	'393 Patent Claim Language	Invalidity Contentions
		discloses the claimed compound in at least two salt forms and further discloses that the sodium salt of the compound is sold as Remodulin® which is an FDA approved treatment. Paragraph [0051].

C. Invalidity of United States Patent No. 7,999,007

United States Patent No. 7,999,007 is entitled "Buffer solutions having selective bactericidal activity against gram negative bacteria and methods of using same." The '007 patent issued on August 16, 2011 and claims the priority date of September 7, 2007. The central feature of each of the asserted claims is the combination of treprostinil and glycine buffer with a pH of greater than 10.

In November 2004, Remodulin (treprostinil) was approved for intravenous use for the treatment of pulmonary hypertension. When administered intravenously, Remodulin must be diluted prior to injection. At the time, the approved diluents were Sterile Water for Injection or 0.9% Sodium Chloride for Injection. Around September 2006, Dr. Robyn Barst, a pulmonary hypertension specialist, contacted UTC and the CDC to inform them she was observing that patients receiving intravenous Remodulin were experiencing higher rates of blood stream infections than patients receiving intravenous administration of another pulmonary hypertension medication called Flolan®. Unlike Remodulin, which was diluted with water or saline, Flolan® was diluted with Sterile Diluent for Flolan®. Sterile Diluent for Flolan® is a glycine buffer with a pH of 10.5. In response, the CDC conducted an investigation and published its results in March, 2007, confirming that the incidence of blood stream infections was greater in patients receiving intravenous Remodulin® than in patients receiving intravenous Flolan®. On September 7, 2007, six months after the CDC report was published and approximately a year

IPR2020-00770
United Therapeutics EX2007
Page 3101 of 7335

after Dr. Barst first raised the infection issue, UTC filed the application that later matured into the '007 patent.

The asserted claims of the '007 patent generally are directed to methods of (i) selectively killing gram negative bacteria and inhibiting the growth of gram positive bacteria in a pharmaceutical preparation comprising supplying an active ingredient with "a buffer comprising glycine having a pH of greater than 10" (claims 1-10); (ii) methods of reducing the "occurrence of blood stream infections" in a mammal comprising "administering to a mammal the active agent with a buffer comprising glycine and having a pH of greater than 10" (claims 11-21); and (iii) pharmaceutical compositions in a solution "comprising glycine and with glycine and having a pH greater than 10" (claims 22-26).

1. Claims 1-5, 7-17 And 19-26 Of The '007 Patent Are Anticipated by EP 0347243A1 Or Obvious Over EP 0347243A1 In View Of Sterile Diluent for Flolan And Knowledge Of One Of Ordinary Skill In The Art.

The asserted patent claims 1-5, 7-17, and 19-26 of the '007 patent are invalid, because they are anticipated by European Patent Application EP 0347243A1 ("EP '243") or obvious over EP '243 in view of Sterile Diluent For Flolan and/or knowledge of one of ordinary skill in the prior art.

EP '243 issued on December 20, 1989, and is, thus, 102(b) prior art. EP '243 patent disclosed and claimed medicaments for the treatment of pulmonary hypertension that could be used subcutaneously or intravenously. EP '243, ¶¶ 22, 25. Example 1 discloses the combination of treprostinil and a "glycine buffer" with a pH of 10.5. EP '243 further describes the use of buffer solutions with treprostinil to treat pulmonary hypertension. EP '243 concludes that treprostinil used with a glycine buffer solution of greater than pH 10 "was found to reduce hypoxia-induced increase in pulmonary arterial pressure and pulmonary vascular resistance in a

IPR2020-00770
United Therapeutics EX2007
Page 3102 of 7335

dose-related manner without appreciably affecting cardiac output or heart rate." *Id.* at ¶¶ 32-34. EP '243 discloses that "sterile" acqueous solutions are preferred and that "[s]uch preparations may conveniently be prepared by admixing the compound with water or a glycine buffer and rendering the resulting solution sterile and isotonic with the blood." *Id.* at ¶ 25. Therefore, EP '243 discloses "a pharmaceutical preparation" or "pharmaceutical composition" comprising "treprostinil" and "a buffer comprising glycine and having a pH of greater than 10." Having a low buffer capcity and the intended purpose—killing bacteria and reducing infections—are inherent properties of a sterile solutions that are sterile and isotonic with the blood. *Id.*

If EP '243 does not anticipate the '007 patent, '007 patent is invalid as obvious over EP '243 patent in view of the commercial embodiment Sterile Diluent for Flolan®. Flolan® is a third party competitive product, containing epoprostenol, which was approved in 1995 for treating pulmonary hypertension. Flolan® is a powder that must be reconstituted with "Sterile Diluent for Flolan" ("SDF"). SDF is a solution containing the amino acid glycine and having a pH greater than 10 that physicians or patients may use to dilute Flolan prior to intravenous infusion. The use of SDF (or a buffer such as SDF) was described, for example, in 1999 Flolan® label and U.S. Patent No. 4,335,139[9]. SDF was available more than 1 year prior to the earliest priority date of the '007 patent and is 102(b) prior art to the '007 patent.

A person of ordinary would have found it obvious to combine Remodulin in combination with SDF, based on EP '243, SDF and knowledge of one of ordinary skill in the art, with a

[9] U.S. Patent No. 4,335,139 was cited by the Examiner during the prosecution of U.S. Patent No. 8,658,694 and appears on the face of 2000 Flolan® label. The '139 patent discloses the use of a prostacyclin with "a pharmaceutically acceptable buffer having a pH value of at least 9 and based on an amino acid as the principal buffering acid in the buffer." '139 patent, col. 1, lines 38-45. "Such a solution and all solutions hereinafter referred to are, for medicinal purposes, to be understood to be sterile solutions." *Id.* at col. 2, lines 4-6. "Glycine" is specifically disclosed as an amino acid of the buffer. *Id.* at Example 1. Example 7 specifically discloses a sterile diluent for injection of a prostacyclin, which contains glycine and has a pH of 10.5. The 2000 Flolan label incorporated by reference the '139 patent as covering Flolan® and SDF.

IPR2020-00770
United Therapeutics EX2007
Page 3103 of 7335

reasonable expectation of success. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). As of the priority date of the '007 patent, Remodulin (treprostinil) was the commercially-available treprostinil product, and SDF was the only commercially-available glycine buffer with a pH of 10.5, already in use with another pulmonary hypertension medication. And as the district court in the related case, *UTC v. Sandoz*, 12-CV-01617, 13-CV-316 (D.N.J. 2014), expressly found, this combination would meet all of the asserted claims of the '007 patent. (Decision at 73.) UTC's expert in the related *Sandoz* matter, Dr. Michael Miller, admitted at trial that a person of ordinary skill in the art, seeking to practice the invention disclosed and claimed in EP '243, could easily have done so by combining Remodulin and Sterile Diluent for Flolan, both of which were commercially available products as of the priority date for the '007 patent.

A person of ordinary skill in the art also would have been motivated to use treprostinil with a high pH buffer comprising glycine with a reasonable expectation of success in inhibiting bacterial growth or reducing the occurrence of blood stream infections. The use of SDF resulted in a high pH glycine buffer solution that was sterile, antibacterial and anti-infective. Moreover, it was well-known in the prior art that glycine is an amino acid that has antibacterial properties. *See e.g.* Foegeding P.M. et al, "Chemical Food Preservatives," Ch. 47 at 825 in Disinfection, Sterilization and Preservation 4th Ed. 1991; Hammes et al., "Mode of Action of Glycine on the Biosynthesis of Peptidoglycoan," J. Bacteriology, Vol. 116, No. 2 pp. 1029-1053 (1973); Strominger et al., "Nucleotide Accumulation Induced in Staphylococcus aureus by Glycine," J. Bacteriology, Vol. 89, No. 4 pp. 1124-1127 (1965). Therefore, as of the priority date, it was also known that a solution in an alkali environment (high pH solutions) with glycine will have bactericidal antiinfective effects. *See, e.g.*, Mendonca, et al, "Destruction of Gram-Negative Food-Borne Pathogens by High pH Involves Disruption of the Cytoplasmic Membrane,: Applied

IPR2020-00770
United Therapeutics EX2007
Page 3104 of 7335

and Environmental Microbiology, vol. 60, No. 11, p. 4009-4014 (1994). ("Mendonca") (disclosed during the prosecution of the '007 patent); Crowther et al., "Growth of Microorganisms in Propofol, Thiopental, and a 1:1 Mixture Of Propofol and Thiopental," Anesth. Analg., 82: 475-478 (1996) ("Crowther") (TEVA_TRE_0004034-7); and Siqueira et al., Mechanisms of antimicrobial activity of calcium hydroxide: a critical review," Intern. Endodontic J., 32, pp. 361-369, (1999) ("Siqueira) (TEVA_TRE_0004298-306).

Consistent with the fact that glycine and high pH solutions have known antibacterial properties, the prior art describes glycine buffer solutions that have high pH used in pharmaceutical formulations. U.S. Appln. No. 10/137,331; 1999 Flolan Package Insert; EP '243; Wade 2005 [0030]; 2005 PDR. Indeed, the prior art specifically describes with treprostinil with high pH glycine buffer solutions for use in pharmaceutical compositions. EP '243; Wade 2005. Moreover, a person of ordinary skill would have been motivated to address possible complications from bacterial infections when the drug is administered intravenously.

A solution having "a low buffer capacity" also would have been known to a person of ordinary skill in the art. Claims 1-5, 7-10, 16-17, and 21 also require that the glycine buffer used in the claimed methods have a low buffer capacity. The '007 patent states that "the buffer capacity should be low to avoid pH changes in the blood upon infusion." Col. 2, lines 34-35. SDF inherently possesses this limitation. Moreover, it would have been obvious to a person of ordinary skill in the art that it is important to maintain the proper pH of blood to avoid possible severe complications. *See e.g.* Petrucci, R. and Harwood, W., General Chemistry Principles and Modern Applications, 6th Ed., 1993, pp. 656-57 (explaining that the normal pH of blood is 7.4 and increased pH of blood can lead to severe vomiting and hyperventilation). Consequently, it would have been obvious to a person of ordinary skill to formulate the high pH buffer solution

IPR2020-00770
United Therapeutics EX2007
Page 3105 of 7335

with a low buffer capacity, so that it would be safe and avoid any complications based on changes of blood pH when the treprostinil solution is administered. *See also* EP '243 at 5.

The dependent claims the depend from claim 1 are obvious for the same reasons as stated above. Furthermore, dependent claim 2 requires that the active agent is treprostinil sodium. The prior art specifically describes the use of glycine buffered solutions with treprostinil. EP '243; Wade 2005 [0030]. Also, the 2006 Remodulin Package Insert describes the use of treprostinil as the active ingredient. Dependent claim 3 requires the buffer to contain sodium hydroxide. SDF contained sodium hydroxide. Moreover, the 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem describes sodium hydroxide used in the glycine buffer solution. Dependent claims 4 and 5 require the buffer solution to have a pH between about 10 to about 12 or 10.2 to 10.8, respectively. The 1999 Flolan Package Insert and the 2005 PDR, and Calbiochem describe the pH of the glycine buffer from 10.2 to 10.8, and EP '243 describes such a formulation at Example 1. Dependent claim 7 requires the active agent to be at a concentration between about 0.001 mg/mL to about 1 mg/mL, and dependent claim 8 requires treprostinil sodium to be at a concentration between about 0.004 mg/mL to about 0.13 mg/mL. EP '243 and the 2006 Remodulin Package Insert disclose concentrations that cover this ranges. EP '243 at 5. Dependent claims 9 and 10 require that pharmaceutical preparation is injected, for claim 10 injected intravenously, into a mammal in need thereof. EP '243, 1999 Flolan Package Insert, the 2005 PDR, the 2006 Remodulin Package Insert, and Wade 2005 all describe the injection of the pharmaceutical preparation into mammals for treatment.

The dependent claims the depend from claim 11 are obvious for the same reasons as stated above. Furthermore, dependent claim 12 requires that a human subject undergoing the method has pulmonary arterial hypertension. EP '243, 1999 Flolan Package Insert, the 2005

IPR2020-00770
United Therapeutics EX2007
Page 3106 of 7335

PDR, the 2006 Remodulin Package Insert, and Wade 2005 all describe the use of the active ingredient to treat pulmonary arterial hypertension. Also, the dependent claims the depend from claim 22 are obvious for the same reasons as stated above.

Plaintiff has not set forth its contentions concerning secondary considerations in this case. If Plaintiff relies on any secondary considerations of non-obviousness, Teva reserves the right to supplement its contentions.

2. Claims 1-5, 7-17, And 19-26 Of The '007 Patent Are Not Enabled And/Or Lack A Written Description

As explained above, a person of ordinary skill in the art would have found the asserted claims anticipated or obvious in view of the prior art. A person of ordinary skill would have been able to take the information in the prior art and apply routine experimentation to arrive at the methods and compositions of the asserted claims. But if Plaintiff contends that that the asserted claims are not invalid because a person of ordinary skill would need to practice undue experimentation from the disclosures in the prior art, then the asserted claims are invalid because they are not enabled and the patent does not contain a sufficient written description.

The '007 patent generally describes solutions with an active ingredient, glycine, a high pH, and a low buffer capacity. Further, it gives general and broad ranges for these ingredients and requirements and specifically does not restrict them to indicate that only a narrow range for those ingredients and requirements will work. For example, it describes glycine concentrations "of about 30% to about 80%" and an active ingredient concentration of preferably 0.004 mg/mL to about 0.13 mg/mL. If Plaintiff contends that the prior art is not enabled or a person of ordinary skill would need to conduct undue experimentation based on the disclosures in the prior art, then the asserted claims of the '007 patent would lack enablement and fail to meet the written description requirement because a person of ordinary skill in the art would need to conduct

IPR2020-00770
United Therapeutics EX2007
Page 3107 of 7335

undue experimentation to enable the full scope of the claims, and the patent lacks any written description as to all of the alleged proper parameters for the claimed methods and compositions.

The following prior art shows all of the limitations of the '007 patent, including the use of glycine buffers to inhibit bacterial growth or reduce bloodbourne infections, prior to September 7, 2007, the priority date of the '007 patent:

- EP '243 (TEVA_TRE_0004270-80)
- U.S. Patent Publication No. 2005/0165110 July 2005, Wade et al. ("Wade 2005") (TEVA_TRE_0004213-218)
- Crowther et al., "Growth of Microorganisms in Propofol, Thiopental, and a 1:1 Mixture Of Propofol and Thiopental," *Anesth. Analg., 82:* 475-478 (1996) ("Crowther") (TEVA_TRE_0004034-7)
- Siqueira et al., Mechanisms of antimicrobial activity of calcium hydroxide: a critical review," Intern. Endodontic J., 32, pp. 361-369, (1999) ("Siqueira) (TEVA_TRE_0004298-306)
- Foegeding P.M. et al, "Chemical Food Preservatives," Ch. 47 in Disinfection, Sterilization and Preservation 4th Ed. 1991. (TEVA_TRE_0004267-9)
- Hammes et al., "Mode of Action of Glycine on the Biosynthesis of Peptidoglycoan," J. Bacteriology, Vol. 116, No. 2 pp. 1029-1053 (1973) (TEVA_TRE_0004042-66)
- Strominger et al., "Nucleotide Accumulation Induced in Staphylococcus aureus by Glycine," J. Bacteriology, Vol. 89, No. 4 pp. 1124-1127 (1965) (TEVA_TRE_0004038-41)
- "Buffers: A guide for the preparation and use of buffers in biological systems" by Calbiochem ("Calbiochem") (TEVA_TRE_0003997-4033)
- 2006 Remodulin Package Insert (TEVA_TRE_0004285-97)
- 1999 Flolan Package Insert (TEVA_TRE_0004281-84)
- The 2005 Physicians' Desk Reference for Flolan® (epoprostenol sodium for injection) ("2005 PDR") (TEVA_TRE_0003991-6)
- Petrucci, R. and Harwood, W., General Chemistry Principles and Modern Applications, 6th Ed., pp. 656-57 (1993) (Teva_TRE_0003971-4)

IPR2020-00770
United Therapeutics EX2007
Page 3108 of 7335

- Prior art disclosed or cited during prosecution of the '007, '137, and '694 patents.

Teva expressly reserves the right to modify and/or supplement the above list at any time as necessary and/or as discovery progresses.

The following chart incorporates the analysis set forth above and identifies where specifically in each alleged item of prior art each limitation of each asserted claim is found:

	'007 Patent Claim Language	Invalidity Contentions
1	A method of selectively killing gram negative bacteria and inhibiting the growth of gram positive bacteria in a pharmaceutical preparation comprising an active agent selected from the group consisting of treprostinil and treprostinil sodium, the method comprising supplying the active agent with a buffer comprising glycine and having a pH of greater than 10 with low buffer capacity.	**Anticipation:** Claim 1 of the '007 patent is invalid, because it is anticipated by European Patent Application EP 0347243A1 ("EP '243") or obvious over EP '243 in view of Sterile Diluent For Flolan and/or knowledge of one of ordinary skill in the prior art. EP '243 issued on December 20, 1989, and is, thus, 102(b) prior art. EP '243 patent disclosed and claimed medicaments for the treatment of pulmonary hypertension that could be used subcutaneously or intravenously. EP '243, ¶¶ 22, 25. Example 1 discloses the combination of treprostinil and a "glycine buffer" with a pH of 10.5. EP '243 further describes the use of buffer solutions with treprostinil to treat pulmonary hypertension. EP '243 concludes that treprostinil used with a glycine buffer solution of greater than pH 10 "was found to reduce hypoxia-induced increase in pulmonary arterial pressure and pulmonary vascular resistance in a dose-related manner without appreciably affecting cardiac output or heart rate." *Id.* at ¶¶ 32-34. EP '243 discloses that "sterile" acqueous solutions are preferred and that "[s]uch preparations may conveniently be prepared by admixing the compound with water or a glycine buffer and rendering the resulting solution sterile and isotonic with the blood." *Id.* at ¶ 25. Therefore, the pharmaceutical preparation of EP '243 inherently inhibits growth of gram positive bacteria and, if given to a person, will inherently kill gram negative bacteria. Therefore, EP '243 discloses "a pharmaceutical preparation" or "pharmaceutical composition" comprising "treprostinil" and "a buffer comprising glycine and having a pH of greater than 10" with the

IPR2020-00770
United Therapeutics EX2007
Page 3109 of 7335

	'007 Patent Claim Language	Invalidity Contentions
		inherent qualities described in the claims. Moreover, having a low buffer capcity is an inherent property of sterile solutions with a high pH that are isotonic with the blood and are intended to be given to humans, as the pH of the pharmaceutical preparation should quickly adjust to the pH of blood, which is substantially lower than pH of 10. *Id.* **Obviousness:** If EP '243 does not anticipate the '007 patent, '007 patent is invalid as obvious over EP '243 patent in view of the commercial embodiment Sterile Diluent for Flolan®. Flolan® is a third-party competitive product, containing epoprostenol, which was approved in 1995 for treating pulmonary hypertension. Flolan® is a powder that must be reconstituted with "Sterile Diluent for Flolan" ("SDF"). SDF is a solution containing the amino acid glycine and having a pH greater than 10 that physicians or patients may use to dilute Flolan prior to intravenous infusion. The use of SDF (or a buffer such as SDF) was described, for example, in 1999 Flolan® label and U.S. Patent No. 4,335,139[10]. SDF was available more than 1 year prior to the earliest priority date of the '007 patent and is 102(b) prior art to the '007 patent. A person of ordinary skill in the art would have found it obvious to combine Remodulin in combination with SDF, based on the teachings of EP '243, the existing knowledge and use of SDF, and knowledge of one of ordinary skill in the art, with a reasonable expectation of success at arriving at the claimed invention. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). As of the priority date of the '007 patent, Remodulin (treprostinil) was the commercially-available treprostinil product, and SDF was the only commercially-available glycine buffer with a pH of 10.5, already in use with another pulmonary hypertension medication. And as the district court in the

[10] U.S. Patent No. 4,335,139 was cited by the Examiner during the prosecution of U.S. Patent No. 8,658,694 and appears on the face of 2000 Flolan® label. The '139 patent discloses the use of a prostacyclin with "a pharmaceutically acceptable buffer having a pH value of at least 9 and based on an amino acid as the principal buffering acid in the buffer." '139 patent, col. 1, lines 38-45. "Such a solution and all solutions hereinafter referred to are, for medicinal purposes, to be understood to be sterile solutions." *Id.* at col. 2, lines 4-6. "Glycine" is specifically disclosed as an amino acid of the buffer. *Id.* at Example 1. Example 7 specifically discloses a sterile diluent for injection of a prostacyclin, which contains glycine and has a pH of 10.5. The 2000 Flolan label incorporated by reference the '139 patent as covering Flolan® and SDF.

IPR2020-00770
United Therapeutics EX2007
Page 3110 of 7335

	'007 Patent Claim Language	Invalidity Contentions
		related case, *UTC v. Sandoz*, 12-CV-01617, 13-CV-316 (D.N.J. 2014), expressly found, this combination would meet all of the asserted claims of the '007 patent. (Decision at 73.) UTC's expert in the related *Sandoz* matter, Dr. Michael Miller, admitted at trial that a person of ordinary skill in the art, seeking to practice the invention disclosed and claimed in EP '243, could easily have done so by combining Remodulin and Sterile Diluent for Flolan, both of which were commercially available products as of the priority date for the '007 patent. A person of ordinary skill in the art also would have been motivated to use treprostinil with a high pH buffer comprising glycine with a reasonable expectation of success in inhibiting bacterial growth or reducing the occurrence of blood stream infections. The use of SDF resulted in a high pH glycine buffer solution that was sterile, antibacterial and anti-infective. Moreover, it was well-known in the prior art that glycine is an amino acid that has antibacterial properties. *See e.g.* Foegeding P.M. et al, "Chemical Food Preservatives," Ch. 47 at 825 in Disinfection, Sterilization and Preservation 4th Ed. 1991; Hammes et al., "Mode of Action of Glycine on the Biosynthesis of Peptidoglycoan," J. Bacteriology, Vol. 116, No. 2 pp. 1029-1053 (1973); Strominger et al., "Nucleotide Accumulation Induced in Staphylococcus aureus by Glycine," J. Bacteriology, Vol. 89, No. 4 pp. 1124-1127 (1965). Therefore, as the following prior art explains, as of the priority date, it was also known that a solution in an alkali environment (high pH solutions) with glycine will have bactericidal antiinfective effects. *See, e.g.*, Mendonca, et al, "Destruction of Gram-Negative Food-Borne Pathogens by High pH Involves Disruption of the Cytoplasmic Membrane,: Applied and Environmental Microbiology, vol. 60, No. 11, p. 4009-4014 (1994). ("Mendonca") (disclosed during the prosecution of the '007 patent); Crowther et al., "Growth of Microorganisms in Propofol, Thiopental, and a 1:1 Mixture Of Propofol and Thiopental," Anesth. Analg., 82: 475-478 (1996) ("Crowther") (TEVA_TRE_0004034-7); and Siqueira et al., Mechanisms of antimicrobial activity of calcium

IPR2020-00770
United Therapeutics EX2007
Page 3111 of 7335

	'007 Patent Claim Language	Invalidity Contentions
		hydroxide: a critical review," Intern. Endodontic J., 32, pp. 361-369, (1999) ("Siqueira) (TEVA_TRE_0004298-306). Consistent with the fact that glycine and high pH solutions have known antibacterial properties, the prior art describes glycine buffer solutions that have high pH for use in pharmaceutical formulations. *See* U.S. Appln. No. 10/137,331 (disclosed during prosecution of the '007 patent); 1999 Flolan Package Insert (TEVA_TRE_0004281-84) (disclosing the use of SDF and SDF's qualities); EP '243 (TEVA_TRE_0004270-80) (discussed in more detail above); U.S. Patent Publication No. 2005/0165110 (July 2005) by Wade et al. at [0030] ("Wade 2005") (TEVA_TRE_0004213-218); and The 2005 Physicians' Desk Reference for Flolan® (epoprostenol sodium for injection) ("2005 PDR") (TEVA_TRE_0003991-6) (disclosing SDF, its use, and qualities). Indeed, as discussed earlier, the prior art specifically describes, suggests, and combines treprostinil with a high pH glycine buffer solutions for use in pharmaceutical compositions for humans. See EP '243; Wade 2005. As is evident from thee disclosures, a person of ordinary skill would have been motivated to address possible complications from bacterial infections when treprostinil is administered intravenously, as suggested by the use of SDF and the disclosures of EP '243. A solution having "a low buffer capacity," if not inherent, also would have been known to a person of ordinary skill in the art. (Claims 1-5, 7-10, 16-17, and 21 also require that the glycine buffer used in the claimed methods have a low buffer capacity, so this analysis applies to the other claims with equal force.) The '007 patent states that "the buffer capacity should be low to avoid pH changes in the blood upon infusion." Col. 2, lines 34-35. SDF inherently possesses this limitation. Moreover, it would have been obvious to a person of ordinary skill in the art that it is important to maintain the proper pH of blood to avoid possible severe complications. *See e.g.* Petrucci, R. and Harwood, W., General Chemistry Principles and Modern Applications, 6th Ed., 1993, pp. 656-57 (explaining that the normal pH of blood is 7.4 and increased pH of blood can lead to

IPR2020-00770
United Therapeutics EX2007
Page 3112 of 7335

	'007 Patent Claim Language	Invalidity Contentions
		severe vomiting and hyperventilation). Consequently, it would have been obvious to a person of ordinary skill to formulate the high pH buffer solution with a low buffer capacity, so that it would be safe and avoid any complications based on changes of blood pH when the treprostinil solution is administered. *See also* EP '243 at 5. Plaintiff has not set forth its contentions concerning secondary considerations in this case. If Plaintiff relies on any secondary considerations of non-obviousness, Teva reserves the right to supplement its contentions.
2	The method of claim 1, wherein the active agent is treprostinil sodium.	Dependent claim 2 incorporates the method of claim 1; therefore, the contentions incorporate the analysis from claim 1 in its entirety. Claim 2 further specifies that the active agent is treprostinil sodium. The prior art specifically describes the use of glycine buffered solutions with treprostinil. EP '243; Wade 2005 [0030]. Also, the 2006 Remodulin Package Insert describes the use of treprostinil as the active ingredient.
3	The method of claim 1, wherein the buffer further comprises sodium hydroxide.	Dependent claim 3 incorporates the method of claim 1, therefore the contentions incorporate the analysis from claim 1 in its entirety. Dependent claim 3 further specifies that the buffer to contain sodium hydroxide. SDF contained sodium hydroxide. Moreover, the 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem describes sodium hydroxide as a basic agent that can be used to adjust the pH of a solution and can be used in the glycine buffer solution.
4	The method of claim 1, wherein the buffer has a pH between about 10 to about 12 with low buffer capacity.	Dependent claim 4 incorporates the method of claim 1, therefore the contentions incorporate the analysis from claim 1 in its entirety. Dependent claim 4 further requires the buffer solution to have a pH between about 10 to about 12. The 1999 Flolan Package Insert and the 2005 PDR, and Calbiochem describe the pH of the glycine buffer from 10.2 to 10.8, and EP '243 describes such a formulation at Example 1. Therefore, the pH range claimed herein is disclosed in the prior art.
5	The method of claim 4, wherein the buffer has a pH between about 10.2 to about 10.8 with low buffer capacity.	Dependent claim 5 incorporates the method of claim 1; therefore, the contentions incorporate the analysis from claim 1 in its entirety. Dependent claims 5 further requires the buffer solution to have a pH between about 10.2 to 10.8. The 1999 Flolan Package Insert and the 2005 PDR, and Calbiochem describe the pH of the glycine buffer from 10.2 to 10.8, and EP '243 describes

IPR2020-00770
United Therapeutics EX2007
Page 3113 of 7335

	'007 Patent Claim Language	Invalidity Contentions
		such a formulation at Example 1. Therefore, the pH range claimed herein is disclosed in the prior art.
7	The method of claim 1, wherein the active agent is supplied at a concentration between about 0.001 mg/mL to about 1 mg/mL.	Dependent claim 7 incorporates the method of claim 1; therefore, the contentions incorporate the analysis from claim 1 in its entirety. Dependent claim 7 further specifies the active agent to be at a concentration between about 0.001 mg/mL to about 1 mg/mL. EP '243 and the 2006 Remodulin Package Insert at dosing instruction disclose concentrations that specifically cover this ranges. *E.g.*, EP '243 at 5.
8	The method of claim 2, wherein the treprostinil sodium is supplied at a concentration between about 0.004 mg/mL to about 0.13 mg/mL.	Dependent claim 8 incorporates the method of claim 1; therefore, the contentions incorporate the analysis from claim 1 in its entirety. Dependent claim 8 further specifies the active agent to be at a concentration between about 0.004 mg/mL to about 0.13 mg/mL. EP '243 and the 2006 Remodulin Package Insert at dosing instruction disclose concentrations that specifically cover this ranges. *E.g.*, EP '243 at 5.
9	The method of claim 1 further comprising injecting the pharmaceutical preparation into a mammal in need thereof.	Dependent claim 9 incorporates the method of claim 1; therefore, the contentions incorporate the analysis from claim 1 in its entirety. Dependent claim 9 requires that pharmaceutical preparation is injected into a mammal in need thereof. This is specifically disclosed, as described in more detail above, in EP '243, 1999 Flolan Package Insert, the 2005 PDR, the 2006 Remodulin Package Insert, and Wade 2005. The prior art describes the injection of the pharmaceutical preparation into mammals for treatment.
10	The method of claim 4, wherein the pharmaceutical preparation is injected intravenously into a mammal in need thereof.	Dependent claim 9 incorporates the method of claim 1; therefore, the contentions incorporate the analysis from claim 1 in its entirety. Dependent claim 10 requires that pharmaceutical preparation is injected intravenously into a mammal in need thereof. This is specifically disclosed, as described in more detail above, in EP '243, 1999 Flolan Package Insert, the 2005 PDR, the 2006 Remodulin Package Insert, and Wade 2005. The prior art describes the injection of the pharmaceutical preparation into mammals for treatment.
11	A method of reducing the occurrence of blood stream infections in a mammal being treated with an active agent comprising administering to the mammal the active agent with a buffer comprising glycine and	Claim 11 is substantially the same as claim 1, except that it is directed to "reducing the occurrence of blood stream infections in a mammal being treated with an active agent." Teva hereby incprorates all analysis from claim 1 into this contention. The purpose of the active agent is an inherent quality of an agent that is injected into a mammal. Moreover, reducing the occurrence of blood

IPR2020-00770
United Therapeutics EX2007
Page 3114 of 7335

	'007 Patent Claim Language	Invalidity Contentions
	having a pH of greater than 10, wherein the active agent is selected from the group consisting of treprostinil and treprostinil sodium, and wherein the administration reduces the gram negative bacteria and inhibits the growth of gram positive bacteria.	stream infections would have been an important quality of any injectable.
12	The method of claim 11, wherein the human subject has pulmonary arterial hypertension.	Dependent claim 12 incorporates the method of claim 11; therefore, the contentions incorporate the analysis from claim 11 in its entirety. Dependent claim 12 further specifies that a human subject undergoing the method has pulmonary arterial hypertension. The prior art specifically discloses this additional limitation, as discussed more fully above, including at EP '243, 1999 Flolan Package Insert, the 2005 PDR, the 2006 Remodulin Package Insert, and Wade 2005. Therefore, the prior art describes the use of the active ingredient to treat pulmonary arterial hypertension. Moreover, this additional limitation would have required only routine optimization of the prior art combinations.
13	The method of claim 11, where in the active agent is administered intravenously.	Dependent claim 13 incorporates the method of claim 11; therefore, the contentions incorporate the analysis from claim 11 in its entirety (which in turn incorporates the analysis of claim 1). The prior art disclosed with respect to the analysis in claims 1 and 11 teaches the active agent that is administered intravenously. Moreover, this additional limitation would have required only routine optimization of the prior art combinations.
14	The method of claim 11, wherein the active agent is treprostinil sodium.	Dependent claim 14 incorporates the method of claim 11; therefore, the contentions incorporate the analysis from claim 11 in its entirety (which in turn incorporates the analysis of claim 1). The prior art disclosed with respect to the analysis in claims 1 and 11 teaches that the active agent is treprostinil sodium. Moreover, this additional limitation would have required only routine optimization of the prior art combinations.
15	The method of claim 11, wherein the buffer further comprises sodium hydroxide and has a pH between about 10.2 to about 10.8.	Dependent claim 15 incorporates the method of claim 11; therefore, the contentions incorporate the analysis from claim 11 in its entirety (which in turn incorporates the analysis of claim 1). The prior art disclosed with respect to the analysis in claims 1 and 11 teach that the buffer further comprises sodium hydroxide and has a pH between about 10.2 to about 10.8. Moreover, this

IPR2020-00770
United Therapeutics EX2007
Page 3115 of 7335

	'007 Patent Claim Language	Invalidity Contentions
		additional limitation would have required only routine optimization of the prior art combinations.
16	The method of claim 11, wherein the buffer has a pH between about 10 to about 12 with low buffer capacity.	Dependent claim 16 incorporates the method of claim 11; therefore, the contentions incorporate the analysis from claim 11 in its entirety (which in turn incorporates the analysis of claim 1). The prior art disclosed with respect to the analysis in claims 1 and 11 teaches that the buffer has a pH between about 10 to about 12 with low buffer capacity. Moreover, this additional limitation would have required only routine optimization of the prior art combinations.
17	The method of claim 16, wherein the buffer has a pH between about 10.2 to about 10.8 with low buffer capacity.	Dependent claim 17 incorporates the method of claim 11; therefore, the contentions incorporate the analysis from claim 11 in its entirety (which in turn incorporates the analysis of claim 1). The prior art disclosed with respect to the analysis in claims 1 and 11 teaches that the buffer has a pH between about 10.2 to about 10.8 with low buffer capacity. Moreover, this additional limitation would have required only routine optimization of the prior art combinations.
19	The method of claim 11, wherein the active agent is supplied at a concentration between about 0.004 mg/mL to about 0.13 mg/ml.	Dependent claim 19 incorporates the method of claim 11; therefore, the contentions incorporate the analysis from claim 11 in its entirety (which in turn incorporates the analysis of claim 1). The prior art disclosed with respect to the analysis in claims 1 and 11 teaches that the active agent is supplied at a concentration between about 0.004 mg/mL to about 0.13 mg/ml. Moreover, this additional limitation would have required only routine optimization of the prior art combinations.
20	The method of claim 14, wherein the treprostinil sodium is supplied at a concentration between about 0.004 mg/mL to about 0.13 mg/mL.	Dependent claim 20 incorporates the method of claim 14; therefore, the contentions incorporate the analysis from claim 14 in its entirety (which in turn incorporates the analysis of claims 1 and 11). The prior art disclosed with respect to the analysis in claims 1 and 11 teaches that treprostinil sodium is supplied at a concentration between about 0.004 mg/mL to about 0.13 mg/mL Moreover, this additional limitation would have required only routine optimization of the prior art combinations.
21	The method of claim 1 wherein the administering is injecting the pharmaceutical preparation into a mammal in need thereof.	Dependent claim 16 incorporates the method of claim 1; therefore, the contentions incorporate the analysis from claim 1 in its entirety. The prior art disclosed with respect to the analysis in claim 1 teaches injecting the pharmaceutical preparation into a mammal in need thereof. Moreover, this additional limitation would have required only routine optimization of the prior art

IPR2020-00770
United Therapeutics EX2007
Page 3116 of 7335

	'007 Patent Claim Language	Invalidity Contentions
		combinations.
22	A pharmaceutical composition comprising an active agent selected from the group consisting of treprostinil and treprostinil sodium in a solution comprising glycine and having a pH greater than 10.	Claim 2 is directed to a pharmaceutical composition comprising treprostinil in a solution comprising glycine having a pH greater than 10. All of the prior art and analysis cited in claim 1 are directly applicable to claim 22, as claim 22 is substantially same as the "pharmaceutical preparation" that is administered in claim 1.
23	The composition of claim 22, wherein the solution further comprises sodium hydroxide.	Dependent claim 23 incorporates the method of composition of 22; therefore, the contentions incorporate the analysis from claim 22 in its entirety (which in turn incorporates the analysis of claim 1). The prior art further discloses the solution has sodium hydroxide.
24	The composition of claim 22, wherein the solution has a pH between about 10 to about 12.	Dependent claim 24 incorporates the method of composition of 22, therefore the contentions incorporate the analysis from claim 22 in its entirety (which in turn incorporates the analysis of claim 1). The prior art further discloses the solution has pH between about 10-12. Moreover, this additional limitations would have required only routine optimization of the prior art combinations.
25	The composition of claim 24, wherein the solution has a pH between about 10.2 to about 10.8.	Dependent claim 25 incorporates the method of composition of 22, therefore the contentions incorporate the analysis from claim 22 in its entirety (which in turn incorporates the analysis of claim 1). The prior art further discloses the solution has pH between about 10.2-10.8. Moreover, this additional limitation would have required only routine optimization of the prior art combinations.
26	The composition of claim 22, wherein the active agent is treprostinil sodium.	Dependent claim 26 incorporates the method of composition of 22; therefore, the contentions incorporate the analysis from claim 22 in its entirety (which in turn incorporates the analysis of claim 1). The prior art further discloses the active agent is treprostinil sodium. Moreover, this additional limitation would have required only routine optimization of the prior art combinations.

D. Invalidity of United States Patent No. 8,653,137

United States Patent No. 8,653,137, entitled "Buffer solutions having selective bactericidal activity against gram negative bacteria and methods of using same," was issued on February 18, 2014 with 13 claims. Claims 1-13 of the '137 patent are directed to methods of

IPR2020-00770
United Therapeutics EX2007
Page 3117 of 7335

reducing the occurrence of a bacterial infection "comprising diluting a starting solution of an active pharmaceutical ingredient other than epoprostenol with a buffer comprising glycine and having a pH of greater than 10" and administering the buffered solution "to the human subject in need thereof."

UTC asserts that Teva infringes claims 1-13 of the '137 patent. Claim 1 is the only independent claim of the '137 patent:

> 1. A method of reducing occurrence of a bacterial infection in a human suffering from pulmonary arterial hypertension, who is undergoing treatment for said pulmonary hypertension, associated with occurrence of a bacterial infection comprising diluting a starting solution of an active pharmaceutical ingredient other than epoprostenol with a buffer comprising glycine and having a pH of greater than 10 to provide a final solution with a pH of greater than 10 and an amount of the active pharmaceutical ingredient other than epoprostenol effective for treating pulmonary arterial hypertension, and administering said final solution to the human subject in need thereof.

The '137 patent shares the same priority date as the '007 patent, substantially the same specification, and is in the same family of patent as the '007 patent. The scope of the claims, accordingly, are substantially similar and comprise generally the same subject matter (e.g., reducing infection with treprostinil plus buffer solution having glycine and having pH greater than 10). Therefore, Teva asserts that the claims of the '137 patent are invalid for substantially the same reasons as the '007 patent.

Teva is not aware of any such secondary considerations that, when considered with the evidence of obviousness, would warrant a finding of non-obviousness of the claims of the '137 patent. During the prosecution of the '137 patent, applicants contended, without any declaration, that the claimed methods showed an unexpected antibacterial effect. But as shown above in the contentions for the '007 patent, the prior art clearly demonstrates that the antibacterial effect of

IPR2020-00770
United Therapeutics EX2007
Page 3118 of 7335

the claimed buffer was well-known and expected. If UTC relies on any secondary considerations of non-obviousness, Teva reserves the right to supplement its contentions.

The following prior art shows all of the limitations of the '137 patent, including the use of glycine buffers to inhibit bacterial growth, prior to September 7, 2007, the priority date of the '137 patent:

- EP '243 (TEVA_TRE_0004270-80)
- U.S. Patent Publication No. 2005/0165110 July 2005, Wade et al. ("Wade 2005") (TEVA_TRE_0004213-218)
- Crowther et al., "Growth of Microorganisms in Propofol, Thiopental, and a 1:1 Mixture Of Propofol and Thiopental," *Anesth. Analg., 82:* 475-478 (1996) ("Crowther") (TEVA_TRE_0004034-7)
- Siqueira et al., Mechanisms of antimicrobial activity of calcium hydroxide: a critical review," Intern. Endodontic J., 32, pp. 361-369, (1999) ("Siqueira) (TEVA_TRE_0004298-306)
- Foegeding P.M. et al, "Chemical Food Preservatives," Ch. 47 in Disinfection, Sterilization and Preservation 4th Ed. 1991. (TEVA_TRE_0004267-9)
- Hammes et al., "Mode of Action of Glycine on the Biosynthesis of Peptidoglycoan," J. Bacteriology, Vol. 116, No. 2 pp. 1029-1053 (1973) (TEVA_TRE_0004042-66)
- Strominger et al., "Nucleotide Accumulation Induced in Staphylococcus aureus by Glycine," J. Bacteriology, Vol. 89, No. 4 pp. 1124-1127 (1965) (TEVA_TRE_0004038-41)
- "Buffers: A guide for the preparation and use of buffers in biological systems" by Calbiochem ("Calbiochem") (TEVA_TRE_0003997-4033)
- 2006 Remodulin Package Insert (TEVA_TRE_0004285-97)
- 1999 Flolan Package Insert (TEVA_TRE_0004281-84)
- The 2005 Physicians' Desk Reference for Flolan® (epoprostenol sodium for injection) ("2005 PDR") (TEVA_TRE_0003991-6)
- Petrucci, R. and Harwood, W., General Chemistry Principles and Modern Applications, 6th Ed., pp. 656-57 (1993) (Teva_TRE_0003971-4)

IPR2020-00770
United Therapeutics EX2007
Page 3119 of 7335

- Prior art disclosed or cited during prosecution of the '007, '137, and '694 patents.

Teva expressly reserves the right to modify and/or supplement the above list at any time as necessary and/or as discovery progresses.

	'137 Patent Claim Language	Invalidity Contentions
1	A method of reducing occurrence of a bacterial infection in a human suffering from pulmonary arterial hypertension, who is undergoing treatment for said pulmonary hypertension, associated with occurrence of a bacterial infection comprising diluting a starting solution of an active pharmaceutical ingredient other than epoprostenol with a buffer comprising glycine and having a pH of greater than 10 to provide a final solution with a pH of greater than 10 and an amount of the active pharmaceutical ingredient other than epoprostenol effective for treating pulmonary arterial hypertension, and administering said final solution to the human subject in need thereof.	Claim 1 of the '137 patent is invalid for the same reasons as the '007 patent and Teva hereby incorporates by reference the analysis set forth for claim 1 of the '007 patent. The '137 patent shares the same priority date as the '007 patent, substantially the same specification, and is in the same family of patent as the '007 patent. The scope of the claims, accordingly, are substantially similar and comprise generally the same subject matter (e.g., reducing infection with treprostinil plus buffer solution having glycine and having pH greater than 10). Claim 1 of the '137 patent specifies that "a human is suffering from pulmonary arterial hypertension, who is undergoing treatment for said pulmonary hypertension, associated with occurrence of a bacterial infection" and that the product is an "active pharmaceutical ingredient other than epoprostenol." The prior art treprostinil formulation is an active pharmaceutical ingredient other than epoprostenol and, as shown below, the teachings of the prior art sufficiently disclose and teach that the person to whom the pharmaceutical composition is administered suffers from PAH and may suffer a bacterial infection (due to having a non-sterile solution). Therefore, the same analysis and prior art would apply to the invalidity contention for the '137 patent, and if the '007 patent is invalid, the '137 patent would be invalid as well. **Anticipation:** Claim 1 of the '137 patent is invalid, because it is anticipated by European Patent Application EP 0347243A1 ("EP '243") or obvious over EP '243 in view of Sterile Diluent For Flolan and/or knowledge of one of ordinary skill in the prior art. EP '243 issued on December 20, 1989, and is, thus, 102(b) prior art. EP '243 patent disclosed and claimed medicaments for the treatment of persons suffering from pulmonary hypertension that could be used subcutaneously or intravenously. EP '243, ¶¶ 22, 25.

IPR2020-00770
United Therapeutics EX2007
Page 3120 of 7335

	'137 Patent Claim Language	Invalidity Contentions
		Example 1 discloses the combination of treprostinil and a "glycine buffer" with a pH of 10.5. EP '243 further describes the use of buffer solutions with treprostinil to treat pulmonary hypertension. EP '243 concludes that treprostinil used with a glycine buffer solution of greater than pH 10 "was found to reduce hypoxia-induced increase in pulmonary arterial pressure and pulmonary vascular resistance in a dose-related manner without appreciably affecting cardiac output or heart rate." *Id.* at ¶¶ 32-34. EP '243 discloses that "sterile" acqueous solutions are preferred and that "[s]uch preparations may conveniently be prepared by admixing the compound with water or a glycine buffer and rendering the resulting solution sterile and isotonic with the blood." *Id.* at ¶ 25. Therefore, the pharmaceutical preparation of EP '243 inherently inhibits growth of gram positive bacteria associated with occurrence of a bacterial infection and, if given to a person, will inherently kill gram negative bacteria. Therefore, EP '243 discloses "a pharmaceutical preparation" or "pharmaceutical composition" comprising "treprostinil" (active ingredient other than epoprostenol") and "a buffer comprising glycine and having a pH of greater than 10" with the inherent qualities described in the claims. Moreover, having a low buffer capcity is an inherent property of a sterile solutions with a high pH that are isotonic with the blood and are intended to be given to humans, as the pH of the pharmaceutical preparation should quickly adjust to the pH of blood, which is substantially lower than pH of 10. *Id.* **Obviousness:** If EP '243 does not anticipate the '137 patent, the '137 patent is invalid as obvious over EP '243 patent in view of the commercial embodiment Sterile Diluent for Flolan®. Flolan® is a third party competitive product, containing epoprostenol, which was approved in 1995 for treating pulmonary hypertension. Flolan® is a powder that must be reconstituted with "Sterile Diluent for Flolan" ("SDF"). SDF is a solution containing the amino acid glycine and having a pH greater than 10 that physicians or patients may use to dilute Flolan prior to intravenous infusion. The use of SDF (or a buffer such

	'137 Patent Claim Language	Invalidity Contentions
		as SDF) was described, for example, in 1999 Flolan® label and U.S. Patent No. 4,335,139. SDF was available more than 1 year prior to the earliest priority date of the '137 patent and is 102(b) prior art to the '137 patent. A person of ordinary would have found it obvious to combine Remodulin in combination with SDF, based on the teachings of EP '243, the existing knowledge and use of SDF, and knowledge of one of ordinary skill in the art, with a reasonable expectation of success at arriving at the claimed invention. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). As of the priority date of the '137 patent, Remodulin (treprostinil) was the commercially-available treprostinil product, and SDF was the only commercially-available glycine buffer with a pH of 10.5, already in use with another pulmonary hypertension medication. And as the district court in the related case, *UTC v. Sandoz*, 12-CV-01617, 13-CV-316 (D.N.J. 2014), expressly found, this combination would meet all of the asserted claims of the '007 patent (and therefore meet the limitations of the '137 patent). (Decision at 73.) UTC's expert in the related *Sandoz* matter, Dr. Michael Miller, admitted at trial that a person of ordinary skill in the art, seeking to practice the invention disclosed and claimed in EP '243, could easily have done so by combining Remodulin and Sterile Diluent for Flolan, both of which were commercially available products as of the priority date for the '137 patent. A person of ordinary skill in the art also would have been motivated to use treprostinil with a high pH buffer comprising glycine with a reasonable expectation of success in inhibiting bacterial growth or reducing the occurrence of blood stream infections. The use of SDF resulted in a high pH glycine buffer solution that was sterile, antibacterial and anti-infective. Moreover, it was well-known in the prior art that glycine is an amino acid that has antibacterial properties. *See e.g.* Foegeding P.M. et al, "Chemical Food Preservatives," Ch. 47 at 825 in Disinfection, Sterilization and Preservation 4th Ed. 1991; Hammes et al., "Mode of Action of Glycine on the Biosynthesis of Peptidoglycoan," J. Bacteriology, Vol. 116, No. 2 pp. 1029-1053 (1973); Strominger et al., "Nucleotide

IPR2020-00770
United Therapeutics EX2007
Page 3122 of 7335

	'137 Patent Claim Language	Invalidity Contentions
		Accumulation Induced in Staphylococcus aureus by Glycine," J. Bacteriology, Vol. 89, No. 4 pp. 1124-1127 (1965). Therefore, as the following prior art explains, as of the priority date, it was also known that a solution in an alkali environment (high pH solutions) with glycine will have bactericidal antiinfective effects. *See, e.g.*, Mendonca, et al, "Destruction of Gram-Negative Food-Borne Pathogens by High pH Involves Disruption of the Cytoplasmic Membrane,: Applied and Environmental Microbiology, vol. 60, No. 11, p. 4009-4014 (1994). ("Mendonca") (disclosed during the prosecution of the '007 patent); Crowther et al., "Growth of Microorganisms in Propofol, Thiopental, and a 1:1 Mixture Of Propofol and Thiopental," Anesth. Analg., 82: 475-478 (1996) ("Crowther") (TEVA_TRE_0004034-7); and Siqueira et al., Mechanisms of antimicrobial activity of calcium hydroxide: a critical review," Intern. Endodontic J., 32, pp. 361-369, (1999) ("Siqueira) (TEVA_TRE_0004298-306). Consistent with the fact that glycine and high pH solutions have known antibacterial properties, the prior art describes glycine buffer solutions that have high pH for use in pharmaceutical formulations. *See* U.S. Appln. No. 10/137,331 (disclosed during prosecution of the '007 patent); 1999 Flolan Package Insert (TEVA_TRE_0004281-84) (disclosing the use of SDF and SDF's qualities); EP '243 (TEVA_TRE_0004270-80) (discussed in more detail above); U.S. Patent Publication No. 2005/0165110 (July 2005) by Wade et al. at [0030] ("Wade 2005") (TEVA_TRE_0004213-218); and The 2005 Physicians' Desk Reference for Flolan® (epoprostenol sodium for injection) ("2005 PDR") (TEVA_TRE_0003991-6) (disclosing SDF, its use, and qualities). Indeed, as discussed earlier, the prior art specifically describes, suggests, and combines treprostinil with a high pH glycine buffer solutions for use in pharmaceutical compositions for humans. See EP '243; Wade 2005. As is evident from thee disclosures, a person of ordinary skill would have been motivated to address possible complications from bacterial infections when treprostinil is administered intravenously, as suggested by the use of SDF and the disclosures of EP '243.

IPR2020-00770
United Therapeutics EX2007
Page 3123 of 7335

	'137 Patent Claim Language	Invalidity Contentions
		A solution having "a low buffer capacity," if not inherent, also would have been known to a person of ordinary skill in the art. (Claims 1-5, 7-10, 16-17, and 21 also require that the glycine buffer used in the claimed methods have a low buffer capacity, so this analysis applies to the other claims with equal force.) The '137 patent states that "the buffer capacity should be low to avoid pH changes in the blood upon infusion." Col. 2, lines 34-35. SDF inherently possesses this limitation. Moreover, it would have been obvious to a person of ordinary skill in the art that it is important to maintain the proper pH of blood to avoid possible severe complications. *See, e.g.*, Petrucci, R. and Harwood, W., General Chemistry Principles and Modern Applications, 6th Ed., 1993, pp. 656-57 (explaining that the normal pH of blood is 7.4 and increased pH of blood can lead to severe vomiting and hyperventilation). Consequently, it would have been obvious to a person of ordinary skill to formulate the high pH buffer solution with a low buffer capacity, so that it would be safe and avoid any complications based on changes of blood pH when the treprostinil solution is administered. *See also* EP '243 at 5. Plaintiff has not set forth its contentions concerning secondary considerations in this case. If Plaintiff relies on any secondary considerations of non-obviousness, Teva reserves the right to supplement its contentions.
2	The method of claim 1, wherein the buffer further comprises sodium hydroxide.	Dependent claim 2 incorporates the method of claim 1, so the contentions incorporate herein by reference the analysis and prior art of claim 1. The additional limitation of sodium hydroxide is disclosed in the prior art cited therein and would have required only routine optimization. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
3	The method of claim 1, wherein the buffer has a pH between 10 and 12.	Dependent claim 3 incorporates the method of claim 1, so the contentions incorporate herein by reference the analysis and prior art of claim 1. The additional pH limitation is disclosed in the prior art cited therein (e.g., EP '243 discloses pH above 10) and would have required only routine optimization. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
4	The method of claim 3, wherein the buffer has a pH between	Dependent claim 4 incorporates the method of claim 1, so the contentions incorporate herein by reference the

IPR2020-00770
United Therapeutics EX2007
Page 3124 of 7335

	'137 Patent Claim Language	Invalidity Contentions
	10.2 and 10.8.	analysis and prior art of claim 1. The additional pH limitation is disclosed in the prior art cited therein (e.g., EP '243 discloses pH above 10) and would have required only routine optimization. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
5	The method of claim 1, wherein the final solution is administered at a concentration between about 0.001 mg/mL to about 1 mg/mL.	Dependent claim 5 incorporates the method of claim 1, so the contentions incorporate herein by reference the analysis and prior art of claim 1. The additional concentration limitation is disclosed in the prior art cited therein (e.g., 2005 PDR discloses the concentrations of Remodulin) and would have required only routine optimization. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
6	The method of claim 1, wherein the final solution is administered at a concentration between about 0.004 mg/mL to about 0.13 mg/mL.	Dependent claim 6 incorporates the method of claim 1, so the contentions incorporate herein by reference the analysis and prior art of claim 1. The additional concentration limitation is disclosed in the prior art cited therein (e.g., EP '243 discloses pH above 10) and would have required only routine optimization. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
7	The method of claim 1, wherein the administering is by injection.	Dependent claim 7 incorporates the method of claim 1, so the contentions incorporate herein by reference the analysis and prior art of claim 1. The additional "injection" limitation is disclosed in the prior art cited therein (e.g., EP '243 discloses injections and Flolan was an injection) and would have required only routine optimization. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
8	The method of claim 7, wherein the injection is intravenous injection.	Dependent claim 8 incorporates the method of claim 7, so the contentions incorporate herein by reference the analysis and prior art of claim 7. The additional intravenous injection limitation is disclosed in the prior art cited therein (e.g., EP '243 discloses intravenous injection and flolan was an intravenous injection) and would have required only routine optimization. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
9	The method according to claim 1, wherein the administration reduces the growth of gram negative bacteria.	Dependent claim 9 incorporates the method of claim 1, so the contentions incorporate herein by reference the analysis and prior art of claim 1. The additional bacterial limitation is disclosed in the prior art cited therein (e.g., EP '243 discloses a sterile solution that would have this inherent quality) and would have required only routine optimization. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.

IPR2020-00770
United Therapeutics EX2007
Page 3125 of 7335

	'137 Patent Claim Language	Invalidity Contentions
10	The method of claim 4, wherein the final solution is administered intravenously.	Dependent claim 10 incorporates the method of claim 4, so the contentions incorporate herein by reference the analysis and prior art of claim 4. The additional intravenous injection limitation is disclosed in the prior art cited therein (e.g., EP '243 discloses intravenous administration and Flolan was an intravenous administration) and would have required only routine optimization. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
11	The method of claim 1, wherein the buffer is a 50 mL solution of 94 mg of glycine, 73.3 mg of sodium chloride, and sodium hydroxide.	Dependent claim 11 incorporates the method of claim 1, so the contentions incorporate herein by reference the analysis and prior art of claim 1. The additional limitation specifying amount of ingredients is disclosed in the prior art cited therein (e.g., SDF) and would have required only routine optimization to arrive at the amounts to achieve the necessary pH and sterile qualities. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
12	The method of claim 11, wherein the administering is by injection.	Dependent claim 12 incorporates the method of claim 11, so the contentions incorporate herein by reference the analysis and prior art of claim 11. The additional injection limitation is disclosed in the prior art cited therein (e.g., EP '243 discloses injection and flolan was an injection) and would have required only routine optimization. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
13	The method of claim 12, wherein the injection is intravenous injection.	Dependent claim 13 incorporates the method of claim 12, so the contentions incorporate herein by reference the analysis and prior art of claim 12. The additional intravenous injection limitation is disclosed in the prior art cited therein (e.g., EP '243 discloses intravenous injection and flolan was an intravenous injection) and would have required only routine optimization. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.

E. Invalidity of United States Patent No. 8,658,694

United States Patent No. 8,658,694, entitled "Buffer solutions having selective bactericidal activity against gram negative bacteria and methods of using same," was issued on February 25, 2014 with 26 claims. UTC asserts that Teva infringes claims 1-26 of the '694 patent. Claims 1 and 11 are the only independent claims of the '694 patent:

IPR2020-00770
United Therapeutics EX2007
Page 3126 of 7335

1. A method of treating pulmonary arterial hypertension comprising diluting a starting solution of treprostinil or treprostinil sodium with a buffer comprising glycine and having a pH of greater than 10 to provide a final solution with a pH of greater than 10 and an effective amount of treprostinol or treprostinil sodium for treating pulmonary arterial hypertension, and administering said final solution to a human subject in need thereof.

11. A method of reducing occurrence of a bacterial infection in a human suffering from pulmonary arterial hypertension, who is undergoing treatment for said pulmonary hypertension, comprising diluting a starting solution of treprostinil or treprostinil sodium with a buffer comprising glycine and having a pH of greater than 10 to provide a final solution with a pH of greater than 10 and an amount of treprostinil or treprostinil sodium effective for treating pulmonary arterial hypertension, and administering said final solution to the human subject in need thereof.

The '694 patent shares the same priority date as the '007 patent, substantially the same specification, and is in the same family of patent as the '007 patent. The scope of the claims, accordingly, is substantially similar and comprises generally the same subject matter (e.g., reducing infection or treating PAH with treprostinil plus buffer solution having glycine and having pH greater than 10). Therefore, Teva asserts that the claims of the '694 patent are invalid for substantially the same reasons as the '007 patent.

No evidence of secondary considerations of non-obviousness were presented during the prosecution of the '694 patent, and Teva is not aware of any such secondary considerations that, when considered with the evidence of obviousness, would warrant a finding of non-obviousness of the claims of the '694 patent. To the extent Plaintiff is relying on their contentions during the prosecution history of the '694 patent, then the prior art rebuts this contention of unexpected results. If UTC relies on any secondary considerations of non-obviousness, Teva reserves the right to supplement its contentions.

IPR2020-00770
United Therapeutics EX2007
Page 3127 of 7335

The following prior art shows all of the limitations of the '694 patent, including the use of glycine buffers to inhibit bacterial growth, prior to September 7, 2007, the priority date of the '694 patent:

- EP '243 (TEVA_TRE_0004270-80)
- U.S. Patent Publication No. 2005/0165110 July 2005, Wade et al. ("Wade 2005") (TEVA_TRE_0004213-218)
- Crowther et al., "Growth of Microorganisms in Propofol, Thiopental, and a 1:1 Mixture Of Propofol and Thiopental," *Anesth. Analg., 82:* 475-478 (1996) ("Crowther") (TEVA_TRE_0004034-7)
- Siqueira et al., Mechanisms of antimicrobial activity of calcium hydroxide: a critical review," Intern. Endodontic J., 32, pp. 361-369, (1999) ("Siqueira) (TEVA_TRE_0004298-306)
- Foegeding P.M. et al, "Chemical Food Preservatives," Ch. 47 in Disinfection, Sterilization and Preservation 4th Ed. 1991. (TEVA_TRE_0004267-9)
- Hammes et al., "Mode of Action of Glycine on the Biosynthesis of Peptidoglycoan," J. Bacteriology, Vol. 116, No. 2 pp. 1029-1053 (1973) (TEVA_TRE_0004042-66)
- Strominger et al., "Nucleotide Accumulation Induced in Staphylococcus aureus by Glycine," J. Bacteriology, Vol. 89, No. 4 pp. 1124-1127 (1965) (TEVA_TRE_0004038-41)
- "Buffers: A guide for the preparation and use of buffers in biological systems" by Calbiochem ("Calbiochem") (TEVA_TRE_0003997-4033)
- 2006 Remodulin Package Insert (TEVA_TRE_0004285-97)
- 1999 Flolan Package Insert (TEVA_TRE_0004281-84)
- The 2005 Physicians' Desk Reference for Flolan® (epoprostenol sodium for injection) ("2005 PDR") (TEVA_TRE_0003991-6)
- Petrucci, R. and Harwood, W., General Chemistry Principles and Modern Applications, 6th Ed., pp. 656-57 (1993) (Teva_TRE_0003971-4)
- Prior art disclosed or cited during prosecution of the '007, '137, and '694 patents.

IPR2020-00770
United Therapeutics EX2007
Page 3128 of 7335

Teva expressly reserves the right to modify and/or supplement the above list at any time as necessary and/or as discovery progresses.

	'694 Patent Claim Language	Invalidity Contentions
1	1. A method of treating pulmonary arterial hypertension comprising diluting a starting solution of treprostinil or treprostinil sodium with a buffer comprising glycine and having a pH of greater than 10 to provide a final solution with a pH of greater than 10 and an effective amount of treprostinol[sic] or treprostinil sodium for treating pulmonary arterial hypertension, and administering said final solution to a human subject in need thereof.	Claim 1 of the '694 patent is invalid for the same reasons as the '007 patent and Teva hereby incorporates by reference the analysis set forth for claim 1 of the '007 patent. The '694 patent shares the same priority date as the '007 patent, substantially the same specification, and is in the same family of patent as the '007 patent. The scope of the claims, accordingly, are substantially similar and comprise generally the same subject matter (e.g., treating pulmonary arterial hypertension with treprostinil plus buffer solution having glycine and having pH greater than 10). Claim 1 of the '694 patent specifies treating a person with pulmonary arterial hypertension and administering the solution with trepsotinil and glycine having pH above 10 to such a person. There is no meaningful patentable difference between claims of the '694 patent and the '007 patent. The prior art teaches that the person to whom the pharmaceutical composition is administered suffers from PAH. Therefore, the same analysis and prior art would apply to the invalidity contention for the '694 patent and if the '007 patent is invalid, so would be the '694 patent. **Anticipation:** Claim 1 of the '694 patent is invalid, because it is anticipated by European Patent Application EP 0347243A1 ("EP '243") or obvious over EP '243 in view of Sterile Diluent For Flolan and/or knowledge of one of ordinary skill in the prior art. EP '243 issued on December 20, 1989, and is, thus, 102(b) prior art. EP '243 patent disclosed and claimed medicaments for the treatment of persons suffering from pulmonary hypertension that could be used subcutaneously or intravenously. EP '243, ¶¶ 22, 25. Example 1 discloses the combination of treprostinil and a "glycine buffer" with a pH of 10.5. EP '243 further describes the use of buffer solutions with treprostinil to treat pulmonary hypertension. EP '243 concludes that treprostinil used with a glycine buffer solution of greater than pH 10 "was found to reduce

IPR2020-00770
United Therapeutics EX2007
Page 3129 of 7335

	'694 Patent Claim Language	Invalidity Contentions
		hypoxia-induced increase in pulmonary arterial pressure and pulmonary vascular resistance in a dose-related manner without appreciably affecting cardiac output or heart rate." *Id.* at ¶¶ 32-34. EP '243 discloses that "sterile" acqueous solutions are preferred and that "[s]uch preparations may conveniently be prepared by admixing the compound with water or a glycine buffer and rendering the resulting solution sterile and isotonic with the blood." *Id.* at ¶ 25. Therefore, the pharmaceutical preparation of EP '243 inherently inhibits growth of gram positive bacteria associated with occurrence of a bacterial infection and, if given to a person, will inherently kill gram negative bacteria. Therefore, EP '243 discloses "a pharmaceutical preparation" or "pharmaceutical composition" comprising "treprostinil" and "a buffer comprising glycine and having a pH of greater than 10" with the inherent qualities described in the claims. Moreover, having a low buffer capcity is an inherent property of a sterile solutions with a high pH that are isotonic with the blood and are intended to be given to humans, as the pH of the pharmaceutical preparation should quickly adjust to the pH of blood, which is substantially lower than pH of 10. *Id.* **Obviousness:** If EP '243 does not anticipate the '694 patent, '694 patent is invalid as obvious over EP '243 patent in view of the commercial embodiment Sterile Diluent for Flolan®. Flolan® is a third-party competitive product, containing epoprostenol, which was approved in 1995 for treating pulmonary hypertension. Flolan® is a powder that must be reconstituted with "Sterile Diluent for Flolan" ("SDF"). SDF is a solution containing the amino acid glycine and having a pH greater than 10 that physicians or patients may use to dilute Flolan prior to intravenous infusion. The use of SDF (or a buffer such as SDF) was described, for example, in 1999 Flolan® label and U.S. Patent No. 4,335,139. SDF was available more than 1 year prior to the earliest priority date of the '694 patent and is 102(b) prior art to the '694 patent. A person of ordinary would have found it obvious to combine Remodulin in combination with SDF, based on the teachings of EP '243, the existing knowledge and use

IPR2020-00770
United Therapeutics EX2007
Page 3130 of 7335

	'694 Patent Claim Language	Invalidity Contentions
		of SDF, and knowledge of one of ordinary skill in the art, with a reasonable expectation of success at arriving at the claimed invention. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). As of the priority date of the '694 patent, Remodulin (treprostinil) was the commercially-available treprostinil product, and SDF was the only commercially-available glycine buffer with a pH of 10.5, already in use with another pulmonary hypertension medication. And as the district court in the related case, *UTC v. Sandoz*, 12-CV-01617, 13-CV-316 (D.N.J. 2014), expressly found, this combination would meet all of the asserted claims of the '007 patent (and therefore would meet the limitations of the '694 patent). (Decision at 73.) UTC's expert in the related *Sandoz* matter, Dr. Michael Miller, admitted at trial that a person of ordinary skill in the art, seeking to practice the invention disclosed and claimed in EP '243, could easily have done so by combining Remodulin and Sterile Diluent for Flolan, both of which were commercially available products as of the priority date for the '694 patent. A person of ordinary skill in the art also would have been motivated to use treprostinil with a high pH buffer comprising glycine with a reasonable expectation of success in inhibiting bacterial growth or reducing the occurrence of blood stream infections. The use of SDF resulted in a high pH glycine buffer solution that was sterile, antibacterial and anti-infective. Moreover, it was well-known in the prior art that glycine is an amino acid that has antibacterial properties. *See e.g.* Foegeding P.M. et al, "Chemical Food Preservatives," Ch. 47 at 825 in Disinfection, Sterilization and Preservation 4th Ed. 1991; Hammes et al., "Mode of Action of Glycine on the Biosynthesis of Peptidoglycoan," J. Bacteriology, Vol. 116, No. 2 pp. 1029-1053 (1973); Strominger et al., "Nucleotide Accumulation Induced in Staphylococcus aureus by Glycine," J. Bacteriology, Vol. 89, No. 4 pp. 1124-1127 (1965). Therefore, as the following prior art explains, as of the priority date, it was also known that a solution in an alkali environment (high pH solutions) with glycine will have bactericidal antiinfective effects. *See, e.g.*, Mendonca, et al, "Destruction of Gram-Negative Food-Borne Pathogens by High pH Involves Disruption of the

IPR2020-00770
United Therapeutics EX2007
Page 3131 of 7335

	'694 Patent Claim Language	Invalidity Contentions
		Cytoplasmic Membrane,: Applied and Environmental Microbiology, vol. 60, No. 11, p. 4009-4014 (1994). ("Mendonca") (disclosed during the prosecution of the '007 patent); Crowther et al., "Growth of Microorganisms in Propofol, Thiopental, and a 1:1 Mixture Of Propofol and Thiopental," Anesth. Analg., 82: 475-478 (1996) ("Crowther") (TEVA_TRE_0004034-7); and Siqueira et al., Mechanisms of antimicrobial activity of calcium hydroxide: a critical review," Intern. Endodontic J., 32, pp. 361-369, (1999) ("Siqueira) (TEVA_TRE_0004298-306). Consistent with the fact that glycine and high pH solutions have known antibacterial properties, the prior art describes glycine buffer solutions that have high pH for use in pharmaceutical formulations. *See* U.S. Appln. No. 10/137,331 (disclosed during prosecution of the '007 patent); 1999 Flolan Package Insert (TEVA_TRE_0004281-84) (disclosing the use of SDF and SDF's qualities); EP '243 (TEVA_TRE_0004270-80) (discussed in more detail above); U.S. Patent Publication No. 2005/0165110 (July 2005) by Wade et al. at [0030] ("Wade 2005") (TEVA_TRE_0004213-218); and The 2005 Physicians' Desk Reference for Flolan® (epoprostenol sodium for injection) ("2005 PDR") (TEVA_TRE_0003991-6) (disclosing SDF, its use, and qualities). Indeed, as discussed earlier, the prior art specifically describes, suggests, and combines treprostinil with a high pH glycine buffer solutions for use in pharmaceutical compositions for humans. See EP '243; Wade 2005. As is evident from thee disclosures, a person of ordinary skill would have been motivated to address possible complications from bacterial infections when treprostinil is administered intravenously, as suggested by the use of SDF and the disclosures of EP '243. A solution having "a low buffer capacity," if not inherent, also would have been known to a person of ordinary skill in the art. (Claims 1-5, 7-10, 16-17, and 21 also require that the glycine buffer used in the claimed methods have a low buffer capacity, so this analysis applies to the other claims with equal force.) The '137 patent states that "the buffer capacity should be low to

IPR2020-00770
United Therapeutics EX2007
Page 3132 of 7335

	'694 Patent Claim Language	Invalidity Contentions
		avoid pH changes in the blood upon infusion." Col. 2, lines 34-35. SDF inherently possesses this limitation. Moreover, it would have been obvious to a person of ordinary skill in the art that it is important to maintain the proper pH of blood to avoid possible severe complications. *See e.g.* Petrucci, R. and Harwood, W., General Chemistry Principles and Modern Applications, 6th Ed., 1993, pp. 656-57 (explaining that the normal pH of blood is 7.4 and increased pH of blood can lead to severe vomiting and hyperventilation). Consequently, it would have been obvious to a person of ordinary skill to formulate the high pH buffer solution with a low buffer capacity, so that it would be safe and avoid any complications based on changes of blood pH when the treprostinil solution is administered. *See also* EP '243 at 5. Plaintiff has not set forth its contentions concerning secondary considerations in this case. If Plaintiff relies on any secondary considerations of non-obviousness, Teva reserves the right to supplement its contentions.
2	The method of claim 1, wherein the buffer further comprises sodium hydroxide.	This dependent claim incorporates the method of claim 1, so the contentions incorporate herein by reference the analysis and prior art of claim 1. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert (disclosing a buffer with sodium hydroxide), the 2005 PDR, and Calbiochem.
3	The method of claim 1, wherein the buffer has a pH between 10 and 12.	This dependent claim incorporates the method of claim 1, so the contentions incorporate herein by reference the analysis and prior art of claim 1. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert (disclosing a solution with pH of over 10), the 2005 PDR, and Calbiochem.
4	The method of claim 3, wherein the buffer has a pH	This dependent claim incorporates the method of claim 1, so the contentions incorporate herein by reference the

IPR2020-00770
United Therapeutics EX2007
Page 3133 of 7335

	'694 Patent Claim Language	Invalidity Contentions
	between 10.2 and 10.8.	analysis and prior art of claim 1. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
5	The method of claim 1, wherein the final solution is administered at a concentration between about 0.004 mg/mL to about 0.13 mg/mL.	This dependent claim incorporates the method of claim 1, so the contentions incorporate herein by reference the analysis and prior art of claim 1. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
6	The method of claim 1, wherein the administering is by injection.	This dependent claim incorporates the method of claim 1, so the contentions incorporate herein by reference the analysis and prior art of claim 1. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
7	The method of claim 6, wherein the injection is intravenous injection.	This dependent claim incorporates the method of claim 6, so the contentions incorporate herein by reference the analysis and prior art of claim 6. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
8	The method of claim 6, wherein the active pharmaceutical ingredient is treprostinil sodium.	This dependent claim incorporates the method of claim 6, so the contentions incorporate herein by reference the analysis and prior art of claim 6. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein.

IPR2020-00770
United Therapeutics EX2007
Page 3134 of 7335

	'694 Patent Claim Language	Invalidity Contentions
		The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
9	The method of claim 4, wherein the final solution is administered intravenously.	This dependent claim incorporates the method of claim 4, so the contentions incorporate herein by reference the analysis and prior art of claim 4. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
10	The method of claim 1, wherein the buffer is a 50 mL solution of 94 mg of glycine, 73.3 mg of sodium chloride, and sodium hydroxide.	This dependent claim incorporates the method of claim 1, so the contentions incorporate herein by reference the analysis and prior art of claim 1. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
11	A method of reducing occurrence of a bacterial infection in a human suffering from pulmonary arterial hypertension, who is undergoing treatment for said pulmonary hypertension, comprising diluting a starting solution of treprostinil or treprostinil sodium with a buffer comprising glycine and having a pH of greater than 10 to provide a final solution with a pH of greater than 10 and an amount of treprostinil or treprostinil sodium effective for treating pulmonary arterial hypertension, and administering said final solution to the human subject in need thereof.	This independent claim is substantially similar to claim 1. Therefore, Teva hereby incorporates herein the analysis set forth in claim 1. The minor differences in claim language, such as "reducing occurrence of a bacterial infection in a human suffering from pulmonary arterial hypertension, who is undergoing treatment for said pulmonary hypertension" has been addressed in the analysis for claim 1, and, therefore, does not require any further explanation here. To the extent that claim 1 is invalid, claim 11 should also be invalid.
12	The method of claim 11,	This dependent claim incorporates the method of claim

IPR2020-00770
United Therapeutics EX2007
Page 3135 of 7335

	'694 Patent Claim Language	Invalidity Contentions
	wherein the buffer further comprises sodium hydroxide.	11, so the contentions incorporate herein by reference the analysis and prior art of claim 11. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
13	The method of claim 11, wherein the buffer has a pH between 10 and 12.	This dependent claim incorporates the method of claim 11, so the contentions incorporate herein by reference the analysis and prior art of claim 11. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
14	The method of claim 13, wherein the buffer has a pH between 10.2 and 10.8.	This dependent claim incorporates the method of claim 13, so the contentions incorporate herein by reference the analysis and prior art of claim 13. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
15	The method of claim 11, wherein the final solution is administered at a concentration between about 0.001 mg/mL to about 1 mg/mL.	This dependent claim incorporates the method of claim 11, so the contentions incorporate herein by reference the analysis and prior art of claim 11. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
16	The method of claim 11, wherein the final solution is administered at a concentration between about 0.004 mg/mL to about 0.13 mg/mL.	This dependent claim incorporates the method of claim 11, so the contentions incorporate herein by reference the analysis and prior art of claim 11. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with

IPR2020-00770
United Therapeutics EX2007
Page 3136 of 7335

	'694 Patent Claim Language	Invalidity Contentions
		respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
17	The method of claim 11, wherein the administering is by injection.	This dependent claim incorporates the method of claim 11, so the contentions incorporate herein by reference the analysis and prior art of claim 11. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
18	The method of claim 17, wherein the injection is intravenous injection.	This dependent claim incorporates the method of claim 11, so the contentions incorporate herein by reference the analysis and prior art of claim 11. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
19	The method of claim 17, wherein the active pharmaceutical ingredient is treprostinil sodium.	This dependent claim incorporates the method of claim 11, so the contentions incorporate herein by reference the analysis and prior art of claim 11. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
20	The method according to claim 11, wherein the administration reduces the growth of gram negative bacteria.	This dependent claim incorporates the method of claim 11, so the contentions incorporate herein by reference the analysis and prior art of claim 11. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
21	The method of claim 14,	This dependent claim incorporates the method of claim

IPR2020-00770
United Therapeutics EX2007
Page 3137 of 7335

	'694 Patent Claim Language	Invalidity Contentions
	wherein the final solution is administered intravenously.	14, so the contentions incorporate herein by reference the analysis and prior art of claim 14. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
22	The method of claim 11, wherein the buffer is a 50 mL solution of 94 mg of glycine, 73.3 mg of sodium chloride, and sodium hydroxide.	This dependent claim incorporates the method of claim 11, so the contentions incorporate herein by reference the analysis and prior art of claim 11. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
23	The method of claim 22, wherein the administering is by injection.	This dependent claim incorporates the method of claim 22, so the contentions incorporate herein by reference the analysis and prior art of claim 22. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
24	The method of claim 23, wherein the injection is intravenous injection.	This dependent claim incorporates the method of claim 23, so the contentions incorporate herein by reference the analysis and prior art of claim 23. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
25	The method of claim 10, wherein the administering is by injection.	This dependent claim incorporates the method of claim 10, so the contentions incorporate herein by reference the analysis and prior art of claim 10. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with

IPR2020-00770
United Therapeutics EX2007
Page 3138 of 7335

	'694 Patent Claim Language	Invalidity Contentions
		respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.
26	The method of claim 25, wherein the injection is intravenous injection.	This dependent claim incorporates the method of claim 25, so the contentions incorporate herein by reference the analysis and prior art of claim 25. Moreover, the additional limitation of this claim is substantially identical to the dependent limitations of the '007 and '137 patent and has been dicussed in full detail with respect to those patents and the dependent claims therein. The additional limitation is disclosed in the prior art cited in those discusions. *See, e.g.*, 1999 Flolan Package Insert, the 2005 PDR, and Calbiochem.

IPR2020-00770
United Therapeutics EX2007
Page 3139 of 7335

Dated: April 24, 2015

WINSTON & STRAWN LLP

By: /s/ Samuel S. Park

LITE DEPALMA GREENBERG, LLC
Michael E. Patunas
Mayra V. Tarantino
Two Gateway Center
Suite 1201
Newark, NJ 07102
Tel. (973) 623-3000
Fax (973) 623-0858
mpatunas@litedepalma.com
mtarantino@litedepalma.com

Attorneys for Defendants
Teva Pharmaceuticals USA, Inc.

Of Counsel:
WINSTON & STRAWN LLP
George C. Lombardi
Samuel S. Park
35 West Wacker Drive
Chicago, Illinois 60601
Tel: (312) 558-5600
Fax: (312) 558-7000
glombardi@winston.com
spark@winston.com

CERTIFICATE OF SERVICE

The undersigned attorney certifies that a copy of Defendant Teva Pharmaceuticals USA, Inc.'s Non-Infringement And Invalidity Contentions was served by electronic mail on the 24th day of April, 2015 upon:

Stephen M. Orlofsky
David C. Kistler
New Jersey Resident Partners
BLANK ROME LLP
301 Carnegie Center, 3d Floor
Princeton, NJ 08540
Telephone: (609) 750-7700

OF COUNSEL:

Douglas Carsten
WILSON SONSINI GOODRICH & ROSATI, P.C.
12235 El Camino Real
Suite 200
San Diego, CA 92130

Bobby Delafield
WILSON SONSINI GOODRICH & ROSATI, P.C.
900 South Capital of Texas Highway
Las Cimas IV, Fifth Floor
Austin, TX 787-5546

William C. Jackson
BOIES, SCHILLER & FLEXNER LLP
5301 Wisconsin Ave, NW
Washington, DC 20015

/s/ Jason Pesick
Jason Pesick
WINSTON & STRAWN LLP
35 West Wacker Drive
Chicago, Illinois 60601
Tel: (312) 558-3262
jpesick@winston.com

IPR2020-00770
United Therapeutics EX2007
Page 3141 of 7335

Organic Process Research & Development 2005, 9, 319–320

A New Purification Process for Pharmaceutical and Chemical Industries

Pandurangan Arumugam and Paramasivan Thirumalai Perumal*

Organic Chemistry Division, Central Leather Research Institute, Adyar, Chennai 600-020, India

Abstract:

A novel separation and purification process suitable for pharmaceutical and chemical industries has been developed. The process is based on the difference in adsorption and solubility of organic compounds. The process was carried out under mechanical stirring, and individual components were isolated in short time with excellent purity. The process can be suitably adopted for the purification of organic compounds in large scale.

The separation and purification of organic compounds are very important to chemical and pharmaceutical industries. It is a challenging task to separate a required product from a mixture of components during industrial production. Even though different distillation[1] and recrystallization[2] techniques are widely employed in industries, the application of the above methods are limited and time-consuming, leading to cost escalation. The column chromatographic method,[3−5] used in some industries, is a process that is too complicated, particularly for large-scale production (Table 1).

To overcome the above barriers, herein we bring a preliminary communication of our new invention for the separation of organic compounds, which can be applied in kilogram reactors to purify drugs and chemicals. The process is very simple and does not require any special kind of glassware. The process is carried out under mechanical stirring in a round-bottom flask.

Thus, the crude reaction mixture to be purified was dissolved in a minimum amount of a suitable solvent, selected preferably from low-boiling solvents such as hexane, dichloromethane, chloroform, ethanol, etc. To this solution 3−4-fold (if the spots are close as in aniline and 4-nitroaniline 5−6-fold) of a selected adsorbent was added and mixed well. Then the solvent was removed completely under vacuum. To the above solvent-free slurry, a selected solvent or mixture of solvent was added and stirred mechanically; the solution was decanted, and the solvent was evaporated. When the quantity of solvent and length of stirring time were increased, comparatively more quantity of a particular compound was isolated. When the polarity of the solvent was slowly increased, successive components were isolated.

* Corresponding author. E-mail: ptperumal@hotmail.com. Fax: 91-44-24911589.

(1) Krell, E. *Handbook of Laboratory Distillation*, 2nd ed.; Lumb, E. C., Ed.; Elsevier: Amsterdam, 1963.

(2) Mersmann, A., Ed. *Crystallisation Technology Handbook*; Marcel Dekker: New York, 1994.

(3) Brown, P. R.; Grushk, E. *Advances in Chromatography*, Marcel Dekker: New York, 1994; Vol 34; 1995; Vol 35.

(4) Heftmann, E., Ed. *Chromatography*, 3rd ed.; Reinhold: New York, 1974.

(5) Braithwaite, A.; Smith, F. J. *Chromatographic Methods*. 4th ed.; Chapman Hall: London, 1985.

10.1021/op048790d CCC: $30.25 © 2005 American Chemical Society
Published on Web 04/27/2005

The success of the process is evident by the fact that it is able to separate a mixture of very close-moving (chromatographically) aniline and 4-nitroaniline. Aniline and 4-nitroaniline are moving in 5% ethyl acetate:petroleum ether, and the R_f difference between aniline and 4-nitroaniline is just 0.09. A variety of organic compounds that were mixed and isolated successfully are summarized in Table 2.

To demonstrate suitability the method for separation of the required component from a chemical reaction mixture, the technique was applied to Biginelli condensation, and pure 6-methyl-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-carboxylic acid ethyl ester was isolated from a mixture of benzaldehyde, ethyl acetoacetate, and 6-methyl-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-carboxylic acid ethyl ester. This reaction was carried out in 1-mole scale, and by employing our technique the quantitative separation of 6-methyl-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-carboxylic acid ethyl ester was achieved with very high purity (99%).

Explanation of the Process with an Example. *p*-Methyl acetophenone (500 g) and resorcinol (500 g) were dissolved in 2 L of ethanol. To this solution 3 kg of neutral alumina activity I−II was added and mixed well; the solvent was removed completely under vacuum. To the above solvent-free slurry was added 2% ethyl acetate:petroleum ether 40−60 °C (7 L); the solution was stirred for 20 min and decanted, and the solvent was evaporated. The residue weighed 120 g of *p*-methyl acetophenone. Thus, five elutions (each elution was carried out with 7 L of solvent and 20 min stirring) in 2% ethyl acetate:petroleum ether at 40−60 °C separated 455 g of *p*-methyl acetophenone with 100% purity (based on gas chromatography). Then the polarity of solvent was increased to 5% ethyl acetate:petroleum ether 40−60 °C. In 5% ethyl acetate:petroleum ether 40−60 °C (7 L) mixture were isolated *p*-methyl acetophenone and resorcinol. The elution in 5% ethyl acetate:petroleum ether 40−60 °C was continued until the isolated resorcinol was single on TLC. Then 7 L of ethyl acetate was added and stirred for 20 min and then decanted; the solvent was evaporated. The elution in ethyl acetate was repeated for three times to complete the isolation of resorcinol. Thus 400 g of pure (100%, based on gas chromatography) resorcinol was isolated. The mixture of *p*-methyl acetophenone and resorcinol isolated in 5% ethyl acetate:petroleum ether 40−60 °C were combined, solvent was removed, and the process was repeated. Thus, each component was isolated in almost pure state in a short time.

The results of our study indicate the following salient features: (1) Direct separation based on solubility differences gave a mixture of two products, whereas adsorption on silica gel followed by elution with same solvent gave separation

IPR2020-00770
United Therapeutics EX2007
Page 3142 of 7335

Table 1. **Comparison between chromatographic method and our new method**

s. no.		purification based on column chromatographic method	purification based on our new method
1	ratio of adsorbent (employed in the purification process) to compound	25−50:1[6]	4−6:1
2	quantity of solvent required	large excess of solvent is required for continuous elution	minimal solvent consumption; 2−3 times the slurry weight is sufficient
3	time (for 1-kg batch)	several hours	10 h
4	apparatus	very large size colum is required	does not require special equipment; performed in reactor vessel.

Table 2. **Separation of some mixed compounds based on our new technique**

				yield[a] %		purity[b]	
s. no.	cmpd 1	cmpd 2	adsorbent	cmpd 1	cmpd 2	cmpd 1	cmpd 2
1	benzophenone	dimedone	silica gel 60−120 mesh	98	97	100	98
2	aniline	4-nitroaniline	neutral alumina activity I−II	98	98	99	98
3	*p*-chlorobenzaldehyde	acetoacetanilide	neutral alumina activity I−II	99	97	100	99
4	*p*-methylacetophenone	resorcinol	neutral alumina activity I−II	97	96	100	100[c]

[a] After purification. [b] Based on gas chromatography. [c] Carried out in 40-g as well as in 1-kg scale.

of the chemical mixture. Example: dimedone and benzophenone.

(2) The nature of the adsorbent plays a vital role in the above separation process.[7] Low-grade adsorbent is preferable when the compounds are not close moving on TLC. When ethyl acetoacetate, benzaldehyde, and 6-methyl-4-phenyl-1,2,3,4-tetrahydropyrimidin-5-carboxylic acid ethyl ester were adsorbed on silica gel, the isolation of product was very easy compared to the adsorption on neutral alumina activity I−II.

(3) High-grade adsorbent is preferable when the compounds are close moving on TLC. For example, aniline and 4-nitroaniline adsorption on silica gel gave a mixture of two compounds, whereas adsorption on neutral alumina activity I−II resulted in the separation of individual compounds.

(4) The eluent for the separation of a particular compound from a mixture was chosen on the basis of a trial and error method. The prepared slurry was collected in different vials, solvent systems of increasing polarity were added, and the eluates were analyzed by TLC to scout for the best solvent system. It is recommended to use a solvent of slightly reduced polarity and then choose one from TLC analysis to perform large-scale elution.

We strongly believe that further intensive research in this technique will enhance its application to the separation of all kinds of organic compounds of industrial importance.

(6) Vogel, A. I. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; revised by Furniss, B. R., Hannaford, A. J., Smith, P. W. G., Tatchell, A. R.; Longman Scientific & Technical: Harlow, England and Wiley: New York, 1989; p 215.

(7) Strain, H. H. *Chromatographic Adsorption Analysis*, 2nd ed.; Interscience: New York, 1945.

Acknowledgment

P.A. dedicates this article to Mr. P. G. Jayapalan, M.A. B.Ed., and Mrs. P. G. J. Vijayalakshmi, Kanchipuram. We thank the Council of Scientific and Industrial Research, India, for financial support.

Received for review November 24, 2004.

OP049790D

IPR2020-00770
United Therapeutics EX2007
Page 3143 of 7335

JOC Note

An Enantioselective Synthesis of (*S*)-(+)-3-Aminomethyl-5-methylhexanoic Acid via Asymmetric Hydrogenation

Mark J. Burk,[†,⊥] Pieter D. de Koning,[‡] Todd M. Grote,[‡] Marvin S. Hoekstra,[‡] Garrett Hoge,[§] Rex A. Jennings,[‡] William S. Kissel,*[,‡] Tung V. Le,[‡] Ian C. Lennon,[†] Thomas A. Mulhern,[‡] James A. Ramsden,*[,†] and Robert A. Wade[‡]

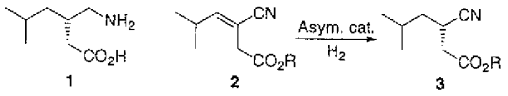
Dowpharma, Chirotech Technology Limited, A Subsidiary of The Dow Chemical Company, Cambridge Science Park, Milton Road, Cambridge CB4 0WG, United Kingdom, Pfizer Global Research and Development, Pfizer Inc., 188 Howard Avenue, Holland, Michigan 49424, and Pfizer Global Research and Development, Pfizer Inc., 2800 Plymouth Road, Ann Arbor, Michigan 48105

jramsden@dow.com

Received March 27, 2003

Abstract: A concise enantioselective synthesis of (*S*)-(+)-3-aminomethyl-5-methylhexanoic acid (**1**, Pregabalin) has been developed. The key step is the asymmetric hydrogenation of a 3-cyano-5-methylhex-3-enoic acid salt **2** with a rhodium Me-DuPHOS catalyst, providing the desired (*S*)-3-cyano-5-methylhexanoate **3** in very high ee. Subsequent hydrogenation of the nitrile **3** with a heterogeneous nickel catalyst provides Pregabalin **1** in excellent overall yield and purity.

(*S*)-(+)-3-Aminomethyl-5-methylhexanoic acid (**1**, Pregabalin) is a potent anticonvulsant related to the inhibitory neurotransmitter γ-aminobutyric acid.[2] Since the biological activity resides in the (*S*)-enantiomer, an enantioselective synthesis is required. During the initial development of Pregabalin **1** several routes were examined in considerable detail.[3] The preferred process to emerge from these studies starts with the condensation of diethyl malonate and isobutyraldehyde. After a further 4 steps, resolution with (*S*)-(+)-mandelic acid provides (*S*)-Pregabalin **1** in 25−29% overall yield. Although this route is cost-effective, the use of a late-stage resolution without the opportunity to efficiently recycle the off-isomer is inefficient and there was clearly scope for developing a more economical process. Asymmetric catalytic hydrogenation of a suitable prochiral precursor such as **2** was identified as a potential route to **1** via intermediate **3**.



1 **2** **3**

Considerable precedent exists for the asymmetric hydrogenation of β-substituted itaconic acid derivatives. Rhodium−phosphine complexes generally provide the desired 2-substituted succinates with high enantioselectivity.[4] In particular, hydrogenation of itaconate salts with Rh-DuPHOS catalysts provides significant rate enhancement, increases the selectivity, and allows mixtures of geometrical isomers to be hydrogenated to a single product. This is in sharp contrast to previous catalyst systems for which considerable differences were noted for the different geometrical isomers. Chiral ruthenium complexes have also found some application, but in general these are less effective than rhodium complexes, and require higher catalyst loading, higher temperatures, and longer reaction times.[5] There are surprisingly few reports on the asymmetric hydrogenation of acrylonitrile derivatives. In one example, (*Z*)-*N*-(1-cyano-2-phenylvinyl)benzamide was hydrogenated in the presence of [(*R*,*R*)-(DIPAMP)Rh(COD)]BF_4, giving the desired product in 89% ee. However, the reaction was less selective and considerably slower than the hydrogenation of the corresponding acrylic acid.[6]

Thus, while there was no direct precedent for the hydrogenation of this class of compounds we had considerable confidence that a suitable catalyst could be identified for this reaction. Herein we report a succinct synthesis of Pregabalin **1**, utilizing a rhodium-catalyzed asymmetric hydrogenation to furnish the key intermediate **3** in high yield and excellent enantiomeric excess.[7]

The required precursor for the hydrogenation reaction was readily prepared following a literature procedure for similar compounds, summarized in Scheme 1.[8] Baylis−Hillman reaction between isobutyraldehyde and acrylonitrile furnished hydroxy nitrile **4**.[9] This was then converted to the ethyl carbonate **5** (the reaction also works with the corresponding acetate), which was used directly in a palladium-catalyzed carbonylation to give 3-cyano-5-methylhex-3-enoic acid ethyl ester (**2a**) as a 3.5:1 (*Z*/*E*) mixture of isomers (83%, Scheme 1). Initial attempts at using the crude product from this reaction in the hydrogenation step failed, presumably due to residual impurities. The ester was further purified by vacuum distillation. The other hydrogenation substrates, *tert*-butylammonium and potassium salts **2b** and **2c**,

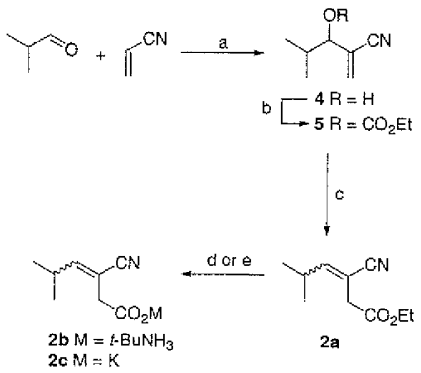
[†] Chirotech Technology Ltd., Cambridge.
[‡] Pfizer Inc., Holland, Michigan.
[§] Pfizer Inc., Ann Arbor, Michigan.
(⊥) Current address: Diversa Corporation, 4995 Directors Place, San Diego, CA 92121.

10.1021/jo034397b CCC: $25.00 © 2003 American Chemical Society
Published on Web 06/06/2003

(2) Yuen, P.; Kanter, G. D.; Taylor, C. P.; Vartanian, M. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 823.
(3) Hoekstra, M. S.; Sobieray, D. M.; Schwindt, M. A.; Mulhern, T. A.; Grote, T. M.; Huckabee, B. K.; Hendrickson, V. S.; Franklin, L. C.; Granger E. J.; Karrick, G. L. *Org. Proc. Res. Dev.* **1997**, *1*, 26.
(4) (a) Jendrella, H.; Henning, R.; Seuring, B.; Herchen, J.; Kulitzscher, B.; Wunner, J. *Synlett* **1993**, 155. (b) Morimoto, T.; Chiba, M.; Achiwa, K. *Tetrahedron* **1993**, *49*, 1793. (c) Burk, M. J.; Bienewald, F.; Harris, M.; Zanotti-Gerosa, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 1931.
(5) (a) Kawano, H.; Ikuriya, T.; Ishii, Y.; Saburi, M.; Yoshikawa, S.; Uchida, Y.; Kumobayashi, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1571. (b) Shao, L.; Miyata, S.; Muramatsu, H.; Kawano, H.; Ishii, Y.; Saburi, M.; Uchida, Y. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1441.
(6) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946.
(7) Burk, M. J.; Gooi, O. P.; Hoekstra, M. S.; Mich, T. F.; Mulhern, T. A.; Ramsden, J. A. Warner-Lambert Company, WO 01/55090 A1, 2001; *Chem. Abstr.* **2001**, *135*, 122750.
(8) Yamamoto, K.; Deguchi, R.; Tsuji, J. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3397.
(9) Basaviah, D.; Gowriswari, V. V. L. *Synth. Commun.* **1987**, *17*, 587.

IPR2020-00770
United Therapeutics EX2007
Page 3144 of 7335

SCHEME 1[a]



[a] Reagents and conditions: (a) DABCO, H_2O, 2,6-di-*tert*-butyl-4-methylphenol, 50 °C, 97%; (b) $ClCO_2Et$, pyridine, CH_2Cl_2, rt, 95%; (c) $Pd(OAc)_2$, PPh_3, EtOH, CO (300 psi), 50 °C, 83%; (d) **2b** (i) LiOH, H_2O, THF, rt; (ii) HCl; (iii) *tert*-$BuNH_2$, EtOAc, 89%; (e) **2c** KOH, MeOH, 45 °C, 88%.

TABLE 1. Asymmetric Hydrogenation of 3-Cyano-5-methylhex-3-enoic Acid Ethyl Ester 2a

entry[a]	precatalyst	temp (°C)	conv (%)[b]	ee (%)[b,c]
1	[(*R,R*)-(Me-DuPHOS)Rh(COD)]BF_4	rt	10	8 (*S*)
2	[(*R,R*)-(Me-BPE)Rh(COD)]OTf	rt	54	10 (*R*)
3	[(*R,R*)-(Me-DuPHOS)Rh(COD)]BF_4	55	100	19 (*R*)
4	[(*R,R*)-(Et-DuPHOS)Rh(COD)]BF_4	55	100	42 (*R*)
5	[(*R,R*)-(*i*Pr-DuPHOS)Rh(COD)]BF_4	55	79	44 (*S*)
6	[(*R,R*)-(Me-BPE)Rh(COD)]OTf	55	100	13 (*R*)
7	[(*R,R*)-(Et-BPE)Rh(COD)]BF_4	55	100	13 (*R*)
8	[(*S,S*)-(*i*Pr-BPE)Rh(COD)]BF_4	55	67	<2
9	[(*R,R*)-(Me-FerroTANE)Rh(COD)]BF_4	rt	51	37 (*S*)
10	[(*R,R*)-(Et-FerroTANE)Rh(COD)]BF_4	rt	41	7 (*S*)

[a] 1 mmol of substrate in 5 mL of methanol was hydrogenated with 10 μmol of precatalyst in a glass lined stainless steel pressure vessel with hydrogen at 90 psi. [b] Conversion and enantiomeric excess were determined by GC (see Experimental Section). [c] The absolute stereochemistry was established by conversion to Pregabalin.

were readily prepared from the ester by standard methods. In both cases, mixtures of geometrical isomers were obtained in approximately the same ratio as observed for ester **2a**. The *tert*-butylammonium salt **2b** could also be prepared directly from the crude ester **2a** (62%), removing the need for vacuum distillation.

Efforts were initially focused on the asymmetric hydrogenation of the ethyl ester **2a**. A range of chiral rhodium complexes were examined under typical hydrogenation conditions (Table 1). Although the hydrogenation reactions proceeded slowly at room temperature, upon heating to 55 °C complete conversion was achieved for the majority of catalyst systems examined. Unfortunately, the enantiomeric excess obtained for this substrate was disappointingly low.

In contrast, however, the hydrogenation of *tert*-butylammonium salt **2b** not only proceeded rapidly at room temperature (reaction complete in under 15 min with some catalysts) but also gave the product with excellent enantioselectivity (Table 2).

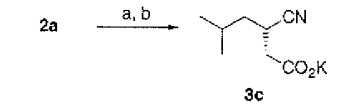
From this initial screen, three precatalysts were clearly outstanding in terms of both high reactivity and selectivity, namely [(Me-DuPHOS)Rh(COD)]BF_4, [(Et-DuPHOS)-Rh(COD)]BF_4, and [(*R,R*)-(Me-FerroTANE)Rh(COD)]BF_4 (entries 1, 2, and 7). In all cases the (*R,R*)-enantiomer of the catalyst provided the desired (*S*)-enantiomer of the product. A similar screen of catalysts was also conducted for the potassium salt **2c**, with comparable results being obtained in terms of rate and selectivity. These screening reactions were conducted at a molar substrate-to-catalyst ratio (S/C) of 100:1. For this to be an economically viable route, comparable rates and selectivity would need to be achieved at much lower S/C ratios. After some scale-up work, [(*R,R*)-(Me-DuPHOS)Rh(COD)]BF_4 was selected as the best catalyst for further development due to a combination of rate and selectivity at reduced catalyst loading. Under slightly modified reaction conditions the hydrogenation of **2b** with [(*R,R*)-(Me-DuPHOS)Rh(COD)]-BF_4 was demonstrated at a molar S/C of 2700/1, which corresponds to a substrate to catalyst w/w ratio of 1000/1. The reaction was complete in 4 h and the crude product was obtained in 97.7% e.e.

TABLE 2. Asymmetric Hydrogenation of *tert*-Butylammonium 3-Cyano-5-methylhex-3-enoate 2b

entry[a]	precatalyst	react. time	conv (%)[b]	ee (%)[b]
1	[(*R,R*)-(Me-DuPHOS)Rh(COD)]BF_4	15 min[c]	100	95.0 (*S*)
2	[(*R,R*)-(Et-DuPHOS)Rh(COD)]BF_4	15 min[c]	100	97.4 (*S*)
3	[(*R,R*)-(*i*Pr-DuPHOS)Rh(COD)]BF_4	6 h	72	24.0 (*R*)
4	[(*R,R*)-(Me-BPE)Rh(COD)]OTf	45 min[c]	100	83.3 (*S*)
5	[(*R,R*)-(Et-BPE)Rh(COD)]BF_4	45 min[c]	100	81.0 (*S*)
6	[(*S,S*)-(*i*Pr-BPE)Rh(COD)]OTf	6 h	59	8.0 (*S*)
7	[(*R,R*)-(Me-FerroTANE)Rh(COD)]BF_4	20 min[c]	100	95.4 (*S*)
8	[(*R,R*)-(Et-FerroTANE)Rh(COD)]BF_4	20 min[c]	100	84.6 (*S*)

[a] 1 mmol of substrate in 5 mL of methanol was hydrogenated with 10 μmol of precatalyst in a glass-lined stainless steel pressure vessel with hydrogen at 90 psi at room temperature. [b] Conversion and enantiomeric excess were determined by GC (see Experimental Section). [c] Time within which hydrogen uptake had ceased.

SCHEME 2[a]

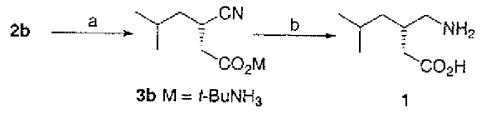


[a] Reagents and conditions: (a) KOH, H_2O, MeOH; (b) [(*R,R*)-(Me-DuPHOS)Rh(COD)]BF_4, H_2 (45 psi), 55 °C, 99% conversion, 96.6% ee.

To circumvent the need to isolate 3-cyano-5-methylhex-3-enoic acid or a salt, ethyl ester **2a** was hydrolyzed with potassium hydroxide in a mixture of methanol and water to give a solution of potassium salt **2c**. Addition of a solution of the precatalyst, [(*R,R*)-(Me-DuPHOS)Rh(COD)]-BF_4 (S/C 2000/1), followed by hydrogenation gave potassium (*S*)-3-cyano-5-methylhexanoate (**3c**) in 96.6% ee (Scheme 2). An important point to note is that this reaction is conducted in a mixed methanol−water solvent system (presumably the water assists in the hydrolysis), demonstrating the utility of the Rh-DuPHOS catalyst under partially aqueous conditions. While this is a more direct approach, the drawback of this procedure is that any residual ethyl ester **2a** that may be present will be hydrogenated to the *opposite* enantiomer of the product **3**, thus reducing the enantiomeric excess. The rate of reaction was also somewhat slower under these reaction

IPR2020-00770
United Therapeutics EX2007
Page 3145 of 7335

SCHEME 3[a]



[a] Reagents and conditions: (a) [(*R,R*)-(Me-DuPHOS)Rh(COD)]-BF_4, H_2 (45 psi), MeOH, 55 °C, 100% conversion, 97.7% ee; (b) (i) Sponge Ni, KOH, H_2 (50 psi), H_2O, EtOH; (ii) AcOH, 61% (two steps), 99.8% ee.

conditions. Thus, the favored process is to prepare the *tert*-butylammonium salt **2b** from the purified ethyl ester **2a**, followed by asymmetric hydrogenation to *tert*-butylammonium salt **3b** (Scheme 3). This process has been scaled up to multi-kilogram quantities without significant difficulties (see Supporting Information).

The final step in the synthesis of (*S*)-(+)-3-aminomethyl-5-methylhexanoic acid (**1**), the reduction of the nitrile group, was accomplished via a heterogeneous hydrogenation of the *tert*-butylammonium salt **3b** over sponge nickel. The crude product was crystallized from a mixture of ethanol, water, and acetic acid to give Pregabalin **1** in 61% yield and 99.8% ee (Scheme 3).

The much higher reactivity and selectivity observed for the asymmetric hydrogenation of salts **2b** and **2c** compared to the ethyl ester **2a** is due to enhanced coordination between the substrate and the catalyst. It is well established that the bisphosphine rhodium catalysts of this type are most effective when the substrate is able to behave as a bidentate ligand **7** (Scheme 4).[10] In the presence of the strongly coordinating nitrile ligand this chelating binding mode is disrupted. The $^{31}P\{^1H\}$ NMR spectrum of the complex formed between the catalytic intermediate [(*R,R*)-(Me-DuPHOS)Rh$(CD_3OD)_2$]-BF_4 (**6**) and *tert*-butylammonium salt **2b** shows a dynamic mixture of species, characterized by complex and broadened signals. Within this is a pair of double doublets at δ 79.3 and 88.6 ppm (J_{PP} = 34 Hz, J_{PRh} = 149 Hz) which can be assigned to the rhodium chelate **7**. The spectroscopic data for this complex are similar to those previously reported for an analogous vinyl acetate complex.[10] Upon treatment with hydrogen, the olefin is reduced and the $^{31}P\{^1H\}$ NMR spectrum collapses to a doublet at δ 95.4 ppm (J_{PRh} = 171 Hz), assigned to the bis-(*S*)-3-cyano-5-methylhexanoate complex **8** as the $^{31}P\{^1H\}$ NMR spectrum is almost identical with that of [(*R,R*)-(Me-DuPHOS)Rh$(NCCH_3)_2$]BF_4 [δ 95.3 (d, J_{PRh} = 175 Hz)]. It is proposed that the small standing concentration of **7** in the reaction mixture (ca. 10%) serves as a conduit through which all the hydrogenation substrate is converted to product. The relatively low reactivity observed in this reaction compared to, for example, itaconic salts[4c] or amido itaconates[11] is attributed to the low levels of the reactive intermediate **7** in the reaction mixture. Similar observations, where a minor component of a mixture gives rise to the major product, are well established in the asymmetric hydrogenation of prochiral olefins by chiral bisphosphine rhodium complexes.[12]

(10) Burk, M. J.; Bienwald, F.; Challenger, S.; Derrick, A.; Ramsden. J. A. *J. Org. Chem.* **1999**, *64*, 3290.

(11) Berens, U.; Burk, M. J.; Gerlach, A.; Hems, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 1981.

(12) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746.

In conclusion we have demonstrated a six-step synthesis of (*S*)-(+)-3-aminomethyl-5-methylhexanoic acid (**1**) that delivers the product in high yield and excellent enantiopurity. The synthetic sequence described is as short as the previously preferred route,[3] but potentially provides significant improvements in cost of goods, waste reduction, and throughput.

Experimental Section

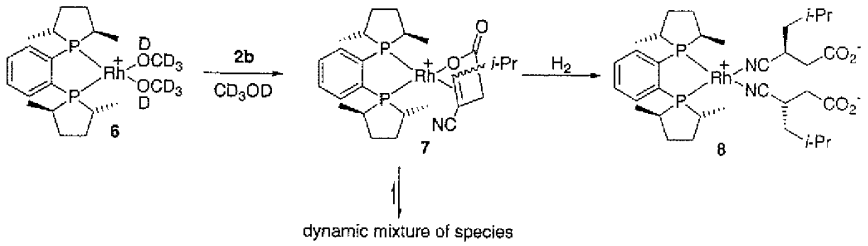
***tert*-Butylammonium 3-Cyano-5-methyl-hex-3-enoate (2b).** Ethyl ester **2a** (20.0 g, 110 mmol, see Supporting Information) and lithium hydroxide hydrate (13.0 g, 310 mmol) were suspended in a mixture of tetrahydrofuran (75 mL) and water (25 mL). The slurry was vigorously stirred for 4 h at room temperature. The mixture was acidified to pH 2 (HCl, 3 N) and extracted into ethyl acetate (3 × 150 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give crude 3-cyano-5-methylhex-3-enoic acid: IR (film) ν_{max} 2222, 1714 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (major isomer) 1.09 (3H, d, J = 7.0 Hz), 2.91 (1H, dheptet, J = 10.0, 7.0 Hz), 3.25 (2H, br), 6.16 (1H, d, J = 10.0 Hz), (minor isomer) 1.05 (3H, d, J = 6.7 Hz), 2.63 (1H, dheptet, J = 10.0, 6.7 Hz), 3.31 (2H, s), 6.40 (1H, d, J = 10.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (major isomer) 22.1, 31.9, 39.0, 104.6, 116.9, 159.7, 175.4 (minor isomer) 21.9, 28.9, 34.2, 104.8, 119.5, 159.1, 175.0. *m/z* 152 (M − H), 305 (2M − H). The acid was dissolved in ethyl acetate (400 mL) and a solution of *tert*-butylamine in ethyl acetate (20 mL) was added. The temperature of the solution rose by approximately 10 °C as the salt **2b** precipitated as a white crystalline solid. The product was collected by filtration and dried in vacuo (22.15 g, 89%): mp 161 °C; IR (KBr) ν_{max} 2216, 1557 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ (major isomer) 1.09 (6H, d, J = 6.5 Hz), 1.37 (9H, s), 2.81 (1H, dheptet, J = 10.0, 6.5 Hz), 3.04 (2H, d, J = 1 Hz), 6.13 (1H, d, J = 10.0 Hz), (minor isomer) 1.05 (6H, d, J = 6.5 Hz), 1.37 (9H, s), 2.74 (1H, dheptet, J = 10.1, 6.5 Hz), 3.11 (2H, s), 6.25 (1H, d, J = 10.1 Hz); ^{13}C NMR (CD_3OD, 100 MHz) δ (major isomer) 22.7, 28.3, 33.0, 44.1, 52.9, 110.3, 119.2, 157.3, 177.1, (minor isomer) 22.1, 28.3, 29.7, 38.8, 52.9, 110.8, 122.1, 157.0, 176.5; *m/z* 74 ($tBuNH_3^+$), 305 (2M + H).

Representative Procedure for Hydrogenation Screening Reactions. A solution of ethyl ester **2a** (0.19 mL, 1.0 mmol) in methanol (4 mL) was placed in a glass-lined 50-mL PARR microreactor modified with an injection septum and valve. The vessel was heated to an internal temperature of 55 °C. A hydrogen atmosphere was established and a solution of [(*R,R*)-(^{i}Pr-DuPHOS)Rh(COD)]BF_4 (7.2 mg, 10 μmol) in methanol (1 mL) was added via syringe. The vessel was pressurized with hydrogen to 100 psi and stirred overnight. The pressure was then released and the solvent was removed in vacuo. ^1H NMR analysis showed approximately 80% conversion to **3a**. GC analysis showed 86.4% conversion, 43.8% ee (*S*): IR (film) ν_{max} 2242, 1738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.96 (3H, d, J = 6.8 Hz), 0.98 (3H, d, J = 6.5 Hz), 1.29 (3H, t, J = 7.1 Hz), 1.34 (1H, ddd, J = 13.4, 9.4, 5.0 Hz), 1.64 (1H, ddd, J = 13.8, 10.9, 4.7 Hz), 1.87 (1H, m), 2.53 (1H, dd, J = 16.6, 6.9 Hz), 2.69 (1H, dd, J = 16.3, 7.3 Hz), 3.06 (1H, m), 4.20 (2H, q, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5, 21.6, 23.2, 25.7, 26.2, 26.5, 37.5, 41.1, 61.6, 121.5, 170.1. Screening reactions at room temperature were carried out via a modified procedure. The liner was charged with a stir bar, the substrate, and catalyst. The vessel was assembled and a hydrogen atmosphere established as described above. Methanol was added via the septum, the vessel was again purged before pressurizing to the reaction pressure and stirring was then initiated.

***tert*-Butylammonium (*S*)-3-Cyano-5-methylhexanoate (3b).** A pressure reactor was charged with a solution of *tert*-butylammonium salt **2b** (125.8 g, 0.56 mol) in methanol (1 L). A hydrogen atmosphere was established and the vessel was heated to 45 °C. A solution of [(*R,R*)-(Me-DuPHOS)Rh(COD)]-BF_4 (0.125 g, 0.206 mmol) in methanol (15 mL) was added via syringe. The vessel was charged with hydrogen to 65 psi and the reaction was stirred at 45 °C until hydrogen uptake ceased

IPR2020-00770
United Therapeutics EX2007
Page 3146 of 7335

SCHEME 4. Proposed Mechanism for the Hydrogenation of *tert*-Butylammonium Salt 2b



(4 h). The solvent was removed in vacuo to give the product as a white crystalline solid (125 g, 99%), GC analysis showed >99% conversion, 97.7% ee: mp 148 °C dec; $[\alpha]^{25}_D$ −16.8° (*c* 1.2, MeOH); IR (KBr) ν_{max} 2238, 1557 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 0.98 (3H, d, J = 5.8 Hz), 1.00 (3H, d, J = 6.1 Hz), 1.37 (9H, s), 1.41 (1H, ddd, J = 13.4, 9.4, 5.0 Hz), 1.59 (1H, ddd, J = 13.8, 10.9, 5.1 Hz), 1.83 (1H, m), 2.39 (1H, dd, J = 15.2, 6.9 Hz), 2.49 (1H, dd, J = 15.5, 7.9 Hz), 3.10 (1H, m); ^{13}C NMR (CD_3OD, 100 MHz) 22.2, 23.9, 27.9, 28.3, 28.7, 42.2, 42.6, 52.9, 124.2, 177.7; *m/z* 74 (tBuNH$_3^+$), 309 (2M + H).

Potassium (*S*)-3-Cyano-5-methylhexanoate (3c) (in situ generation of salt). A pressure reactor was charged with a solution of ethyl ester **2a** (10.8 g, 59.7 mmol) in methanol (100 mL) and water (18 mL). A solution of potassium hydroxide in methanol (5 M, 11.7 mL, 58.4 mol) was added, a nitrogen atmosphere was established, and the vessel was heated to 55 °C and held at this temperature for 2 h. A hydrogen atmosphere was established and a solution of [(*R*,*R*)-(Me-DuPHOS)Rh(COD)]-BF_4 (0.018 g, 0.030 mmol) in methanol (20 mL) was added via syringe. The vessel was charged with hydrogen to 60 psi and the reaction was stirred at 55 °C until hydrogen uptake ceased (5 h). The solvent was removed in vacuo to give the product as a white crystalline solid (11.2 g, 99%), GC analysis showed >99% conversion, 97.7% ee: mp 102 °C dec; $[\alpha]^{25}_D$ −20.6° (*c* 1.1, MeOH); IR (KBr) ν_{max} 2240, 1580 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 0.98 (3H, d, J = 6.6 Hz), 1.00 (3H, d, J = 6.6 Hz), 1.41 (1H, ddd, J = 13.5, 9.7, 5.2 Hz), 1.58 (1H, ddd, J = 15.2, 10.7, 4.8 Hz), 1.84 (1H, m), 2.39 (1H, dd, J = 15.2, 6.9 Hz), 2.49 (1H, dd, J = 15.2, 7.6 Hz), 3.11 (1H, m); ^{13}C NMR (CD_3OD, 100 MHz) 22.2, 23.8, 27.9, 28.7, 42.2, 42.5, 124.6, 178.0; *m/z* 154 (M), 309 (2M + H).

(*S*)-3-Aminomethyl-5-methylhexanoic Acid (1). A solution of *tert*-butylammonium salt **3b** (8.0 g, 35.0 mmol) in water (15 mL) and ethanol (11 mL) was added to nickel sponge (A-7000, 5 g, water wet), followed by potassium hydroxide (91% flake, 2.2 g, 35.6 mmol), and the resulting slurry was shaken under 50 psi of hydrogen overnight. The mixture was filtered (Supercel) and the cake was rinsed with water (20 mL) and ethanol (7 mL). Acetic acid (4.1 mL, 71.6 mmol) was added to the combined filtrates which were then heated to 70 °C, then cooled slowly to room temperature over several hours, followed by aging for 6 h at 0−5 °C. The product was collected by filtration, rinsed with propan-2-ol (50 mL), and dried under vacuum to give 1 as a white crystalline solid (3.4 g, 61%, 99.8% ee), identical with that prepared previously.[3] Anal. Calcd for $C_8H_{17}NO_2$: C, 60.35; H, 10.76; N, 8.80. Found: C, 60.59; H, 10.78; N, 8.80.

Acknowledgment. The authors thank Cara Dykstra (Pfizer) and Will Spearing and Jonathan Hill (Chirotech) for analytical support.

Supporting Information Available: Experimental details for the synthesis of **4**, **5**, **2a**, **2c**, and **3c** and for the multikillogram conversion of **2b** to **1**, copies of the ^{31}P NMR spectra of **6**−**8**, and ^1H and ^{13}C NMR spectra of **2a**−**c**, **3a**−**c**, 3-cyano-5-methylhex-3-enoic acid, and 3-cyano-5-methyl-hexanoic acid. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034397B

IPR2020-00770
United Therapeutics EX2007
Page 3147 of 7335

Stereochemistry of Organic Compounds

ERNEST L. ELIEL
Department of Chemistry
The University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

SAMUEL H. WILEN
Department of Chemistry
The City College of the City University of New York
New York, New York

With a Chapter on Stereoselective Synthesis by

LEWIS N. MANDER
Research School of Chemistry
Australian National University
Canberra, Australia

A Wiley-Interscience Publication
JOHN WILEY & SONS, INC.
New York • Chichester • Brisbane • Toronto • Singapore

IPR2020-00770
United Therapeutics EX2007
Page 3148 of 7335

This text is printed on acid-free paper.

Copyright © 1994 by John Wiley & Sons, Inc.

All rights reserved. Published simultaneously in Canada.

Reproduction or translation of any part of this work beyond that permitted by Section 107 or 108 of the 1976 United States Copyright Act without the permission of the copyright owner is unlawful. Requests for permission or further information should be addressed to the Permissions Department, John Wiley & Sons, Inc., 605 Third Avenue, New York, NY 10158-0012.

Library of Congress Cataloging in Publication Data:

Eliel, Ernest Ludwig, 1921-
Stereochemistry of organic compounds / Ernest L. Eliel, Samuel H. Wilen, Lewis N. Mander.
p. cm.
"A Wiley-Interscience publication."
Includes index.
ISBN 0-471-01670-5
1. Stereochemistry. 2. Organic compounds. I. Wilen, Samuel H. II. Mander, Lewis N. III. Title.
QD481.E52115 1993
547.1'223--dc20 93-12476

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

this type of enantiomerization has much in common with asymmetric transformations of diastereomers. The latter are described in Section 7-3.c.

7-3. CHEMICAL SEPARATION OF ENANTIOMERS VIA DIASTEREOMERS

a. Formation and Separation of Diastereomers. Resolving Agents

The largest number of recorded resolutions has been effected by conversion of a racemate to a mixture of diastereomers. In this type of reaction, the substrate to be resolved is treated with one enantiomer of a chiral substance (the resolving agent). The first such resolution, described by Pasteur in 1853, is outlined in Figure 7.17 (Jacques et al., 1981a, pp. 253, 257). Diastereomer pairs prepared in connection with resolutions may be ionic (diastereomeric salts), covalent, charge-transfer complexes, or inclusion compounds. The latter two types of diastereomers are discussed in Section 7-3.c.

The vast majority of resolutions mediated by diastereomers (diastereomeric salt mixtures, in particular) have been based on solubility differences of solids; however, in the contemporary literature, covalent diastereomer separations based on chromatography in all of its variants are used with great frequency. Chromatography has freed resolutions from the constraint of dependency on crystallization as the technique on which diastereomer separation has traditionally depended. As a result, resolutions in general are much more successful at present than they were in the past.

Not infrequently oily covalent diastereomer mixtures eventually crystallize and their resolution may then be performed in the more traditional way by taking advantage of solubility differences. Separation of diastereomeric salt mixtures by chromatography is also now possible (Section 7-3.d). Because of this interplay between ionic and covalent structure and the several ways of separating diastereomer mixtures, we have chosen in this section not to treat resolving agents separately according to whether they form covalent or ionic diastereomer mixtures.

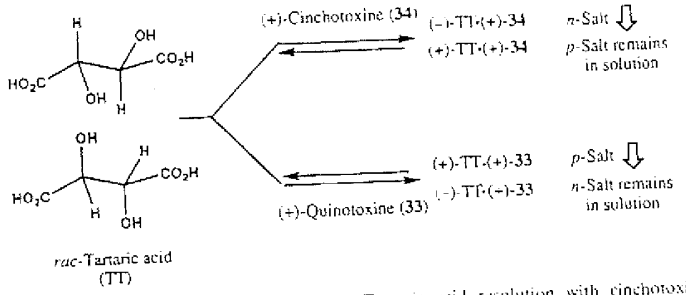


Figure 7.17. First resolution via diastereomers. Tartaric acid resolution with cinchotoxine and quinotoxine (Fig. 7.19) as resolving agents (Pasteur, 1853). The *n* and *p* symbols are defined on p. 326.

IPR2020-00770
United Therapeutics EX2007
Page 3150 of 7335

Details of chromatographic resolutions are examined in Section 7-3.d. The differential stability of diastereomers is another basis for their separation. Transient diastereomeric species are formed in chromatographic columns as flowing racemate samples interact with chiral stationary phases or with achiral stationary phases in the presence of nonracemic chiral mobile phases. This type of resolution is also dealt with in Section 7-3.d. Section 7-3 concludes with an examination of the asymmetric transformation of diastereomers (Section 7-3.e).

In this section, our analysis focuses on resolving agents with emphasis on the recent literature and with examples of their use. The desirable characteristics of a good resolving agent are (Wilen, 1971):

(a) Ready availability
(b) Stability of supply
(c) Stability in use and in storage
(d) Low price or ease of preparation
(e) Ease of recovery and reuse
(f) Low molecular weight
(g) Availability in high enantiomeric purity
(h) Availability of both enantiomers
(i) Low toxicity
(j) Reasonable solubility

α-Methyl-β-phenylethylamine, $C_6H_5CH_2CH(NH_2)CH_3$, illustrates the application of feature (a). This amine is a potentially useful resolving agent (for a recent application to the resolution of gossypol, see Kai, Liang, et al., 1985). However, the amine (amphetamine) is a central nervous system (CNS) active compound, and accordingly it is a controlled substance. Like all such substances (e.g., deoxyephedrine and morphine) it is difficult to obtain. The acquisition of controlled substances for use as resolving agents is so complicated and time consuming (at least in the United States) that their use for this purpose is essentially precluded.

The supply of resolving agents that are derived from natural sources, such as brucine and 10-camphorsulfonic acid, may be shut off by economic or political problems that impede access to the sources (feature b).

Some resolving agents are awkward to use and to store without precaution. Liquid primary amines, such as α-methylbenzylamine and dehydroabietylamine (Fig. 7.19), readily form solid carbamates on exposure to air (Rosan, 1989). It may consequently be desirable to store these amines as salts [feature (c)]; if so, one may profitably choose salts that are conglomerates, since enantiomer purification of such salts would be concomitant with chemical purification (e.g., during recovery). α-Methylbenzylamine hydrogen sulfate (Fig. 7.1) and α-(1-naphthyl)-ethylamine phenylacetate are examples of salts that are conglomerates (Jacques et al., 1981a). All other things being equal, high expense is a negative feature in the choice of a resolving agent, although this feature (d) may be mitigated by the possibility of recovery and reuse (feature e). When preparation of a resolving

IPR2020-00770
United Therapeutics EX2007
Page 3151 of 7335

agent is required, the yield and complexity of the synthesis is likely to be a consideration.

Since resolving agents are purchased by weight but are used on a molar basis, low molecular weight (feature f) is an advantage. This is a significant consideration especially in resolutions carried out on an industrial scale. Unfortunately, many naturally occurring resolving agents, notably alkaloids, have high molecular weights (e.g., brucine, MW 394.4); this is less likely to be the case for synthetic ones (for lists of resolving agents giving molecular weights, see Jacques et al., 1981a, pp. 255–256). Moreover, synthetic resolving agents are usually obtainable in both enantiomeric forms and this feature (h) is advantageous, since it permits the preparation of both enantiomers of a compound by means of mirror-image resolutions (*Marckwald principle*, Marckwald, 1896; type a in Table 7.3). A fair number of such pairs of enantiomers are available commercially (e.g., α-methylbenzylamine, ephedrine, tartaric acid, or 10-camphorsulfonic acid). Some synthetic resolving agents have been designed that explicitly incorporate many of the features listed above (e.g., ten Hoeve and Wynberg, 1985).

Use of synthetic resolving agents requires their prior resolution. This requirement leads us to discuss the possibility of effecting *reciprocal resolutions*: If *rac*-*N*-benzyloxycarbonylalanine [(±)-Z-Ala] is resolvable with (−)-ephedrine [(−)-Eph], then, as is often (but not invariably) the case, the resolving agent (±)-Eph will be resolvable with either (+)- or (−)-Z-Ala (type b in Table 7.3; Overby and Ingersoll, 1960; Jacques et al., 1981a, p. 306).

TABLE 7.3 Types of Diastereomer-mediated Resolutions[a]

Type of Resolution[b]	Resolution Substrate	Resolving Agent	Diastereomeric Products: Less Soluble	Diastereomeric Products: More Soluble
a. Normal	(±)-**Z-Ala**	+ (−)-Eph ⟶	(−)-**Z-Ala**·(−)-Eph	+ (+)-Z-Ala·(−)-Eph
Marckwald	(±)-**Z-Ala**	+ (+)-Eph ⟶	(+)-**Z-Ala**·(+)-Eph	+ (−)-Z-Ala·(+)-Eph
b. Normal	(±)-**Z-Ala**	+ (−)-Eph ⟶	(−)-**Z-Ala**·(−)-Eph	+ (+)-Z-Ala·(−)-Eph
Reciprocal	(±)-**Eph**	+ (+)-Z-Ala ⟶	(+)-Z-Ala·(+)-**Eph**	+ (±)-Z-Ala·(−)-Eph
c. Mutual	(±)-**Z-Ala**[c]	+ (±)-Eph ⟶	(+)-**Z-Ala**·(±)-Eph	+ (±)-Z-Ala·(−)-Eph
d. Mutual	(±)-**Z-Ala**	+ (±)-**Eph** ⟶	(+)-**Z-Ala**·(±)-**Eph**[d] + (−)-Z-Ala·(−)-Eph[e]	(−)-**Z-Ala**·(−)-**Eph**[d] + (+)-Z-Ala·(+)-Eph[e]

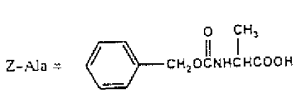
[a] Types of resolutions: (a) Normal and Marckwald resolutions. (b) Normal and reciprocal resolutions (Overby and Ingersoll, 1960); (c) Mutual resolution; see text (Ingersoll, 1925); (d) Mutual resolutions (Wong and Wang, 1978). Resolution substrates and products are in boldface.

[b] This resolution was carried out on partially resolved Ala enriched in (+)-Z-Ala.

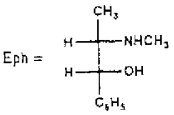
[c] On seeding with (+, +) salt.

[d] On seeding with (−, −) salt.

[e] The (+)-Z-Ala·(−)-Eph and (−)-Z-Ala·(+)-Eph diastereomeric salts did not crystallize.



N-Benzyloxycarbonylalanine



(1*R*,2*S*)-(−)-Ephedrine

IPR2020-00770
United Therapeutics EX2007
Page 3152 of 7335

The reciprocal resolutions shown in Table 7.3 (type b) lead to diastereomeric combinations of salt pairs (the two sets of resolution products). It follows that separability of the diastereomeric salts in one case does not guarantee such separability in the other (Mislow, 1962). However, it does not preclude it either; reciprocal resolutions very often are successful. Moreover, the likelihood of success in reciprocal resolutions has served as a guide in the design of new resolvings agents (including the design of new enantioselective stationary phases for chromatography; Section 7-3.c). Factors leading to the prediction of success in reciprocal resolutions have been evaluated (Fogassy et al., 1981).

Another potentially useful approach to the preparation of synthetic resolving agents is the application of *mutual resolution*. The idea of effecting the mutual resolution of a racemic acid and of a racemic base was first advanced by Ingersoll (1925) in connection with the resolution of phenylglycine with (+)-10-camphorsulfonic acid. The compound (−)-phenylglycine was recovered from the less soluble diastereomeric salt and (+)-phenylglycine (ee = 63%) was recovered from the mother liquor. Reaction of the latter with *rac*-10-camphorsulfonic acid led to formation of a precipitate from which pure (+)-phenylglycine *and* (−)-10-camphorsulfonic were recovered. This process is schematically illustrated in Table 7.3 (type c) for partially resolved (+)-Z-Ala (admixed with *rac*-Z-Ala) recovered from the more soluble product (+)-Z-Ala·(−)-Eph (method a, top line). The less soluble product isolated from reaction with (±)-Eph contains both pure (+)-Z-Ala and resolved "resolving agent" (+)-Eph. Although the method is attractive for the isolation of the substrate enantiomer incorporated in the more soluble diastereomeric product (Table 7.3), we are unaware of any application of this process other than the cases described by Ingersoll (1925).

Although it is not implicit in Table 7.3 (type a), only *one* enantiomer of the substrate is readily obtained in conventional (hence, also in reciprocal) diastereomer-mediated resolutions, for example, (−)-Z-Ala in the resolution of (±)-Z-Ala with (−)-Eph, and (+)-Eph in the reciprocal resolution of (±)-Eph with (+)-Z-Ala (a and b in Table 7.3). In either case, it is only the enantiomer incorporated in the less soluble product that is readily obtained. A change in resolving agent or use of the enantiomeric resolving agent [(+)-Eph as in Table 7.3 (type a), second line (Marckwald principle)] is usually required to obtain the other enantiomer of the substrate to be resolved (see, e.g., Saigo et al., 1986b). On the other hand, crystallization of solutions containing equivalent amounts of *racemic* substrate and *racemic* "resolving agent" may permit the isolation of either enantiomer of the material to be resolved and simultaneously either enantiomer of the "resolving agent" provided that the racemic salt is a conglomerate. Wong and Wang (1978) demonstrated the possibility of effecting such mutual resolutions by alternately seeding racemic solutions containing the four possible salts with crystals of one of the less soluble salts and then with crystals of the enantiomeric salt. In each case, the salt that precipitated had the same composition as that of the seeds; the enantiomers of only one of two possible diastereomeric salts crystallized (d in Table 7.3). As expected, on admixture, the two precipitated enantiomers formed a conglomerate. Hence, mutual resolution, though performed on diastereomeric salts, has the attributes of preferential crystallization. The mutual resolution of (±)-malic acid and of (±)-α-methylbenzylamine has

IPR2020-00770
United Therapeutics EX2007
Page 3153 of 7335

EXPERIMENTAL ORGANIC CHEMISTRY
PRINCIPLES AND PRACTICE

LAURENCE M. HARWOOD
BSc, MSc, PhD (Manch) MA (Oxon), CChem, FRSC
The Dyson Perrins Laboratory and Merton College, Oxford

CHRISTOPHER J. MOODY
BSc (Lond), PhD (L'pool), DSc (Lond), CChem, FRSC
Department of Chemistry, Imperial College of
Science, Technology and Medicine, London

BLACKWELL SCIENTIFIC PUBLICATIONS
OXFORD LONDON
EDINBURGH BOSTON MELBOURNE

IPR2020-00770
United Therapeutics EX2007
Page 3154 of 7335

The authors cannot be held responsible in any way whatsoever for mishaps incurred during experimentation

sci
QD
261
.H2651
1990

© 1989 by Blackwell Scientific Publications
Editorial offices:
Osney Mead, Oxford OX2 0EL
(*Orders*: Tel: 0865 240201)
8 John Street, London WC1N 2ES
23 Ainslie Place, Edinburgh EH3 6AJ
3 Cambridge Center, Suite 208,
Cambridge, Massachusetts 02142, USA
107 Barry Street, Carlton,
Victoria 3053, Australia

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording or otherwise without the prior permission of the copyright owner

First published 1989

Set by Times Graphics, Singapore
and printed and bound in Great Britain by
Butler & Tanner Ltd
Frome, Somerset and London

DISTRIBUTORS

USA
Publishers' Business Services
PO Box 447
Brookline Village
Massachusetts 02147
(*Orders*: Tel: (617) 524 7678)

Canada
Oxford University Press
70 Wynford Drive
Don Mills
Ontario M3C 1J9
(*Orders*: Tel: (416) 441 2941)

Australia
Blackwell Scientific Publications
(Australia) Pty Ltd
107 Barry Street
Carlton, Victoria 3053
(*Orders*: Tel: (03) 347 0300)

British Library
Cataloguing in Publication Data

Harwood, Laurence
Experimental organic chemistry.
1. Organic chemistry. Experiments
I. Title II. Moody, Christopher
547'.00724

ISBN 0-632-02016-4
ISBN 0-632-02017-2 pbk

Library of Congress
Cataloging-in-Publication Data

Harwood, Laurence
Experimental organic chemistry.
Includes index.
1. Chemistry, Organic--Laboratory manuals. I. Moody, Christopher. II. Title.
QD261.H265 1989 547'.0078 88-7680
ISBN 0-632-02016-4
ISBN 0-632-02017-2

Contents

IPR2020-00770
United Therapeutics EX2007
Page 3156 of 7335

The most important factor in drying organic solutions is the choice of drying agent. Ideally the solid drying agent should be totally insoluble in organic solvents, inert to a wide range of organic compounds (including solvents) and able to take up water quickly and efficiently to give a hydrated form which is an easily filterable solid. The most commonly used drying agents are listed in Table 3.5, which gives information on their *capacity* (how much water they can take up), *speed* (rate of water uptake), *efficiency* (how dry they leave the solution) and *applicability* (suitability for different classes of compound). Clearly the choice will depend on a number of factors, the most crucial of which is the nature of the organic compound that is dissolved in the solvent, and that is ultimately to be isolated. As a good general purpose drying agent, magnesium sulfate finds the widest use.

It is important to note that drying agents that are suitable for drying *organic solutions* are not usually appropriate for drying *organic solvents* for use with moisture-sensitive compounds (see pp. 77–87). The drying of organic solvents is an entirely separate problem that is referred to on p. 79, and dealt with specifically in Appendix 2.

Crystallization

The simplest and most effective technique for the purification of solid organic compounds is crystallization. Crystalline compounds are easy to handle, their purity is readily assessed (Chapter 4) and they are often easier to identify than liquids or oils. Crystals can be obtained in one of three ways: from the melted solid on cooling, by sublimation (pp. 154–155) or from a supersaturated solution. The last method is by far the most common in the organic laboratory.

Crystallization of Organic Compounds

A general plan for the purification of an organic compound by *crystallization* is shown in Figure 3.37. The process involves five stages: dissolution, filtration, crystallization, collection of the crystals and drying the crystals. The purity of the crystals can then be determined (Chapters 4 and 5), and if necessary further purification by *recrystallization* can be carried out. Before discussing each of the stages in the process in detail, we should briefly consider how crystallization succeeds in purifying compounds at all.

How crystallization works

The technique involves dissolving the impure solid in the minimum volume of a hot solvent and filtering to remove insoluble impurities. The resulting hot saturated solution of the compound, together with any soluble impurities, is set aside to cool slowly, whereupon crystals of pure compound will separate from solution. The solution remaining after crystallization is usually known as the *mother liquor*. Why are the crystals

IPR2020-00770
United Therapeutics EX2007
Page 3157 of 7335

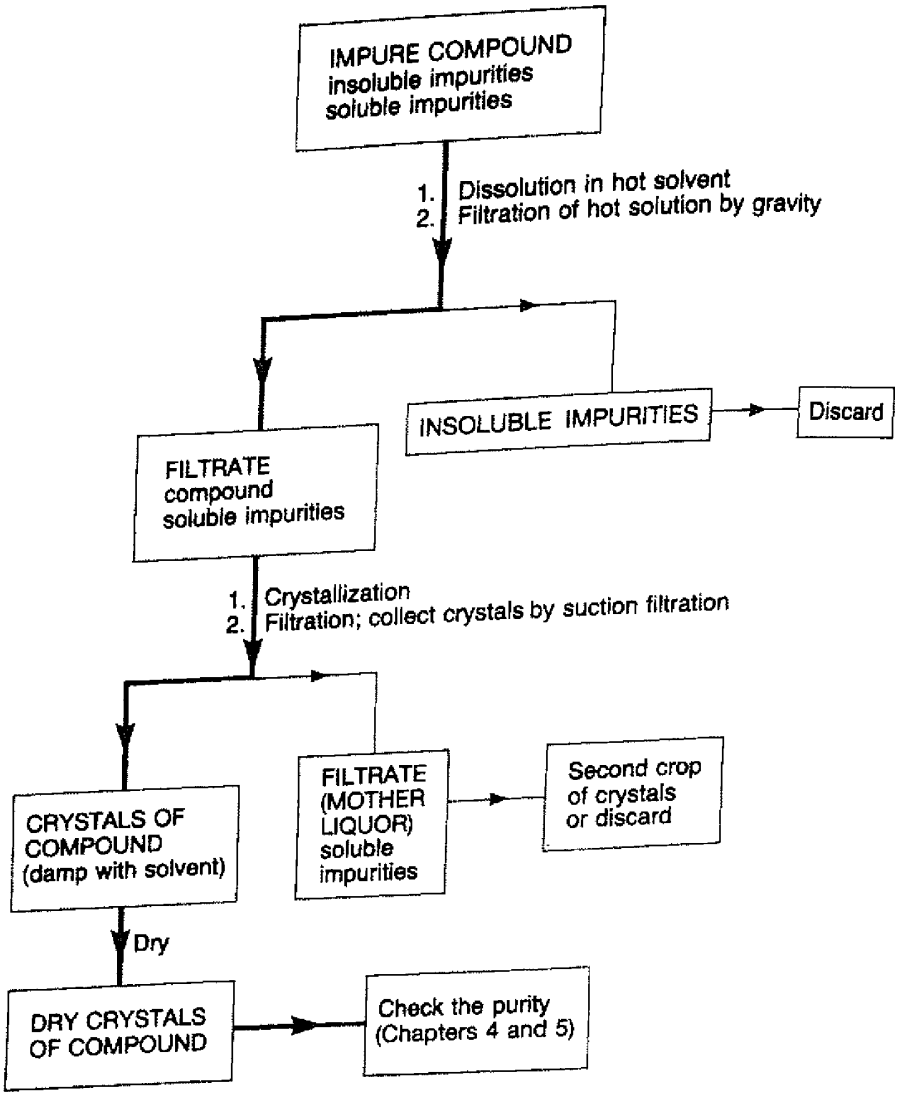


Figure 3.37. Plan for purification of an organic compound by crystallization.

pure? The process of crystallization is an equilibrium: molecules in solution are in equilibrium with those in the crystal lattice. Since a crystal lattice is highly ordered, other different molecules, such as impurities, will be excluded from the lattice and will return to the solution. Therefore only molecules of the required compound are retained in the crystal lattice and the impurities will remain in solution. For a crystallization to be successful, *the solution must be allowed to cool slowly*, so that the crystals are formed slowly, and the equilibrium process which excludes the impurities is allowed to operate. If a solution is cooled rapidly, impurity molecules will be trapped or included in the rapidly growing crystal lattice. This rapid

ooling

IPR2020-00770
United Therapeutics EX2007
Page 3158 of 7335

formation of solid material from solution is *precipitation*, and is not the same as crystallization.

At this stage it should be pointed out that crystallization does not always work. Substances which are grossly impure will often refuse to crystallize, and in these cases some preliminary purification by another technique, such as extraction (pp. 114–125) or chromatography (pp. 155–205), may be necessary.

Dissolution

The first problem is to dissolve the impure substance in a suitable solvent. The ideal solvent for a crystallization should not react with the compound, should be fairly volatile so that it is easy to remove from the crystals, should have a boiling point that is lower than the melting point of the compound to be crystallized, should be nontoxic and nonflammable, but most important of all, the compound should be very soluble in hot solvent and insoluble in cold solvent. In many cases, particularly when crystallizing known compounds, you will know what solvent to use because the literature or your laboratory text will tell you. In other cases, you will have to decide what solvent to use. Choosing a solvent for crystallization is not always easy, but organic chemists tend to follow the rule that 'like dissolves like'. So, for the crystallization of nonpolar substances such as hydrocarbons, use a nonpolar solvent such as hexane or light petroleum. Compounds containing polar groups such as OH are best crystallized from polar OH containing solvents such as ethanol. Indeed polar solvents are often preferred for other compounds because they tend to give better crystals. Some suggestions for crystallization solvents for the most common classes of organic compound, arranged in order of increasing polarity, are given in Table 3.6.

Like dissolves like

If the crystallization solvent is not known for certain, do not commit all your solid and attempt to dissolve it up. Rather, carry out some preliminary solubility tests. To do this, place a small quantity of the solid

Test the solubility

Table 3.6. Suggested solvents for crystallization.

Class of compound	Suggested solvents
Hydrocarbons	Light petroleum, hexane, cyclohexane, toluene
Ethers	Ether, dichloromethane
Halides	Dichloromethane, chloroform
Carbonyl compounds	Ethyl acetate, acetone
Alcohols, acids	Ethanol
Salts	Water

IPR2020-00770
United Therapeutics EX2007
Page 3159 of 7335

Use a hood if the solvent is toxic

Use a steam bath for heating flammable solvents

(*ca.* 20 mg or the amount that fits on the tip of a micro-spatula) in a small test tube — an ignition tube or a 10 × 75 mm test tube is ideal — and add a few drops of solvent to the tube. If the substance dissolves easily in cold solvent, try again with a different solvent. If the substance is insoluble in cold solvent, warm the tube on a steam or water bath, and if the substance remains insoluble, add more solvent with continued heating. If the compound still refuses to dissolve, try again with a different solvent. Once you have found a solvent that dissolves the compound when hot, you need to check that the solid will separate again on cooling. Place the tube in a beaker of ice-water, and leave it to stand for a minute or two. If a solid forms on cooling, the solvent is probably suitable for crystallization of the bulk material. With experience, these preliminary solubility tests can be carried out quickly, and provide a satisfactory guide to the choice of crystallization solvent.

Always keep a seed crystal

Once you have found a suitable solvent, you are ready to dissolve up the solid for crystallization. Before doing so, it is a good idea to weigh the solid, if you have not already done so, so that the recovery of material from the crystallization process can be determined. If the substance is already crystalline, do not dissolve all of it. Always retain a few crystals in case they are needed for seeding purposes (see p. 132). Large crystals are often difficult to dissolve, and should be ground up before adding the crystallization solvent.

Mixed solvents for crystallization

If a suitable crystallization solvent cannot be found, then you may have to use a *mixed solvent system*. A mixed solvent system is a pair of miscible solvents, chosen so that one of them (the good solvent) dissolves the compound readily, and the other (the poor solvent) does not. For example, many moderately polar organic compounds are soluble in ether, but not in light petroleum, and therefore a mixture of the two solvents may be suitable for crystallization. There are two schools of thought on how to carry out a crystallization using mixed solvents. One method is to dissolve the solid in the minimum volume of hot good solvent, add the poor solvent dropwise until the solution starts to become slightly turbid or cloudy, and then set the solution aside to crystallize. The second method is to suspend the solid in hot poor solvent, and then add the good solvent dropwise with continued heating until the solid *just* dissolves; then set the solution aside as before. Typical mixed solvent systems that often work quite well include ether–light petroleum, dichloromethane–light petroleum, ether–acetone and ethanol–water. If possible choose a system in which the good solvent is the lower boiling solvent. One final word of warning: the use of mixed solvents often encourages *oiling out* (see p. 132), and therefore crystallization from a single solvent is preferred.

Filtration

Once your compound is in solution in a hot solvent, the solution should be filtered to remove any insoluble material. This material may be an

IPR2020-00770
United Therapeutics EX2007
Page 3160 of 7335

insoluble impurity or by-product or may simply be pieces of extraneous material such as dust, glass or paper. The solution should be filtered under gravity through a fluted filter paper into an Erlenmeyer flask using the technique described in pp. 74–75.

Use hand protection for hot filtration

In some cases the solution of your organic compound will be strongly colored by impurities. This is not a problem provided that the colored impurities remain in solution. However, occasionally they are adsorbed by the crystals as they form, to give an impure, colored product. Luckily the fact that such impurity molecules are easily adsorbed can be used to remove them from solution. This process is usually known as *decolorization*, and involves treating the hot solution with activated charcoal, often known as decolorizing carbon or under the tradename Norit®. To decolorize a solution add a small quantity of activated charcoal, usually about 2% by weight of the sample, to the hot, but not boiling, solution. If the solution is at or close to its boiling point, the addition of the finely divided charcoal will cause it to boil over. Continue to heat the solution containing the charcoal for about 5–10 min with occasional swirling or stirring. By this time the impurity molecules responsible for the color should have been adsorbed by the charcoal, and filtration of the mixture should give a decolorized solution of the organic compound. The filtration can be carried out under gravity through a fluted filter paper, although a second filtration may be necessary to remove all the fine particles of charcoal.

Decolorization

Use a steam bath for flammable solvents

Crystallization and What To Do if No Crystals are Formed

Having filtered your hot solution into an Erlenmeyer flask, cover the flask with a watch glass to prevent contamination by atmospheric dust, and then set it aside so that the solution can cool slowly. The rate of cooling determines the size of the crystals, rapid cooling favoring the formation of a lot of small crystals, and slow cooling encouraging the growth of fewer, but much larger, crystals. A convenient compromise between speed of crystallization and crystal quality is to allow the hot solution to cool to room temperature by placing the flask on a surface such as glass or cork that does not conduct the heat away too quickly. The *rate* of crystallization is usually greatest at about 50 °C below the melting point of the substance, and maximum formation of crystals occurs at about 100 °C below the melting point. Once the crystals have formed, it is usually a good idea to cool the solution from room temperature to about 0 °C by placing the Erlenmeyer in an ice bath. This will ensure that the maximum amount of crystals are obtained. It is not usually good practice to cool the solution below 0 °C, unless there are special problems in getting crystals to form in the first place (see p. 132), because this results in condensation of water vapor into the solution unless special precautions are taken.

What do you do when no crystallization occurs after cooling the solution to room temperature? You should attempt to induce crystalliza-

IPR2020-00770
United Therapeutics EX2007
Page 3161 of 7335

Seeding

Scratching

Cooling

tion by one of the following methods. Add a seed crystal which was saved from the original material before dissolution. This will provide a nucleus on which other crystals can grow. If this fails, try scratching the side of the flask with a glass rod. This is thought to produce micro-fragments of glass which then serve as nuclei to induce crystallization. If this fails, try cooling the flask in an acetone–solid CO_2 bath (see p. 104), and then scratch the side of the flask as the solution warms up to room temperature. If the substance still refuses to crystallize, it probably means that you have too much solvent; the excess solvent should be boiled off (**hood — check for flames in the vicinity**), and the reduced volume of solution should be set aside again until crystallization occurs.

Oiling out

The final problem that may be encountered in crystallization is the separation of the substance as an oil rather than as crystals. This is known as *oiling out*, and usually occurs when the compound is very impure or when it has a melting point that is lower than the boiling point of the solvent. Even if the oil eventually solidifies, the compound will not be pure, and the material should be redissolved by heating the solution. You may need to add a little more solvent at this stage, or more good solvent if mixed solvents are being used. Indeed, crystallization from a slightly more dilute solution may prevent oiling out. Slower cooling also favors the formation of crystals rather than oils. If the compound completely refuses to crystallize, the chances are that it is too impure, and it should be purified by some other means such as chromatography.

Collecting the Crystals

After crystallization the crystals are separated from the *mother liquor* by suction filtration, a technique which has already been discussed in detail on pp. 75–77. After filtration, the crystals should be washed with a little fresh solvent. Remember that if the crystallization has been performed using mixed solvents, the wash solvent should be the same mixture.

Second crop will be less pure

The mother liquor from the crystallization (which is now the filtrate) may still contain a significant quantity of your organic product. In this case a second batch of crystals, known as the *second crop*, can often be obtained by concentrating the mother liquor by boiling off some of the solvent (**hood — check for flames in the vicinity**) and then allowing the solution to cool and crystallize as before. However, be warned, the second crop is usually less pure than the first simply because the impurities were concentrated in the mother liquor during the first crystallization. Do not combine the two crops of crystals until you have checked the purity of each batch.

Drying the Crystals

After filtration and washing, the crystals should be dried to constant weight. Techniques for drying solids are discussed in pp. 136–138.

IPR2020-00770
United Therapeutics EX2007
Page 3162 of 7335

Special Crystallization Techniques

Crystallization of Very Small Quantities

When the amount of material to be crystallized is less than about 100 mg, the normal techniques of crystallization are inappropriate because of the losses of material that would occur, particularly during filtration. To crystallize small quantities (10–100 mg) of organic compounds, place the solid in a *very small* test tube, and dissolve it up in the minimum volume of hot solvent in the usual way. It is impossible to filter very small volumes of solution using the normal technique, so another method is needed. One way is to put a small plug of cotton wool in the tip of a Pasteur pipet and then slowly draw the hot solution through the cotton wool into the pipet (Figure 3.38(a)). The cotton wool will retain all but the finest of insoluble impurities. Quickly remove the wool from the end of the pipet using a pair of tweezers, and then release the hot solution from the pipet into the *pre-weighed* vessel where it will be allowed to crystallize. To avoid spills, it is safer to hold the Pasteur pipet over the crystallization vessel whilst removing the cotton wool. The ideal vessels for the crystallization of small quantities of material are small conical-bottomed centrifuge tubes or tubes specially designed for the purpose known as *Craig tubes*. The idea is to minimize the number of transfers and to avoid having to collect the crystals by filtration. If the crystallization is allowed to take place in a

Craig tubes

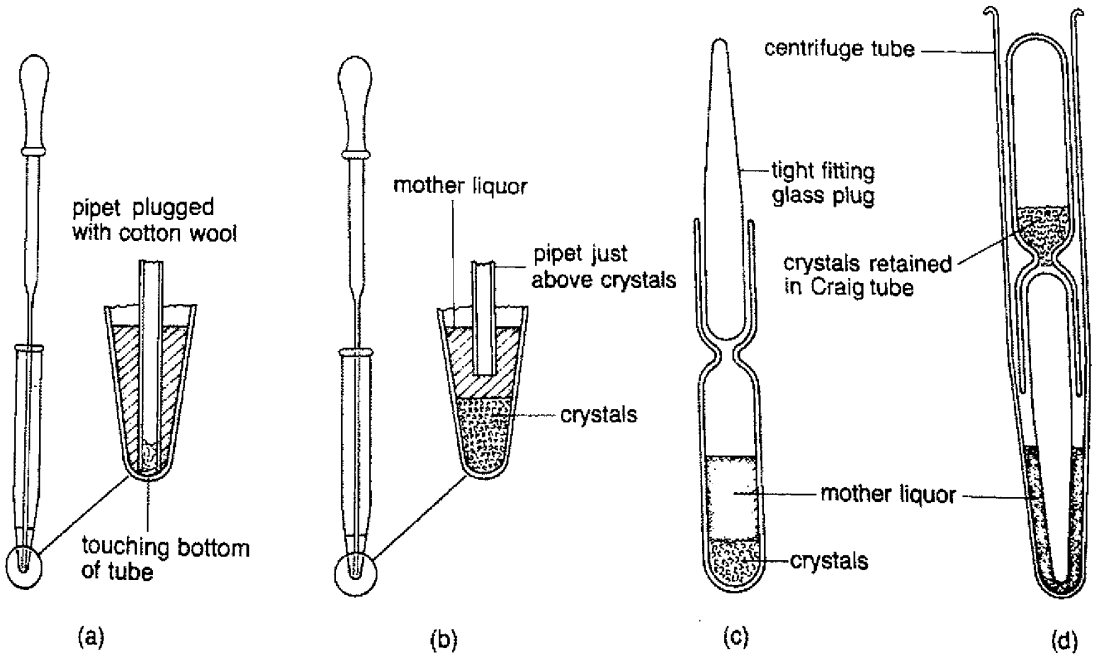


Figure 3.38. (a) Using a Pasteur pipet and cotton wool for filtration; (b) removing the mother liquor with a Pasteur pipet; (c) Craig tube before centrifugation; (d) Craig tube after centrifugation.

IPR2020-00770
United Therapeutics EX2007
Page 3163 of 7335

small centrifuge tube, the mother liquor should be removed using a Pasteur pipet, taking care not to suck up any crystals (Figure 3.38(b)). A small amount of wash solvent can be added, and can then be removed by pipet. The damp crystals should be dried in the same tube by placing it in a suitable drying apparatus (Figure 3.40).

Craig tubes (Figure 3.38(c, d)) are designed so that the mother liquor from the crystallization can be removed by *centrifugation*. The hot filtrate is transferred to the Craig tube as described above, and the crystallization is allowed to proceed. When crystallization is complete, insert the well-fitting glass 'plug' of the Craig tube, place an empty inverted centrifuge tube over the Craig tube, and invert the whole, making sure that the two parts of the Craig tube do not separate. Place the tube in the centrifuge, make sure the centrifuge is balanced, and turn it on for 20–30 s. The centrifugation will force the mother liquor past the glass plug, but the crystals will be retained by the plug (Figure 3.38(d)). The Craig tube plus crystals is then placed in a suitable drying apparatus to dry the crystals.

Always balance the centrifuge rotor arm

When the crystals are dry, the crystallization tube can be weighed, and provided that the empty weight was recorded, the weight of crystals can be determined. The crystals can be removed from the tube by inverting it over a piece of filter or weighing paper, and gently tapping it.

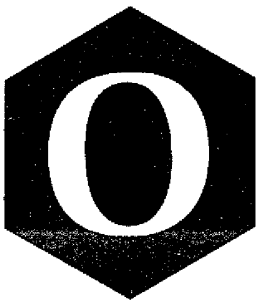
Fractional Crystallization

Fractional crystallization is a rather special technique for separating two compounds by repeated crystallization. Although chromatography has largely supplanted fractional crystallization as a separation method, the technique still has its uses, particularly in the resolution of racemic acids or bases by separation of their crystalline diastereomeric salts formed by reaction with optically active bases or acids respectively. A schematic plan for a fractional crystallization is shown in Figure 3.39. The first crystallization gives crystals (C_1) and mother liquor (ML_1). These are separated in the normal way, and the crystals are recrystallized to give crystals C_2 and mother liquor ML_2'. The first mother liquor is evaporated to dryness, and the residue is redissolved and crystallized to give crystals C_2' and mother liquor ML_2. The crystals C_2' are combined with ML_2'; the solvent is evaporated, and the residue is crystallized further. As the scheme unfolds, pure crystals of the less soluble component are obtained and the mother liquor becomes enriched in the more soluble component. In practice it is fairly easy to obtain a pure, less soluble component after two or three crystallizations, but the more soluble component may require further purification by some other technique.

Crystals for X-Ray Crystallography

Good crystals are an essential requirement if the material is to be submitted for X-ray structure analysis. Therefore the growth of X-ray

IPR2020-00770
United Therapeutics EX2007
Page 3164 of 7335



Organic Chemistry

Second Edition

MAITLAND JONES, Jr. Princeton University

W · W · NORTON & COMPANY NEW YORK · LONDON

IPR2020-00770
United Therapeutics EX2007
Page 3165 of 7335

Copyright © 2000, 1997 by W. W. Norton & Company, Inc.

All rights reserved
Printed in the United States of America

Editor: Joseph Wisnovsky
Manuscript editor: Jeannette Stiefel
Project editor: Katherine Barry
Editorial assistants: Paul Fyfe, Amy Sievers
Manufacturing director: Roy Tedoff
Illustrations: J/B Woolsey Associates, TSI Graphics
Composition: TSI Graphics
Manufacturing: R.R. Donnelly & Sons Company
Text design: Jack Meserole
Cover design: Maitland Jones, III
Cover blackboard photographs: Nat Clymer
Cover molecular image: Greg Hart

The text of this book is composed in Trump Medieval with the display set in Helvetica

Library of Congress Cataloging-in-Publication Data
Jones, Maitland, Jr., 1937–
Organic chemistry / Maitland Jones, Jr.—2nd ed.
p. cm.
Includes bibliographical references and index.
ISBN 0-393-97405-7
1. Chemistry, Organic. I. Title.
QD253.J65 2000 99-052222
547—dc21

W. W. Norton & Company, Inc., 500 Fifth Avenue, New York, N.Y. 10110
www.wwnorton.com

W. W. Norton & Company Ltd., 10 Coptic Street, London, WC1A 1PU

1 2 3 4 5 6 7 8 9 0

IPR2020-00770
United Therapeutics EX2007
Page 3166 of 7335

4.8 PHYSICAL PROPERTIES OF DIASTEREOMERS: OPTICAL RESOLUTION

The formation of diastereomers allows the separation of enantiomers. Separation of enantiomers, called **resolution**, is a serious experimental difficulty. So far we have ignored it. Enantiomers have identical physical properties (except for the ability to rotate the plane of plane-polarized light), and one might legitimately wonder how in the world we are ever going to get them apart. At several points we used a single enantiomer without giving any hint of how a pair of enantiomers might be separated. The key to this puzzle is that diastereomers, unlike enantiomers, have different physical properties—melting point, boiling point, and so on.

One general procedure for separating enantiomers is to allow them to react with a naturally occurring chiral molecule to form a pair of diastereomers.* These can then be separated by taking advantage of one of their different physical properties. One typically can separate such a pair by crystallization, because the members of the diastereomeric pair will have different solubilities. Then, if the original chemical reaction can be reversed, we have the pair of enantiomers separated. Figure 4.42 outlines the general scheme and begins with a schematic recapitulation of Figure 4.33, which first described the reaction of a single enantiomer with a racemic mixture to give a pair of diastereomers. Be sure to compare the two figures.

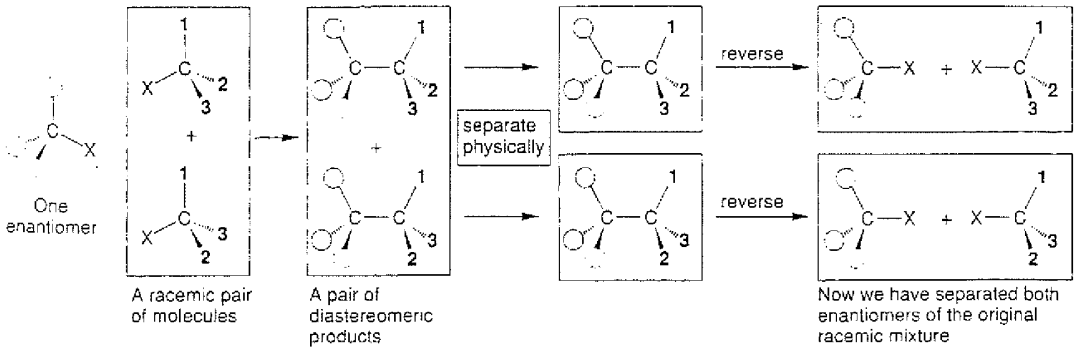


FIGURE 4.42 Resolution is a general method for separating the constituent enantiomers of a racemic mixture. A single enantiomer of a chiral molecule is used to form a pair of diastereomers, which can be separated physically. If the original chemical reaction can be reversed, the enantiomers can be isolated.

It is not even necessary to form covalent bonds. For example, in the traditional method for separating enantiomers of organic acids, optically active nitrogen-containing molecules, called alkaloids, are used to form a pair of diastereomeric salts, which can then be separated by crystallization. These alkaloids have wondrously complex structures (for more on these fascinating molecules, see Chapter 20, pp. 1047–51). Two examples, brucine and the notorious strychnine, are shown in Figure 4.43 along with the general procedure for this kind of resolution.

*Of course, there is no magic in using a molecule derived from natural sources. One made in the laboratory will do as well. However, many molecules found in Nature are easily isolable as pure enantiomers, and it is often convenient to use them.

IPR2020-00770
United Therapeutics EX2007
Page 3167 of 7335

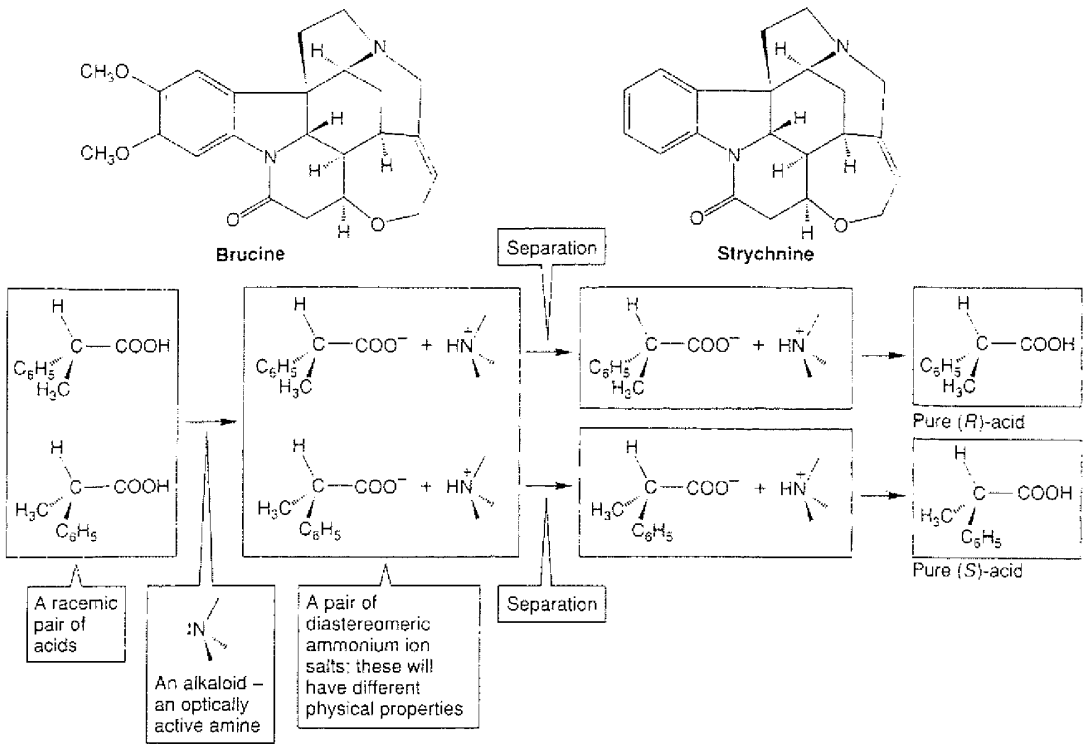
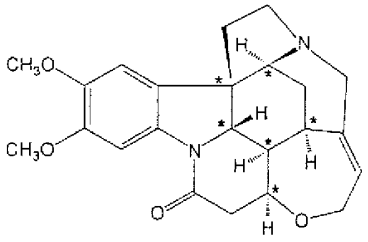


FIGURE 4.43 Two alkaloids, brucine and strychnine, are commonly used to separate the enantiomers of chiral organic acids. Diastereomeric salts are first formed, then separated by crystallization, and the individual enantiomeric acids are regenerated.

PROBLEM 4.20 Identify with an asterisk (*) all the stereogenic carbons in brucine.

ANSWER



PROBLEM 4.21 Identify each stereogenic carbon in brucine as (*R*) or (*S*).

These days, this general procedure has been extended so that all manner of enantiomeric pairs can be separated by chromatography. In such a technique, covalent chemical bonds are not formed, as they are not in the salt formation shown in Figure 4.43. Rather, advantage is taken of the formation of partial bonds—complexes—as the pair of enantiomers passes over an optically active substrate. The complexes are diastereomeric and

IPR2020-00770
United Therapeutics EX2007
Page 3168 of 7335

thus one will be more stable (contain a stronger partial bond) than the other. One enantiomer will be held more tightly than the other and will pass through the chromatography apparatus more slowly (Fig. 4.44).

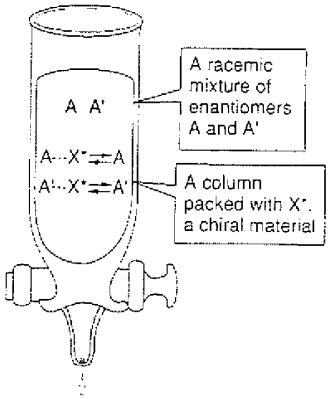


FIGURE 4.44 A chromatography column for separating enantiomers. The column is packed with an optically active substrate (X*) that forms a complex with the enantiomers A and A'. These complexes are diastereomers and have different physical properties, including bond strengths of A···X and A'···X. Both AX and A'X are in equilibrium with the free enantiomers, and these equilibria will be different for the two diastereomeric complexes. Therefore, A and A' will move through the column at different rates and emerge at different times.

4.9 DETERMINATION OF ABSOLUTE CONFIGURATION (*R* OR *S*)

Now that we have achieved the separation of our racemic mixture of enantiomers into a pair of optically active stereoisomers, we face the difficult task of finding out which enantiomer is (*R*) and which is (*S*). This problem is not trivial! Indeed, in Chapter 23, when we deal with sugars, we'll find that until rather recently, there was *no* way to be certain, and one just had to guess (correctly in the case of the sugars, it turns out). One would like to peer directly at the structures, of course, and under some circumstances this is possible.

X-ray crystallography can determine the relative positions of atoms in a crystal, and a special kind of X-ray diffraction called "anomalous dispersion" can tell the absolute configuration of the molecule. But this is not a generally applicable technique—one needs a crystalline compound, for example. It does serve to give us some benchmarks, though. If we know the absolute configuration (*R* or *S*) of some compounds, we may be able to determine the absolute configurations of other molecules by relating them to the few compounds of known absolute configuration. We must be very careful, however. The chemical reactions that interconvert the molecules of known and unknown absolute configurations must not alter the stereochemical arrangement at the stereogenic atoms, or if they do, it must be in a known fashion. How do we know whether a given chemical reaction will or will not change the stereochemistry? We need to know the reaction mechanism—to know how the chemical changes occur—in order to answer this question. This reason is just one of many for the study of reac-

IPR2020-00770
United Therapeutics EX2007
Page 3169 of 7335

Benzindene Prostaglandins. Synthesis of Optically Pure 15-Deoxy-U-68,215 and Its Enantiomer via a Modified Intramolecular Wadsworth-Emmons-Wittig Reaction

Chiu-Hong Lin,* Paul A. Aristoff,* Paul D. Johnson, James P. McGrath, Joseph M. Timko, and André Robert

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

Received June 11, 1987

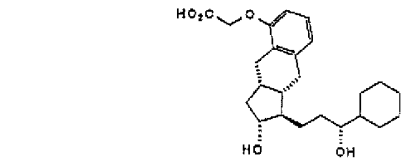
The optically pure [[1(*R*)-(3-cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2(*R*)-hydroxy-(3a*S*,9a*S*)-1*H*-benz[*f*]-inden-5-yl]oxy]acetic acid (**2a**) and its 1,2,3a,9a-tetraepi isomer (**2b**), 15-deoxy analogues (prostaglandin numbering) of the potent antiulcer agent **1** (U-68,215), have been synthesized. The resolution of the optical isomers was accomplished by LC (liquid chromatography) separation of the 2(*RS*)-(*S*)-α-methylbenzyl carbamates **8a,b**, which were obtained from the racemic alcohols **7a,b**. The racemic alcohols **7a,b** were initially synthesized via condensation of the enol lactone **4** with the phosphonate **3c** followed by the catalytic hydrogenation and sodium borohydride reduction of the adduct **5**. A second and improved route involved the coupling reaction of the anion of the phosphonate **3c** and the enolate of the γ-keto ester **12a**, both generated in situ in the presence of the excess lithium diisopropylamide, to give cyclopentenone **5** directly in 75% yield. The absolute configuration of the resolved isomers **7a** and **7b** was confirmed by comparison with authentic samples which were synthesized independently via selective deoxygenation of the side chain hydroxyl group from **16a** and **16b**, prepared with known absolute configuration. The racemic alcohols **7a,b** and the resolved optically pure isomers **7a** and **7b** were then converted separately in three steps to the racemic analogue **2a,b** and the optically pure isomers **2a** and **2b**, respectively. The absolute configuration of the optically pure isomers **2a** and **2b** was further established by comparing with the authentic samples synthesized independently from the authentic alcohols **7a** and **7b**, prepared from **16a** and **16b**, respectively. Interestingly, most of the biological activity seemed to reside with **2b**, the "unnatural" isomer in terms of prostaglandin analogues.

Introduction

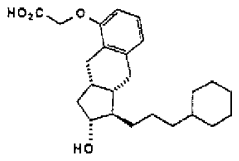
A benzindene prostaglandin analogue with a cyclohexyl side chain (**1**, U-68,215) was recently shown by us to be a potent antiulcer agent.[1,2] Moreover, unlike most prostaglandin analogues of interest in the gastrointestinal area, this compound is considerably more stable and exhibits no enteropooling, uterotonic, or gastrointestinal mucosa cellular proliferative activity.[1] However, it does have significant cardiovascular effects which could limit its therapeutic utility in antiulcer therapy. We were therefore interested in synthesizing some selected analogues of **1** in hopes of completely separating out the cardiovascular activity while maintaining the potent antiulcer behavior. The side chain deoxy analogue of **1** was chosen as one of the analogues to examine this possibility and was initially prepared in racemic form for the initial biological screening. Encouragingly, the racemate **2a,b** was found to demonstrate significant cytoprotective and gastric antisecretory activity while having only minor effects on blood pressure. However, unlike the corresponding dihydroxy analogue **1**, the racemic analogue **2a,b** exhibited enteropooling (the accumulation of fluid in the small intestine, an index of the diarrheogenic activity of prostaglandin) activity. We therefore set out to synthesize the optically pure isomer **2a** with natural configuration and its enantiomer (**2b**). The biological activity of each isomer, then, would enable us to determine which component of the racemate was responsible for the desirable cytoprotective/antisecretory activity and which one contributed to the undesirable enteropooling activity.

Results and Discussion

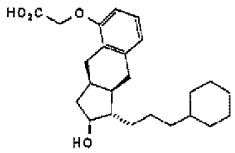
The synthesis of the racemic side chain deoxy analogue **2a,b** was accomplished in a straightforward manner as shown in Scheme I. Bromination of alcohol **3a** followed



1 (U-68,215)



2a



2b

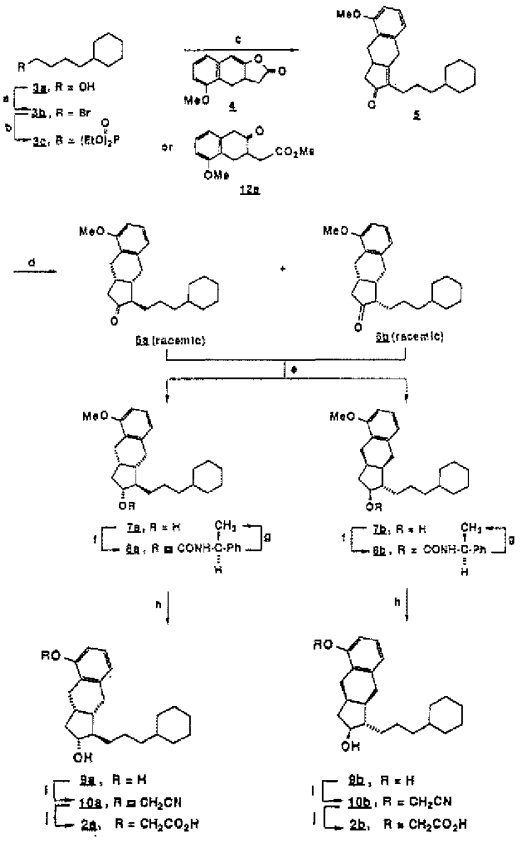
by displacement of the bromide **3b** with the anion of diethyl phosphite afforded the phosphonate reagent **3c** in 78% overall yield. The anion of this phosphonate, **3d**, generated in situ by reacting **3c** with 1 equiv of *n*-butyllithium at −78 °C, was coupled with 0.5 equiv of enol lactone **4**.[2] When the reaction mixture was warmed to room temperature, protonated with 0.5 equiv of acetic acid, and heated, the coupled product undergoes the intramolecular Wadsworth-Emmons-Wittig reaction to give cyclopentenone derivative **5** in 68% yield. A similar transformation has already been described in detail in the synthesis of the dihydroxy analogue **1**.[2] As shown in Scheme II, the mechanism of the coupling reaction of the enol lactone **4** with 2 equiv of the phosphonate anion **3d** proceeds via the initial adduct **13a**, a hemiketal intermediate which collapses to intermediate **13b**, which rapidly reacts with excess phosphonate anion **3d** to generate the dianion **13d**. Addition of 1 equiv of acetic acid (against 2 equiv of base used) as an external proton source upon warming to room temperature generates the monoanion **13e**. This monoanion undergoes an intramolecular Wadsworth-Emmons-Wittig reaction upon heating at 65

(1) Robert, A.; Aristoff, P. A.; Wendling, M. G.; Kimball, F. A.; Miller, W. L.; Gorman, R. R. *Prostaglandins* **1985**, *30*, 619.
(2) Aristoff, P. A.; Johnson, P. D.; Harrison, A. W. *J. Am. Chem. Soc.* **1985**, *107*, 7967.

0022-3263/87/1952-5594$01.50/0 © 1987 American Chemical Society

IPR2020-00770
United Therapeutics EX2007
Page 3170 of 7335

Scheme I[a]

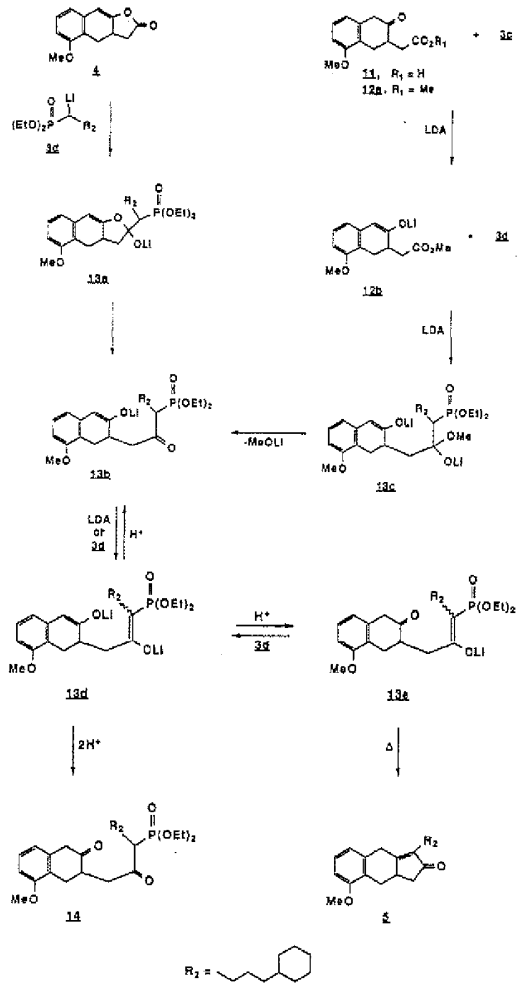


[a] (a) PBr_3, Δ; (b) $(EtO)_2P(O)Li$, THF, Δ; (c) 4 or 12a (see Scheme II), base, THF; HOAc, Δ; (d) Pd/C, H_2, K_2CO_3, EtOH; (e) $NaOH/H_2O/EtOH/NaBH_4$, −10 °C; (f) phosgene, triethylamine, (S)-(−)-α-methylbenzylamine, toluene; (g) $LiAlH_4$/THF, Δ; (h) Ph_2PLi, THF, Δ; (i) K_2CO_3, $ClCH_2CN$, acetone, Δ; (j) KOH, EtOH, H_2O, Δ.

°C to give the desired cyclopentenone derivative **5**.

More recently, on the basis of this postulated mechanism, we have developed an improved process (Scheme II) which involves the direct coupling of the anion **3d** of the phosphonate **3c** and the lithium enolate **12b** of the γ-keto ester **12a**.[3] We rationalized that the enolate ester **12b** can also undergo a similar coupling reaction with the phosphonate anion **3d**. If the resulting coupled hemiketal intermediate, **13c**, suffers loss of lithium methoxide, intermediate **13b** would be obtained, which is then converted to **5** as described previously. This mechanistic consideration prompted us to try an in situ generation of both anions **3d** and **12b**. Since the enolate formation of the ketone is much faster than of the ester with a base such as lithium diisopropylamide, we decided to try this possibility. Thus, when 3 equiv of lithium diisopropylamide in tetrahydrofuran were added to a tetrahydrofuran solu-

Scheme II



tion containing 1 equiv of keto ester **12a**[3] and 1.5 equiv of phosphonate **3c** at −78 °C, followed by slow warming to room temperature, addition of 1.5–1.8 equiv of acetic acid, and heating at 65 °C, the desired cyclopentenone derivative **5** was isolated in 75% yield after chromatography. This result indicates that the deprotonation of **3c** and **12a** to form the phosphonate anion **3d** and the enolate anion **12b**, respectively, is much faster than the deprotonation to form the enolate of the ester in **12a**. Actually, when we monitored the reaction by quenching an aliquot with saturated aqueous ammonium chloride, 5–10 min after the addition of lithium diisopropylamide at −78 °C, the keto phosphonate **14** was isolated, indicating that the coupling reaction of **3d** and **12b** occurs rather rapidly. When the reaction was interrupted by quenching with excess acid before undergoing intramolecular Wadsworth–Emmons–Wittig reaction, i.e., before protonation with acetic acid and heating, the coupled product **14** was isolated in 75% yield after chromatography. This result shows that the intramolecular Wadsworth–Emmons–Wittig reaction (**13e** to **5**) is a high-yield process. Although the overall yield of this process, from the keto acid **11** to the enone **5** via the γ-keto ester **12a** (49%), is no better than the original

(3) The γ-keto ester **12a** used in the modified process was easily obtained in 66% yield from the keto acid **11**, which is the precursor to enol lactone **4** and an intermediate in the synthesis of 15-hydroxy analogue 1[2] (see Experimental Section). This successful conversion, in conjunction with the modified phosphonate chemistry described in this report, has provided the more viable and improved synthesis of the benzindene analogs.

IPR2020-00770
United Therapeutics EX2007
Page 3171 of 7335

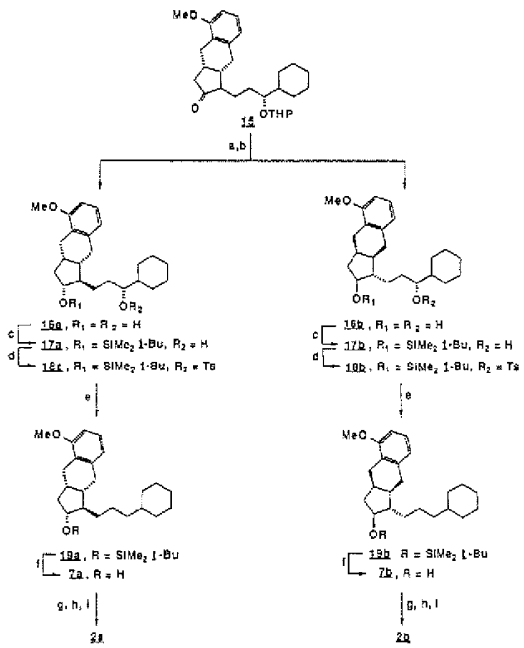
process via enol lactone (57%), in the large-scale preparation (>300 g), the process via the γ-keto ester has been found to have the following advantages: (1) the reproducibility of the conversion of the γ-keto ester **12a** to enone **5** was far better than the enol lactone **11**; (2) the conversion of the keto acid **11** to the γ-keto ester **12a** was much easier to accomplish on large scale than the conversion to the somewhat labile enol lactone, which required removal of large quantities of acetic anhydride in the workup; (3) when the resolved phosphonate is used for the condensation–cyclization, as in the case of synthesizing 15-hydroxy analogue **1**, there is a distinctive advantage in using less phosphonate for the reaction. Overall, this remarkable result indicates that this reaction is a potentially useful method for achieving the direct synthesis of cyclopentenone or cyclohexenone derivatives from γ- or δ-keto esters, respectively. We are currently examining the scope and limitations of this transformation.[4]

Hydrogenation of the enone **5** (Scheme I) using 10% palladium on carbon in ethanol with a catalytic amount of potassium carbonate present gave after 2 days at room temperature a difficultly separated mixture of the initial product **6b** (racemic) and its equilibrated isomer **6a** (racemic) in 80% yield (3:1 ratio of **6a** to **6b**). Apparently the long reaction time allowed significant equilibration of the initially formed product **6b** to **6a** in the presence of potassium carbonate. When the same hydrogenation was carried out with a different lot of 10% palladium on carbon, the hydrogenation was completed in 7 h, and the product ratio was reversed to 1:3 for **6a** to **6b**. Thus, the variations in activity of the catalyst play an important role in this hydrogenation reaction. The more active catalyst, however, also lowered the yield of **6a,b** to 73% and caused the formation of the side products such as overreduction to the alcohol (9%) and the deoxy compound (17%).

The mixture of racemic ketones **6a** and **6b** was converted directly in a one-pot operation to the racemic alcohol mixture **7a,b** in 84% yield by treatment with aqueous sodium hydroxide and sodium borohydride in ethanol. This reaction succeeds because whereas equilibration of **6b** to **6a** is fast, hydride reduction of **6b** is slow and that of **6a** is relatively fast.[2] The net effect is therefore that all of **6b** is converted to the racemic mixture of alcohols **7a,b**. Without resolution of the optical isomers **7a** and **7b**, initially the alcohol mixture **7a,b** was converted in three steps (90% overall yield) to the racemic 15-deoxy benzindene analogue **2a,b**, by using the same chemistry developed to prepare the parent 15-hydroxy compound **1**.[2] Thus, the alcohols **7a,b** were first demethylated with lithium diphenylphosphide in tetrahydrofuran (70 °C, 7 h) to give the diols **9a,b** in 95% yield.[5] The racemic diol mixture **9a,b** was then selectively alkylated with chloroacetonitrile in the presence of potassium carbonate in acetone (65 °C, 24 h) to afford the cyanomethyl ethers **10a,b** (99%). Finally, the hydrolysis of the cyano group was smoothly accomplished by heating **10a,b** in 25% aqueous potassium hydroxide in methanol or ethanol (90 °C, 5 h) in 97% yield. Thus, keto ester **12a** was converted in six steps and 46% overall yield to the racemic benzindene analogue **2a,b** (13 steps and 25% overall yield from 5-methoxy-2-tetralone).

For the synthesis of the optically active isomer **2a** with natural configuration and its enantiomer (**2b**), the resolution of the racemic mixtures at some stage of the synthesis was necessary. We decided to pursue the resolution of the racemic alcohols **7a,b** by reacting the alcohols with a chiral reagent and separating the diastereomers chromatographically. The absolute configuration of these two diastereomers was then determined by matching the HPLC peaks with the authentic diastereomer synthesized independently from the established route (vide infra). On an analytical scale, the carbamate formation from the racemic **7a,b**, and authentic **7a** and **7b** (vide infra), was initially carried out by using (*S*)-(−)-α-methylbenzyl isocyanate[6,7] in toluene at room temperature with dibutyltin acetate as the catalyst.[8] Apparently the catalyst was very effective for this transformation, and the reaction could be completed in 3–4 h at room temperature. Without this catalyst, however, refluxing in toluene for an extended period of time was required. From this analytical scale carbamate formation the absolute configuration of each carbamate was assigned by matching the HPLC peaks of the carbamates **8a** and **8b**, obtained from the authentic alcohols **7a** and **7b**, prepared from compounds of known configuration as shown in Scheme III. The less polar carbamate corresponded to the diastereomer **8a** and the more polar carbamate to the diastereomer **8b**. When the reaction was scaled-up for the synthesis, however, the reaction conditions to form carbamates **8a** and **8b** were altered to use the less expensive (*S*)-(−)-α-methylbenzylamine. Thus, the racemic alcohol mixture **7a,b** was reacted

Scheme III[a]



[a] (a) NaOH, H_2O, EtOH, $NaBH_4$, −10 °C; (b) HOAc–THF–H_2O (3:1.5:1), 45 °C, 3 h; (c) *t*-BDMSiCl, imidazole, THF; (d) TsCl, pyridine; (e) $LiAlH_4$, Et_2O; (f) HCl, 2-PrOH, H_2O; (g) Ph_2PLi, THF, Δ; (h) K_2CO_3, $ClCH_2CN$, acetone, Δ; (i) KOH, EtOH, H_2O, Δ.

(4) The direct conversion of a γ-keto ester with a hindered carbonyl group to a cyclopentenone derivative has also been reported, see: Haltman, R. L.; Vollhardt, K. P. C. *Tetrahedron Lett.* **1986**, 1461.

(5) Ireland, R. E.; Walba, D. M. *Tetrahedron Lett.* 1976, 1071. See, for a useful review: Bhatt, M. V.; Kulkami, S. U. *Synthesis* 1983, 249.

(6) Pirkle, W. H.; Hoekstra, M. S. *J. Org. Chem.* 1974, 39, 3904 and references cited therein.

(7) Morrison, J. D., Ed. In *Asymmetric Synthesis*; Academic: Orlando, 1983; Vol. 1, Chapter 6.

(8) Thomas, F.; Thorne, M. P. *Can. J. Chem.* 1976, *54*, 24.

IPR2020-00770
United Therapeutics EX2007
Page 3172 of 7335

in toluene with phosgene, triethylamine, and the optically active amine, to form the mixture of carbamates **8a** and **8b**.[6] Preparative LC separation (liquid chromatography) afforded >99% pure **8a** and **8b** (see Experimental Section). Each of these carbamates **8a** and **8b**, was then converted back to the optically pure alcohols **7a** and **7b**, respectively, in 100% yield by treating the carbamates in tetrahydrofuran with lithium aluminum hydride. Each of these alcohols **7a** and **7b** was then converted in three steps, as described earlier for the synthesis of the racemic **2a,b**, to the optically pure **2a** and **2b**, respectively. These optically pure **2a** and **2b** showed physical properties identical with those of the racemic **2a,b** except for optical rotation and melting point (**2a,b**, mp 158–160 °C; **2a**, mp 133.5–135.5 °C; **2b**, mp 133.5–135.5 °C). The specific rotations of **2a** ($[\alpha]_D$ + 30.69°) and **2b** ($[\alpha]_D$ −28.16°) also showed **2a** and **2b** are enantiomers. The HPLC analyses also confirmed that **2a** and **2b** exhibited retention times identical with those of the authentic samples synthesized from the material with known absolute configuration.

The confirmation of the absolute configuration of **2a** and **2b** synthesized from the resolved alcohols **7a** and **7b** via chiral carbamates shown in Scheme I required the synthesis of authentic acids **2a** and **2b** for comparison. As shown in Scheme III, the 15-hydroxy intermediates **16a** and **16b** were synthesized from optically pure 15[2] and separated during the course of the synthesis of 1.[2] The diols 16a (98.5% pure) and **16b** (>99% pure) were independently converted to alcohols **7a** and **7b**, respectively, via selective removal of the side chain hydroxyl group. These alcohols were then used as the reference for matching the peaks with the resolved alcohols **7a** and **7b**, thereby establishing the absolute configuration of each isomer. This selective removal was made possible based on the observation that the ring hydroxyl group was preferentially silylated over the side chain hydroxyl group. Thus, as shown in Scheme III, the diols **16a** and **16b** were therefore separately silylated using *tert*-butyldimethylsilyl chloride and imidazole in tetrahydrofuran.[9] The major products obtained were assigned as **17a** and **17b**, respectively. Each of these isomers was then subjected to tosylation (*p*-toluenesulfonyl chloride/pyridine) to give the tosylates **18a** and **18b** from **17a** and **17b**, respectively. The tosylates 18a and 18b were then treated with lithium aluminum hydride in ether to give the silyloxy products **19a** and **19b**, respectively. The removal of the silyl group from **19a** and **19b** in aqueous hydrochloric acid/2-propanol resulted in the formation of the authentic alcohols **7a** and **7b**, respectively. Alcohols **7a** and **7b** exhibited the opposite specific rotations but otherwise were spectroscopically and chromatographically identical. Finally, the alcohols **7a** and **7b** prepared from 16a and **16b**, respectively, were converted to the authentic acids **2a** and **2b**, respectively, as previously described. The spectroscopic data, specific rotations, and retention times by HPLC of **2a** and **2b** obtained by the resolution process (Scheme I) matched the authentic acids 2a and **2b** formed via the route shown in Scheme III.

The biological activities of the racemate **2a,b**, the "natural" isomer **2a**, and the "unnatural isomer" **2b** were tested orally in rats. The racemate **2a,b** was found to be cytoprotective (against ethanol-induced lesions, ED_{50} = 40 μg/kg), antiulcer (against aspirin-induced ulcers, ED_{50} = 35 μg/kg) and antisecretory (ED_{50} = 500 μg/kg). This racemate **2a,b** also did not lower blood pressure when given orally to anesthesized rats at 20 times the antisecretory ED_{50}. However, orally in rats, it was enteropooling (ED_{50} = 50 μg/kg) and diarrheogenic (ED_{50} < 150 μg/kg). When given subcutaneously, **2a,b** was not cytoprotective, enteropooling, nor antisecretory. Its two optical isomers, **2a** and **2b**, were also cytoprotective orally (ED_{50}'s = 65 and 15 μg/kg, respectively). Paradoxically, the isomer with an unnatural configuration, **2b**, was much more active than the isomer with a natural configuration, **2a** (antisecretory ED_{50}'s = 150 and 3000 μg/kg, respectively, for **2b** and **2a**). The unnatural isomer **2b** was also more enteropooling than the natural isomer **2a** when administered orally (ED_{50}'s = 50 and 2000 μg/kg, respectively). However, both were inactive at 5000 μg/kg when administered subcutaneously.

In conclusion, the synthesis of the racemic (**2a,b**) as well as the optically pure side chain deoxy analogue (**2a**) of a potent antiulcer agent 1 and its enantiomer (**2b**) has been achieved via the modification of the synthesis of 1 reported previously. The benzindene nucleus has been formed via a convergent cyclopentane annulation route, the key step either involving formation of **5** from enol lactone **4** or, via an improved process, from the keto ester **12a**. The synthesis of the optically pure isomers **2a** and **2b** has been achieved by resolving the intermediates **7a,b** via the preparative liquid chromatographic separation of their carbamates, **8a** and **8b**. The absolute configuration of each optically pure isomer has been established by comparing the physical and HPLC properties with the authentic samples, synthesized independently via deoxygenation from the side chain of the intermediates **16a** and **16b** with known configuration. It has also been found, for the first time, that the isomer with the "unnatural" configuration among the benzindene prostaglandin analogues has shown more potent biological activity than the isomer with the "natural" configuration.

Experimental Section[10]

1-Bromo-4-cyclohexylbutane (3b). To 8.1 mL (47 mmol) of 4-cyclohexyl-1-butanol (3a) was added dropwise 2.2 mL (23 mmol) of phosphorus tribromide. The mixture was stirred at 0 °C for 15 min, at room temperature for 2 h, and then at 100 °C for 1.5 h, cooled to 0 °C, quenched with 50 g of ice, diluted with 100 mL of brine, and extracted with ether. The organic layer was washed with brine, dried (Na_2SO_4), filtered, concentrated, and bulb-to-bulb distilled at 100 °C at 2 mmHg, to give 9.84 g (96%)

(9) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190. In this particular case, however, we found tetrahydrofuran to be a superior solvent to dimethylformamide for the selective silylation.

(10) All melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. The ^1H NMR spectra of chloroform-*d* solutions were obtained on a Varian EM-390 spectrometer operating at 90 MHz. Chemical shifts are reported in δ (parts per million) relative to internal tetramethylsilane. Combustion analyses, mass spectra (including high resolution), and infrared spectra (IR) were obtained by the Physical and Analytical Chemistry Unit of The Upjohn Company with IR spectra being obtained either on neat samples (oils) or on Nujol mulls (solids). GC/MS were obtained with a Hewlett-Packard 5992A GC/MS system. HPLC analyses were obtained with a Varian 5500 or 5560 HPLC chromatograph with appropriate columns and solvent systems. Optical rotations were measured by a Perkin-Elmer 241 polarimeter. Thin-layer chromatography (TLC) was conducted with silica gel GF plates (Analtech Uniplates). The TLC plates were visualized first by UV light (Mineralight UVS-11) and then sprayed with either 50% aqueous or methanolic sulfuric acid followed by heating. For the phosphonates, 0.5% zinc chloride/0.5% diphenylamine in acetone was used as the spraying agent. For flash chromatography and preparative liquid chromatography (LC), silica gel 60 (40–63 μm, E. Merck) was used. The liquid chromatography (LC) was performed either by various sizes of Michel-Miller columns (Ace Glass, Inc.) dry-packed with silica gel or by prepacked columns (E. Merck). The solvents were delivered by Milton-Roy pumps. For gravity column chromatography, silica gel 60 (63–200 μm, E. Merck) was used. The analyses of fractions were performed by TLC using an appropriate solvent or a mixture of solvents. All solvents were reagent grade or reagent grade distilled from glass (Burdick and Jackson). The dry solvents used in reactions, such as THF, DMF, and DMSO, were Burdick and Jackson brand high-purity solvents dried over 4-Å molecular sieves. All reactions were degassed and were conducted under an inert atmosphere.

IPR2020-00770
United Therapeutics EX2007
Page 3173 of 7335

of **3b** as a colorless liquid: ^{1}H NMR ($CDCl_3$, TMS) δ 3.43 (t, J = 7 Hz, 2 H), 2.3–0.6 (m, 17 H); IR (film) ν_{max} 732,648 cm^{-1}; high-resolution MS, m/z calcd for $C_{10}H_{19}{}^{79}Br$ (M^+) 218.0671, found 218.0664; R_f 0.54 (hexane).

Diethyl (4-Cyclohexylbutyl)phosphonate (3c). A solution of 6.7 mL (52 mmol) of diethyl phosphite in 400 mL of THF was cooled to −78 °C, and 36.4 mL (57 mmol) of n-butyllithium in hexane (1.57 M) was added dropwise. The resulting mixture was stirred at −78 °C for 30 min and at 0 °C for 30 min and then treated with 9.4 g (43 mmol) of 1-bromo-4-cyclohexylbutane (**3b**) in 50 mL of THF dropwise over 10 min. The resulting solution was stirred at room temperature for 1 h and at 60 °C for 4 h and then quenched with 500 mL of brine containing 40 mL of 1 N aqueous hydrochloric acid. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude product was flash chromatographed on 200 g of silica gel 60, eluting with 1 L of 50%, 1 L of 60%, and 2 L of 70% ethyl acetate in hexane to give 9.6 g (81%) of **3c** as a colorless oil: ^{1}H NMR ($CDCl_3$, TMS) δ 4.13 (2 overlapping q, J = 7 Hz, J_{P-H} = 7 Hz, 4 H), 1.9–0.5 (m, including t at 1.33, 25 H); IR (film) ν_{max} 1392, 1244, 1229, 1164, 1098, 1059, 1032 cm^{-1}; high-resolution MS, m/z calcd for $C_{14}H_{29}O_3P$ (M^+) 276.1854, found 276.1852; R_f 0.14 (50% ethyl acetate/hexane). Anal. Calcd for $C_{14}H_{29}O_3P$: C, 60.84; H, 10.58. Found: C, 61.01; H, 10.96.

Methyl 5-Methoxy-2-oxo-1,2,3,4-tetrahydro-3-naphthaleneacetate (12a). The keto acid 11[2] (33.1 mmol) dissolved in 27 mL of acetonitrile was treated with a solution of anhydrous hydrochloric acid in methanol, prepared by adding 3.7 mL of acetyl chloride to 23 mL of methanol at 0 °C.[11] The mixture was stirred at room temperature for 3 h and then treated with 5.7 mL of water. The resulting mixture was stirred at room temperature overnight, quenched with saturated aqueous sodium bicarbonate to pH 5, and concentrated in vacuo. The residue was extracted with ethyl acetate, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue (7.4 g) was purified by column chromatography on 200 g silica gel (63–200 μm), eluting with 15% ethyl acetate/hexane, and then recrystallized from *tert*-butyl methyl ether/hexane, to give in the first crop 4.93 g and in the second crop 0.5 g, with a total of 5.43 g (66%), of pure keto ester **12a** as a pale yellow solid: mp 71–72 °C; ^{1}H NMR ($CDCl_3$) δ 7.40–6.68 (m, 3 H), 3.84 (s, 3 H), 3.72 (s, 3 H), 3.72–2.32 (m, 7 H); IR (mull) 1731, 1709, 1588 cm^{-1}; high-resolution MS, m/z calcd for $C_{14}H_{16}O_4$ (M^+) 248.1049, found 248.1046, other ions at 217, 216, 188, 175, 174, 160, 146, 131, 115, 104, 91; R_f 0.35 (25% ethyl acetate/hexane). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.50; H, 6.60.

(3a*RS*)-1-(3-Cyclohexylpropyl)-3,3a,4,9-tetrahydro-5-methoxy-2*H*-benz[*f*]inden-2-one (5). Method A. A solution of 496.5 mg (2.0 mmol) of keto ester **12a**, 829.1 mg (3.0 mmol) of phosphonate **3c**, and 10 mL of THF at −78 °C was treated dropwise over 1–2 h with 6.0 mmol of lithium diisopropylamide in 6 mL of 2:1 hexane/THF. The resulting light pink solution was stirred at −78 °C for 3 h and then at room temperature overnight, treated with 0.21 mL (3.6 mmol) of glacial acetic acid, and then heated to reflux (bath temperature, 70 °C). TLC analysis showed R_f 0.71, 0.66, and 0.21 for **12a**, **5**, and **14**, respectively, in 50% ethyl acetate/hexane. The phosphonate **3c** stayed at the origin in the same solvent system. After 7 h the mixture was cooled to 0–5 °C and quenched with 10% aqueous sodium bisulfate to pH 7–8. The THF was removed in vacuo, and the residue was extracted with ethyl acetate. The organic extract was washed with water, brine, and saturated aqueous sodium bicarbonate, dried (Na_2SO_4), filtered, and concentrated to give the crude product as a yellow oil. This oil was purified by liquid chromatography (LC), eluting with 2.8 L of 10% ethyl acetate/hexane and 3 L of ethyl acetate, to give 504.5 mg (74.5%) of pure cyclopentenone **5** as a near colorless oil and 220 mg (26.5%) of the recovered phosphonate **3c** as a light brown oil.

Method B. A solution of 2.17 g (7.85 mmol) of phosphonate **3c** and 150 mL of THF at −78 °C was treated with 5 mL (8.0 mmol) of 1.6 M n-butyllithium, in hexane, stirred at −78 °C for 1 h, and then treated dropwise with a solution of 0.80 g (3.7 mmol) of enol lactone **4**[2] in 20 mL of THF. The resulting mixture was stirred for 1 h at −78 °C and 2 h while warming to 0 °C, then treated with 0.21 mL (3.6 mmol) of glacial acetic acid, stirred at 0 °C for 15 min and at 55–60 °C for 6 h, cooled to 0 °C, and quenched with 250 mL of brine containing 6 mL of 1 N aqueous hydrochloric acid. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine/saturated aqueous sodium bicarbonate (3:1) and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was flash chromatographed on 200 g of silica gel 60, eluting with 1 L 10%, 1 L 15%, 1 L 20%, 2 L 50%, and 2 L 75% ethyl acetate in hexane to give 0.855 g (68%) of pure **5** as a near colorless oil.

The physical properties of compound **5** were as follows: ^{1}H NMR ($CDCl_3$, TMS) δ 7.30–6.60 (m, 3 H), 3.87 (s, 3 H), 4.10–3.40 (m, 3 H), 3.10–0.60 (m, 21 H); IR (film) ν_{max} 1700, 1655, 1595 cm^{-1}; high-resolution MS, m/z calcd for $C_{23}H_{30}O_2$ (M^+) 338.2246, found 338.2252; R_f 0.50 and 0.66 (25% and 50% ethyl acetate/hexane, respectively). Anal. Calcd for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93. Found: C, 81.66; H, 9.42.

Diethyl [1-(3-Cyclohexylpropyl)-2-oxo-3-(2-oxo-5-methoxy-1,2,3,4-tetrahydro-3-naphthyl)propyl]phosphonate (14). The reaction was run in an identical manner as in the previous experiment (method A) for the preparation of cyclopentenone **5**. However, the reaction was interrupted by quenching with 10% aqueous sodium bisulfate (to pH 7) after the reaction mixture was stirred overnight at room temperature rather than treating with acetic acid and heating. The reaction mixture was then extracted with ethyl acetate, and the organic extract was washed with saturated sodium bicarbonate and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give a brown oil. The oil was purified by LC on 200 g silica gel 60, eluting with 50% ethyl acetate/hexane to give 740.2 mg (75%) of **14** as a near colorless oil: ^{1}H NMR ($CDCl_3$, TMS) δ 7.34–6.65 (m, 3 H), 4.16 (quintet, J = 7 Hz, 4 H), 3.80 (s, 3 H), 3.78–0.78 (m, 25 H), 1.40 (t, J = 7 Hz, 6 H); IR (film) ν_{max} 1713, 1589, 1265, 1250 cm^{-1}; high-resolution MS, m/z calcd for $C_{27}H_{41}O_6P$ (M^+) 492.2641, found 492.2639; R_f 0.44 in 66% ethyl acetate/hexane. This material appeared to be unstable. The color of this oil turned to deep brown even though it was stored in the refrigerator at 0–5 °C.

1(*R*)-(3-Cyclohexylpropyl)-1,3,3a,4,9,9a-hexahydro-5-methoxy-(3a*S*,9a*S*)-2*H*-benz[*f*]inden-2-one and Its 1,3a,9a-Triepi Isomer (6a) and 1(*S*)-(3-Cyclohexylpropyl)-1,3,3a,4,9,9a-hexahydro-5-methoxy-(3a*S*,9a*S*)-2*H*-benz[*f*]inden-2-one and Its 1,3a,9a-Triepi Isomer (6b). A mixture of 1.37 g (4.05 mmol) of enone **5**, 490 mg of 10% palladium on carbon, and 50 mg (0.36 mmol) of anhydrous potassium carbonate in 75 mL of absolute ethanol was hydrogenated at 50 psi. After 46 h at room temperature, the mixture was filtered through a Celite pad, the pad being washed with ethyl acetate. The filtrate was concentrated in vacuo and then chromatographed on 100 g of silica gel 60, eluting with 10% ethyl acetate in hexane to give 1.10 g (80%) of 3:1 mixture of **6a** and **6b** as a colorless oil: ^{1}H NMR ($CDCl_3$, TMS) δ 7.30–6.60 (m, 3 H), 3.83 (s, 3 H), 3.30–0.60 (m, 26 H); IR (film) 1740, 1595 cm^{-1}; high-resolution MS, m/z calcd for $C_{23}H_{32}O_2$ (M^+) 340.2402, found 340.2427; R_f 0.55 (20% ethyl acetate/hexane). HPLC analyses were carried out by using a Varian 5560 with HP 3390A integrator, with Waters Resolve 3.9 × 150 mm column (5-μm SiO_2), eluting with 1% THF/hexane with 2 mL/min flow rate and detecting at 278 nm (0.05 AU/mV). Two peaks with retention times 5.80 and 6.60 min in a 3:1 ratio were assigned as **6a** and **6b**, respectively. Anal. Calcd for $C_{23}H_{34}O_2$: C, 81.15; H, 9.47; Found: C, 80.76; H, 9.55. When the hydrogenation was carried out by using a different lot of palladium on carbon, presumably more active, the reaction was completed in 7 h. The ratio was reversed to 1:3 for **6a** to **6b**, indicating the shorter reaction time gave nonequilibrated mixture in favor of the unnatural isomer **6b**.

1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-5-methoxy-(3a*S*,9a*S*)-1*H*-benz[*f*]inden-2(*R*)-ol and Its 1,2,3a,9a-Tetraepi Isomer (7a,b). A solution of 400 mg (1.17 mmol) of the mixture of **6a** and **6b**, 40 mL of absolute ethanol, and 4 mL of methylene chloride was cooled to −10 °C, treated with 8 mL of 10% aqueous sodium hydroxide, and stirred for 15 min, and 60 mg (1.59 mmol) of sodium borohydride was added.

(11) Fieser, L. F.; Fieser, M. In *Reagents for Organic Synthesis*; Vol. 1, p 11.

IPR2020-00770
United Therapeutics EX2007
Page 3174 of 7335

At 1, 3, and 6 h, an additional 60 mg (1.59 mmol) of sodium borohydride was added to the reaction mixture at −10 °C. After being stirred for an additional 2 h at −10 °C, the mixture was quenched with 2.9 mL of glacial acetic acid, diluted with 250 mL of brine, and extracted with ethyl acetate. The organic layers were combined, washed with saturated sodium bicarbonate and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using 250 g of silica gel 60, eluting with 10% ethyl acetate/hexane, to give 373 mg (93%) of **7a,b** as a white oily solid: ^1H NMR ($CDCl_3$, TMS) δ 7.30–6.60 (m, 3 H), 3.83 (s, 3 H), 3.96–3.34 (m, 1 H), 2.90–0.60 (m, 27 H); IR (film) 3350, 1595 cm^{-1}; high-resolution MS, m/z calcd for $C_{23}H_{34}O_2$ (M^+) 342.2599, found 342.2547; R_f (20% ethyl acetate/hexane). Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01; Found: C, 80.70; H, 10.23.

1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-(3a*S*,9a*S*)-1*H*-benz[*f*]indene-2(*R*),5-diol and Its 1,2,3a,9a-Tetraepi Isomer (9ab). A solution of 0.9 mL of diphenylphosphine and 30 mL of THF at 0 °C was treated with 3.2 mL (5.1 mmol) of *n*-butyllithium (1.6 M in hexane). After the mixture was stirred for 30 min, 557 mg (1.6 mmol) of **7a,b** in 10 mL of THF was added, and the resulting mixture was heated at 70 °C for 7 h, then cooled to 0 °C, treated with an additional 0.9 mL (5 mmol) of diphenylphosphine and 3.2 mL (5.2 mmol) of *n*-butyllithium in hexane, and stirred at room temperature for 30 min and then at 70 °C for 18 h. The mixture was then cooled to 0 °C, diluted with 100 mL of brine containing 10 mL of 1 N aqueous hydrochloric acid, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on 200 g of silica gel 60, eluting with 5% acetone/methylene chloride to give 509 mg (95%) of **9a,b** as a white foam: ^1H NMR ($CDCl_3$, TMS) δ 7.20–6.50 (m, 3 H), 3.90–3.40 (m, 1 H), 2.90–0.50 (m, 28 H); IR (mull) 3430, 3160, 1600 cm^{-1}; high-resolution MS, m/z calcd for $C_{22}H_{32}O_2$ (M^+) 328.2402, found 328.2409; R_f 0.24 (5% acetone/methylene chloride). Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82; Found: C, 80.09; H, 10.14.

[[1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2-(*R*)-hydroxy-(3a*S*,9a*S*)-1*H*-benz[*f*]inden-5-yl]oxy]acetonitrile and Its 1,2,3a,9a-Tetraepi Isomer (10a,b). A mixture of 450 mg (1.37 mmol) of **9a,b**, 1.8 mL (28 mmol) of chloroacetonitrile, 2.2 g (16 mmol) of anhydrous potassium carbonate, and 20 mL of acetone was heated at 65 °C for 24 h, then cooled, diluted with brine, and extracted with ethyl acetate. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on 200 g of silica gel 60, eluting with 25% ethyl acetate/hexane, to give 498 mg (99%) of **10a,b** as a colorless oil, which solidified in the refrigerator: ^1H NMR ($CDCl_3$, TMS) δ 7.30–6.70 (m, 3 H), 4.74 (s, 2 H), 3.90–3.50 (m, 1 H), 3.0–0.6 (m, 27 H); IR (film) 3400, 1595 cm^{-1}; high-resolution MS, m/z calcd for $C_{24}H_{33}NO_2$ 367.2511, found 367.2500; R_f 0.33 (30% ethyl acetate/hexane). Anal. Calcd for $C_{24}H_{33}O_2N$: C, 78.43; H, 9.06; N, 3.81. Found: C, 78.18; H, 9.08; N, 3.97.

[[1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2-(*R*)-hydroxy-(3a*S*,9a*S*)-1*H*-benz[*f*]inden-5-yl]oxy]acetic Acid and Its 1,2,3a,9a-Tetraepi Isomer (2a,b). A solution of 450 mg (1.22 mmol) of **10a,b**, 30 mL of methanol, and 10 mL of 25% aqueous potassium hydroxide was heated at 90 °C for 5 h, then cooled to 0 °C, acidified to pH 5–6 with 1 N aqueous hydrochloric acid, diluted with brine, and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was chromatographed on 90 g of CC-4 acid-washed silica gel, eluting with 250 mL of 20%, 30%, 40%, and 50% ethyl acetate/hexane, to give 461 mg (97%) of **2a,b**, which was crystallized from hot THF/hexane (1:2, 3 mL/100 mg) to give 305 mg of **2a,b** as a white solid (mp 158–160 °C), and 156 mg of a white solid (mp 150–155 °C) from the mother liquor: ^1H NMR ($CDCl_3$, TMS) δ 7.30–6.70 (m, 3 H), 4.73 (s, 2 H), 4.60–3.40 (m, 3 H), 3.0–0.6 (m, 26 H); IR (film) 3420, 1735, 1590 cm^{-1}; high-resolution MS, m/z calcd for $C_{30}H_{50}O_4Si_2$ (as $(TMS)_2$ derivative) 530.3247, found 530.3227; R_f 0.57 (ethyl acetate/acetic acid/cyclohexane/water (9:2:5:10)). HPLC analyses were carried out by using a Varian 5560 with an HP 3390A integrator equipped with an Altex Ultrasphere ODS C18 10 × 250 mm column, eluting with water/acetonitrile/methanol/85% phosphoric acid (500:350:150:1) with a 3-mL/min flow rate and detection at 217 nm (0.02 AU/mV). A single peak at retention time of 48.89 min was observed. Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.57; H, 9.12.

[[1(*R*)-(Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-5-methoxy-1*H*-(3a*S*,9a*S*)-benz[*f*]inden-2(*R*)-yl]oxy]-(*S*)-α-methylbenzyl Carbamate (8a) and Its 1,2,3a,9a-Tetraepi Isomer (8b). A solution of 572.4 mg (1.67 mmol) of **7a,b** and 75 mL of toluene was treated with 1.66 mL of 12.5% solution of phosgene in toluene and 0.59 mL of triethylamine. After 1.25 h, the resulting mixture was treated with 1.3 mL of 98% (*S*)-(−)-α-methylbenzylamine. The reaction was exothermic and the mixture became gelatinous within 1 min after the addition. After 25 min the mixture was diluted with 100 mL of Skellysolve B and filtered through a medium frittered disk Buchner funnel, washing with Skellysolve B. The filtrate was concentrated in vacuo at 35 °C to give 1.11 g of a yellow oil. This oil was chromatographed on 100 g of silica gel 60, which was slurry packed, and eluted with 5% acetone/Skellysolve B to give 785.1 mg of the mixture of **8a** and **8b**. This mixture was chromatographed on two Merck columns (size B) connected in series, conditioned, and eluted with 15% *tert*-butyl methyl ether/hexane. The mixture was applied to the column in toluene, eluting at 7 mL/min to give 328 mg (40%) of compound **8a** as a white solid (mp 108 °C, R_f 0.31 (15% *tert*-butyl methyl ether/Skellysolve B)), 117.3 mg of the mixture of **8a** and **8b**, and 273.8 mg (33.5%) of compound **8b** as a white solid (mp 115 °C, R_f 0.28 (the same solvent system as **8a**)). HPLC analyses were carried out by using a Varian 5560 with a Varian 4270 integrator equipped with an Altex Ultrasphere ODS C18, 10 × 250 mm column, eluting with acetonitrile/methanol/water (45:40:15), with a 3 mL/min flow rate and detection at 217 nm (0.05 AU/mV). The compound **8a** showed a single peak at 34.12 min whereas the compound **8b** showed a peak at 35.36 min with a minor contaminant at 34.08. The assignment of carbamates **8a** and **8b** was based on the comparison of the HPLC peaks with authentic carbamates **8a** and **8b**, prepared independently from authentic alcohols **7a** and **7b**, respectively. The carbamates were prepared in analytical scale by dissolving ca. 1 mg of these alcohols in 0.5 mL of toluene and adding 1 μL of dibutyltin diacetate and 5 μL of (*S*)-(−)-α-methylbenzyl isocyanate. After the mixture was stirred at room temperature for 4 h, the reaction was quenched with brine and extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered, and concentrated in vacuo.

1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-5-methoxy-(3a*S*,9a*S*)-1*H*-benz[*f*]inden-2(*R*)-ol (7a). A solution of 328 mg (0.67 mmol) of **8a** and 25 mL of THF was treated with lithium aluminum hydride (102.6 mg, 2.7 mmol), and the resulting mixture was heated at 60–65 °C for 4 h. The mixture was then cooled to room temperature and carefully quenched with 1 mL of water. Addition of brine was followed by aqueous sodium bisulfate until pH was 4. The mixture was then extracted three times with ethyl acetate, and the combined organic extracts were filtered through anhydrous sodium sulfate powder. The filtrate was concentrated in vacuo to give 285.9 mg of a yellow oil, which was chromatographed on 64 g of silica gel 60, eluting with 12% ethyl acetate/hexane to give 229.5 mg (100%) of pure **7a** as a colorless glass: ^1H NMR and IR spectra were identical with those of **7a,b**; $[\alpha]_D$ 30.6° (c 1.215, 95% ethanol); R_f 0.36 (15% ethyl acetate/Skellysolve B) and 0.20 (15% *tert*-butyl methyl ether/Skellysolve B); HPLC analysis (same condition as in the analyses of **8a** and **8b**) as in previous experiment, but eluting with acetonitrile/water/methanol (60:20:20), gave a single peak at 41.06 min.

1(*S*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-5-methoxy-(3a*R*,9a*R*)-1*H*-benz[*f*]inden-2(*S*)-ol (7b). A 273.8 mg (0.56 mmol) sample of **8b** was reacted and worked up in an identical manner as the reaction of **8a** to **7a** to obtain 267.2 mg of crude product as a yellow glass. This material was chromatographed on 65 g of silica gel 60, which was eluted with 10% ethyl acetate/hexane to give 191.8 mg (100%) of pure **7b** as a colorless glass: $[\alpha]_D$ −27.7° (c 1.139, 95% ethanol); HPLC analysis gave a single peak at 41.38 min.

1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-(3a*S*,9a*S*)-1*H*-benz[*f*]indene-2(*R*),5-diol (9a). A 233.9 mg (0.68 mmol) sample of **7a** was converted to **9a** in an identical manner as in the preparation of **9a,b** from **7a,b** to give 212.0 mg

IPR2020-00770
United Therapeutics EX2007
Page 3175 of 7335

(94.5%) of **9a** as a white foam: ^{1}H NMR and IR spectra were identical with those of **9a,b**; $[\alpha]_D$ 30.6° (*c* 1.09, 95% ethanol); R_f 0.25 (25% ethyl acetate/hexane).

1(*S*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-(3a*R*,9a*R*)-1*H*-benz[*f*]indene-2(*S*),5-diol (9b). A 194.6 mg (0.57 mmol) sample of **7b** was converted to **9b** in an identical manner as in the preparation of **9a,b** from **7a,b** to give 167.6 mg (90%) of **9b** as a white foam: ^{1}H NMR and IR spectra were identical with those of **9a,b**; $[\alpha]_D$ −29.2° (*c* 1.17, 95% ethanol); R_f 0.25 (25% ethyl acetate/hexane).

[[1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2-(*R*)-hydroxy-(3a*S*,9a*S*)-1*H*-benz[*f*]inden-5-yl]oxy]acetonitrile (10a). A 212.0 mg (0.65 mmol) sample of **9a** was converted to **10a** in a similar manner as in the alkylation of **9a,b** to **10a,b** to give 211.6 mg (89%) of **10a**: mp 99–99.5 °C; ^{1}H NMR spectrum was identical with that of **10a,b**; $[\alpha]_D$ 30.5° (*c* 1.032, 95% ethanol); R_f 0.34 (25% ethyl acetate/Skellysolve B).

[[1(*S*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2-(*S*)-hydroxy-(3a*R*,9a*R*)-1*H*-benz[*f*]inden-5-yl]oxy]acetonitrile (10b). A 167.6 mg (0.51 mmol) sample of **9b** was converted to **10b** in a similar manner as to conversion of **9a,b** to **10a,b** to give 164.9 mg (88%) of **10b**: mp 99.5–100 °C; ^{1}H NMR spectrum was identical with that of **10a,b**; $[\alpha]_D$ −28.4° (*c* 1.017, 95% ethanol); R_f 0.34 (25% ethyl acetate/Skellysolve B).

[[1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2-(*R*)-hydroxy-(3a*S*,9a*S*)-1*H*-benz[*f*]inden-5-yl]oxy]acetic Acid (2a). A 211.6 mg (0.58 mmol) sample of **10a** was converted to **2a** in an identical manner as the conversion of **10a,b** to **2a,b** to give 203.3 mg of a pale yellow solid, which was recrystallized from ethyl acetate/hexane to give 156.1 mg (70%) of pure **2a** as a white solid: mp 133.5–135.5 °C, mixed mp with **2a** obtained from **16a** (Scheme III) was unchanged; ^{1}H NMR spectrum was identical with that of **2a,b**; MS, *m/z* calcd for $C_{24}H_{34}O_4$ (M^+) 386; other ions 368, 309, 243, 203, 157; $[\alpha]_D$ 30.69° (*c* 1.167, 95% ethanol), R_f 0.19 (acetone/methylene chloride/acetic acid (4:95:1)), 0.27 (the organic phase of ethyl acetate/acetic acid/2,2,4-trimethylpentane/water (9:2:5:10)), and 0.35 (ethyl acetate/Skellysolve B/acetic acid (35:64:1)).

[[1(*S*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2-(*S*)-hydroxy-(3a*R*,9a*R*)-1*H*-benz[*f*]inden-5-yl]oxy]acetic Acid (2b). A 164.9 mg (0.45 mmol) sample of **10b** was converted to **2b** in an identical manner as the synthesis of **2a** from **10a** to give 139.7 mg (80%) of pure **2b** as a white solid: mp 133.5–135.5 °C, mixed mp with **2b** obtained from **16b** (Scheme III) was unchanged; ^{1}H NMR and MS spectra and R_f's in three-solvent system as described in the previous experiment were identical with those of **2a**; $[\alpha]_D$ −28.16 (*c* 1.079, 95% ethanol).

1(*R*)-(3-Cyclohexyl-3(*R*)-hydroxypropyl)-2,3,3a,4,9,9a-hexahydro-2(*R*)-[(*tert*-butyldimethylsilyl)oxy]-5-methoxy-(3a*S*,9a*S*)-1*H*-benz[*f*]indene (17a). A solution of 229.5 mg (0.64 mmol) of **16a** (98.5% pure, contaminated with 1.5% **16b**),[2] 87.1 mg (1.28 mmol) of imidazole, and 6.4 mL of THF at 0–5 °C was treated with 192.9 mg (1.28 mmol) of *tert*-butyldimethylsilyl chloride dissolved in 3.2 mL of THF. After the mixture was stirred 30 h at room temperature another portion of imidazole (17.4 mg, 0.256 mmol) and *tert*-butyldimethylsilyl chloride (38.6 mg, 0.256 mmol) was added, and the mixture was stirred for an additional 18 h, quenched at 0–5 °C with 5 mL of water, stirred for 30 min, and extracted with ethyl acetate. The organic extract was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give a near colorless oil. The oil was purified by LC on 215 g of silica gel 60, eluting with 2.4 L of 9% ethyl acetate/hexane and 600 mL ethyl acetate to give 21.2 mg (6.4%) of bis-silylated product, 197.9 mg (65.4%) of **17a**, and 46.2 mg (20%) of the recovered starting material **16a**. This material was resilylated by reacting with 122.5 mg (1.8 mmol) of imidazole and 271.3 mg (1.8 mmol) of *tert*-butyldimethylsilyl chloride in 5 mL of THF at room temperature for 48 h. Workup and LC purification using 52.5 g silica gel 60, as described above, gave an additional 56.5 mg of **17a**. The combined products yielded 254.2 mg (84%) of the desired monosilylated product **17a** as a colorless oil: ^{1}H NMR ($CDCl_3$, TMS) δ 7.30–6.68 (m, 3 H), 3.80 (s, 3 H), 3.86–3.12 (m, 2 H), 3.08–0.95 (m, 24 H), 0.88 (s, 9 H), 0.04 (s, 6 H); IR (film) 3430, 1580, 870, 840, 775, 730 cm^{-1}; R_f 0.48 (17% ethyl acetate/hexane).

1(*S*)-(3-Cyclohexyl-3(*R*)-hydroxypropyl)-2,3,3a,4,9,9a-hexahydro-2(*S*)-[(*tert*-butyldimethylsilyl)oxy]-5-methoxy-(3a*R*,9a*R*)-1*H*-benz[*f*]indene (17b). A 358.5 mg (1.0 mmol) sample of **16b** (>99% pure)[2] was converted to **17b** in an identical manner as the silylation of **16a** to **17a** to give 29.7 mg (5.1%) of bis-silylated product, 385.8 mg (81.6%) of **17b** as a colorless oil, and 40.7 mg (11.4%) of the recovered starting material **16b**. Spectral properties of **17b** were identical with those of **17a**.

1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2-(*R*)-[(*tert*-butyldimethylsilyl)oxy]-5-methoxy-(3a*S*,9a*S*)-1*H*-benz[*f*]indene (19a). A solution of 245.9 mg (0.52 mmol) of **17a** and 5.2 mL of pyridine at 0–5 °C was treated with 594.8 mg (3.12 mmol) of *p*-toluenesulfonyl chloride. The resulting pink-colored solution was stirred at room temperature for 24 h, cooled to 0–5 °C again, treated with 0.52 mL of water, stirred for 30 min at room temperature, and extracted with ethyl acetate. The combined organic extracts were washed with water, 10% aqueous sodium bisulfate, saturated aqueous sodium bicarbonate, and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give 0.33 g of tosylate **18a** as a light brown oil: ^{1}H NMR ($CDCl_3$, TMS) δ 7.94–6.68 (m, 7 H), 4.62–4.32 (m, 1 H), 3.80 (s, 3 H), 3.90–3.40 (m, 1 H), 3.04–0.95 (m, 24 H), 2.38 (s, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H); R_f 0.56 (17% ethyl acetate/hexane). Without further purification of the tosylate **18a**, this material was dissolved in 26.0 mL of anhydrous ether, cooled to 0–5 °C with an ice–water bath, and treated over 5 min with 197.3 mg (5.2 mmol) of lithium aluminum hydride. The cooling bath was then removed, and the gray suspension was stirred at room temperature for 24 h, cooled again to 0–5 °C, and treated carefully with 1 N hydrochloric acid until the pH of the mixture was about 7. The resulting mixture was extracted with ethyl acetate and the combined organic extracts were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give an oil. This oil was purified on 215 g of LC grade silica gel 60, eluting with 1.5 L of 5% and 1 L of 33% ethyl acetate/hexane to give 187.4 mg (78.9%) of pure **19a** as a colorless oil: ^{1}H NMR ($CDCl_3$, TMS) δ 7.24–6.66 (m, 3 H), 3.82 (s, 3 H), 3.92–3.50 (m, 1 H), 3.10–0.95 (m, 26 H), 0.88 (s, 9 H), 0.02 (s, 6 H); IR (film) 1600, 1580, 870, 835, 770 cm^{-1}; R_f 0.89 (17% ethyl acetate/hexane).

1(*S*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2-(*S*)-[(*tert*-butyldimethylsilyl)oxy]-5-methoxy-(3a*R*,9a*R*)-1*H*-benz[*f*]indene (19b). A 378.2 mg (0.8 mmol) sample of **17b** was converted to **19b** in an identical manner as the conversion of **17a** to **19a**. However, the lithium aluminum hydride reduction was run in tetrahydrofuran instead of diethyl ether. This change of solvent resulted in isolation of 214.0 mg (58.6%) of the desired **19b** as a colorless oil: ^{1}H NMR and IR spectra and R_f were identical with those of **19a**.

1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-5-methoxy-(3a*S*,9a*S*)-1*H*-benz[*f*]inden-2(*R*)-ol (7a). A solution of 182.7 mg (0.40 mmol) of **19a**, 3.0 mL of 2-propanol, 2 mL of THF, and 1 mL of 3 N hydrochloric acid was stirred at room temperature for 24 h, treated with saturated aqueous sodium bicarbonate to pH 7–8, and extracted with ethyl acetate. The organic extract was washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to give a colorless oil. This oil was chromatographed on 215 g of LC grade silica gel 60, eluting with 20% ethyl acetate/hexane to give 123.8 mg (90.4%) of **7a** as a colorless oil: ^{1}H NMR and IR spectra and R_f were identical with those of **7a,b**; $[\alpha]_D$ 31.8° (*c* 1.22, 95% ethanol). The carbamate **8a** of compound **7a** had an identical HPLC retention time as the carbamate **8a** resolved by liquid chromatography from the mixture **8a,b**.

1(*S*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-5-methoxy-(3a*R*,9a*R*)-1*H*-benz[*f*]inden-2(*S*)-ol (7b). A 205.6 mg (0.45 mmol) sample of **19b** was converted to **7b** in an identical manner as in the conversion of **19a** to **7a** to give 125.6 mg (81.5%) of **7b** as a colorless oil: ^{1}H NMR and IR spectra and R_f were identical with those of **7a,b**; $[\alpha]_D$ −31.5° (*c* 1.24, 95% ethanol). The carbamate **8b** of compound **7b** had an identical HPLC retention time as the carbamate **8b**, resolved by liquid chromatography from the mixture **8a,b**.

[[1(*R*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2-(*R*)-hydroxy-(3a*S*,9a*S*)-1*H*-benz[*f*]inden-5-yl]oxy]acetic Acid (2a). Compound **7a** (obtained from **16a**) was converted to **2a** in an identical manner as previously described for the conversion of **7a** (obtained via resolution of **7a,b**) to **2a**. The specific

IPR2020-00770
United Therapeutics EX2007
Page 3176 of 7335

rotations of each intermediate were recorded: **9a**, $[\alpha]_D$ 31.4° (c 0.873, 95% ethanol); **10a**, $[\alpha]_D$ 29.5° (c 0.818, 95% ethanol). The HPLC analysis of the final product **2a** showed an identical retention time as that of **2a** obtained from the resolution of intermediate **7a,b** as shown on Scheme I. The spectral properties were also identical: $[\alpha]_D$ 31.3° (c 0.713, 95% ethanol); high-resolution MS (as TMS derivative), m/z calcd for $C_{36}H_{50}O_4Si_2$ 530.3247, found 530.3248.

[[1(*S*)-(3-Cyclohexylpropyl)-2,3,3a,4,9,9a-hexahydro-2-(*S*)-hydroxy-(3a*R*,9a*R*)-1*H*-benz[*f*]inden-5-yl]oxy]acetic Acid (2b). Compound **7b** (obtained from **16b**) was converted to **2b** in an identical manner as previously described for the conversion of **7b** (obtained via resolution of **7a,b**) to **2b**. The specific rotations of each intermediate were recorded: **9b**, $[\alpha]_D$ −31.8° (c 0.916, 95% ethanol); **10b**, $[\alpha]_D$ −30.0° (c 0.83, 95% ethanol). The HPLC analysis of the final product **2b** showed an identical retention time as that of **2b** obtained from the resolution of intermediate **7a,b** as shown in Scheme I. The spectral properties were also identical: $[\alpha]_D$ −31.4° (c 0.72, 95% ethanol); high-resolution MS (as TMS derivative), m/z calcd for $C_{30}H_{50}O_4Si_2$ 530.3247, found 530.3237.

Acknowledgment. Helpful discussions with Dr. D. R. Morton are acknowledged. The supply of the intermediates as well as the technical assistance of D. L. Alexander, A. W. Harrison, P. G. Brewer, and D. P. Carvell are gratefully acknowledged. We also thank C. Lancaster, A. S. Olafsson, and K. P. Kolbasa for their assistance in providing the biological data.

Novel Mitomycin C Amidines:[1] Synthesis and Their Reactions with Amines

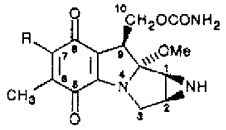
D. M. Vyas,* Y. Chiang,[2] D. Benigni, and T. W. Doyle

Bristol-Myers Company, Pharmaceutical Research and Development Division, Wallingford, Connecticut 06492

Received April 10, 1987

Reactions of formamide acetals (e.g., DMFDMA, **10**, **12**) with mitomycin C (**1**) has afforded novel amidine derivatives (e.g., 7–9, 11, 13). Investigation of reactions of amines with bisamidine **8** in both polar and nonpolar solvents (e.g., MeOH vs $CHCl_3$) has led to the discovery that **8**, in its reactions with primary amines in methanol, behaves as a mitomycin A (**2**) equivalent to afford 7-*N*-substituted mitosanes (e.g., **16**–**19**). In contrast, bisamidine **8** undergoes a selective deamidination reaction with primary amines in chloroform to afford monoamidine **14**.

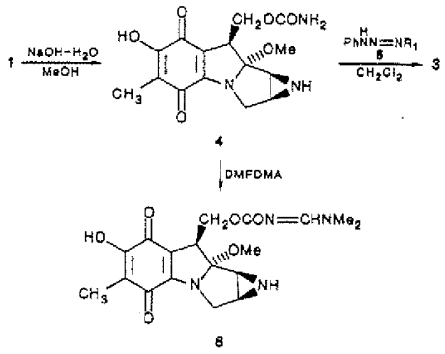
Fermentation-derived[3] antineoplastic antibiotics, mitomycin C (**1**) and mitomycin A (**2**),[4] are of great significance in cancer chemotherapy. While **1** is currently[5] in clinical use for the management of a variety of neoplasms, mitomycin A (**2**) is continuing to play a pivotal role in analogue research[6] which is directed toward discovery of new clinical agents endowed with less myelosuppressive properties and a broader spectrum of antitumor activity.



1: R = NH_2
2: R = OCH_3
3: R = OR_1

Recently,[7] we reported a practical approach to the synthesis of **2** and its analogues, namely 7-alkoxymitosanes **3**[8] from mitomycin C. The key reaction of this process

Scheme I



(Scheme I) involves O-alkylation of 7-hydroxymitosane (**4**) with an appropriate triazene (**5**) in a nonpolar solvent. During a similar attempt to methylate **4** with another well-established methylating agent, namely *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA),[9] an amidine derivative, **6**, was obtained as the sole product in place of the desired product **2**. This finding was not surprising in light of the fact that DMFDMA is known to react with amines, amides, and urethanes to yield corresponding amidines. However, the observed functionalization[10] of the carbamoyl moiety of **4** is unprecedented. This encouraged us to investigate the reactions of formamide acetals with mitomycin C, which bears potentially three reactive amino

(1) Presented in part at the 187th National Meeting of the American Chemical Society, St. Louis, MO, April 8–13, 1984; Abstracts, MEDI 30.
(2) Present address: Hoechst-Roussel Pharmaceuticals, Inc. Somerville, NJ 08876.
(3) Remers, W. A. In *Chemistry of Antitumor Antibiotics*; Wiley: New York, 1979; Vol 1, pp 221–276 and references therein.
(4) According to the trivial system of nomenclature, which has found wide use in mitomycin literature, mitomycin C (**1**) is named as 7-amino-9a-methoxymitosane and mitomycin A (**2**) as 7,9a-dimethoxymitosane.
(5) Carter, S. K.; Crooke, S. T. *Mitomycin C, Current Status and New Developments*; Academic: New York, 1979; Chapter 15.
(6) Sami, S. M.; Iyengar, S. E.; Tarnow, S. E.; Remers, W. A.; Bradner, W. T.; Schurig, J. E. *J. Med. Chem.* **1984**, *27*, 701 and references cited therein.
(7) Vyas, D. M.; Benigni, D.; Partyka, R. A.; Doyle, T. W. *J. Org. Chem.* **1986**, *51*, 4307.
(8) Sami, S. M.; Iyengar, B. S.; Remers, W. A.; Bradner, W. T. *J. Med. Chem.* **1987**, *30*, 168.
(9) For a review on the chemistry of formamide acetals, see: Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675.
(10) Under reductive conditions, thionucleophiles are known to displace the carbamoyl moiety. See: Bean, M.; Kohn, H. *J. Org. Chem.* **1985**, *50*, 293.

0022-3263/87/1952-5601$01.50/0 © 1987 American Chemical Society

IPR2020-00770
United Therapeutics EX2007
Page 3177 of 7335

was obtained as a colorless, crystalline solid from water, yield 33.4 g. (91%), m.p. 211–211.5° with decomposition.[15]

Anal. Calcd. for $C_6H_6N_6$: C, 49.0; H, 3.4; N, 47.6. Found: C, 49.2; H, 3.7; N, 47.8.

5-(3'-Pyridyl)tetrazole was prepared from 3-cyanopyridine. Using the same quantities of reagents as in the foregoing example, the product was obtained as a colorless, crystalline solid from water, yield 33.3 g. (91%), m.p. 234–235° with decomposition.[15]

Anal. Calcd. for $C_6H_6N_6$: C, 49.0; H, 3.4; N, 47.6. Found: C, 49.2; H, 3.4; N, 47.7.

5-(4'-Pyridyl)tetrazole was prepared from 4-cyanopyridine in the same way with the same quantities of reagents. It crystallized from water as a colorless solid, yield 34.3 g. (93%), m.p. 253–254° with decomposition.[15]

Anal. Calcd. for $C_6H_6N_6$: C, 49.0; H, 3.4; N, 47.6. Found: C, 49.2; H, 3.6; N, 47.3.

2,6-Di(5'-tetrazolyl)pyridine. A solution of 27.5 g. (0.21 mole) of 2,6-dicyanopyridine in 100 ml. of *n*-butyl alcohol was refluxed for 2 days with 38.2 g. (0.59 mole) of sodium azide and 38 ml. of glacial acetic acid.[14] At this point another 10 g. of sodium azide and 20 ml. of glacial acetic acid were added. Refluxing continued for 2 days. The crude product, 45.6 g. (99%), was obtained by diluting the reaction mixture with water, distilling and acidifying as in the foregoing examples. The product was purified by dissolving it in aqueous sodium hydroxide and reprecipitating from the hot, colorless solution with acid. The analytical sample was recrystallized from hot water in which the product was only sparingly soluble, m.p. 290° with decomposition.

Anal. Calcd. for $C_7H_5N_9$: C, 39.1; H, 2.3; N, 58.6. Found: C, 39.2; H, 2.6; N, 58.6.

5-(2'-Piperidyl)tetrazole. A suspension of 11 g. of 5-(2'-pyridyl)tetrazole in 150 ml. of glacial acetic acid was shaken with 250 mg. of platinum oxide and hydrogen at an initial pressure of 50 p.s.i. Hydrogenation was complete in 24 hr. After removal of the catalyst by filtration the solution was evaporated to a small volume and diluted with ether to precipitate the product. Purification was effected by dissolving the colorless solid in the minimum amount of warm water, treating with Norit and reprecipitating with acetone, yield 10.5 g. (92%), m.p. 287° with decomposition.

Anal. Calcd. for $C_6H_{11}N_5$: C, 47.1; H, 7.2; N, 45.7. Found: C, 47.0; H, 7.1; N, 46.0.

The *acetyl* derivative was prepared by refluxing for 2 hrs. in glacial acetic acid with an equimolar amount of acetic anhydride. After removal of the solvent under reduced pressure, the residue of acetyl derivative was obtained as a colorless, crystalline solid from water, m.p. 135.5–136.5°.

Anal. Calcd. for $C_8H_{13}N_5O$: C, 49.2; H, 6.7; N, 35.9. Found: C, 49.1; H, 6.6; N, 35.6.

For preparative purposes it was advantageous to form the acetyl derivative directly by hydrogenation of the pyridyltetrazole as just described; after removal of the catalyst, acetic anhydride was added to the glacial acetic acid solution and acetylation was completed as just described. The over-all yield from the pyridyltetrazole was 84%.

5-(3'-Piperidyl)tetrazole was obtained in almost quantitative yield as a colorless, crystalline solid by hydrogenation of the pyridyltetrazole in a completely analogous manner, m.p. 296–297° with decomposition. The analytical sample was recrystallized from the minimum amount of water; the remainder of the product was precipitated from water with acetone.

Anal. Calcd. for $C_6H_{11}N_5$: C, 47.1; H, 7.2; N, 45.7. Found: C, 47.1; H, 7.3; N, 45.7.

The *acetyl* derivative, prepared as described for the isomer, separated from isopropyl alcohol as a colorless, crystalline solid, m.p. 170–171°.

Anal. Calcd. for $C_8H_{13}N_5O$: C, 49.2; H, 6.7; N, 35.9. Found: C, 49.5; H, 6.7; N, 36.1.

5-(4'-Piperidyl)tetrazole was obtained in 86% yield by hydrogenation of the pyridyltetrazole in a completely analogous manner. The product crystallized from water as dense colorless prisms; it did not decompose below 370° but showed some shrinking and browning at 237°.

Anal. Calcd. for $C_6H_{11}N_5$: C, 47.1; H, 7.2; N, 45.7. Found: C, 47.0; H, 7.2; N, 46.0.

The *acetyl* derivative, obtained as described for the isomers, separated from isopropyl alcohol as a colorless, crystalline solid, m.p. 156.5–157.5°.

Anal. Calcd. for $C_8H_{13}N_5O$: C, 49.2; H, 6.7; N, 35.9. Found: C, 49.3; H, 6.8; N, 35.8.

EAST LANSING, MICHIGAN

(15) B. Brouwer-van Straater, D. Solinger, C. van de Westeringh, and H. Veldstra, *Rec. trav. chim.*, 77, 1129 (1958).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MICHIGAN STATE UNIVERSITY]

Tetrazole Analogs of Plant Auxins[1]

J. M. McMANUS[2,3] AND ROBERT M. HERBST

Received March 30, 1959

A group of chlorinated 5-phenoxymethyltetrazoles has been prepared as analogs of the corresponding substituted phenoxyacetic acids. Two methods of synthesis were used to corroborate the structure of the products. The tetrazole analog of the natural plant auxin, 3-indolylacetic acid, in which the carboxyl group is replaced by the acidic tetrazole moiety, has been prepared from the corresponding nitrile. An improved method for the synthesis of phenoxyacetonitriles is described.

The isolation and identification of 3-indolylacetic acid as a natural growth hormone in plants[4] initiated a search for other substances which could elicit this type of activity. Among those synthetic materials shown to stimulate growth was a group of chlorinated compounds derived from phenoxyacetic acid. Varying degrees of activity were demonstrated depending on the number and position of the chlorine atoms in the benzenoid portion of the structure; the most active are 2,4-dichloro-

(1) Based on a doctoral thesis submitted to Michigan State University in 1958 by James M. McManus.

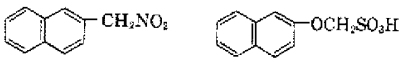
(2) White Laboratories Fellow, 1956–1958.

(3) Present address: Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

(4) F. Kögl, A. J. Haagen-Smit and H. Erxleben, *Z. physiol. Chem.*, 228, 90 (1934).

IPR2020-00770
United Therapeutics EX2007
Page 3178 of 7335

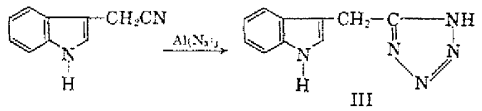
phenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T).[5] The requirement that there be a carboxyl group on the side chain[6] finds exception in that the corresponding aldehydes, nitriles, esters and amides also show, to a certain extent, hormonal activity. Exceptions to the carboxylic acid rule have been shown by active compounds in which the carboxyl group is replaced by a nitro group (I) or a sulfonic acid moiety (II).[7]



I II

Because of the acidic nature of 5-mono substituted tetrazoles,[8,9,10,11] it appeared of interest to incorporate a tetrazole nucleus into the chemical structure of an active plant auxin in place of the carboxyl group. In this study the tetrazole analogs of 3-indolylacetic acid and various chlorophenoxyacetic acids were synthesized.

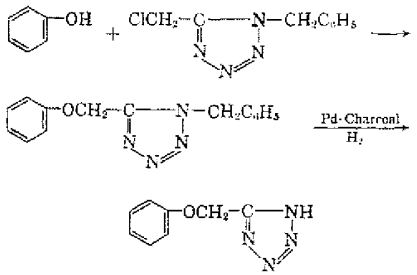
Behringer and Kohl[12] have shown that certain nitriles will react with aluminum azide in tetrahydrofuran to form 5-substituted tetrazoles. The preparation of 5-(3′-indolylmethyl)tetrazole (III) was accomplished by application of this general procedure to 3-indolylacetonitrile. It was found advantageous to modify the isolation technique recommended by these authors. Better results were obtained when the tetrahydrofuran was displaced from the reaction mixture by distillation while constant volume was maintained by simultaneous addition of water. The insoluble aluminum salt of the tetrazole which remained after all the tetrahydrofuran had been removed was decomposed with dilute hydrochloric acid, leaving an aqueous suspension of the tetrazole.



III

The substituted 5-phenoxymethyltetrazoles were synthesized by application of two general procedures: The first involved interaction of nitriles with sodium azide and acetic acid in *n*-butyl alcohol[10]; the second, interaction of nitriles with aluminum azide in tetrahydrofuran.[12] The first procedure was used successfully for the synthesis of 5-phenoxymethyltetrazole and the corresponding 2,4-dichloro- and 2,4,5-trichlorophenoxymethyl analogs from the appropriate nitriles. Attempts to prepare 5-(2′,4′,6′-trichlorophenoxymethyl)tetrazole in this way were not successful; the reaction mixture became very dark because of extensive decomposition, and no definite product was isolated. The interaction of 2-chloro-, 4-chloro-, and 2,4,6-trichlorophenoxyacetonitrile with aluminum azide in refluxing tetrahydrofuran resulted in good yields of the corresponding tetrazoles. After completion of this work an improved technique involving interaction of nitriles with lithium or an ammonium azide in dimethylformamide appeared.[13]

An alternate method used for the preparation of some of the phenoxymethyltetrazoles involved interaction of the appropriately substituted phenol with 1-benzyl-5-chloromethyltetrazole in an alkaline medium, followed by hydrogenolytic removal of the benzyl group with palladium on charcoal and hydrogen. In several instances, namely 5-(2,′4′-dichloro- and 2′,4′,6′-trichlorophenoxymethyl)-1-benzyltetrazole, debenzylation was accompanied by partial dehalogenation and possibly reduction. Isolation of pure compounds of unequivocal structure for comparison with the compounds prepared by other routes was not feasible in these two cases. In other instances compounds identical with those formed from the nitriles were obtained by this method.



The tetrazole analogs are similar to the phenoxyacetic acids in physical properties. All are solids with melting points in the same range as and similar solubilities to the corresponding carboxylic acids. No regular differences in melting points are noted, some are slightly higher some lower than those of the corresponding phenoxyacetic acids.

The nitriles used as intermediates for the phenoxymethyltetrazole syntheses were prepared from the phenol, chloroacetonitrile and potassium carbonate in refluxing acetone. This method of preparation offered a distinct advantage over methods which involved synthesis of the nitrile either from

(5) R. M. Muir, C. H. Hansch and A. H. Gallup, *Plant Physiol.*, 24, 359 (1949).
(6) J. Koepfli, K. Thimann and F. Went, *J. Biol. Chem.*, 122, 763 (1937–38).
(7) R. Wain, *Ann. Appl. Biol.*, 36, 558 (1949).
(8) E. Oliveri-Mandala, *Gazz. chim. ital.*, 44, 175 (1914).
(9) J. S. Mihina and R. M. Herbst, *J. Org. Chem.*, 15, 1082 (1950).
(10) R. M. Herbst and K. R. Wilson, *J. Org. Chem.*, 22, 1142 (1957).
(11) R. M. Herbst, *Essays in Biochemistry*, S. Graff, Ed., John Wiley and Sons, Inc., New York, 1956, p. 141.
(12) H. Behringer and K. Kohl, *Chem. Ber.*, 89, 2648 (1956).
(13) W. G. Finnegan, R. A. Henry and R. Lofquist, *J. Am. Chem. Soc.*, 80, 3908 (1958).

IPR2020-00770
United Therapeutics EX2007
Page 3179 of 7335

TABLE I

PHENOXYACETONITRILES ARYL-OCH_2CN

Aryl	M.P.	Yield, %	Formula	Analyses Calcd. Cl	Calcd. N	Found Cl	Found N
C_6H_5	[a]	82					
2-ClC_6H_4	[b]	44	C_8H_6ClNO	21.2	8.4	21.1	8.1
4-ClC_6H_4	46.5–47.5	93	C_8H_6ClNO	21.2	8.4	21.2	8.2
2,4-$Cl_2C_6H_3$	48.5–49[c]	85	$C_8H_5Cl_2NO$	35.1	6.9	35.2	6.8
2,4,5-$Cl_3C_6H_2$	91.5–92.5	88	$C_8H_4Cl_3NO$	45.0	5.9	44.8	5.8
2,4,6-$Cl_3C_6H_2$	102–103[d]	98	$C_8H_4Cl_3NO$	45.0	5.9	44.9	5.7

[a] B.p. 73–76° at 1 mm., Powell and Adams[18] reported b.p. 132° at 30 mm. [b] B.p. 109° at 1 mm. [c] M.p. 44–46° previously reported.[14] [d] M.p. 103° previously reported.[19]

the acid by way of the acid chloride and amide or from phenoxymethyl chloride and sodium cyanide[14] as these latter methods involved a series of steps. The structure of the phenoxyacetonitriles was established by comparison of physical constants with those recorded in the literature, elemental analysis and, in several cases, by hydrolysis to the known phenoxyacetic acids.

5-(3′-Indolylmethyl)tetrazole appears to stimulate cell elongation in the *Avena* test at concentrations about 200 times as great as those of 3-indolylacetic acid required to produce the same effect. 5(2′,4′-Dichlorophenoxymethyl)tetrazole is inactive but appears to be a competitive antagonist for 2,4-dichlorophenoxyacetic acid in the *Avena* test. Details of these studies are to be published elsewhere.[15]

The preparation of both 5-(3′-indolylmethyl)- and 5-(2′,4′-dichlorophenoxymethyl)tetrazole by somewhat different techniques has just been reported by van de Westeringh and Veldstra.[16]

EXPERIMENTAL[17]

5-(3′-Indolylmethyl)tetrazole. Seven and eight-tenths g. (0.12 mole) of sodium azide and 5.3 g. (0.04 mole) of anhydrous aluminum chloride were refluxed together in 120 ml. of dry tetrahydrofuran for 1 hr. 5.8 g. (0.04 mole) of 3-indolylacetonitrile was added to the mixture and refluxing with stirring continued for 24 hrs. The tetrahydrofuran was then distilled from the reaction mixture while water was added slowly at such a rate that the volume remained constant. After the organic solvent had been removed, the suspended solid was filtered off, resuspended in 250 ml. of water, and treated with sufficient hydrochloric acid to bring the suspension to *p*H 2. After 10 min. stirring, the solid was filtered off and washed with water. Drying gave 6.5 g. of crude product which was recrystallized first from ethylene chloride and then from water, yield 4.5 g. (61%), m.p. 179–180° with decomposition.

Anal. Calcd. for $C_{10}H_9N_5$: C, 60.3; H, 4.6; N, 35.2. Found: C, 60.3; H, 4.8; N, 35.0.

The *monopicrate* crystallized from water, m.p. 131–132°.

Anal. Calcd. for $C_{16}H_{12}N_8O_7$: C, 44.9; H, 2.8; N, 26.2. Found: C, 45.5; H, 3.2; N, 25.8.

Phenoxyacetonitriles. The preparation of phenoxyacetonitrile will serve as a typical example. A mixture of 23.5 g. of phenol, 18.7 g. of chloroacetonitrile and 34.5 g. of anhydrous potassium carbonate in 75 ml. of dry acetone was heated under reflux for 8 hr. The mixture was then poured into 200 ml. of water containing 10 g. of sodium hydroxide and extracted with ether. The ether layer was separated and dried over sodium sulfate, and the ether was removed by distillation. Fractionation of the residual reddish oil gave the product as a colorless, oily liquid, yield 27.2 g. Physical properties, yields, and analytical data for the phenoxyacetonitriles prepared in this way are given in Table I. Except for 2,4,6-trichlorophenoxyacetonitrile, which was recrystallized from absolute ethanol, the solid chlorophenoxyacetonitriles were recrystallized from petroleum ether.

Phenoxyacetic acid. Phenoxyacetonitrile (5.3 g.) was refluxed in 100 ml. of 25% sodium hydroxide solution for 12 hr. The resulting solution was filtered and the filtrate was cooled and acidified with 6*N* hydrochloric acid. The yield of product after recrystallization from water was 4.9 g. (81%), m.p. 98–99°. Sabanejeff and Dworkowitsch[20] report m.p. 97°.

2,4-Dichlorophenoxyacetic acid, m.p. 138.5–139° was obtained from the nitrile in similar manner; previously reported[21] m.p. 138°.

2,4,5-Trichlorophenoxyacetic acid was obtained from the nitrile in similar manner and recrystallized from benzene, m.p. 150.5–152°. Porkorny[21] reported m.p. 153°.

Preparation of Phenoxymethyltetrazoles. 5-Phenoxymethyltetrazole. Procedure Ia. A mixture of 16.3 g. (0.125 mole) of phenoxyacetonitrile, 11 g. (0.165 mole) of sodium azide and 10 g. (0.165 mole) of glacial acetic acid in 60 ml. of *n*-butyl alcohol was heated under reflux for 4 days. Heating was continued for 2 days after addition of 2.5 g. of sodium azide and 5 g. of glacial acetic acid. The reaction mixture was diluted with 200 ml. of water, and the mixture was distilled until the alcohol was removed. Acidification of the residual aqueous solution with dilute sulfuric acid gave the product as a colorless solid, yield 22 g. Recrystallization from water gave the pure product, m.p. 127.5–129°.

(14) H. Barber, R. Fuller, M. Green and H. Zwartouw *J. Appl. Chem. (London)*, 3, 266 (1953).

(15) We are indebted to Mr. R. H. Hamilton, Dr. A. Kivilaan and Dr. R. S. Bandurski of the Department of Botany at Michigan State University for their enthusiastic cooperation in these studies. Their results will be published separately in *Plant Physiology*.

(16) C. van de Westeringh and H. Veldstra, *Rec. trav. chim.*, 77, 1107 (1958).

(17) Microanalyses were done on all compounds by Micro-Tech Laboratories, Skokie, Ill. Melting points were taken in open capillaries and are not corrected.

(18) S. Powell and R. Adams, *J. Am. Chem. Soc.*, 42, 646 (1920).

(19) D. Drain, D. Peak, and F. Whitmont, *J. Chem. Soc.*, 2680 (1949).

(20) A. Sabanejeff and P. Dworkowitsch, *Ann.*, 216, 284 (1883).

(21) R. Porkorny, *J. Am. Chem. Soc.*, 63, 1768 (1941).

IPR2020-00770
United Therapeutics EX2007
Page 3180 of 7335

Anal. Calcd. for $C_8H_8N_4O$: C, 54.5; H, 4.6; N, 31.8. Found: C, 54.5; H, 4.7; N, 31.9.

5-(2'-Chlorophenoxymethyl)tetrazole. Procedure Ib. To a suspension of 16.7 g. (0.1 mole) of 2-chlorophenoxyacetonitrile and 19.5 g. (0.3 mole) of sodium azide in 50 ml. of dry tetrahydrofuran was added a solution of 13.3 g. (0.1 mole) of anhydrous aluminum chloride in 160 ml. of the same solvent. The mixture was refluxed with continuous stirring for 24 hr. The tetrahydrofuran was then distilled from the reaction mixture while water was added slowly at such a rate that the volume of the mixture remained constant. The solid which had separated was filtered off, resuspended in 250 ml. of water and treated with 30 ml. of concentrated hydrochloric acid. After being stirred for 1 hr. the solid was filtered off and dried, yield 18.8 g. of crude product which was recrystallized from toluene, m.p. 134.5–135.5°.

Anal. Calcd. for $C_8H_7ClN_4O$: C, 45.6; H, 3.4; Cl, 16.8; N, 26.6. Found: C, 45.9; H, 3.6; Cl, 16.9; N, 26.6.

5-(4'-Chlorophenoxymethyl)tetrazole. Following *Procedure Ib* a mixture of 16.7 g. (0.1 mole) of 4-chlorophenoxyacetonitrile, 19.5 g. (0.3 mole) of sodium azide, and 13.3 g. (0.1 mole) of anhydrous aluminum chloride in 210 ml. of dry tetrahydrofuran gave 20.6 g. of crude product. Recrystallization from aqueous ethanol gave 13.9 g. (66%) of pure product, m.p. 165–166°.

Anal. Calcd. for $C_8H_7ClN_4O$: C, 45.6; H, 3.4; Cl, 16.8; N, 26.6. Found: C, 45.7; H, 3.6; Cl, 16.8; N, 26.5.

5-(2' 4'-Dichlorophenoxymethyl)tetrazole. Using *Procedure Ia* a mixture of 25.2 g. (0.125 mole) of 2,4-dichlorophenoxyacetonitrile, 11 g. (0.165 mole) of sodium azide, and 10 g. of glacial acetic acid in 60 ml. of *n*-butyl alcohol gave 25.6 g. of crude product which was purified by recrystallization from toluene, m.p. 124.5–125.5°.

Anal. Calcd. for $C_8H_6Cl_2N_4O$: C, 39.2; H, 2.5; Cl, 28.9; N, 22.9. Found: C, 39.4; H, 2.6; Cl, 29.0; N, 23.0.

5-(2',4',5'-Trichlorophenoxymethyl)tetrazole. Following *Procedure Ia* a mixture of 29.6 g. (0.125 mole) of 2,4,5-trichlorophenoxyacetonitrile, 11 g. (0.165 mole) of sodium azide, and 10 g. of glacial acetic acid in 60 ml. of *n*-butyl alcohol gave 25.4 g. of crude product that was purified by recrystallization from toluene, m.p. 163.5–165°.

Anal. Calcd. for $C_8H_5Cl_3N_4O$: C, 34.4; H, 1.8; Cl, 38.1; N, 20.1. Found: C, 34.7; H, 1.8; Cl, 38.3; N, 20.1.

5-(2',4',6'-Trichlorophenoxymethyl)tetrazole. Using *Procedure Ib* 5.8 g. (0.025 mole) of 2,4,6-trichlorophenoxyacetonitrile, 4.8 g. (0.074 mole) of sodium azide, and 2.98 g. (0.025 mole) of anhydrous aluminum chloride in 90 ml. of dry tetrahydrofuran gave 6.6 g. of crude product which was recrystallized first from toluene and then from ethanol, m.p. 164–165°.

Anal. Calcd.: for $C_8H_5Cl_3N_4O$: C, 34.4; H, 1.8; Cl, 38.1; N, 20.1. Found: C, 34.6; H, 2.1; Cl, 37.9; N, 20.0.

Several attempts to prepare this compound using *Procedure Ia* were accompanied by extensive decomposition; no definite product was isolated from the reaction mixtures.

1-Benzyl-5-phenoxymethyltetrazole. A mixture of 8.3 g. (0.04 mole) of 1-benzyl-5-chloromethyltetrazole,[22] 4.7 g. (0.05 mole) of phenol, and 2.7 g. (0.05 mole) of sodium methoxide in 75 ml. of absolute methanol was heated under reflux with stirring for 10 hr. The contents of the flask were then poured into 150 ml. of water, the precipitate was filtered off and recrystallized from aqueous methanol to give 3.8 g. (36%) of the desired product, m.p. 66.5–67°.

Anal. Calcd. for $C_{15}H_{14}N_4O$: C, 67.7; H, 5.3; N, 21.0. Found: C, 67.4; H, 5.4; N, 21.1.

1-Benzyl-5-(2',4'-dichlorophenoxymethyl)tetrazole. Under similar conditions 8.3 g. of 1-benzyl-5-chloromethyltetrazole, 8.15 g. of 2,4-dichlorophenol, and 2.7 g. of sodium methoxide in 75 ml. of absolute methanol gave 12.4 g. of crude product from which, after recrystallization from methanol, 8.6 g. of pure product, m.p. 107.5–108°, was obtained.

Anal. Calcd. for $C_{15}H_{12}Cl_2N_4O$: C, 53.8; H, 3.6; Cl, 21.2; N, 16.7. Found: C, 53.8; H, 3.9; Cl, 21.0; N, 16.8.

1-Benzyl-5-(2',4',5'-trichlorophenoxymethyl)tetrazole. In similar manner 6.9 g. of 1-benzyl-5-chloromethyltetrazole, 8.2 g. of 2,4,5-trichlorophenol, and 2.2 g. of sodium methoxide in 75 ml. of absolute methanol gave 10.6 g. of crude product which on recrystallization from methanol gave 6.4 g. of pure product, m.p. 113.5–114.5°.

Anal. Calcd. for $C_{15}H_{11}Cl_3N_4O$: C, 48.7; H, 3.0; Cl, 28.8; N, 15.2. Found: C, 48.6; H, 3.1; Cl, 28.7; N, 15.3.

1-Benzyl-5-(2',4',6'-trichlorophenoxymethyl)tetrazole. Similarly 6.9 g. of 1-benzyl-5-chloromethyltetrazole, 8.15 g. of 2,4,6-trichlorophenol, and 2.2 g. of sodium methoxide in 75 ml. of absolute methanol gave 12.3 g. of crude product and after recrystallization from methanol, 9.1 g. of pure material, m.p. 112–113°.

Anal. Calcd. for $C_{15}H_{11}Cl_3N_4O$: C, 48.7; H, 3.0; Cl, 28.8; N, 15.2. Found: C, 48.8; H, 3.0; Cl, 28.9; N, 15.0.

Debenzylation of 1-Benzyl-5-phenoxymethyltetrazole. A solution of 2.7 g. (0.01 mole) of 1-benzyl-5-phenoxymethyltetrazole in 100 ml. of absolute ethanol was shaken for 12 hr. with 1 g. of 5% palladium on charcoal at an initial hydrogen pressure of 50 p.s.i. The catalyst was filtered off and the solvent was removed from the filtrate in a vacuum. The residue was treated with dilute sodium hydroxide and filtered. From the alkali insoluble solid, 1.3 g. (49%) of the starting material was recovered. Acidification of the alkaline solution with dilute hydrochloric acid gave a precipitate of 5-phenoxymethyltetrazole, 400 mg. (43%), which was recrystallized from water, m.p. and mixture m.p. 127.5–128.5°.

Debenzylation of 1-benzyl-5-(2',4',5'-trichlorophenoxymethyl)tetrazole. A mixture of 1.8 g. of 1-benzyl-5-(2',4',5'-trichlorophenoxymethyl)tetrazole and 1 g. of palladium on charcoal in 75 ml. of absolute ethanol was shaken for 12 hr. at an initial hydrogen pressure of 50 p.s.i. The catalyst was filtered and washed with warm ethanol. Removal of the solvent from the combined filtrate and washings in a vacuum left a residue which after repeated crystallization from toluene gave 5-(2',4',5'-trichlorophenoxymethyl)tetrazole, m.p. and mixture m.p. 160–162°.

Both 1-benzyl-5-(2',4'-dichloro- and 2',4',6'-trichlorophenoxymethyl)tetrazole were debenzylated in a similar manner, but in neither case was a pure product isolated from the resulting mixture of products. Apparently debenzylation was accompanied by dehalogenation and possibly reduction in varying degrees which would have vitiated this approach as an unequivocal synthesis.

EAST LANSING, MICH.

(22) E. K. Harvill, R. M. Herbst, and E. C. Schreiner, *J. Org. Chem.*, 17, 1597 (1952).

IPR2020-00770
United Therapeutics EX2007
Page 3181 of 7335

Advanced Organic Synthesis

METHODS AND TECHNIQUES

RICHARD S. MONSON

DEPARTMENT OF CHEMISTRY
CALIFORNIA STATE COLLEGE, HAYWARD
HAYWARD, CALIFORNIA

ACADEMIC PRESS
New York and London

IPR2020-00770
United Therapeutics EX2007
Page 3182 of 7335

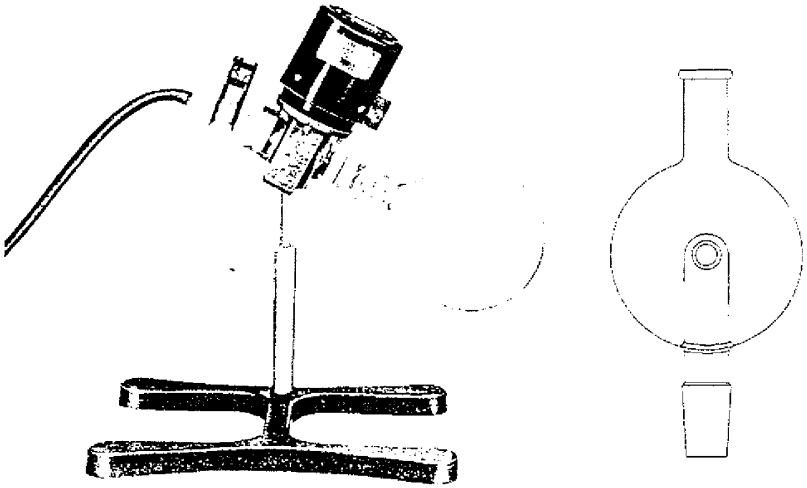
COPYRIGHT © 1971, BY ACADEMIC PRESS, INC.
ALL RIGHTS RESERVED
NO PART OF THIS BOOK MAY BE REPRODUCED IN ANY FORM,
BY PHOTOSTAT, MICROFILM, RETRIEVAL SYSTEM, OR ANY
OTHER MEANS, WITHOUT WRITTEN PERMISSION FROM
THE PUBLISHERS.

ACADEMIC PRESS, INC.
111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS, INC. (LONDON) LTD.
Berkeley Square House, London W1X 6BA

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 75-165531

PRINTED IN THE UNITED STATES OF AMERICA



(a) (b)

FIG. A3.12. (a) Rotary evaporator (Buchler Instruments) (b) Trap used with rotary evaporator.

walls of the rotating flask provides a large surface area for rapid evaporation, while the rotation action mixes the solution and inhibits actual boiling. Figure A3.12b illustrates a trap which may be used with the rotary evaporator to prevent loss of the solution in case of bumping. The trap may also be cooled, if desired, for recovery of the solvent.

III. Purification of the Product

A. DISTILLATION (*2*)

Setups for simple and fractional distillation at atmospheric pressure are shown (Fig. A3.13). A 30-cm Vigreux column (Fig. A3.13b) is convenient if the components boil at least 50° apart at atmospheric pressure. For better separation, a column packed with glass helices is suitable. All columns employed in fractional distillation should be wrapped or jacketed to minimize heat loss.

Heat sources for distillation must be closely controlled to prevent overheating or too rapid distillation. The best heat sources are electrically heated liquid baths. Mineral oil or wax is a satisfactory medium for heat exchange up to about 240°. The medium may be

IPR2020-00770
United Therapeutics EX2007
Page 3184 of 7335

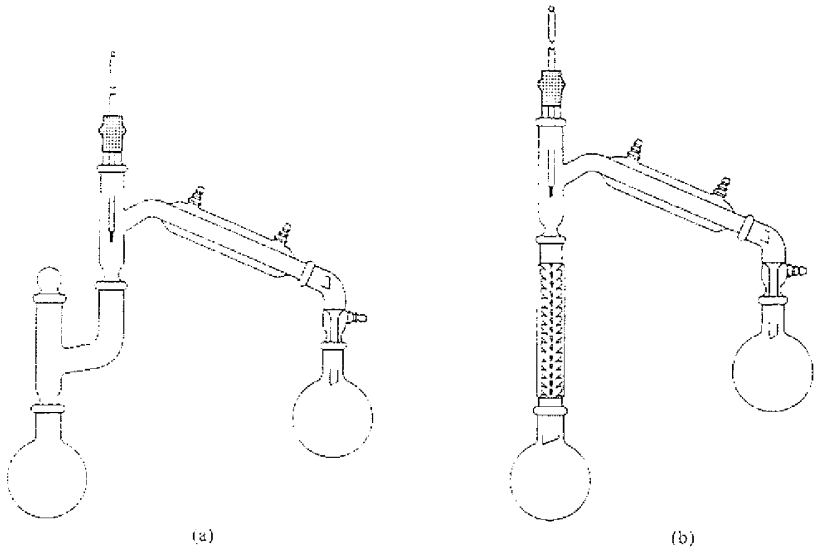


FIG. A3.13. Setups for atmospheric pressure distillation (a) for simple distillation (b) Vigreux column for fractional distillation.

contained in a stainless steel beaker or sponge dish and heated by an electric hot plate or immersion coil. The bath temperature (20–80° above the boiling point) is easily monitored by an immersed thermometer.

Distillation at reduced pressure is advisable with the majority of organic compounds boiling above 150° at 1 atmosphere. Aspirator pressure (20–30 mm depending on water temperature and system leaks) is sufficient for many reduced pressure distillations. A liquid boiling at 200°/1 atm, for example, will have a boiling point of approximately 100° at 30 mm. (Estimates of observed boiling points at reduced pressure can be made by use of the pressure-temperature alignment chart shown in Fig. A3.14). The aspirator pump is simple and is not affected by organic or acid vapors. The pressure in such a system is best monitored by a manometer.

A vacuum system employing an oil pump is shown schematically in Fig. A3.15. Protection of the pump requires that the system be well trapped between the pump and the distillation setup. The pressure can be regulated by introducing an air leak through a needle valve (a bunsen burner needle valve is satisfactory). The pressure is monitored by use of a tipping McLeod gauge (Fig. A3.16) which gives intermittant (as opposed to continuous) reading of pressure down to about 0.05 mm, of sufficient precision for the purpose.

IPR2020-00770
United Therapeutics EX2007
Page 3185 of 7335

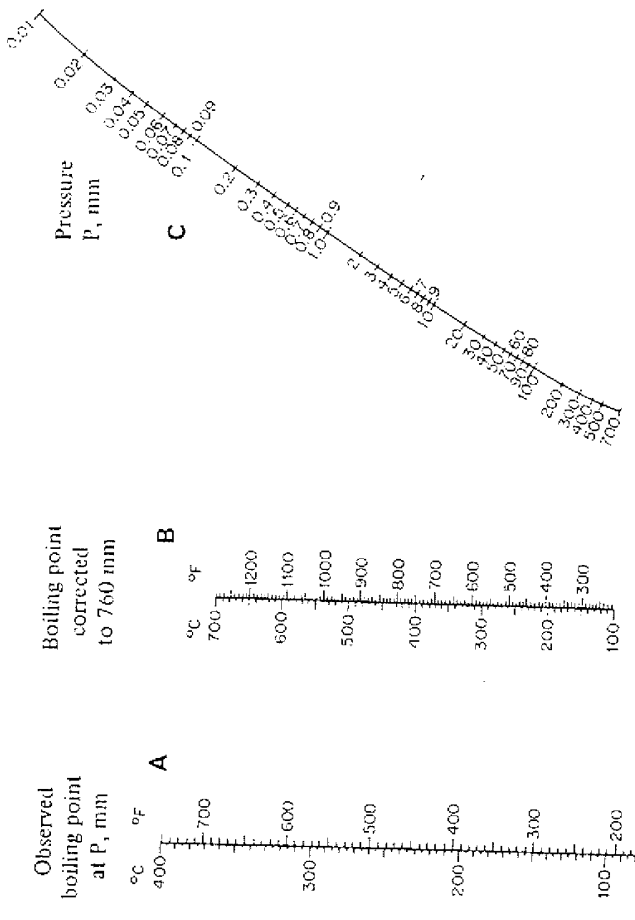


FIG. A3.14. Pressure–temperature alignment chart (reprinted by permission from MCR Manufacturing Chemists, Norwood, Ohio).

IPR2020-00770
United Therapeutics EX2007
Page 3186 of 7335

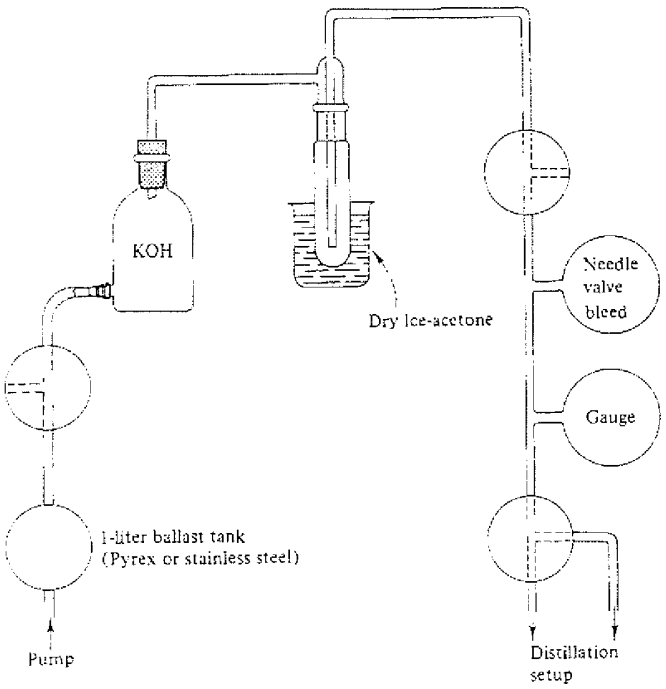


FIG. A3.15. Schematic diagram of a vacuum system for distillation.

The prevention of bumping in reduced pressure distillations requires special precautions. Boiling chips rarely function well over the course of a long distillation under vacuum, and one of several alternative techniques should be employed. The following methods are listed in decreasing order of effectiveness: (1) Introduction of a fine stream of air or nitrogen through a capillary bleed tube (Fig. A3.17); (2) the use of 12–15 microporous boiling chips (Todd Scientific Co.); (3) covering the boiling liquid with a mesh of Pyrex wool; (4) the use of boiling sticks.

B. CRYSTALLIZATION AND RECRYSTALLIZATION

Several techniques are usually employed to induce crystallization from saturated solutions of organic solids. The introduction of seed crystals will invariably work, although with new compounds such crystals are not available. Seeding with crystals of a

IPR2020-00770
United Therapeutics EX2007
Page 3187 of 7335

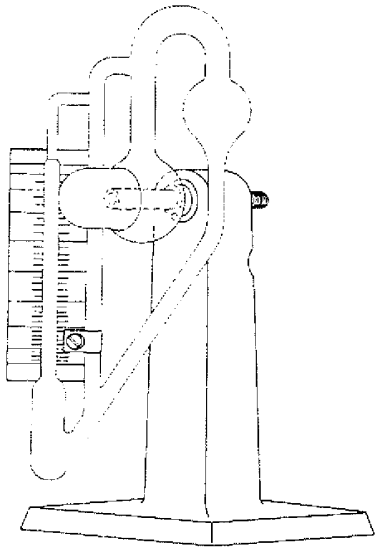


FIG. A3.16. Tipping McLeod guage.

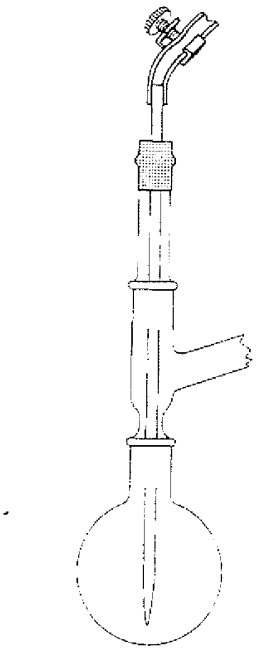


FIG. A3.17. Capillary bleed tube for reduced pressure distillation.

compound with related molecular or crystal structure is frequently successful. Alternatively, cooling the solution and scratching the interior of the vessel with a glass rod is successful in a surprising number of cases.

The technique of trituration is frequently useful. The organic product is stripped of solvent and the oily residue is placed in a mortar and covered with a layer of a solvent in which it is only slightly soluble. The mass is ground with a pestle mixing in the solvent as thoroughly as possible. In favorable cases, the solvent removes traces of impurities that may be inhibiting crystallization, and grinding action induces crystallization.

Successful recrystallization of an impure solid is usually a function of solvent selection. The ideal solvent, of course, dissolves a large amount of the compound at the boiling point but very little at a lower temperature. Such a solvent or solvent mixture must exist (one feels) for the compound at hand, but its identification may necessitate a laborious trial and error search. Solvent polarity and boiling point are probably the most important factors in selection. Benzhydrol, for example, is only slightly soluble in 30–60° petroleum ether at the boiling point but readily dissolves in 60–90° petroleum ether at the boiling point.

IPR2020-00770
United Therapeutics EX2007
Page 3188 of 7335

Until one develops a "feel" for recrystallization, the best procedure for known compounds is to duplicate a selection in the literature. For new compounds, a literature citation of a solvent for an analogous structure is often a good beginning point. To assist in the search, Table A3.4 lists several of the common recrystallizing solvents with useful data. The dielectric constant can be taken to be a rough measure of solvent polarity.

TABLE A3.4
RECRYSTALLIZING SOLVENTS

Solvent	B.P. (°C)	Dielectric constant	Water solubility (g 100 g)
Acetic acid	188	6.2	Misc.
Acetone	56.5	21	Misc.
Acetonitrile	82	38	Misc.
Benzene	80	2.3	0.07
t-Butyl alcohol	82	17	Misc.
Carbon tetrachloride	77	2.2	0.08
Chloroform	61	4.8	1.0
Cyclohexane	81	2.0	Sl. sol.
DMF	154	38	Misc.
Dioxane	101	2.2	Misc.
DMSO	189	45	Misc.
Ethanol	78	25	Misc.
Ethyl acetate	77	6.0	9
Ethyl ether	35	4.3	7.5
Ethylene chloride	83	10	0.83
Heptane	98	2.0	Insol.
Hexane	69	1.9	Insol.
Isopropyl alcohol	82	18	Misc.
Methanol	65	34	Misc.
Methylene chloride	40	9.1	2.0
Nitromethane	101	38	10
Pentane	36	2.0	0.03
Pyridine	115	12	Misc.
Water	100	80	—

C. DRYING OF SOLIDS

A solid insensitive to air is easily dried by spreading the material over a large piece of filter paper and allowing moisture or solvent to evaporate. However, many organic solids are sensitive to air or moisture and must be dried under reduced pressure in a vacuum desiccator or vacuum oven. Moreover, complete drying of a sample to be analyzed by combustion analysis necessitates vacuum drying. For vacuum drying of small samples, an Abderhalden (drying pistol) is a convenient arrangement (Fig. A3.18).

IPR2020-00770
United Therapeutics EX2007
Page 3189 of 7335

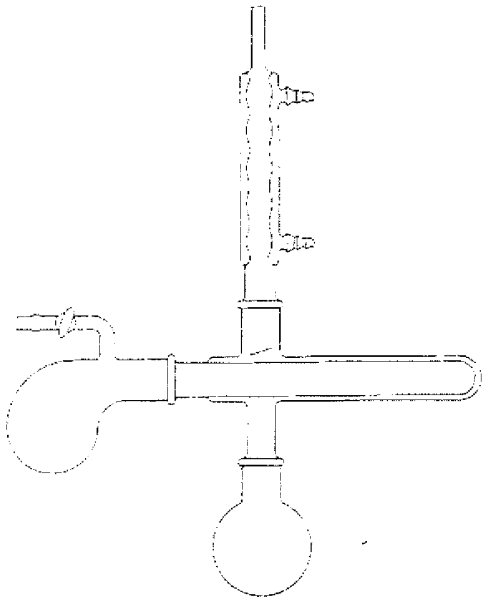


FIG. A3.18. Abderhalden (drying pistol).

The sample is placed in the barrel of the pistol and a drying agent (usually P_2O_5) placed in the "handle." The evacuated system is heated by refluxing a liquid of the desired boiling point over the sample.

D. SUBLIMATION

When a solid compound possesses a relatively high vapor pressure below its melting point, it may be possible to purify it by sublimation. Selenium dioxide, for example, is easily purified prior to use by sublimation at atmospheric pressure (Chapter 1, Section XI). More commonly, the method of choice is sublimation at reduced pressure, which allows more ready evaporation of solids with limited volatility. A convenient vacuum sublimation apparatus is shown in Fig. A3.19. The impure sample is placed in the lower cup, which is attached to the condenser by an O-ring seal and spring. Water is run through the condenser and the system is evacuated. The cup is heated gradually with an oil bath, and sublimation follows. The sublimate is recovered by scraping it off the walls of the condenser with a spatula.

IPR2020-00770
United Therapeutics EX2007
Page 3190 of 7335

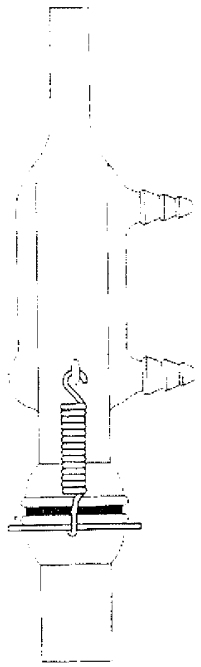


FIG. A3.19. Apparatus for vacuum sublimation.

E. CHROMATOGRAPHY

1. *Column Chromatography:* Column Chromatography is a useful separation technique for mixtures resulting from intermediate to small scale synthetic processes. For example, nitroferrocene is conveniently isolated from a mixture of the product, ferrocene, and 1,1'-dinitroferrocene by chromatography on Activity I basic alumina at about the 100-g scale (Chapter 7, Section XI).

The column (20–30 cm by 1–2 cm diameter or larger in the proportion 10:1) is prepared by filling it with a dry solvent of low polarity (e.g., pentane), pushing a plug of cotton to the bottom, covering the cotton with a layer of sand, and dusting in the adsorbant. About 25 g of adsorbant per gram of mixture is a good approximation for a first trial. The adsorbant is covered with a layer of sand, excess solvent is drained, and the sample, dissolved in a minimum amount of a suitable solvent, is introduced with a dropper.

IPR2020-00770
United Therapeutics EX2007
Page 3191 of 7335

Alumina is the most frequently employed adsorbant. Its activity (i.e., the extent to which it adsorbs polar compounds) is largely a function of the amount of water present. Alumina of Activity I is prepared by heating the material in an oven to 200–230° and allowing it to cool in a desiccator. Addition of water to the extent of 3%, 6%, 10%, or 15% to the dry material gives alumina of Activity II, III, IV, and V, respectively.

The column is eluted with dry solvents of gradually increasing eluting power. The order of eluting power of the common dry solvents is shown in Table A3.5. The compounds are eluted from the column in order of their increasing polarity. The usual order of elution of organic compounds is shown in Table A3.6. The progress of the

TABLE A3.5
ORDER OF ELUTING POWER OF COMMON DRY SOLVENTS

1. 30–60° Petroleum ether	8. Chloroform
2. 60–90° Petroleum ether	9. Ethyl acetate
3. Carbon tetrachloride	10. Ethylene chloride
4. Cyclohexane	11. Ethanol
5. Benzene	12. Methanol
6. Ether	13. Water
7. Acetone	14. Acetic acid

TABLE A3.6
ORDER OF ELUTION OF ADSORBED COMPOUNDS

1. Aliphatic hydrocarbons	7. Ketones
2. Alkyl halides	8. Aldehydes
3. Olefins	9. Thiols
4. Aromatic hydrocarbons	10. Amines
5. Ethers	11. Alcohols
6. Esters	12. Carboxylic acids

elution is followed by collecting small samples of the eluant and evaporating the solvent. The melting points and spectra of the residual materials serve as a guide to the development of the column. When one compound has been completely eluted, changing to a solvent or a solvent mixture of higher eluting power will hasten the recovery of subsequent fractions.

2. *Thin-Layer Chromatography (TLC)*: The function of TLC in organic synthesis is primarily one of allowing the experimenter to follow the progress of the reaction without actually interrupting the reaction. Since successful TLC can be carried out on a minute scale, only a very small fraction of the reaction mixture need be withdrawn and subjected to analysis. The following example of the TLC analysis of the chromic acid oxidation of borneol, described by Davis (3), is a useful model.

IPR2020-00770
United Therapeutics EX2007
Page 3192 of 7335

(a) *Preparation of the plates* (4): Microscope slides are washed thoroughly with soap, rinsed with distilled water followed by methanol, and allowed to dry on edge. A suspension of 35 g of Silica Gel G in 100 ml of chloroform is placed in a wide-mouth bottle. Two slides, held face to face with forceps, are immersed in the suspension which is briefly stirred. The slides are withdrawn evenly, resulting in a smooth deposit of the adsorbant. The rate of withdrawal of the slides controls the thickness of the silica gel layer. The slides are separated and allowed to dry. Each slide is then held in a slow stream of steam for 5 seconds to allow the binder to set. Prior to use, the slides are activated by heating for 45 minutes in an oven at 125° or by placing them on a hot plate over a wire gauze for the same length of time.

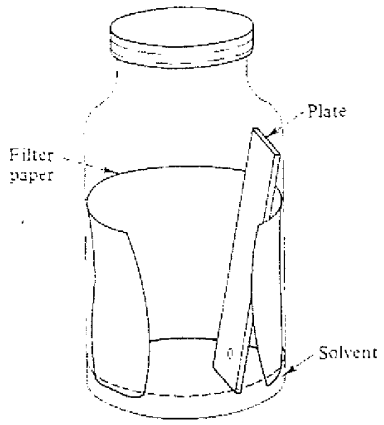


FIG. A3.20. Apparatus for the development of TLC plates.

(b) *Chromic acid oxidation of borneol:* The following solutions are prepared: 2% borneol in ether; 10% chromic anhydride and 5%, sulfuric acid in water; 2% camphor in ether.

One milliliter each of the borneol solution and the oxidizing solution are mixed in a test tube and briefly shaken. A TLC slide is spotted with the borneol solution, the camphor solution, and the ether layer of the reaction mixture. Spotting is done by means of a capillary melting point tube used as a dropper and filled with a 5 mm sample. The slide is developed in a wide-mouth jar containing a filter paper liner and a few milliliters of chloroform (Fig. A3.20). After development (the solvent front rises to within 1 cm of the top), the slide is removed, the solvent is allowed to evaporate, and the slide is placed in a covered wide-mouth jar containing a few crystals of iodine. The spots readily become visible and the progress of the reaction can easily be followed. With periodic shaking, the oxidation is complete in about 30 minutes.

IPR2020-00770
United Therapeutics EX2007
Page 3193 of 7335

A variety of reaction mixtures can be analyzed by this simple technique, although a suitable solvent or solvent mixture for the development of the slide must be determined for the particular compounds involved.

3. *Gas–Liquid Phase Chromatography (glpc):* glpc is certainly a technique of high utility to the synthetic chemist, both for analysis of reaction mixtures and for their separation on a synthetic scale. However, a detailed treatment of the techniques of glpc would be beyond the intention of the present book, since, by and large, such matters as sampling techniques, flow rates, column temperature and packing, as well as other variables, can usually be determined only in connection with the problem at hand. Instead, the student is advised to consult the instruction manuals of individual commercial instruments for operating details. An excellent discussion of the practical aspects of glpc by Ettre and Zlatkis is also available (5). Finally, a useful summary of column packing materials with many references is published periodically by Analabs, Inc. (6).

REFERENCES

1. The two most comprehensive works are A. Weissberger, ed., "Technique of Organic Chemistry," Interscience, New York, 1945; and E. Müller, ed., "Methoden der organische Chemie (Houben-Weyl)," 4th ed. Georg Thieme, Stuttgart. An excellent brief summary of many important techniques is to be found in K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill, New York, 1960.
2. A thorough discussion of the methods of conducting distillation will be found in A. Weissberger, ed., "Technique of Organic Chemistry," Vol. IV: Distillation, Interscience, New York, 1951. *Cf.* Wiberg, *op. cit.*, Chap. 1.
3. M. Davis, *J. Chem. Educ.* 45, 192 (1968).
4. J. J. Peiffer, *Mikrochim. Acta*, p. 529 (1962); J. F. Janssen, *J. Chem. Educ.* 46, 717 (1969).
5. L. S. Ettre and A. Zlatkis, eds., "The Practice of Gas Chromatography," Interscience, New York, 1967.
6. T. R. Lyon, C. L. Hoffman, and M. M. Austin, "Guide to Stationary Phases for Gas Chromatography," Analabs, Inc., Hamden, Connecticut.

IPR2020-00770
United Therapeutics EX2007
Page 3194 of 7335

Development of Dual-Acting Benzofurans for Thromboxane A_2 Receptor Antagonist and Prostacyclin Receptor Agonist: Synthesis, Structure−Activity Relationship, and Evaluation of Benzofuran Derivatives

Michihiro Ohno,* Mitsuko Miyamoto, Kazuhiro Hoshi, Takahiro Takeda, Naohiro Yamada, and Atsushi Ohtake

Pharmaceutical Research Laboratories, Toray Industries, Inc., 1,111 Tebiro, Kamakura, Kanagawa, 248-8555, Japan

Received March 3, 2005

Prostacyclin (PGI_2) is an unstable, powerful endogenous inhibitor of platelet aggregation, and thromboxane A_2 (TXA_2) is an unstable endogenous arachidonic acid metabolite that plays a pivotal role in platelet aggregation and vasoconstriction. The balance between TXA_2 and PGI_2 greatly affects maintenance of the homeostasis of the circulatory system. A novel series of benzofuran-7-yloxyacetic acid derivatives was discovered as potent dual-acting agents to block the thromboxane A_2 receptor and to activate the prostacyclin receptor. Synthesis, structure−activity relationship, and in vitro and ex vivo pharmacology of this series of compounds are described. The most potent in the series was {3-[2-(1,1-diphenylethylsulfanyl)ethyl]-2-hydroxymethylbenzofuran-7-yloxy}acetic acid diethanolamine salt (**7**) with K_i of 4.5 nM for thromboxane receptor antagonism and K_i of 530 nM for prostacyclin receptor agonism. Remarkably, compound **7** is a promising candidate for novel treatment as an antithrombotic agent with other cardiovascular actions to avoid hypotensive side effects.

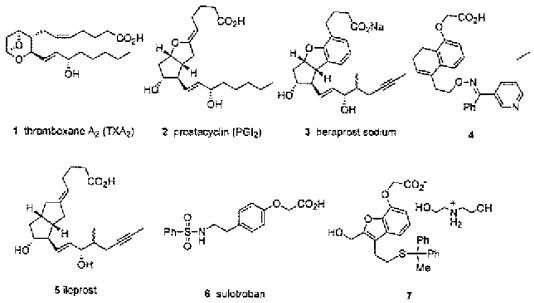
Introduction

Thromboxane A_2 (TXA_2) (**1**), discovered by Samuelsson, is an unstable endogenous arachidonic acid metabolite that plays a pivotal role in platelet aggregation and vasoconstriction[1] and has been implicated as a contributor to cardiovascular, renal, and pulmonary diseases.[2,3] Because of the lack of clinical efficacy with these agents,[4] a combined therapy using thromboxane receptor antagonists (TRAs) and thromboxane synthase inhibitors (TSIs) has been developed. This therapy has the advantage that its TSI activity would prevent the biosynthesis of TXA_2 while the accumulated PGH_2 would be redirected to produce beneficial prostaglandin metabolites such as prostacyclin (PGI_2), PGD_2, and PGE_2. However, this conventional TRA/TSI therapy exhibits unsatisfactory clinical effects.[5]

Prostacyclin (**2**), discovered by Vane, is a powerful endogenous inhibitor of platelet aggregation and also plays an important role in biological homeostasis as an endogenous autacoid distributed widely in various tissues.[6] Although these actions attract notice in the cardiovascular field, the therapeutic application of PGI_2 itself is limited by both chemical and metabolic instability because of its labile enol−ether moiety. Thus, the extensive efforts that have been focused on the synthesis of PGI_2 mimics were directed toward the stabilization of the enol−ether moiety (i.e., **3**).[7,8] Recently, nonprostanoids PGI_2 mimetics with chemical and metabolic instability have been reported (i.e., **4**)[9−14] (Chart 1).

TXA_2 and PGI_2, both of which are synthesized from arachidonic acid, have opposite effects on platelet aggregation. Also, the balance between TXA_2 and PGI_2 greatly affects maintenance of the homeostasis of the circulatory system. In the case of ischemic disorders, the TXA_2/PGI_2 balance is shifted to the TXA_2 side, and phenomena such as platelet activation, subsequent thrombogenesis, and vascular contraction appear. Thus, it is clinically important to achieve the proper TXA_2/PGI_2 balance. A combination of an agent for inhibiting TXA_2 activity and an agent acting as a PGI_2 receptor agonist is thought to be effective. Moreover, researchers at Schering AG reported that the PGI_2 mimetic **5** (iloprost) showed strong antithrombotic action when it was combined with the TXA_2/PGH_2 receptor antagonist **6** (sulotroban).[15,16] Therefore, we are interested in developing agents that combine the TXA_2 receptor (TP) antagonist activity with prostacyclin receptor (IP) agonist activity within a single molecule. Such agents would not only maximize the beneficial effects of each agent but also address the potential clinical problem of using two drugs with different pharmacokinetics. Moreover, one could expect a synergistic effect from combining two therapeutic actions in a single chemical entity to avoid the hypotensive effect of PGI_2.

Chart 1. Chemical Structures of Thromboxane A_2, Prostacyclin, Prostacyclin Mimetics, and Thromboxane A_2 Antagonists

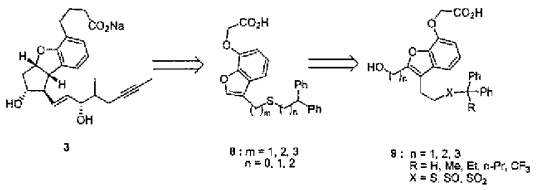


* To whom correspondence should be addressed. Phone: +81-(467)-32-2111. Fax: +81-(467)-32-4791. E-mail: michihiro_ono@nts.toray.co.jp.

10.1021/jm050194z CCC: $30.25 © 2005 American Chemical Society
Published on Web 07/15/2005

IPR2020-00770
United Therapeutics EX2007
Page 3195 of 7335

Chart 2. Molecular Design of Benzofuran Derivatives from **3**



In this paper, we report the first dual-acting benzofuran **7** that possesses TXA_2 antagonism and PGI_2 agonism within a single molecule. We describe the design, synthesis, and the biological evaluation of benzofuran derivatives.

Chemistry

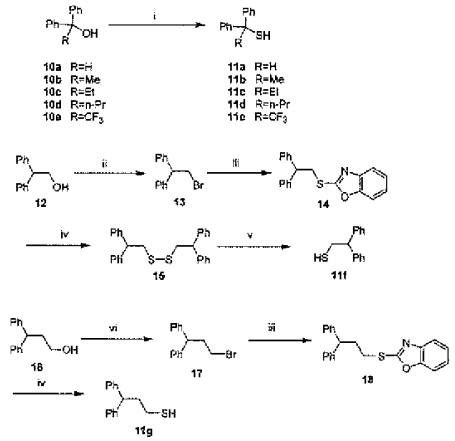
We started to design our new compounds from **3**. To avoid enantiomeric problems, we chose benzofuran, which is regarded as a characteristic structure of **3**, for our scaffold. We chose an oxyacetic acid group for the α-chain and attached it at the 7-position of benzofuran for the following reasons: (1) This derivatization at the 7-position is known to maintain the PGI_2 agonistic properties. (2) This derivatization can avoid ω-oxidation as a route of metabolic degradation of the α-chain. (3) It enables us to shorten synthetic steps. For comparison, we also attached the ω-side chain at the 3-position of benzofuran. A wide range of ω-side chains was screened from a series of functional groups, which we examined in the course of research on **3**. We began with the synthesis and evaluation of compound **8**, which have a sulfide ω-side chain, because some thromboxane antagonists have sulfide groups or sulfonamide groups (i.e., **6**) in their ω-chains.

In the following optimization, we introduced a hydroxyl group at the 2-position of compound **8** through the carbon chain and designed compound **9** to enhance the TXA_2 antagonism and/or the PGI_2 agonism. The hydroxyl group at the 2-position of benzofuran corresponds to that of the 11-position of PGI_2. The product in which the sulfide in compound **9** was oxidized was also screened in the optimization (Chart 2).

Compounds in Tables 1 and 2 were prepared as described in Schemes 1−8. The exploration of conventional methods for thiol synthesis was the first key objective of this project. First, we tried to synthesize thiols **11a−e** by alkali hydrolysis of the 2-alkylated isothioureas but only succeeded in the case of **11a**. Isothioureas for **11b−e** have undergone elimination reactions to produce styrenes under hydrolytic conditions. Primary thiols (**11f** and **11g**) were synthesized by hydrolysis of 2-mercaptobenzoxazole derivatives. Compounds **11b−d** were also obtained in poor yield by this method.

Nishio reported the single-step conversion from secondary and tertiary alcohols to the corresponding thiols by treatment with Lawesson's reagent.[17,18] The original procedure, reported by Nishio, worked well for **11a** but gave low yields for **11b−d**. We isolated styrene-type byproducts in the reaction mixtures of **11b−d**, which suggests that the thiols produced had undergone elimination reactions to produce styrenes. Moreover, the reaction rate under the original conditions (using DME)

Scheme 1[a]



[a] Reagents: (i) Lawesson's reagent, toluene−H_2O; (ii) Ph_3P, CBr_4; (iii) 2-mercaptobenzoxazole, K_2CO_3; (iv) NaOH; (v) Zn, AcOH; (vi) Ph_3P, NBS.

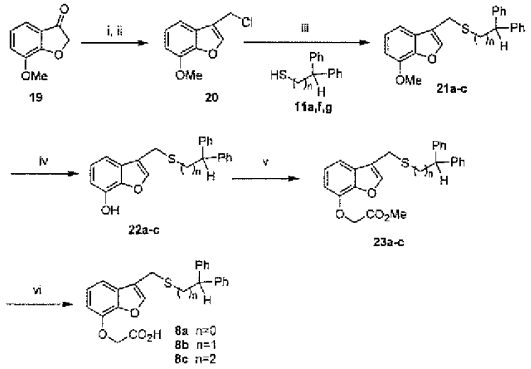
was fast, and the thiol conversion reaction at room temperature was complete within 15 min, which made the control of the reaction difficult. We later found that the addition of a small amount of the water would slow both the thiol conversion and the elimination reactions. By heating the corresponding alcohols with Lawesson's reagent in toluene with water (1 equiv for Lawesson's reagent), we succeeded in obtaining **11b−e** in good yield, and our condition also enabled the large-scale preparation of **11b**.

The second key objective of this project was the synthesis of 3-substituted 7-oxybenzofurans. The preparation of compounds **8a−c** is described in Scheme 2. We began the synthesis from 7-methoxy-2*H*-benzofuran-3-one (**19**), which was easily prepared by the procedure of Bryant.[19] Thus, compound **19** was treated with lithium chloromethylene to obtain compound **20** in 10% yield. The low yield occurred because the carbonyl group of **19** was easily enolized upon treatment with base, and compound **19** was subject to intermolecular aldol condensation. Compound **20** was coupled with thiols, and the methyl protection of the phenol group at the 7-position of **21a−c** was removed using *n*-PrSK. Compounds **22a−c** were treated with methyl bromoacetate to introduce the oxyacetic α-chain moiety. Methyl esters of **23a−c** were hydrolyzed to give **8a−c**.

The preparation of compounds **8d−f** and **8j** is described in Scheme 3. To avoid the aldol side reaction described in the synthesis of **8a−c**, we used the stable Wittig ylide for the preparation of compound **24**. Since this reagent was isolated as a neutral salt-free form, the reaction did not require any base, resulting in the isolation of compound **24** in 46% yield. By use of BBr_3, the methyl protection of phenol group at the 7-position of **24** was selectively removed. The methyl ester of **25** was reduced to the alcohol using $LiAlH_4$, and the resulting compound **26** was treated with methyl bromoacetate to selectively introduce the oxyacetic α-chain moiety at the 7-position of **26**. The alcohol **27** was treated with mesyl chloride, and the resulting mesylate **28** was coupled with thiols. Compounds **8d−f** and **8j**

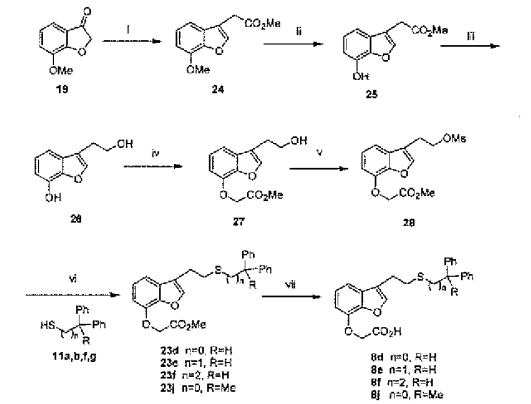
IPR2020-00770
United Therapeutics EX2007
Page 3196 of 7335

Scheme 2[a]



[a] Reagents: (i) *n*-BuLi, CH_2BrCl; (ii) *p*-toluenesulfonic acid, toluene; (iii) *t*-BuOK, thiols, DMF; (iv) *t*-BuOK, *n*-PrSH, DMF; (v) $BrCH_2CO_2Me$, K_2CO_3, DMF; (vi) NaOH.

Scheme 3[a]



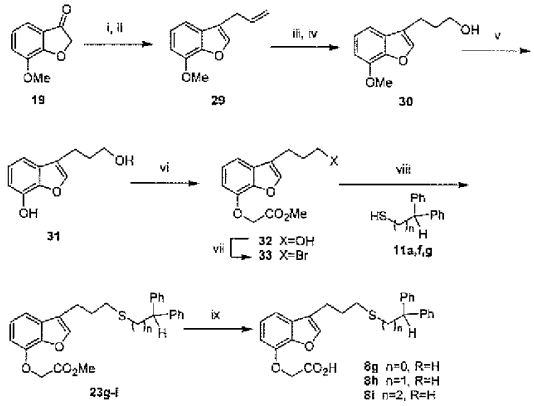
[a] Reagents: (i) Ph_3PCHCO_2Me, xylene; (ii) BBr_3, CH_2Cl_2; (iii) $LiAlH_4$, THF; (iv) $BrCH_2CO_2Me$, K_2CO_3, DMF; (v) methanesulfonyl chloride, Et_3N; (vi) *t*-BuOK, thiols, DMF; (vii) NaOH.

were obtained upon hydrolysis of the methyl ester groups of **23d−f** and **23j**.

The preparation of compounds **8g−i** is described in Scheme 4. To avoid aldol side reactions described in the synthesis of **8a−c**, we used an organocerium reagent, which was prepared in situ from $CeCl_3$ and allylmagnesium bromide.[20,21] Since the basicity of the allylcerium reagent was lower than that in Grignard reagent, compound **29** was obtained in 72% yield, including the dehydration step. The alcohol group was introduced using a hydroboration procedure on **29**. After cleaving the methyl protection of the phenol group at the 7-position of **30** using BBr_3, the oxyacetic α-chain moiety was introduced selectively at the 7-position of **31** by treating with methyl bromoacetate. The alcohol group of **32** was converted to bromine using *N*-bromosuccinimde-Ph_3P, and the resulting compound **33** was coupled with thiols. Compounds **8g−i** were obtained by hydrolysis of the methyl ester groups of **23g−i**.

The preparation of compounds **9a−e** is described in Scheme 5. The 2-substituted benzofuran scaffold was synthesized from **34** using a Dieckmann condensation. The methyl ester of **35** was selectively reduced to the

Scheme 4[a]



[a] Reagents: (i) allylmagnesium bromide, $CeCl_3$, THF; (ii) *p*-toluenesulfonic acid, benzene; (iii) BH_3-Me_2S, THF; (iv) H_2O_2, NaOH; (v) BBr_3, CH_2Cl_2; (vi) $BrCH_2CO_2Me$, K_2CO_3, DMF; (vii) Ph_3P, *N*-bromosuccinimde; (viii) *t*-BuOK, thiols, DMF; (ix) NaOH.

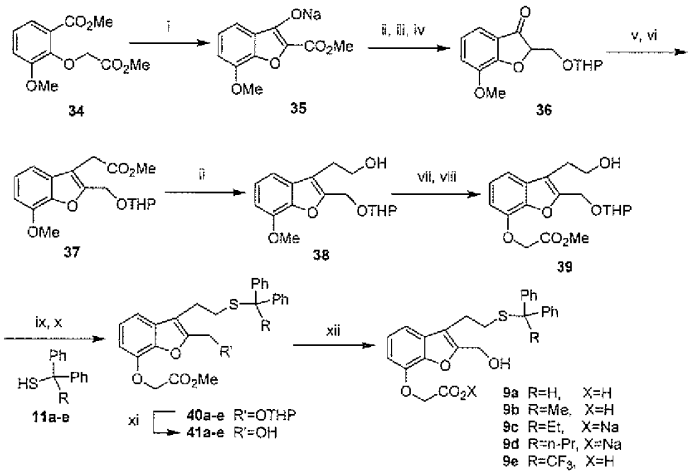
alcohol using $LiAlH_4$ because the carbonyl group of the 3-position was protected as sodium enolate. During the acidic workup, the carbonyl group of the 3-position was restored. After the protection of the primary alcohol at the 2-position of benzofuran by THP, compound **36** was obtained in 75% yield as a 1:1 mixture of diastereomers. In the synthesis of this series, we also tried a Wittig reaction using the stable ylides to avoid the aldol side reaction as described in the synthesis of **8d**, but the stable Wittig ylide did not react with **36** because of the steric interference by 2-position substitution. Then we performed Reformatski reaction. The reactivity of the Reformatski reagent with each diastereomer was similar, so we used the 1:1 diastereomers mixture of **36** for the scale-up synthesis. The dehydration of the Reformatski product was achieved by using Tf_2O−pyridine in toluene, and compound **37** was obtained in 78% yield in two steps. The methyl ester of compound **37** was reduced to the alcohol using $LiAlH_4$. After cleaving the methyl protection of the phenol group at the 7-position of **38** was cleaved using *n*-PrSK, the oxyacetic α-chain moiety was introduced selectively at this position by treating with methyl bromoacetate. The alcohol **39** was coupled with thiols **11a−e** via the mesylate. The THP group of **40a−e** was removed under mild acidic conditions, and compounds **9a−e** were obtained by hydrolysis of methyl ester groups of **41a−e**.

The preparation of compounds **7** and **9h−i** is described in Scheme 6. Compound **7** was obtained in 71% yield by treating **9b** with diethanolamine and crystallizing from ethanol. The sulfoxide analogue **9h** was synthesized by direct oxidation of **9b** with H_2O_2. The sulfone analogue **9i** was synthesized by oxidation of **41b** with *m*-CPBA followed by hydrolysis of the methyl ester.

The preparation of **9f** is described in Scheme 7. The 2-hydroxyethylbenzofuran scaffold was also synthesized from **35**, and the side chain at the 2-position of benzofuran was introduced using a Claisen rearrangement. First, the hydroxyl group of enolate **35** was allylated by treating with allyl bromide, and the allylic group then migrated to the 2-position upon heating to give **43**. The ester group of compound **43** underwent hydrolysis

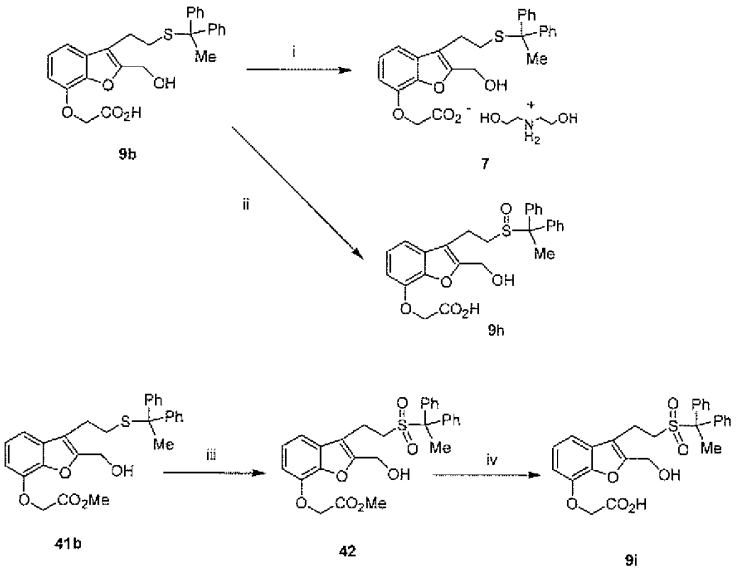
IPR2020-00770
United Therapeutics EX2007
Page 3197 of 7335

Scheme 5[a]



[a] Reagents: (i) NaH, toluene; (ii) $LiAlH_4$, THF; (iii) HCl (aq); (iv) 3,4-dihydro-2*H*-pyran, pyridinium *p*-toluenesulfonate; (v) Zn, $BrCH_2CO_2Me$; (vi) Tf_2O, pyridine; (vii) *t*-BuOK, *n*-PrSH, DMF; (viii) $BrCH_2CO_2Me$, K_2CO_3, DMF; (ix) methanesulfonyl chloride, Et_3N; (x) *t*-BuOK, thiols, DMF; (xi) pyridinium *p*-toluenesulfonate, MeOH; (xii) NaOH.

Scheme 6[a]



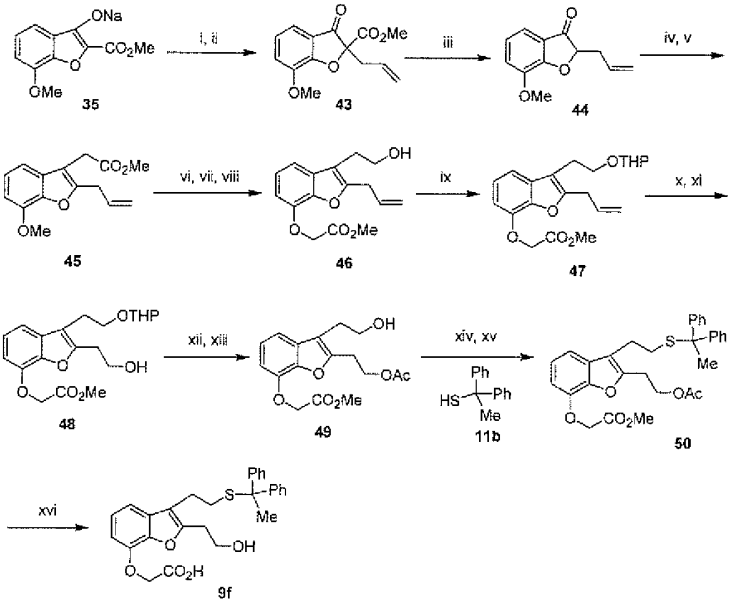
[a] Reagents: (i) diethanol amine, EtOH; (ii) H_2O_2, MeOH; (iii) *m*-CPBA; (iv) NaOH.

and decarboxylation under acidic condition. The side chain at the 3-position of benzofuran was introduced using Reformatski reaction, and the dehydration of the Reformatski product was performed using *p*-toluenesulfonic acid. After cleaving the methyl protection of the phenol group at the 7-position of **45** using BBr_3, the methyl ester was reduced to the alcohol by $LiAlH_4$. Then, the oxyacetic α-chain moiety was introduced selectively at the 7-position by treating with methyl bromoacetate. The primary alcohol of **46** was protected with THP, followed by cleavage of the olefin at the 2-position of **47** using OsO_4–$NaIO_4$. The alcohol of the 2-position side chain of compound **48** was protected with acetyl group, and the THP group was removed. After the coupling with thiol **11b** via the mesylate of **49**, compound **9f** was obtained by hydrolysis of the methyl ester and the acetyl group.

The preparation of **9g** is described in Scheme 8. We planned to introduce a hydroxyl group by using hydroboration of the olefin. After the reduction of the methyl ester on the side chain of compound **45** to alcohol **51** by $LiAlH_4$, the methyl protection of the phenol group at 7-position was removed using *n*-PrSK instead of BBr_3, which was accompanied by double bond isomerization of the olefin at the 2-position. Then, we changed the original plan by introducing the hydroxyl group via bromination at the allylic position. We isolated **52** after the introduction of the oxyacetic α-chain moiety at the

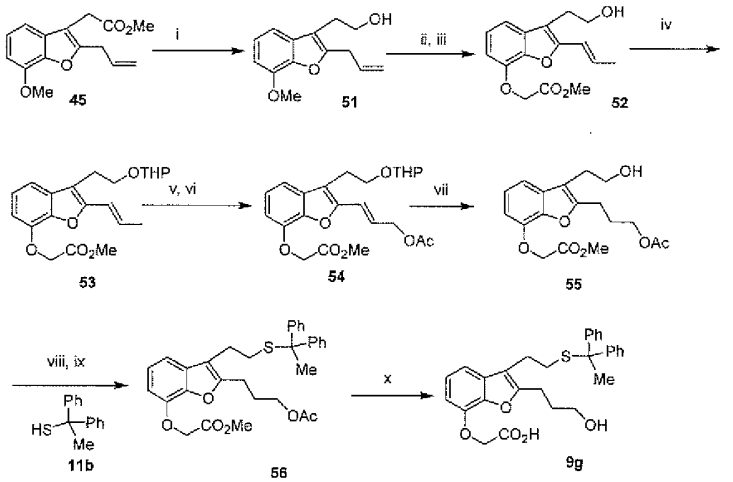
IPR2020-00770
United Therapeutics EX2007
Page 3198 of 7335

Scheme 7[a]



[a] Reagents: (i) allyl bromide; (ii) toluene, reflux; (iii) H_2SO_4, *t*-BuOH; (iv) Zn, $BrCH_2CO_2Me$; (v) *p*-toluenesulfonic acid; (vi) BBr_3, CH_2Cl_2; (vii) $LiAlH_4$, THF; (viii) $BrCH_2CO_2Me$, K_2CO_3, DMF; (ix) 3,4-dihydro-2*H*-pyran, *p*-toluenesulfonic acid; (x) OsO_4, $NaIO_4$; (xi) $NaBH_4$, THF; (xii) Ac_2O, pyridine; (xiii) HCl, MeOH; (xiv) methanesulfonyl chloride, Et_3N; (xv) *t*-BuOK, **11b**, DMF; (xvi) NaOH.

Scheme 8[a]



[a] Reagents: (i) $LiAlH_4$, THF; (ii) *t*-BuOK, *n*-PrSH, DMF; (iii) $BrCH_2CO_2Me$, K_2CO_3, DMF; (iv) 3,4-dihydro-2*H*-pyran, pyridinium *p*-toluenesulfonate; (v) *N*-bromosuccinimide, AIBN; (vi) AcOK, DMF; (vii) H_2, 10% Pd/C, MeOH; (viii) methanesulfonyl chloride, Et_3N; (ix) NaH, **11b**, DMF; (x) NaOH.

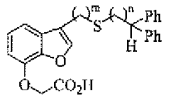
7-position by treating with methyl bromoacetate. After THP protection of the primary alcohol on the side chain, the allylic position on the side chain of **53** was brominated by *N*-bromosuccinimide and compound **54** was obtained by treatment with potassium acetate. The double bond on the side chain was reduced by catalytic hydrogenation, which was accompanied by removal of the THP group. After coupling with thiol **11b** via mesylate of **55**, compound **9g** was obtained by hydrolysis of the methyl ester and the acetyl group.

Pharmacology

All compounds synthesized were evaluated as the sodium salt, diethanolamine salt, or free acid. Compounds synthesized were evaluated in terms of inhibition of aggregation in human platelet rich plasma (PRP) induced by the P2Y receptor agonist adenosine diphosphate (ADP) or by a stable TXA_2 agonist (U46619). To confirm the mechanistic profile of these compounds, we also performed receptor binding assays in the

IPR2020-00770
United Therapeutics EX2007
Page 3199 of 7335

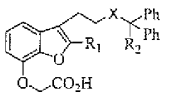
Table 1. In Vitro Activities of Benzofuran Sulfides



compd	m	n	antiaggregatory activity IC_{50} (μM)[a] ADP[b]	antiaggregatory activity IC_{50} (μM)[a] U46619[c]	receptor affinty K_i (μM) IP	receptor affinty K_i (μM) TP
8a	1	0	>100	>100	4.7 ± 1.4	5.1 ± 0.4
8b	1	1	19.9 ± 6.4	17.3 ± 0.6	0.68 ± 0.07	2.5 ± 0.1
8c	1	2	12.8 ± 3.2	10.0 ± 3.6	0.58 ± 0.02	3.1 ± 0.2
8d	2	0	5.9 ± 1.8	0.56 ± 0.02	0.41 ± 0.05	0.31 ± 0.02
8e	2	1	0.73 ± 0.24	0.51 ± 0.01	0.08 ± 0.02	3.1 ± 0.2
8f	2	2	5.2 ± 1.4	5.4 ± 0.14	0.56 ± 0.09	>10
8g	3	0	1.9 ± 0.2	1.6 ± 0.1	0.27 ± 0.03	3.1 ± 0.3
8h	3	1	1.7 ± 0.3	1.4 ± 0.2	0.40 ± 0.07	>15
8i	3	2	>100	>100	2.9 ± 0.5	>15

[a] IC_{50} represents the concentration that inhibits induced aggregation by 50%. [b] Inhibition of platelet aggregation induced by ADP (5 μM) in human platelet rich plasma. [c] Inhibition of platelet aggregation induced by U46619 (2μM) in human platelet rich plasma.

Table 2. In Vitro Activities of 2-Substituted Benzofuran Sulfides



compd	R_1	R_2	X	antiaggregatory activity IC_{50} (μM)[a] ADP[b]	antiaggregatory activity IC_{50} (μM)[a] U46619[c]	receptor affinty K_i (μM) IP	receptor affinty K_i (μM) TP
8d	H	H	S	5.9 ± 1.8	0.56 ± 0.02	0.41 ± 0.05	0.31 ± 0.02
8j	H	Me	S	8.1 ± 1.1	0.58 ± 0.03	0.57 ± 0.07	0.026 ± 0.001
9a	CH_2OH	H	S	3.3 ± 0.6	0.46 ± 0.08	0.75 ± 0.07	0.088 ± 0.012
9b	CH_2OH	Me	S	2.2 ± 0.4	0.17 ± 0.01	0.53 ± 0.07	0.0045 ± 0.0002
9c[d]	CH_2OH	Et	S	56 ± 8	3.8 ± 0.8	3.40 ± 0.15	0.180 ± 0.01
9d[d]	CH_2OH	*n*-Pr	S	>100	56 ± 2	>2.3	>5.9
9e	CH_2OH	CF_3	S	1.5 ± 0.2	0.52 ± 0.01	0.76 ± 0.19	0.150 ± 0.04
9f	$(CH_2)_2OH$	Me	S	0.71 ± 0.07	0.54 ± 0.01	0.21 ± 0.01	0.078 ± 0.008
9g	$(CH_2)_3OH$	Me	S	9.0 ± 0.7	2.9 ± 0.2	5.80 ± 0.09	0.072 ± 0.003
9h	CH_2OH	Me	SO	7.9 ± 1.7	1.7 ± 0.1	>10	0.051 ± 0.012
9i	CH_2OH	Me	SO_2	3.0 ± 0.8	0.31 ± 0.09	1.90 ± 0.22	0.0043 ± 0.0004

[a] IC_{50} represents the concentration that inhibits induced aggregation by 50%. [b] Inhibition of platelet aggregation induced by ADP (5 μM) in human platelet rich plasma. [c] Inhibition of platelet aggregation induced by U46619 (2 μM) in human platelet rich plasma. [d] This compound was provided as sodium salt.

human platelet membrane fraction. These receptor binding assays were carried out by using [^{3}H]-SQ-29548 (a selective TXA_2 receptor (TP) antagonist) and [^{3}H]-APS314d sodium salt (a selective PGI_2 receptor (IP) agonist), which is one of the component of **3**. Scatchard analysis of binding of [^{3}H]-SQ-29548 revealed a single binding site (K_d = 10.2 ± 0.51 nM, B_{max} = 5.89 ± 0.62 nM/mg protein). [^{3}H]-APS314d sodium salt also had one binding site (K_d = 14.3 ± 0.51 nM, B_{max} = 6.08 ± 0.60 nM/mg protein).

Results and Discussion

We screened a wide range of ω-side chain functionality based on our work with **3**. We identified lead compound **8e**, which contains sulfide in its ω-side chain. The sulfide side chain in conjunction with the benzofuran scaffold results in a PGI_2 receptor agonist. To probe the width and depth of the ω-side chain binding pocket, various lengths of carbon chains were tested (Table 1).

In this series, compound **8e** possesses the lowest inhibitory potency of ADP-induced platelet aggregation, which was derived from its agonism at the PGI_2 receptor. Compound **8d** possesses the second lowest inhibitory potency of U46619-induced platelet aggregation, which was derived from its antagonism at the TXA_2 receptor and its agonism at the PGI_2 receptor. Agonism at PGI_2 receptor proved to be tolerated on the length of the side chain, and compounds **8b**−**h** showed inhibitory potency (induced by ADP). On the other hand, TXA_2 receptor antagonism is very sensitive to the length of the side chain. Only compound **8d** shows significant TXA_2 antagonistic property (K_i = 0.31 μM) (Table 1).

Compound **8j**, which has a diphenylethyl sulfide group at the end of its side chain, and compound **9a**, which has a hydroxymethyl group at the 2-position of benzofuran, also display TXA_2 receptor antagonistic and PGI_2 receptor agonistic properties (Table 2). This is evidence of the utility of terminal sulfide group on the ω-side chain in the search for dual prostanoids.

We investigated the influence of alkyl substitution groups at the end of the side chain on compound **9a**. The methyl analogue **9b**, ethyl analogue **9c**, *n*-propyl analogue **9d**, and trifluoromethyl analogue **9e** were synthesized. Compound **9b** shows excellent potency as both a PGI_2 receptor agonist and a TXA_2 receptor

IPR2020-00770
United Therapeutics EX2007
Page 3200 of 7335

Table 3. Solubility of Compound **9b** with Diethanolamine Salt and Sodium Salt

salt form of **9b**	solubility (mg/mL) in distilled H_2O	saline	5% xylitol
diethanolamine salt (**7**)	>30	<0.5[a]	10
sodium salt	10	<0.5	1

[a] The compound was precipitated as a sodium salt.

antagonist. Other compounds were not as potent as **9b** at these receptors. Compound **9b** is the best dual prostanoid in this series.

Next we checked the influence of carbon chain length of the hydroxymethyl group attached to the 2-position on the benzofuran ring, which was designed to correspond to the 11-position hydroxyl group of PGI_2. Compound **8j**, which lacks the hydroxymethyl group, has almost the same agonist potency as compound **9b** at the PGI_2 receptor, but it is less potent as a TXA_2 receptor antagonist. In contrast, compound **9f**, which bears a hydroxyethyl group instead of hydroxymethyl, is more potent than compound **9b** as a PGI_2 receptor agonist but is also less potent as a TXA_2 receptor antagonist. The hydroxypropyl-bearing compound **9g** is less potent in both properties.

We also tested oxidized forms of the sulfide in compound **9b**. The sulfoxide analogue **9h** and the sulfone analogue **9i** were synthesized. Compound **9h** completely loses efficacy at the PGI_2 receptor and is a pure TXA_2 receptor antagonist. Compound **9i** has almost the same potency as compound **9b** as a TXA_2 receptor antagonist, but its potency as a PGI_2 receptor agonist is less than that of compound **9b**.

In the next study, we examined the pharmacological profile of compound **9b** in terms of its antiplatelet effects. Compound **9b** is a novel compound having potent TXA_2 receptor antagonistic activity together with a moderate PGI_2 receptor agonist activity. In fact, compound **9b** shows 117-fold higher affinity compared to TP receptor than to IP receptor, as evidenced by the K_d values determined in binding assays using human platelet membrane.

To eliminate the effect of DMSO in pharmacological experiments, we made the sodium salt and the diethanolamine salt and compared the solubility of these salts. (Table 3). Both salts dissolve well in distilled water. Compound **9b** having two aromatic rings at the end of the side chain, however, is highly lipophilic, so sodium salt does not dissolve well in saline and 5% xylitol. Otherwise, the diethanolamine salt of compound **9b** (**7**), which could be easily crystallized from ethanol, showed excellent solubility in the 5% xylitol. In saline, neither salt dissolved more than 0.5 mg/mL, since the diethanolamine salt turned into the sodium salt. From these results, we found out that compound **7** with 5% xylitol is the practical formula for pharmacological experiments.

The TXA_2 receptor antagonistic and PGI_2 receptor agonistic activities of compound **7** were examined in in vitro platelet aggregation (Table 4). Compound **7** exhibited inhibitory effects on the ADP and U46619-induced aggregation. The IC_{50} value of inhibitory effects on the ADP-induced aggregation was about 18-fold less potent than that on the U46619-induced aggregation. A similar tendency was observed with the TXA_2 receptor

Table 4. Effects of Compounds **7**, **3**, **4**, and SQ-29548 on in Vitro Platelet Aggregation in Human PRP[a]

aggregating agent	IC_{50} (nM) **7**	**3**	**4**	SQ-29548
U46619	120 ± 30	7.6 ± 0.7	170 ± 11	21 ± 3
ADP	2200 ± 320	5.7 ± 1.0	170 ± 3	>10000

[a] The platelet aggregation was induced by U46619 (4 μM) or by ADP (5 μM). Values are the mean ± SE of three to four determinations.

antagonist SQ-29548. On the other hand, the IC_{50} value of inhibitory effects by the selective PGI_2 receptor agonists **3** and compound **4** were almost the same on both ADP and U46619 induced platelet aggregation. These results are consistent with the fact that compound **7** has PGI_2 receptor agonistic activity in addition to the TXA_2 receptor antagonistic activity. This is also supported by the evidence that these results, together with the results of binding assay, indicate that the PGI_2 receptor agonistic activity of compound **7** is relatively weaker than its TXA_2 receptor antagonistic activity.

To confirm the antithrombotic character of compound **7**, we tried ex vivo platelet aggregation experiment by monitoring blood pressure and heart rate. The inhibitory effects observed with cynomolgus monkey PRP were IC_{50} = 3.7 ± 1.5 μM (induced by 5 μM of ADP) and IC_{50} = 0.14 ± 0.20 μM (induced by 600 μM of arachidonic acid). Since these data were quite similar to those observed with human PRP, the ex vivo experiment was carried out in monkeys (Figure 1). In the ex vivo experiment, the arachidonic acid induced aggregation was completely inhibited by the infusion of compound **7** even at the lowest dose examined (3 $\mu g\ kg^{-1}\ min^{-1}$). Infusion of **7** also caused dose-dependent inhibitions of the ADP-induced platelet aggregation, which was completely inhibited at the highest dose examined (30 $\mu g\ kg^{-1}\ min^{-1}$). In the similar manner, the IP receptor agonist **4** showed dose-dependent inhibition of ADP-induced platelet aggregation but did not show clear inhibition of arachidonic acid induced aggregation. Furthermore, compound **4** showed a dose-dependent decrease in blood pressure in the examined dose range, and the decrease was accompanied by an increase in heart rate. The antiplatelet activity of compound **4** is linked to its potent vasodilation. On the other hand, compound **7** does not show any significant change in blood pressure and heart rate even at the highest dose examined (30 $\mu g\ kg^{-1}\ min^{-1}$). These results suggest that the antiplatelet activity of compound **7** is not related to vasodilation.

In conclusion, a variety of benzofuran-7-oxyacetic acid analogues with many kinds of 2- and 3-position side chains were prepared by versatile synthetic routes, which allow large-scale preparation. Among the benzofuran analogues synthesized, we found the first dual-acting benzofuran **7** possessing a potent TXA_2 antagonism and a moderate PGI_2 agonism. The TP receptor antagonistic and IP receptor agonistic activities of compound **7** are also demonstrated in in vitro platelet aggregation induced by various platelet stimulating agents. The ex vivo experiment of compound **7** illustrated the beneficial properties of PGI_2 stable mimetics in terms of avoiding hypotensive side effects. Remarkably, compound **7** was found to be a promising

IPR2020-00770
United Therapeutics EX2007
Page 3201 of 7335

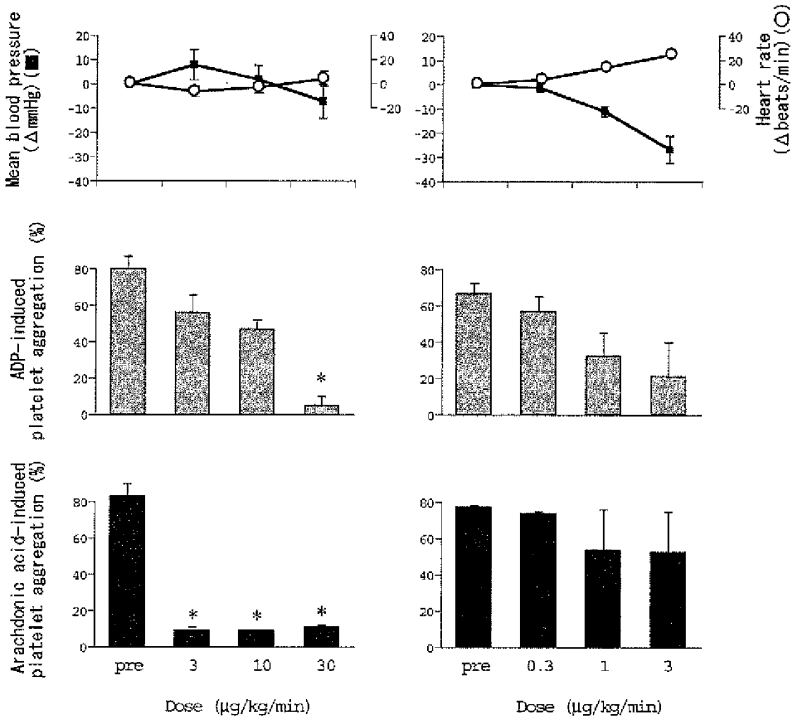


Figure 1. Effects of compound **7** (left) and compound **4** (right) on blood pressure, heart rate, and ex vivo platelet aggregation in monkey. Drugs were infused for 30 min at each of the doses in a dose-escalation manner. Platelet aggregation was induced by ADP (10 μM) or by arachidonic acid (600 μM). Data are expressed as the mean ± SE of three to four determinations: (*) significantly different from the vehicle group ($p < 0.01$).

candidate as novel medicine in antithrombotic and cardiovascular fields. Further experimental evaluations are now in progress on pharmacological properties.

Experimental Section

All of the reagents and solvents used were reagent grade or were purified by standard methods before use. All melting points were obtained with Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were measured on a JASCO FT/IR-410 infrared spectrophotometer. ^{1}H NMR spectra were recorded with Varian Gemini-2000 spectrometer (300 MHz) with tetramethylsilane as an internal standard. Low mass spectra (MS) or high-resolution mass spectra (HR-MS) were obtained with a JEOL JMS-DX303 mass spectrometer. The fast atom bombardment mass spectra (FAB-MS) were obtained by using glycerol as the matrix. Optical rotations were determined at the sodium D line using a HORIBA high-sensitivity polarimeter. Elemental analysis was performed by Toray Research Center. Thin-layer chromatography was performed on precoated TLC plates (silica gel 60 F-254, layer thickness of 0.25 mm, or DIOL F-254s) manufactured by E. Merck. Silica gel column chromatography was performed on silica gel 60 (0.063−0.200 mm) manufactured by E. Merck. Synthetic reagents were purchased from Aldrich (Milwaukee, WI), Kanto Kagaku Co. (Tokyo, Japan), TCI (Tokyo, Japan), and Sigma Chemical Co. (St. Louis, MO). Anhydrous tetrahydrofuran, methanol, dichloromethane, dimethylformamide, and pyridine were purchased from Kanto Kagaku Co. (Tokyo, Japan). The active isomer of beraprost, [^{3}H]APS-314d sodium, and [^{3}H]SQ-29548 were synthesized at Daiichi Pure Chemicals (Tokyo, Japan). SQ-29548 and U46619 were purchased from Cayman Chemical (MI), ADP from Sigma (MO), 3.8% sodium citrate was purchased from Yamanouchi Pharmaceutical (Tokyo, Japan), and a low molecular weight heparin sodium dalteparin was purchased from Kissei Pharmaceutical (Nagano, Japan).

In general, reactions were carried out in dry solvents under an argon atmosphere unless otherwise mentioned. All reactions that required anhydrous conditions were performed under argon or nitrogen, and all glassware was either oven-dried or flame-dried before use.

[3-[2-(1,1-Diphenylethylsulfanyl)ethyl]-2-hydroxymethylbenzofuran-7-yloxy]acetic Acid Diethanolamine Salt (7). To a stirred solution of **9b** (886 mg, 1.92 mmol) in EtOH (10 mL) was added diethanolamine (230 mg, 2.19 mmol) in EtOH (3 mL), which was stood at room temperature. The resulting crystals were collected and were washed with small amount of cold EtOH to afford **7** (776 mg, 71%). Colorless plates, mp 181.5 °C; ^{1}H NMR (D_2O) δ 1.95 (3H, s), 2.61 (4H, m), 3.36 (4H, bs), 4.01 (4H, bs), 4.61 (2H, s), 4.71 (2H, s), 6.79 (2H, m), 7.04 (1H, m), 7.18 (6H, bs), 7.36 (4H, bs). Anal. ($C_{31}H_{37}NO_7S$) C, H, N, S.

General Procedure for Hydrolysis of Methyl Ester. [3-Benzhydrylsulfanylmethylbenzofuran-7-yloxy]acetic Acid (8a). To a stirred solution of **23a** (73 mg, 0.17 mmol) in MeOH (3.0 mL) was added 1.0 N NaOH (aq) (0.010 mL, 0.49 mmol) and stirred at room temperature for 1 h. The reaction mixture was poured into 1 N HCl (aq) and was extracted with AcOEt. The organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent gave an oily residue, which was recrystallized from AcOEt/*n*-hexane to afford **8a** (70 mg, 99%). White powder, mp 135.5−137 °C; ^{1}H NMR ($CDCl_3$) δ 3.64 (2H, d, J = 1.0 Hz), 4.92 (2H, s), 5.00 (1H, s), 6.83 (1H, d, J = 6.0 Hz), 7.14−7.39 (13H, m); IR (KBr) 1742 cm^{-1} (COOH); LR-MS (EI) 404 (M^+). Anal. ($C_{24}H_{20}O_4S$) C, H, N, S.

IPR2020-00770
United Therapeutics EX2007
Page 3202 of 7335

[3-(2,2-Diphenylethylsulfanylmethyl)benzofuran-7-yloxy]acetic Acid (8b). Compound **8b** (70%) was prepared from **23b**. White powder, mp 91.0−93.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.13 (2H, d, J = 8.0 Hz), 3.65 (2H, s), 4.11 (1H, t, J = 8.0 Hz), 4.92 (2H, s), 6.83 (1H, d, J = 8.0 Hz), 7.13−7.31 (13H, m); IR (KBr) 1738 cm^{-1} (COOH); LR-MS (EI) 418 (M^+). Anal. ($C_{25}H_{22}O_4S$) C, H, N, S.

[3-(3,3-Diphenylpropylsulfanylmethyl)benzofuran-7-yloxy]acetic Acid (8c). Compound **8c** (96%) was prepared from **23c**. White powder, mp 154.5−155.5 °C; ^{1}H NMR (DMSO-d_6) δ 2.15−2.35 (4H, m), 3.82 (2H, s), 4.02 (1H, t, J = 6.0 Hz), 4.85 (2H, s), 6.84 (1H, d, J = 8.0 Hz), 7.10−7.30 (13H, m), 7.70 (1H, s); IR (KBr) 1748 cm^{-1} (COOH); LR-MS (EI) 432 (M^+). Anal. ($C_{26}H_{24}O_4S$) C, H, N, S.

[3-(2-Benzhydrylsulfanylethyl)benzofuran-7-yloxy]acetic Acid (8d). Compound **8d** (97%) was prepared from **23d**. Colorless prisms, mp 139−141 °C; ^{1}H NMR ($CDCl_3$) δ 2.57 (2H, t, J = 8.0 Hz), 2.88 (2H, t, J = 8.0 Hz), 4.90 (2H, s), 5.17 (1H, s), 6.78 (1H, dd, J = 1.0, 8.0 Hz), 6.97 (1H, dd, J = 1.0, 8.0 Hz), 7.09 (1H, t, J = 8.0 Hz), 7.21−7.41 (11H, m); IR (KBr) 1738 cm^{-1} (COOH); LR-MS (EI) 418 (M^+). Anal. ($C_{25}H_{22}O_4S$) C, H, N, S.

{3-[2-(2,2-Diphenylethylsulfanyl)ethyl]benzofuran-7-yloxy}acetic Acid (8e). Compound **8e** (78%) was prepared from **23e**. Colorless prisms, mp 116−118 °C; ^{1}H NMR ($CDCl_3$) δ 2.74−2.79 (2H, m), 2.87−2.91 (2H, m), 3.24 (2H, d, J = 8.0 Hz), 4.16 (1H, t, J = 8.0 Hz), 4.91 (2H, s), 6.82 (1H, dd, J = 2.0, 7.0 Hz), 7.12−7.32 (12H, m), 7.40 (1H, m); IR (KBr) 1744 cm^{-1} (COOH); LR-MS (EI) 432 (M^+). Anal. ($C_{26}H_{24}O_4S$) C, H, N, S.

{3-[2-(3,3-Diphenylpropylsulfanylmethyl)ethyl]-benzofuran-7-yloxy}acetic Acid (8f). Compound **8f** (97%) was prepared from **23f**. White powder, mp 61−62 °C; ^{1}H NMR ($CDCl_3$) δ 2.29−2.36 (2H, m), 2.49 (2H, dd, J = 7.0, 9.0 Hz), 2.78−2.89 (4H, m), 4.07 (1H, t, J = 8.0 Hz), 4.91 (2H, s), 6.82 (1H, dd, J = 2.0, 7.0 Hz), 7.11−7.30 (12H, m), 7.44 (1H, m); IR (KBr) 1734 cm^{-1} (COOH); LR-MS (EI) 446 (M^+). Anal. ($C_{27}H_{26}O_4S$) C, H, N, S.

[3-(3-Benzhydrylsulfanylpropyl)benzofuran-7-yloxy]-acetic Acid (8g). Compound **8g** (85%) was prepared from **23g**. Colorless needles, mp 116−118 °C; ^{1}H NMR ($CDCl_3$) δ 1.93 (2H, sept, J = 7.0 Hz), 2.46 (2H, t, J = 7.0 Hz), 2.72 (2H, t, J = 7.0 Hz), 4.91 (2H, s), 5.14 (1H, s), 6.81 (1H, d, J = 7.0 Hz), 7.10−7.42 (13H, m); IR (KBr) 1738 cm^{-1} (COOH); LR-MS (EI) 432 (M^+). Anal. ($C_{26}H_{24}O_4S$) C, H, N, S.

{3-[3-(2,2-Diphenylethylsulfanyl)propyl]benzofuran-7-yloxy}acetic Acid (8h). Compound **8h** (84%) was prepared from **23h**. Colorless needles, mp 94 °C; ^{1}H NMR ($CDCl_3$) δ 1.94 (2H, quint, J = 7.0 Hz), 2.51 (2H, t, J = 7.0 Hz), 2.72 (2H, t, J = 7.0 Hz), 3.21 (2H, d, J = 8.0 Hz), 4.17 (1H, t, J = 8.0 Hz), 4.92 (2H, s), 6.81 (1H, d, J = 7.0 Hz), 7.10−7.40 (13H, m); IR (KBr) 1740 cm^{-1} (COOH); LR-MS (EI) 446 (M^+). Anal. ($C_{27}H_{26}O_4S$) C, H, N, S.

{3-[3-(3,3-Diphenylpropylsulfanyl)propyl]benzofuran-7-yloxy}acetic Acid (8i). Compound **8i** (85%) was prepared from **23i**. Colorless prisms, mp 94 °C; ^{1}H NMR ($CDCl_3$) δ 1.92 (2H, quint, J = 7.0 Hz), 2.32 (2H, q, J = 7.0 Hz), 2.45 (2H, t, J = 7.0 Hz), 2.54 (2H, t, J = 7.0 Hz), 2.74 (2H, t, J = 7.0 Hz), 4.08 (1H, t, J = 8.0 Hz), 4.91 (2H, s), 6.81 (1H, d, J = 7.0 Hz), 7.10−7.40 (13H, m); IR (KBr) 1738 cm^{-1} (COOH); LR-MS (EI) 460 (M^+). Anal. ($C_{28}H_{28}O_4S$) C, H, N, S.

{3-[2-(1,1-Diphenylethylsulfanyl)ethyl]benzofuran-7-yloxy}acetic Acid (8j). Compound **8j** (70%) was prepared from **23j**. Colorless prisms, mp 117 °C; ^{1}H NMR ($CDCl_3$) δ 2.11 (3H, s), 2.60 (2H, m), 2.70 (2H, m), 4.89 (2H, s), 6.79 (1H, dd, J = 1.0, 7.5 Hz), 6.99 (1H, dd, J = 1.0, 7.5 Hz), 7.10 (1H, t, J = 7.5 Hz), 7.18−7.33 (6H, m), 7.38−7.43 (5H, m); IR (KBr) 1740 cm^{-1} (COOH); LR-MS (EI) 432 (M^+). Anal. ($C_{26}H_{24}O_4S$) C, H, N, S.

[3-(2-Benzhydrylsulfanylethyl)-2-hydroxymethylbenzofuran-7-yloxy]acetic Acid (9a). Compound **9a** (80%) was prepared from **41a**. Colorless plates, mp 144 °C; ^{1}H NMR ($CDCl_3$) δ 2.66 (2H, t, J = 7.0 Hz), 2.88 (2H, t, J = 7.0 Hz), 4.65 (2H, s), 4.85 (2H, s), 5.04 (1H, s), 6.77 (1H, d, J = 8.0 Hz), 6.92 (1H, d, J = 8.0 Hz), 7.07 (1H, t, J = 8.0 Hz), 7.19−7.36 (10H, m); IR (KBr) 1736 cm^{-1} (COOH); LR-MS (EI) 448 (M^+). Anal. ($C_{26}H_{24}O_5S$) C, H, N, S.

[3-[2-(1,1-Diphenylethylsulfanyl)ethyl]-2-hydroxymethylbenzofuran-7-yloxy]acetic Acid (9b). Compound **9b** (89%) was prepared from **41b**. Colorless plates, mp 140.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.00 (3H, s), 2.59 (2H, m), 2.67 (2H, m), 4.62 (2H, s), 4.85 (2H, s), 6.76 (1H, d, J = 7.0 Hz), 6.92 (1H, d, J = 7.0 Hz), 7.06 (1H, t, J = 7.0 Hz), 7.16−7.28 (6H, m), 7.33 (4H, m); IR (KBr) 1742 cm^{-1} (COOH); LR-MS (FAB, negative) 461 (M^+ − H). Anal. ($C_{27}H_{26}O_5S$) C, H, N, S.

[3-[2-(1,1-Diphenylpropylsulfanyl)ethyl]-2-hydroxymethylbenzofuran-7-yloxy]acetic Acid Sodium Salt (9c). Compound **9c** (83%) was prepared from **41c**. White powder, mp 193 °C; ^{1}H NMR (D_2O) δ 0.52 (3H, bs), 2.07 (2H, bs), 2.20 (2H, m), 2.35 (2H, m), 4.34 (2H, s), 4.46 (2H, s), 6.50 (1H, m), 6.58 (1H, m), 6.80 (1H, m), 6.97 (6H, bs), 7.10 (4H, bs); LR-MS (FAB, negative) 475 (M^+ − Na). Anal. ($C_{28}H_{27}O_5SNa$) C, H, N, S.

[3-[2-(1,1-Diphenylbutylsulfanyl)ethyl]-2-hydroxymethylbenzofuran-7-yloxy]acetic Acid Sodium Salt (9d). Compound **9d** (76%) was prepared from **41d**. Colorless needles, mp 178 °C; ^{1}H NMR (D_2O) δ 0.48 (3H, m), 0.93 (2H, m), 2.02 (2H, m), 2.22 (4H, m), 4.21 (2H, bs), 4.36 (2H, s), 6.35 (1H, s), 6.48 (1H, m), 6.67 (1H, m), 6.90 (6H, m), 7.09 (4H, m); LR-MS (FAB, positive) 513 (M^+ + H). Anal. ($C_{29}H_{29}O_5SNa$) C, H, N, S.

{2-Hydroxymethyl-3-[2-(2,2,2-trifluoro-1,1-diphenylethylsulfanyl)ethyl]benzofuran-7-yloxy}acetic Acid (9e). Compound **9e** (93%) was prepared from **41e**. Colorless prisms, mp 129−131 °C; ^{1}H NMR ($CDCl_3$) δ 2.61 (2H, m), 2.74 (2H, m), 4.64 (2H, s), 4.89 (2H, s), 6.77 (1H, dd, J = 0.8, 8.0 Hz), 6.83 (1H, dd, J = 0.8, 8.0 Hz), 7.06 (1H, t, J = 8.0 Hz), 7.24−7.29 (6H, m), 7.32−7.39 (4H, m); IR (KBr) 1738 cm^{-1} (COOH); LR-MS (EI) 516 (M^+). Anal. ($C_{27}H_{23}F_3O_5S$) C, H, N, S.

[3-[2-(1,1-Diphenylethylsulfanyl)-ethyl]-2-(2-hydroxyethyl)benzofuran-7-yloxy]acetic Acid (9f). Compound **9f** was prepared from **50** (87%). Colorless prisms, mp 129−131 ° C; ^{1}H NMR (CD_3OD) δ 2.01 (3H, s), 2.56 (2H, m), 2.69 (2H, m), 2.89 (2H, t, J = 6.9 Hz), 3.83 (2H, t, J = 6.9 Hz), 4.83 (2H, s), 6.74 (1H, dd, J = 7.8, 1.0 Hz), 6.81 (1H, dd, J = 7.8, 1.0 Hz), 7.01 (1H, t, J = 7.8 Hz), 7.15−7.40 (10H, m); IR (KBr) 1742 cm^{-1} (COOH); LR-MS (EI) 476 (M^+). Anal. ($C_{28}H_{23}O_5S$) C, H, N, S.

[3-[2-(1,1-Diphenylethylsulfanyl)ethyl]-2-(3-hydroxypropyl)benzofuran-7-yloxy]acetic Acid (9g). Compound **9g** was prepared from **55** (84%). Colorless prisms, mp 152−153 ° C; ^{1}H NMR (CD_3OD) δ 1.90 (2H, m), 2.00 (3H, s), 2.54 (2H, m), 2.66 (2H, m), 2.74 (2H, t, J = 7.5 Hz), 3.57 (2H, t, J = 6.4 Hz), 4.84 (2H, s), 6.73 (1H, dd, J = 7.8, 1.0 Hz), 6.81 (1H, dd, J = 7.8, 1.0 Hz), 7.01 (1H, t, J = 7.8 Hz), 7.15−7.39 (10H, m); IR (KBr) 1748 cm^{-1} (COOH); LR-MS (EI) 490 (M^+). Anal. ($C_{29}H_{30}O_5S$) C, H, N, S.

{3-[2-(Diphenylethanesulfonyl)ethyl]-2-hydroxymethylbenzofuran-7-yloxy}acetic Acid (9i). Compound **9i** (84%) was prepared from **42**. Colorless prisms, mp 156−158 °C; ^{1}H NMR (CD_3OD) δ 2.20 (3H, s), 2.96−3.10 (4H, m), 4.60 (2H, s), 4.83 (2H, s), 6.80 (1H, dd, J = 0.8, 8.0 Hz), 6.86 (1H, dd, J = 0.8, 8.0 Hz), 7.07 (1H, t, J = 8.0 Hz), 7.33−7.42 (6H, m), 7.55−7.64 (4H, m); IR (KBr) 1740 cm^{-1} (COOH); LR-MS (EI) 494 (M^+). Anal. ($C_{27}H_{26}O_7S$) C, H, N, S.

{3-[2-(Diphenylethanesulfinyl)ethyl]-2-hydroxymethylbenzofuran-7-yloxy}acetic Acid (9h). To a stirred solution of **9b** (197 mg, 0.43 mmol) in MeOH (3 mL) was added 30% H_2O_2 (0.5 mL), and the reaction mixture was stirred at room temperature for 4.5 h. The reaction mixture was poured into 1 N HCl (aq) and was extracted with AcOEt. The organic layer was sequentially washed with water and brine and dried over $MgSO_4$. Removal of the solvent gave an oily residue, which was recrystallized from AcOEt/*n*-hexane to afford **9h** (164 mg, 81%). Colorless prisms, mp 131−132 °C; ^{1}H NMR (CD_3OD) δ 1.94 (3H, s), 2.51 (2H, t, J = 7.4 Hz), 3.00−3.10 (2H, m), 4.62 (2H, s), 4.86 (2H, s), 6.82 (1H, dd, J = 0.8, 7.9 Hz), 6.83 (1H, dd, J = 0.8, 7.9 Hz), 7.04 (1H, t, J = 7.9 Hz), 7.20−7.42

IPR2020-00770
United Therapeutics EX2007
Page 3203 of 7335

(10H, m); IR (KBr) 1745 cm^{-1} (COOH); LR-MS (EI) 478 (M^+). Anal. ($C_{27}H_{26}O_6S$) C, H, N, S.

1,1-Diphenylpropane-1-ol (10c). To a stirred solution of benzophenone (3.50 g, 19.2 mmol) in THF (30 mL) was added 1.0 M EtMgBr in THF (24.5 mL, 24.5 mmol), and the mixture was stirred at 0 °C for 5.0 h. The reaction mixture was poured into 5% citric acid (aq) and was extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and was dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/4) to afford **10c** (635 mg, 16%). Colorless oil; ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, J = 7.5 Hz), 2.08 (1H, s), 2.32 (2H, q, J = 7.5 Hz), 7.19−7.34 (6H, m), 7.39−7.44 (4H, m); LR-MS (EI) 212 (M^+).

1,1-Diphenylbutane-1-ol (10d). By the procedure used in **10c**, compound **10d** (80%) was prepared from benzophenone and *n*-PrMgBr. Colorless oil; ^1H NMR ($CDCl_3$) δ 0.93 (3H, t, J = 7.0 Hz), 1.30 (2H, m), 2.09 (1H, s), 2.26 (2H, m), 7.19−7.33 (6H, m), 7.39−7.43 (4H, m); LR-MS (EI) 226 (M^+).

2,2,2-Trifluoro-1,1-diphenylethanol (10e). By the procedure used in **10c**, compound **10e** (96%) was prepared from trifluoroacetophenone and PhMgBr. Colorless oil; ^1H NMR ($CDCl_3$) δ 2.87 (1H, s), 7.33−7.39 (6H, m), 7.46−7.53 (4H, m); LR-MS (EI) 252 (M^+).

General Procedure for Preparation of Thiols. 1,1-Diphenylethanthiol (11b). To solution of 1,1-diphenylethane-1-ol (50 g) and Lawesson's reagent (50 g) in toluene (1300 mL) was added water (6.5 mL), and the reaction mixture was stirred at 50 °C. Water (200 mL) was added, and the resulting mixture was cooled to room temperature. The organic layer was separated and sequentially washed with saturated $NaHCO_3$ (200 mL) and brine (200 mL). The organic layer was dried over Na_2SO_4 and evaporated. The resulting oil was purified by silica gel chromatography (eluent: *n*-hexane), which afforded **11b** (25.0 g, 46%). Colorless solid; ^1H NMR ($CDCl_3$) δ 2.16 (3H, s), 2.49 (1H, s), 7.20−7.34 (6H, m), 7.41−7.45 (4H, m); LR-MS (CI) 213 ($M^+ - H$).

Diphenylmethanethiol (11a). Compound **11a** (94%) was prepared from diphenylmethanol. Colorless oil; ^1H NMR ($CDCl_3$) δ 2.27 (1H, d, J = 5.0 Hz), 5.44 (1H, d, J = 5.0 Hz), 7.20−7.45 (10H, m); LR-MS (FAB) 200 (M^+), 199 ($M^+ - H$).

1,1-Diphenylpropane-1-thiol (11c). Compound **11c** (49%) was prepared from **10c**. Colorless oil; ^1H NMR ($CDCl_3$) δ 0.86 (3H, t, J = 7.0 Hz), 2.25 (1H, s), 2.51 (2H, q, J = 7.0 Hz), 7.19−7.40 (10H, m); LR-MS (EI) 228 (M^+).

1,1-Diphenylbutane-1-thiol (11d). Compound **11d** (44%) was prepared from **10d**. Colorless oil; ^1H NMR ($CDCl_3$) δ 0.91 (3H, t, J = 7.0 Hz), 1.24 (2H, m), 1.55 (1H, s), 2.42 (2H, m), 7.16−7.40 (10H, m); LR-MS (EI) 242 (M^+).

2,2,2-Trifluoro-1,1-diphenylethanol (11e). Compound **11e** (20%) was prepared from **10e**. Colorless oil; ^1H NMR ($CDCl_3$) δ 2.86 (1H, s), 7.30−7.39 (6H, m), 7.40−7.49 (4H, m); LR-MS (EI) 268 (M^+).

2,2-Diphenylethanethiol (11f). To a stirred solution of **15** (30 mg, 0.07 mmol) in AcOH (5 mL) was added zinc powder (5 mg, 0.08 mmol), and the reaction mixture was stirred at 90 °C for 1 h. The reaction mixture was filtered, and the solvent was removed under reduced pressure. The resulting oily residue was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/5) to afford **11f** (27 mg, 90%). Colorless oil; ^1H NMR ($CDCl_3$) δ 1.35 (1H, t, J = 8.0 Hz), 3.18 (2H, q, J = 8.0 Hz), 4.13 (1H, t, J = 8.0 Hz), 7.10−7.42 (10H, m); LR-MS (EI) 214 (M^+).

3,3-Diphenylpropane-1-thiol (11g). To a stirred solution of **18** (5.16 g, 15 mmol) in EtOH (50 mL) and H_2O (20 mL) was added NaOH (950 mg, 24 mmol), and the reaction mixture was refluxed for 5.5 h. The solvent was removed, and the residue was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/12) to afford **11g** (2.94 g, 86%). Colorless oil; ^1H NMR ($CDCl_3$) δ 2.28−2.51 (5H, m), 4.09 (1H, t, J = 8.0 Hz), 7.15−7.32 (10H, m); LR-MS (EI) 228 (M^+).

1-Bromo-2,2-diphenylethane (13). To a stirred solution of 2,2-diphenylethanol (**12**) (10.0 g, 50 mmol) in dichloromethane (200 mL) was added Ph_3P (16.0 g, 61 mmol) and CBr_4 (25 g, 75.6 mmol). After being stirred at room temperature for 4 h, the reaction mixture was sequentially washed with saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and evaporated. The resulting oil was distilled under reduced pressure to afford **13** (10.9 g, 83%). Colorless oil, bp 170−171 °C at 0.40 mmHg; ^1H NMR ($CDCl_3$) δ 3.87−4.00 (2H, m), 4.29−4.40 (1H, m), 7.00−7.50 (10H, m); LR-MS (EI) 260, 262 (M^+) (relative peak height ratio is 1:1).

2-(2,2-Diphenylethylsulfanyl)benzoxazole (14). To a stirred solution of **13** (2.03 g, 7.77 mmol) in DMF (15 mL) was added 2-mercaptobenzoxazole (1.31 g, 8.66 mmol) and K_2CO_3 (1.47 g, 10.6 mmol), and the reaction mixture was stirred at room temperature for 4 h. Saturated aqueous NH_4Cl (5 mL) was added to the reaction mixture and was extracted with AcOEt. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue that was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/50 to 1/20) to afford **14** (694 mg, 27%). Colorless prisms, mp 89.0−90.5 °C; ^1H NMR ($CDCl_3$) δ 3.95−4.05 (2H, m), 4.42−4.52 (1H, m), 7.00−7.70 (14H, m); LR-MS (EI) 331(M^+).

Di-(2,2-diphenylethyl) Disulfide (15). To a stirred solution of **14** (110 mg, 0.33 mmol) in EtOH (5 mL) and THF (1 mL) was added 1 N NaOH (1.0 mL), and the reaction mixture was stirred at 40 °C for 4 h. Saturated aqueous NH_4Cl (5 mL) was added to the reaction mixture and was extracted with AcOEt. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue that was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/25) to afford **15** (60 mg, 85%). Colorless oil; ^1H NMR ($CDCl_3$) δ 3.31 (4H, d, J = 8.0 Hz), 4.28 (2H, t, J = 8.0 Hz), 7.16−7.30 (20H, m); LR-MS (EI) 426 (M^+).

1-Bromo-3,3-diphenylpropane (17). To a stirred solution of 3,3-diphenylpropan-1-ol (**16**) (10.8 g, 48 mmol) and Ph_3P (15.2 g, 58 mmol) in THF (120 mL) was added *N*-bromosuccinimide (10.1 g, 57 mmol). After being stirred at 0 °C for 2 h, the reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (dichloromethane) to afford **17** (13.4 g, 96%). Colorless plates, mp 35−37 °C; ^1H NMR ($CDCl_3$) δ 2.58 (2H, q, J = 7.0 Hz), 3.32 (2H, t, J = 7.0 Hz), 4.20 (1H, t, J = 7.0 Hz), 7.15−7.34 (10H, m); LR-MS (EI) 274, 276 (M^+) (relative peak height ratio is 1:1).

2-(3,3-Diphenylpropylsulfanyl)benzoxazole (18). By the procedure used in **14**, compound **18** (90%) was prepared from **17**. Colorless plates, mp 91 °C; ^1H NMR ($CDCl_3$) δ 2.61 (2H, q, J = 7.0 Hz), 3.23 (2H, t, J = 7.0 Hz), 4.20 (1H, t, J = 7.0 Hz), 7.15−7.60 (14H, m); LR-MS (EI) 345 (M^+).

3-Chloromethyl-7-methoxybenzofuran (20). To a solution of 7-methoxy-2*H*-benzofuran-3-one (**19**) (7.13 g, 43.4 mmol) and bromochloromethane (11.3 mL) in THF (200 mL) was added *n*-BuLi (1.6 M in *n*-hexane) (80 mL, 128 mmol) at −78 °C, and the reaction mixture was stirred at −78 °C for 2 h. AcOH (7.3 mL) was added to the reaction mixture, and the solvent was removed. To the resulting oil was added toluene (100 mL) and *p*-toluenesulfonic acid monohydrate (20 mg), and the mixture was stirred at 50 °C for 2 h. The reaction mixture was sequentially washed with saturated $NaHCO_3$ and brine and was dried over Na_2SO_4 and evaporated. The resulting oil was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/8 then 1/4) to afford **20** (0.88 g, 10%). Colorless prisms, mp 43−44 °C; ^1H NMR ($CDCl_3$) δ 4.00 (3H, s), 4.72 (2H, d, J = 3.0 Hz), 6.80 (1H, d, J = 3.0 Hz), 6.87 (1H, d, J = 3.0 Hz), 7.11−7.27 (1H, m), 7.65 (1H, s); LR-MS (EI) 196 (M^+).

General Procedure for Coupling with Thiols. 3-Benzhydrylsulfanylmethyl-7-methoxybenzofuran (21a). To a solution of diphenylmethanethiol (**11a**) (121 mg, 0.604 mmol) in DMF (2.0 mL) was added *t*-BuOK (81 mg, 0.722 mmol) and **20** (118 mg, 0.600 mmol), and the reaction mixture was stirred at room temperature for 1 h. Saturated aqueous NH_4Cl was added to the reaction mixture and was extracted with AcOEt. The combined organic layer was sequentially washed with

IPR2020-00770
United Therapeutics EX2007
Page 3204 of 7335

water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue that was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/20) to afford **21a** (183 mg, 85%). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.63 (2H, s), 4.02 (3H, s), 5.00 (1H, s), 6.83 (1H, dd, J = 1.0, 8.0 Hz), 7.15−7.39 (13H, m); LR-MS (EI) 360 (M^+).

3-(2,2-Diphenylethylsulfanylmethyl)-7-methoxybenzofuran (21b). Compound **21b** (99%) was prepared from **20**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.12 (2H, d, J = 8.0 Hz), 3.65 (2H, s), 4.00 (3H, s), 4.11 (1H, t, J = 8.0 Hz), 6.82 (1H, d, J = 8.0 Hz), 7.13−7.29 (12H, m), 7.46 (1H, s); LR-MS (EI) 374 (M^+).

3-(3,3-Diphenylpropylsulfanylmethyl)-7-methoxybenzofuran (21c). Compound **21c** (62%) was prepared from **20**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.20−2.60 (4H, m), 3.74 (2H, s), 4.00 (3H, s), 3.90−4.20 (1H, m), 6.81 (1H, dd, J = 2.0, 8.0 Hz), 7.10−7.50 (12H, m), 7.47 (1H, s); LR-MS (EI) 388 (M^+).

General Procedure for Deprotection of Methyl on Phenolic Hydroxyl Group Using *n*-PrSH. 3-Benzhydrylsulfanylmethylbenzofuran-7-ol (22a). To a solution of **21a** (45 mg, 0.125 mmol) in DMF (3.0 mL) was added *t*-BuOK (47 mg, 0.42 mmol) and *n*-PrSH (0.20 mL), and the reaction mixture was stirred at 100 °C for 4 h. Saturated aqueous NH_4Cl was added to the reaction mixture and was extracted with AcOEt. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue that was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/5) to afford **22a** (26 mg, 60%). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.63 (2H, s), 5.02 (1H, s), 5.47 (1H, s), 6.85 (1H, dd, J = 1.0, 8.0 Hz), 7.15−7.39 (13H, m); LR-MS (EI) 346 (M^+).

3-(2,2-Diphenylethylsulfanylmethyl)benzofuran-7-ol (22b). Compound **22b** (98%) was prepared from **21b**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.13 (2H, d, J = 7.5 Hz), 3.65 (2H, d, J = 1.0 Hz), 4.12 (1H, t, J = 7.5 Hz), 5.26 (1H, s), 6.83−6.86 (1H, m), 7.11−7.30 (12H, m), 7.45 (1H, s); LR-MS (EI) 360 (M^+).

3-(3,3-Diphenylpropylsulfanylmethyl)benzofuran-7-ol (22c). Compound **22c** (89%) was prepared from **21c**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.10−2.60 (4H, m), 3.74 (2H, d, J = 1.0 Hz), 3.90−4.20 (1H, m), 5.60−6.20 (1H, s), 6.70−6.90 (1H, m), 6.90−7.40 (13H, m); LR-MS (EI) 374 (M^+).

General Procedure for Reaction with Methyl Bromoacetate. [3-Benzhydrylsulfanylmethylbenzofuran-7-yloxy]acetic Acid Methyl Ester (23a). To a solution of **22a** (67 mg, 0.19 mmol) in DMF (2.0 mL) was added methyl bromoacetate (0.18 mL) and K_2CO_3 (145 mg, 1.05 mmol), and the reaction mixture was stirred at room temperature for 1.5 h. Saturated aqueous NH_4Cl was added to the reaction mixture and was extracted with AcOEt. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue that was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/5) to afford **23a** (73 mg, 90%). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.63 (2H, d, J = 0.5 Hz), 3.82 (3H, s), 4.88 (2H, s), 5.00 (1H, s), 7.12−7.40 (14H, m); IR (neat) 1748 cm^{-1} (COOMe); LR-MS (EI) 418 (M^+).

[3-(2,2-Diphenylethylsulfanylmethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (23b). Compound **23b** (93%) was prepared from **22b**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 3.12 (2H, d, J = 7.5 Hz), 3.64 (2H, d, J = 1.0 Hz), 3.81 (3H, s), 4.11 (1H, t, J = 7.5 Hz), 4.88 (2H, s), 6.78 (1H, d, J = 7.0 Hz), 7.11−7.30 (12H, m), 7.47 (1H, s); IR (neat) 1760 cm^{-1} (COOMe); LR-MS (EI) 432 (M^+).

[3-(3,3-Diphenylpropylsulfanylmethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (23c). Compound **23c** (70%) was prepared from **22c**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.20−2.60 (4H, m), 3.78 (2H, d, J = 2.0 Hz), 3.80 (3H, s), 3.90−4.20 (1H, m), 4.86 (2H, s), 6.77 (1H, dd, J = 1.0, 7.5 Hz), 7.00−7.50 (13H, m); IR (neat) 1763 cm^{-1} (COOMe); LR-MS (EI) 446 (M^+).

[3-(2-Benzhydrylsulfanylethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (23d). By the procedure used in **21a**, compound **23d** (80%) was prepared from **28**. Colorless prisms, mp 94−95 °C; ^{1}H NMR ($CDCl_3$) δ 2.59−3.02 (4H, m), 3.79 (3H, s), 4.87 (2H, s), 5.17 (1H, s), 6.69−7.45 (14H, m); IR (KBr) 1763 cm^{-1} (COOMe); LR-MS (EI) 432 (M^+).

{3-[2-(2,2-Diphenylethylsulfanyl)ethyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (23e). By the procedure used in **21a**, compound **23e** (80%) was prepared from **28**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.73−2.80 (2H, m), 2.85−2.92 (2H, m), 3.24 (2H, d, J = 8.0 Hz), 3.80 (3H, s), 4.17 (1H, t, J = 8.0 Hz), 4.88 (2H, s), 6.76−6.79 (1H, m), 7.12−7.33 (12H, m), 7.40 (1H, m); IR (neat) 1736 cm^{-1} (COOMe); LR-MS (EI) 446 (M^+).

{3-[2-(3,3-Diphenylpropylsulfanylmethyl)ethyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (23f). By the procedure used in **21a**, compound **23f** (29%) was prepared from **28**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.30−2.36 (2H, m), 2.46−2.52 (2H, m), 2.76−2.89 (4H, m), 3.80 (3H, s), 4.08 (1H, t, J = 8.0 Hz), 4.87 (2H, s), 6.77 (1H, dd, J = 2.0, 7.0 Hz), 7.11−7.31 (12H, m), 7.44 (1H, m); IR (neat) 1742 cm^{-1} (COOMe); LR-MS (EI) 460 (M^+).

[3-(3-Benzhydrylsulfanylpropyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (23g). By the procedure used in **21a**, compound **23g** (89%) was prepared from **33**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.93 (2H, sept, J = 7.0 Hz), 2.46 (2H, t, J = 7.0 Hz), 2.72 (2H, t, J = 7.0 Hz), 3.82 (3H, s), 4.88 (2H, s), 5.13 (1H, s), 6.77 (1H, dd, J = 2.0, 6.0 Hz), 7.00−7.50 (13H, m); IR (neat) 1763 cm^{-1} (COOMe); LR-MS (EI) 446 (M^+).

{3-[3-(2,2-Diphenylethylsulfanyl)propyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (23h). By the procedure used in **21a**, compound **23h** (67%) was prepared from **33**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.94 (2H, quint, J = 7.0 Hz), 2.50 (2H, t, J = 7.0 Hz), 2.71 (2H, t, J = 7.0 Hz), 3.20 (2H, d, J = 8.0 Hz), 3.81 (3H, s), 4.15 (1H, t, J = 8.0 Hz), 4.89 (2H, s), 6.77 (1H, dd, J = 1.0, 7.0 Hz), 7.09−7.34 (13H, m); IR (neat) 1765 cm^{-1} (COOMe); LR-MS (EI) 460 (M^+).

{3-[3-(3,3-Diphenylpropylsulfanyl)propyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (23i). By the procedure used in **21a**, compound **23i** (53%) was prepared from **33**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.92 (2H, quint, J = 7.0 Hz), 2.31 (2H, q, J = 7.0 Hz), 2.45 (2H, t, J = 7.0 Hz), 2.54 (2H, t, J = 7.0 Hz), 2.74 (2H, t, J = 7.0 Hz), 3.81 (3H, s), 4.08 (1H, t, J = 8.0 Hz), 4.88 (2H, s), 6.77 (1H, d, J = 7.0 Hz), 7.05−7.35 (12H, m), 7.39 (1H, s); IR (neat) 174 cm^{-1} (COOMe); LR-MS (EI) 474 (M^+)

{3-[2-(1,1-Diphenylethylsulfanyl)ethyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (23j). By the procedure used in **21a**, compound **23j** (74%) was prepared from **28**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.07 (3H, s), 2.61 (2H, m), 2.70 (2H, m), 3.80 (3H, s), 4.87 (2H, s), 6.75 (1H, dd, J = 1.0, 8.0 Hz), 6.97 (1H, dd, J = 1.0, 8.0 Hz), 7.08 (1H, t, J = 8.0 Hz), 7.19−7.34 (6H, m), 7.38−7.43 (5H, m); IR (neat) 1765 cm^{-1} (COOMe); LR-MS (EI) 446 (M^+).

(7-Methoxybenzofuran-3-yl)acetic Acid Methyl Ester (24). To a solution of 7-mehtoxy-3(2*H*)-benzofuranone (**19**) (1.80 g, 11.0 mmol) in xylene (40 mL) was added $Ph_3PCHCOOMe$ (4.10 g, 12.3 mmol), and the mixture was stirred at 140 °C for 18 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/3) to afford **24** (1.11 g, 46%). Pale-yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.70 (2H, d, J = 1.0 Hz), 3.73 (3H, s), 4.01 (3H, s), 6.82 (1H, dd, J = 2.0, 7.0 Hz), 7.15 (1H, dd, J = 2.0, 7.0 Hz), 7.19 (1H, t, J = 7.0 Hz), 7.64 (1H, s); IR (KBr) 1742 cm^{-1} (COOMe); LR-MS (EI) 220 (M^+).

(7-Hydroxybenzofuran-3-yl)acetic Acid Methyl Ester (25). To a solution of **24** (5.35 g, 24.3 mmol) in dichloromethane (100 mL) was added 1.0 M BBr_3 in dichloromethane (55 mL, 55 mmol) at −78 °C, and the mixture was stirred at 0 °C for 90 min. The reaction mixture was poured into water and was extracted with dichloromethane. The combined organic layer was sequentially washed with water and brine and dried over $MgSO_4$. Removal of the solvent afforded **25** (5.00 g, 99%). Pale-brown prisms, mp 48−50 °C; ^{1}H NMR ($CDCl_3$) δ 3.71 (2H, d, J = 1.0 Hz), 3.74 (3H, s), 5.30 (1H, bs), 6.82−6.88 (1H, m), 7.10−7.17 (2H, m), 7.64 (1H, t, J = 1.0 Hz); IR (KBr) 1696 cm^{-1} (COOMe); LR-MS (EI) 206 (M^+).

IPR2020-00770
United Therapeutics EX2007
Page 3205 of 7335

3-(2-Hydroxyethyl)benzofuran-7-ol (26). To a solution of **25** (8.11 g, 39 mmol) in THF (600 mL) was added $LiAlH_4$ (1.53 g, 40 mmol) at 0 °C and was stirred at 0 °C for 6 h. The reaction mixture was poured into 1.0 N HCl and was extracted with AcOEt. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. The solvent was removed, and the residue was recrystallized from AcOEt to afford **26** (5.37 g, 77%). Colorless prisms, mp 113.0 °C; ^1H NMR ($CDCl_3$) δ 2.94 (2H, dt, J = 1.0, 6.0 Hz), 3.94 (2H, t, J = 6.0 Hz), 5.26 (1H, bs), 6.85 (1H, m), 7.12–7.14 (2H, m), 7.52 (1H, d, J = 1.0 Hz); LR-MS (EI) 178 (M^+).

[3-(2-Hydroxyethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (27). By the procedure used in **23a**, compound **27** (80%) was prepared from **26**. Pale-yellow oil; ^1H NMR ($CDCl_3$) δ 2.94 (2H, dt, J = 1.0, 6.0 Hz), 3.81 (3H, s), 3.93 (2H, t, J = 6.0 Hz), 4.89 (2H, s), 6.79 (1H, dd, J = 1.0, 8.0 Hz), 7.15 (1H, t, J = 8.0 Hz), 7.22 (1H, dd, J = 1.0, 8.0 Hz), 7.54 (1H, d, J = 1.0 Hz); IR (KBr) 1746 (COOMe); LR-MS (EI) 250 (M^+).

[3-(2-Methanesulfonyloxyethyl)benzofuran-7-yloxy]-acetic Acid Methyl Ester (28). To a stirred solution of **27** (4.12 g, 16.5 mmol) in CH_2Cl_2 (120 mL) was added Et_3N (3.0 mL, 21.6 mmol) and methanesulfonyl chloride (1.35 mL, 17.4 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 3.5 h. The solvent was removed under reduced pressure, and the residue was poured into 1 N HCl and was extracted with ethyl acetate. The combined organic layer was sequentially washed with water, saturated $NaHCO_3$, water, and brine and dried over Na_2SO_4. The solvent was removed, and the residue was recrystallized from AcOEt/*n*-hexane to afford **28** (5.25 g, 97%). Colorless prisms, mp 102.0 °C; ^1H NMR ($CDCl_3$) δ 3.15 (2H, dt, J = 1.0, 7.0 Hz), 3.81 (3H, s), 3.92 (3H, s), 4.48 (2H, t, J = 7.0 Hz), 4.89 (2H, s), 6.79 (1H, dd, J = 1.5, 7.5 Hz), 7.17 (1H, t, J = 7.5 Hz), 7.21 (1H, dd, J = 1.5, 7.5 Hz), 7.56 (1H, s); IR (KBr) 1763 (COOMe); LR-MS (EI) 328 (M^+).

3-Allyl-7-methoxybenzofuran (29). $CeCl_3$ (5.63 g, 22.8 mmol) was dried with stirring at 150 °C for 4 h under reduced pressure. Anhydrous THF (30 mL) was added to this flask and was stirred at room temperature overnight. Allylmagnesium bromide (0.79 M in diethyl ether) (28.9 mL, 22.8 mmol) was added to this suspension at 0 °C dropwise, which afforded an orange suspension. To this suspension was added **19** (2.5 g, 22.8 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 1.5 h. The reaction mixture was poured into water (200 mL) and AcOH (3.0 mL) and was extracted with ethyl acetate. The combined organic layer was sequentially washed with saturated $NaHCO_3$ and brine and dried over Na_2SO_4. The solvent was removed, and to the residue was added benzene (20 mL) and *p*-TsOH (50 mg). The mixture was stirred at 60 °C for 0.5 h. The reaction mixture was sequentially washed with saturated $NaHCO_3$ and brine and was dried over Na_2SO_4 and evaporated. The residue was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/20) to afford **29** (2.05 g, 72%). Pale-yellow oil; ^1H NMR ($CDCl_3$) δ 3.40–3.44 (2H, m), 4.10 (3H, s), 5.09–5.23 (2H, m), 5.95–6.10 (1H, m), 6.80 (1H, dd, J = 3.0, 6.0 Hz), 7.13–7.16 (2H, m), 7.42 (1H, s); LR-MS (EI) 188 (M^+).

3-(7-Methoxybenzofuran-3-yl)propan-1-ol (30). To a stirred solution of **29** (2.19 g, 11.65 mmol) in THF (25 mL) was added BH_3-Me_2S (2.0 M in THF) (6.1 mL, 12.2 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 2 h. To the reaction mixture was added EtOH (20 mL), 3 N NaOH (5 mL), and 30% H_2O_2 (1.5 mL), and the resulting solution was stirred at room temperature for 30 min. The reaction mixture was poured into saturated NH_4Cl and was extracted with ethyl acetate. The combined organic layer was sequentially washed with water, saturated $NaHCO_3$, water, and brine and dried over Na_2SO_4. The solvent was removed and the residue was purified by silica gel chromatography (AcOEt/cyclohexane = 1/3) to afford **30** (1.42 g, 59%). Colorless oil; ^1H NMR ($CDCl_3$) δ 1.49 (1H, bs), 1.98 (2H, m), 2.77 (2H, dt, J = 1.0, 8.0 Hz), 3.74 (2H, t, J = 6.0 Hz), 4.01 (3H, s), 6.81 (1H, m), 7.16 (2H, m), 7.44 (1H, s); LR-MS (EI) 206 (M^+).

3-(3-Hydroxypropyl)benzofuran-7-ol (31). By the procedure used in **25**, compound **31** (90%) was prepared from **30**. Colorless prisms, mp 101.0–101.5 °C; ^1H NMR ($CDCl_3$) δ 1.90 (2H, quint, J = 7.0 Hz), 2.72 (2H, t, J = 7.0 Hz), 3.62 (2H, t, J = 7.0 Hz), 6.70 (1H, dd, J = 2.0, 7.0 Hz), 7.03 (2H, m), 7.49 (1H, s); LR-MS (EI) 192 (M^+).

[3-(3-Hydroxypropyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (32). By the procedure used in **23a**, compound **32** (83%) was prepared from **31**. Colorless powder, mp 72–73 °C; ^1H NMR ($CDCl_3$) δ 1.98 (2H, quint, J = 6.0 Hz), 2.78 (2H, t, J = 6.0 Hz), 3.74 (2H, t, J = 6.0 Hz), 3.82 (3H, s), 4.89 (2H, s), 6.78 (1H, d, J = 7.0 Hz), 7.14 (1H, m), 7.22 (1H, m), 7.45 (1H, s); IR (KBr) 1715 cm^{-1} (COOMe); LR-MS (EI) 264 (M^+).

[3-(3-Bromopropyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (33). By the procedure used in **17**, compound **33** (95%) was prepared from **32**. Colorless oil; ^1H NMR ($CDCl_3$) δ 2.24 (2H, quint, J = 6.0 Hz), 2.86 (2H, t, J = 6.0 Hz), 3.45 (2H, t, J = 6.0 Hz), 3.82 (3H, s), 4.89 (2H, s), 6.78 (1H, dd, J = 1.0, 8.0 Hz), 7.15 (1H, t, J = 8.0 Hz), 7.21 (1H, dd, J = 1.0, 8.0 Hz), 7.48 (1H, s); IR (neat) 1769 cm^{-1} (COOMe); LR-MS (EI) 326, 328 (M^+) (relative peak hight ratio is 1:1).

7-Methoxy-2-(tetrahydropyran-2-yloxymethyl)benzofuran-3-one (36). Sodium hydride (60% in mineral oil, 5.60 g, 0.140 mmol), which was washed with *n*-hexane before use, was suspended in toluene (100 mL). To this suspension was added a solution of 3-methoxy-2-methoxycarbonylmethoxybenzoic acid methyl ester (**34**) (35.6 g, 0.140 mol) in toluene (400 mL), and the reaction mixture was refluxed for 22 h. After the mixture was cooled to room temperature, the precipitate was collected and washed with a small amount of toluene to give **35** (34.18 g, 100%) as pale-red powder.

To a stirred solution of **35** (11.3 g, 46.4 mmol) in THF (1100 mL) was added $LiAlH_4$ (1.83 g, 49 mmol) in four portions at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, and 1 N HCl (200 mL) and brine (200 mL) were added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was dissolved in CH_2Cl_2 (180 mL). To this solution was added 3,4-dihydro-2*H*-pyran (7.26 g, 86 mmol) and pyridinium *p*-toluenesulfonate (2.50 g, 110 mmol), and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was diluted with CH_2Cl_2 (180 mL) and was sequentially washed with water and brine and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/3) to afford **36** (9.71 g, 75%) as a 1:1 mixture of two diastereomers.

Polar Isomer of 36. Pale-yellow solid; ^1H NMR ($CDCl_3$) δ 1.35–1.65 (6H, m), 3.50 (1H, m), 3.78 (1H, m), 3.97 (3H, s), 3.99 (1H, dd, J = 2.7, 11.5 Hz), 4.21 (1H, dd, J = 4.1, 11.5 Hz), 4.67 (1H, m), 4.76 (1H, dd, J = 2.7, 4.1 Hz), 7.03 (1H, t, J = 7.8 Hz), 7.13 (1H, dd, J = 1.2, 7.8 Hz), 7.27 (1H, dd, J = 1.2, 7.8 Hz); LR-MS (EI) 278 (M^+).

Less Polar Isomer of 36. Pale-yellow liquid; ^1H NMR ($CDCl_3$) δ 1.42–1.65 (6H, m), 3.52 (1H, m), 3.84 (1H, dd, J = 5.8, 11.5 Hz), 3.85 (1H, m), 3.97 (3H, s), 4.29 (1H, dd, J = 2.5, 11.5 Hz), 4.69 (1H, m), 4.82 (1H, dd, J = 2.5, 5.8 Hz), 7.02 (1H, t, J = 7.7 Hz), 7.12 (1H, dd, J = 1.4, 7.7 Hz), 7.25 (1H, dd, J = 1.4, 7.7 Hz); LR-MS (EI) 278 (M^+).

[7-Methoxy-2-(tetrahydropyran-2-yloxymethyl)benzofuran-3-yl]acetic Acid Methyl Ester (37). To a stirred suspension of zinc powder (7.81 g, 120 mmol) and catalytic amount of iodine in THF (10 mL) was added a solution of **36** (16.1 g, 58 mmol) and methyl bromoacetate (11.0 mL, 116 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 60 min and at 50 °C for 30 min. The reaction was quenched by addition of acetic acid (5.5 mL), and the mixture was filtered. The filtrate was concentrated under reduced pressure, and the residue was dissolved in toluene (140 mL) and pyridine (140 mL). The solution was cooled to 0 °C, and Tf_2O (14.5 mL, 88 mmol) was added. The reaction mixture was stirred at 0 °C for 90 min. The reaction was

IPR2020-00770
United Therapeutics EX2007
Page 3206 of 7335

quenched by addition of brine (400 mL), and the mixture was extracted with ethyl acetate. The combined organic layer was sequentially washed with water, 5% citric acid, water, and brine and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/2) to afford **37** (15.0 g, 78%). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.45−1.90 (6H, m), 3.56 (1H, m), 3.69 (3H, s), 3.76 (2H, s), 3.90 (1H, m), 4.01 (3H, s), 4.70 (1H, d, J = 13.0 Hz), 4.72 (1H, t, J = 3.0 Hz), 4.85 (1H, d, J = 13.0 Hz), 6.81 (1H, dd, J = 1.0, 8.0 Hz), 7.11−7.20 (2H, m); IR (neat) 1742 cm^{-1} (COOMe); LR-MS (EI) 334 (M^+).

2-[7-Methoxy-2-(tetrahydropyran-2-yloxymethyl)benzofuran-3-yl]ethanol (38). By the procedure used in **26**, compound **38** (51%) was prepared from **37**. Pale-yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.49−1.87 (6H, m), 2.98 (2H, t, J = 6.0 Hz), 3.57 (1H, m), 3.87 (2H, t, J = 6.0 Hz), 3.92 (1H, m), 4.01 (3H, s), 4.64 (1H, d, J = 13.0 Hz), 4.81 (1H, t, J = 3.0 Hz), 4.86 (1H, d, J = 13.0 Hz), 6.83 (1H, dd, J = 1.0, 8.0 Hz), 7.12 (1H, dd, J = 1.0, 8.0 Hz), 7.17 (1H, t, J = 8.0 Hz); IR (neat) 1734 cm^{-1} (COOMe); LR-MS (EI) 306 (M^+).

[3-(2-Hydroxyethyl)-2-(tetrahydropyran-2-yloxymethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (39). To a stirred mixture of *t*-BuOK (9.71 g, 87 mmol) and **38** (7.67 g, 25 mmol) in DMF (150 mL) was added *n*-PrSH (8.50 mL, 94 mmol), and the reaction mixture was stirred at 140 °C for 1 h. The solvent was removed under reduced pressure, and the residue was poured into 5% citric acid and extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was dissolved in DMF (100 mL). To this solution was added K_2CO_3 (10.23 g, 74 mmol) and methyl bromoacetate (5.0 mL, 54 mmol), and the reaction mixture was stirred at room temperature for 15 h. The solvent was removed under reduced pressure, and the residue was poured into 5% citric acid and was extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/1, then 2/1) to afford **39** (7.54 g, 84%). Pale-yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.47−1.88 (6H, m), 2.31 (1H, t, J = 3.0 Hz), 2.98 (2H, t, J = 6.0 Hz), 3.81 (3H, s), 3.83−3.96 (3H, m), 4.65 (1H, d, J = 13.0 Hz), 4.81 (1H, t, J = 3.0 Hz), 4.85 (1H, d, J = 13.0 Hz), 4.90 (2H, s), 6.78 (1H, dd, J = 1.5, 7.5 Hz), 7.14 (1H, t, J = 7.5 Hz), 7.18 (1H, dd, J = 1.5, 7.5 Hz); IR (neat) 1763 cm^{-1} (COOMe); LR-MS (EI) 364 (M^+).

[3-[2-(1,1-Diphenylethylsulfanyl)ethyl]-2-(tetrahydropyran-2-yloxymethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (40b). Compound **39** was mesylated by the procedure used in **28**. And by the procedure used in **23d**, compound **40b** (80% in two steps) was synthesized from **39**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.47−1.82 (6H, m), 2.04 (3H, s), 2.57 (2H, t, J = 7.0 Hz), 2.77 (2H, t, J = 7.0 Hz), 3.54 (1H, m), 3.80 (3H, s), 3.89 (1H, m), 4.55 (1H, d, J = 13.0 Hz), 4.68 (1H, t, J = 3.0 Hz), 4.73 (1H, d, J = 13.0 Hz), 4.87 (2H, s), 6.74 (1H, dd, J = 1.0, 8.0 Hz), 6.89 (1H, dd, J = 1.0, 8.0 Hz), 7.06 (1H, t, J = 8.0 Hz), 7.18−7.30 (6H, m), 7.39 (4H, m); LR-MS (FAB, positive) 583 (M^+ + Na).

[3-(2-Benzhydrylsulfanylethyl)-2-(tetrahydropyran-2-yloxymethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (40a). By the procedure used in **40b**, compound **40a** (73%) was synthesized from **39**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.47−1.82 (6H, m), 2.66 (2H, t, J = 7.0 Hz), 2.95 (2H, t, J = 7.0 Hz), 3.54 (1H, m), 3.80 (3H, s), 3.89 (1H, m), 4.54 (1H, d, J = 13.0 Hz), 4.68 (1H, t, J = 3.0 Hz), 4.72 (1H, d, J = 13.0 Hz), 4.88 (2H, s), 5.15 (1H, s), 6.78 (1H, dd, J = 1.0, 8.0 Hz), 6.83 (1H, dd, J = 1.0, 8.0 Hz), 7.08 (1H, t, J = 8.0 Hz), 7.19−7.33 (6H, m), 7.37−7.41 (4H, m); LR-MS (FAB, positive) 569 (M^+ + Na).

[3-[2-(1,1-Diphenylpropylsulfanyl)ethyl]-2-(tetrahydropyran-2-yloxymethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (40c). By the procedure used in **40b**, compound **40c** (40%) was synthesized from **39**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.77 (3H, t, J = 7.0 Hz), 1.45−1.82 (6H, m), 2.33 (2H, q, J = 7.0 Hz), 2.40 (2H, t, J = 7.0 Hz), 2.69 (2H, t, J = 7.0 Hz), 3.54 (1H, m), 3.80 (3H, s), 3.88 (1H, m), 4.52 (1H, d, J = 13.0 Hz), 4.68 (1H, t, J = 3.0 Hz), 4.71 (1H, d, J = 13.0 Hz), 4.87 (2H, s), 6.73 (1H, dd, J = 1.0, 8.0 Hz), 6.84 (1H, dd, J = 1.0, 8.0 Hz), 7.05 (1H, t, J = 8.0 Hz), 7.16−7.29 (m, 6H), 7.33 (m, 4H); LR-MS (FAB, positive) 597 (M^+ + Na).

[3-[2-(1,1-Diphenylbutylsulfanyl)ethyl]-2-(tetrahydropyran-2-yloxymethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (40d). By the procedure used in **40b**, compound **40d** (86%) was synthesized from **39**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.82 (3H, t, J = 7.0 Hz), 1.14 (2H, m), 1.45−1.88 (6H, m), 2.25 (2H, m), 2.41 (2H, t, J = 7.0 Hz), 2.68 (2H, t, J = 7.0 Hz), 3.53 (1H, m), 3.80 (3H, s), 3.88 (1H, m), 4.52 (1H, d, J = 13.0 Hz), 4.68 (1H, t, J = 3.0 Hz), 4.70 (1H, d, J = 13.0 Hz), 4.87 (2H, s), 6.73 (1H, dd, J = 1.0, 8.0 Hz), 6.84 (1H, dd, J = 1.0, 8.0 Hz), 7.45 (1H, t, J = 8.0 Hz), 7.16−7.28 (6H, m), 7.34 (4H, m); LR-MS (FAB, positive) 611 (M^+ + Na).

{2-(Tetrahydropyran-2-yloxymethyl)-3-[2-(2,2,2-trifluoro-1,1-diphenylethylsulfanyl)ethyl]benzofuran-7-yloxy}-acetic Acid Methyl Ester (40e). By the procedure used in **40b**, compound **40e** (56%) was synthesized from **39**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.42−1.95 (6H, m), 2.59 (2H, m), 2.78 (2H, m), 3.56 (1H, m), 3.80 (3H, s), 3.89 (1H, m), 4.53 (1H, d, J = 13.0 Hz), 4.68 (1H, t, J = 3.3 Hz), 4.72 (1H, d, J = 13.0 Hz), 4.87 (2H, s), 6.73 (1H, dd, J = 0.8, 7.9 Hz), 6.78 (1H, dd, J = 0.8, 7.9 Hz), 7.03 (1H, t, J = 8.0 Hz), 7.25−7.30 (6H, m), 7.36−7.42 (4H, m); LR-MS (EI) 614 (M^+).

General Procedure for Deprotection of the THP Group. [3-[2-(1,1-Diphenylethylsulfanyl)ethyl]-2-hydroxymethylbenzofuran-7-yloxy]acetic Acid Methyl Ester (41b). To a stirred solutoin of **40b** (550 mg, 0.98 mmol) in THF (10 mL) and MeOH (10 mL) was added pyridinium *p*-toluenesulfonate (103 mg, 0.41 mmol), and the reaction mixture was stirred at 80 °C for 6.5 h. The solvent was removed under reduced pressure, and the residue was poured into 5% citric acid and was extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and was dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/1) to afford **41b** (387 mg, 83%). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.00 (3H, s), 2.26 (1H, t, J = 6.5 Hz), 2.60 (2H, m), 2.69 (2H, m), 3.81 (3H, s), 4.63 (2H, d, J = 6.5 Hz), 4.88 (2H, s), 6.74 (1H, dd, J = 1.0, 7.0 Hz), 6.92 (1H, dd, J = 1.0, 7.0 Hz), 7.07 (1H, t, J = 7.0 Hz), 7.16−7.29 (6H, m), 7.34 (m, 4H); LR-MS (FAB, positive) 477 (M^+ + H).

[3-(2-Benzhydrylsulfanylethyl)-2-hydroxymethylbenzofuran-7-yloxy]acetic Acid Methyl Ester (41a). Compound **41a** (73%) was prepared from **40a**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.15 (1H, t, J = 7.0 Hz), 2.67 (2H, t, J = 7.0 Hz), 2.92 (2H, t, J = 7.0 Hz), 3.80 (3H, s), 4.68 (2H, d, J = 7.0 Hz), 4.88 (2H, s), 5.04 (1H, s), 6.81 (1H, dd, J = 1.0, 8.0 Hz), 6.89 (1H, dd, J = 1.0, 8.0 Hz), 7.11 (1H, t, J = 8.0 Hz), 7.18−7.36 (10H, m); LR-MS (FAB, positive) 463 (M^+ + H).

[3-[2-(1,1-Diphenylpropylsulfanyl)ethyl]-2-hydroxymethylbenzofuran-7-yloxy]acetic Acid Methyl Ester (41c). Compound **41c** (78%) was prepared from **40c**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.73 (3H, t, J = 7.0 Hz), 2.27 (1H, t, J = 6.0 Hz), 2.31 (2H, q, J = 7.0 Hz), 2.47 (2H, m), 2.55 (2H, m), 3.81 (3H, s), 4.59 (2H, d, J = 6.0 Hz), 4.88 (2H, s), 6.74 (1H, dd, J = 1.0, 8.0 Hz), 6.88 (1H, dd, J = 1.0, 8.0 Hz), 7.06 (1H, t, J = 8.0 Hz), 7.14−7.32 (10H, m); LR-MS (FAB, positive) 491 (M^+ + H).

[3-[2-(1,1-Diphenylbutylsulfanyl)ethyl]-2-hydroxymethylbenzofuran-7-yloxy]acetic Acid Methyl Ester (41d). Compound **41d** (91%) was prepared from **40d**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.80 (3H, t, J = 7.0 Hz), 1.11 (2H, m), 2.23 (2H, m), 2.26 (1H, t, J = 6.5 Hz), 2.48 (2H, m), 2.55 (2H, m), 3.81 (3H,s), 4.59 (2H, d, J = 6.5 Hz), 4.88 (2H, s), 6.74 (1H, dd, J = 1.0, 8.0 Hz), 6.88 (1H, dd, J = 1.0, 8.0 Hz), 7.06 (1H, t, J = 8.0 Hz), 7.15−7.32 (10H, m); LR-MS (FAB, positive) 505 (M^+ + H).

IPR2020-00770
United Therapeutics EX2007
Page 3207 of 7335

{2-Hydroxymethyl-3-[2-(2,2,2-trifluoro-1,1-diphenylethylsulfanyl)ethyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (41e). Compound **41e** (84%) was prepared from **40e**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.98 (1H, t, J = 6.3 Hz), 2.57−2.65 (2H, m), 2.70−2.78 (2H, m), 3.81 (3H, s), 4.64 (2H, d, J = 6.3 Hz), 4.87 (2H, s), 6.73 (1H, dd, J = 0.8, 8.0 Hz), 6.81 (1H, dd, J = 0.8, 8.0 Hz), 7.05 (1H, t, J = 8.0 Hz), 7.24−7.29 (6H, m), 7.35−7.40 (4H, m); LR-MS (EI) 530 (M^+).

2-(3-(2-(1,1-Diphenylethylsulfonyl)ethyl)-2-(hydroxymethyl)benzofuran-7-yloxy)acetic Acid Methyl Ester (42). To a stirred solution of **41b** (216 mg, 0.45 mmol) in dichloromethane (3 mL) was added *m*-CPBA (196 mg) at 0 °C. The reaction mixture was stirred at this temperature for 3.5 h and was poured into water. The organic layer was separated, and the water layer was extracted twice with dichloromethane. The combined organic layer was sequentially washed with water and brine and dried over $MgSO_4$. Removal of the solvent gave an oily residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane = 2/3) to afford **42** (183 mg, 79%). Colorless prisms, mp 53−54 °C; ^{1}H NMR ($CDCl_3$) δ 2.17 (3H, s), 2.49 (1H, t, J = 6.3 Hz), 2.97−3.12 (4H, m), 3.80 (3H, s), 4.69 (2H, d, J = 6.3 Hz), 4.87 (2H, s), 6.78 (1H, dd, J = 0.8, 8.0 Hz), 6.88 (1H, dd, J = 0.8, 8.0 Hz), 7.08 (1H, t, J = 8.0 Hz), 7.32−7.40 (6H, m), 7.52−7.60 (4H, m); LR-MS (EI) 508 (M^+).

2-Allyl-7-methoxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylic Acid Methyl Ester (43). Compound **35** (18.6 g, 76.4 mmol) was dissolved in DMF (150 mL). To this solution was added allyl bromide (8.6 mL, 99 mmol), and the reaction mixture was stirred at room temperature for 15.5 h. Acetic acid (2.0 mL) was added to the reaction mixture, and the solvent was removed under reduced pressure. The residue was dissolved in toluene (200 mL) and was refluxed for 1 h. The reaction mixture was cooled to room temperature and poured into water (200 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was sequentially washed with saturated $NaHCO_3$, water, and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/3) to afford **43** (18.4 g, 92%). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.91 (1H, ddt, J = 14.5, 7.0, 1.0 Hz), 3.08 (1H, ddt, J = 14.5, 7.0, 1.0 Hz), 3.75 (3H, s), 3.99 (3H, s), 5.11−5.07 (1H, m), 5.27−5.20 (1H, m), 5.67 (1H, ddt, J = 17.0, 10.0, 7.0 Hz), 7.06 (1H, t, J = 8.0 Hz), 7.15 (1H, dd, J = 8.0, 1.5 Hz), 7.24 (1H, dd, J = 8.0, 1.5 Hz); LR-MS (EI) 262 (M^+).

2-Allyl-7-methoxybenzofuran-3-one (44). To a solution of **43** (18.42 g, 70 mmol) in *t*-BuOH (150 mL) was added concentrated H_2SO_4 (2 mL), and the mixture was refluxed for 22.5 h. The reaction mixture was cooled to room temperature and was poured into saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was sequentially washed with saturated aqueous $NaHCO_3$, water, and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/4) to afford **44** (11.39 g, 80%). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.55−2.66 (1H, m), 2.78−2.89 (1H, m), 3.96 (3H, s), 4.68 (1H, dd, J = 7.0, 5.0 Hz), 5.09−5.14 (1H, m), 5.24 (1H, ddd, J = 7.0, 2.0, 1.5 Hz), 5.82 (1H, ddt, J = 17.0, 10.0, 7.0 Hz), 7.02 (1H, t, J = 8.0 Hz), 7.15 (1H, dd, J = 8.0, 1.0 Hz), 7.24 (1H, dd, J = 8.0, 1.0 Hz); LR-MS (EI) 204 (M^+).

(2-Allyl-7-methoxybenzofuran-3-yl)acetic Acid Methyl Ester (45). By the procedure used in **37**, the Reformatski reaction of compound **44** was performed. The intermediate was dissolved in toluene (100 mL), and *p*-toluenesulfonic acid monohydrate (536 mg, 2.8 mmol) was added. The reaction mixture was stirred at room temperature for 2 h and was poured into water and extracted with ethyl acetate. The combined organic layer was washed with brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/3) and was recrystallized from AcOEt/*n*-hexane to afford **45** (5.23 g, 67%). Colorless prisms, mp 65−66 °C; ^{1}H NMR ($CDCl_3$) δ 3.57 (2H, dt, J = 6.0, 1.5 Hz), 3.63 (2H, s), 3.68 (3H, s), 3.99 (3H, s), 5.15 (1H, dq, J = 25.0, 1.5 Hz), 5.24 (1H, m), 5.82 (1H, ddt, J = 17.0, 10.0, 6.0 Hz), 6.77 (1H, dd, J = 7.7, 1.4 Hz), 7.09 (1H, dd, J = 7.7, 1.4 Hz), 7.15 (1H, t, J = 7.7 Hz); LR-MS (EI) 260 (M^+).

[2-Allyl-3-(2-hydroxyethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (46). To a solution of **45** (464 mg, 1.78 mmol) in dichloromethane (4 mL) was added 1.0 M BBr_3 dichloromethane solution (3.9 mL, 3.9 mmol) at −78 °C, and the mixture was stirred at 0 °C for 2 h. The reaction mixture was poured into saturated $NaHCO_3$ and was extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was dissolved in THF (15 mL). To this solution was added $LiAlH_4$ (91 mg, 2.40 mmol), and the mixture was stirred at 0 °C for 30 min and at room temperature for 1.5 h. The reaction mixture was poured into saturated $NaHCO_3$ and extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was dissolved in DMF (5 mL). To this solution was added methyl bromoacetate (0.5 mL, 5.28 mmol) and K_2CO_3 (606 mg, 4.38 mmol), and the mixture was stirred at room temperature for 17 h. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/1) to afford **46** (450 mg, 87%). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.89 (2H, t, J = 6.3 Hz), 3.56 (2H, dt, J = 6.0, 1.5 Hz), 3.81 (3H, s), 3.85 (2H, t, J = 6.3 Hz), 4.89 (2H, s), 5.10−5.19 (2H, m), 5.99 (1H, ddt, J = 17.0, 10.0, 6.0 Hz), 6.73 (1H, dd, J = 7.0, 1.5 Hz), 7.08−7.16 (2H, m); LR-MS (EI) 290 (M^+).

{2-Allyl-3-[2-(tetrahydropyran-2-yloxy)ethyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (47). To a solution of **46** (450 mg, 1.55 mmol) in THF (2 mL) were added 3,4-dihydro-2*H*-pyran (0.21 mL, 2.30 mmol) and *p*-toluenesulfonic acid monohydrate (15 mg, 0.08 mmol), and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was poured into water and was extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/3) to afford **47** (544 mg, 94%). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.45−1.84 (6H, m), 2.92 (2H, t, J = 7.0 Hz,), 3.41−3.49 (1H, m), 3.53−3.61 (3H, m), 3.72−3.80 (1H, m), 3.81 (3H, s), 3.94 (1H, dt, J = 9.5, 7.0 Hz), 4.57−4.59 (1H, m), 4.88 (2H, s), 5.09−5.20 (2H, m), 5.98 (1H, ddt, J = 17.0, 10.2, 6.3 Hz), 6.70 (1H, dd, J = 8.0, 1.0 Hz), 7.09 (1H, t, J = 8.0 Hz), 7.16 (1H, dd, J = 8.0, 1.0 Hz); LR-MS (EI) 374 (M^+).

{2-(2-Hydroxyethyl)-3-[2-(tetrahydropyran-2-yloxy)-ethyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (48). To a solution of **47** (0.97 g, 2.59 mmol) in dioxane (15 mL) and water (5 mL) was added 0.07 M OsO_4 in *t*-BuOH (0.37 mL, 26 umol) at 0 °C. $NaIO_4$ (1 38 g 6 45 mmol) was added to this solution in several portions, and the mixture was stirred at 0 °C for 30 min and at room temperature for 30 min. The reaction mixture was filtered, and the filtrate was diluted with THF (12 mL). To this solution was added $NaBH_4$ (98 mg, 2.59 mmol), and the mixture was stirred at room temperature for 40 min. The reaction mixture was poured into water and was extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by silica gel column chromatography (AcOEt/*n*-hexane = 1/1) to afford **48** (412 mg, 42%). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.42−1.76 (6H, m), 2.96 (2H, t, J = 6.0 Hz), 3.05 (2H, t, J = 5.8 Hz), 3.35−3.43 (1H, m), 3.58−3.71 (2H, m), 3.81 (3H, s), 3.93 (2H, t, J = 5.8 Hz), 4.04−4.11 (1H, m), 4.52−4.54 (1H, m), 4.87 (2H, s), 6.70 (1H, dd, J =

IPR2020-00770
United Therapeutics EX2007
Page 3208 of 7335

8.0, 1.5 Hz), 7.09 (1H, t, J = 8.0 Hz), 7.14 (1H, dd, J = 8.0, 1.5 Hz); LR-MS (EI) 378 (M^+).

[2-(2-Acetoxyethyl)-3-(2-hydroxyethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (49). To a solution of **48** (403 mg, 1.06 mmol) in THF (5 mL) were added pyridine (0.13 mL, 1.61 mmol) and acetic anhydride (0.3 mL, 3.18 mmol). The reaction mixture was stirred at room temperature for 16 h and was poured into water and extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was dissolved in MeOH (4 mL). To this solution was added 1 N HCl (1 mL), and the reaction mixture was stirred at room temperature for 2 h and was poured into water and extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane = 2/1) and recrystallized from AcOEt/*n*-hexane to afford **49** (283 mg, 79%). Colorless prisms, mp 80−81 °C; ^{1}H NMR ($CDCl_3$) δ 2.03 (3H, s), 2.90 (2H, t, J = 6.3 Hz), 3.13 (2H, t, J = 6.6 Hz), 3.81 (3H, s), 3.87 (2H, t, J = 6.3 Hz), 4.43 (2H, t, J = 6.6 Hz), 4.88 (2H, s), 6.74 (1H, dd, J = 7.5, 2.5 Hz), 7.09−7.14 (2H, m); LR-MS (EI) 336 (M^+).

{2-(2-Acetoxyethyl)-3-[2-(1,1-diphenylethylsulfanyl)-ethyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (50). By the procedure used in the preparation of **40b**, compound **50** (87%) was prepared from **49** and **11b**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.99 (3H, s), 2.04 (3H, s), 2.50−2.59 (2H, m), 2.62−2.70 (2H, m), 2.98 (2H, t, J = 6.6 Hz), 3.81 (3H, s), 4.32 (2H, t, J = 6.6 Hz), 4.87 (2H, s), 6.69 (1H, dd, J = 8.0, 1.0 Hz), 6.85 (1H, dd, J = 8.0, 1.0 Hz), 7.04 (1H, t, J = 8.0 Hz), 7.18−7.32 (6H, m), 7.36−7.42 (4H, m); LR-MS (EI) 532 (M^+).

2-(2-Allyl-7-methoxybenzofuran-3-yl)ethanol (51). By the procedure used in **26**, compound **51** (86%) was prepared from **45**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.90 (2H, t, J = 6.4 Hz), 3.56 (2H, dt, J = 4.6, 1.6 Hz), 3.86 (2H, t, J = 6.4 Hz), 4.00 (3H, s), 5.09−5.15 (1H, m), 5.18 (1H, q, J = 1.6 Hz), 5.99 (1H, ddt, J = 17.0, 9.9, 6.3 Hz), 6.77 (1H, dd, J = 7.4, 1.4 Hz), 7.08−7.17 (2H, m); LR-MS (EI) 232 (M^+).

[3-(2-Hydroxyethyl)-2-propenylbenzofuran-7-yloxy]-acetic Acid Methyl Ester (52). By the procedure used in **39**, compound **52** (35%) was prepared from **51**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.94 (3H, dd, J = 6.6, 1.4 Hz), 2.93 (2H, t, J = 6.5 Hz), 3.82 (3H, s), 3.85 (2H, t, J = 6.5 Hz), 4.92 (2H, s), 6.38−6.61 (2H, m), 6.76 (1H, dd, J = 7.0, 1.5 Hz), 7.08−7.14 (2H, m); LR-MS (EI) 290 (M^+).

{2-Propenyl-3-[2-(tetrahydropyran-2-yloxy)ethyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (53). By the procedure used in **47**, compound **53** (92%) was prepared from **52**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.44−1.86 (6H, m), 1.93 (3H, d, J = 5.2 Hz), 2.95 (2H, t, J = 7.0 Hz), 3.40−3.48 (1H, m), 3.58 (1H, dt, J = 9.5, 7.0 Hz), 3.72−3.82 (1H, m), 3.81 (3H, s), 3.93 (1H, dt, J = 9.5, 7.0 Hz), 4.56−4.59 (1H, m), 4.91 (2H, s), 6.35−6.56 (2H, m), 6.73 (1H, dd, J = 8.0, 1.0 Hz), 7.07 (1H, t, J = 8.0 Hz), 7.15 (1H, dd, J = 8.0, 1.0 Hz); LR-MS (EI) 374 (M^+).

{2-(3-Acetoxypropenyl)-3-[2-(tetrahydropyran-2-yloxy)ethyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (54). To a solution of **53** (523 mg, 1.40 mmol) in benzene (5 mL) were added *N*-bromosuccimide (299 mg, 1.68 mmol) and AIBN (23 mg, 0.14 mmol). The reaction mixture was stirred at room temperature for 4 h and was poured into water and extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was dissolved in DMF (4 mL). To this solution was added KOAc (205 mg, 2.09 mmol), and the mixture was stirred at room temperature for 50 min. The reaction mixture was poured into water and was extracted with ethyl acetate. The combined organic layer was sequentially washed with water and brine and dried over Na_2SO_4. Removal of the solvent afforded an oily residue, which was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/2) to afford **54** (217 mg, 36%). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.44−1.84 (6H, m), 2.12 (3H, s), 2.98 (2H, t, J = 7.0 Hz), 3.39−3.47 (1H, m), 3.59 (1H, dt, J = 9.5, 7.0 Hz), 3.69−3.77 (1H, m), 3.82 (3H, s), 3.95 (1H, dt, J = 9.5, 7.0 Hz), 4.57 (1H, m), 4.77 (2H, dd, J = 6.0, 1.5 Hz), 4.90 (2H, s), 6.52 (1H, dt, J = 16.0, 6.0 Hz), 6.69 (1H, dt, J = 16.0, 1.5 Hz), 6.77 (1H, dd, J = 8.0, 1.0 Hz), 7.10 (1H, t, J = 8.0 Hz), 7.18 (1H, dd, J = 8.0, 1.0 Hz); LR-MS (EI) 432 (M^+).

[2-(3-Acetoxypropyl)-3-(2-hydroxyethyl)benzofuran-7-yloxy]acetic Acid Methyl Ester (55). To a solution of **54** (199 mg, 0.460 mmol) in MeOH (4 mL) was added 5% Pd/C (28 mg), and the reaction mixture was stirred at room temperature for 50 min under hydrogen atmosphere. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography (AcOEt/*n*-hexane = 1/1) to afford **55** (80 mg, 50%). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.03 (3H, s), 2.09 (2H, quint, J = 7.0 Hz), 2.87 (4H, m), 3.81 (3H, s), 3.86 (2H, t, J = 7.0 Hz), 4.12 (2H, t, J = 7.0 Hz), 4.88 (2H, s), 6.71 (1H, dd, J = 7.0, 2.0 Hz), 7.07−7.14 (2H, m); LR-MS (EI) 350 (M^+).

{2-(3-Acetoxypropyl)-3-[2-(1,1-diphenylethylsulfanyl)-ethyl]benzofuran-7-yloxy}acetic Acid Methyl Ester (56). By the procedure used in the preparation of **40b**, compound **56** (78%) was prepared from **55**. Colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.92 (2H, m), 2.01 (3H, s), 2.05 (3H, s), 2.50−2.57 (2H, m), 2.65−2.70 (2H, m), 2.76 (2H, t, J = 7.3 Hz), 3.80 (s, 3H), 4.05 (2H, t, J = 6.0 Hz), 4.86 (2H, s), 6.68 (1H, dd, J = 8.0, 1.0 Hz), 6.86 (1H, dd, J = 8.0, 1.0 Hz), 7.04 (1H, t, J = 8.0 Hz), 7.18−7.31 (6H, m), 7.36−7.41 (4H, m); LR-MS (EI) 546 (M^+).

Blood Samples. Blood samples were collected from healthy male human volunteers under the approval by the Institutional Ethics Committee of the Pharmaceutical Research Laboratories, Toray Industries, Inc. Written informed consent was obtained from each of the volunteers. The volunteers did not take any drugs at least within 2 weeks before their participation in this study. Blood samples were also collected from male cynomolgus monkeys (Japan SLC, Shizuoka, Japan) in accordance with the guidelines for the animal care and use established at the Pharmaceutical Research Laboratories, Toray Industries, Inc.

Binding Assay for TP and IP Receptors in Human Platelet Membrane. Blood was collected from human volunteers by venous puncture. An amount of nine volumes of the collected blood was mixed with one volume of a solution containing 85 mM sodium citrate, 65 mM citric acid, 2% glucose, and 0.1 mM indomethacin. Platelet-rich plasma (PRP) was prepared by centrifugation at 120*g* for 10 min at 4 °C. The platelets were washed twice in washing buffer, pH 6.5, containing 115 mM NaCl, 4.3 mM K_2HPO_4, 24.4 mM Na_2HPO_4, 5 mM glucose, 1 mM EDTA-2Na, and 0.01 mM indomethacin, and resuspended in 10 mM Tris buffer, pH 7.4, containing 5 mM $MgCl_2$, and 2 mM EDTA-2Na. The platelets were alternately frozen and thawed three times and then centrifuged at 40000*g* for 20 min at 4 °C. The membrane preparation was resuspended at 4 °C in assay buffer, pH 7.4, containing 50 mM Tris and 5 mM $MgCl_2$, and stored at −80 °C until use. For TP receptor binding assay, human platelet membrane (10 μg of protein) was incubated in assay buffer in the presence of the selective TP receptor antagonist, [^{3}H]SQ-29548, and **7** for 30 min at 25 °C. For IP receptor binding assay, human platelet membrane (10 μg of protein) was incubated in assay buffer in the presence of the selective IP receptor agonist, [^{3}H]APS-314d sodium, and **7** for 60 min at 4 °C. The reaction mixture was separated into bound and free radiolabeled ligand by rapid filtration through GF/C filters presoaked in 10 mM Tris-HCl buffer. Filters were washed, and the residual [^{3}H]SQ-29548 or [^{3}H]APS-314d sodium bound to the filter was determined by liquid scintillation counting. Specific binding was defined as the difference between total binding and nonspecific binding, which was determined in the presence of 10 μM SQ-29548 or 10 μM APS-314d sodium. K_i was calculated using the equation $K_i = IC_{50}/(1 + L/K_d)$, where L is the concentration of ligand.

IPR2020-00770
United Therapeutics EX2007
Page 3209 of 7335

Platelet Aggregation in PRP. Nine volumes of blood collected from human volunteers were mixed with one volume of 3.8% sodium citrate in a tube. The citrated blood samples were immediately centrifuged at 90−140*g* for 10 min at room temperature. The resulting supernatant was used as the PRP fraction. The remaining blood was further centrifuged at 1400*g* for 10 min. The resulting supernatant was used as the platelet-poor plasma fraction. Human PRP were pretreated with compound at various concentrations for 1 min before the addition of U46619 (2 μM), arachidonic acid (600 μM), collagen (1 μg/mL), or ADP (5 μM). The platelet stimulation with ADP was carried out in the presence or absence of SQ-29548 (10 μM).

Platelet aggregation was monitored by recording transmittance on a four-channel light transmission aggregometer (NBS Hematracer 601, MC Medical, Japan) for 5 min after the addition of a platelet-stimulating agent. For evaluating the effect of the test drugs, the percent inhibition values of platelet aggregation were calculated from the increases in transmittance observed with the test drugs ($N = 3$), on the assumption that no inhibition was observed in the control incubation of PRP with vehicle alone. And the optical density of platelet-poor plasma was taken to represent 100% aggregation.

Blood Pressure, Heart Rate, and ex Vivo Platelet Aggregation in Monkeys. Cynomolgus monkeys were anesthetized with sodium pentobarbital (35 mg/kg iv) and given compound **7** at doses of 3, 10, and 30 μg kg^{-1} min^{-1} or compound **4** at doses of 0.3, 1, and 3 μg kg^{-1} min^{-1} both in a manner of dose escalation by infusion for 30 min for each dose via the catheter inserted into the forearm or saphenous vein. Arterial blood pressure and heart rate were monitored with a polygraph system through a femoral catheter and during the infusion period, and the blood pressure and heart rate were recorded at baseline and at the end of the infusion at each dose. Arterial blood was drawn to examine ex vivo platelet aggregation at baseline and at the end of the infusion at each dose. The collected blood samples were processed to prepare PRP for determining by the light transmission method, as described above.

Statistics. The data are shown as the mean ± standard error. Statistical comparisons between mean values were performed by one-way ANOVA and Dunnett's test at a significance level of $p < 0.05$.

Acknowledgment. We thank Dr. Katsuhiko Iseki (Toray, Kamakura) and Dr. Kiyotaka Ohno (Toray, Kamakura) for helpful discussions. We thank Dr. Masafumi Isogaya and Mika Nukaya for providing us with the biological data. We thank Dr. Kenneth A. Jacobson and Heng T. Duong (NIDDK, Bethesda, MD) for helpful discussions and proofreading of the manuscript.

Supporting Information Available: Results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Hamberg, M.; Svensson, J.; Samuelsson, B. Thromboxanes: A new group of biologically active compounds derived from prostaglandin endoperoxides. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72*, 2994−2998.

(2) Hall, S. E. Thromboxane A_2 receptor antagonists. *Med. Res. Rev.* **1991**, *11* (5), 503−579.

(3) Rote, W. E.; Mu, D. X.; Lucchesi, B. R. Thromboxane antagonism in experimental canine carotid artery thrombosis. *Stroke* **1993**, *24*, 820−828.

(4) Serruys, P. W.; Rutsch, W.; Heyndrickx, G. R.; Danchin, N.; Mast, E. G.; Wijns, W.; Rensing, B. J.; Vos, J.; Stibbe, J. (CARPORT Study Group). Prevention of restenosis after percutaneous transluminal coronary angioplasty with thromboxane A_2 receptor blockade. *Circulation* **1991**, *84*, 1568−1580.

(5) The RAPT Investigators (Van de Werf, F.). Randomized trial of ridogrel, a combined thromboxane A_2 synthase inhibitor and thromboxane A_2/prostaglandin endoperoxide receptor antagonist, versus aspirin as adjunct to thrombolysis in patient with acute myocardial infarction. *Circulation* **1994**, *89*, 588−595.

(6) Moncada, S.; Gryglewski, R.; Bunting, S.; Vane, J. R. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. *Nature* **1976**, *263*, 663−665.

(7) Collins, P. W.; Djuric, S. W. Synthesis of therapeutic useful prostaglandin and prostacyclin analogs. *Chem. Rev.* **1993**, *93*, 1533−1564.

(8) Narita, S.; Takahashi, A.; Aoki, T.; Sato, H.; Satoh, S.; Yamada, S.; Kudo, M.; Yamaguchi, T.; Kogi, K.; Shibasaki, M. Synthesis and biological activities of chemically stable prostacyclin mimics with *cis*-bicyclo[4.3.0]nonene ring system: the novel homoisocarbacyclin analogues. *Bioorg. Med. Chem.* **1993**, *1* (2), 77−118.

(9) Meanwell, N. A.; Romine, J. L.; Seiler, S. M. Non-prostanoid prostacyclin mimetics. *Drugs Future* **1994**, *19* (4), 361−385.

(10) Wise, H.; Jones, R. L. Focus on prostacyclin and its novel mimetics. *Trends. Pharmacol. Sci.* **1996**, *17*, 17−21.

(11) Hayashi, K.; Nagamatsu, T.; Oka, T.; Suzuki, Y. Modulation of anti-glomerular basement membrane nephritis in rats by ONO-1301, a non-prostanoid prostaglandin I_2 mimetic compound with inhibitory activity against thromboxane A_2 synthase. *Jpn. J. Pharmacol.* **1997**, *73* (1), 73−82.

(12) Minamoto, K. Beneficial effect of a stable PGI_2 analogue (ONO-1301) on prostanoid release after reperfusion in canine left single lung allotransplantation model. *Nippon Kyobu Geka Gakkai Zasshi.* **1997**, *45* (12), 1931−1942.

(13) Kondo, K.; Hamanaka, N. Prostacyclin mimetics with non-prostanoid structure. *Folia Pharmacol. Jpn.* **1995**, *106*, 181−191.

(14) Tsubaki, K.; Taniguchi, K.; Tabuchi, S.; Okitsu, O.; Hattori, K.; Seki, J.; Sakane, K.; Tanaka, H. A novel pyridazinone derivative as a nonprostanoid PGI_2 agonist. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2787−2790.

(15) Sturzebecher, S.; Witt, W. The PGI_2-analogue iloprost and the TXA_2-receptor antagonist sulotroban synergistically inhibit TXA_2-dependent platelet activation. *Prostaglandins* **1988**, *36*, 751−760.

(16) Klar, U.; Pletsch, A.; Rehwinkel, H.; Schreyer, R. An attempt to synthesize prostanoid thromboxane A_2 antagonists with an additional prostacyclin like quality. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1215−1218.

(17) Nishio, T. A novel transformation of alcohols to thiol. *J. Chem. Soc., Chem. Commun.* **1989**, 205−206.

(18) Nishio, T. Direct conversion of alcohol into thiols. *J. Chem. Soc., Perkin. Trans. 1* **1993**, 1113−1117.

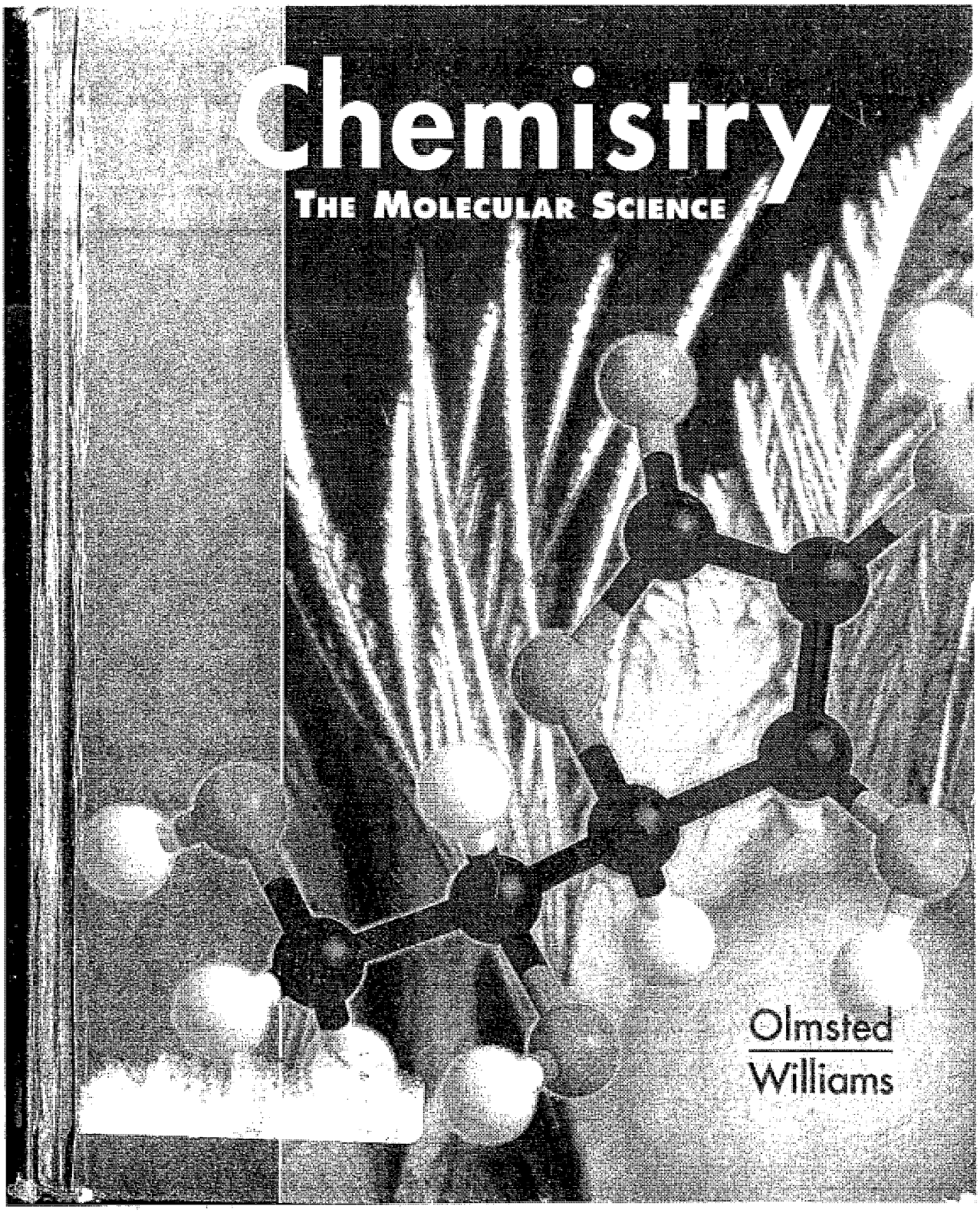
(19) Bryant, W. M., III; Hahn, G. F. A practical preparation of 7-methoxy-3(2*H*)-benzofuranone. *Synth. Commun.* **1995**, *25* (6), 915−920.

(20) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, K.; Kamiya, Y. Reactions of carbonyl compounds with Grignard reagents in the presence of cerium chloride. *J. Am. Chem. Soc.* **1989**, *111*, 4392−4398.

(21) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. Carbon−carbon bond-forming reactions using cerium metal or organocerium(III) reagents. *J. Org. Chem.* **1984**, *49*, 3904−3912.

JM050194Z

IPR2020-00770
United Therapeutics EX2007
Page 3210 of 7335

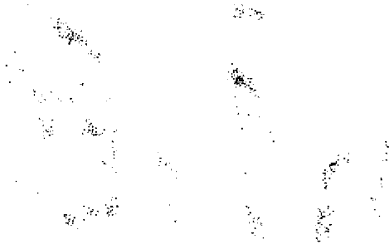

Chemistry
THE MOLECULAR SCIENCE
Olmsted
Williams

Chemistry
THE MOLECULAR SCIENCE

John Olmsted III
CALIFORNIA STATE UNIVERSITY, FULLERTON
FULLERTON, CALIFORNIA

Gregory M. Williams
CALIFORNIA STATE UNIVERSITY, FULLERTON
FULLERTON, CALIFORNIA

with 1033 illustrations, including 920 in color



Mosby

St. Louis Baltimore Boston Chicago London Madrid Philadelphia Sydney Toronto

IPR2020-00770
United Therapeutics EX2007
Page 3212 of 7335

Mosby
Dedicated to Publishing Excellence

Editor-in-Chief: James M. Smith
Developmental Editor: John S. Murdzek
Project Manager: Carol Sullivan Wiseman
Senior Production Editor: Pat Joiner
Designer: William A. Seabright
Design Manager: Betty Schulz
Manufacturing Supervisor: John Babrick
Art Developer: John S. Murdzek
Illustrations: ArtScribe, Inc., and J/B Woolsey Associates
Photo Researchers: Patrick Watson, John S. Murdzek
Photographer: Patrick Watson
Cover Design: David Zielinski, Jill Papke

Copyright © 1994 by Mosby–Year Book, Inc.

All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without prior written permission from the publisher.

Permission to photocopy or reproduce solely for internal or personal use is permitted for libraries or other users registered with the Copyright Clearance Center, provided that the base fee of $4.00 per chapter plus $0.10 per page is paid directly to the Copyright Clearance Center, 27 Congress Street, Salem, MA 01970. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collected works, or for resale.

Printed in the United States of America
Composition by Graphic World, Inc.
Printing/binding by Von Hoffmann Press

Mosby–Year Book, Inc.
11830 Westline Industrial Drive
St. Louis, Missouri 63146

Library of Congress Cataloging in Publication Data

Olmsted, John III
Chemistry, the molecular science / John Olmsted III, Gregory M. Williams
p. cm.
Includes index.
ISBN 0-8016-7485-9
1. Chemistry. I. Williams, Gregory M. II. Title.
QD33.046 1994
540—dc20 93-37165
CIP

94 95 96 97 98 / 9 8 7 6 5 4 3 2

IPR2020-00770
United Therapeutics EX2007
Page 3213 of 7335

CHAPTER 10 EFFECTS OF INTERMOLECULAR FORCES

The properties of ice crystals, icebergs, and liquid water are consequences of intermolecular forces.

IPR2020-00770
United Therapeutics EX2007
Page 3214 of 7335

As we have developed ideas about chemistry, we have emphasized the forces that bind atoms together into molecules. In Chapters 8 and 9, for example, we described the bonding forces that exist *within molecules*. These are called **intramolecular forces.** In Chapter 5, on the other hand, we described the properties of a gas using the ideal gas model, which assumes that the forces acting *between molecules* of a gas are negligible. In reality, there are indeed forces between molecules. These forces are called **intermolecular forces.** They affect the properties of gases and explain the existence and properties of liquids and solids.

Intermolecular forces are considerably weaker than intramolecular forces. In a liquid, for example, intermolecular forces are weak enough to allow individual molecules to move about relatively freely. On the other hand, intramolecular forces are strong enough to prevent atoms from breaking away from the molecules to which they are bonded.

Our discussion of bonding ignored relatively weak intermolecular interactions, but to understand the properties of liquids and solids, we must take these interactions into account. Intermolecular forces "lock" molecules into the fixed positions that characterize a solid and prevent vaporization of molecules in the liquid phase. This chapter is devoted to describing intermolecular forces and their role in the world of chemistry.

10.1 THE NATURE OF INTERMOLECULAR FORCES

We can begin an exploration of intermolecular forces by considering the properties of the elements. At room temperature and pressure, all but 13 of the elements are solids. Two others, mercury and bromine, are liquids, leaving only 11 elements that are gases. Only for these 11 gases are intermolecular forces small enough to neglect at room temperature. More commonly, intermolecular forces are strong enough to lock molecules in place in the solid state.

THE HALOGENS

The halogens, the elements from column VII of the periodic table, provide a good introduction to intermolecular forces. The halogens are most stable as diatomic molecules: F_2, Cl_2, Br_2, I_2, and At_2. At room temperature and pressure, fluorine and chlorine are gases, bromine is a liquid, and iodine is a solid. Figure 10-1 shows the strikingly different physical appearances of these elements.

The bonding patterns of the four halogens are identical. Each molecule contains two atoms held together by a single covalent bond that can be described by the overlap of valence *p* orbitals. In contrast to this common bonding pattern, bromine and iodine differ from chlorine and fluorine in their macroscopic physical appearance and in their molecular behavior, as Figure 10-2 illustrates.

Fluorine and chlorine molecules move freely throughout their gaseous volume, traveling many molecular diameters before colliding with one another or with the

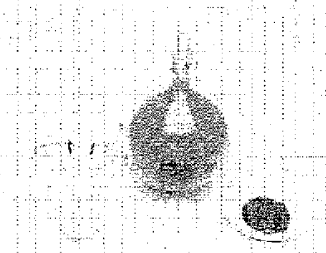


FIGURE 10-1
Under ambient conditions, chlorine is a pale yellow-green gas, bromine is a dark red liquid, and iodine is a purple crystalline solid.

The heaviest halogen, astatine, is a highly unstable radioactive element. Astatine is extremely rare and has no chemical applications.

A bonding description of F_2 is given in Chapters 8 and 9. The other diatomic molecules form bonds in an analogous manner, using valence p orbitals.

IPR2020-00770
United Therapeutics EX2007
Page 3215 of 7335

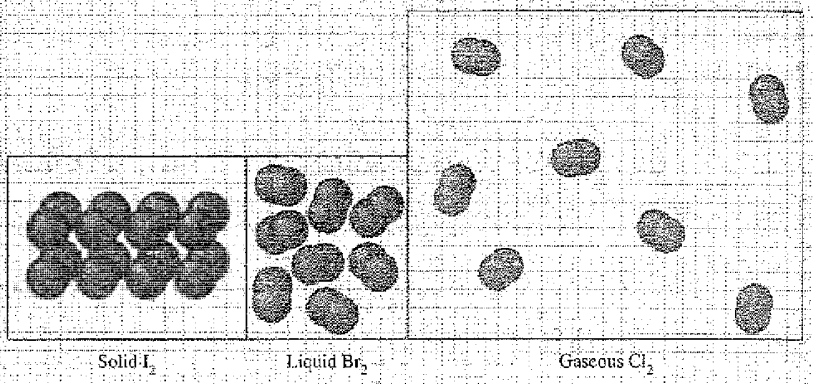


FIGURE 10-2
Molecular representations of solid I_2, liquid Br_2, and gaseous Cl_2 demonstrate why gases, liquids, and solids behave differently. A gas is mostly empty space, so the molecules are free to move about the entire volume of their container. Molecules in a liquid, on the other hand, are packed closely together but can still move past one another. A crystalline solid contains a regular array of molecules that vibrate about favored positions but cannot move freely by one another.

walls of their container. Because much of the volume of a gas is empty space, samples of gaseous F_2 and Cl_2 readily expand or contract in response to changes in pressure. This freedom of motion indicates that the intermolecular forces between these molecules are quite small.

Molecules of liquid bromine also move about relatively freely, but there is not much empty space between molecules. A liquid cannot be compressed significantly by increasing the pressure because molecules are already in close contact with one another. Also, a liquid does not expand significantly if the pressure above it is reduced. This is because intermolecular forces in a liquid are large enough to prevent the molecules from breaking away from one another.

Solid iodine has even less empty space between molecules than liquid bromine. Furthermore, the molecules in this solid do not move freely past one another. A sample of solid iodine contains highly regular crystals in which I_2 molecules are arranged in ordered arrays. Each molecule vibrates back and forth about a single lowest-energy position, but it cannot slide easily past its neighbors. Like liquids, solids do not expand or contract significantly when pressure decreases or increases.

Bromine does not exist as a gas at room temperature and iodine molecules cannot move freely because intermolecular forces between these molecules are relatively strong. Attractive intermolecular forces pull molecules toward one another, and energy is released as they get closer together. Molecules in a gas remain separated from one another because they have sufficient kinetic energy to overcome these attractive forces. Molecules in a liquid or solid remain close to one another because they lack sufficient kinetic energy to overcome these attractive forces. Hence whether a substance is a gas, liquid, or solid depends on the balance between the energy of motion of its molecules and the stabilization energy generated by its intermolecular forces.

The graph in Figure 10-3 shows that the intermolecular stabilization energy is substantially greater for Br_2 than for F_2. At room temperature, fluorine molecules have more kinetic energy of motion than the stabilization energy of F_2-F_2 interactions, whereas bromine molecules have enough kinetic energy to move freely about but insufficient energy of motion to overcome the intermolecular forces that hold them together in the liquid phase. At room temperature, iodine molecules are locked in position in the solid state because the stabilization energy between I_2 molecules is even larger than that between Br_2 molecules. To summarize, whether a substance is a gas, a liquid, or a solid depends on the balance between its intermolecular stabilization energy and its average molecular energy of motion.

IPR2020-00770
United Therapeutics EX2007
Page 3216 of 7335

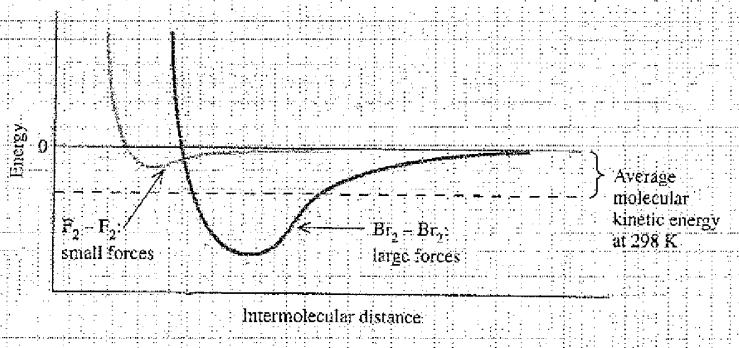


FIGURE 10-3
Intermolecular attractive forces stabilize molecules that are close to one another. The plot shows that there are larger attractive energies between bromine molecules than between fluorine molecules. This is the reason that at room temperature, fluorine is more stable as a gas, but bromine is more stable as a liquid.

Because the energy of motion depends on temperature, changing the temperature changes the balance between interaction energy and energy of motion and eventually changes the stable form of matter. For example, liquid bromine boils when it is heated to 59 °C at atmospheric pressure, forming gaseous bromine. Similarly, gaseous chlorine condenses when it is cooled to −34 °C at atmospheric pressure, forming liquid chlorine. At −101 °C, moreover, liquid chlorine becomes a solid. Fluorine liquefies at −188 °C and solidifies at −220 °C.

The link between kinetic energy and temperature is described in Chapter 5.

REAL GASES

Fluorine and chlorine are gases under ambient conditions. Yet both gases can be liquefied by lowering the temperature sufficiently. This shows the existence of attractive forces sufficient to hold molecules in the confined volume of the liquid phase at low temperature. Therefore the assumption of the ideal gas model—that intermolecular forces in a gas can be neglected—cannot be correct under conditions that cause a gas to liquefy. In other words, neither Cl_2 nor F_2 behaves ideally under all conditions.

The ideal gas model also assumes that molecular sizes can be neglected, yet no substance can be compressed indefinitely. When the distance between molecules gets small enough, repulsive forces among their electron clouds strongly resist further reduction of the volume. This is shown by the steeply rising plots of Figure 10-3. Thus finite molecular sizes also lead to deviations from ideal gas behavior.

What effect do intermolecular forces and molecular volumes have on real gases? In other words, how close do real gases come to ideal behavior? To see how far real gases stray from the ideal gas model, we can compare experimental values of real gas properties with those computed from the ideal gas equation. A convenient way to make these comparisons is to examine the experimental ratio, PV/nRT. For an ideal gas, this ratio, which is called the *compressibility*, must equal 1.

Figure 10-4 shows how compressibility varies with pressure for chlorine gas at room temperature. If chlorine were ideal, the compressibility would always be 1, as shown by the red line on the graph. Notice in the inset of Figure 10-4 that chlorine behaves very nearly ideally at pressures around 1 atmosphere (atm). In fact, its compressibility deviates from 1.0 by less than 4% at pressures below 4 atm. As the pressure increases, however, the deviations become increasingly significant. At 100 atm, chlorine is far from ideal because chlorine molecules are close enough together for attractive forces to play a significant role. Figure 10-4 also indicates that up to about 375 atm pressure, the compressibility of Cl_2 is *smaller* than 1, which means that intermolecular attractions hold chlorine molecules somewhat closer

IPR2020-00770
United Therapeutics EX2007
Page 3217 of 7335

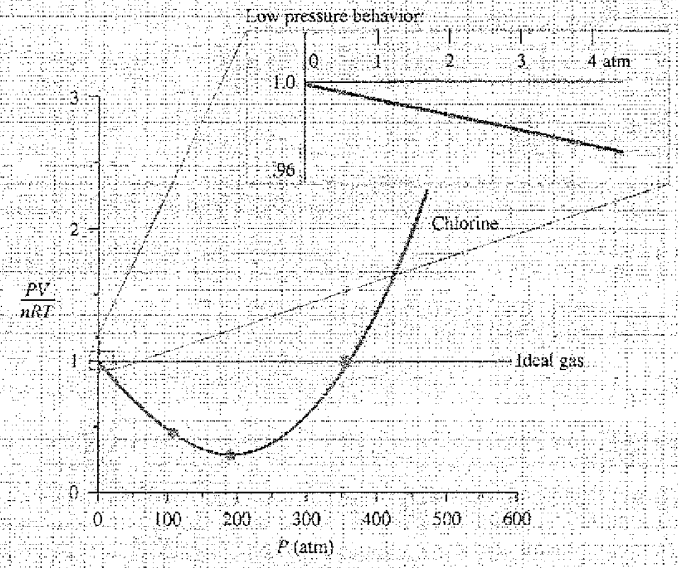


FIGURE 10-4
Variation in PV/nRT with pressure for chlorine gas at room temperature. The inset at the upper right shows the low-pressure region on an expanded scale.

together, on average, than would be the case for an ideal gas. At pressures greater than 375 atm, the compressibility becomes *larger* than 1. This is the effect of finite molecular size. At high enough pressure, molecules are so close together that repulsive interactions outweigh attractive ones.

Every gas deviates from ideal behavior. Given this fact, does it make sense to use the ideal gas model to discuss the properties of real gases? The answer is "yes," as long as conditions do not become too extreme. The gases that chemists usually work with, such as chlorine, helium, and nitrogen, are nearly ideal at and above room temperature at pressures below about 10 atm.

At high pressure, every gas shows deviations from ideal behavior. Figure 10-5 shows compressibilities of He, F_2, CH_4, and N_2, which are gases at room temperature. Notice that the compressibility of helium increases steadily as pressure increases. Interatomic forces are too small to reduce the compressibility below 1, but the finite size of helium atoms generates deviations from ideality that become significant at pressures above 100 atm.

Deviations from ideal behavior always decrease as temperature increases. Figure 10-6 shows compressibility plots for fluorine at several temperatures. Notice that

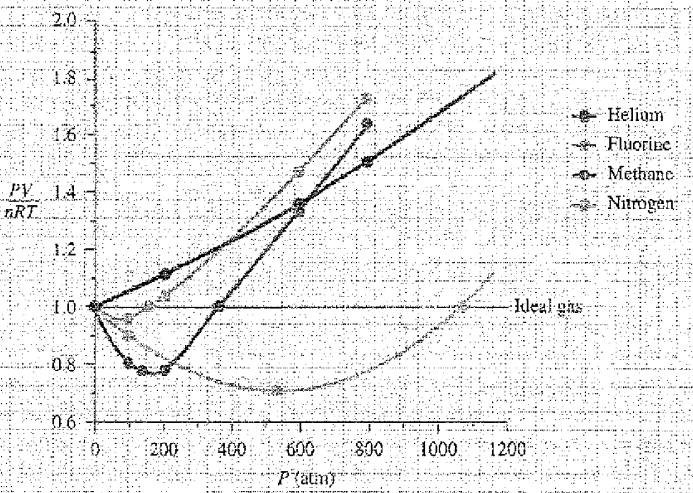


FIGURE 10-5
Compressibilities of He, F_2, CH_4, and N_2 at 300 K. Even substances that we normally think of as gases are not completely ideal.

IPR2020-00770
United Therapeutics EX2007
Page 3218 of 7335

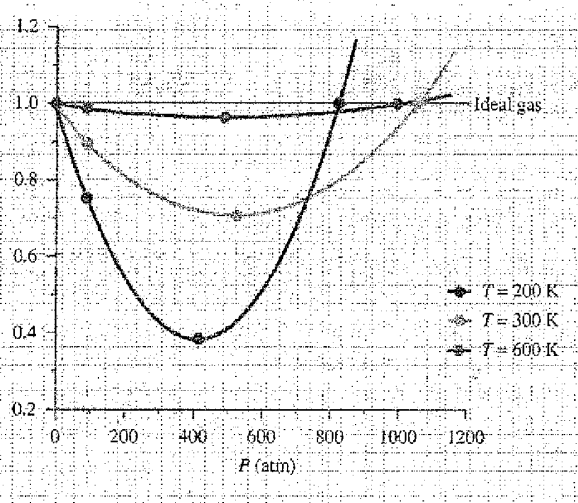


FIGURE 10-6
Variation in PV/nRT with pressure for fluorine gas at several temperatures. As temperature increases, the behavior of all gases becomes more nearly ideal.

fluorine deviates considerably from ideal behavior at 200 K and high pressure but that it is nearly ideal at 600 K, even at 1000 atm. High temperature means high average kinetic energy, and molecules with high energy have more than enough energy to overcome intermolecular forces of attraction.

DISPERSION FORCES

The strength of intermolecular interactions in a liquid determines its normal boiling point, which is the temperature at which liquid converts to vapor at a pressure of 1.00 atm. A liquid boils when the average kinetic energy of its molecules becomes larger than the stabilization energy between molecules. Thus a low boiling point signifies small intermolecular forces, whereas a high boiling point signifies large intermolecular forces. Among the halogens, fluorine boils at −188 °C, chlorine at −34 °C, bromine at 59 °C, and iodine at 185 °C. These boiling points indicate that intermolecular forces between halogen molecules increase with atomic number.

To explain this trend in forces, we can examine what happens when two halogen molecules approach each other. Each molecule contains positive nuclei surrounded by a cloud of negative electrons. As two molecules approach each other, the nucleus of one molecule attracts the electron cloud of the other. At the same time the two electron clouds repel each other. Because electrons are highly mobile, however, their orbitals can change shape to minimize electron-electron repulsion, as shown in Figure 10-7. This distortion of the electron cloud creates a temporary charge imbalance, giving the molecule a slight positive charge at one end and a slight negative charge at the other. The net attractive forces generated by all these temporary charge imbalances are called **dispersion forces.**

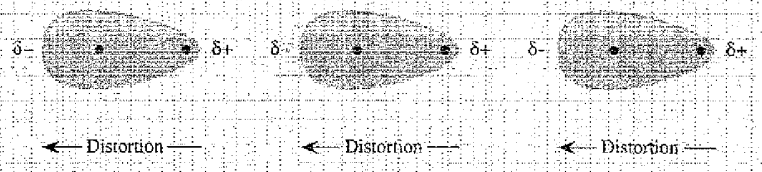


FIGURE 10-7
Schematic view of how dispersion forces arise. As the molecule in the center approaches the one on the left, its electron cloud distorts slightly in response to coulombic attraction to the nuclei of the other molecule. This creates a small, temporary positive charge at the right end of the center molecule, which in turn distorts the electron cloud of the molecule on the right.

IPR2020-00770
United Therapeutics EX2007
Page 3219 of 7335

FIGURE 10-8
Iodine's electron cloud is much larger and much more polarizable than fluorine's. Iodine therefore has stronger dispersion forces than fluorine, which is why F_2 is a gas and I_2 is a solid at room temperature.

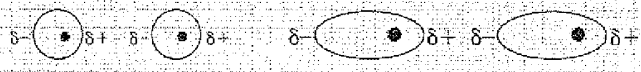
The magnitude of dispersion forces depends on how easy it is to distort the electron cloud of the molecule. The ease of distortion is called molecular **polarizability** because distortion of an electron cloud generates a temporary polarity within the molecule. As Figure 10-8 illustrates, the large electron cloud of an I_2 molecule distorts more readily than the small electron cloud of F_2. Both F_2 and I_2 contain 14 valence electrons, but those of F_2 are in relatively compact $n = 2$ orbitals, whereas those of I_2 occupy highly diffuse $n = 5$ orbitals. As a result, the valence orbitals of I_2 distort much more readily than those of F_2, generating large dispersion forces that make I_2 a solid at room temperature. This reasoning is extended to include the elemental rare gases in Sample Problem 10-1.

SAMPLE PROBLEM 10-1 BOILING POINT TRENDS

At room temperature, neon and xenon are gases, but both become liquids if the temperature is low enough. Draw a molecular picture showing the relative sizes and polarizabilities of atoms of neon and xenon, and use the picture to determine which substance has a lower boiling point.

METHOD: The boiling point of a substance depends on the magnitude of its intermolecular forces, which in turn depend on the polarizability of its electron cloud. Monatomic gases contain atoms rather than molecules, so we must assess *interatomic* forces for these substances.

The only force acting between atoms of rare gases is due to the polarizability of their electron clouds. The valence electrons of neon are in small, $n = 2$ atomic orbitals that have low polarizability, whereas those of xenon are in relatively large, polarizable $n = 5$ orbitals. The smaller electron cloud of neon distorts less than the larger electron cloud of xenon when two atoms approach each other, as a molecular picture illustrates.



Neon ($n = 2$) Xenon ($n = 5$)

Less polarizability means smaller partial charges and weaker intermolecular forces. Thus neon has the lower boiling point.

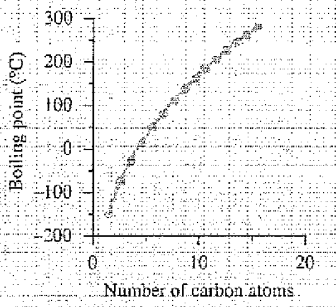


FIGURE 10-9
The boiling points of alkanes increase with the length of their carbon chains.

It is easier to distort the electron cloud of a large molecule than of a small molecule. Thus size also affects polarizability. Figure 10-9 shows how the boiling points of alkanes change as the carbon chain gets longer. As alkanes get longer, their electron clouds become larger and more polarizable, making dispersion forces larger and raising the boiling point. For example, at room temperature methane (CH_4) is a gas, pentane (C_5H_{12}) is a liquid, and eicosane ($C_{20}H_{42}$) is a waxy solid. Figure 10-10 compares the polarizabilities of pentane and decane.

Among otherwise similar substances, more extended molecules have higher polarizabilities than more compact molecules. This trend is illustrated by the boiling points of the three isomers with the formula C_5H_{12}. Figure 10-11 shows that the

IPR2020-00770
United Therapeutics EX2007
Page 3220 of 7335

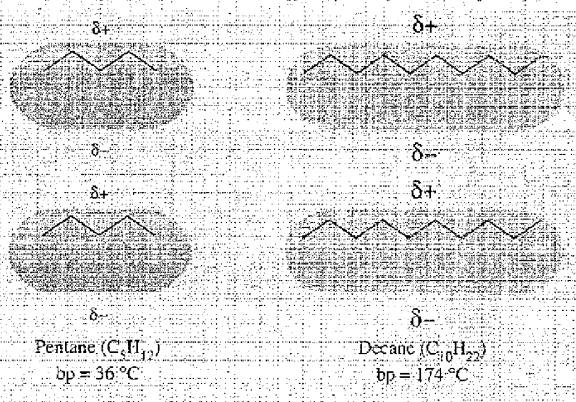


FIGURE 10-10
Large alkanes have higher boiling points than small alkanes. Their dispersion forces are larger because of the increased polarizability of their larger electron clouds.

highest-boiling isomer, pentane, is most extended and the lowest-boiling isomer, 2,2-dimethylpropane, is most compact, with 2-methylbutane in between in compactness and boiling point.

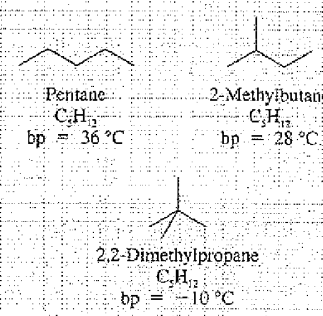
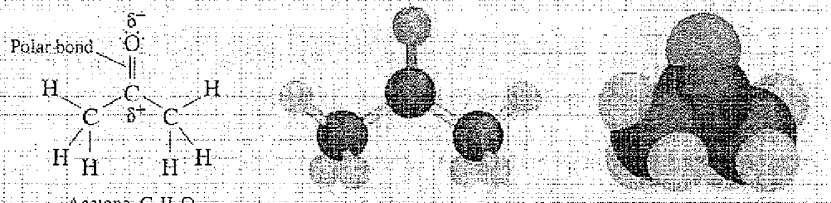


FIGURE 10-11
The three isomers with chemical formula C_5H_{12} have somewhat different boiling points because polarizability increases as molecules become more extended.

DIPOLAR FORCES

Dispersion forces exist between all molecules, but some substances remain liquid at much higher temperatures than can be accounted for by dispersion forces alone. As examples, consider 2-methylpropane and acetone, whose structures are shown in Figure 10-12. These two molecules have the same molar mass, similar shape, and nearly the same number of valence electrons (34 vs. 32). They are so similar that we might expect the two compounds to have similar boiling points, but acetone is a liquid at room temperature, whereas 2-methylpropane is a gas. Acetone boils at 56 °C, whereas 2-methylpropane boils at −12 °C. Why does acetone remain a liquid at temperatures well above the boiling point of 2-methylpropane? The cause is charge asymmetry in the molecular structure of acetone.



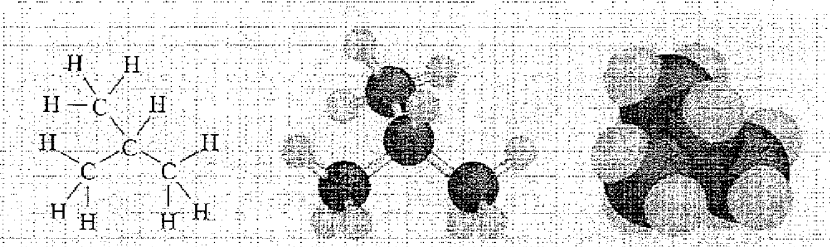


FIGURE 10-12
Models and Lewis structures of 2-methylpropane and acetone show that they have similar molecular shapes. The important difference between them is the polar bond in acetone.

IPR2020-00770
United Therapeutics EX2007
Page 3221 of 7335

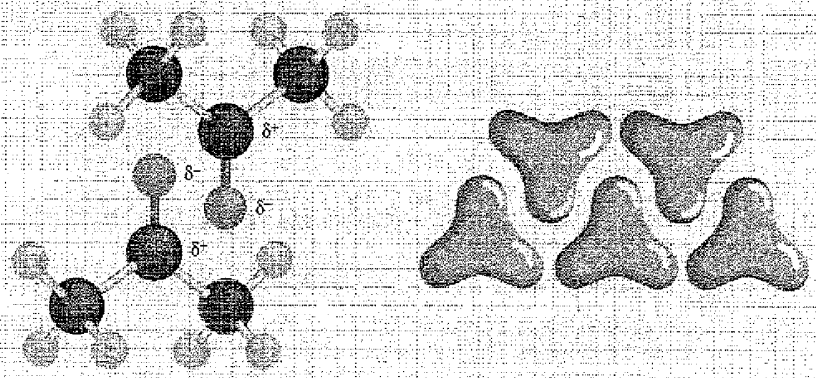


FIGURE 10-13
In liquid acetone the permanent dipoles tend to align with positive ends nearer negative ones and negative ends nearer positive ones.

Electronegativity and polarized bonds were introduced in Section 8.2.

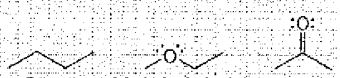
Remember from the bonding picture presented in Chapter 8 that chemical bonds are polarized toward the more electronegative atom. Whereas carbon ($\chi = 2.5$) and hydrogen ($\chi = 2.2$) have nearly equal electronegativity, the electronegativity of oxygen is considerably larger ($\chi = 3.4$). Thus a C—O bond is highly polarized, with a partial negative charge on the oxygen atom and a partial positive charge on the carbon atom.

When two polar acetone molecules approach each other, they align with the positive end of one molecule close to the negative end of the other. In a liquid array, this repeating pattern of head-to-tail alignment gives rise to significant net attractive **dipolar forces** among the molecules. Figure 10-13 illustrates this schematically.

The dispersion forces in acetone are about the same as those in 2-methylpropane, but the addition of dipolar forces makes the total amount of intermolecular attraction between acetone molecules substantially greater than that between molecules of 2-methylpropane. Consequently, acetone boils at a considerably higher temperature than 2-methylpropane. Sample Problem 10-2 provides some additional comparisons of dispersion forces and dipole forces.

SAMPLE PROBLEM 10-2 BOILING POINTS AND STRUCTURE

The line structures of butane, methyl ethyl ether, and acetone are as follows. Explain the trend in boiling points: butane (0 °C), methyl ethyl ether (8 °C), and acetone (56 °C).



METHOD: We can explain these boiling points in terms of dispersion forces and dipolar forces. First, assess the magnitudes of dispersion forces, which are present in all substances, and then look for molecular polarity.

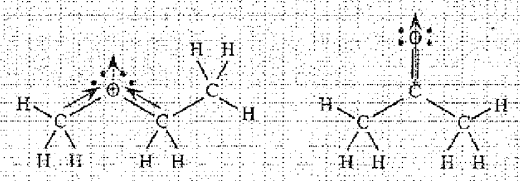
Dispersion forces depend primarily on the size of the electron cloud and secondarily on the shape of the molecule. A table helps organize the available information.

Substance	Boiling point	Electrons	Shape
Butane	0 °C	34	Elongated
Methyl ethyl ether	8 °C	34	Elongated
Acetone	56 °C	32	Compact

IPR2020-00770
United Therapeutics EX2007
Page 3222 of 7335

The table shows that dispersion forces alone cannot account for the range in boiling temperatures. Methyl ethyl ether and butane have the same number of electrons and similar shapes; yet their boiling points are different. Acetone, which has fewer electrons and a more compact shape than the other compounds, has smaller dispersion forces; yet it boils at a higher temperature. The order of boiling points indicates that acetone is a more polar molecule than methyl ethyl ether, which in turn is more polar than butane.

We expect butane to have a low polarity because of the small electronegativity difference between carbon and hydrogen. Acetone and methyl ethyl ether, on the other hand, contain polar C—O bonds. The molecular geometry about the polar C—O bonds reveals why acetone is more polar than methyl ethyl ether. The full Lewis structures of these molecules show that the oxygen atom in the ether has a steric number of four and bent geometry. Arrows show the charge displacement for each polar bond.



Methyl ethyl ether Acetone

Notice that the two C—O bond dipoles in methyl ethyl ether partially cancel each other, leaving a relatively small polarity, whereas the polar C—O bond in acetone is unopposed. Thus acetone is more polar than methyl ethyl ether.

SECTION EXERCISES

10.1.1 On the basis of the behavior of the other elements of Group VII, predict whether At$_2$ will be a gas, liquid, or solid at room temperature. Sketch its intermolecular stabilization energy curve relative to that of F_2.

10.1.2 From the compressibility curves shown in Figure 10-5, determine which of the four gases has the largest intermolecular forces and which has the smallest. State your reasoning.

10.1.3 Explain the following differences in normal boiling points:
(a) Kr boils at −152 °C, and propane boils at −42 °C.
(b) $C(CH_3)_4$ boils at 10 °C, and CCl_4 boils at 77 °C.
(c) N_2 boils at −196 °C, and CO boils at −91.5 °C.

10.2 HYDROGEN BONDING

Methyl ethyl ether is a gas at room temperature (boiling point, or bp, = 8 °C), whereas 1-propanol, whose structure is shown in Figure 10-14, is a liquid (bp = 97 °C). Both compounds have the same molecular formula, C_3H_8O, and both have chains of four atoms, C—O—C—C and O—C—C—C. Consequently, the electron clouds of these two molecules are about the same size, and their dispersion forces are comparable. Each molecule has an sp^3-hybridized oxygen atom with two polar single bonds, so their dipolar forces should be similar. The very different boiling points of 1-propanol and methyl ethyl ether make it clear that dispersion and dipolar forces do not reveal the entire story of intermolecular attractions.

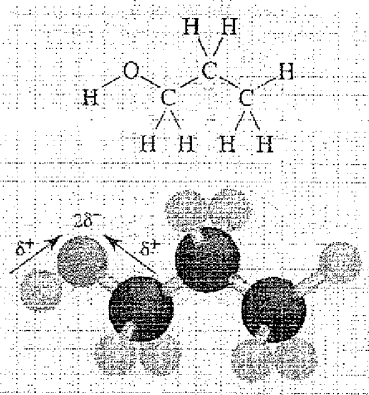


FIGURE 10-14
The Lewis structure and ball-and-stick model of 1-propanol. Polar bonds to the oxygen atom have been highlighted in the ball-and-stick model.

IPR2020-00770
United Therapeutics EX2007
Page 3223 of 7335

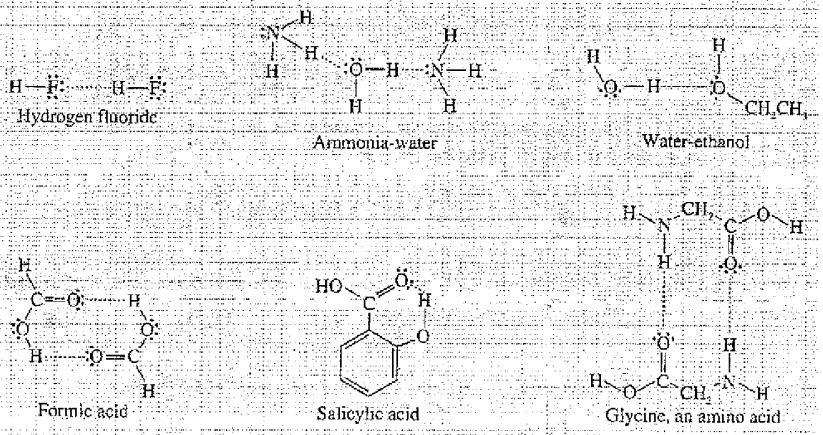


FIGURE 10-15
Examples of hydrogen bonding among some small molecules.

The forces of attraction between 1-propanol molecules are stronger than those between methyl ethyl ether molecules because of a special intermolecular interaction called a **hydrogen bond.** A hydrogen bond occurs when electrons from a highly electronegative atom are partially shared with a positively polarized hydrogen atom. Hydrogen bonds are only 5% to 10% as strong as covalent bonds, but they are comparable to and sometimes stronger than dipolar and dispersion interactions.

There are two requirements for hydrogen bond formation. The covalent bond to hydrogen must be highly polar, and there must be nonbonding electrons on a highly electronegative atom. These requirements restrict hydrogen bond formation to molecules that have hydrogen atoms bonded to fluorine, oxygen, and nitrogen. The presence of any of these elements signals that hydrogen bonding may occur. Figure 10-15 shows representative examples of hydrogen bonding. Dashed lines designate hydrogen bonds to indicate the partially bonding nature of these interactions.

Chlorine and sulfur atoms are also sufficiently electronegative to participate in hydrogen bonding, and there is some evidence for such bonding in HCl. However, the nonbonding electrons on these atoms are in diffuse 3p orbitals that do not interact as strongly with a hydrogen atom as electrons in more compact 2p orbitals.

Notice from the examples shown in Figure 10-15 that hydrogen bonds can form between *different* molecules (for example NH_3···H_2O) and *identical* molecules (for example, HF···HF). Also notice that molecules can form more than one hydrogen bond (for example, glycine) and that hydrogen bonds can form within a molecule (for example, salicylic acid) and between molecules. Sample Problem 10-3 explores the possibilities for hydrogen bond formation.

SAMPLE PROBLEM 10-3 FORMATION OF HYDROGEN BONDS

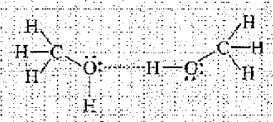
In which of the following systems will hydrogen bonding play an important role: CH_3F, $(CH_3)_2CO$ (acetone), CH_3OH, and NH_3 dissolved in $(CH_3)_2CO$?

METHOD: Hydrogen bonds occur when both polar H—X bonds and electronegative atoms with nonbonding pairs of electrons are present. Lewis structures provide the best starting point in determining whether these requirements are met:

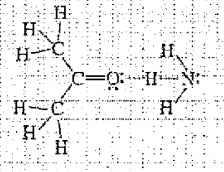
IPR2020-00770
United Therapeutics EX2007
Page 3224 of 7335

Acetone and CH_3F each has an electronegative atom with nonbonding pairs, but neither has highly polar H—X bonds. Thus there is no hydrogen bonding between molecules of these substances.

Its O—H bond gives CH_3OH an electronegative atom with nonbonding pairs and a polar O—H bond. Hydrogen bonding occurs between the O—H hydrogen atom on one molecule and the oxygen atom of a neighboring molecule:



For a solution of ammonia in acetone, we must examine both components. Acetone has an electronegative oxygen atom with nonbonding pairs, whereas NH_3 has a polar N—H bond. Consequently, a mixture of these two compounds will display hydrogen bonding between ammonia's hydrogen atoms and acetone's oxygen atoms:



For extra practice, draw a similar picture that shows the hydrogen bonding in a solution of acetone in water.

BINARY HYDROGEN COMPOUNDS

The graph in Figure 10-16 shows that there are regular periodic trends in the boiling points of the binary hydrogen compounds. For each column of the periodic table the boiling points of the binary hydrogen compounds increase from top to bottom of the column. This trend can be attributed to increasing dispersion forces: The more electrons the molecule has, the stronger the dispersion forces and the higher the boiling

Many elements in the *p* block of the periodic table have electronegativities close to that of hydrogen. This means that the H-X bonds have low bond polarity, so dispersion forces dominate the intermolecular interactions.

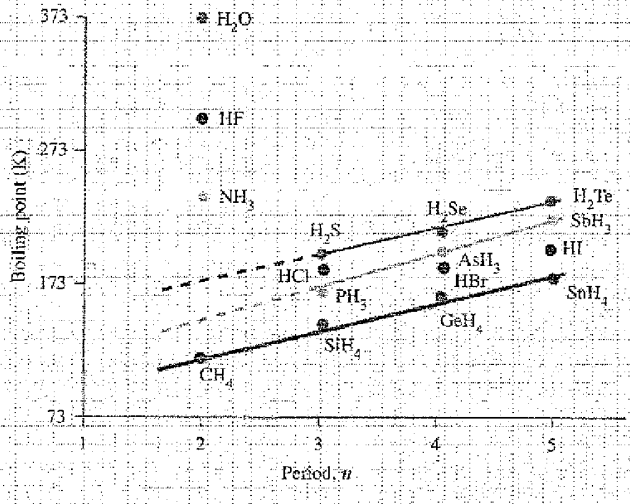


FIGURE 10-16
Periodic trends in the boiling points of binary hydrogen compounds. Notice that H_2O, HF, and NH_3 are exceptions to the trends.

IPR2020-00770
United Therapeutics EX2007
Page 3225 of 7335

point. For example, H_2S (18 electrons) boils at −60 °C, whereas H_2Se (36 electrons) and H_2Te (54 electrons) boil at −41 °C and −4 °C, respectively.

Ammonia, water, and hydrogen fluoride depart dramatically from the periodic behavior illustrated in Figure 10-16. This is because their molecules experience particularly large intermolecular forces resulting from hydrogen bonding. In hydrogen fluoride, for instance, partial donation of an electron pair from the highly electronegative fluorine atom of one HF molecule to the electron-deficient hydrogen atom of another HF molecule creates a hydrogen bond. Similar interactions among many HF molecules result in a network of hydrogen bonds that gives HF a boiling point much higher than those of HCl, HBr, and HI.

Water has a substantially higher boiling point than hydrogen fluoride, which indicates that the overall strength of hydrogen bonding in H_2O is greater than that in HF. Fluorine has the highest electronegativity, however, so the strongest *individual* hydrogen bonds are those in HF. The higher boiling point of water reflects the fact that it forms more hydrogen bonds *per molecule* than hydrogen fluoride.

Every hydrogen atom in liquid HF is involved in a hydrogen bond, but there is only one polar hydrogen atom per molecule. Thus each HF molecule participates in two hydrogen bonds with two other HF partners. There is one hydrogen bond involving the partially positive hydrogen atom and a second involving the partially negative fluorine atom. In contrast, a water molecule has *two* hydrogen atoms that can form hydrogen bonds and *two* nonbonding electron pairs on each oxygen atom. This permits every water molecule to form *four* hydrogen bonds.

Hydrogen bonding in liquid water and, even more strikingly, in solid ice creates a three-dimensional network that puts each oxygen atom at the center of a distorted tetrahedron. Figure 10-17 shows that two arms of the tetrahedron are regular covalent O—H bonds, whereas the other two arms of the tetrahedron are hydrogen bonds to two different water molecules.

HYDROGEN BONDING IN BIOMOLECULES

Hydrogen bonding is particularly important in biochemical systems because biomolecules contain many oxygen and nitrogen atoms that participate in hydrogen bonding. For example, the amino acids from which proteins are made contain NH_2

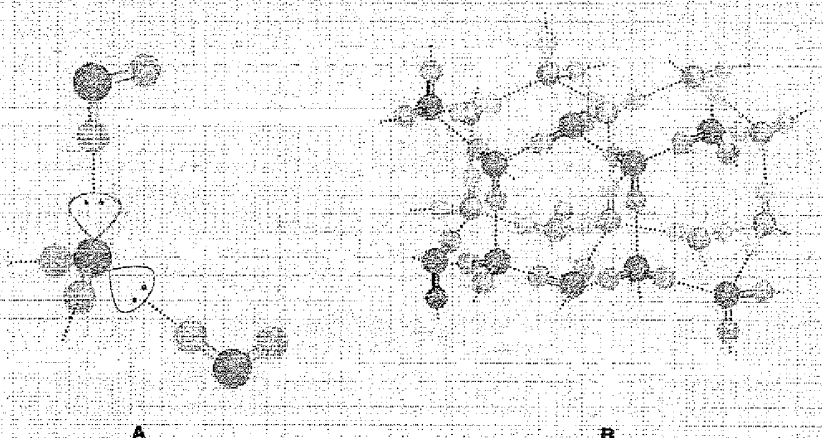


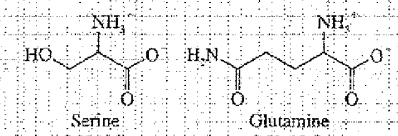
FIGURE 10-17
The structure of ice. **A,** Each oxygen atom is at the center of a distorted tetrahedron of hydrogen atoms. The tetrahedron is composed of two short covalent O····H bonds and two long H—O hydrogen bonds. **B,** Water molecules are held in a network of these tetrahedra.

IPR2020-00770
United Therapeutics EX2007
Page 3226 of 7335

(amino) and CO_2H (carboxylic acid) groups. Four different types of hydrogen bonds exist in these systems: O—H···N, N—H···O, O—H···O and N—H···N. Hydrogen bonding between glycine molecules is shown in Figure 10-15, and Sample Problem 10-4 provides further illustrations. We examine more details of hydrogen bonding in biomolecules in Chapter 11.

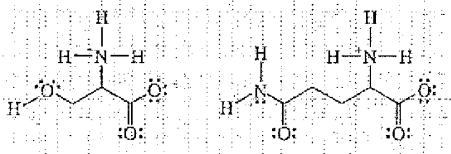
SAMPLE PROBLEM 10-4 HYDROGEN BONDING IN AMINO ACIDS

In aqueous solution, amino acids undergo intramolecular proton transfer to form ions. The line structures of two amino acid ions, serine and glutamine, follow. For each molecule, identify the hydrogen atoms that can form hydrogen bonds and the electronegative atoms to which hydrogen bonds can form.

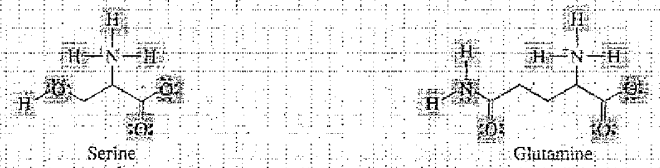


Serine $C_3H_7NO_3$ Glutamine $C_5H_{10}N_2O_3$

METHOD: Hydrogen atoms in polar H—X bonds can form hydrogen bonds with lone pairs on other nitrogen, oxygen, or fluorine atoms. To identify hydrogen bonding possibilities, we need Lewis structures to determine the locations of nonbonding pairs of electrons. Carbon atoms are never involved in hydrogen bonds, so we can ignore the carbon framework of the molecules. The following partial Lewis structures show the nonbonding pairs of electrons and the polar H—X bonds:



Any N—H or O—H hydrogen atom in these molecules can participate in hydrogen bonding. These are highlighted in blue in the following structures. The N atoms and O atoms with lone pairs of electrons can also participate in hydrogen bonding. These atoms are highlighted in yellow.



Serine Glutamine

Dispersion forces, dipole interactions, and hydrogen bonds are all much weaker than covalent intramolecular bonds. For example, the average C—C bond energy is 345 kJ/mol, whereas dispersion forces are just 0.1 to 5 kJ/mol for small alkanes such as propane. Moreover, dipolar interactions between polar molecules such as acetone range from 5 to 20 kJ/mol, and hydrogen bonds vary from 5 to 50 kJ/mol.

Recall from Chapter 9 that bond energy is the amount of energy required to break 1 mol of a particular bond. Table 9-2 lists bond energies.

IPR2020-00770
United Therapeutics EX2007
Page 3227 of 7335

SECTION EXERCISES

10.2.1 Which has a higher boiling point, CH_3F or CH_3OH? Why? Illustrate your answer with a molecular picture.

10.2.2 Acetone and methanol have nearly equal boiling points. What types of intermolecular forces does each exhibit? What does the similarity in boiling points tell you about the relative magnitudes of each type of force in these two compounds?

10.2.3 There are nine important hydrogen bonding interactions. One of them is O—H···O. Draw the other eight. For each of the nine, draw a Lewis structure of a specific example using real molecules.

10.3 PROPERTIES OF LIQUIDS

Liquids are intermediate in behavior between gases and solids. Whereas intermolecular forces among gas molecules are weak enough to allow molecules of a gas to move freely throughout their container, intermolecular forces in a solid are strong enough to hold the molecules fixed in place. In a liquid, intermolecular forces confine the molecules to a specific volume, but they are insufficient to keep the molecules from moving from place to place within the body of the liquid. Table 10-1 summarizes the physical properties of the three states of matter. Notice how the properties of liquids fall in between those of gases and solids.

SURFACE TENSION

Water drips from a faucet in nearly spherical liquid droplets rather than in a film. Drops are more stable than films because of intermolecular attractions. The physical property describing this increased stability is **surface tension,** which is the resistance of a liquid to an increase in its surface area.

Figure 10-18 illustrates at the molecular level why liquids exhibit surface tension. A molecule in the *interior* of a liquid is completely surrounded by other molecules, each of which exerts attractive forces as described in the previous sections. A molecule at a liquid *surface*, on the other hand, has other molecules beside it and beneath it but *none above it*. As a result, the net intermolecular force on molecules at the surface pulls them toward the interior of the liquid.

Molecules at the surface of a liquid are less stable than those within it, so a liquid is most stable when the fewest molecules are at its surface. This occurs when the liquid has minimum surface area. Spheres have less area per unit volume than any

It is not absolutely correct to say that there are *no* molecules above a surface, for there are always molecules in the gas above the liquid. However, the concentration of molecules in the gas phase is so low that they can be ignored.

TABLE 10-1 PHYSICAL PROPERTIES OF THE STATES OF MATTER

PROPERTY	GAS	LIQUID	SOLID
Volume	Variable	Fixed	Fixed
Shape	Variable	Variable	Fixed
Compressibility	Large	Almost zero	Almost zero
Fluidity	Very high	High	Very low
Diffusion rate	High	Moderate	Very low

IPR2020-00770
United Therapeutics EX2007
Page 3228 of 7335

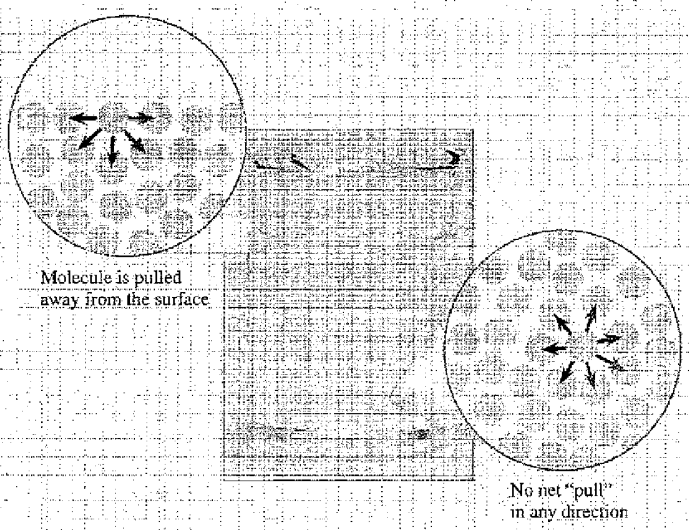
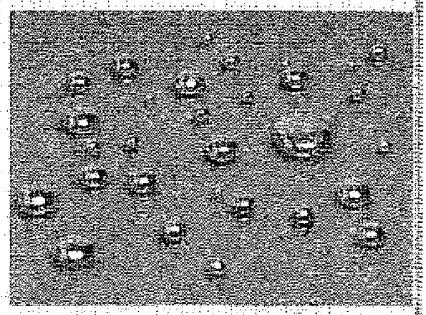


FIGURE 10-18
In the interior of a liquid *(right)*, each molecule experiences equal forces in all directions. A molecule at the surface of a liquid *(left)* is pulled back into the liquid by intermolecular forces.

other shape, so small drops of a liquid tend to be spheres. Large drops are affected by gravitational forces, which distort them from spheres.



A small drop of mercury adopts a spherical shape, which minimizes the number of atoms at the surface. Gravitational force "flattens out" larger, more massive drops.

ADHESIVE FORCES

Molecules in liquids in contact with the solid surfaces of their containers experience two different sets of forces. First, they are attracted to the other molecules in the liquid, as just described. The intermolecular forces between liquid molecules are called **cohesive forces.** Second, they are attracted to molecules in the container walls. The intermolecular forces between molecules in the wall of a container and the molecules of a liquid are called **adhesive forces.**

One manifestation of adhesive forces is the curved surface of an aqueous solution contained in a narrow glass tube. Glass surfaces are mostly silicates with many exposed oxygen atoms and O—H groups. These form strong hydrogen bonds with water molecules. As a result, water adheres well to glass. The liquid maximizes its contact with the walls by forming a concave surface.

Figure 10-19 shows that the curvature of the liquid surface increases as the diameter of the tubing becomes smaller. When the tube diameter is smaller than a few millimeters, water actually "climbs the walls," pulled upward by forces of adhesion. The upward movement of water against the force of gravity is called **capillary action.** Capillary action can also operate in reverse. For example, water molecules do not adhere well to a surface coated with a film of wax, so immersing a wax-coated capillary tube in water will cause the water level to fall rather than rise. Sample Problem 10-5 treats another example of reverse capillary action.

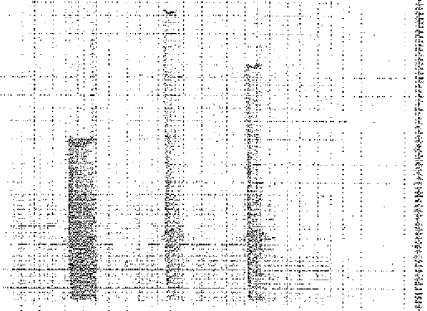


FIGURE 10-19
When adhesive forces exceed cohesive forces, a liquid takes on a shape that maximizes its contact with the walls of the container. Water forms a concave surface in cylindrical glass containers and rises inside narrow-diameter tubing.

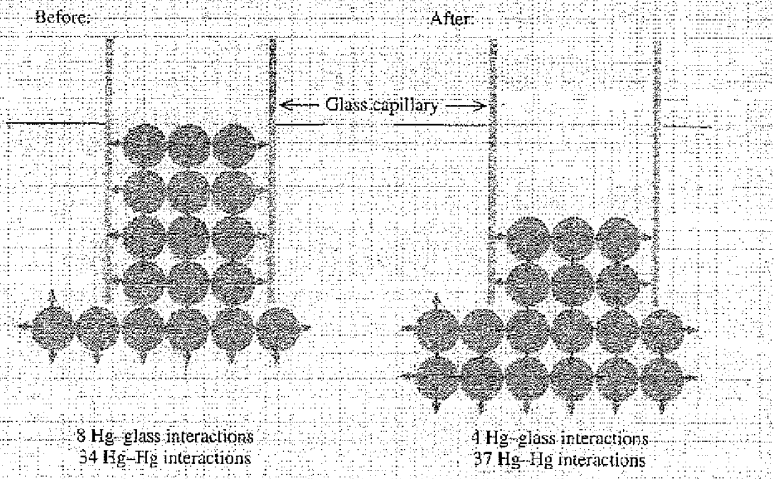
SAMPLE PROBLEM 10-5 CAPILLARY ACTION IN MERCURY

When a narrow tube is inserted into liquid mercury, the liquid level inside the tube *drops*. Explain this observation in terms of intermolecular forces, and illustrate it with a drawing.

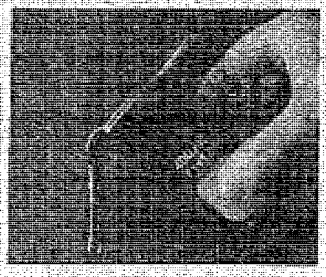
IPR2020-00770
United Therapeutics EX2007
Page 3229 of 7335

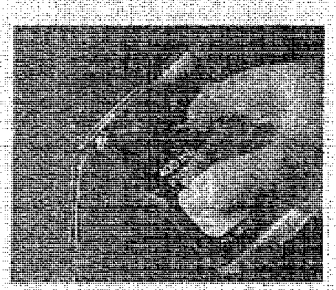
METHOD: The balance between cohesive intermolecular forces (within the liquid) and adhesive intermolecular forces (between liquid and solid molecules) determines how a liquid behaves in contact with a solid surface. We must interpret the observation in terms of the contacts between liquid and solid molecules.

The observation is that the liquid level *drops* when a tube is inserted into liquid mercury. A picture helps show what takes place.



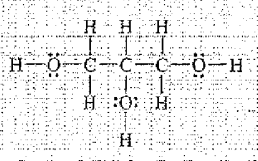
When the liquid inside the tube falls to a lower height, the number of *adhesive* interactions decreases, because fewer liquid atoms are in contact with the solid glass surface. Conversely, the number of *cohesive* interactions increases because the mercury now has less surface area. We conclude that cohesive forces in liquid mercury are *greater* than adhesive forces between mercury atoms and glass.





Honey is far more viscous than water.

Glycerol is highly viscous because its molecules are large enough for some tangling to occur and because it forms extensive hydrogen bonding networks via its three polar O—H bonds:



VISCOSITY

Water can be poured very quickly from one container to another, salad oil pours more slowly, and honey on a cold day seems to take forever. A liquid's resistance to flow is called its **viscosity**; the larger its viscosity, the more slowly the liquid pours. Viscosity can be determined by measuring the time it takes for a specific amount of liquid to flow through a tube of known diameter under the force of gravity.

Viscosity measures how easily molecules slide by one another, and this depends on molecular shapes and intermolecular forces. Molecular shape strongly influences viscosity. Liquids such as water, acetone, and benzene, whose molecules are small and compact, have low viscosity. In contrast, large molecules such as the hydrocarbons found in oils tend to get tangled up with each other. Tangling inhibits the flow of molecules and leads to high viscosity. In addition, strong cohesive forces make it harder for molecules to move about. As a result, substances whose molecules form hydrogen bonds have higher viscosity than those whose molecules do not. Hydrogen bonding makes water more viscous than acetone (C_3H_6O). Glycerol, whose molecules combine a hydrocarbon's tendency to tangle with the "stickiness" of hydrogen bonding, has a very high viscosity.

Molecules move faster as temperature increases, and this allows them to slide by one another more easily. Consequently, viscosity decreases as temperature increases. This dependence is quite noticeable for highly viscous substances such as honey and syrup, which are much easier to pour when hot than when cold.

IPR2020-00770
United Therapeutics EX2007
Page 3230 of 7335

SECTION EXERCISES

10.3.1 Water forms a film on the surface of a "clean" buret and drains without forming droplets. Water forms beads on the surface of a "dirty" buret. What can you conclude about the nature of the forces between clean glass and water molecules and those between dirty glass and water molecules?

10.3.2 Aqueous solutions do not adhere well to polyethylene because polyethylene contains very long chains of nonpolar CH_2 groups: $CH_3—(CH_2)_n—CH_3$, where n is larger than 200. Does the water rise or fall when a polyethylene straw is dipped into a glass of water? Draw a picture that shows what happens to the water molecules inside the straw. You need not show the details of structure of the surface or water molecules, but your drawing should indicate the adhesive and cohesive interactions.

10.3.3 In what way is a beaker of octadecane like a plate of spaghetti? Octadecane is the C_{18} linear alkane.

10.4 PROPERTIES OF SOLIDS

One of the most active areas of research in modern chemistry, physics, and engineering is the development of new solid materials. Solids play an ever-expanding role in modern society, from complex materials that act as high-temperature superconductors, to heat-resistant tiles for the outer "skin" of the space shuttle, to new tissue-compatible solids used for surgical implants.

BONDING IN SOLIDS

In preceding chapters, we introduced ionic, metallic, and covalent solids; each is held together by a different type of interaction. As described in Chapter 7, ionic solids contain cations and anions strongly attracted to each other through coulombic interactions. These forces are *interionic* rather than *intermolecular*. As we described in Chapter 9, the solid structure of metals comes from electrons in highly delocalized valence orbitals. Each metal atom can be viewed as a cation embedded in a "sea" of mobile valence electrons. Semimetals such as silicon and germanium also contain delocalized orbitals extending throughout their entire structures. Covalent solids such as quartz, graphite, and diamonds, described in Chapters 8 and 9, contain infinite arrays of atoms, all linked by covalent bonds in a single huge three-dimensional network.

A fourth type of solid contains individual molecules that are held in place by combinations of dispersion and dipolar forces, with hydrogen bonding playing an important role when it is present. Examples of such molecular solids include iodine, ice, table sugar, and wax. Molecular solids tend to have relatively low melting points as a consequence of the relatively small forces that hold their molecules in place.

Solids are classified as **crystalline** or **amorphous**. Crystalline solids have a highly regular appearance because they contain ordered arrays of atoms, molecules, or ions at the microscopic level. Diamonds, sugar crystals, quartz, and table salt are examples of crystalline solids. Amorphous solids, on the other hand, show much less regularity in appearance because their molecules are distributed irregularly throughout the solid. Cotton candy, glass, and wax are examples of amorphous solids.

IPR2020-00770
United Therapeutics EX2007
Page 3231 of 7335

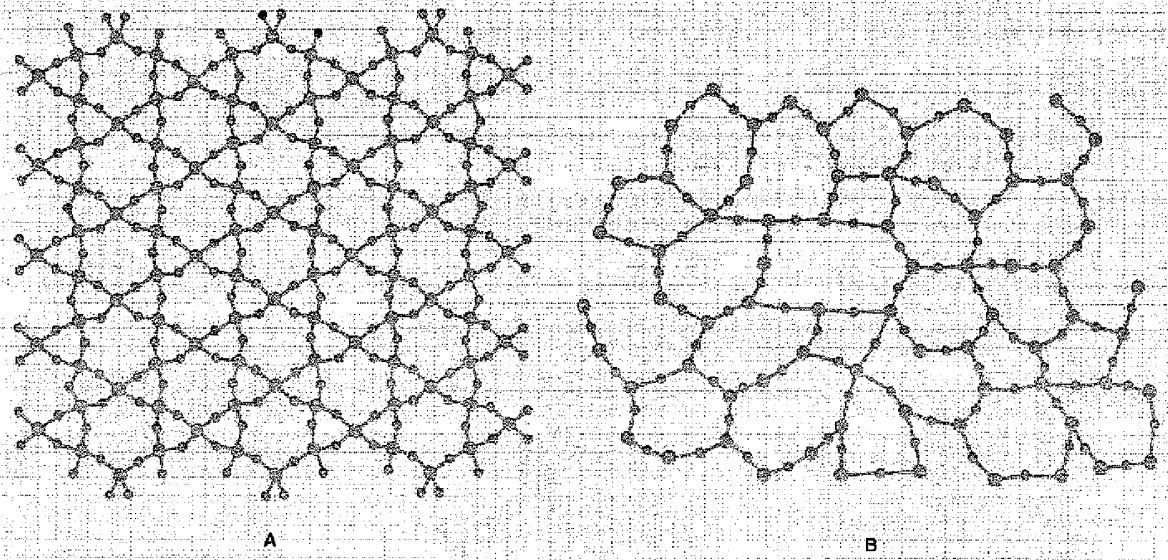
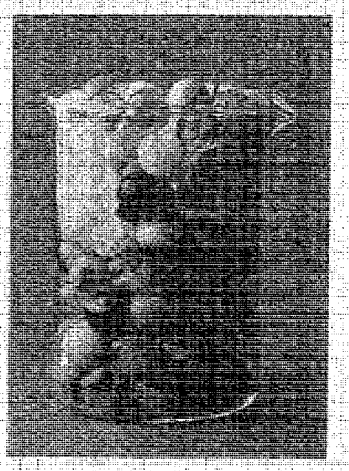


FIGURE 10-20
A, Quartz is a crystalline form of silicon dioxide containing a three-dimensional array of SiO_2 units linked by highly regular covalent bonding. **B,** Glass also has a three-dimensional array of SiO_2 units, but in this case bond arrangement is irregular, and the solid is amorphous. Both **A** and **B** are two-dimensional representations. The actual structures are three-dimensional.

Silicon dioxide forms crystalline and amorphous solids. Quartz is a crystalline form of silicon dioxide found in minerals all over the world. Each tetrahedral silicon atom is bonded to a total of four oxygens in a highly symmetrical three-dimensional network. This strong bonding network gives silicon dioxide its high melting point of 1710 °C. Slow cooling of molten SiO_2 gives crystalline quartz, but rapid cooling gives an amorphous material called *glass*. Figure 10-20 shows representations of quartz and glass. Both structures are three-dimensional networks, but the two-dimensional view given in the figure is sufficient to show the differences between crystalline and amorphous solids.



A close-packed arrangement of marbles packs the maximum number into the minimum volume.

CRYSTALLINE SOLIDS

Crystals (Figure 10-21) often have a high degree of symmetry. Some of the most valued materials of society are precious gemstones, which are crystals of rare and richly colored minerals. The following general features characterize crystalline solids:

- Crystals are uniform in structure. Crystals of a particular substance have common geometric features regardless of how they are formed.
- The shape of a crystal is characterized by its parallel faces and edges. The edges of a crystal usually intersect at fixed angles.
- When a crystal breaks into smaller pieces, fragmentation occurs along crystal edges. The smaller pieces have the same characteristic angles as the original crystal.
- Crystals have a high degree of symmetry.

CLOSE-PACKED CRYSTALS

A solid is most stable when each atom or molecule is close to as many others as possible. An arrangement that accomplishes this is described as a **close-packed**

IPR2020-00770
United Therapeutics EX2007
Page 3232 of 7335

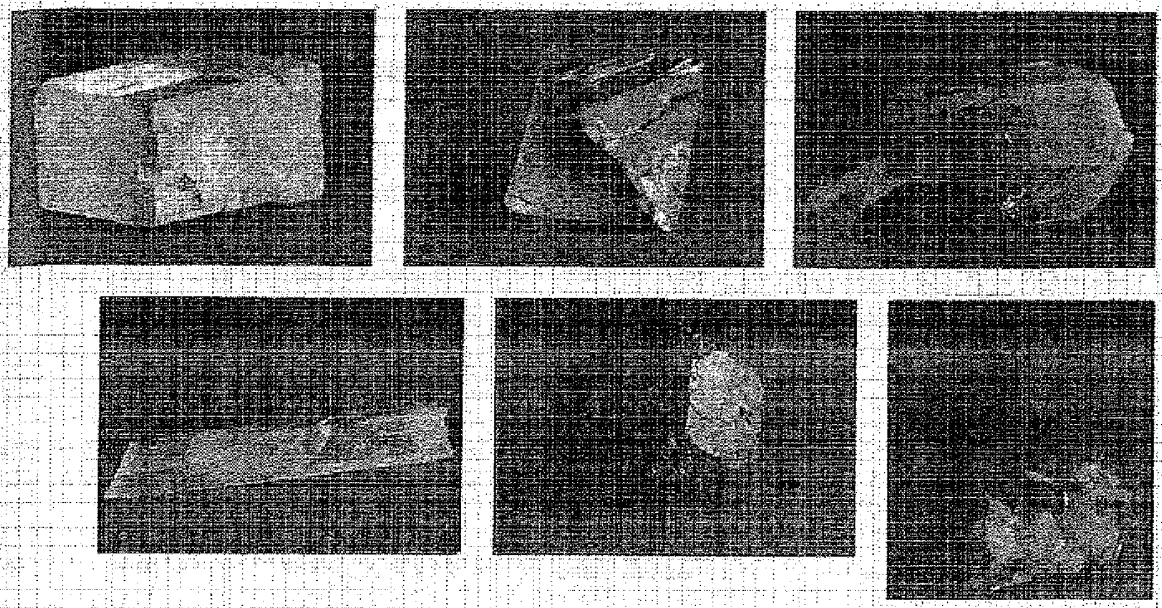


FIGURE 10-21
Crystalline materials can have many shapes. Often, they are highly regular and strikingly beautiful.

structure. Close-packed structures have atoms or molecules arranged so that the empty space around them is minimized.

To visualize a close-packed atomic solid, think of the atoms as spheres that are packed as compactly as possible. Begin by assembling a single planar layer as shown in Figure 10-22, *A*. Notice that the most compact planar arrangement places each sphere within a regular hexagon formed by six others. Now add a second layer of spheres. To achieve a most compact arrangement, each sphere will nestle in one of the "dimples" between a trio of spheres in the first layer, as shown in Figure 10-22, *B*. As additional spheres are added, the second layer eventually looks identical to the lower layer, except that it is offset slightly to allow the spheres to nestle in the dimples formed by the layer below.

Now consider adding a third layer of spheres. This new layer will look just like the other two, but it can nest in two different ways because there are two sets of dimples in the second layer. As Figure 10-22, *C* shows, one set is located directly above the spheres in the first layer. If spheres in the third layer lie in these dimples, the third layer is directly above the first, and the resulting three-dimensional structure is a **hexagonal close-packed structure.** If spheres in the third layer lie in the other set of dimples, the third layer is offset from both of the lower layers. This arrangement is a **cubic close-packed structure.**

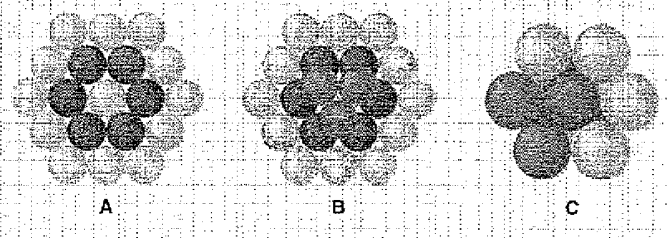
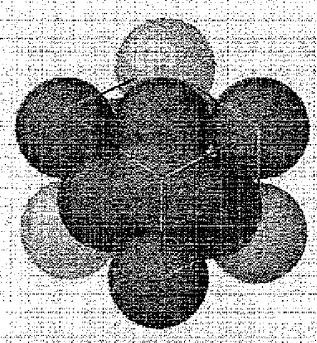
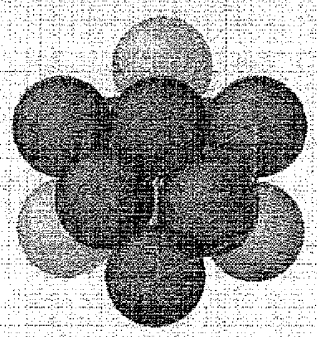


FIGURE 10-22
A, Spheres close-packed in a layer generate a hexagonal pattern. **B,** When a second layer is packed on top of the first, each sphere in the second layer nestles in the dimple created by three adjacent spheres in the lower layer. **C,** The second layer has two different sets of dimples, one directly above the spheres in the first layer (shaded in blue) and the other offset from the spheres in the first layer (shaded in orange).

IPR2020-00770
United Therapeutics EX2007
Page 3233 of 7335



A



B

FIGURE 10-23
A cubic close-packed array viewed at an angle to reveal its cubic structure. **A,** Two faces of the cube have been outlined. A sphere sits in the center of each face. **B,** One corner sphere has been removed to show more clearly the underlying hexagonal plane of spheres.

To see the cubes in a cubic close-packed structure, we need to rotate the array so that the hexagonal planes tilt upward at a 45-degree angle, as shown in Figure 10-23, *A*. Notice that we have rotated the entire array but have not changed the relative positions of the spheres. From this perspective, three spheres from one hexagonal plane lie along a diagonal of a square, with one sphere from each adjacent plane forming the other two corners of the square. At right angles to this first square are other sets of squares that form cubes. Figure 10-23, *B* shows one such cube with one corner sphere removed to reveal the original hexagonal planar array.

The exploded views in Figure 10-24 show yet another way of looking at the hexagonal close-packed and cubic close-packed crystal types. In the hexagonal close-packed structure, notice that the *third* layer lies directly above the first, the fourth above the second, and so on. Thus we can label the layers ABAB, and so on. In the cubic close-packed structure, the third layer is offset from the other two, but the *fourth* layer is directly above the first. Thus this arrangement can be labelled ABCABC, and so on.

Atoms and molecules with spherical symmetry often form crystals with hexagonal close-packed or cubic close-packed geometry. For instance, magnesium and zinc crystallize with their atoms in a hexagonal close-packed array. Silver, aluminum, and gold, on the other hand, crystallize in the cubic close-packed arrangement. Argon solidifies at low temperature as a cubic close-packed crystal, and neon can solidify in either form.

The packing in ionic crystals requires that ions of opposite charges alternate with one another to maximize interionic attraction. For many 1:1 ionic crystals such as NaCl, the most stable arrangement is two interlocking face-centered cubic arrays, as is illustrated in Figure 10-25.

Another type of arrangement, which is shown in Figure 10-26, *A*, is a **body-centered cubic structure.** A body-centered cube can be constructed by assembling a set of spheres in a *square* planar array, as shown in Figure 10-26, *B*, and then nesting a second set of spheres in the dimples of the first set, as shown in Figure

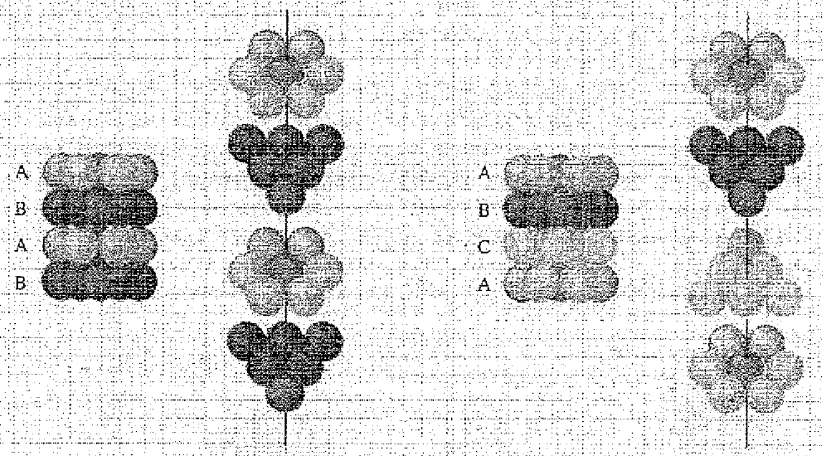


FIGURE 10-24
Side and expanded views of the hexagonal close-packed and cubic close-packed crystal types. In the hexagonal close-packed structure, spheres on both sides of any plane are in the same positions, and the third layer is directly above the first. In the cubic close-packed structure, layers take up three different positions, and the fourth layer is directly above the first.

IPR2020-00770
United Therapeutics EX2007
Page 3234 of 7335

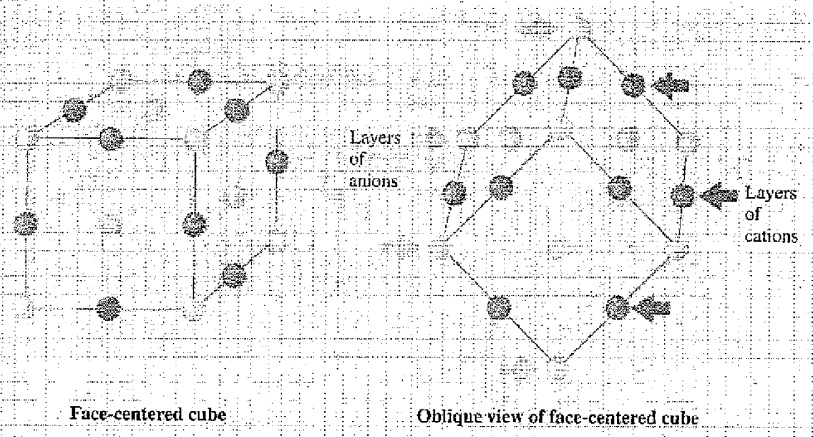


FIGURE 10-25
Ionic crystals such as NaCl contain face-centered cubic arrangements of each ion. In this view a cube is drawn with the cations, shown as yellow spheres, at its corners and in the centers of the faces. The anions, shown as blue spheres, occupy positions at the center of each edge of the cube. A view from an oblique angle reveals that this structure contains alternating hexagonal planar arrays of cations and anions.

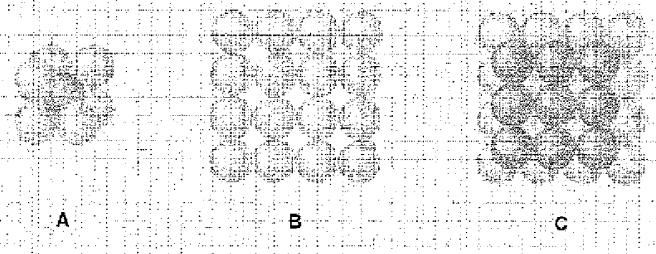


FIGURE 10-26
A body-centered cubic array is made up of layers of spheres arranged in a square pattern. The basic pattern **(A)** has one corner sphere removed to reveal the sphere nested in the center of the cube. The array can be constructed by laying down a square layer of spheres **(B)**, and then placing a second square layer in the dimples between the spheres **(C)**. A third layer directly above the first completes the cubes.

10-26, *C*. This arrangement gives a second square array, on which yet another set can be nested.

UNIT CELLS

Any crystal is a near-infinite array of atoms, molecules, or ions arranged in some regular repeating pattern. Because of this repeating pattern, every crystal has one smallest unit from which the entire pattern can be assembled. This minimum unit is called a **unit cell**. The idea of the unit cell is illustrated in two dimensions by the art of M.C. Escher, as shown in Figure 10-27. Escher often used symmetrical patterns aligned together to create an overall design. The repeating units can be visualized as "tiles" placed edge to edge. A unit cell in a crystal is a three-dimensional fragment stacked together like a set of blocks.

The body-centered cubic crystal provides a good illustration of three-dimensional unit cells. A drawing of the unit cell of this crystal is shown in Figure 10-28, *A*. Notice that it is a cube defined by the centers of eight iron atoms that surround a central iron atom. This cube contains a central Fe atom and portions of additional Fe atoms. The body-centered cubic crystal is built up by stacking together many unit cells, as shown in Figure 10-28, *B*. It takes eight unit cells stacked together to complete one of the corner atoms, so each unit cell contains one eighth of an atom at each of its corners. The cell has eight such corners, so each unit cell contains two complete iron atoms.

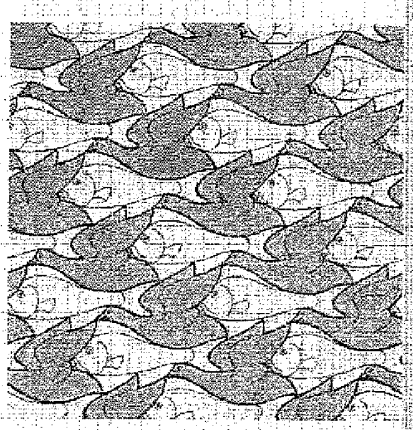


FIGURE 10-27
M.C. Escher used repeating patterns to create works of art with exquisite symmetry. The repeating patterns in Escher's work are two-dimensional analogs of the unit cells that define the symmetry of a crystalline solid.

IPR2020-00770
United Therapeutics EX2007
Page 3235 of 7335

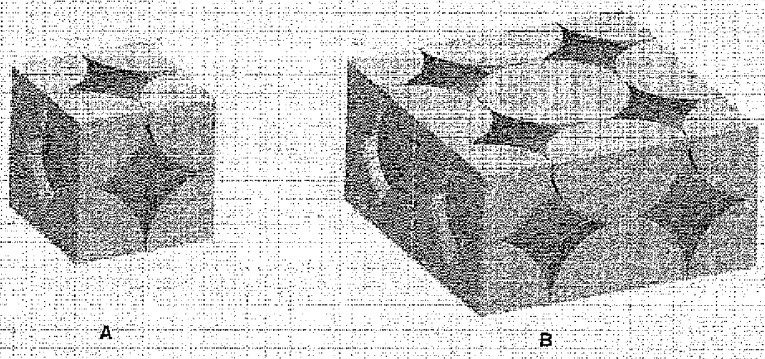


FIGURE 10-28
A, The unit cell of iron, which forms body-centered cubic crystals. There is an iron atom at the center of the unit cell, and each of the eight corners contains one eighth of an iron atom, giving a total of one complete atom. **B,** Four unit cells stacked together. The four unit cells touch at the center, forming half of an iron atom. When a second set of four unit cells is placed on top of the first, the iron atom becomes complete and is surrounded by eight other iron atoms.

MOLECULAR SOLIDS

Up to now, we have described the crystalline arrays favored by spherical objects such as atoms, but most molecules are far from spherical. The photo of stacks of produce in Figure 10-29 illustrates that nonspherical objects require more elaborate arrays to achieve maximum stability. Compare the stack of bananas in the figure with the stack of oranges. Just as the stacking pattern for bananas is less symmetrical than that for oranges, the structural patterns of most molecular crystals are less symmetrical than crystals of spherical atoms, reflecting the lower symmetry of the molecules that make up the crystal.

Dispersion forces, dipolar forces, and hydrogen bonds hold the molecules of molecular crystals in place. Two examples of molecular crystals are naphthalene and benzoic acid. Naphthalene, which is sold as moth balls, forms white crystals in which the planar naphthalene molecules are held in place only by dispersion forces. The lattice structure of this crystal is shown in Figure 10-30. Benzoic acid forms white crystals, too, but its molecules are held in place by a combination of dispersion and hydrogen bonding forces, as illustrated in Figure 10-31.

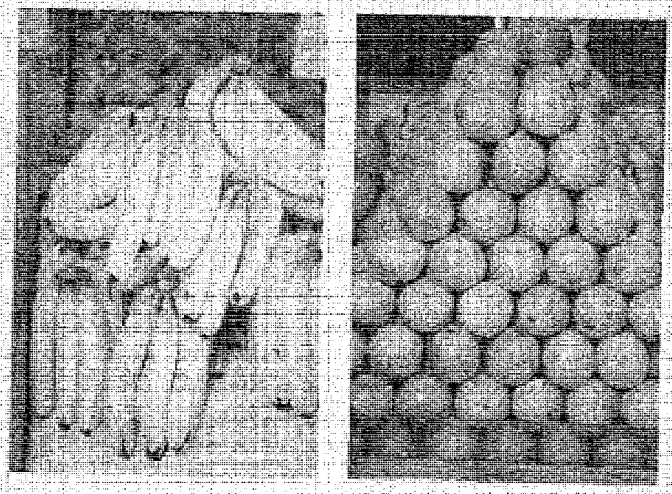
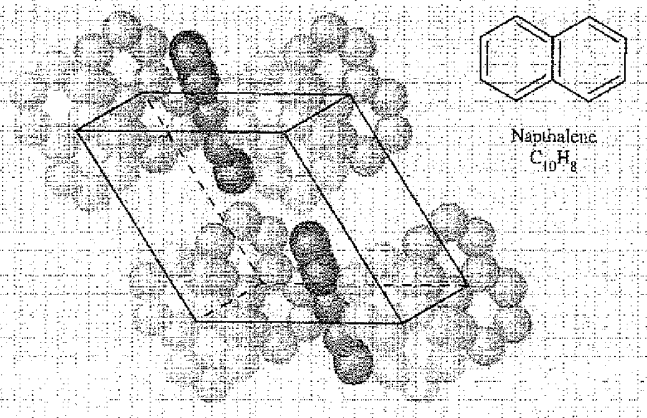


FIGURE 10-29
Nonspherical objects such as bananas require more elaborate packing schemes than spherical objects such as oranges.

IPR2020-00770
United Therapeutics EX2007
Page 3236 of 7335



Naphthalene
$C_{10}H_8$

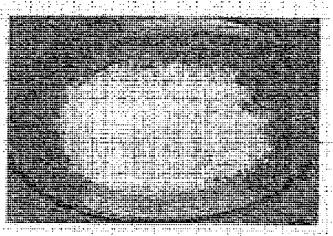
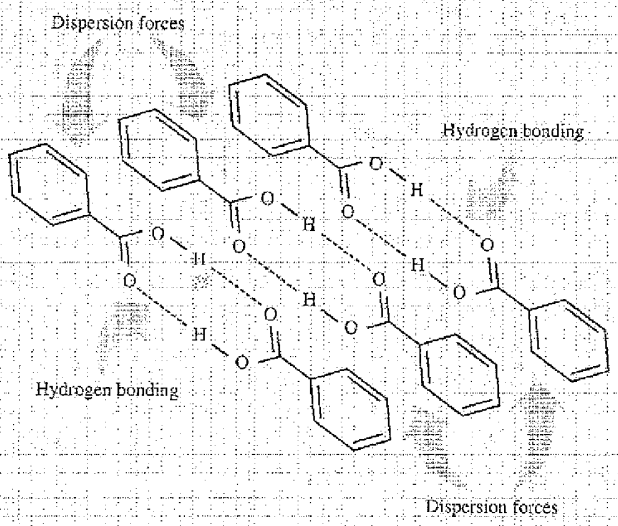


FIGURE 10-30
Naphthalene is a planar molecule. It forms crystals whose unit cell has a molecule at each corner of a prism and two molecules tilted at an angle inside the prism. The crystal is held together by dispersion forces generated primarily by the electrons of the delocalized π system.



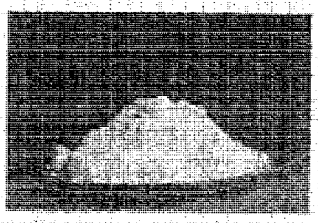


FIGURE 10-31
Crystals of benzoic acid contain pairs of molecules held together head-to-head by hydrogen bonds. These pairs then form stacks, which are held together by dispersion forces.

COVALENT SOLIDS

We described the covalent network structure of silicon dioxide in Chapter 8 and at the beginning of this section. Two other covalent solids, diamond and graphite, were introduced in Chapter 9. These two forms of carbon have very different structures (see Box 9-3), but both contain near-infinite arrays of atoms bonded covalently to one another.

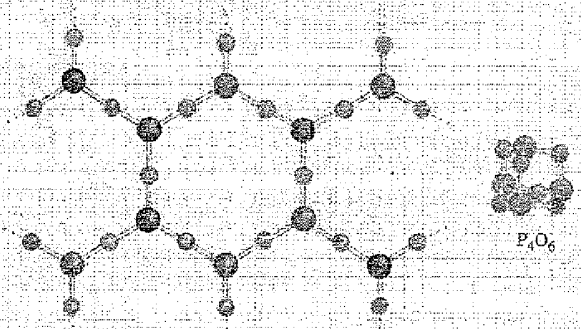
Covalent bonds make covalent solids extremely durable. Examples include the "everlasting sands" and the longevity of granite formations such as the Rock of Gibraltar. Diamonds and other valuable gemstones are covalent solids, too. Rubies and sapphires are covalent crystals of aluminum oxide with small amounts of colored transition metal ion impurities. Carborundum is a 1:1 covalent solid of silicon and

IPR2020-00770
United Therapeutics EX2007
Page 3237 of 7335

carbon that has the same lattice structure as diamonds. Carborundum is considerably less expensive than diamond but almost as strong and wear-resistant, so it is used for the edges of cutting tools. Sample Problem 10-6 compares the structures and properties of a covalent solid and a molecular solid.

SAMPLE PROBLEM 10-6 COVALENT AND MOLECULAR SOLIDS

Whereas SiO_2 melts at 1710 °C, other nonmetal oxides melt at much lower temperatures. For example, As_2O_3 sublimes directly to the gas phase at 315 °C, and P_4O_6 melts at 25 °C. Referring to the following bonding pictures and to the bonding pattern of silica in Figure 10-20, describe the forces that hold these solids together.



As_2O_3

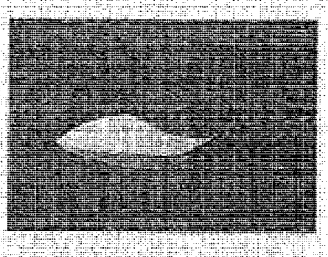
P_4O_6

METHOD: Solids may be covalent, ionic, metallic, or molecular, with different forces accounting for the stability of each type of solid. Because these are nonmetal oxides, they cannot be described as metallic. None of these oxides contains ions, so they must be covalent or molecular. The bonding patterns provide the information we need to categorize them and explain their melting temperatures.

SiO_2: The bonding pattern in silica is a three-dimensional array of strong covalent bonds. Many of these bonds must be broken before silica melts. Silica melts at 1710 °C because its three-dimensional covalent bonding network is highly stable.

As_2O_3: The bonding picture shows a two-dimensional network of covalent bonds, with no bonding between molecular planes. In this respect, arsenic trioxide is similar to graphite. It sublimes at a relatively low temperature, indicating that a small amount of energy is required to disrupt this planar bonding network. This is a covalent solid with weak covalent bonds. Actually, when As_2O_3 sublimes, it forms As_4O_6 molecules whose bonding pattern resembles that of P_4O_6. Thus much of the energy required to break the planar bonding network is recovered through the formation of new As—O bonds.

P_4O_6: The molecular structure shows that P_4O_6 is composed of discrete molecular units rather than arrays of covalent bonds. Strong covalent bonding holds the atoms in each molecule together, but each molecular unit is attracted to others only by dispersion forces. This is a molecular solid, so very little energy is required to overcome dispersion forces and allow P_4O_6 molecules to move around in the liquid state.



AMORPHOUS SOLIDS

Solid materials are most stable in crystalline form, so when a liquid is cooled slowly, it generally solidifies as crystals. When solids form rapidly, on the other hand, their atoms or molecules may become locked into positions other than those of a regular crystal, giving amorphous materials. Ordinary cane sugar is crystalline as it comes

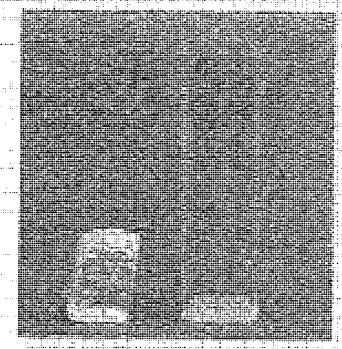
IPR2020-00770
United Therapeutics EX2007
Page 3238 of 7335

from the package, but it forms an amorphous solid when it is carefully heated until it melts and then is rapidly cooled. Cotton candy contains long threads of amorphous sugar.

Amorphous comes from Greek, *a* meaning "without," and *morph*, meaning "form."

What we call "glass" turns out to be an entire family of amorphous solids based on silica (SiO_2). Pure silica is usually found as crystals containing the regular array of covalent bonds shown in Figure 10-20. Quartz contains crystals of pure silica, whereas sand is generally crystals of silica and other minerals. When quartz is melted and then quickly cooled, however, it forms fused silica, an amorphous solid glass. Silica glass resists corrosion, transmits light well, and withstands wide variations in temperature, but it is very difficult to work with because its melting point of 1710 °C is so high. Despite its advantageous properties, therefore, pure silica glass is used only for special applications.

Sodium oxide (Na_2O) is mixed with silica to make glass that can be shaped at a lower temperature. Sodium oxide is ionic, and it breaks the Si—O—Si chain of covalent bonds. This weakens the lattice strength of the glass, lowers its melting point, and reduces the viscosity of the resulting liquid. Unfortunately, it also reduces the resistance to chemical attack so much that a stoichiometric mixture of sodium oxide and silica, Na_2SiO_3, dissolves in water and is called *water glass*.



An important scientific application of silica glass is in high-precision spectrophotometer cells for measuring ultraviolet absorption spectra.

The most desirable glass melts at a reasonable temperature and is easy to work with, yet is chemically inert. Such a glass can be prepared by adding a third component that has bonding characteristics intermediate between those of purely ionic sodium oxide and those of purely covalent silicon dioxide. Several different components are used, depending on the properties desired in the glass.

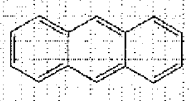
The glass used for windowpanes and bottles is soda-lime-silica glass, a composite of sodium oxide, calcium oxide, and silicon dioxide. The addition of CaO strengthens the lattice enough to make it chemically inert to most common substances. (Strong bases and HF, however, attack this glass.) Pyrex, the glass used in coffeepots and laboratory glassware, can withstand rapid temperature changes that would crack soda-lime-silica glass. Pyrex is a composite of B_2O_3, CaO, and SiO_2. Lenses and other optical components are made from glass that contains PbO. Light rays are strongly bent as they pass through lenses made of this glass. Colored glasses are obtained by adding small amounts of colored metal oxides such as Cr_2O_3 (amber), NiO (green), or CoO (brown).

Many materials that we use in this age of plastics are amorphous solids composed of extremely large molecules called *polymers*. Polymeric solids are intermediate between molecular and covalent solids. They have discrete but extremely large molecular units held together by dispersion forces. Because the molecules are so large, their covalent bonding plays an important role in determining the properties of the solid. A "plastic" can be shaped and molded because of the weak dispersion forces between polymer molecules, but it has relatively high strength because its long-chain molecules are held together by strong covalent bonds.

We discuss giant molecules in Chapter 11.

SECTION EXERCISES

10.4.1 Describe the forces that exist in (a) solid CO_2 (dry ice); (b) crystalline yellow elemental sulfur, S_8; (c) triacontane, the linear C_{30} hydrocarbon, whose melting point is 65 °C; and (d) anthracene ($C_{14}H_{10}$), whose line structure follows:



IPR2020-00770
United Therapeutics EX2007
Page 3239 of 7335

10.4.2 Predict the angles found in the crystalline fragments broken from a hexagonal close-packed crystal. What additional angles would be found in fragments from cubic close-packed crystals?

10.4.3 The unit cell of cubic close-packed crystals is a cube defined by the centers of spheres at its eight corners; there is an additional sphere embedded in the center of each face (see Figure 10-22 on p. 447). Draw this unit cell. Determine what fraction of each type of atom (corner and center of face) is within the unit cell. (HINT: How many unit cells must be stacked together to give one complete face atom?)

10.5 THE NATURE OF SOLUTIONS

Our discussion so far has focused primarily on pure substances, but much of the chemistry that occurs in the world around us involves mixtures of substances. Recall from Chapter 1 that a homogeneous mixture of chemical substances is commonly called a **solution.** The component that determines the state of the solution is the **solvent.** Normally, this component is present in greatest quantity. All other substances in the solution are called **solutes.** Solutions have special properties that we describe in the next several sections.

Most of us think of solutions as liquid mixtures. The oceans, for example, are liquid solutions in which water is the solvent and dissolved ions, gases, and molecules are the solutes. Vinegar is a liquid solution of acetic acid in water, and gasoline is a liquid solution that contains many different hydrocarbons. Gases can be solutions, as well. Two examples are the Earth's atmosphere, a solution of nitrogen, oxygen, and small amounts of several other gases, as well as natural gas, a solution of methane, ethane, and minor amounts of other hydrocarbons. Even solids can be solutions. For instance, brass is a solution of copper and zinc, and steel is a solution of a small amount of carbon dissolved in iron.

A solution is characterized by its concentration, which can vary. For example, if we add more sugar to a cup of coffee, the solution becomes more concentrated in sugar. The concentration of pollutants in the air is higher in urban areas than in rural ones. Steel can be made harder and stronger by controlling the concentration of carbon in iron. Concentration is usually expressed as molarity or as mole fraction of the solute.

Molarity (M) was first described in Section 3.7, and mole fraction (X) was defined in Section 5.5.

Except for gaseous solutions, there is usually an upper limit to the amount of solute that will dissolve in a given amount of solvent. When that limit has been reached, the solution can hold no more solute. It is then said to be a **saturated solution.** The concentration of a saturated solution is called the **solubility** of the substance in that particular solvent.

Solubilities vary widely because they depend on the intermolecular forces in the solute and solvent. For example, the solubility of NaCl in water is about 6 mol/L (M), the solubility of AgCl in water is only 10^{-5} M, and the solubility of NaCl in gasoline is virtually zero. Some substances form solutions in all proportions and are said to be completely **miscible.** Acetone and water, for example, can be mixed in any proportion from pure water to pure acetone. A few salts, such as $FeCl_3 \cdot 6H_2O$, mix with hot water in any proportion. The energetic interactions involved in the solution process underlie such variations in solubility.

IPR2020-00770
United Therapeutics EX2007
Page 3240 of 7335

"LIKE DISSOLVES LIKE"

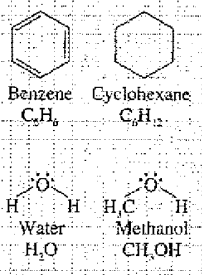
Whether or not a given substance dissolves in a liquid depends primarily on intermolecular coulombic forces of attraction. These interactions are of three types: those between ions or molecules of the pure solute, those between solvent molecules, and those between solvent and solute in the solution.

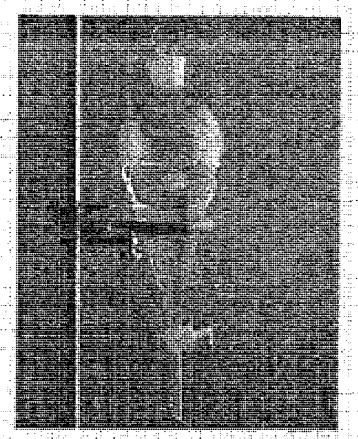
A substance dissolves if the forces of attraction between the solvent molecules and the solute molecules are comparable to or greater than the solute-solute and solvent-solvent interactions. Substances that dissolve in each other usually have similar types of intermolecular interactions, a generalization that can be summarized by the expression *like dissolves like*.

When two liquids are mixed, all three sets of intermolecular interactions are important. Consider water, methanol, benzene, and cyclohexane, which are all liquids at room temperature. Water and methanol are miscible because molecules in the pure liquids and their mixtures form many hydrogen bonds. Benzene and cyclohexane are also completely miscible because molecules in the pure liquids and their mixtures interact through the dispersion forces caused by their polarizable electron clouds. In contrast, water and benzene are nearly insoluble in each other. When mixed, benzene and water partition into distinct layers, one of nearly pure water and the other of nearly pure benzene. Water and cyclohexane are also insoluble in each other and form two layers when mixed.

The solubilities of water, methanol, benzene, and cyclohexane in one another are examples of like dissolving like. Water and methanol form hydrogen bonds. When these liquids are mixed, the degree of hydrogen bonding in the solution is about the same as that in the pure liquids. Likewise, dispersion forces in solutions of benzene and cyclohexane are about the same as those in the pure liquids. As Figure 10-32 shows, however, benzene molecules cannot dissolve in water unless they disrupt part of water's hydrogen bonding network. Because benzene does not form hydrogen bonds, the only forces of attraction between water molecules and benzene molecules are dispersion forces, and for water, hydrogen bonds are much stronger than dispersion forces. The cost of disrupting water's hydrogen bonding network is far greater than the stability gained from benzene-water dispersion forces.

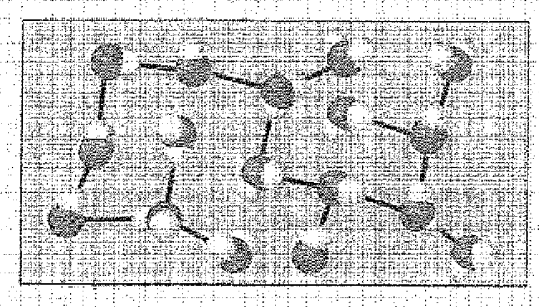
Some liquids can interact with other substances in multiple ways. Acetone, for instance, has a polar C═O double bond and a three-carbon bonding framework. The bonding framework is similar to a hydrocarbon, so acetone will mix with cyclohexane. The polar C═O group makes acetone compatible with other polar molecules such as acetonitrile (CH_3CN). Finally, the polar oxygen atom in acetone has two lone pairs of electrons that can form hydrogen bonds with hydrogen atoms from ammonia or water. Because of its versatility as a solvent, acetone is widely used to clean and rinse laboratory glassware. Sample Problem 10-7 treats several alcohols, which also display multiple types of interactions.

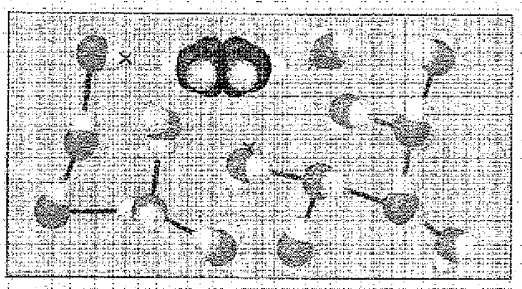




Water and benzene, which are insoluble in each other, form two layers when mixed.

FIGURE 10-32
A collection of water molecules *(left)* has an intricate hydrogen bonding network *(blue lines)*. The presence of the benzene molecule *(right)* disrupts all the hydrogen bonds marked with *x*'s.





IPR2020-00770
United Therapeutics EX2007
Page 3241 of 7335

SAMPLE PROBLEM 10-7 SOLUBILITY TRENDS

Give a molecular explanation for the following trend in alcohol solubilities in water:

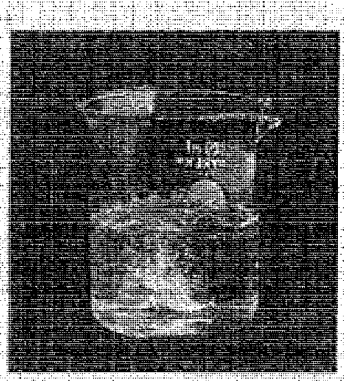
Propanol	$CH_3CH_2CH_2OH$	Completely miscible
Butanol	$CH_3CH_2CH_2CH_2OH$	1.1 M
Pentanol	$CH_3CH_2CH_2CH_2CH_2OH$	0.30 M
Hexanol	$CH_3CH_2CH_2CH_2CH_2CH_2OH$	0.056 M

METHOD: Solubility limits depend on the relative magnitude of the destabilization that occurs when solvent bonding networks and solute bonding networks are disrupted, compared with the stabilization generated by solute-solvent interactions. This problem refers to a series of aqueous solutions, which are dominated by hydrogen bonding interactions.

When any alcohol dissolves in water, the hydrogen-bonding network of water is disrupted by the nonpolar hydrocarbon part of the alcohol. Counterbalancing these disruptions, hydrogen-bonding interactions are generated in the solution between the OH groups of the alcohol and water molecules.

As the nonpolar region of an alcohol grows longer, more and more hydrogen bonds are disrupted by each solute molecule. At the same time, each alcohol listed has only one OH group, so the amount of compensating solute-solvent hydrogen bonding is the same for all the alcohols.

This explains why longer-chain alcohols are progressively less soluble in water. As the hydrocarbon chain gets longer, more destabilization is involved in inserting the alcohol into the water matrix, so the alcohol gets increasingly less soluble as the chain grows.



Zinc methyl reacts with aqueous acids.

The network bonding of metals was discussed in Section 9.6.

Recall from Section 4.6 that strong acids generate hydronium ions in aqueous solution.

SOLUBILITY OF SOLIDS

Like dissolves like also describes the solubility properties of solids. There are four different kinds of solids: covalent, ionic, molecular, and metallic. Each is held together by a different kind of interaction, and each has its own solubility characteristics.

Covalent solids such as diamond, graphite, or silica cannot dissolve without breaking covalent chemical bonds. Because intermolecular forces of attraction are always much weaker than covalent bonds, solvent-solute interactions are never strong enough to offset the energy cost of breaking bonds. Covalent solids are insoluble in all solvents, but they may be chemically attacked by some liquids or vapors.

Metals are the next most difficult solids to dissolve because they contain extensive delocalized bonding networks that must be disrupted before the metal can dissolve.

When an alkali metal contacts water or when other metals such as Ca, Zn, or Fe are treated with aqueous acid, the metal *reacts* with the solution, producing hydrogen gas and a solution of the metal cation (for example, Na^+ and Ca^{2+}). A chemical reaction has occurred, so the aqueous medium has *not* dissolved the metal. Zinc metal, for example, reacts with hydrochloric acid to generate H_2 gas and displace Zn^{2+} cations in solution:

$$Zn_{(s)} + 2\,H_3O^+_{(aq)} \rightarrow Zn^{2+}_{(aq)} + H_{2(g)} + 2\,H_2O_{(l)}$$

The solution produced when zinc reacts with hydrochloric acid is an aqueous solution of zinc ions from the chemical reaction and chloride ions from HCl, not a solution of zinc metal in water. If this solution is boiled to dryness, the remaining solid is $ZnCl_2$, not zinc metal.

IPR2020-00770
United Therapeutics EX2007
Page 3242 of 7335

A few metals *react* with water, and several *react* with aqueous acids, but no metals will simply *dissolve* in water. Likewise, metals do not dissolve in nonpolar liquid solvents.

Metals are insoluble in common liquid solvents but can dissolve in each other (like dissolves like). A mixture of substances with metallic properties is called an **alloy.** Some alloys are solutions, and others are heterogeneous mixtures. Brass, for instance, is a homogeneous solution of copper (20% to 97%) and zinc (80% to 3%), but common plumber's solder is a heterogeneous alloy of lead (67%) and tin (33%). When solder is examined under a microscope, separate regions of solid lead and solid tin can be seen. When brass is examined, no such regions can be seen.

Mercury, the only metal that is a liquid at room temperature, dissolves a number of metals to give liquid solutions. Any solution of another metal in mercury is called an **amalgam.** Metals close to mercury in the periodic table, such as silver, gold, zinc, and tin, are particularly soluble in mercury. An amalgam of silver, tin, and mercury has been widely used to make dental fillings. When the intermetallic compound Ag_3Sn is ground with mercury, it forms a semisolid amalgam that can be shaped to fill a cavity. On standing, mercury reacts with the other metals to form a hard solid mixture of Ag_2Hg_8 and Sn_7Hg_8. The mixture expands slightly during reaction, forming a tight fit within the cavity.

The mercury atoms in dental fillings are chemically bound and do not dissolve, so they are safe for the wearer, despite the fact that mercury is highly toxic. Dentists who mix the amalgams, however, may be at risk of mercury poisoning.

As described in Section 7.7, *ionic solids* contain cations and anions held in a three-dimensional ionic lattice by strong coulombic attractions. Thus ionic solids do not dissolve unless considerable solvent-ion interactions exist to counterbalance the energy cost of breaking the ions free from the lattice. There are no ionic liquids at room temperature, so at first we might think there are no solvents suitable for ionic solids. Some ionic solids dissolve in water, however, because water is a *highly polar* liquid in which strong ion-dipole interactions exist between water molecules and ions in aqueous solution. Figure 10-33 illustrates the solvation of Na^+ and Cl^- ions as NaCl dissolves in water.

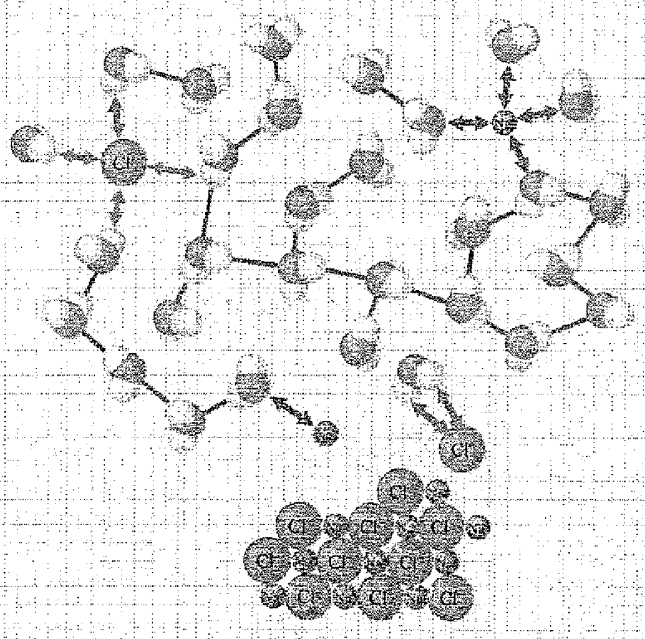


FIGURE 10-33
A molecular picture showing the ion-dipole interactions that help a solid ionic crystal dissolve in water. Arrows indicate ion-dipole interactions.

IPR2020-00770
United Therapeutics EX2007
Page 3243 of 7335

The solubility guidelines presented in Chapter 4 categorize ionic solids as soluble or insoluble. For soluble salts the stabilization due to ion-dipole interactions compares favorably with the coulombic forces of the ionic solid. For insoluble salts, ion-dipole interactions provide too little stabilization to overcome the forces that hold the ions in the solid lattice.

Molecular solids are held together by dispersion forces, dipole forces, and sometimes hydrogen bonds. Such solids dissolve readily in solvents with similar types of intermolecular forces. Nonpolar iodine, for instance, dissolves readily in a nonpolar liquid such as carbon tetrachloride (CCl_4). Many organic compounds are molecular solids that dissolve in organic liquids such as benzene or cyclohexane.

Hydrogen bonding in the aqueous environment allows water to dissolve materials that can form hydrogen bonds. For example, we have seen that acetone is fully miscible with water because of significant hydrogen bonding between the polar C=O oxygen atoms of acetone and the hydrogen atoms of water molecules. Hydrogen bonding also makes sugars such as sucrose and glucose very soluble in water. Glucose, whose structure is shown in Figure 10-34, is an organic molecule with five polar O—H groups, each of which forms hydrogen bonds with water molecules. Thus glucose ($C_6H_{12}O_6$) is quite soluble in water, whereas a hydrocarbon such as benzene (C_6H_6), which cannot form hydrogen bonds, is nearly insoluble in water.

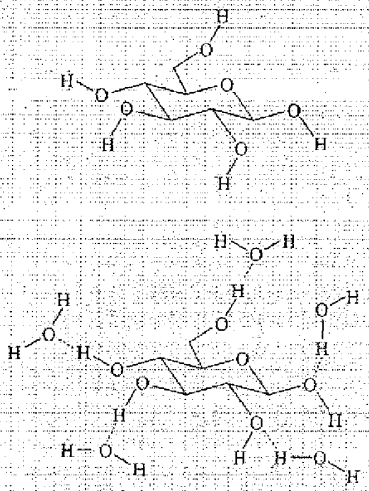


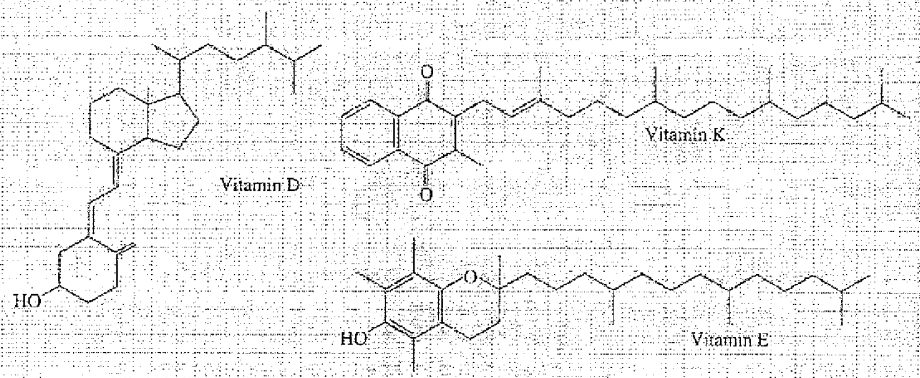
FIGURE 10-34
The line structure of glucose (top). All five polar O—H groups can form hydrogen bonds with water molecules (dotted lines, bottom).

Glucose and other sugars are discussed in more detail in Section 11.7.

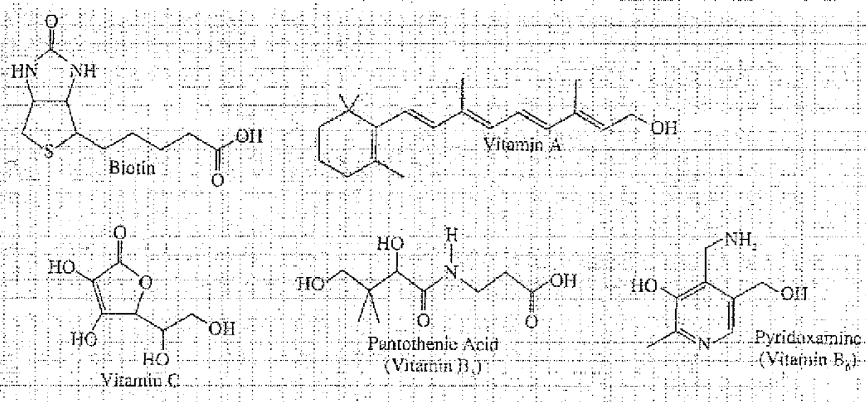
The best solvent for a molecular solid is one whose intermolecular forces match the forces holding the molecules in the crystal. For a solid held together by dispersion forces, good solvents are nonpolar liquids such as CCl_4 and C_6H_6. For polar solids a polar solvent such as acetone works well. The best solvent for ionic salts is water. This does not mean, however, that *every* polar solid dissolves in acetone or that *every* ionic salt dissolves in water. A substance dissolves when there is a favorable balance of coulombic forces. We can predict that the balance will be *unfavorable* for a salt in a nonpolar solvent or a nonpolar organic molecule in water, but there is no foolproof method for predicting a *favorable* balance for potentially favorable cases. Solubility guidelines are only guidelines, and they are highly empirical. Sample Problem 10-8 provides some practice in recognizing solubility types.

SAMPLE PROBLEM 10-8 SOLUBILITIES OF VITAMINS

Vitamins, organic molecules required by the body for proper function but not synthesized by the body, must be present in the foods we eat. Vitamins can be grouped into two categories: fat-soluble, which dissolve in fatty hydrocarbon-like tissues, and water-soluble. The structures of several vitamins are shown below. Assign each one to the appropriate category.



IPR2020-00770
United Therapeutics EX2007
Page 3244 of 7335



METHOD: At first glance, it may seem that the like-dissolves-like guideline does not apply here. Certainly, none of these complex molecules look like water, and the resemblance to simple hydrocarbons such as cyclohexane is also remote. Keep in mind, however, that the basis for the like-dissolves-like principle is that similar compounds dissolve in each other because they have *common patterns* of intermolecular interactions. We have seen, for instance, that alcohols with large nonpolar segments do not dissolve well in water. We can categorize vitamins similarly by the amount of the structure that can be stabilized by hydrogen bonding to water molecules.

A hydrogen bond donor must have a hydrogen atom bonded to F, O, or N, and a hydrogen bond acceptor is an electronegative atom with a lone pair of electrons. By these criteria, all the vitamins shown above are capable of some hydrogen bonding. However, vitamins A, D, E, and K have large regions where there are only nonpolar C—C and C—H bonds. Like the longer alcohols, these molecules have too few hydrogen bonding sites for them to be soluble in water. As a result, these are fat-soluble vitamins.

The four remaining molecules, vitamin C, biotin, pantothenic acid, and pyridoxamine, have a comparatively large number of O—H and N—H groups. These groups make these vitamins strong hydrogen bonders, so they are all water soluble. (In fact, all the B vitamins are soluble in water.)

The different solubilities of these two kinds of vitamins have important metabolic consequences. Fat-soluble vitamins can be stored in fatty body tissue for a long time because they do not dissolve in aqueous body fluids. As a result, too much of a fat-soluble vitamin can overload the storage capabilities and lead to a toxic reaction. Water-soluble vitamins, on the other hand, cannot be stored, and the body will excrete anything more than the amount it can use immediately. We must therefore have a regular supply of water-soluble vitamins in our diets to remain healthy.

SOLUBILITY OF GASES IN LIQUIDS

Substances are gases when their intermolecular forces are negligible. Molecular oxygen is a typical example. Oxygen molecules are nonpolar, so they do not form dipole-dipole or hydrogen-bonding interactions. The valence electrons in O_2 molecules have $n = 2$, which means that they are in compact orbitals that generate small dispersion interactions. Intermolecular interactions between oxygen molecules and molecules of a solvent such as water are minimal, so oxygen is not very soluble in water. Water in contact with the Earth's atmosphere contains O_2 at a concentration of only about 3×10^{-4} M.

A few gases interact strongly with water to form concentrated aqueous solutions. For example, a 12 M solution can be prepared by bubbling HCl gas through water.

IPR2020-00770
United Therapeutics EX2007
Page 3245 of 7335

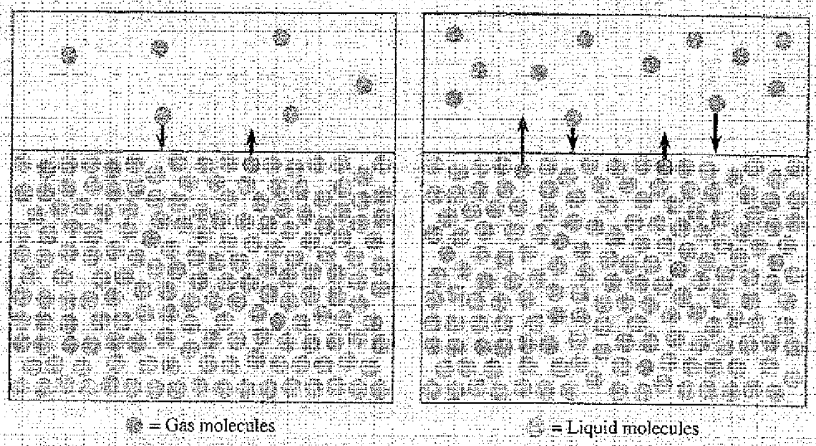


FIGURE 10-35
When the partial pressure of a gas above a solution increases *(right)*, the capture rate goes up, so the concentration of gas in the solution increases.

This is because when HCl gas dissolves in water, proton transfer occurs to generate H_3O^+ ions:

$$HCl_{(g)} + H_2O_{(l)} \rightarrow Cl^-_{(aq)} + H_3O^+_{(aq)}$$

Although this is a chemical reaction, we say that HCl dissolves in water rather than reacts with water because boiling the solution regenerates HCl and H_2O vapors.

Ammonia is another gas that is very soluble in water, giving solutions as concentrated as 14.8 M. Ammonia dissolves because it forms hydrogen bonds with water molecules. When an ammonia molecule displaces a water molecule, one hydrogen-bonding interaction is exchanged for another.

Gas solubility increases with the partial pressure of the gas in contact with the solution. The molecular view of a solution in Figure 10-35 shows the reasons. Gas molecules that collide with a liquid surface can be captured into solution, and as the partial pressure increases, the number of collisions between gas molecules and the solution surface also increases. This, in turn, causes more gas molecules to be captured by the solution and increases the concentration of dissolved gas.

At the same time that gas molecules are being captured at the liquid surface, dissolved gas molecules escape from the liquid if their motion brings them to the surface. As more and more gas molecules enter the solution, the escape rate of molecules returning to the gas phase increases accordingly. At any given partial pressure, the concentration of gas dissolved in the liquid changes until the number of gas molecules that leave the solution matches the number of molecules that enter the solution. The gas-liquid system is then in a condition of dynamic equilibrium, in which molecules are continually transferred between phases without any net change in concentrations.

Dynamic equilibrium was introduced in Section 2.1 and is treated in detail in Chapter 15.

The rate of capture from the gas phase is directly proportional to pressure, and the rate of escape from the solution is directly proportional to the concentration of dissolved gas molecules. The solubility of a gas is the concentration at which these two rates exactly balance. Thus gas solubility is directly proportional to partial pressure. **Henry's law** expresses this quantitatively:

$$C_i = K_H p_i \qquad (10\text{-}1)$$

IPR2020-00770
United Therapeutics EX2007
Page 3246 of 7335

TABLE 10-2 HENRY'S LAW CONSTANTS

GAS	K_H (10^{-3} M/atm) 0 °C	25 °C	30 °C
N_2	1.1	0.67	0.40
O_2	2.5	1.3	0.89
CO	1.6	0.96	0.44
Ar	2.5	1.5	1.0
He	0.41	0.38	0.40
CO_2	78	34	16

Aqueous solutions.

We usually express dissolved gas concentration in molarity and gas pressure in atmospheres, so K_H has units of molarity/atmosphere.

Here, C_i is the concentration of gas in the solution, and p_i is the partial pressure of the same gas in the vapor phase above the solution. These two variables are linked by the Henry's law constant (K_H). The value of K_H depends on the identity of the gas, the solvent, and on the temperature of the system. Table 10-2 lists values for the Henry's law constants for several gases dissolving in water. Sample Problem 10-9 makes use of Henry's law to determine the concentrations of atmospheric gases that dissolve in water, and Box 10-1 discusses how Henry's law applies to deep-sea diving.

SAMPLE PROBLEM 10-9 SOLUBILITIES OF ATMOSPHERIC GASES

The Earth's atmosphere is 78% N_2, 21% O_2, and minor amounts of other gases, including CO_2 (0.31%). Find the concentration of N_2, O_2, and CO_2 in water at equilibrium with the Earth's atmosphere at 25 °C.

METHOD: Each gas establishes its own dynamic equilibrium with water. The concentration depends on the partial pressure of the gas in the atmosphere and on the value of the Henry's law constant at 25 °C.

Recall from Chapter 5 that the partial pressure of any gas in a mixture is given by the mole fraction (X_i) multiplied by total pressure. Using 1.0 atmosphere (atm) for the total pressure:

$$p_{O_2} = X_{O_2} P = \left(\frac{21\%\ O_2}{100\%}\right) \times (1.0\ \text{atm}) = 0.21\ \text{atm}\ O_2$$

Likewise, the partial pressure of N_2 is 0.78 atm and that of CO_2 is 3.1×10^{-3} atm.

Now we can use Henry's law to calculate the concentrations of dissolved gas:

$$C_{N_2} = \left(6.7 \times 10^{-4} \frac{\text{M}}{\text{atm}}\right)(0.78\ \text{atm}) = 5.2 \times 10^{-4}\ \text{M}\ N_2$$

$$C_{O_2} = \left(1.3 \times 10^{-3} \frac{\text{M}}{\text{atm}}\right)(0.21\ \text{atm}) = 2.7 \times 10^{-4}\ \text{M}\ O_2$$

$$C_{CO_2} = \left(3.4 \times 10^{-2} \frac{\text{M}}{\text{atm}}\right)(3.1 \times 10^{-3}\ \text{atm}) = 1.1 \times 10^{-4}\ \text{M}\ CO_2$$

IPR2020-00770
United Therapeutics EX2007
Page 3247 of 7335

BOX 10-1

HENRY'S LAW AND THE BENDS

According to Henry's law, gases become more soluble as pressure increases. Normally, this variation has few consequences because atmospheric pressure varies slowly with changing altitude or weather. However, very large pressure changes are routine in deep-sea diving. As a result, divers returning from the depths to the surface must take special precautions to allow their bodies to adjust to changes in the solubility of the gases in their blood.

Carbonated beverages illustrate what happens when a gas dissolved in a liquid experiences a rapid drop in pressure. Soft drinks, soda water, champagne, and beer are all bottled under several atmospheres' pressure of carbon dioxide. When a bottle is uncapped, the total pressure quickly falls to 1 atm, and the partial pressure of CO_2 drops to 0.003 atm. At this lower pressure, the concentration of CO_2 in the solution is much higher than its solubility, so the excess CO_2 forms gas bubbles and escapes from the liquid.

Deep-sea divers experience pressure changes similar to those of bottled drinks. For every 30 feet a diver descends, the pressure increases by 1 atmosphere. As a result, the amount of nitrogen gas dissolved in the diver's blood increases significantly as the diver descends. If a diver returns to the surface too quickly after a deep dive, gas dissolved in the blood may form bubbles in the same way as the CO_2 in a freshly opened carbonated drink. These bubbles interfere with the transmission of nerve impulses and restrict the flow of blood. This condition, known as *the bends*, is extremely painful and can cause paralysis or death.

Divers avoid the bends by returning to the surface slowly, taking short "decompression stops" at intermediate depths to allow excess gas to escape from the blood without forming bubbles. Another way of preventing the bends is by using helium-oxygen gas mixtures instead of air in divers' breathing apparatus. Helium is only half as soluble as nitrogen in blood, so less extra gas dissolves in blood.

SECTION EXERCISES

10.5.1 List the types of intermolecular interactions that stabilize a solution of acetone in methanol, and draw molecular pictures that illustrate any dipole-dipole and hydrogen-bonding interactions that exist between molecules of these substances.

10.5.2 Gases can be collected by bubbling them through water into an evacuated container. If 0.18 mol of CO_2 at $P = 0.98$ atm is bubbled through 450 mL of water into an empty glass vessel at 298 K, what fraction of the gas dissolves in the water?

10.5.3 On the basis of their molecular structures, predict which of the following silicon-containing materials are water soluble: elemental Si, SiO_2, Na_2SiO_3, and $SiCl_4$.

10.6 DUAL-NATURE MOLECULES: SURFACTANTS AND BIOLOGICAL MEMBRANES

Now that we have described intermolecular forces, solutions, and solubility properties, we can apply these concepts to examples of solute-solvent interactions of key importance in the chemical industry and in biology.

IPR2020-00770
United Therapeutics EX2007
Page 3248 of 7335

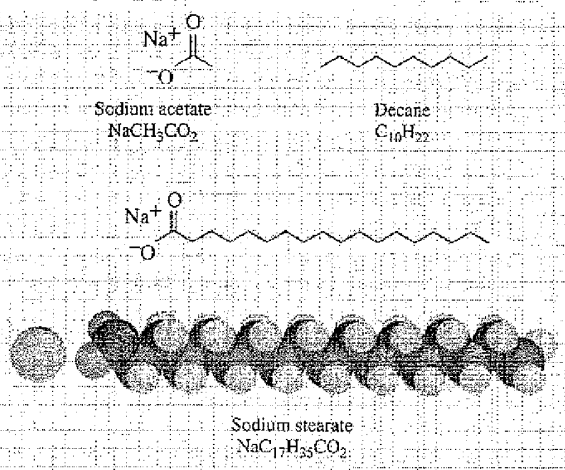


FIGURE 10-36
Sodium stearate is a typical dual-nature molecule. It has a hydrophilic polar head that resembles sodium acetate and a hydrophobic nonpolar tail that is a hydrocarbon similar to decane.

Substances that do not dissolve in water, such as organic fats and oils, are called **hydrophobic.** Substances that are miscible with water, such as the organic but hydrogen-bonding molecules methanol and acetone, are called **hydrophilic.** Some molecules contain both hydrophilic and hydrophobic regions. Such dual-nature molecules may have a polar or ionic "head" that is compatible with water and a long hydrocarbon "tail" that is incompatible with water. Sodium stearate, whose structure is shown in Figure 10-36, is a dual-nature molecule. The head of the stearate anion resembles the water soluble acetate anion, and the tail is a hydrocarbon chain containing 17 carbon atoms.

Figure 10-37 shows three different structures that dual-nature molecules such as sodium stearate can form when they are placed in water. They may form a molecular **monolayer** on the surface, in which the polar head groups are immersed in the water while the nonpolar tails are aggregated together on the surface. Agitating the solution may cause the molecules to arrange into spherical aggregates called **micelles,** in which the hydrophobic tails point inward and the polar heads lie on the outside of the structure, where they interact with the aqueous solvent. Dual-nature molecules may also form enclosed **bilayers,** called **vesicles,** which have two parallel rows of molecules oriented so that their hydrocarbon tails are clustered together.

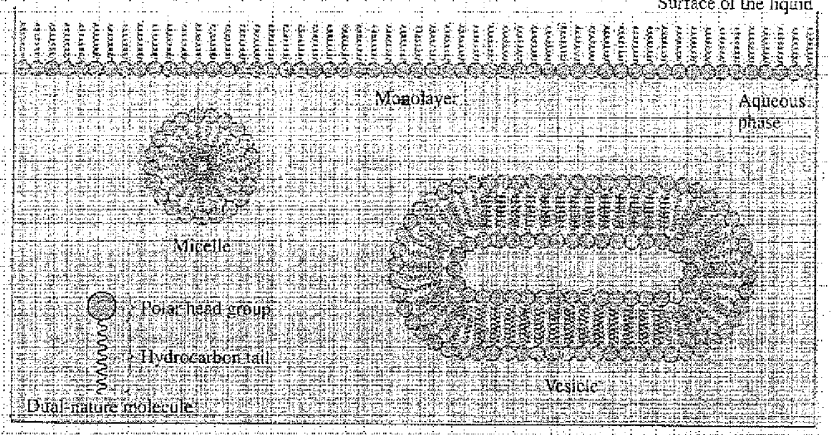


FIGURE 10-37
Cross-sectional molecular views of the structures that can form when dual-nature molecules are placed in water. The molecules may form a monolayer at the surface, spherical clusters called *micelles*, or bilayer structures called *vesicles*. In all three structures the hydrocarbon tails cluster together to minimize their interactions with water molecules, and the polar head groups are positioned to maximize their interactions with water molecules.

IPR2020-00770
United Therapeutics EX2007
Page 3249 of 7335

All these arrangements obey the principle of like dissolving like. The hydrocarbon tails aggregate through dispersion forces because they are incompatible with the aqueous medium. The hydrogen-bonding network of the solvent would be disrupted by incorporating these tails into the solution. The polar heads, on the other hand, interact strongly with water to maximize hydrogen bonding and ion-dipole interactions.

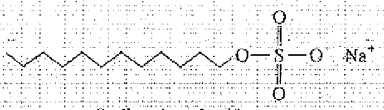
SURFACTANTS

Dual-nature molecules are widely used in industrial chemistry to modify the behavior of aqueous solutions. In this context they are called **surfactants.** Common surfactant head groups include carboxylate ($-CO_2^-$), sulfonate ($-SO_3^-$), sulfate ($-OSO_3^-$), and ammonium ($-NH_3^+$). Sodium is the most common counter-ion for anionic surfactants and chloride for cationic surfactants because these ions are nontoxic and their salts are highly soluble.

Surfactants are widely used as soaps and detergents. Clothing becomes soiled by a wide variety of substances; some are water soluble, and others are not. Surfactants remove water-insoluble grease (for example, butter, fat, and oil) from solid surfaces. Dispersion forces stabilize grease particles in the hydrocarbon tails of surfactant aggregates. Agitation removes these aggregates from the fabric, suspending them in solution as a large number of tiny micelles with grease particles trapped inside. The micelles do not redeposit on the fabric because their hydrophilic heads hold them in solution. When water is drained from the washing machine, the grease-containing micelles are swept away, leaving clean clothes behind.

Soaps are carboxylate surfactants derived from natural sources such as animal fats that contain stearic acid and other long-chain organic acids. These carboxylate surfactants form insoluble salts with Ca^{2+} and Mg^{2+}. In regions where water is "hard," these soaps precipitate calcium and magnesium stearate as a "scum" that inhibits cleansing action and is responsible for bathtub rings. Detergents, on the other hand, contain sulfonate and sulfate surfactants that are "synthetic" compounds, originally prepared in the laboratory. Detergents such as sodium lauryl sulfate do not form precipitates with divalent cations, but they have a tendency to lather and foam. Foaming is a disadvantage in washing machines but is considered to be an advantage in hair shampoos. The cleaning action of soaps and detergents is similar, but detergents have largely replaced soaps because of their superior behavior in hard water.

Soap made by boiling animal fat in an alkaline solution obtained from ashes has been known since the time of the ancient Sumerians, 2500 BC.



Sodium lauryl sulfate
(common ingredient in shampoo)

Surfactants are used in such a wide variety of ways that billions of dollars are spent on them every year. They appear in many household products, including cleansing agents and shampoos. Some surfactants are used as emulsifiers in processed foods such as bottled salad dressing. An emulsifier causes normally incompatible liquids such as the oil and water in salad dressing to disperse in each other. Surfactants emulsify by forming molecular connections between the liquids. Their hydrophobic tails interact with oil molecules, whereas their hydrophilic heads interact with water molecules.

Gasoline contains surfactants designed to prevent the accumulation of high-boiling compounds on the surfaces of fuel injectors and carburetors. These deposits interfere with the flow of air and cause rough idling and poor gas mileage. In this case the hydrophilic polar ends interact strongly with the solid surface, and the hydrophobic ends are compatible with liquid gasoline. The polar ends adhere to the metal walls of the injection system, whereas their tails extend into the fuel mixture. This creates a thin nonpolar film that protects the surface from gummy deposits. These same films help prevent the formation of rust by screening the metal surface from water molecules.

IPR2020-00770
United Therapeutics EX2007
Page 3250 of 7335

Figure 10-38 illustrates that surfactants also decrease the surface tension of water. In the figure, the drop of water that contains a surfactant is flattened and deformed, giving it a larger surface area than the drop of water that contains no surfactant. Surfactant molecules reduce surface tension by forming a monolayer on the aqueous surface. Unlike water molecules at the surface, this monolayer does not experience an attractive force drawing molecules back into the bulk of the liquid.

A surfactant also causes water to form a film coating on any surface it contacts. In this sense, surfactants make water "wetter." Because of its improved ability to coat surfaces, surfactant-treated water is used occasionally to fight fires.

Chemists and engineers in the petroleum industry are studying ways to use surfactants to increase the amount of oil that can be recovered from wells. The goal is to develop inexpensive, environmentally safe surfactants that can be mixed with water and injected into existing oil wells. The surfactant will promote formation of an oil-water emulsion that has a lower viscosity than oil and should be easier to extract from the well.

Approximately half of the surfactants produced in the United States are used in household and industrial cleaning products, but the remaining half are used in a wide range of industries. In agriculture, surfactants are used as wetting agents that assist in the uniform application of sprayed pesticides. They also are used to prevent caking of fertilizers. Surfactants used in agricultural products must not interfere with the active agents and must be biodegradable and environmentally benign. In the food industry, different surfactants are used as emulsifiers, cleaners, foaming agents, and antifoaming agents. Paints are dispersions of dyes, binding agents, and fillers. Most paints contain surfactants that convey improved flow and mixing properties. Surfactants are used widely in the plastics industry as foaming agents to assist in the production of plastic foams and to improve moldability and extrudability of specially shaped products. In the manufacture of textiles, surfactants are used to clean natural fibers, as lubricants that reduce friction during the spinning and weaving processes, emulsifiers that improve the application of dyes and finishes, and antistatic agents.

This is just a sampling of the industrial applications of these versatile materials. A host of other industries also uses surfactants in significant amounts. Examples include pharmaceuticals, paper, mining, petroleum, tanning, photography, electroplating, and adhesives.

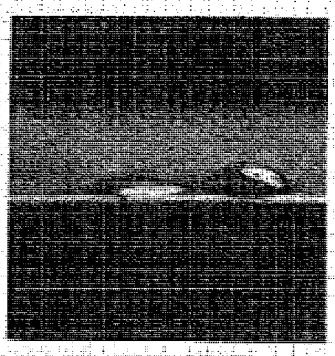


FIGURE 10-38
Surfactants reduce surface tension by forming a monolayer at the water-air interface. The water droplet on the left contains a surfactant, making its surface tension lower and causing it to flatten and spread out.

CELL MEMBRANES

It may seem like a huge conceptual leap from industrial surfactants to biological cell membranes, but the same principles apply to both sets of substances.

Every biological cell is surrounded by a thin membrane only a few molecules thick. Among the major components of membranes are molecules called *phospholipids*, which are dual-nature molecules. Although their chemical structures are much more complex than simple surfactants such as sodium stearate, phospholipids nevertheless have hydrophilic heads and hydrophobic tails. Figure 10-39 shows the structure of lecithin, which is a common membrane phospholipid. The hydrophilic end of lecithin has a cationic $N(CH_3)_3^+$ group and eight oxygen atoms with nonbonding pairs of electrons, all of which form hydrogen bonds with water molecules. The hydrophobic portion of lecithin consists of two hydrocarbon tails.

Phospholipids form bilayers in aqueous media. The molecules form two approximately parallel rows with tails aligned and heads in contact with the solution. This arrangement, shown in Figure 10-40, is analogous to the vesicles in Figure 10-37. The bilayer forms a closed sac that contains the aqueous cytoplasm and all the cellular components. Thus a cell can be viewed as a large and complex vesicle.

IPR2020-00770
United Therapeutics EX2007
Page 3251 of 7335

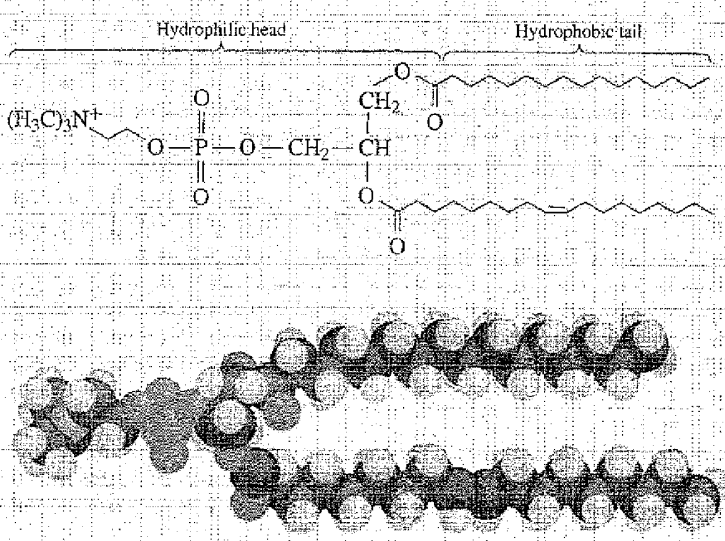
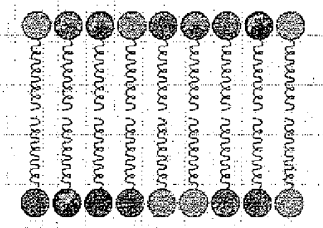
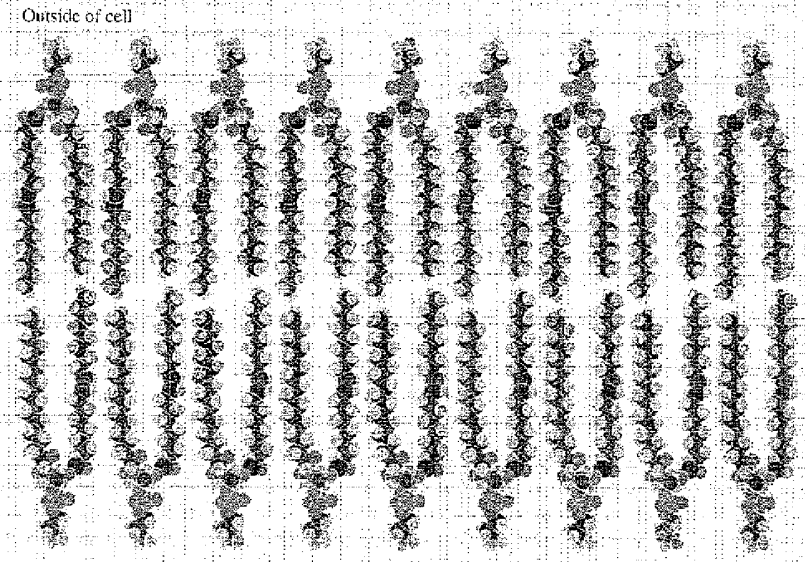


FIGURE 10-39
The chemical structure of lecithin. Lecithin is one of the most common phospholipids used for the construction of cell membranes. It is also used as a "natural" emulsifier in beauty products.

FIGURE 10-40
A lipid bilayer contains two layers of dual-nature molecules arranged tail to tail. The polar head groups face outward and are stabilized by dipolar and hydrogen-bonding interactions with water molecules.



A Schematic of a lipid bilayer



B Space-filling model of a lipid bilayer

One purpose of a cellular lipid bilayer is to control which molecules pass into and out of the cell. Uncharged small molecules such as water, ammonia, and oxygen can diffuse through the membrane. Hydrophobic molecules such as hydrocarbons can also pass through because they are soluble in the overlapping tails that make up the interior of the bilayer. Ions and water-soluble polar molecules such as glucose and urea, on the other hand, cannot get through the membrane.

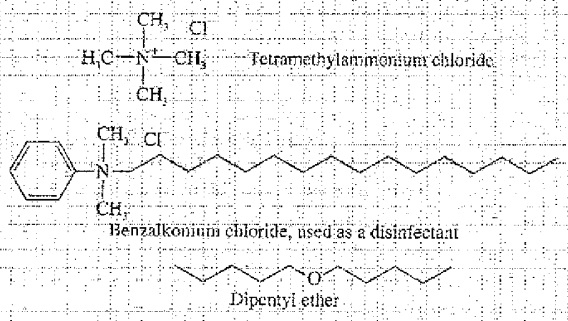
IPR2020-00770
United Therapeutics EX2007
Page 3252 of 7335

For cells to carry out their functions, glucose and other nutrients must be brought in, and urea and other waste products must be expelled. This would be an impossible task if cell membranes were composed only of phospholipids. Specific large biomolecules act as molecular "gates" through the membranes. These proteins are embedded in the bilayers but protrude into the surrounding water and/or into the cell interiors.

The structures of proteins are described in Chapter 11.

SECTION EXERCISES

10.6.1 Line drawings of some molecules follow. Identify the hydrophilic and hydrophobic regions of each, and determine which are surfactants.



10.6.2 Explain why glucose and other large, water-soluble molecules cannot pass through a lipid bilayer. (The structure of glucose is shown in Figure 10-34.)

10.7 PROPERTIES OF AQUEOUS SOLUTIONS

Solute molecules alter many properties of a liquid. For instance, adding salt to water gives a solution that boils at a higher temperature than pure water, and adding ethylene glycol to the water in an automobile radiator gives a solution that protects against freezing because the solution freezes at a lower temperature than pure water. Changes such as these in the behavior of liquids can be understood from a molecular perspective if we first describe phase changes from a molecular viewpoint and then examine the effect of added solute molecules. We consider aqueous solutions specifically because they are by far the most important in general chemistry, biology, and geology.

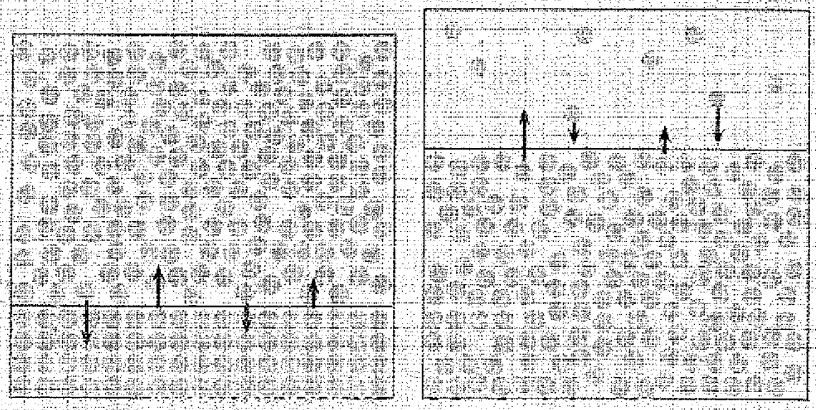
PHASE EQUILIBRIA

If pure water at 0 °C is cooled, it freezes, and if ice at 0 °C is warmed, it melts. The temperature at which this transformation between the liquid and solid forms of H_2O occurs is the freezing point of water. At exactly 0 °C, solid ice and liquid water are equally stable, so in a thoroughly insulated container, ice and water could coexist at 0 °C indefinitely.

The molecular view shown in Figure 10-41, *A*, reveals that two processes occur in a mixture of ice and water at 0 °C. First, water molecules in the liquid that collide

The temperature 0 °C can also be characterized as the melting point of ice.

IPR2020-00770
United Therapeutics EX2007
Page 3253 of 7335



A Solid–pure liquid equilibrium **B** Pure liquid–gas equilibrium

FIGURE 10-41
Molecular views of the dynamic equilibria between pure phases. **A,** The equilibrium between liquid and solid. **B,** The equilibrium between liquid and gas. At the equilibrium temperature, exactly the same number of molecules escape from the liquid phase as are captured by the liquid phase. Remember that all molecules are constantly in motion; for clarity, however, the motions of molecules confined within a phase have not been shown.

Dynamic equilibrium is consistent with the kinetic theory of molecular motion. One proof of molecular transfer between phases comes from radioactivity studies. If radioactive ice is placed in nonradioactive water at 0 °C, the water slowly becomes radioactive because of molecular transfer of radioactive water molecules between phases.

When water boils in an open container, the steam diffuses into the surrounding atmosphere, leading to a continual escape of molecules. Consequently, the liquid-vapor equilibrium can be observed only when the gas is confined to a closed space.

with the crystals are sometimes captured and added to the solid phase. Second, molecules on the surface of the ice crystals sometimes become detached and enter the surrounding liquid. The mixture reaches a state of dynamic equilibrium when equal numbers of molecules move in each direction in any given time. When the pressure exerted on the mixture is 1 atm, this ice-water equilibrium exists only at 0 °C because any change of temperature throws the rates out of balance. Lowering the temperature decreases the rate at which molecules escape from the surface of the ice, whereas raising the temperature increases the rate of escape.

A dynamic equilibrium also exists between liquid water and steam when the pressure exerted on the liquid is 1 atm and the temperature is 100 °C (Figure 10-41, *B*). Some molecules at the liquid surface have sufficient energy to escape into the gas phase, and some molecules in the gas phase are captured when they strike the liquid surface. Under conditions of dynamic equilibrium, equal numbers of molecules move in each direction in any given time. At a pressure of 1 atm, this equilibrium exists only at 100 °C because lowering the temperature reduces the rate at which molecules escape from the liquid phase and condensation occurs. Raising the temperature, on the other hand, increases the rate of escape from the liquid phase, and the liquid boils.

These two equilibria provide the basis for precise definitions of the normal freezing point and the normal boiling point. The **normal freezing point** *(fp)* of a substance is the temperature at which solid and liquid coexist at equilibrium under a pressure of 1 atm. The **normal boiling point** *(bp)* of a liquid is the temperature at which liquid and vapor coexist at equilibrium under a pressure of 1 atm.

EFFECT OF SOLUTES

Four common properties of solutions are modified by the presence of solute molecules. These properties are freezing point, boiling point, vapor pressure, and osmotic pressure. They are called the *colligative properties*.

The molecular view of freezing and boiling provides a basis for determining the influence of dissolved substances on melting and boiling points. In a solution, solute molecules displace some of the solvent molecules, so a given volume of a solution contains a smaller number of solvent molecules than the same volume of pure solvent. Consequently, the presence of solute molecules reduces the rate at which solvent molecules leave the liquid phase. Figure 10-42 shows that changing one rate without changing the other rate throws the dynamic equilibrium out of balance.

The addition of solutes *decreases* the freezing point of a solution because collisions between solvent molecules and crystals of solid solvent occur less frequently

IPR2020-00770
United Therapeutics EX2007
Page 3254 of 7335

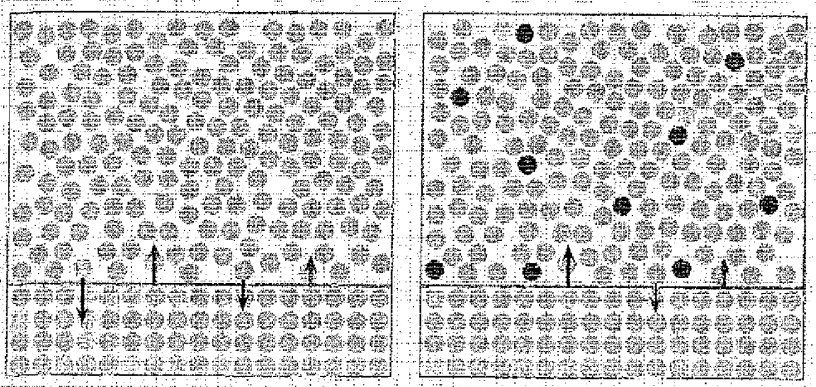


FIGURE 10-42
Molecular views of the rates of solid-liquid phase transfer of a pure liquid and a solution at the normal freezing point. The addition of solute does not change the rate of escape from the solid, but it decreases the rate at which the solid captures solvent molecules from the solution. This disrupts the dynamic equilibrium between escape and capture.

than in the pure solvent. Consequently, fewer molecules are captured by the solid phase than escape from the solid to the liquid. Cooling the solution restores dynamic equilibrium because it simultaneously reduces the number of molecules that have sufficient energy to break away from the surface of the solid and increases the number of molecules in the liquid with low enough kinetic energy to be captured by the solid.

Experiments show that at low solute concentration the change in freezing point of a solution, ΔT_f, obeys a simple equation:

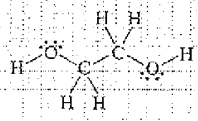
$$\Delta T_f = K_f X_{\text{solute}} \qquad \textbf{(10-2)}$$

where X_{solute} is the total mole fraction of solutes and K_f is a constant, called the **freezing point depression constant.** The constant is different for different *solvents* but does not depend on the identity of the *solutes.* For water, K_f is 105.0 °C. Sample Problem 10-10 illustrates the use of Equation 10-2.

Equation 10-2 can be derived from our simple molecular picture and principles of kinetic molecular theory. The derivation is independent of the nature of solute and solvent, so Equation 10-2 is valid for other solvents besides water, except that K_f has a different value for each solvent.

SAMPLE PROBLEM 10-10 FREEZING POINT DEPRESSION

Ethylene glycol (1,2-ethanediol) is added to automobile radiators to prevent cooling water from freezing. What is the freezing point of radiator coolant that contains 2.00 kg of ethylene glycol and 5.00 L of water?


Ethylene glycol

METHOD: The question asks for the freezing point of a solution. The phrase *to prevent the water from freezing* reveals that we are dealing with the depression of the freezing point of water. Equation 10-2 describes this process quantitatively: $\Delta T_f = K_f X_{\text{solute}}$.

The freezing point depression constant for water is known from experiments and can be found in tables: $K_f = 105.0$ °C. To calculate the freezing point, we must first determine the mole fraction of the solute in this solution.

IPR2020-00770
United Therapeutics EX2007
Page 3255 of 7335

The mole fraction of solute is defined to be moles of solute divided by total moles of solution. The number of moles of solute is found from the mole-mass relationship, and the number of moles of solvent can be found from the density of water and the mole-mass relationship. The molar mass (MM) of ethylene glycol is obtained from its chemical formula, $C_2H_6O_2$: $MM = 62.07$ g/mol:

$$n(\text{ethylene glycol}) = \frac{(2.00\text{ kg})(10^3\text{ g/kg})}{62.07\text{ g/mol}} = 32.22\text{ mol}$$

We find the mass of water from its density, 1.00 g/mL, and then convert to moles using the molar mass of water, $MM = 18.02$ g/mol:

$$m(\text{water}) = dV = (1.00\text{ g/mL})(5.00\text{ L})(10^3\text{ mL/L}) = 5.000 \times 10^3\text{ g}$$

$$n(\text{water}) = \frac{5.000 \times 10^3\text{ g}}{18.02\text{ g/mol}} = 277.5\text{ mol}$$

Now calculate the mole fraction of ethylene glycol:

$$X_{\text{solute}} = \frac{n_{\text{solute}}}{n_{\text{solute}} + n_{\text{solvent}}} = \frac{32.22\text{ mol}}{32.22\text{ mol} + 277.5} = 0.1040$$

Substitute this value for the mole fraction into Equation 10-2 to find the difference between the freezing point of the solution and that of pure water:

$$\Delta T_f = K_f X_{\text{solute}} = (105.0\text{ °C})(0.1040) = 10.9\text{ °C}$$

The result is rounded to three significant figures to be consistent with the data given in the problem. This is the amount by which the freezing point of the solution *differs* from that of pure water. Because the freezing point of water is 0 °C and freezing points are depressed by adding solutes, the new freezing point is below 0 °C: $T_f = -10.9$ °C.

A nonvolatile solute is one that has a negligible vapor pressure at the boiling point of the solution.

The effect of a solute on the boiling point of a solution is opposite to its effect on the freezing point. A boiling point is *increased* by adding a nonvolatile solute. This is because the solute reduces the rate of escape of solvent molecules into the gas phase. To get back to dynamic equilibrium, the solution must be heated so that more molecules acquire sufficient energy to escape from the liquid phase.

Molecular analysis and experimental studies show that the change in the boiling point of a solution obeys the same type of equation as the change in the freezing point:

$$\Delta T_b = K_b X_{\text{solute}} \qquad (10\text{-}3)$$

In Equation 10-3, ΔT_b is the elevation of the boiling point, and K_b is a constant called the **boiling point elevation constant.** The constant depends on the identity of the *solvent* but not on the identities of the nonvolatile *solutes*. Thus there is a different boiling point elevation constant for every solvent; for water, $K_b = 28.9$ °C. As Sample Problem 10-11 illustrates, Equation 10-3 is used in the same way as Equation 10-2.

SAMPLE PROBLEM 10-11 BOILING POINT ELEVATION

Determine the mole fraction of ethylene glycol required to raise the boiling point of radiator coolant to 110 °C, and calculate the mass of ethylene glycol that must be mixed with 5.00 L of water to give a solution with this mole fraction.

IPR2020-00770
United Therapeutics EX2007
Page 3256 of 7335

METHOD: The problem asks for the amount of solute required to raise the boiling point of a solution. Equation 10-3 applies, but it must be rearranged to solve for mole fraction:

$$\Delta T_b = K_b X_{solute} \qquad \textit{from which} \qquad X_{solute} = \frac{\Delta T_b}{K_b}$$

The tabulated value of K_b is 28.9 °C. We find ΔT_b from the normal boiling point of water and the desired boiling point of the solution:

$$\Delta T_b = (110\ °C - 100\ °C) = 10\ °C \qquad X_{solute} = \frac{10\ °C}{28.9\ °C} = 0.346$$

To apply this to an actual solution of radiator coolant containing 5.00 L of water, we must convert from mole fraction to mass using the definition of mole fraction. First, we calculate the number of moles of ethylene glycol required to give a solution whose mole fraction is 0.346. We determined in Sample Problem 10-10 that 5.00 L of water contains 277.5 moles:

$$0.346 = \frac{n_{solute}}{n_{solute} + n_{solvent}} = \frac{n_{solute}}{n_{solute} + 277.5\ mol}$$

Solving for n_{solute} requires some algebra:

$$n_{solute} = (0.346)(n_{solute} + 277.5\ mol) = (0.346)(n_{solute}) + 96.02\ mol$$

$$96.02\ mol = n_{solute} - (0.346)(n_{solute}) = (0.654)(n_{solute})$$

$$n_{solute} = 149\ mol$$

Finally, we convert from moles to mass using the molar mass of ethylene glycol:

$$m = n(MM) = (149\ mol)(62.07\ g/mol) = 9.2 \times 10^3\ g$$

The result is rounded to two significant figures to be consistent with ΔT_b.

Traditionally, K_b and K_f values have been expressed by using a different concentration unit called *molality* (c_m). *Molality* is moles of solute divided by kilograms of solvent. Then, $\Delta T_f = K_f c_m$ and $\Delta T_b = K_b c_m$. For water, $K_b = 0.512\ °C/c_m$ and $K_f = 1.858\ °C/c_m$. We prefer to use *mole fraction*, however, because it is a concentration measure that is already familiar to you. Furthermore, the mole fraction emphasizes the molecular nature of these effects. Keep in mind, however, that tabulations in reference sources are likely to be in molality units.

IONIC SOLUTIONS

Equations 10-2 and 10-3 describe how the freezing and boiling points of a solution depend on the mole fraction of solute. These changes occur because each solute species reduces the concentration of solvent molecules, thereby reducing the rate of escape of solvent molecules from the solution phase. This effect is cumulative, meaning that if two types of solute species are present, each reduces the rate of escape of solvent molecules. The change in freezing and boiling points of a solution is therefore determined by the *total* mole fraction of *all* solute species present.

This cumulative effect is particularly important for solutions of ionic substances because these solutions always contain cations and anions. As a result, the total mole fraction of solutes in an aqueous salt solution is always greater than the mole fraction of the salt itself. For example, when sodium chloride dissolves in water, each mole of the salt yields 1 mol of Na^+ ions and 1 mol of Cl^- ions, making the mole fraction of all solutes twice the mole fraction of the salt. This is taken into account by including an additional term in Equations 10-2 and 10-3:

$$\Delta T_f = i K_f X_{solute} \qquad \Delta T_b = i K_b X_{solute}$$

The factor i is a dimensionless number that gives the number of ions generated in solution by one formula unit of solute. For NaCl, $i = 2$ because each NaCl unit generates two ions in solution. For a salt such as $MgCl_2$, $i = 3$, reflecting the fact that each $MgCl_2$ unit yields one Mg^{2+} cation and two Cl^- anions.

IPR2020-00770
United Therapeutics EX2007
Page 3257 of 7335

OSMOSIS

Water molecules can pass through cell membranes, but most solutes cannot. This is a **semipermeable membrane**, and the movement of water through it is **osmosis**.

If a semipermeable membrane separates two identical solutions, solvent molecules move in both directions at the same rate, and there is no net osmosis. The two sides of the membrane are at dynamic equilibrium. The situation changes when the solution on the two sides of the membrane are different. Consider the membrane in Figure 10-43, which has pure water on one side and a solution of sugar in water on the other. The sugar molecules in the solution reduce the concentration of solvent molecules in the solution. Consequently, more solvent molecules pass through the membrane from the solvent side to the solution side than from the solution side to the solvent side. Now water flows from the solvent side to the solution side, and there is a net rate of osmosis.

What can be done to increase the rate of solvent flow from the solution side of the membrane? An increase in pressure on the solution side accomplishes this, because as pressure increases, the flow rate of any liquid also increases. An increase in pressure on the solution side of the membrane increases the rate of transfer of water molecules from the solution side to the solvent side.

Figure 10-44 shows that when the pressure is increased until the rate of solvent transfer is equal in both directions, dynamic equilibrium has been reestablished and net osmosis falls to zero. The pressure increase needed to equalize the transfer rates is called the **osmotic pressure** (Π). Osmotic pressure is a pressure *difference*. Both sides of a semipermeable membrane have some pressure exerted on them, and Π is the *extra pressure* that must be exerted on the solution to maintain dynamic equilibrium.

Like freezing point depression and boiling point elevation, osmotic pressure is proportional to the concentration of solute molecules. Osmotic pressure does not involve a temperature change, however, so there is no disadvantage in using the usual measure of solution concentration, molarity. Experiments also show that osmotic pressure increases as temperature increases:

$$\Pi = MRT \qquad (10\text{-}4)$$

The osmotic pressure equation seems very simple, but its derivation requires the molecular model, differential calculus, and detailed principles of physical chemistry that are beyond the scope of this book.

In Equation 10-4, M is the total molarity of all solutes, T is the temperature in kelvins, and R is the gas constant. If osmotic pressure is expressed in atmospheres, the fact that molarity is in moles per liter requires us to use $R = 0.08206$ L atm/mol K.

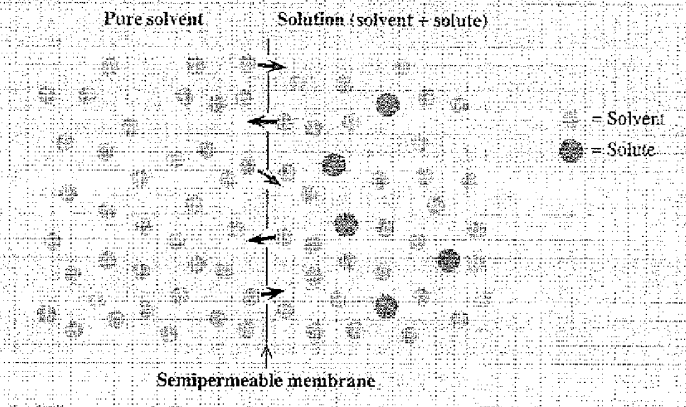


FIGURE 10-43
Small solvent molecules can pass back and forth freely through the pores of a semipermeable membrane, but solute molecules cannot. The presence of solute molecules in a solution reduces the concentration of solvent molecules, and this in turn reduces the rate at which solvent molecules pass out of the solution. There is an imbalance in transfer rates, which leads to osmosis.

IPR2020-00770
United Therapeutics EX2007
Page 3258 of 7335

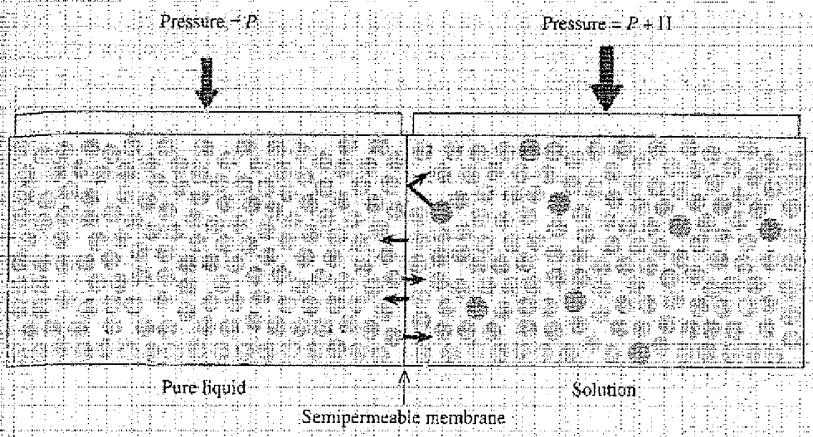


FIGURE 10-44
To equalize the rates of transfer of solvent molecules from a solution and from pure solvent, an additional pressure Π (osmotic pressure) must be exerted on the solution.

Osmotic pressure effects can be substantial. For example, the waters of the oceans contain dissolved salts at a total ionic molarity of about 1.13 M. We can calculate the osmotic pressure of ocean water:

$$\Pi = MRT = (1.13 \text{ mol/L})(0.08206 \text{ L atm/mol K})(298 \text{ K}) = 27.6 \text{ atm}$$

Thus the osmotic pressure of ocean water is *more than 25 times atmospheric pressure*. By comparison the freezing point of ocean water is depressed by only about 1% from the freezing point of pure water, from 273 K to about 271 K (−2 °C).

Osmotic pressure plays a key role in biological chemistry because the cells of the human body are encased in semipermeable membranes and bathed in body fluids. Under normal physiological conditions the body fluid outside the cells has the same total solute molarity as the fluid inside the cells, and there is no *net* osmosis across cell membranes. Solutions with the same solute molarity are isotonic solutions.

The situation changes if a molarity imbalance is created. Figure 10-45 shows red blood cells immersed in solutions of different molarities. When the fluid outside the cell is at *higher* solute molarity, transport of water across the membrane into the cell slows. The result is that water leaves the cell, causing it to shrink. When the fluid

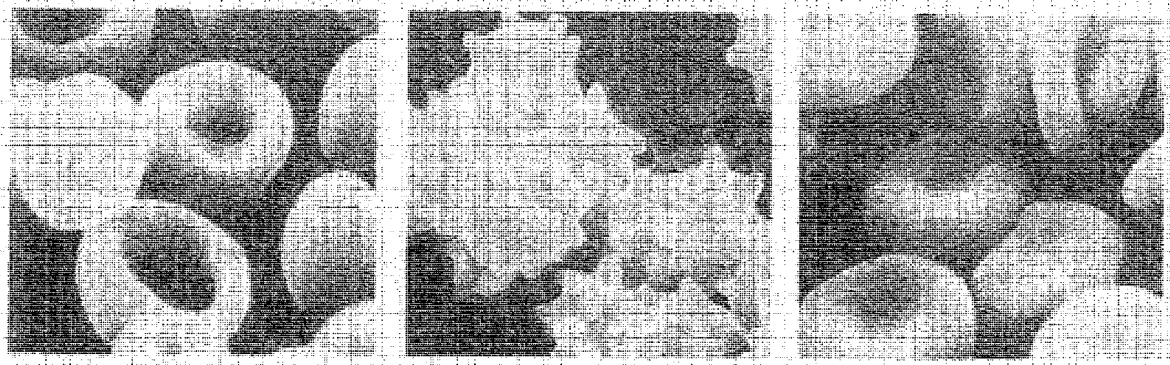


FIGURE 10-45
When bathed in isotonic solution *(left)*, red blood cells retain their normal shape because there is no net osmosis across their membranes. In a solution of higher concentration *(center)*, the net osmotic flow removes water from the cell interior, causing cells to shrink and wrinkle. In a solution of lower concentration *(right)*, the net osmotic flow pumps water into cells, expanding them until they may rupture.

IPR2020-00770
United Therapeutics EX2007
Page 3259 of 7335

outside the cell is at *lower* molarity, movement of water into the cell increases. The extra water in the cell causes an increase in internal pressure. Eventually, the internal pressure of the cell matches the osmotic pressure, and water transport reaches dynamic equilibrium. Unfortunately, osmotic pressures are so large that cells can burst under the increased pressure before they reach equilibrium.

Red blood cells are particularly susceptible to these potentially damaging concentration changes because they are suspended in the aqueous medium of the blood. Consequently, solutions used for intravenous feeding must be isotonic. Sample Problem 10-12 deals with isotonic solutions.

SAMPLE PROBLEM 10-12 ISOTONIC SOLUTIONS

Isotonic intravenous solutions contain 49 g/L of glucose ($C_6H_{12}O_6$). What is the osmotic pressure of blood?

METHOD: Isotonic solutions, by definition, exert equal osmotic pressure. Therefore Π for blood is the same as Π for the glucose solution. We can calculate Π from Equation 10-4 after converting the concentration into moles per liter:

$$\Pi = MRT \qquad M = \frac{\text{mol}}{\text{L}} = \frac{m}{(MM)(\text{L})}$$

According to the formula of glucose, MM is 180 g/mol. Substituting, we find the molarity of the glucose solution:

$$\frac{49\ \text{g}}{(180\ \text{g/mol})(1\ \text{L})} = 0.272\ \text{M}$$

Because we are working with blood in the human body, T is human body temperature, which is 37 °C.

$$T = 37\ ^\circ\text{C} = 37 + 273 = 310\ \text{K} \qquad R = 0.08206\ \text{L atm/mol K}$$

$$P = (0.272\ \text{mol/L})(0.08206\ \text{L atm/mol K})(310\ \text{K}) = 6.9\ \text{atm}$$

The result is rounded to two significant figures to match the initial data (49 g/L).

An additional pressure of 6.9 atm is more than enough to destroy the cell membrane, so it is hardly surprising that red blood cells burst when immersed in dilute solutions.

DETERMINATION OF MOLAR MASS

The magnitude of osmotic pressure is large enough that measurements of Π provide a convenient way to determine the molar mass of a compound. We can solve the osmotic pressure equation (Equation 10-4) for molar mass after expressing molarity in terms of mass and molar mass:

$$\Pi = MRT \qquad \Pi = \frac{mRT}{(MM)(V)}$$

A simple rearrangement gives an equation for calculating molar mass:

$$MM = \frac{mRT}{\Pi V} \tag{10-5}$$

To determine the molar mass of an unknown compound, a measured mass of material is dissolved to give a measured volume of solution. The system is held at constant temperature, and the osmotic pressure is determined by using an apparatus such as the one shown in Figure 10-46. Osmotic pressure measurements are particularly useful for determining the molar mass of large molecules such as polymers and biological materials, as Sample Problem 10-13 illustrates.

IPR2020-00770
United Therapeutics EX2007
Page 3260 of 7335

SAMPLE PROBLEM 10-13 DETERMINING MOLAR MASSES

A 25.00 mL aqueous solution containing 0.420 g of hemoglobin has an osmotic pressure of 4.6 torr at 27 °C. What is the molar mass of hemoglobin?

METHOD: Equation 10-5, which is used to calculate the molar mass by osmometry, is derived from the osmotic pressure expression, Equation 10-4.

All of the necessary data are given in the problem:

$$m_{solute} = 0.420\ \text{g} \qquad R = 0.08206\ \text{L atm/mol K} \qquad T = 27\ ^\circ\text{C} + 273 = 300\ \text{K}$$

$$\Pi = (4.6\ \text{torr})(1\ \text{atm}/760\ \text{torr}) = 0.00605\ \text{atm}$$

$$V_{solution} = (25.00\ \text{mL})(1\ \text{L}/1000\ \text{mL}) = 0.02500\ \text{L}$$

$$MM = \frac{mRT}{\Pi V} = \frac{(0.420\ \text{g})(0.08206\ \text{L atm/mol K})(300\ \text{K})}{(0.00605\ \text{atm})(0.02500\ \text{L})}$$

$$MM = 6.8 \times 10^4\ \text{g/mol}$$

As in any calculation, be careful to express all data in appropriate units. The osmotic pressure was measured to two significant figures, so the result has two significant figures.

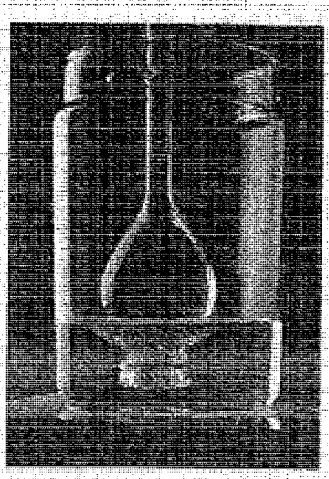


FIGURE 10-16
In a standard thistle-tube osmometer the liquid level of the solution at equilibrium is higher than that of the exterior solvent, generating an additional pressure equal to the osmotic pressure.

SECTION EXERCISES

10.7.1 A water-soluble protein molecule has a molar mass of 985 g/mol. Calculate the freezing point depression, boiling point elevation, and osmotic pressure at 300 K of an aqueous solution containing 0.750 g/L of this protein. (Assume that the solution has a density of 1.000 g/mL.)

10.7.2 The process called **reverse osmosis** occurs when a solution in contact with pure solvent across a semipermeable membrane is subjected to an external pressure that is *greater* than its osmotic pressure. Reverse osmosis can be used to desalinate seawater. Redraw Figure 10-44 using arrows to represent water movement across the membrane during reverse osmosis.

10.7.3 In your own words, write a detailed, molecular-level description of how reverse osmosis can be used to desalinate seawater.

10.8 SEPARATION PROCESSES

Water leaving a community is contaminated with a variety of impurities that must be removed before the water is pure enough to be used again. When a synthetic chemist makes a new compound, it is likely to be contaminated with by-products and unreacted starting materials, which must be removed before the new compound can be identified and studied. An oil refinery is a huge chemical plant that separates the components of petroleum and converts them into useful fuels. A biochemist who wants to study the properties of a particular enzyme must first isolate the molecule from its natural source. These are but four scenarios out of many in which separation and purification are essential parts of the chemical operations.

Phase behavior is at the heart of most purification techniques. When a solution goes through a phase change, its different components are likely to move between the phases at different rates. Chemists take advantage of these differences to purify chemical compounds. In this section, we survey purification techniques.

IPR2020-00770
United Therapeutics EX2007
Page 3261 of 7335

RECRYSTALLIZATION

Most laboratory syntheses are carried out in liquid solution. If the product is a solid, it may spontaneously precipitate from the reaction solvent, or it may be isolated by boiling off the solvent. In either case the solid product almost always contains impurities. Recrystallization is the classic way of removing impurities from a crude solid.

Recrystallization takes advantage of the way in which the solubilities of solids vary with temperature. Most solid solutes are more soluble in hot than in cold solvent because fast-moving, high-energy molecules are less likely to be captured by the solid phase than slow-moving ones, and solute molecules move faster in hot than in cold solutions.

If a solid substance is dissolved in a minimum volume of hot solvent that is then allowed to cool, the solubility of the solid is exceeded, and it crystallizes from the solution. In favorable cases the impurities remain dissolved in the cold solvent, and the solid has been purified. Purification by recrystallization works best when the crude solid contains a low percentage of impurities. If a large amount of an impurity is present, the impurity is likely to crystallize with the desired substance. The example in Sample Problem 10-14 illustrates this feature.

SAMPLE PROBLEM 10-14 PURIFICATION BY RECRYSTALLIZATION

A chemist has synthesized 10.0 g of crude organic solid that contains an estimated 10% impurities. The desired product is less soluble in cold ethanol (5.0 g/100 mL) than in hot ethanol (15 g/100 mL). The chemist estimates that the impurity is similar to the product and therefore has the same solubility properties. Can the compound be purified by recrystallization from ethanol?

METHOD: If the sample is dissolved in the minimum amount of hot ethanol, chilling the solution will cause the solid to precipitate. This will purify the compound if none of the impurity precipitates at the same time. We need to determine the minimum volume of hot solvent needed to dissolve the entire sample and then find out whether the impurity precipitates when that volume of solvent is chilled.

Because 10% of the crude sample is impurity, the 10.0-g sample contains 9.00 g of the desired compound. From the solubility of 15 g/100 mL in hot ethanol, we can calculate the minimum volume of solvent that will dissolve the entire sample:

$$(9.0\text{ g})\left(\frac{100\text{ mL}}{15\text{ g}}\right) = 60\text{ mL}$$

There is an estimated 1.0 g of impurities in the sample. If the impurities have solubility properties similar to those of the desired product, 60 mL of hot ethanol will dissolve 9.0 g of impurities, too, so both the desired product and the impurities will dissolve completely in 60 mL of hot ethanol.

When the ethanol is cooled, the mass of solid that it can hold can be calculated from the solubility in cold ethanol:

$$(60\text{ mL})\left(\frac{5\text{ g}}{100\text{ mL}}\right) = 3.0\text{ g}$$

The cold solution can contain 3.0 g each of the desired solid and its impurity.

Of the 9.0 g of the desired substance, 6.0 g will recrystallize on cooling. All of the 1.0 g of impurity will remain dissolved. A single recrystallization of the contaminated sample will give 6.0 g of pure compound.

Chemists frequently recover a "second crop" of substance by boiling off some of the solvent and then rechilling the solution. You should be able to determine how much additional pure substance could be recovered from this solution before the impurity begins to precipitate.

IPR2020-00770
United Therapeutics EX2007
Page 3262 of 7335

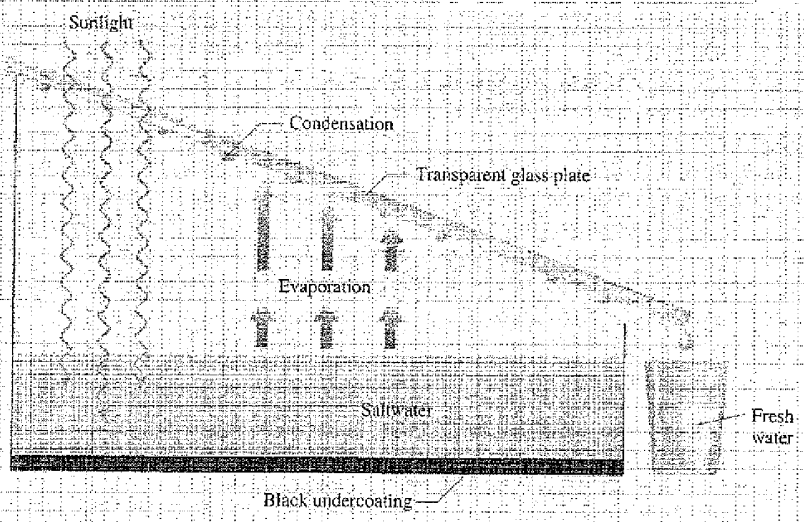


FIGURE 10-47
A simple solar saltwater still. Stills designed along these lines find commercial use in areas where sunlight and saltwater are plentiful and natural supplies of fresh water are scarce.

As Sample Problem 10-14 shows, some product is always lost during recrystallization. In the single recrystallization described, 3.0 g of the original material remains in solution. Thus the yield of the one-step process is 67%. By taking a second crop, an additional 2.0 g can be recovered, increasing the yield to 89%, but the remaining 1.0 g remains mixed with 1.0 g of impurity and cannot be recovered by further recrystallization. Chemical syntheses seldom give 100% yields, in part because the process of purifying the product always results in some losses.

DISTILLATION

The most common method for purifying liquids is **distillation,** which is based on a liquid-vapor phase change. A liquid solution is heated until it boils, and if the solutes remain nonvolatile, pure solvent boils off. This pure solvent vapor is captured by condensing it on a chilled surface.

Fresh water can be obtained by distilling saltwater. Figure 10-47 shows a simple solar still, in which the energy needed to vaporize the water comes from sunlight absorbed by the black coating on the bottom of the still. As the solution is heated, water evaporates, leaving the nonvolatile salt behind. The water vapor comes into contact with the underside of the glass plate, which is cooled by natural air flow. Fresh water condenses on the cool plate and trickles down to a collection vessel at the bottom of the still.

Obtaining high-purity liquids in the laboratory often requires a more elaborate procedure because many liquids decompose or react with oxygen at high temperature. For this reason, high-boiling liquids are often distilled under reduced pressure to lower the boiling temperature. Figure 10-48 shows a common laboratory apparatus used for reduced-pressure distillation.

When a liquid is contaminated with volatile impurities, simple boiling gives a mixture of compounds rather than a pure solvent. In these cases, chemical treatment of the solution can be used to convert the volatile impurity into a nonvolatile solid. For example, small amounts of water are removed from organic solvents such as cyclohexane and diethyl ether by placing a piece of sodium metal in the distilling flask. Water in the solution reacts with sodium to give sodium hydroxide, which is nonvolatile, and hydrogen gas, which does not recondense. Air is excluded from the still, moreover, to prevent immediate contamination of the distilled solvent with

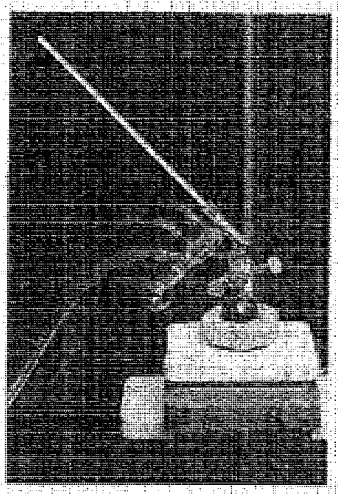


FIGURE 10-48
Liquids susceptible to oxidation or thermal decomposition can be purified by distilling them under reduced pressure.

The effect of pressure on boiling points is considered in Chapter 13. Qualitatively, reducing the pressure reduces the rate of capture of molecules from the gas phase, and this lowers the temperature at which liquid-vapor equilibrium exists.

$2\ Na + 2\ H_2O \rightarrow 2\ NaOH + H_2$. Dry solvents are needed for reactions that give undesirable side products when water is present.

IPR2020-00770
United Therapeutics EX2007
Page 3263 of 7335

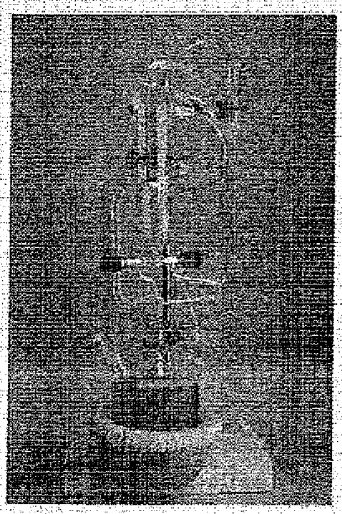


FIGURE 10-49
To produce scrupulously dry solvents, the solvent must be treated with a chemical purifying agent and then distilled under an atmosphere of a dry inert gas. The blue color in the distillation flask is due to the drying agent. Diethyl ether, which is colorless, is collected by condensing the solvent into a bulb above the boiling solvent.

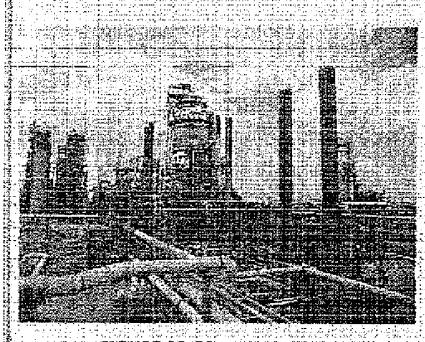


FIGURE 10-50
Oil refineries use immense distillation towers to separate crude oil into its various useful fractions.

The different fractions of hydrocarbons that can be obtained from petroleum are listed in Table 8-2.

water vapor from the atmosphere. Figure 10-49 shows a laboratory still for producing scrupulously dry diethyl ether.

Distillations in the chemical industry are performed on an enormous scale. Distillation is an essential step in the refining of petroleum, for example. Crude oil is a complex mixture of hydrocarbons without a single well-defined boiling point. Instead, crude oil boils over a broad range of temperatures as the lighter, more volatile hydrocarbons boil off first. As the temperature increases gradually, heavier and heavier components of the oil distill out of the mixture. The end product is asphalt, a gooey black tar. In the first step of petroleum refining, crude oil is separated into several fractions according to specific ranges of boiling point. Figure 10-50 shows the huge distillation towers used for these kinds of separations.

CHROMATOGRAPHY

There are many types of **chromatography,** but all are based on the same essential principles. A *mobile phase* carries the compounds to be separated, and a *stationary phase* binds these compounds through intermolecular forces.

Figure 10-51 shows how chromatography separates compounds. The mobile phase dissolves the compounds of interest and carries them over the stationary phase. The rate of movement of compounds depends on how strongly they interact with the stationary phase. Because solutes move only when in the mobile phase, molecules that have a very low affinity for the stationary phase move quickly, whereas those that bind tightly to the stationary phase lag behind. After the materials have traveled a sufficient distance, they become separated into distinct "bands"; each band may contain one pure material. As the mobile phase comes off the lower end of the column, it can be collected in small volumes called *fractions* or *cuts.* When the separations are complete, the various components of the original mixture are found in different fractions.

Chromatography is extremely versatile because the stationary phase and the mobile phase can be varied to match the types of compounds that need to be separated. For example, some stationary phases separate solutes according to their polarity. Polar groups on the stationary phase bind solutes through dipole-dipole or hydrogen-bonding interactions. The binding is reversible, and eventually the solvent washes the solutes off the stationary phase. The more polar the solute, the tighter it binds to the stationary phase. Thus the faster the solutes move through the column, the lower their polarity.

In other cases the stationary phase binds solutes according to their size. Here, the stationary phase is made up of particles that are perforated with holes or channels, much like a sponge or a Wiffle ball (Figure 10-52). Small molecules can pass through the holes into the interior of the particle. Eventually these molecules make their way back out of the stationary phase. The smallest molecules move into and out of particles many times as they travel along the column. Larger molecules enter fewer times because they do not fit inside the pores as easily. The more particles a solute molecule enters, the more time it spends bound to the stationary phase, and the more slowly it moves along the column. Thus the largest solute molecules emerge from the chromatography column first, and the smallest molecules emerge last. Pore size in these stationary phases can be controlled to accommodate an enormous range of molecular sizes, from mixtures of small gas molecules to huge biomolecules with molar masses in excess of 100,000 g/mol.

METHODS OF CHROMATOGRAPHY

Chromatographic techniques are classified according to the nature of their mobile and stationary phases. Gas chromatography (GC) is used to separate mixtures of

IPR2020-00770
United Therapeutics EX2007
Page 3264 of 7335

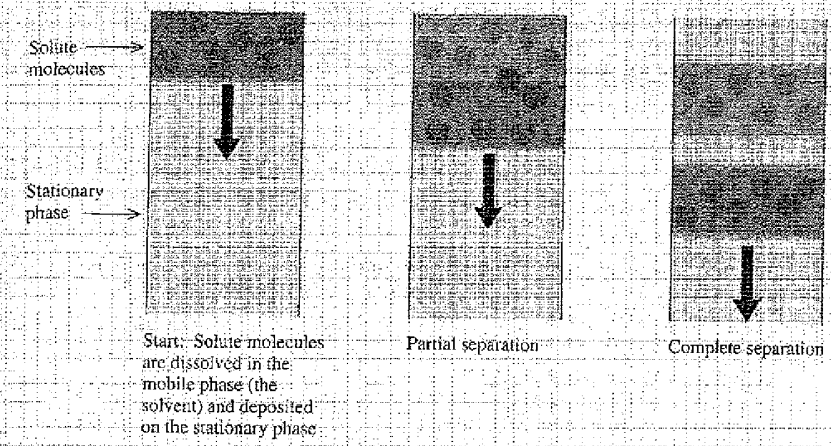


FIGURE 10-51
Diagrammatic view of how column chromatography works. Solute molecules that bind strongly to the stationary phase (*red circles*) move down the column more slowly than those that bind only weakly (*blue circles*). For clarity, solvent molecules and the detailed structure of the stationary phase are not shown.

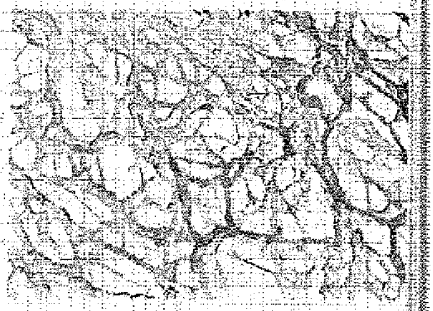
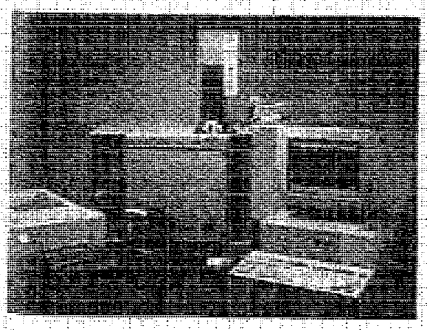


FIGURE 10-52
Chromatographic columns that separate substances according to molecular sizes have stationary phases made up of many tiny porous beads. This image was magnified 50,000 times.

gases or volatile liquids. The mixture to be separated is vaporized in an oven, and the gaseous mobile phase passes through a long, narrow column packed with a finely divided solid that may be impregnated with a nonvolatile liquid (stationary phase). As the components of the mixture emerge from the column, their presence is sensed by a detector and displayed as a graph on a computer screen. Figure 10-53 shows a photograph of a gas chromatograph. The most widespread use of GC is in identifying trace components of a mixture. Among other things, GC is used to test urine for the presence of illegal drugs, identify pollutants and measure their concentrations in groundwater, assay the purity of a volatile compound isolated in the laboratory, and follow the progress of a chemical reaction by monitoring the disappearance of starting materials or the appearance of products.

Liquid chromatography (LC) uses a liquid mobile phase that passes down the stationary phase of a finely divided solid. An LC apparatus is shown in Figure 10-54. This technique is widely used to purify chemical substances on a multigram scale.

In thin-layer chromatography (TLC) a minute amount of a mixture is placed as a small spot at the bottom of a plate coated with a thin layer of a solid stationary phase, usually SiO_2 or Al_2O_3. The plate is placed "spotted" end down in a chamber containing a small amount of a suitable liquid solvent that acts as the mobile phase. Capillary action carries the solvent and the mixture up the plate, and the dissolved



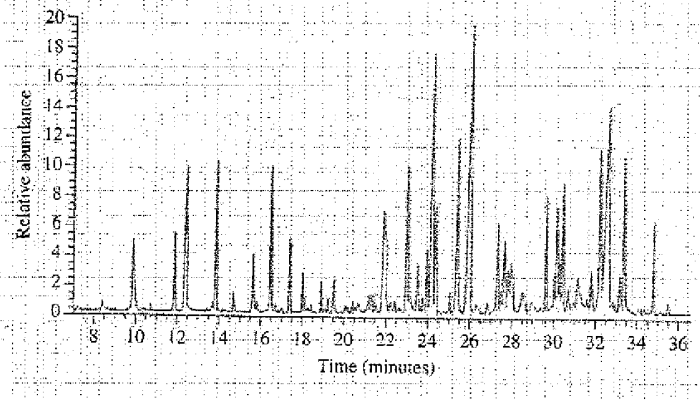


FIGURE 10-53
A gas chromatograph separates a small sample of a mixture into its individual components. The printout shown here highlights the large number of compounds used to make perfume.

IPR2020-00770
United Therapeutics EX2007
Page 3265 of 7335

BOX 19-2

ION-EXCHANGE CHROMATOGRAPHY

The cations or anions in solutions of ionic compounds can be exchanged for other cations or anions by using the technique of *ion-exchange chromatography*. The stationary phases used in ion-exchange columns are large polymer molecules with charged functional groups. In an anion-exchange column the polymer is linked covalently to a positively charged group. Negative counter-ions are loosely associated with the polymer through ion-ion attractions. In a cation-exchange column the polymer contains covalently bound substituents with a negative charge, and the positive counter-ions are loosely associated through ion-ion attractions.

Before an ion exchange column can be used, the stationary phase must first be *charged*. In the charging process a highly concentrated solution of a specific cation or anion is passed through the column. All the mobile ions associated with the resin are replaced by the specific cation or anion. For example, to charge a cation-exchange resin with sodium ions, the column is treated with concentrated aqueous sodium chloride. After the column is charged, an aqueous solution containing other cations (for example, calcium cations) can be passed through the column, and the column will attract these cations, releasing sodium ions to enter the solution. Cations have exchanged places between solution and polymer, hence the term **ion exchange.**

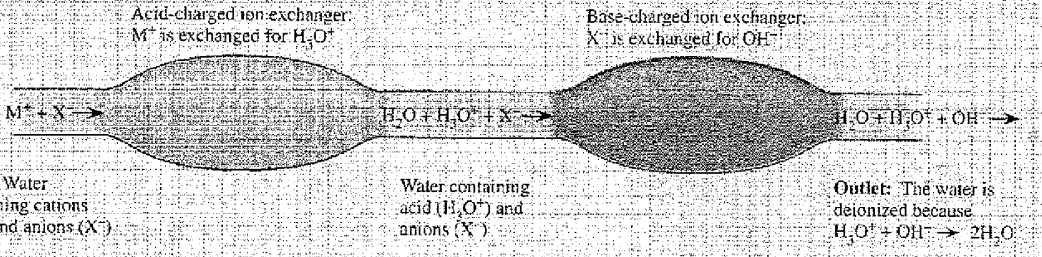
As this description suggests, ion-exchange chromatography does not *remove* ions from a solution. Instead, it *replaces* them with other ions. Nonetheless, this method is used widely in the water treatment industry to soften and deionize water.

"Hard" water has high concentrations of divalent Mg^{2+} and Ca^{2+} cations. We explained earlier that the large molecules that make up soaps contain negatively charged groups that form precipitates with these divalent metal cations. The sodium salts of soaps, on the other hand, do not precipitate from solution. The function of a water softener is to exchange the "hard" Ca^{2+} and Mg^{2+} cations for the "soft" Na^+ cation. Thus even though soft water is no more pure than hard water, it dissolves soaps better. This makes soft water a better medium than hard water for household and industrial cleaning.

Deionization, shown below, removes ions from solution. An aqueous salt solution passes in sequence through a cation-exchange column charged with hydronium ions and an anion-exchange column charged with hydroxide ions. In the first column H_3O^+ replaces metal cations in the solution. In the second column OH^- replaces the anions present in the original salt solution. Hydroxide ions and hydronium ions immediately combine to give water:

$$H_3O^+_{(aq)} + OH^-_{(aq)} \rightarrow 2\,H_2O_{(l)}$$

Although ion exchange is a cost-effective way to produce ion-free water for laboratory and home use, it cannot be applied economically to the desalinization of seawater. After a short period of use, the columns become depleted of H_3O^+ and OH^- ions and must be recharged by passing aqueous HCl through the cation exchanger and aqueous NaOH through the anion exchanger. Because seawater is much higher in total ion content than fresh water, the cost of the chemicals for recharging quickly becomes prohibitive.



IPR2020-00770
United Therapeutics EX2007
Page 3266 of 7335

solutes spread out according to their polarity. The plate is removed from the chamber when the solvent nears the top. The plate dries as the solvent evaporates, leaving the nonvolatile components of the mixture as spots located at different positions on the plate. The TLC in Figure 10-55 shows that common blue ink is a mixture of several different colored compounds. TLC is often used to monitor the progress of chemical reactions. It is also used to determine the optimum separation conditions for larger-scale chromatographic techniques such as LC. Box 10-2 explains another chromatographic technique, ion-exchange chromatography.

FIGURE 10-54
A liquid chromatograph involves the same principles as GC but on a larger scale.

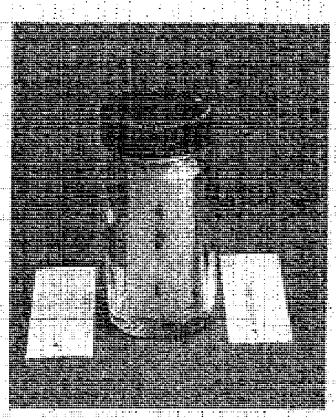


FIGURE 10-55
In thin-layer chromatography a solvent moves along a plate by capillary action, carrying different components with it at different rates. The photograph shows the separation of a blue ink into its component pigments.

SECTION EXERCISES

Explain in molecular terms the following features of purification techniques.

10.8.1 When a precipitate forms too quickly, it is likely to be less pure than if it is allowed to crystallize slowly from the same solution.

10.8.2 Distillation of an organic liquid that contains a volatile impurity always gives a distilled liquid that still contains some of the impurity.

10.8.3 If your home water softener runs out of salt, your water soon feels hard again.

CHAPTER SUMMARY

1. Attractive forces between molecules cause most substances to be liquids or solids under normal conditions, as well as leading to nonideal behavior of gases at high pressure and low temperature. These forces include dispersion forces, dipole-dipole interactions, and hydrogen bonding.
2. Hydrogen bonds, which are particularly important in aqueous environments, involve partial sharing of electrons between a fluorine, oxygen, or nitrogen atom and a hydrogen atom in a highly polar bond.
3. The molecules in liquids cohere but move freely. Liquid properties include surface tension, capillary action, and viscosity. Solids, on the other hand, are held in fixed structures by ionic, metallic, covalent, or intermolecular interactions.
4. Amorphous solids lack a regular structure, but any crystalline solid is composed of a repeating pattern whose smallest complete part is a unit cell. The simplest of these repeat patterns, adopted by many atomic and metallic solids, are hexagonal close-packed, face-centered cubic, and body-centered cubic structures.
5. A solution is a homogeneous mixture of varying amounts of solutes contained in a solvent. Substances that are subject to similar intermolecular forces tend to dissolve in each other, leading to the generalization, like dissolves like.
6. Gaseous solutions have unrestricted composition ranges, but most liquid solutions have an upper limit on the amount of solute they can hold. The solubility of a gas in a liquid depends not only on the natures of solvent and solute, but also on the partial pressure of solute in the gas phase.
7. Surfactants, which are molecules that contain water-compatible and water-incompatible structures, form monolayers, micelles, and vesicles in aqueous media.
8. Solutes depress the freezing point, raise the boiling point, and generate an osmotic pressure of a solution. The magnitudes of these colligative properties are concentration-dependent.
9. Transfers between phases form the basis for separation and purification techniques, including recrystallization, distillation, and chromatography.

IPR2020-00770
United Therapeutics EX2007
Page 3267 of 7335

KEY TERMS

adhesive forces
cohesive forces
dipolar forces
dispersion forces
hydrogen bond
intermolecular forces
intramolecular forces
polarizability

capillary action
surface tension
viscosity

amorphous
body-centered cubic structure
close-packed structure
crystalline
cubic close-packed structure
hexagonal close-packed structure
unit cell

alloy
amalgam
Henry's law
miscible
saturated solution
solubility
solute
solution
solvent

bilayer
hydrophilic
hydrophobic
micelle
monolayer
surfactant
vesicle

boiling point elevation constant
freezing point depression constant
normal boiling point (bp)
normal freezing point (fp)
osmosis
osmotic pressure (Π)
semipermeable membrane

chromatography
distillation
ion exchange

SKILLS TO MASTER

- Explaining variations in boiling points
- Identifying hydrogen bonds
- Describing surface tension, capillary action, and viscosity
- Recognizing types of solids
- Depicting simple crystal types
- Predicting solubility patterns
- Calculating gas solubilities
- Describing surfactant properties
- Calculating colligative properties
- Drawing molecular pictures of solutions
- Describing separation techniques

LEARNING EXERCISES

10.1 Write a chapter summary of two pages or less that summarizes the important ideas and concepts presented in this chapter.

10.2 List all the types of interactions that can act to hold a solid together. Organize the list from strongest to weakest.

10.3 Draw molecular pictures that show every type of hydrogen bond that exists in a solution containing methanol, water, and ammonia.

10.4 Write a paragraph that describes the factors that make glycerol highly viscous and explains why its viscosity falls as temperature rises.

10.5 Define and give an example of each of the following: (a) close-packed structure; (b) unit cell; (c) molecular solid; (d) covalent solid; (e) amorphous solid; and (f) surfactant.

10.6 Update your list of memory-bank equations. Be sure to mention how the equations in this chapter are used.

10.7 Write a paragraph that describes the types of substances that form monolayers, micelles, and vesicles in water. Explain the differences among these structures.

10.8 Describe how each of the following separation processes works: recrystallization, distillation, and chromatography.

10.9 Prepare a list of the terms in Chapter 10 that are new to you. Write a one-sentence definition for each, using your own words. If you need help, consult the glossary.

IPR2020-00770
United Therapeutics EX2007
Page 3268 of 7335

PROBLEMS

THE NATURE OF INTERMOLECULAR FORCES

10.1 Methane condenses at 121 K, but carbon tetrachloride boils at 350 K. Sketch an energy-distance plot similar to that of Figure 10-3 that shows the behavior of both of these substances.

10.2 Draw pictures showing the atomic arrangements in samples of $Ag_{(s)}$, $Ar_{(g)}$, and $Hg_{(l)}$.

10.3 Predict whether intermolecular attractions become more or less significant when the following changes are imposed:
(a) A gas is expanded to a larger volume at constant temperature.
(b) More gas is forced into the same volume at constant temperature.
(c) The temperature of the gas is lowered at constant volume.

10.4 Predict whether molecular volume becomes more or less significant when each of the changes in Problem 10.3 is imposed.

10.5 From the following experimental data, calculate the percent deviation from ideal behavior for each gas:
(a) 1.00 mol CO_2 in a 1.20-L container at 40.0 °C exerts 19.7 atm pressure.
(b) 3.00 g H_2 at 0.00 °C and 200 atm occupies a volume of 189.18 cm^3.

10.6 Arrange the following in order of increasing boiling point: Ar, He, Ne, and Xe. Explain your ranking.

10.7 Arrange the following in order of ease of liquefaction: CCl_4, CH_4, and CF_4. Explain your ranking.

10.8 Benzene (C_6H_6), naphthalene ($C_{10}H_8$), and anthracene ($C_{14}H_{10}$) are three ring compounds with similar molecular structures. One is a liquid, another is a relatively volatile solid, and the third is a less volatile solid. Which is which? Explain your assignments.

Benzene C_6H_6 — Napthalene $C_{10}H_8$ — Anthracene $C_{14}H_{10}$

10.9 Which of the following ions have the stronger interaction with water molecules in an aqueous solution? Explain your choices. (a) Na^+ or Mg^{2+}; (b) Na^+ or K^+; and (c) SO_4^{2-} or SO_3^{2-}.

HYDROGEN BONDING

10.10 Draw Lewis structures that show the hydrogen bonding interactions for each of the following: (a) two NH_3 molecules; (b) two CH_3OH molecules; and (c) an HF molecule and an acetone molecule [$(CH_3)_2C{=}O$].

10.11 List ethanol (C_2H_5OH), propane (C_3H_8), and *n*-pentane (C_5H_{12}) in order of increasing boiling point, and explain what features determine this order.

10.12 How many hydrogen bonds can be formed by one glycerol molecule ($HOCH_2CHOHCH_2OH$)? Draw Lewis structures that show the hydrogen bonding of a glycerol molecule dissolved in water.

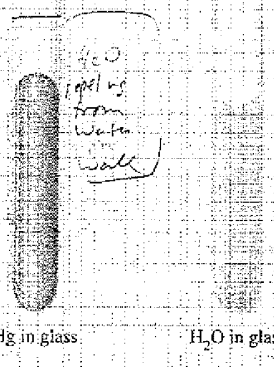
10.13 Which of the following will hydrogen bond? (a) CH_2Cl_2; (b) H_2SO_4; (c) H_3COCH_3; and (d) $H_2NCH_2CO_2H$.

PROPERTIES OF LIQUIDS

10.14 Given that a lubricant must flow easily to perform its function, which grade of motor oil is preferred for winter use: high or low viscosity? Why?

10.15 Pentane is a C_5 hydrocarbon, gasoline contains mostly C_8 hydrocarbons, and fuel oil contains hydrocarbons in the C_{12} range. List these three hydrocarbons in order of increasing viscosity, and explain what molecular feature accounts for the variation.

10.16 Water in a glass tube takes on a concave shape, whereas mercury in a glass tube takes on a convex shape. Explain why the two liquids display different shapes.



Hg in glass — H_2O in glass

10.17 To make a good solder joint, the liquid metal solder must adhere well to the metal surfaces being joined. "Flux" is used to clean the metal surfaces. What types of substances must flux remove?

IPR2020-00770
United Therapeutics EX2007
Page 3269 of 7335

10.18 A pipet is considered to be "dirty" when water forms beads on its walls rather than forming a thin film that drains well. Which of the following on the surface of a pipet wall will make it dirty? In each case, explain the intermolecular forces underlying your classification. (a) grease; (b) Mg^{2+} ions; (c) acetone; and (d) SiO_2.

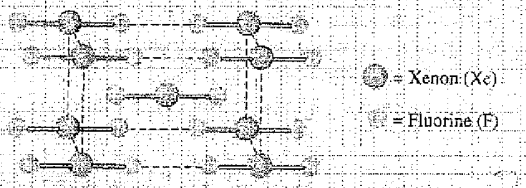
PROPERTIES OF SOLIDS

10.19 Classify each of the following as ionic, covalent, molecular, or metallic solids: Sn, S_8, Se, SiO_2, and Na_2SO_4.

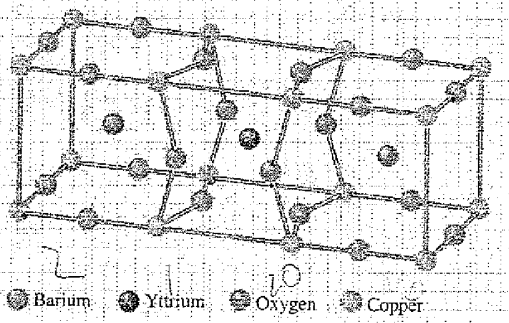
10.20 Amorphous silica has a density of around 2.3 g/cm^3, whereas crystalline quartz has a density of 2.65 g/cm^3. Why do these two forms of the same substance have different densities?

10.21 Construct part of the Lewis structure of carborundum, the diamondlike compound of empirical formula SiC.

10.22 The unit cell of a compound of xenon and fluorine follows. What is the formula of the compound?



10.23 Recently, a new group of solids was prepared that can act as superconductors at temperatures near the boiling point of liquid nitrogen. (A superconductor is a material whose electrical resistance is zero.) The unit cell of one of these new superconductors is shown here. Identify the formula of the compound.



10.24 Draw the unit cell of the NaCl crystal and determine the number of nearest neighbors of opposite charge for each ion in these unit cells.

THE NATURE OF SOLUTIONS

10.25 Do you expect gasoline to dissolve in water? Knowing that gasoline is less dense than water, would you use water to fight a gasoline fire? Explain.

10.26 Acetone, $(CH_3)_2CO$, is miscible with both water and cyclohexane (C_6H_{12}), but water and cyclohexane are nearly insoluble in each other. Explain.

10.27 Ammonia can be condensed to a liquid at low temperature. What kinds of solids would you expect to be soluble in liquid ammonia?

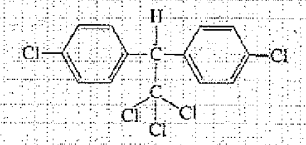
10.28 One of the detrimental effects of the "thermal pollution" of water supplies is that a rise in temperature reduces the amount of dissolved oxygen available for fish. Using the information in Table 10-2, calculate the number of liters of water a fish requires at 30 °C to obtain the same amount of oxygen that it could obtain from 1 L of water at 25 °C.

10.29 Using the information in Table 10-2, calculate the number of grams of CO_2 that can be dissolved in 250 mL of a carbonated beverage at 1.10 atm pressure and 25 °C.

10.30 If a bottle of the carbonated beverage in Problem 10.29 is stored in an ice chest at 0 °C, what is the partial pressure of CO_2 in the gas space above the liquid?

DUAL-NATURE MOLECULES: SURFACTANTS AND BIOLOGICAL MEMBRANES

10.31 Dichlorodiphenyltrichloroethane (DDT) has the following structure:



Is this compound hydrophilic or hydrophobic? Is it readily excreted by animals, or will it concentrate in fatty tissues? Does your answer explain why DDT has been banned as a pesticide?

10.32 Of the following compounds, which will be the best and which will be the worst surfactant? Support your choices with molecular pictures. (a) propionic acid, $H_3CCH_2CO_2H$; (b) lauryl alcohol, $H_3C(CH_2)_{11}OH$; and (c) sodium lauryl sulfate $H_3C(CH_2)_{11}OSO_3^-Na^+$.

10.33 Some surfactants form membranes that span small holes between two aqueous solutions. These membranes are liquid bilayers two molecules thick. Draw a molecular picture of one of these membranes.

10.34 Stearic acid forms a monolayer on the surface of gasoline. Draw a molecular picture that shows how stearic acid molecules are arranged in this monolayer.

IPR2020-00770
United Therapeutics EX2007
Page 3270 of 7335

PROPERTIES OF AQUEOUS SOLUTIONS

10.35 Compute the freezing point of a wine that is 12% ethanol by mass. (Ignore all other solutes.)

10.36 Do you have enough information to calculate the boiling point of the wine in Problem 10.35? If so, calculate it. If not, explain what feature of wine prevents you from doing this calculation.

10.37 An aqueous solution contains 1.00 g/L of a derivative of the detergent lauryl alcohol. The osmotic pressure of this solution at 25 °C is 17.8 torr.
(a) What is the molar mass of the detergent?
(b) The hydrocarbon portion of the molecule is an 11-carbon chain. What is the molar mass of the polar portion?

10.38 Calculate the boiling point of a solution that contains 2.50 g NaCl in 155 mL of water.

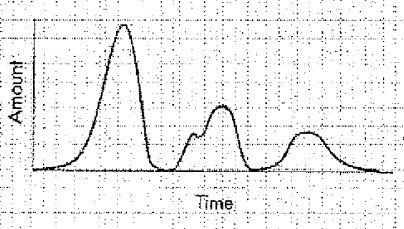
SEPARATION PROCESSES

10.39 Describe how you would purify diethyl ether, $(C_2H_5)_2O$, which is contaminated with a small amount of water.

10.40 You have prepared a new, highly colored solid compound and want to determine whether your product is pure or contains several components. What technique would provide this information most conveniently? Describe how the technique works.

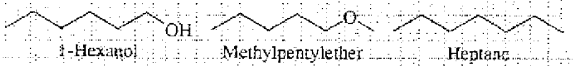
10.41 The solubility of $HgCl_2$ in water is 380 g/L at 100 °C and 30 g/L at 0 °C. What is the minimum volume of water needed to recrystallize a crude sample of this compound whose mass is 250 g? What fraction of the crude sample will be recovered? (For calculation purposes, assume that the crude sample is 95% $HgCl_2$ and that the impurity is more soluble than $HgCl_2$.)

10.42 You have prepared a sample of polymer and have performed liquid chromatography using molecular sieves to determine its molecular size. The chromatogram follows:



(a) How many components does your sample contain?
(b) Is there a larger amount of long-, medium-, or short-chain polymer molecules in the sample? Explain.

10.43 A sample for gas chromatography contains the following compounds:



If the GC column separates molecules according to their polarity, in what order will the compounds come off the column? Explain.

ADDITIONAL PROBLEMS

10.44 Will water, ethanol, or acetone rise the highest in a glass capillary tube? Which will rise the least? Explain why in terms of intermolecular forces.

10.45 An aqueous solution containing 1.00 g of a sugar in 100 mL of solution has an osmotic pressure of 1.36 atm at 25 °C. What is the molar mass of this sugar?

10.46 Classify each of the following solids as covalent, metallic, ionic, or molecular: (a) a solid that conducts electricity; (b) a solid that does not conduct electricity but dissolves in water to give a conducting solution; and (c) a solid that does not conduct electricity and melts below 100 °C to give a nonconducting liquid.

10.47 Rank the following substances in order of increasing solubility in water, and state the reasons for your rankings: C_6H_6 (benzene), $HOCH_2CH(OH)CH(OH)CH_2OH$ (erythritol), and $C_5H_{11}OH$ (pentanol).

10.48 What mole fraction of ethanol is required to protect the water in an automobile cooling system from freezing at −20 °C?

10.49 Aqueous solutions of 0.5 M acetic acid and 0.5 M $MgSO_4$ each have freezing points higher than the freezing point of 1 M glucose but lower than the freezing point of 0.5 M glucose. Explain these observations.

10.50 The osmotic pressure of a 0.10 M solution of H_3PO_4 at 300 K is 3.03 atm. What is the *total* molarity of the solutes under these conditions? On the basis of this result, would you call H_3PO_4 a strong acid?

10.51 The solubility of NaCl is 26 g/100 mL at 0 °C and 28 g/100 mL at 100 °C. Is it practical to purify NaCl by recrystallization from water? Explain your answer.

10.52 Why is the boiling point of H_2S lower than the boiling point of H_2O? Why is it also lower than the boiling point of H_2Te?

IPR2020-00770
United Therapeutics EX2007
Page 3271 of 7335

10.53 List the following liquids in order of increasing viscosity at room temperature, and explain the order of your list: (a) butanol, C_4H_9OH; (b) pentane, C_5H_{12}; and (c) propane-1,3-diol, $HOCH_2CH_2CH_2OH$.

10.54 Rank the following substances in order of increasing solubility in cyclohexane (C_6H_{12}) and explain the order of your list: KCl; C_4H_9OH; and C_4H_8.

10.55 Approximately what value of *total* solute molarity would you expect to find for 0.1 M aqueous solutions of each of the following: (a) citric acid (a weak organic acid); (b) $FeCl_3$; (c) NaOH; and (d) $(NH_4)_2CO_3$.

10.56 Brackish water, with a salt content around 0.5% by mass, is found in semiarid regions such as the American Southwest. Assuming that brackish water contains only sodium chloride, estimate the osmotic pressure of brackish water.

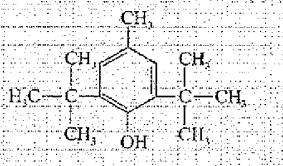
10.57 The freezing point of 0.050 M $KHSO_3$ is −0.19 °C. Which of the following equations best represents what happens when this compound dissolves in water? Explain your choice.

(a) $KHSO_{3\,(s)} \rightarrow KHSO_{3\,(aq)}$

(b) $KHSO_{3\,(s)} \rightarrow K^+_{(aq)} + HSO_{3\,(aq)}^-$

(c) $KHSO_{3\,(s)} + H_2O \rightarrow K^+_{(aq)} + H_2O^+_{(aq)} + SO_3^{2-}{}_{(aq)}$

10.58 Butylated hydroxytoluene (BHT) is used as a food preservative. It has the following molecular structure:



Would you expect to find this compound in urine or stored in body fat? BHT is nontoxic to humans.

10.59 Water and carbon tetrachloride are not miscible. When mixed, they form two layers, like water and oil. If an aqueous solution of I_2 is shaken with CCl_4, the iodine is "extracted" into the CCl_4 layer. Explain this behavior on the basis of your knowledge of intermolecular forces.

10.60 Some chemists interpret the boiling point of HCl as evidence for hydrogen bonding in this compound. How does the location of HCl on the graph in Figure 10-16 suggest that it may form hydrogen bonds? Draw a molecular picture that shows the possible hydrogen bonds between HCl molecules.

10.61 List the following aqueous solutions in order of increasing osmotic pressure, and explain your rankings: (a) 3.0×10^{-3} M KBr; (b) 3.0×10^{-3} M glucose; and (c) 4.0×10^{-3} M glucose.

10.62 Identify two elements that form molecular crystals, two that form metallic crystals, and two that form covalent crystals. Identify regions of the periodic table where elements of these three kinds are located.

10.63 One of the earliest methods of preserving fish was by salting. Explain what happens when fish is placed in a strong salt solution.

10.64 Would water dissolve salts as well as it does if it had a linear structure (such as CO_2) instead of a bent one? Explain.

10.65 List all the intermolecular forces that stabilize the liquid phase of each of the following compounds: (a) NH_3; (b) Xe; (c) SF_4; (d) CF_4; and (e) CH_3CO_2H (acetic acid).

10.66 Fish have blood that is isotonic with seawater, which freezes at −2.30 °C. What is the osmotic pressure of fish blood at 15 °C?

10.67 Homemade ice cream is frozen by churning it in a bucket suspended in an ice-water-salt mixture. A typical mix calls for 1.1 kg of rock salt (NaCl) and 7.25 kg of ice. Compute the mole fraction of NaCl in this mixture after all the ice melts, and estimate its freezing point.

10.68 Compute the molar mass of vitamin C if a solution containing 22.0 g in 100 g of water freezes at −2.33 °C.

10.69 For each of the following pairs, identify which has the higher boiling point, and identify the type of force that is responsible: (a) CH_3OCH_3 and CH_3OH; (b) SO_2 and SiO_2; (c) HF and HCl; and (d) Br_2 and I_2.

10.70 When an aqueous solution is cooled to a low temperature, part of the water freezes as pure ice. What happens to the freezing point of the remaining solution when this occurs? A glass of wine placed in a freezer at −10 °C for a very long time forms some ice crystals but does not completely freeze. Compute the mole fraction of ethanol in the remaining liquid phase.

10.71 Molecular hydrogen and atomic helium have two electrons, but He boils at 4.2 K, whereas H_2 boils at 20 K. Neon boils at 27.1 K, whereas methane, which has the same number of electrons, boils at 114 K. Explain why molecular substances boil at a higher temperature than atomic substances with the same number of electrons.

10.72 Arrange the following liquids in order of increasing viscosity, and state the factors that determine the ranking: 1-butanol, $CH_3CH_2CH_2CH_2OH$; *n*-pentane, $CH_3CH_2CH_2CH_2CH_3$; 2,2-dimethylpropane, $(CH_3)_4C$; and propane-1,3-diol, $HOCH_2CH_2CH_2OH$.

10.73 The structures and boiling points of *n*-pentane and 2,2-dimethylpropane follow:

Pentane	2,2-Dimethylpropane
C_5H_{12}	C_5H_{12}
bp = 36 °C	bp = 10 °C

Use the boiling point data and molecular drawings to explain how shape affects the magnitude of dispersion forces. (See Figures 10-10 and 10-11.)

IPR2020-00770
United Therapeutics EX2007
Page 3272 of 7335

INTRODUCTION TO

Organic Laboratory Techniques

SMALL-SCALE APPROACH

FIRST EDITION

Donald L. Pavia
Gary M. Lampman
George S. Kriz
Western Washington University, Bellingham, Washington

Randall G. Engel
Edmonds Community College, Lynnwood, Washington

Saunders Golden Sunburst Series
SAUNDERS COLLEGE PUBLISHING
Harcourt Brace College Publishers

Fort Worth Philadelphia San Diego New York Orlando Austin
San Antonio Toronto Montreal London Sydney Tokyo

IPR2020-00770
United Therapeutics EX2007
Page 3273 of 7335

Copyright © 1998 by Harcourt Brace & Company

All rights reserved. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without permission in writing from the publisher.

Requests for permission to make copies of any part of the work should be mailed to: Permissions Department, Harcourt Brace & Company, 6277 Sea Harbor Drive, Orlando, Florida 32887-6777.

Publisher: John Vondeling
Developmental Editor: Sandra Kiselica
Cover Designer: Kathleen Flanagan
Cover Photo Credit: Reginald Wickham Photography
Production Services: York Production Services
Product Manager: Angus McDonald

Printed in the United States of America
Introduction to Organic Laboratory Techniques: Small Scale Approach
ISBN: 0-03-024519-2
Library of Congress Catalog Card Number: 94-066238
890123 039 109876543

"WARNINGS ABOUT SAFETY PRECAUTIONS

Some of the experiments contained in this Laboratory Manual involve a degree of risk on the part of the instructor and student. Although performing the experiments is generally safe for the college laboratory, unanticipated and potentially dangerous reactions are possible for a number of reasons, such as improper measurement or handling of chemicals, improper use of laboratory equipment, failure to follow laboratory safety procedures, and other causes. Neither the Publisher nor the Authors can accept any responsibility for personal injury or property damage resulting from the use of this publication."

4.8 CENTRIFUGATION

Sometimes centrifugation is more effective in removing solid impurities than are conventional filtration techniques. Centrifugation is particularly effective in removing suspended particles which are so small that the particles would pass through most filtering devices. Another situation in which centrifugation may be useful is when the mixture must be kept hot to prevent premature crystallization while the solid impurities are removed.

Centrifugation is performed by placing the mixture in one or two centrifuge tubes (be sure to balance the centrifuge) and centrifuging for several minutes. The supernatant liquid is then decanted (poured off) or removed with a Pasteur pipet.

PROBLEMS

1. In each of the following situations, what type of filtration device would you use?
   (a) Remove powdered decolorizing charcoal from 20 mL of solution.
   (b) Collect crystals obtained from crystallizing a substance from about 1 mL of solution.
   (c) Remove a very small amount of dirt from 1 mL of liquid.
   (d) Isolate 2.0 g of crystals from about 50 mL of solution after performing a crystallization.
   (e) Remove dissolved colored impurities from about 3 mL of solution.
   (f) Remove solid impurities from 5 mL of liquid at room temperature.

TECHNIQUE 5

Crystallization: Purification of Solids

Organic compounds that are solid at room temperature are usually purified by crystallization. The general technique involves dissolving the material to be crystallized in a *hot* solvent (or solvent mixture) and cooling the solution slowly. The dissolved material has a decreased solubility at lower temperatures and will separate from the solution as it is cooled. This phenomenon is called either **crystallization** if the crystal growth is relatively slow and selective or **precipitation** if the process is rapid and nonselective. Crystallization is an equilibrium process and produces very pure material. A small seed crystal is formed initially, and it then grows layer by layer in a reversible manner. In a sense, the crystal "selects" the correct molecules from the solution. In precipitation, the crystal lattice is formed so rapidly that impurities are trapped within the lattice. Therefore, any attempt at purification with too rapid a process should be avoided.

The method of crystallization described in detail in this chapter is called **standard-scale crystallization.** This technique, which is carried out with an Erlenmeyer flask to dissolve the material and a Büchner funnel to filter the crystals, is normally used when the weight of solid to be crystallized is more than 0.1 g. Another method, which is performed with a Craig tube, is used with smaller amounts of solid. Referred to as **microscale crystallization,** this technique is discussed briefly in Section 5.4.

IPR2020-00770
United Therapeutics EX2007
Page 3275 of 7335

PDR®

59 EDITION

2005

PHYSICIANS' DESK REFERENCE®

Executive Vice President, PDR: David Duplay

Vice President, Sales and Marketing: Dikran N. Barsamian
Senior Director, Pharmaceutical Sales: Anthony Sorce
National Account Manager: Marion Reid, RPh
Senior Account Managers: Frank Kerkowsky, Suzanne E. Yarrow, RN
Account Managers: Marjorie A. Jaxel, Kevin McGlynn, Elaine Musco, Lois Smith, Eileen Sullivan, Richard Zwickel
Senior Director, Brand and Product Management: Valerie E. Berger
Director, Brand and Product Management: Carmen Mazzatta
Associate Product Managers: Michael Casale, Andrea Colavecchio
Senior Director, Publishing Sales and Marketing: Michael Bennett
Director of Trade Sales: Bill Gaffney
Associate Director of Marketing: Jennifer M. Fronzaglia
Senior Marketing Manager: Kim Marich
Direct Mail Manager: Lorraine M. Loening
Manager of Marketing Analysis: Dina A. Maeder
Promotion Manager: Linda Levine
Vice President, Regulatory Affairs: Mukesh Mehta, RPh
Vice President, PDR Services: Brian Holland
Director of PDR Operations: Jeffrey D. Schaefer
Director of Operations: Robert Klein
Clinical Content Operations Manager: Thomas Fleming, PharmD
Manager, Editorial Services: Bette LaGow
Drug Information Specialists: Min Ko, PharmD; Greg Tallis, RPh
Project Editors: Nell Chesanow, Harris Fleming
Senior Editor: Lori Murray
Production Editor: Gwynned L. Kelly
Manager, Production Purchasing: Thomas Westburgh
Production Manager: Gayle Graizzaro
Production Specialist: Christina Klinger
Senior Production Coordinator: Gianna Caradonna
Production Coordinator: Yasmin Hernández
Senior Index Editors: Noel Deloughery, Shannon Reilly
Format Editor: Michelle S. Guzman
Traffic Assistant: Kim Condon
PDR Sales Coordinators: Nick W. Clark, Gary Lew
Production Design Supervisor: Adeline Rich
Senior Electronic Publishing Designer: Livio Udina
Electronic Publishing Designers: Bryan C. Dix, Rosalia Sbema
Production Associate: Joan K. Akerlind
Digital Imaging Manager: Christopher Husted
Digital Imaging Coordinator: Michael Labruyere
Finance Director: Mark S. Ritchin
Director of Client Services: Stephanie Struble

THOMSON PDR

Copyright © 2005 and published by Thomson PDR at Montvale, NJ 07645-1742. All rights reserved. None of the content of this publication may be reproduced, stored in a retrieval system, resold, redistributed, or transmitted in any form or by any means (electronic, mechanical, photocopying, recording, or otherwise) without the prior written permission of the publisher. Physicians' Desk Reference®, PDR®, Pocket PDR®, PDR Family Guide to Prescription Drugs®, PDR Family Guide to Women's Health and Prescription Drugs®, and PDR Family Guide to Nutrition and Health® are registered trademarks used herein under license. PDR® for Ophthalmic Medicines, PDR® for Nonprescription Drugs and Dietary Supplements, PDR® Companion Guide, PDR® Pharmacopoeia, PDR® for Herbal Medicines, PDR® for Nutritional Supplements, PDR® Medical Dictionary, PDR® Nurse's Drug Handbook, PDR® Nurse's Dictionary, PDR® Family Guide Encyclopedia of Medical Care, PDR® Family Guide to Natural Medicines and Healing Therapies, PDR® Family Guide to Common Ailments, PDR® Family Guide to Over-the-Counter Drugs, PDR® Family Guide to Nutritional Supplements, and PDR® Electronic Library are trademarks used herein under license.

Officers of Thomson Healthcare, Inc.: President and Chief Executive Officer: Robert Cullen; *Chief Financial Officer:* Paul Hilger; *Chief Technology Officer:* Fred Lauber; *Executive Vice President, Medical Education:* Jeff MacDonald; *Executive Vice President, Micromedex:* Jeff Reihl; *Executive Vice President, PDR:* David Duplay; *Senior Vice President, Business Development:* Robert Christopher; *Senior Vice President, Marketing:* Timothy Murray; *Vice President, Human Resources:* Pamela M. Bilash

ISBN: 1-56363-497-X

C

IPR2020-00770
United Therapeutics EX2007
Page 3277 of 7335

Aplisol—Cont.

A separate, sterile, single-use disposable syringe and needle should be used for each individual patient to prevent possible transmission of serum hepatitis virus and other infectious agents from one person to another.

Special care should be taken to ensure that the product is injected intradermally and not into a blood vessel.

Before administration of Aplisol, a review of the patient's history with respect to possible immediate-type hypersensitivity to the product, determination of previous use of Aplisol and the presence of any contraindication to the test should be made (see CONTRAINDICATIONS).

As with any biological product, epinephrine should be immediately available in case an anaphylactoid or acute hypersensitivity reaction occurs.

Failure to store and handle Aplisol as recommended may result in a loss of potency and inaccurate test results.[1,2,3]

Reactivity to the test may be depressed or suppressed for as long as 5–6 weeks in individuals following immunization with certain live viral vaccines, viral infections or discontinuation of corticosteroids or immunosuppressive agents.[4,5]

Information to Patients

Patients should be instructed to report adverse events such as vesiculation, ulceration or necrosis which may occur at the test site in highly sensitive individuals. Patients should be informed that pain, pruritus and discomfort may occur at injection site.

Patient should be informed of the need to return to their physician or health care provider for the reading of the test and of the need to keep and maintain a personal immunization record.

Drug Interactions

In patients who are receiving corticosteroids or immunosuppressive agents, reactivity to the test may be depressed or suppressed. This reduced reactivity may be present for as long as 5–6 weeks after discontinuation of therapy (see PRECAUTIONS—General).[2]

The reactivity to PPD may be temporarily depressed by certain live virus vaccines. Therefore, if a tuberculin test is to be performed, it should be administered either before or simultaneously with the use of oral polio and/or injection of measles, mumps and rubella vaccines in combined form or as separate antigens, or testing should be postponed for 4–6 weeks.[10]

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long term studies have been conducted in animals or in humans to evaluate carcinogenic or mutagenic potential or effects on fertility with Aplisol.

Pregnancy

Teratogenic effects: Pregnancy Category C. Animal reproduction studies have not been conducted with Aplisol. It is also not known whether Aplisol can cause fetal harm when administered to a pregnant woman or can affect the reproduction capacity. Aplisol should be given to a pregnant woman only if clearly needed.

However, the risk of unrecognized tuberculosis and the postpartum contact between a mother with active disease and an infant leaves the infant in grave danger of tuberculosis and complications such as tuberculous meningitis. Although there have not been any reported adverse effects upon the fetus recognized as being due to tuberculosis skin testing, the prescribing physician will want to consider if the potential benefits outweigh the possible risks for performing the tuberculin test on a pregnant woman or a woman of childbearing age, particularly in certain high risk populations.

Tuberculin skin testing is considered valid and safe throughout pregnancy.[8]

ADVERSE REACTIONS

In highly sensitive individuals, strongly positive reactions including vesiculation, ulceration or necrosis may occur at the test site; however, there were no reports of these reactions for the period 1995 through 1998. Cold packs or topical steroid preparations may be employed for symptomatic relief of the associated pain, pruritus and discomfort.

Strongly positive test reactions may result in scarring at the test site.

Immediate erythematous or other reactions may occur at the injection site.

DOSAGE AND ADMINISTRATION

Aplisol vials should be inspected visually for both particulate matter and discoloration prior to administration and discarded if either is seen. Vials in use for more than 30 days should be discarded.

Standard Method (Mantoux Test)

The Mantoux test is performed by intradermally injecting with a syringe and needle exactly 0.1mL of Aplisol. The result is read 48 to 72 hours later and induration only is considered in interpreting the test. Induration is a hard, raised area with clearly defined margins at and around the injection site. Erythema may develop at the injection site but has no diagnostic value. The standard test is performed as follows:

1. The site of the test is usually the flexor or dorsal surface of the forearm about 4" below the elbow. Other skin sites may be used, but the flexor surface of the forearm is preferred. The use of a skin area free of lesions and away from any veins is recommended.[7]
2. The skin at the injection site is cleansed with 70% alcohol and allowed to dry.
3. The test material is administered with a tuberculin syringe (0.5 or 1.0mL) fitted with a short (1/2") 26 or 27 gauge needle.
4. A separate, sterile, single-use disposable syringe and needle should be used for each individual patient.
5. The diaphragm of the vial-stopper should be wiped with 70% alcohol.
6. The needle is inserted through the stopper diaphragm of the inverted vial. Exactly 0.1mL is filled into the syringe with care being taken to exclude air bubbles and to maintain the lumen of the needle filled.
7. The point of the needle is inserted into the most superficial layers of the skin with the needle bevel pointed upward. As the Tuberculin solution is injected, a pale bleb 6 to 10mm in size (1/3") will rise over the point of the needle. This is quickly absorbed and no dressing is required.

In the event the injection is delivered subcutaneously (i.e., no bleb will form), or if a significant part of the dose leaks from the injection site, the test should be repeated immediately at another site at least 5 cm (2") removed.

The Mantoux test is the standard of comparison for all other tuberculin tests.

Interpretation of Tuberculin Reaction

Readings of Mantoux reactions should be made during the period from 48 to 72 hours after the injection. Induration only should be considered in interpreting the test. The diameter of induration should be measured transversely to the long axis of the forearm and recorded in millimeters. Erythema has no diagnostic value and should be disregarded. The presence and size of necrosis and edema if present should be recorded although not used in the interpretation of the test. In the absence of induration, an area of erythema greater than 10 mm is diameter may indicate the injection was made too deeply and retesting is indicated.

Reactions should be interpreted as follows:

Positive—A positive reaction to the tuberculin skin test may not be seen until 2–10 weeks after the infection.[9] Based in current guidelines,[8,12] interpretation of positive reactions (depending on the age, immune status or risk factors of the persons tested) is:

1. An induration of >5 mm is classified as positive in the following:
   - Persons who have had recent close contact with persons who have active TB;
   - Persons who have human immunodeficiency virus (HIV) infection or risk factors for HIV infection but unknown HIV status;
   - Persons who have fibrotic chest radiographs consistent with healed TB.
2. An induration of >10 mm is classified as positive in all persons who do not meet any of the above criteria, but who belong to one or more of the following groups at high risk for TB:
   - Injecting-drug users known to be HIV seronegative;
   - Persons who have other medical conditions that have been reported to increase the risk for progressing from latent TB infection to active TB. These medical conditions include diabetes mellitus, conditions requiring prolonged high-dose corticosteroid therapy and other immunosuppressive therapy (including bone marrow and organ transplantation), chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head or neck), weight loss of >10% below ideal body weight, silicosis, gastrectomy, jejunoileal bypass;
   - Residents and employees of high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, health-care facilities (including some residential mental health facilities), and homeless shelters;
   - Foreign-born persons recently arrived (i.e., within the last 5 years) from countries having a high prevalence or incidence of TB;
   - Some medically underserved, low-income populations, including migrant farm workers and homeless persons;
   - High-risk racial or ethnic minority populations, as defined locally;
   - Children <4 years of age or infants, children and adolescents exposed to adults in high-risk categories.
3. An induration of > 15mm is classified as positive in persons who do not meet any of the above criteria.

Negative—Induration of less than 5 mm. This indicates a lack of hypersensitivity to tuberculoprotein and tuberculous infection is highly unlikely.

Booster Effect—Infection of an individual with tubercle bacilli or other mycobacteria or BCG vaccination results in a delayed hypersensitivity response to tuberculin which is demonstrated by the skin test. The delayed hypersensitivity response may gradually wane over a period of years. If a person receives a tuberculin test at this time, a significant reaction may not be detected. However, the stimulus of the test may boost or increase the size of the reaction to a second test, sometimes causing an apparent conversion or development of sensitivity. This booster effect can be seen on a second test done one week after the initial stimulating test and can persist for a year, and perhaps longer. When routine periodic tuberculin testing of adults is done, initially two-stage testing should be considered to minimize the likelihood of interpreting a boosted reaction as a conversion.[13,14]

It should be noted that reactivity to tuberculin may be depressed or suppressed for as long as 5–6 weeks by viral infections, live virus vaccines (i.e., measles, smallpox, polio, rubella and mumps), or after discontinuation of therapy with corticosteroids or immunosuppressive agents. Malnutrition may also have a similar effect. When of diagnostic importance, a negative test should be accepted as proof that hypersensitivity is absent only after normal reactivity to non-specific irritants has been demonstrated. A primary injection of tuberculin may possibly have a boosting effect on subsequent tuberculin reactions. A pediatric patient who is known to have been exposed to a person with tuberculosis must not be adjudged free of infection until that patient has a negative tuberculin reaction at least ten weeks after contact with tuberculous person has ceased.[15] Annual testing is generally recommended for pediatric patients in high risk populations, such as persons from countries with a high prevalence of tuberculosis and low-income groups.[16,17]

A positive tuberculin reaction does not necessarily signify the presence of active disease. Further diagnostic procedures (e.g., chest radiograph, sputum smear and/or culture examination) should be carried out before a diagnosis of tuberculosis is made. A small percentage of responders may not have been infected with *M. tuberculosis* but by some other mycobacterium. The negative tuberculin skin test should never be used to exclude the possibility of active tuberculosis among persons for whom the diagnosis is being considered (symptoms compatible with tuberculosis).

HOW SUPPLIED

Tuberculin PPD-Aplisol bioequivalent to 5US units (TU) PPD-S per test dose (0.1mL) is available in the following presentations:

NDC 64029-4525-1 (Bio. 1525)
1 mL (10 tests) – rubber-diaphragm-capped vial

NDC 64029-4525-2 (Bio. 1607)
5 mL (50 tests) – rubber-diaphragm-capped vial

This product is ready for use without further dilution.

Storage

DO NOT FREEZE

This product should be stored at 2°–8°C (36°–46°F) and protected from light.

Vials in use more than 30 days should be discarded due to possible oxidation and degradation which may affect potency.

REFERENCES

1. Seibert, F.B.: Am Rev Tuberc, 30:713, 1934
2. Seibert, F.B., and Glenn, J.T.: Am Rev Tuberc, 44:9, 194
3. MMWR, 1995;44 RR-11
4. MMWR, 1996;45 RR-4
5. Huebner RE, Shein MF, Bass JB, The Tuberculin Skin Test; *Clin Infect Dis*, 1993;17:988–75
6. AHFS Drug Information, 1997, 36:84 pp 1962–1968
7. American Thoracic Society: Diagnostic Standards and classification of tuberculosis, 1990 Am Rev Respir Dis 142:725–735
8. Am Rev Respir Dis, 1995;886
9. Brickman HF et.Al., The Timing of Tuberculin Tests in Relation to Immunization with Live Viral Vaccines, *Pediatrics*; 1975;55:892
10. Red Book Report of the Committee on Infectious Disease (1994)
11. Landi S, Held HR, Stability of a dilute solution of tuberculin purified derivative at extreme temperatures, *J Biol Stand*, 1981; 9:195
12. Diagnosis of TB Infection and TB Disease, Centers for Disease Control and Prevention(CDC), March 21, 1996 Doc# 2250102
13. Sewell E.M., O'Hare, D., and Kendig, E.L., Jr.: The Tuberculin Test, Pediatrics, Vol.54, No. 5, Nov.1974.
14. Advisory Committee of Elimination of Tuberculosis (ACET/CDC: Prevention and control of tuberculosis in facilities providing long-term care to the elderly), 1990 MMWR 39(10): 7–13,15.
15. ACET(CDC): The use of preventative therapy for tuberculosis infection in the United States, 1990. MMWR 39(8):9–12.
16. ACET(CDC): Screening for tuberculosis and tuberculosis infection in high risk populations. Recommendations of the ACET, 1990, MMWR 39(8):1–7.

Rx only.

Prescribing Information as of May 2002

PARKEDALE PHARMACEUTICALS

Manufactured by:
Parkedale Pharmaceuticals, Inc.
Rochester, MI 48307

Shown in Product Identification Guide, page 379

BICILLIN® L-A
(bi-sil' in)
(penicillin G benzathine suspension)
INJECTION
FOR DEEP IM INJECTION ONLY

DESCRIPTION

Bicillin L-A (penicillin G benzathine suspension) is prepared by the reaction of dibenzylethylene diamine with two molecules of penicillin G. It is chemically designated as 6*R*, 6*R*) 3,3-Dimethyl-7-oxo -6- (2-phenylacetamido)-1-azabicyclo[3.2.0]heptane-2-carboxylic acid compound with *N,N'*-dibenzylethylenediamine (2:1), tetrahydrate. It is available for deep intramuscular injection. It contains penicillin G benzathine in aqueous suspension with sodium

IPR2020-00770
United Therapeutics EX2007
Page 3278 of 7335

citrate buffer and, as w/v, approximately 0.5% lecithin, 0.6% carboxymethylcellulose, 0.6% povidone, 0.1% methylparaben, and 0.01% propylparaben. It occurs as a white, crystalline powder and is very slightly soluble in water and sparingly soluble in alcohol.

Bicillin L-A suspension in the multiple-dose vial formulation, disposable syringe formulation and TUBEX formulation is viscous and opaque. The multiple-dose vial formulation contains the equivalent of 300,000 units per mL of penicillin G as the benzathine salt. The disposable syringe formulation is available in a 4 mL size containing the equivalent of 2,400,000 units of penicillin G as the benzathine salt. The TUBEX formulation is available in 1 mL and 2 mL TUBEX Sterile Cartridge-Needle Units containing the equivalent of 600,000 units and 1,200,000 units respectively of penicillin G as the benzathine salt. Read CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections prior to use.

CLINICAL PHARMACOLOGY

General

Penicillin G benzathine has an extremely low solubility and, thus, the drug is slowly released from intramuscular injection sites. The drug is hydrolyzed to penicillin G. This combination of hydrolysis and slow absorption results in blood serum levels much lower but much more prolonged than other parenteral penicillins.

Intramuscular administration of 300,000 units of penicillin G benzathine in adults results in blood levels of 0.03 to 0.05 units per mL, which are maintained for 4 to 5 days. Similar blood levels may persist for 10 days following administration of 600,000 units and for 14 days following administration of 1,200,000 units. Blood concentrations of 0.003 units per mL may still be detectable 4 weeks following administration of 1,200,000 units.

Approximately 60% of penicillin G is bound to serum protein. The drug is distributed throughout the body tissues in widely varying amounts. Highest levels are found in the kidneys with lesser amounts in the liver, skin, and intestines. Penicillin G penetrates into all other tissues and the spinal fluid to a lesser degree. With normal kidney function, the drug is excreted rapidly by tubular excretion. In neonates and young infants and in individuals with impaired kidney function, excretion is considerably delayed.

Microbiology

Penicillin G exerts a bactericidal action against penicillin-susceptible microorganisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell-wall mucopeptide. It is not active against the penicillinase-producing bacteria, which include many strains of staphylococci.

The following *in vitro* data are available, but their clinical significance is unknown. Penicillin G exerts high *in vitro* activity against staphylococci (except penicillinase-producing strains), streptococci (Groups A, C, G, H, L, and M), and pneumococci. Other organisms susceptible to penicillin G are *Neisseria gonorrhoeae*, *Corynebacterium diphtheriae*, *Bacillus anthracis*, Clostridia species, *Actinomyces bovis*, *Streptobacillus moniliformis*, *Listeria monocytogenes*, and *Leptospira* species. *Treponema pallidum* is extremely susceptible to the bactericidal action of penicillin G.

Susceptibility Test: If the Kirby-Bauer method of disc susceptibility is used, a 20-unit penicillin disc should give a zone greater than 28 mm when tested against a penicillin-susceptible bacterial strain.

INDICATIONS AND USAGE

Intramuscular penicillin G benzathine is indicated in the treatment of infections due to penicillin-G-sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to this particular dosage form. Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

The following infections will usually respond to adequate dosage of intramuscular penicillin G benzathine:

Mild-to-moderate infections of the upper respiratory tract due to susceptible streptococci.

Venereal infections—Syphilis, yaws, bejel, and pinta.

Medical Conditions in which Penicillin G Benzathine Therapy is Indicated as Prophylaxis:

Rheumatic fever and/or chorea—Prophylaxis with penicillin G benzathine has proven effective in preventing recurrence of these conditions. It has also been used as follow-up prophylactic therapy for rheumatic heart disease and acute glomerulonephritis.

CONTRAINDICATIONS

A history of a previous hypersensitivity reaction to any of the penicillins is a contraindication.

Do not inject into or near an artery or nerve.

WARNINGS

Penicillin G benzathine should only be prescribed for the indications listed in this insert.

SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTIC) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH BICILLIN L-A, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS AND OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, BICILLIN L-A SHOULD BE DISCONTINUED AND APPROPRIATE THERAPY INSTITUTED. SERIOUS ANAPHYLACTIC REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including penicillin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alter the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Inadvertent intravascular administration, including inadvertent direct intra-arterial injection or injection immediately adjacent to arteries, of Bicillin L-A and other penicillin preparations has resulted in severe neurovascular damage, including transverse myelitis with permanent paralysis, gangrene requiring amputation of digits and more proximal portions of extremities, and necrosis and sloughing at and surrounding the injection site. Such severe effects have been reported following injections into the buttock, thigh, and deltoid areas. Other serious complications of suspected intravascular administration which have been reported include immediate pallor, mottling, or cyanosis of the extremity both distal and proximal to the injection site, followed by bleb formation; severe edema requiring anterior and/or posterior compartment fasciotomy in the lower extremity. The above-described severe effects and complications have most often occurred in infants and small children. Prompt consultation with an appropriate specialist is indicated if any evidence of compromise of the blood supply occurs at, proximal to, or distal to the site of injection.[1-3] See CONTRAINDICATIONS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections.

Quadriceps femoris fibrosis and atrophy have been reported following repeated intramuscular injections of penicillin preparations into the anterolateral thigh.

Injection into or near a nerve may result in permanent neurological damage.

PRECAUTIONS

General

Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

Care should be taken to avoid intravenous or intra-arterial administration, or injection into or near major peripheral nerves or blood vessels, since such injection may produce neurovascular damage. See CONTRAINDICATIONS, WARNINGS, and DOSAGE AND ADMINISTRATION sections.

Prolonged use of antibiotics may promote the overgrowth of nonsusceptible organisms, including fungi. Should superinfection occur, appropriate measures should be taken.

Laboratory Tests

In streptococcal infections, therapy must be sufficient to eliminate the organism; otherwise, the sequelae of streptococcal disease may occur. Cultures should be taken following completion of treatment to determine whether streptococci have been eradicated.

Drug Interactions

Tetracycline, a bacteriostatic antibiotic, may antagonize the bactericidal effect of penicillin, and concurrent use of these drugs should be avoided.

Concurrent administration of penicillin and probenecid increases and prolongs serum penicillin levels by decreasing the apparent volume of distribution and slowing the rate of excretion by competitively inhibiting renal tubular secretion of penicillin.

Pregnancy Category B

Reproduction studies performed in the mouse, rat, and rabbit have revealed no evidence of impaired fertility or harm to the fetus due to penicillin G. Human experience with the penicillins during pregnancy has not shown any positive evidence of adverse effects on the fetus. There are, however, no adequate and well-controlled studies in pregnant women showing conclusively that harmful effects of these drugs on the fetus can be excluded. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Soluble penicillin G is excreted in breast milk. Caution should be exercised when penicillin G benzathine is administered to a nursing woman.

Carcinogenesis, Mutagenesis, Impairment Of Fertility

No long-term animal studies have been conducted with this drug.

Pediatric Use

See INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION.

ADVERSE REACTIONS

As with other penicillins, untoward reactions of the sensitivity phenomena are likely to occur, particularly in individuals who have previously demonstrated hypersensitivity to penicillins or in those with a history of allergy, asthma, hay fever, or urticaria.

As with other treatments for syphilis, the Jarisch-Herxheimer reaction has been reported.

The following have been reported with parenteral penicillin G:

General: Hypersensitivity reactions including the following: skin eruptions (maculopapular to exfoliative dermatitis), urticaria, laryngeal edema, fever, eosinophilia; other serum sickness-like reactions (including chills, fever, edema, arthralgia, and prostration); and anaphylaxis including shock and death. Note: Urticaria, other skin rashes, and serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, penicillin G should be discontinued unless, in the opinion of the physician, the condition being treated is life-threatening and amenable only to therapy with penicillin G. Serious anaphylactic reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Gastrointestinal: Pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. See WARNINGS.

Hematologic: Hemolytic anemia, leukopenia, thrombocytopenia.

Neurologic: Neuropathy.

Urogenital: Nephropathy.

The following adverse events have been temporally associated with parenteral administration of penicillin G benzathine:

Body as a Whole: Hypersensitivity reactions including allergic vasculitis, pruritus, fatigue, asthenia, and pain; aggravation of existing disorder; headache.

Cardiovascular: Cardiac arrest; hypotension; tachycardia; palpitations; pulmonary hypertension; pulmonary embolism; vasodilatation; vasovagal reaction; cerebrovascular accident; syncope.

Gastrointestinal: Nausea, vomiting; blood in stool; intestinal necrosis.

Hemic and Lymphatic: Lymphadenopathy.

Injection Site: Injection site reactions including pain, inflammation, lump, abscess, necrosis, edema, hemorrhage, cellulitis, hypersensitivity, atrophy, ecchymosis, and skin ulcer. Neurovascular reactions including warmth, vasospasm, pallor, mottling, gangrene, numbness of the extremities, and neurovascular damage.

Metabolic: Elevated BUN, creatinine, and SGOT.

Musculoskeletal: Joint disorder; periostitis; exacerbation of arthritis; myoglobinuria; rhabdomyolysis.

Nervous System: Nervousness; tremors; dizziness; somnolence; confusion; anxiety; euphoria; transverse myelitis; seizures; coma. A syndrome manifested by a variety of CNS symptoms such as severe agitation with confusion, visual and auditory hallucinations, and a fear of impending death (Hoigne's syndrome), has been reported after administration of penicillin G procaine and, less commonly, after injection of the combination of penicillin G benzathine and penicillin G procaine. Other symptoms associated with this syndrome, such as psychosis, seizures, dizziness, tinnitus, cyanosis, palpitations, tachycardia, and/or abnormal perception in taste, also may occur.

Respiratory: Hypoxia; apnea; dyspnea.

Skin: Diaphoresis.

Special Senses: Blurred vision; blindness.

Urogenital: Neurogenic bladder; hematuria; proteinuria; renal failure; impotence; priapism.

OVERDOSAGE

Penicillin in overdosage has the potential to cause neuromuscular hyperirritability or convulsive seizures.

DOSAGE AND ADMINISTRATION

Due to the viscous nature of this medication, a 23 gauge or larger bore needle should be used to withdraw medication from the vial and for patient administration. A smaller bore needle, such as a 24 or 25 gauge, is not recommended.

Streptococcal (Group A) Upper-respiratory infections (for example, pharyngitis)

Adults—a single injection of 1,200,000 units; older pediatric patients—a single injection of 900,000 units; infants and pediatric patients under 60 lbs.—300,000 to 600,000 units.

Syphilis

Primary, secondary, and latent—2,400,000 units (1 dose).

Late (tertiary and neurosyphilis)—2,400,000 units at 7-day intervals for three doses.

Congenital—under 2 years of age: 50,000 units/kg/body weight; ages 2 to 12 years: adjust dosage based on adult dosage schedule.

Yaws, Bejel, and Pinta—1,200,000 units (1 injection).

Prophylaxis—for rheumatic fever and glomerulonephritis. Following an acute attack, penicillin G benzathine (parenteral) may be given in doses of 1,200,000 units once a month or 600,000 units every 2 weeks.

Continued on next page

IPR2020-00770
United Therapeutics EX2007
Page 3279 of 7335

Bicillin L-A—Cont.

Administer by DEEP INTRAMUSCULAR INJECTION in the upper, outer quadrant of the buttock. In neonates, infants and small children, the midlateral aspect of the thigh may be preferable. When doses are repeated, vary the injection site.

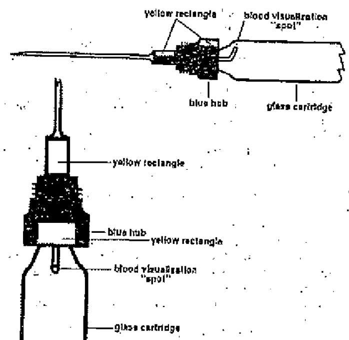
When using the multiple-dose vial:

After selection of the proper site and insertion of the needle into the selected muscle, aspirate by pulling back on the plunger. While maintaining negative pressure for 2 to 3 seconds, carefully observe the barrel of the syringe immediately proximal to the needle hub for appearance of blood or any discoloration. Blood or "typical blood color" may *not* be seen if a blood vessel has been entered—only a mixture of blood and Bicillin L-A. The appearance of any discoloration is reason to withdraw the needle and discard the syringe. If it is elected to inject at another site, a new syringe and needle should be used. If no blood or discoloration appears, inject the contents of the syringe slowly. Discontinue delivery of the dose if the subject complains of severe immediate pain at the injection site or if, especially in neonates, infants and young children symptoms or signs occur suggesting onset of severe pain.

Because of the high concentration of suspended material in this product, the needle may be blocked if the injection is not made at a slow, steady rate.

When using the TUBEX cartridge:

The Wyeth-Ayerst TUBEX® cartridge for this product incorporates several features that are designed to facilitate the visualization of blood on aspiration if a blood vessel is inadvertently entered.



The design of this cartridge is such that blood which enters its needle will be quickly visualized as a red or dark-colored "spot." This "spot" will appear on the barrel of the glass cartridge immediately proximal to the blue hub. The TUBEX is designed with two orientation marks, in order to determine where the "spot" can be seen. First insert and secure the cartridge in the TUBEX injector in the usual fashion. Locate the yellow rectangle at the base of the blue hub. This yellow rectangle is aligned with the blood visualization "spot." An imaginary straight line, drawn from this yellow rectangle to the shoulder of the glass cartridge, will point to the area on the cartridge where the "spot" can be visualized. When the needle cover is removed, a second yellow rectangle will be visible. The second yellow rectangle is also aligned with the blood visualization "spot" to assist the operator in locating this "spot." If the 2 mL metal or plastic syringe is used, the glass cartridge should be rotated by turning the plunger of the syringe clockwise until the yellow rectangle is visualized. If the 1 mL metal syringe is used, it will not be possible to continue to rotate the glass cartridge clockwise once it is properly engaged and fully threaded; it can, however, then be rotated counterclockwise as far as necessary to properly orient the yellow rectangles and locate the observation area. (In this same area in some cartridges, a dark spot may sometimes be visualized prior to injection. This is the proximal end of the needle and does not represent a foreign body in, or other abnormality of, the suspension.)

Thus, before the needle is inserted into the selected muscle, it is important for the operator to orient the yellow rectangle so that any blood which may enter after needle insertion and during aspiration can be visualized in the area on the cartridge where it will appear and not be obscured by any obstructions.

After selection of the proper site and insertion of the needle into the selected muscle, aspirate by pulling back on the plunger. While maintaining negative pressure for 2 to 3 seconds, carefully observe the barrel of the cartridge in the area previously identified (see above) for the appearance of a red or dark-colored "spot."

Blood or "typical blood color" may not be seen if a blood vessel has been entered—only a mixture of blood and Bicillin L-A. The appearance of any discoloration is reason to withdraw the needle and discard the glass TUBEX cartridge. If it is elected to inject at another site, a new cartridge should be used. If no blood or discoloration appears, inject the contents of the cartridge slowly. Discontinue delivery of the dose if the subject complains of severe immediate pain at the injection site or if, especially in infants and young children, symptoms or signs occur suggesting onset of severe pain.

Some TUBEX cartridges may contain a small air bubble which may be disregarded, since it does not affect administration of the product.

DO NOT clear any air bubbles from the cartridge or needle as this may interfere with the visualization of any blood or discoloration during aspiration.

Because of the high concentration of suspended material in this product, the needle may be blocked if the injection is not made at a slow, steady rate.

When using the disposable syringe:

The Wyeth-Ayerst disposable syringe for this product incorporates several features that are designed to facilitate its use.

A single, small indentation, or "dot," has been punched into the metal ring that surrounds the neck of the syringe near the base of the needle. It is important that this "dot" be placed in a position so that it can be easily visualized by the operator following the intramuscular insertion of the syringe needle.

After selection of the proper site and insertion of the needle into the selected muscle, aspirate by pulling back on the plunger. While maintaining negative pressure for 2 to 3 seconds, carefully observe the barrel of the syringe immediately proximal to the location of the "dot" for appearance of blood or any discoloration. Blood or "typical blood color" may *not* be seen if a blood vessel has been entered—only a mixture of blood and Bicillin L-A. The appearance of any discoloration is reason to withdraw the needle and discard the syringe. If it is elected to inject at another site, a new syringe should be used. If no blood or discoloration appears, inject the contents of the syringe slowly. Discontinue delivery of the dose if the subject complains of severe immediate pain at the injection site or if, especially in neonates, infants and young children, symptoms or signs occur suggesting onset of severe pain.

Some disposable syringes may contain a small air bubble which may be disregarded, since it does not affect administration of the product. DO NOT clear any air bubbles from the disposable syringe or needle as this may interfere with the visualization of any blood or discoloration during aspiration.

Because of the high concentration of suspended material in this product, the needle may be blocked if the injection is not made at a slow, steady rate.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

Bicillin® L-A (penicillin G benzathine suspension) is supplied in packages of 10 TUBEX® Sterile Cartridge-Needle Units as follows:

1 mL size, containing 600,000 units per TUBEX® (21 gauge, thin-wall 1 inch needle for pediatric use), NDC 61570-146-10.

2 mL size, containing 1,200,000 units per TUBEX® (21 gauge, thin-wall 1–1/4 inch needle), NDC 61570-147-10.

Store in a refrigerator.

Keep from freezing.

ALSO AVAILABLE

Bicillin L-A (penicillin G benzathine suspension) is also available in packages of 10 disposable syringes as follows:

4 mL size, containing 2,400,000 units per syringe (18 gauge × 2 inch needle), NDC 61570-148-10

Store in a refrigerator.

Keep from freezing.

Shake multiple-dose vials well before using.

REFERENCES

1. SHAW, E.: Transverse myelitis from injection of penicillin. *Am. J. Dis. Child., 111:* 548, 1966.
2. KNOWLES, J.: Accidental intra-arterial injection of penicillin. *Am. J. Dis. Child., 111:* 552, 1966.
3. DARBY, C., et al: Ischemia following an intragluteal injection of benzathine-procaine penicillin G mixture in a one-year-old boy. *Clin. Pediatrics, 12:* 485, 1973.
4. BROWN, L. & NELSON, A.: Postinfectious intravascular thrombosis with gangrene. *Arch. Surg., 94:* 652, 1967.
5. BORENSTINE, J.: Transverse myelitis and penicillin (Correspondence). *Am. J. Dis. Child., 112:* 166, 1966.
6. ATKINSON, J.: Transverse myelopathy secondary to penicillin injection. *J. Pediatrics, 75:* 867, 1969.
7. TALBERT, J. et al: Gangrene of the foot following intramuscular injection in the lateral thigh: A case report with recommendations for prevention. *J. Pediatrics, 70:* 110, 1967.
8. FISHER, T.: Medicolegal affairs. *Canad. Med. Assoc. J., 112:* 395, 1975.
9. SCHANZER, H. et al: Accidental intra-arterial injection of penicillin G. *JAMA, 242:* 1289, 1979.

Manufactured by:
Wyeth Laboratories
A Wyeth-Ayerst Company
Philadelphia, PA 19101
Distributed by:
Monarch Pharmaceuticals, Inc.
Bristol, TN 37620

Refer to the Tubex® Closed Injection System instructions in the Wyeth-Ayerst section of the 2002 PDR®.

Revised March 14, 2001 CI 4656-4

BREVITAL® SODIUM Ⓒ ℞

[*brĕ-vĭ-tŏl*]

METHOHEXITAL SODIUM FOR INJECTION, USP

For Intravenous Use in Adults

For Rectal and Intramuscular Use Only in Pediatric Patients

Prescribing Information as of November 2003.

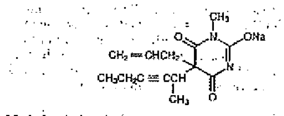
WARNING

Brevital should be used only in hospital or ambulatory care settings that provide for continuous monitoring of respiratory (e.g. pulse oximetry) and cardiac function. Immediate availability of resuscitative drugs and age- and size-appropriate equipment for bag/valve/mask ventilation and intubation and personnel trained in their use and skilled in airway management should be assured. For deeply sedated patients, a designated individual other than the practitioner performing the procedure should be present to continuously monitor the patient. (See WARNINGS)

DESCRIPTION

Brevital® Sodium (Methohexital Sodium for Injection, USP) is 2,4,6 (1*H*, 3*H*, 5*H*)-Pyrimidinetrione, 1-methyl-5-(1-methyl-2-pentynyl)-5-(2-propenyl)-, (±)-, monosodium salt, and has the empirical formula $C_{14}H_{17}N_2NaO_3$. Its molecular weight is 284.29.

The structural formula is as follows:



Methohexital sodium is a rapid, ultrashort-acting barbiturate anesthetic. Methohexital sodium for injection is a freeze-dried, sterile, nonpyrogenic mixture of methohexital sodium with 6% anhydrous sodium carbonate added as a buffer. It contains not less than 90% and not more than 110% of the labeled amount of methohexital sodium. It occurs as a white, freeze-dried plug that is freely soluble in water.

This product is oxygen sensitive. The pH of the 1% solution is between 10 and 11; the pH of the 0.2% solution in 5% dextrose is between 9.5 and 10.5.

Methohexital sodium may be administered by direct intravenous injection or continuous intravenous drip, intramuscular or rectal routes (see PRECAUTIONS—*Pediatric Use*). Reconstituting instructions vary depending on the route of administration (see DOSAGE AND ADMINISTRATION).

CLINICAL PHARMACOLOGY

Compared with thiamylal and thiopental, methohexital is at least twice as potent on a weight basis, and its duration of action is only about half as long. Although the metabolic fate of methohexital in the body is not clear, the drug does not appear to concentrate in fat depots to the extent that other barbiturate anesthetics do. Thus, cumulative effects are fewer and recovery is more rapid with methohexital than with thiobarbiturates. In experimental animals the drug cannot be detected in the blood 24 hours after administration.

Methohexital differs chemically from the established barbiturate anesthetics in that it contains no sulfur. Little analgesia is conferred by barbiturates; their use in the presence of pain may result in excitation.

Intravenous administration of methohexital results in rapid uptake by the brain (within 30 seconds) and rapid induction of sleep.

Following intramuscular administration to pediatric patients, the onset of sleep occurs in 2 to 10 minutes. A plasma concentration of 3 μg/mL was achieved in pediatric patients 15 minutes after an intramuscular dose (10 mg/kg) of a 5% solution. Following rectal administration to pediatric patients, the onset of sleep occurs in 5 to 15 minutes. Plasma methohexital concentrations achieved following rectal administration tend to increase both with dose and with the use of more dilute solution concentrations when using the same dose. A 25 mg/kg dose of a 1% methohexital solution yielded plasma concentrations of 6.9 to 7.9 μg/mL 15 minutes after dosing. The absolute bioavailability of rectal methohexital sodium is 17%.

With single doses, the rate of redistribution determines duration of pharmacologic effect. Metabolism occurs in the liver through demethylation and oxidation. Side-chain oxidation is the most important biotransformation involved in termination of biologic activity. Excretion occurs via the kidneys through glomerular filtration.

INDICATIONS AND USAGE

Brevital Sodium can be used in adults as follows:

1. For *intravenous* induction of anesthesia prior to the use of other general anesthetic agents.

IPR2020-00770
United Therapeutics EX2007
Page 3280 of 7335

Brief Articles

Piperidine Analogues of 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine (GBR 12909): High Affinity Ligands for the Dopamine Transporter

Thomas Prisinzano,[†] Elisabeth Greiner,[†] Edward M. Johnson II,[†] Christina M. Dersch,[‡] Jamila Marcus,[‡] John S. Partilla,[‡] Richard B. Rothman,[‡] Arthur E. Jacobson,[†] and Kenner C. Rice*[,†]

Laboratory of Medicinal Chemistry, NIDDK, National Institutes of Health, Bethesda, Maryland 20892, and Clinical Psychopharmacology Section, Intramural Research Program, NIDA, NIH, Baltimore, Maryland 21224

Received June 21, 2002

A series of 4-[2-[bis(4-fluorophenyl)methoxy]ethylpiperidines were examined for their ability to bind to the dopamine transporter (DAT), the norepinephrine transporter, and the serotonin transporter (SERT). In particular, the role of the *N*-substituent on affinity and selectivity for the DAT was probed. 4-[2-[Bis(4-fluorophenyl)methoxy]ethyl-1-(2-naphthylmethyl)piperidine was found to possess subnanomolar affinity (K_i = 0.7 nM) and good selectivity for the DAT (SERT/DAT = 323).

Introduction

Cocaine is a widely abused drug, and its abuse has had great effects on public health, through the spread of human immunodeficiency virus (HIV), hepatitis, and tuberculosis.[1−9] Unfortunately, there are no U.S. Food and Drug Administration (FDA)-approved therapeutic agents available for the treatment of cocaine abuse or for the prevention of relapse.[10] Among the various agents tested clinically, the best results appear to have been achieved with dextroamphetamine,[11] supporting the hypothesis that agonist substitution therapy is a reasonable approach to developing pharmacotherapies for cocaine dependence.

On a molecular level, cocaine inhibits the reuptake of dopamine (DA), serotonin (5-HT), and norepinephrine (NE). Evidence suggests, however, that its binding to the dopamine transporter (DAT) and subsequent inhibition of DA reuptake may be responsible for its reinforcing properties and a good target for the design of an agonist substitution type medication for cocaine abuse.[12−16]

Our approach to developing this type of potential therapeutic for cocaine abuse is to find a competitive inhibitor of the DAT that dissociates very slowly.[17] 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)-piperazine (GBR 12909) (**1**, Figure 1) was among the first agents to be characterized as a high-affinity and selective inhibitor of DA reuptake.[18,19] Studies with rhesus monkeys have shown that in cocaine and food self-administration studies, **1** decreases cocaine-maintained responding without affecting food-maintained responding.[20,21] Given the promising properties of **1** and its analogues, these compounds have been identified as novel agents for the potential pharmacotherapy of cocaine abuse in humans.

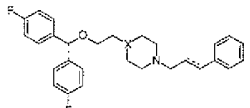


Figure 1. Structure of 1-{2-[bis-(4-fluoro-phenyl)methoxy]-ethyl}-4-(3-phenylpropyl)piperazine analogues.

The binding of these agents at the transporter for norepinephrine (NET) is a possible source of sympathomimetic side effects. In our continuing efforts to develop new agents that might reduce cocaine self-administration, we are attempting to find more selective and high-affinity DAT inhibitors.[20−26] Our efforts were focused on analogues, where a piperidine ring was substituted for the piperazine ring in **1**. Several piperidine analogues have been prepared.[27] Compound **2** was reported to have good affinity for the DAT but was not very selective.[27] Previous reports have shown that modification of this compound may lead to analogues with enhanced selectivity for the DAT over the serotonin transporter (SERT).[28,29]

Chemistry

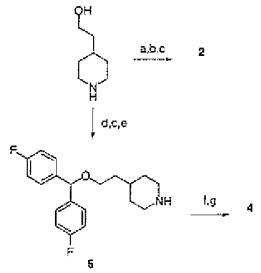
The *N*-substituted piperidines were synthesized from the commercially available 4-piperidineethanol (Scheme 1). The reaction of 4-piperidineethanol with hydrocinnamoyl chloride, followed by reduction of the corresponding amide with LAH, and ether formation using 4,4′-difluorobenzhydrol in toluene under azeotropic distillation conditions gave **2** in good yield.[27] Alternately, a three step sequence of *N*-protection, ether formation, and *N*-deprotection afforded **5**.[27,30] The coupling of piperidine **5** with *trans*-cinnamic acid using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI), followed by reduction of the corresponding amide with AlH_3, afforded alkene **4**.[31,32]

* To whom correspondence should be addressed. Tel: 301-496-1856. Fax: 301-402-0589. E-mail: kr21f@nih.gov.
† National Institutes of Health.
‡ Addiction Research Center.

10.1021/jm020264r This article not subject to U.S. Copyright. Published 2002 by the American Chemical Society
Published on Web 08/17/2002

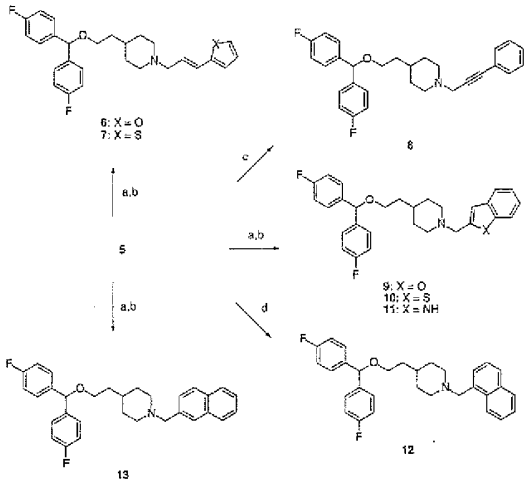
IPR2020-00770
United Therapeutics EX2007
Page 3281 of 7335

Scheme 1[a]



[a] Reagents: (a) Hydrocinnamoyl chloride, NEt_3, CH_2Cl_2. (b) LAH, THF. (c) 4,4-Difluorobenzhydrol, *p*-TsOH·H_2O, toluene. (d) Benzoyl chloride, NEt_3, CH_2Cl_2. (e) NaOH, EtOH. (f) *trans*-Cinnamic acid, EDCI, CH_2Cl_2. (g) LAH, H_2SO_4, THF.

Scheme 2[a]



[a] Reagents: (a) Appropriate acid, EDCI, CH_2Cl_2. (b) LAH, H_2SO_4, THF. (c) Phenylacetylene, $(CH_2O)_n$, $CuSO_4$, THF. (d) 1-Chloromethylnaphthalene, K_2CO_3, DMF.

Targets **6**, **7**, **9**−**11**, and **13** were prepared from **5** using a procedure similar to the preparation of **4** (Scheme 2). The coupling of **5** with the appropriate acid using EDCI followed by reduction of the corresponding amide with AlH_3 gave **6**, **7**, **9**−**11**, and **13**.[33,34] A modified Mannich reaction using **5**, phenylacetylene, and paraformaldehyde gave **8**. The treatment of **5** with 1-chloromethylnaphthalene under basic conditions afforded **12**.

Results and Discussion

We resynthesized **2** to compare (Table 1) its binding affinities with those of our new analogues. It was hoped that the introduction of different functional groups into the *N*-alkyl group of **2** would give us a compound with high affinity and better selectivity than **1**. These analogues might represent a second generation cocaine abuse treatment agent.

We found that the affinity of **2** in our binding assay (Table 1) was higher than previously reported.[27] It had higher affinity (K_i = 1.1 nM) for the DAT and greater selectivity over the SERT (68-fold) than **1**. This might be due to the use of [^{125}I]RTI-55 to label a site on the DAT rather than the formerly used[27] [^{3}H]WIN 35,428.

Table 1. Binding Affinities at the DAT and SERT Labeled with [^{125}I]RTI-55 of **2**, **4**, and **6**−**13** ($K_i \pm$ SD, nM)

compds[a]	DAT[b]	SERT[b]	SERT/DAT
1	3.7 ± 0.4	126 ± 27	34
2	1.1 ± 0.1	68 ± 8	65
4	0.45 ± 0.03	47 ± 2	104
6	0.99 ± 0.07	41 ± 6	41
7	1.3 ± 0.1	45 ± 5	35
8	5.3 ± 0.4	164 ± 26	31
9	1.01 ± 0.18	85 ± 10	84
10	1.61 ± 0.15	246 ± 33	153
11	0.73 ± 0.07	88 ± 10	121
12	16 ± 1	370 ± 27	23
13	0.71 ± 0.06	229 ± 21	323

[a] Prepared and tested as oxalate salt. [b] Values determined as in ref 23 using [^{125}I]RTI-55 as radioligand for the DAT and SERT.

On the basis of this observation and our previous discovery that 1-{2-[bis-(4-fluorophenyl)methoxy]ethyl}-4-(3-phenylallyl)piperazine (GBR 13069, **3**) also had higher affinity for the DAT than **1**,[23] we thought it might be of great interest to prepare **4**. Although it was prepared previously, we thought it possible that **4** might have greater affinity for the DAT in our assay. We found that **4** had higher affinity for the DAT (K_i = 0.45 nM) than **2** (K_i = 1.1 nM). This result, however, was also in contrast to previous findings where the affinity of **4** was reported to be 41.4 nM.[32] In an attempt to better understand these results, we evaluated several additional analogues with *N*-substituents that had been previously investigated in the piperazine series.[22] In particular, we chose to examine *N*-substituents in the piperidine series that displayed high affinity ($K_i \leq$ 10 nM) in the piperazine series, such as a 3-furan-2-ylallyl and a 3-thiophen-2-ylallyl substituent, as well as several others.[22] It was hoped that these specific alterations might provide an explanation for the mode of binding of the two series relative to one another.

The binding results showed that the replacement of the phenyl ring in **4** with a 2-furyl, **6**, or 2-thienyl, **7**, group resulted in a decrease in affinity for the DAT as compared to **4**. These compounds were similar to **4** in their affinity for the SERT.

The role of the trans-alkene in **4** was then tested. The introduction of an alkyne, i.e., **8**, decreased affinity for the DAT (10-fold) as compared to **4**. This seemed to indicate that a trans-alkene was favored over a linear conformation, i.e., **8**. Furthermore, the trans-alkene in **4** was then incorporated into several heterocycles, **9**−**11**. These modifications decreased affinity for the DAT and the SERT as compared to **4**. We noted that the introduction of an indole moiety, **11**, was optimal for affinity (K_i = 0.73 nM) among the heterocycles, **9**−**11**. However, the benzothiophene analogue, **10**, had the best selectivity over the SERT (153-fold).

In an attempt to further investigate the binding region of the *N*-substituent, we synthesized two naphthalene isomers. 1-Naphthylmethyl analogue **12** had the least affinity for the DAT (K_i = 16 nM) and the SERT (K_i = 370 nM) of this series of ligands. Remarkably, 2-naphthylmethyl analogue, **13**, was found to have subnanomolar affinity (K_i = 0.71 nM) for the DAT and the best selectivity over the SERT (323-fold) of the compounds examined.

The functional binding assays (Table 2) were carried out for two of the most interesting ligands, **10** and **13**.

IPR2020-00770
United Therapeutics EX2007
Page 3282 of 7335

Table 2. Reuptake Inhibition Studies of **1**, **10**, and **13** ($IC_{50} \pm$ SD, nM)

compds[a]	DA[b]	5-HT[b]	NE[b]	5-HT/DA	NE/DA
1	4.3 ± 0.3	73 ± 2	79 ± 5	17	18
10	11.9 ± 1.0	1037 ± 92	260 ± 21	87	22
13	7.2 ± 0.4	277 ± 15	93 ± 8	38	13

[a] Prepared and tested as oxalate salt. [b] Values determined as in ref 23b.

These compounds were chosen because they had the best selectivity over the SERT in this series. The uptake assay showed that both **10** and **13** had slightly lower potency than **1** in inhibiting DA uptake. However, both had increased selectivity over inhibiting 5-HT uptake as compared to **1**, and **10** showed the desired increase in selectivity over NE.

In comparison with the piperazine series, the piperidine analogues generally had higher affinity for both the DAT and the SERT.[22] In agreement with the piperazine series,[22] 2-furyl analogue **6** (K_i = 0.99 nM) had slightly higher affinity for the DAT than the 2-thienyl analogue **7** (K_i = 1.3 nM). Compounds **9** and **10** had higher affinity and better selectivity than the corresponding piperazine analogues. Compound **11** was nearly identical to its piperazine counterpart. The only difference was a slightly higher affinity for the SERT that was responsible for a lower selectivity. Compounds **12** and **13** showed very different results. In the piperazine series, the 2-naphthylmethyl derivative had lower affinity for the DAT than the 1-naphthylmethyl derivative. It was thought that if the piperidine series was binding in an identical manner to the piperazine series, then compound **12** would have higher affinity than **13** for the DAT. Interestingly, **13** had subnanomolar affinity for the DAT and the best selectivity over the SERT in this series of ligands. Apparently, an extended conformation is preferred in the piperidine series. It also appears that previous piperazine structure–activity relationships (SAR) may not be applicable to the piperidine series, suggesting that these two series are not binding in an identical manner at the DAT.

Conclusions

A series of 4-[2-[bis(4-fluorophenyl)methoxy]ethylpiperidines were synthesized and evaluated. Several ligands were identified with subnanomolar affinity to DAT. The 2-naphthyl derivative (**13**) was more than 300-fold selective for DAT over the SERT, and in reuptake inhibition studies, the benzothiophene compound **10** was found to have somewhat better selectivity for DAT over the NET than **1**. This study indicates that previous SAR seen in the GBR-12909 piperazine series do not hold for the corresponding piperidine series. Further exploration of this is currently underway.

Experimental Section

Unless otherwise indicated, all reagents were purchased from commercial suppliers and were used without further purification. The instrumentation used has been previously noted.[26]

4-{2-[Bis-(4-fluorophenyl)methoxy]ethyl}piperidine Oxalate (5). A solution of benzoyl chloride (16.3 g, 116.1 mmol) in dry CH_2Cl_2 (200 mL) was added in a dropwise manner to a solution of 4-piperidineethanol (15.0 g, 116.1 mmol) and triethylamine (11.7 g, 116.1 mmol) in dry CH_2Cl_2 (400 mL) at 0 °C. The mixture was stirred at room temperature overnight, washed successively with H_2O (3 × 100 mL), 2 N HCl (3 × 100 mL), and saturated NaCl (2 × 200 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a crude oil that was used without further purification. A mixture of crude oil, *p*-toluenesulfonic acid monohydrate (13.8 g, 72.6 mmol), and 4,4-difluorobenzhydrol (26.8 g, 121.9 mmol) in dry toluene (800 mL) was heated at reflux under azeotropic distillation conditions overnight. The solvent was removed under reduced pressure, and EtOAc (600 mL) was added. The EtOAc portion was washed with H_2O (3 × 100 mL) and saturated NaCl (2 × 100 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a crude oil that solidified upon addition of hexane. A solution of the crude solid, NaOH (21.2 g, 529 mmol), H_2O (50 mL), and absolute EtOH (500 mL) was heated at reflux for 36 h. The solvent was removed under reduced pressure, and H_2O (300 mL) was added to the residue. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined CH_2Cl_2 portion was washed with saturated NaCl (2 × 100 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a crude oil that was dissolved in dry acetone. Oxalic acid (1.1 equiv) was added, and precipitate was collected and dried to afford 36.1 g (74%) of **5** as a white solid; mp 146–148 °C. ^{1}H NMR (DMSO-d_6): δ 7.1–7.4 (m, 8H, aromatic); 5.5 (s, 1H, CH–O); 3.9 (bs, NH); 3.1–3.4 (m, 4H); 2.5–2.9 (m, 5H); 1.1–2.0 (m, 5H).

4-{2-[Bis-(4-fluorophenyl)methoxy]ethyl}-1-(3-phenylallyl)piperidine Oxalate (4). A solution of the free base of **5** (1.5 g, 4.5 mmol), *trans*-cinnamic acid (0.7 g, 4.5 mmol), and EDCI (0.9 g, 5.0 mmol) in dry CH_2Cl_2 (25 mL) was stirred at room temperature overnight. The solvent was removed under reduced pressure, and the ethyl acetate (125 mL) was added to the residue. The ethyl acetate solution was washed successively with 1 N HCl (2 × 50 mL), 10% K_2CO_3 (2 × 50 mL), and saturated NaCl (50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford 2.0 g (96%) of the corresponding amide as an oil that was used without further characterization. A 100% amount of H_2SO_4 (d = 1.84) (1.1 g, 11.0 mmol) was added cautiously to a suspension of LAH (0.8 g, 22 mmol) in dry tetrahydrofuran (THF, 100 mmol) at 0 °C. After the addition was complete, the mixture was stirred at room temperature for 1 h. A solution of the crude amide in dry THF (50 mL) was added in a dropwise manner. The resulting mixture was stirred for 2 h, and 10% NaOH (150 mL) was added cautiously. The layers separated, and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic portion was washed with H_2O (100 mL) and saturated NaCl (2 × 100 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a crude oil that was dissolved in dry acetone. Oxalic acid (1.1 equiv) was added, and the solvent was removed under reduced pressure. Anhydrous Et_2O was added, and the precipitate was collected and dried to afford 1.6 g (67%) of **4** as a white solid; mp 158–160 °C (literature[2] 162.7–163.5 °C). Anal. ($C_{29}H_{31}F_2NO \cdot C_2H_2O_4 \cdot 0.5H_2O$): C, H, N.

4-{2-[Bis-(4-fluorophenyl)methoxy]ethyl}-1-(3-phenylprop-2-ynyl)piperidine Oxalate (8). A mixture of the free base of **5** (1.5 g, 4.7 mmol), phenylacetylene (0.7 g, 7.1 mmol), $CuSO_4$ (0.8 g, 4.7 mmol), and paraformaldehyde (0.4 g, 14.1 mmol) in dry THF (45 mL) was heated at reflux for 2 h. Et_2O (100 mL) was added, and the mixture was filtered through a pad of Celite. The filtrate was evaporated to dryness under reduced pressure, and the residue was dissolved in CH_2Cl_2 (100 mL). The CH_2Cl_2 portion was washed with H_2O (5 × 50 mL) and saturated NaCl (2 × 50 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure affording a crude oil that was dissolved in anhydrous Et_2O. Oxalic acid (1.1 equiv) was added, and the precipitate was collected, washed with cold absolute EtOH (20 mL), and dried to afford 2.0 g (80%) of **8** as a white solid; mp 134–136 °C. ^{1}H NMR (DMSO-d_6): δ 7.1–7.6 (m, 13H, aromatic); 5.5 (s, 1H, CH–O); 4.0 (s, 2H, NCH_2); 3.1–3.4 (m, 4H); 2.5–2.9 (m, 5H); 1.0–2.0 (m, 5H). Anal. ($C_{29}H_{29}F_2NO \cdot C_2H_2O_4$): C, H, N.

IPR2020-00770
United Therapeutics EX2007
Page 3283 of 7335

4-{2-[Bis-(4-fluorophenyl)methoxy]ethyl}-1-naphthalen-1-ylmethylpiperidine Oxalate (12). A suspension of **5** (1.0 g, 2.4 mmol), K_2CO_3 (1.0 g, 7.2 mmol), a catalytic amount of NaI, and 1-chloromethylnaphthalene (0.5 g, 2.6 mmol) in dimethylformamide (DMF, 30 mL) was stirred at 100 °C overnight. The mixture was poured into H_2O (200 mL) and extracted with ethyl acetate (3 × 60 mL). The combined ethyl acetate portion was washed with H_2O (2 × 75 mL) and saturated NaCl (2 × 75 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a residue that was dissolved in anhydrous Et_2O. Oxalic acid (1.1 equiv) was added, and the precipitate was collected, recrystallized from absolute EtOH, and dried to afford 0.9 g (67%) of **12** as a white solid; mp 176−178 °C. ^1H NMR (DMSO-d_6): δ 7.1−8.4 (m, 15H, aromatic); 5.5 (s, 1H, CH−O); 4.5 (s, 2H, $ArCH_2$-); 3.1−3.4 (m, 4H); 2.5−2.9 (m, 5H); 1.1−2.0 (m, 5H). Anal. ($C_{31}H_{31}F_2NO\cdot C_2H_2O_4$): C, H, N.

Acknowledgment. We (LMC, NIDDK) thank the National Institute on Drug Abuse, NIH, for partial support of this work.

References

(1) (a) Redda, K. K.; Walker, C. A.; Barnett, G. *Cocaine, Marijuana, Designer Drugs: Chemistry, Pharmacology and Behavior*; CRC Press: Boca Raton, FL, 1990; pp 1−5. (b) Benowitz, N. L. Clinical Pharmacology and Toxicology of Cocaine. *Pharmacol. Toxicol.* **1993**, *72*, 3−12.

(2) Das, G. Cocaine Abuse in North America: A Milestone in History. *J. Clin. Pharmacol.* **1993**, *33*, 296−310.

(3) Musto, D. F. Opium, Cocaine, and Marihuana in American History. *Sci. Am.* **1991**, *265*, 40−47.

(4) Warner, E. A. Cocaine Abuse. *Ann. Intern. Med.* **1993**, *119*, 226−235.

(5) Tims, F. M.; Leukfeld, C. G. Treatment of Cocaine Abusers: Issues and Perspectives. In *Cocaine Treatment: Research and Clinical Perspectives*; Tims, F. M., Leukfeld, C. G., Eds.; U. S. Department of Health and Human Services: Washington, DC, 1993; pp 1−14.

(6) White, P. T. Coca − An Ancient Herb Turns Deadly. *Natl. Geographic* **1989**, *175*, 3−47.

(7) McCoy, C. B.; Inciardi, J. A. *Sex, Drugs and the Continuing Spread of AIDS*; Roxbury Publishing Co.: Los Angeles, CA, 1995. (b) Hser, Y. I.; Chih-Ping, C.; Hoffman, V.; Anglin, M. D. Cocaine Use and High Risk Sexual Behavior Among STD Clinic Patients. *Sex. Transm. Dis.* **1999**, *26*, 82−86. (c) McCoy, C. B.; Metsch, L. R.; Inciardi, J. A.; Anwyl, R. S.; Wingerd, J.; Bletzer, K. Sex, Drugs, and the Spread of HIV/AIDS in Belle Glade, Florida. *Med. Anthrop. Quart.* **1996**, *10*, 83−93.

(8) Mitscher, L. A.; Baker, W. Tuberculosis: A Search for Novel Therapy Starting with Natural Products. *Med. Res. Rev.* **1998**, *18*, 363−374.

(9) Fischman, M. W.; Schuster, C. R. Cocaine Self-Administration in Humans. *Fed. Proc.* **1988**, *41*, 241−246.

(10) Gorelick, D.A. Pharmacologic Therapies for Cocaine and Other Stimulant Addiction. In *Principles of Addiction Medicine*; Graham, A. W., Schultz, T. K., Eds.; American Society of Addiction Medicine: Chevy Chase, MD, 1997.

(11) Grabowski, J.; Rhoades, H.; Schmitz, J.; Stotts, A.; Daruzska, L. A.; Creson, D.; Moeller, F. G. Dextroamphetamine for Cocaine-dependence Treatment: A Double-blind Randomized Clinical Trial. *J. Clin. Psychopharmacol.* **2001**, *21*, 522−526.

(12) Johanson, C. E.; Fischman, M. W. The Pharmacology of Cocaine Related to its Abuse. *Pharmacol. Rev.* **1989**, *41*, 3−52.

(13) Koob, G. F.; Bloom, F. E. *Science* **1988**, *242*, 715−723.

(14) Ritz, M. C.; Lamb, R. J.; Goldberg, S. R.; Kuhar, M. J. Cocaine Receptors on Dopamine Transporters are Related to Self-Administration of Cocaine. *Science* **1987**, *237*, 1219−1223.

(15) Bergman, J.; Madras, B. K.; Johnson, S. E.; Spealman, R. D. Effects of Cocaine and Related Drugs in Nonhuman Primates. 3. Self-Administration by Squirrel Monkeys. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 150−155.

(16) Giros, B.; Jaber, M.; Jones, S. R.; Wightman, R. M.; Caron, M. G. Hyperlocomotion and Indifference to Cocaine and Amphetamine in Mice Lacking the Dopamine Transporter. *Nature* **1996**, *379*, 606−612.

(17) Rothman, R. B.; Mele, A.; Reid, A. A.; Akunne, H. C.; Greig, N.; Thurkauf, A.; de Costa, B. R.; Rice, K. C.; Pert, A. GBR 12909 Antagonizes the Ability of Cocaine to Elevate Extracellular Levels of Dopamine. *Pharmacol. Biochem. Behav.* **1991**, *40*, 387−397.

(18) Van der Zee, P.; Koger, H. S.; Gooijtes, J.; Hespe, W. Aryl-1,4-Dialk(en)ylpiperazines as Selective and Very Potent Inhibitors of Dopamine Uptake. *Eur. J. Med. Chem.* **1980**, *15*, 363−370.

(19) Andersen, P. H. The Dopamine Uptake Inhibitor GBR 12909: Selectivity and Molecular Mechanism of Action. *Eur. J. Pharmacol.* **1989**, *166*, 493−504.

(20) Glowa, J. R.; Wojnicki, F. H. E.; Matecka, D.; Rice, K. C.; Rothman, R. B. Effects of Dopamine Reuptake Inhibitors on Food- and Cocaine-Maintained Responding: II. Comparison with Other Drugs and Repeated Administrations. *Exp. Clin. Psychopharmacol.* **1995**, *3*, 232−239.

(21) Glowa, J. R.; Fantegrossi, W. E.; Lewis, D. B.; Matecka, D.; Rice, K. C.; Rothman, R. B. Sustained Decrease in Cocaine-Maintained Responding in Rhesus Monkeys with 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-hydroxy-3-phenylpropyl)piperazinyl Decanoate, a Long-Acting Ester Derivative of GBR 12909. *J. Med. Chem.* **1996**, *39*, 4689−4691.

(22) Matecka, D.; Lewis, D. B.; Rothman, R. B.; Dersch, C. M.; Wojnicki, F. H. E.; Glowa, J. R.; DeVries, A. C.; Pert, A.; Rice, K. C. Heteroaromatic Analogues of 1-[2-(Diphenylmethoxy)-ethyl]- and 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazines (GBR 12935 and GBR 12909) as High-Affinity Dopamine Reuptake Inhibitors *J. Med. Chem.* **1997**, *40*, 705−716.

(23) Lewis, D. B.; Matecka, D.; Zhang, Y.; Hsin, L. W.; Dersch, C. M.; Stafford, D.; Glowa, J. R.; Rothman, R. B.; Rice, K. C. Oxygenated Analogues of 1-[2-(Diphenyl)methoxy]ethyl- and 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl-4-(3-phenylpropyl)piperazines (GBR 12935 and GBR 12909) as Potential Extended-Action Cocaine-Abuse Therapeutic Agents. *J. Med. Chem.* **1999**, *42*, 5029−5042. (b) Rothman, R. B.; Lewis, B.; Dersch, C. M.; Xu, H.; Radesca, L.; de Costa, B. R.; Rice, K. C.; Kilburn, R. B.; Akunne, H. C.; Pert, A. Identification of a GBR 12935 Homolog, LR1111, Which is Over 4, 000-Fold Selective for the Dopamine Transporter, Relative to Serotonin and Norepinephrine Transporters. *Synapse* **1993**, *14*, 34−39.

(24) Zhang, Y.; Rothman, R. B.; Dersch, C. M.; de Costa, B. R.; Jacobson, A. E.; Rice, K. C. Synthesis and Transporter Binding Properties of Bridged Piperazine Analogues of 1-{2-[Bis(4-fluorophenyl)methoxy]ethyl}-4-(3-phenylpropyl)piperazine (GBR 12909). *J. Med. Chem.* **2000**, *43*, 4840−4849.

(25) Zhang, Y.; Joseph, D. B.; Bowen, W. D.; Flippen-Anderson, J. L.; Dersch, C. M.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. Synthesis and Biological Evaluation of Tropane-like 1-{2-[Bis-(4-fluorophenyl)methoxy]ethyl}-4-(3-phenylpropyl)piperazine (GBR 12909) Analogues. *J. Med. Chem.* **2001**, *44*, 3937−3945.

(26) Hsin, L. W.; Dersch, C. M.; Stafford, D.; Glowa, J. R.; Rothman, R. B.; Jacobson, A. E.; Rice, K. C. The Development of a Long-Acting Dopamine Transporter Ligands as Potential Cocaine-Abuse Therapeutic Agents: Chiral Hydroxy-Containing Derivatives of 1-[2-[Bis(4-fluorophenyl)methoxy]ethyl-4-(3-phenylpropyl)piperazine and 1-[2-(Diphenyl)methoxy]ethyl-4-(3-phenylpropyl)piperazine (GBR 12909 and GBR 12935). *J. Med. Chem.* **2002**, *45*, 1321−1329.

(27) Dutta, A. K.; Meltzer, P. C.; Madras, B. K. Positional Importance of the Nitrogen Atom in Novel Piperidine Analogues of GBR 12909: Affinity and Selectivity for the Dopamine Transporter. *Med. Chem. Res.* **1993**, *3*, 209−222.

(28) Dutta, A. K.; Xu, C.; Reith, M. E. A. Tolerance in the Replacement of the Benzhydrylic O Atom in 4-[2-Diphenylmethoxy)-ethyl]-1-benzylpiperidine Derivatives by an N Atom: Development of New-Generation Potent and Selective N-Analogue Molecules for the Dopamine Transporter. *J. Med. Chem.* **1998**, *41*, 3293−3297.

(29) Dutta, A. K.; Fei, X. S.; Beardsley, P. M.; Newman, J. L.; Reith, M. E. A. Structure−Activity Relationship Studies of 4-[2-Diphenylmethoxy)ethyl]-1-benzylpiperidine Derivatives and Their N-Analogues: Evaluation of Behavioral Activity of O- and N-Analogues and Their Binding to Monoamine Transporters. *J. Med. Chem.* **2001**, *44*, 937−948.

(30) Lygo, B.; Crosby, J.; Lowdon, T.; Wainwright, P. G. Asymmetric Approaches to 2-Hydroxymethylquinuclidine Derivatives. *Tetrahedron* **1999**, *55*, 2795−2810.

(31) Goldstein, S. W.; McDermott, R. E.; Makowski, M. R.; Eller, C. α-Azido Acids in Heterocyclic Synthesis. *Tetrahedron Lett.* **1991**, *32*, 5493−5496.

(32) Dutta, A. K.; Coffey, L. L.; Reith, M. E. A. Potent and Selcetive Ligands for the Dopamine Transporter (DAT): Structure−Activity Relationships of Novel 4-[2-(Diphenylmethoxy)ethyl]-1-(3-phenylpropyl)piperidine Analogues. *J. Med. Chem.* **1998**, *41*, 669−705.

(33) All of the new compounds were found to be within ±0.4 of the theoretical values for C, H, and N. ^1H NMR (300 MHz, DMSO-d_6) was in agreement with assigned structures.

(34) Uncorrected melting points of oxalate salts: **4**, mp 158−160 °C; **5**, mp 146−148 °C; **6**, mp 148−149 °C; **7**, mp 150−152 °C; **8**, mp 134−136 °C; **9**, mp 156−159 °C; **10**, mp 155−159 °C; **11**, mp 180−183 °C; **12**, mp 176−178 °C; **13**, mp 161−162 °C.

JM020264R

IPR2020-00770
United Therapeutics EX2007
Page 3284 of 7335

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use REMODULIN safely and effectively. See full prescribing information for REMODULIN.

REMODULIN® (treprostinil) Injection, for subcutaneous or intravenous use
Initial U.S. Approval: May 2002

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.1, 2.5) 12/2014

----------INDICATIONS AND USAGE----------

Remodulin is a prostacyclin vasodilator indicated for:

- Treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%) (1.1)
- Patients who require transition from Flolan®, to reduce the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition. (1.2)

----------DOSAGE AND ADMINISTRATION----------

PAH in patients with NYHA Class II-IV symptoms:

- Initial dose for patients new to prostacyclin infusion therapy: 1.25 ng/kg/min, increase based on clinical response (increments of 1.25 ng/kg/min per week for the first 4 weeks of treatment, later 2.5 ng/kg/min per week). Avoid abrupt cessation. (2.2, 2.3)
- Mild to moderate hepatic insufficiency: Decrease initial dose to 0.625 ng/kg/min.
- Severe hepatic insufficiency: No studies performed. (2.4)

Transition from Flolan:

Increase the Remodulin dose gradually as the Flolan dose is decreased, based on constant observation of response. (2.6)

Administration:

Continuous subcutaneous infusion (undiluted) is the preferred mode. Use intravenous (IV) infusion (dilution required) if subcutaneous infusion is not tolerated. (2.1, 2.5)

----------DOSAGE FORMS AND STRENGTHS----------

- Remodulin is supplied in 20 mL vials containing 20, 50, 100, or 200 mg of treprostinil (1, 2.5, 5 or 10 mg/mL). (3)

----------CONTRAINDICATIONS----------

None

----------WARNINGS AND PRECAUTIONS----------

- For intravenous infusion use an indwelling central venous catheter. This route is associated with the risk of blood stream infections (BSIs) and sepsis, which may be fatal. (5.1)
- Do not abruptly lower the dose or withdraw dosing. (5.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence >3%) reported in clinical studies with Remodulin: subcutaneous infusion site pain and reaction, headache, diarrhea, nausea, jaw pain, vasodilatation, edema, and hypotension. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact United Therapeutics Corp. at 1-866-458-6479 or contact FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Blood pressure lowering drugs (e.g., diuretics, antihypertensive agents, or vasodilators): Risk of increased reduction in blood pressure (7.1)
- Remodulin inhibits platelet aggregation. Potential for increased risk of bleeding, particularly among patients on anticoagulants. (7.2)
- Remodulin dosage adjustment may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn. (7.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1 Pulmonary Arterial Hypertension

Remodulin is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%) *[see Clinical Studies (14.1)]*.

It may be administered as a continuous subcutaneous infusion or continuous intravenous (IV) infusion; however, because of the risks associated with chronic indwelling central venous catheters, including serious blood stream infections (BSIs), reserve continuous intravenous infusion for patients who are intolerant of the subcutaneous route, or in whom these risks are considered warranted *[see Warnings and Precautions 5.1]*.

1.2 Pulmonary Arterial Hypertension in Patients Requiring Transition from Flolan®

In patients with pulmonary arterial hypertension requiring transition from Flolan (epoprostenol sodium), Remodulin is indicated to diminish the rate of clinical deterioration. Consider the risks and benefits of each drug prior to transition.

2 DOSAGE AND ADMINISTRATION

2.1 General

Remodulin can be administered without further dilution for subcutaneous administration, or diluted for intravenous infusion with Sterile Diluent for Remodulin or similar approved high-pH glycine diluent (e.g. Sterile Diluent for Flolan or Sterile Diluent for Epoprostenol Sodium), Sterile Water for Injection, or 0.9% Sodium Chloride Injection prior to administration. See Table 1 below for storage and administration time limits for the different diluents.

Table 1. Selection of Diluent

Route	Diluent	Storage limits	Administration limits
SC	None	See section 16	72 hours at 37°C
IV	Sterile Diluent for Remodulin Sterile Diluent for Flolan Sterile Diluent for Epoprostenol Sodium	14 days at room temperature	48 hours at 40 °C
	Sterile water for injection 0.9% Sodium Chloride for injection	4 hours at room temperature or 24 hours refrigerated	48 hours at 40°C

2.2 Initial Dose for Patients New to Prostacyclin Infusion Therapy

Remodulin is indicated for subcutaneous (SC) or intravenous (IV) use only as a continuous infusion. Remodulin is preferably infused subcutaneously, but can be administered by a central intravenous line if the subcutaneous route is not tolerated, because of severe site pain or reaction. The infusion rate is initiated at 1.25 ng/kg/min. If this initial dose cannot be tolerated because of systemic effects, reduce the infusion rate to 0.625 ng/kg/min.

2.3 Dosage Adjustments

The goal of chronic dosage adjustments is to establish a dose at which PAH symptoms are improved, while minimizing excessive pharmacologic effects of Remodulin (headache, nausea, emesis, restlessness, anxiety and infusion site pain or reaction).

The infusion rate should be increased in increments of 1.25 ng/kg/min per week for the first four weeks of treatment and then 2.5 ng/kg/min per week for the remaining duration of infusion, depending on clinical response. Dosage adjustments may be undertaken more often if tolerated. Avoid abrupt cessation of infusion *[see Warnings and Precautions (5.4)]*. Restarting a Remodulin infusion within a few hours after an interruption can be done using the same dose rate. Interruptions for longer periods may require the dose of Remodulin to be re-titrated.

2.4 Patients with Hepatic Insufficiency

In patients with mild or moderate hepatic insufficiency, decrease the initial dose of Remodulin to 0.625 ng/kg/min ideal body weight. Remodulin has not been studied in patients with severe hepatic insufficiency *[see Warnings and Precautions (5.3), Use In Specific Populations (8.6)* and *Clinical Pharmacology (12.3)]*.

2.5 Administration

Inspect parenteral drug products for particulate matter and discoloration prior to administration whenever solution and container permit. If either particulate matter or discoloration is noted, do not use.

Subcutaneous Infusion

Remodulin is administered subcutaneously by continuous infusion without further dilution, via a subcutaneous catheter, using an infusion pump designed for subcutaneous drug delivery. To avoid potential interruptions in drug delivery, the patient must have immediate access to a backup infusion pump and subcutaneous infusion sets. The ambulatory infusion pump used to administer Remodulin should: (1) be small and lightweight, (2) be adjustable to approximately 0.002 mL/hr, (3) have occlusion/no delivery, low battery, programming error and motor malfunction alarms, (4) have delivery accuracy of ±6% or better and (5) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass.

Remodulin is administered subcutaneously by continuous infusion at a calculated subcutaneous infusion rate (mL/hr) based on a patient's dose (ng/kg/min), weight (kg), and the vial strength (mg/mL) of Remodulin being used. During use, a single reservoir (syringe) of undiluted Remodulin can be administered up to 72 hours at 37°C. The subcutaneous infusion rate is calculated using the following formula:

$$\textbf{Subcutaneous Infusion Rate (mL/hr)} = \frac{\textbf{Dose (ng/kg/min)} \times \textbf{Weight (kg)} \times \textbf{0.00006*}}{\textbf{Remodulin Vial Strength (mg/mL)}}$$

**Conversion factor of 0.00006 = 60 min/hour x 0.000001 mg/ng*

Example calculations for ***Subcutaneous Infusion*** are as follows:

Example 1:

For a 60 kg person at the recommended initial dose of 1.25 ng/kg/min using the 1 mg/mL Remodulin, the infusion rate would be calculated as follows:

$$\text{Subcutaneous Infusion Rate (mL/hr)} = \frac{1.25 \text{ ng/kg/min} \times 60 \text{ kg} \times 0.00006}{1 \text{ mg/mL}} = 0.005 \text{ mL/hr}$$

Example 2:

For a 65 kg person at a dose of 40 ng/kg/min using the 5 mg/mL Remodulin, the infusion rate would be calculated as follows:

$$\text{Subcutaneous Infusion Rate (mL/hr)} = \frac{40 \text{ ng/kg/min} \times 65 \text{ kg} \times 0.00006}{5 \text{ mg/mL}} = 0.031 \text{ mL/hr}$$

Intravenous Infusion

Diluted Remodulin is administered intravenously by continuous infusion via a surgically placed indwelling central venous catheter using an infusion pump designed for intravenous drug delivery. If clinically necessary, a temporary peripheral intravenous cannula, preferably placed in a large vein, may be used for short term administration of Remodulin. Use of a peripheral intravenous infusion for more than a few hours may be associated with an increased risk of thrombophlebitis. To avoid potential interruptions in drug delivery, the patient must have immediate access to a backup infusion pump and infusion sets. The ambulatory infusion pump used to administer Remodulin should: (1) be small and lightweight, (2) have occlusion/no delivery, low battery, programming error and motor malfunction alarms, (3) have delivery accuracy of ±6% or better of the hourly dose, and (4) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass.

Infusion sets with an in-line 0.22 or 0.2 micron pore size filter should be used.

Diluted Remodulin has been shown to be stable at ambient temperature when stored for up to 14 days using high-pH glycine diluent at concentrations as low as 0.004 mg/mL (4,000 ng/mL).

Select the intravenous infusion rate to allow for a desired infusion period length of up to 48 hours between system changeovers. Typical intravenous infusion system reservoirs have volumes of 50 or 100 mL. With this selected intravenous infusion rate (mL/hr) and the patient's dose (ng/kg/min) and weight (kg), the diluted intravenous Remodulin concentration (mg/mL) can be calculated using the following formula:

Step 1

$$\text{Diluted Intravenous Remodulin Concentration (mg/mL)} = \frac{\text{Dose (ng/kg/min)} \times \text{Weight (kg)} \times 0.00006}{\text{Intravenous Infusion Rate (mL/hr)}}$$

The volume of Remodulin Injection needed to make the required diluted intravenous Remodulin concentration for the given reservoir size can then be calculated using the following formula:

Step 2

$$\text{Volume of Remodulin Injection (mL)} = \frac{\text{Diluted Intravenous Remodulin Concentration (mg/mL)}}{\text{Remodulin Vial Strength (mg/mL)}} \times \text{Total Volume of Diluted Remodulin Solution in Reservoir (mL)}$$

The calculated volume of Remodulin Injection is then added to the reservoir along with the sufficient volume of diluent to achieve the desired total volume in the reservoir.

Example calculations for ***Intravenous Infusion*** are as follows:

Example 3:

For a 60 kg person at a dose of 5 ng/kg/min, with a predetermined intravenous infusion rate of 1 mL/hr and a reservoir of 50 mL, the diluted intravenous Remodulin concentration would be calculated as follows:

Step 1

$$\text{Diluted Intravenous Remodulin Concentration (mg/mL)} = \frac{5 \text{ ng/kg/min} \times 60 \text{ kg} \times 0.00006}{1 \text{ mL/hr}} = 0.018 \text{ mg/mL (18,000 ng/mL)}$$

The volume of Remodulin Injection (using 1 mg/mL Vial Strength) needed for a total diluted Remodulin concentration of 0.018 mg/mL and a total volume of 50 mL would be calculated as follows:

Step 2

$$\text{Volume of Remodulin Injection (mL)} = \frac{0.018 \text{ mg/mL}}{1 \text{ mg/mL}} \times 50 \text{ mL} = 0.9 \text{ mL}$$

The diluted intravenous Remodulin concentration for the person in Example 3 would thus be prepared by adding 0.9 mL of 1 mg/mL Remodulin Injection to a suitable reservoir along with a sufficient volume of diluent to achieve a total volume of 50 mL in the reservoir. The pump flow rate for this example would be set at 1 mL/hr.

Example 4:

For a 75 kg person at a dose of 30 ng/kg/min, with a predetermined intravenous infusion rate of 2 mL/hr, and a reservoir of 100 mL, the diluted intravenous Remodulin concentration would be calculated as follows:

Step 1

$$\text{Diluted Intravenous} = \frac{30 \text{ ng/kg/min} \times 75 \text{ kg} \times 0.00006}{} = 0.0675 \text{ mg/mL (67,500 ng/mL)}$$

Remodulin Concentration (mg/mL) = $\frac{\text{0.0675 mg/mL}}{\text{2.5 mg/mL}} \times \text{100 mL} = \text{2.7 mL}$ / 2 mL/hr

The volume of Remodulin Injection (using 2.5 mg/mL Vial Strength) needed for a total diluted Remodulin concentration of 0.0675 mg/mL and a total volume of 100 mL would be calculated as follows:

Step 2

Volume of Remodulin Injection (mL) = $\frac{\text{0.0675 mg/mL}}{\text{2.5 mg/mL}} \times \text{100 mL} = \text{2.7 mL}$

The diluted intravenous Remodulin concentration for the person in Example 4 would thus be prepared by adding 2.7 mL of 2.5 mg/mL Remodulin Injection to a suitable reservoir along with a sufficient volume of diluent to achieve a total volume of 100 mL in the reservoir. The pump flow rate for this example would be set at 2 mL/hr.

2.6 Patients Requiring Transition from Flolan

Transition from Flolan to Remodulin is accomplished by initiating the infusion of Remodulin and increasing it, while simultaneously reducing the dose of intravenous Flolan. The transition to Remodulin should take place in a hospital with constant observation of response (e.g., walk distance and signs and symptoms of disease progression). Initiate Remodulin at a recommended dose of 10% of the current Flolan dose, and then escalate as the Flolan dose is decreased (see Table 2 for recommended dose titrations).

Patients are individually titrated to a dose that allows transition from Flolan therapy to Remodulin while balancing prostacyclin-limiting adverse events. Increases in the patient's symptoms of PAH should be first treated with increases in the dose of Remodulin. Side effects normally associated with prostacyclin and prostacyclin analogs are to be first treated by decreasing the dose of Flolan.

Table 2: Recommended Transition Dose Changes

Step	Flolan Dose	Remodulin Dose
1	Unchanged	10% Starting Flolan Dose
2	80% Starting Flolan Dose	30% Starting Flolan Dose
3	60% Starting Flolan Dose	50% Starting Flolan Dose
4	40% Starting Flolan Dose	70% Starting Flolan Dose
5	20% Starting Flolan Dose	90% Starting Flolan Dose
6	5% Starting Flolan Dose	110% Starting Flolan Dose
7	0	110% Starting Flolan Dose + additional 5-10% increments as needed

3 DOSAGE FORMS AND STRENGTHS

20-mL vial containing 20 mg treprostinil (1 mg per mL).

20-mL vial containing 50 mg treprostinil (2.5 mg per mL).
20-mL vial containing 100 mg treprostinil (5 mg per mL).
20-mL vial containing 200 mg treprostinil (10 mg per mL).

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Catheter-Related Bloodstream Infection

Chronic intravenous infusions of Remodulin are delivered using an indwelling central venous catheter. This route is associated with the risk of blood stream infections (BSIs) and sepsis, which may be fatal. Therefore, continuous subcutaneous infusion (undiluted) is the preferred mode of administration.

In an open-label study of IV treprostinil (n=47), there were seven catheter-related line infections during approximately 35 patient years, or about 1 BSI event per 5 years of use. A CDC survey of seven sites that used IV treprostinil for the treatment of PAH found approximately 1 BSI (defined as any positive blood culture) event per 3 years of use. Administration of IV Remodulin with a high pH glycine diluent has been associated with a lower incidence of BSIs when compared to neutral diluents (sterile water, 0.9% sodium chloride) when used along with catheter care guidelines.

5.2 Worsening PAH upon Abrupt Withdrawal or Sudden Large Dose Reduction

Avoid abrupt withdrawal or sudden large reductions in dosage of Remodulin, which may result in worsening of PAH symptoms.

5.3 Patients with Hepatic or Renal Insufficiency

Titrate slowly in patients with hepatic or renal insufficiency, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic or renal function *[see Dosage and Administration (2.4, 2.5), Use In Specific Populations (8.6, 8.7), and Clinical Pharmacology (12.3)]*.

5.4 Effect of Other Drugs on Treprostinil

Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) increases exposure (both C_{max} and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) decreases exposure to treprostinil *[see Drug Interactions (7.5)* and *Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in labeling: Infections associated with intravenous administration *[see Warnings and Precautions (5.1)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Events with Subcutaneously Administered Remodulin

Patients receiving Remodulin as a subcutaneous infusion reported a wide range of adverse events, many potentially related to the underlying disease (dyspnea, fatigue, chest pain, right ventricular heart failure, and pallor). During clinical trials with subcutaneous infusion of Remodulin, infusion site pain and reaction were the most common adverse events among those treated with Remodulin. Infusion site reaction was defined as any local adverse event other than pain or bleeding/bruising at the infusion site and included symptoms such as erythema, induration or rash. Infusion site reactions were sometimes severe and could lead to discontinuation of treatment.

Table 3: Percentages of subjects reporting subcutaneous infusion site adverse events

	Reaction		Pain	
	Placebo	Remodulin	Placebo	Remodulin
Severe	1	38	2	39
Requiring narcotics*	NA[†]	NA[†]	1	32
Leading to discontinuation	0	3	0	7

* based on prescriptions for narcotics, not actual use

† medications used to treat infusion site pain were not distinguished from those used to treat site reactions

Other adverse events included diarrhea, jaw pain, edema, vasodilatation and nausea, and these are generally considered to be related to the pharmacologic effects of Remodulin, whether administered subcutaneously or intravenously.

Adverse Reactions during Chronic Dosing

Table 4 lists adverse reactions defined by a rate of at least 3% more frequent in patients treated with subcutaneous Remodulin than with placebo in controlled trials in PAH.

Table 4: Adverse Reactions in Controlled 12-Week Studies of Subcutaneous Remodulin and at least 3% more frequent than on Placebo.

Adverse Reaction	Remodulin (N=236) Percent of Patients	Placebo (N=233) Percent of Patients
Infusion Site Pain	85	27
Infusion Site Reaction	83	27
Headache	27	23
Diarrhea	25	16
Nausea	22	18
Rash	14	11
Jaw Pain	13	5
Vasodilatation	11	5
Edema	9	3

Reported adverse reactions (at least 3% more frequent on drug than on placebo) are included except those too general to be informative, and those not plausibly attributable to the use of the drug, because they were associated with the condition being treated or are very common in the treated population.

While hypotension occurred in both groups, the event was experienced twice as frequently in the Remodulin group as compared to the placebo group (4% in Remodulin treatment group verses 2% in placebo-controlled group). As a potent vasodilator, hypotension is possible with the administration of Remodulin.

The safety of Remodulin was also studied in a long-term, open-label extension study in which 860 patients were dosed for a mean duration of 1.6 years, with a maximum exposure of 4.6 years. Twenty-nine (29%) percent achieved a dose of at least 40 ng/kg/min (max: 290 ng/kg/min). The safety profile during this chronic dosing study was similar to that observed in the 12-week placebo controlled study except for the following suspected adverse drug reactions (occurring in at least 3% of patients): anorexia, vomiting, infusion site infection, asthenia, and abdominal pain.

Adverse Events Attributable to the Drug Delivery System

In controlled studies of Remodulin administered subcutaneously, there were no reports of infection related to the drug delivery system. There were 187 infusion system complications reported in 28% of patients (23% Remodulin, 33% placebo); 173 (93%) were pump related and 14 (7%) related to the infusion set. Eight of these patients (4 Remodulin, 4 Placebo) reported non-serious adverse events resulting from infusion system complications. Adverse events resulting from problems with the delivery systems were typically related to either symptoms of excess Remodulin (e.g., nausea) or return of PAH symptoms (e.g., dyspnea). These events were generally resolved by correcting the delivery system pump or infusion set problem such as replacing the syringe or battery, reprogramming the pump, or straightening a crimped infusion line. Adverse events resulting from problems with the delivery system did not lead to clinical instability or rapid deterioration. In addition to these adverse events due to the drug delivery system during subcutaneous administration, the following adverse events may be attributable to the IV mode of infusion including arm swelling, paresthesias, hematoma and pain *[see Warnings and Precautions (5.1)]*.

6.2 Post-Marketing Experience

In addition to adverse reactions reported from clinical trials, the following events have been identified during post-approval use of Remodulin. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The following events have been chosen for inclusion because of a combination of their seriousness, frequency of reporting, and potential connection to Remodulin. These events are thrombophlebitis associated with peripheral intravenous infusion, thrombocytopenia bone pain, pruritus and dizziness. In addition, generalized rashes, sometimes macular or papular in nature, and cellulitis have been infrequently reported.

7 DRUG INTERACTIONS

Pharmacokinetic/pharmacodynamic interaction studies have been conducted with treprostinil administered subcutaneously (Remodulin) and orally (treprostinil diethanolamine).

Pharmacodynamics

7.1 Antihypertensive Agents or Other Vasodilators

Concomitant administration of Remodulin with diuretics, antihypertensive agents or other vasodilators may increase the risk of symptomatic hypotension.

7.2 Anticoagulants

Since treprostinil inhibits platelet aggregation, there may be an increased risk of bleeding, particularly among patients receiving anticoagulants.

Pharmacokinetics

7.3 Bosentan

In a human pharmacokinetic study conducted with bosentan (250 mg/day) and an oral formulation of treprostinil (treprostinil diethanolamine), no pharmacokinetic interactions between treprostinil and bosentan were observed.

7.4 Sildenafil

In a human pharmacokinetic study conducted with sildenafil (60 mg/day) and an oral formulation of treprostinil (treprostinil diethanolamine), no pharmacokinetic interactions between treprostinil and sildenafil were observed.

7.5 Effect of Treprostinil on Cytochrome P450 Enzymes

In vitro studies of human hepatic microsomes showed that treprostinil does not inhibit cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A. Additionally, treprostinil does not induce cytochrome P450 isoenzymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A. Thus Remodulin is not expected to alter the pharmacokinetics of compounds metabolized by CYP enzymes.

7.6 Effect of Cytochrome P450 Inhibitors and Inducers on Treprostinil

Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diethanolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor gemfibrozil increases exposure (both C_{max} and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer rifampin decreases exposure to treprostinil. It has not been determined if the safety and efficacy of treprostinil by the parenteral (subcutaneously or intravenously) route are altered by inhibitors or inducers of CYP2C8 *[see Warnings and Precautions (5.4)]*.

Remodulin has not been studied in conjunction with Flolan or Tracleer® (bosentan).

7.7 Effect of Other Drugs on Treprostinil

Drug interaction studies have been carried out with treprostinil (oral or subcutaneous) co-administered with acetaminophen (4 g/day), warfarin (25 mg/day), and fluconazole (200 mg/day), respectively in healthy volunteers. These studies did not show a clinically significant effect on the pharmacokinetics of treprostinil. Treprostinil does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S- warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous infusion of treprostinil at an infusion rate of 10 ng/kg/min.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B - In pregnant rats, continuous subcutaneous infusions of treprostinil during organogenesis and late gestational development, at rates as high as 900 ng treprostinil/kg/min (about 117 times the starting human rate of infusion, on a ng/m^2 basis and about 16 times the average rate achieved in clinical trials), resulted in no evidence of harm to the fetus. In pregnant rabbits, effects of continuous subcutaneous infusions of treprostinil during organogenesis were limited to an increased incidence of fetal skeletal variations (bilateral full rib or right rudimentary rib on lumbar 1) associated with maternal toxicity (reduction in body weight and food consumption) at an infusion rate of 150 ng treprostinil/kg/min (about 41 times the starting human rate of infusion, on a ng/m^2 basis, and 5 times the average rate used in clinical trials). In rats, continuous subcutaneous infusion of treprostinil from implantation to the end of lactation, at rates of up to 450 ng treprostinil/kg/min, did not affect the growth and development of offspring. Animal reproduction studies are not always predictive of human response.

8.2 Labor and Delivery

No treprostinil treatment-related effects on labor and delivery were seen in animal studies. The effect of treprostinil sodium on labor and delivery in humans is unknown.

8.3 Nursing Mothers

It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Many drugs are excreted in human milk.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Clinical studies of Remodulin did not include sufficient numbers of patients aged ≤16 years to determine whether they respond differently from older patients.

8.5 Geriatric Use

Clinical studies of Remodulin did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Patients with Hepatic Insufficiency

Remodulin clearance is reduced in patients with hepatic insufficiency. In patients with mild or moderate hepatic insufficiency, decrease the initial dose of Remodulin to 0.625 ng/kg/min ideal body weight, and monitor closely. Remodulin has not been studied in patients with severe hepatic insufficiency *[see Dosage and Administration (2.4), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

8.7 Patients with Renal Insufficiency

No studies have been performed in patients with renal insufficiency. No specific advice about dosing in patients with renal impairment can be given *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Signs and symptoms of overdose with Remodulin during clinical trials are extensions of its dose-limiting pharmacologic effects and include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Most events were self-limiting and resolved with reduction or withholding of Remodulin.

In controlled clinical trials, seven patients received some level of overdose and in open-label follow-on treatment seven additional patients received an overdose; these occurrences resulted from accidental bolus administration of Remodulin, errors in pump programmed rate of administration, and prescription of an incorrect dose. In only two cases did excess delivery of Remodulin produce an event of substantial hemodynamic concern (hypotension, near-syncope).

One pediatric patient was accidentally administered 7.5 mg of Remodulin via a central venous catheter. Symptoms included flushing, headache, nausea, vomiting, hypotension and seizure-like activity with loss of consciousness lasting several minutes. The patient subsequently recovered.

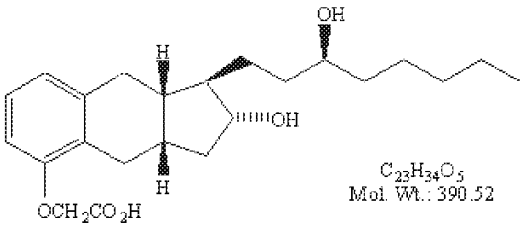
11 DESCRIPTION

Remodulin (treprostinil) Injection is a sterile solution of treprostinil formulated for subcutaneous or intravenous administration. Remodulin is supplied in 20 mL multidose vials in four strengths, containing 20 mg, 50 mg, 100 mg, or 200 mg (1 mg/mL, 2.5 mg/mL, 5 mg/mL or 10 mg/mL) of treprostinil. Each mL also contains 5.3 mg sodium chloride (except for the 10 mg/mL strength which contains 4.0 mg sodium chloride), 3 mg metacresol, 6.3 mg sodium citrate, and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

Treprostinil is chemically stable at room temperature and neutral pH.

Treprostinil is (1R,2R,3aS,9aS)-[[2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]acetic acid. Treprostinil has a molecular weight of 390.52 and a molecular formula of $C_{23}H_{34}O_5$.

The structural formula of treprostinil is:



Sterile Diluent for Remodulin is a high-pH (pH~10.4) glycine diluent supplied in a 50 mL vial containing 50 mL of Sterile Diluent for Remodulin. Each vial contains 94 mg glycine, 73.3 mg sodium chloride, sodium hydroxide (to adjust pH), and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds, and inhibition of platelet aggregation.

12.2 Pharmacodynamics

In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. Other studies have shown that treprostinil causes a dose-related negative inotropic and lusitropic effect. No major effects on cardiac conduction have been observed.

Treprostinil produces vasodilation and tachycardia. Single doses of treprostinil up to 84 mcg by inhalation produce modest and short-lasting effects on QTc, but this is apt to be an artifact of the rapidly changing heart rate. Treprostinil administered by the subcutaneous or intravenous routes has the potential to generate concentrations many-fold greater than those generated via the inhaled route; the effect on the QTc interval when treprostinil is administered parenterally has not been established.

12.3 Pharmacokinetics

The pharmacokinetics of continuous subcutaneous Remodulin are linear over the dose range of 1.25 to 125 ng/kg/min (corresponding to plasma concentrations of about 15 pg/mL to 18,250 pg/mL) and can be described by a two-compartment model. Dose proportionality at infusion rates greater than 125 ng/kg/min has not been studied.

Subcutaneous and intravenous administration of Remodulin demonstrated bioequivalence at steady state at a dose of 10 ng/kg/min.

Absorption

Remodulin is relatively rapidly and completely absorbed after subcutaneous infusion, with an absolute bioavailability approximating 100%. Steady-state concentrations occurred in approximately 10 hours. Concentrations in patients treated with an average dose of 9.3 ng/kg/min were approximately 2,000 pg/mL.

Distribution

The volume of distribution of the drug in the central compartment is approximately 14L/70 kg ideal body weight. Remodulin at *in vitro* concentrations ranging from 330-10,000 mcg/L was 91% bound to human plasma protein.

Metabolism and Excretion

Treprostinil is substantially metabolized by the liver, primarily by CYP2C8. In a study conducted in healthy volunteers using [^{14}C] treprostinil, 78.6% and 13.4% of the subcutaneous dose was recovered in the urine and feces, respectively, over 10 days. Only 4% was excreted as unchanged treprostinil in the urine. Five metabolites were detected in the urine, ranging from 10.2% to 15.5% and representing 64.4% of the dose administered. Four of the metabolites are products of oxidation of the 3-hydroxyloctyl side chain and one is a glucuroconjugated derivative (treprostinil glucuronide). The identified metabolites do not appear to have activity.

The elimination of treprostinil (following subcutaneous administration) is biphasic, with a terminal elimination half-life of approximately 4 hours using a two compartment model. Systemic clearance is approximately 30 L/hr for a 70 kg person.

Based on in vitro studies treprostinil does not inhibit or induce major CYP enzymes *[see Drug Interactions (7.5)]*.

Special Populations

Hepatic Insufficiency

In patients with portopulmonary hypertension and mild (n=4) or moderate (n=5) hepatic insufficiency, Remodulin at a subcutaneous dose of 10 ng/kg/min for 150 minutes had a C_{max} that was 2-fold and 4-fold, respectively, and an AUC_{0-} that was 3-fold and 5-fold, respectively, values observed in healthy subjects. Clearance in patients with hepatic insufficiency was reduced by up to 80% compared to healthy adults.

Renal Insufficiency

No studies have been performed in patients with renal insufficiency, so no specific advice about dosing in such patients can be given. Although only 4% of the administered dose is excreted unchanged in the urine, the five identified metabolites are all excreted in the urine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies have not been performed to evaluate the carcinogenic potential of treprostinil. *In vitro* and *in vivo* genetic toxicology studies did not demonstrate any mutagenic or clastogenic effects of treprostinil. Treprostinil did not affect fertility or mating performance of male or female rats given continuous subcutaneous infusions at rates of up to 450 ng treprostinil/kg/min [about 59 times the recommended starting human rate of infusion (1.25 ng/kg/min) and about 8 times the average rate (9.3 ng/kg/min) achieved in clinical trials, on a ng/m^2 basis]. In this study, males were dosed from 10 weeks prior to mating and through the 2-week mating period. Females were dosed from 2 weeks prior to mating until gestational day 6.

14 CLINICAL STUDIES

14.1 Clinical Trials in Pulmonary Arterial Hypertension (PAH)

Two 12-week, multicenter, randomized, double-blind studies compared continuous subcutaneous infusion of Remodulin to placebo in a total of 470 patients with NYHA Class II (11%), III (81%), or IV (7%) pulmonary arterial hypertension (PAH). PAH was idiopathic/heritable in 58% of patients, associated with connective tissue diseases in 19%, and the result of congenital systemic-to-pulmonary shunts in 23%. The mean age was 45 (range 9 to 75 years). About 81% were female and 84% were Caucasian. Pulmonary hypertension had been diagnosed for a mean of 3.8 years. The primary endpoint of the studies was change in 6-minute walking distance, a standard measure of exercise capacity. There were many assessments of symptoms related to heart failure, but local discomfort and pain associated with Remodulin may have substantially unblinded those assessments. The 6-minute walking distance and an associated subjective measurement of shortness of breath during the walk (Borg dyspnea score) were administered by a person not participating in other aspects of the study. Remodulin was administered as a subcutaneous infusion, described in Section 2, DOSAGE AND ADMINISTRATION, and the dose averaged 9.3 ng/kg/min at Week 12. Few subjects received doses > 40 ng/kg/min. Background therapy,

determined by the investigators, could include anticoagulants, oral vasodilators, diuretics, digoxin, and oxygen but not an endothelin receptor antagonist or epoprostenol. The two studies were identical in design and conducted simultaneously, and the results were analyzed both pooled and individually.

Hemodynamic Effects

As shown in Table 5, chronic therapy with Remodulin resulted in small hemodynamic changes consistent with pulmonary and systemic vasodilation.

Table 5: Hemodynamics during Chronic Administration of Remodulin in Patients with PAH in 12-Week Studies

Hemodynamic Parameter	Baseline		Mean change from baseline at Week 12	
	Remodulin (N=204-231)	Placebo (N=215-235)	Remodulin (N=163-199)	Placebo (N=182-215)
CI ($L/min/m^2$)	2.4 ± 0.88	2.2 ± 0.74	+0.12 ± 0.58*	-0.06 ± 0.55
PAPm (mmHg)	62 ± 17.6	60 ± 14.8	-2.3 ± 7.3*	+0.7 ± 8.5
RAPm (mmHg)	10 ± 5.7	10 ± 5.9	-0.5 ± 5.0*	+1.4 ± 4.8
PVRI ($mmHg/L/min/m^2$)	26 ± 13	25 ± 13	-3.5 ± 8.2*	+1.2 ± 7.9
SVRI ($mmHg/L/min/m^2$)	38 ± 15	39 ± 15	-3.5 ± 12*	-0.80 ± 12
SvO_2 (%)	62 ± 100	60 ± 11	+2.0 ± 10*	-1.4 ± 8.8
SAPm (mmHg)	90 ± 14	91 ± 14	-1.7 ± 12	-1.0 ± 13
HR (bpm)	82 ± 13	82 ± 15	-0.5 ± 11	-0.8 ± 11

*Denotes statistically significant difference between Remodulin and placebo, $p<0.05$.
CI = cardiac index; PAPm = mean pulmonary arterial pressure; PVRI = pulmonary vascular resistance indexed; RAPm = mean right atrial pressure; SAPm = mean systemic arterial pressure; SVRI = systemic vascular resistance indexed; SvO2 = mixed venous oxygen saturation; HR = heart rate.

Clinical Effects

The effect of Remodulin on 6-minute walk, the primary end point of the 12-week studies, was small and did not achieve conventional levels of statistical significance. For the combined populations, the median change from baseline on Remodulin was 10 meters and the median change from baseline on placebo was 0 meters from a baseline of approximately 345 meters. Although it was not the primary endpoint of the study, the Borg dyspnea score was significantly improved by Remodulin during the 6-minute walk, and Remodulin also had a significant effect, compared with placebo, on an assessment that combined walking distance with the Borg dyspnea score. Remodulin also consistently improved indices of dyspnea, fatigue and signs and symptoms of pulmonary hypertension, but these indices were difficult to interpret in the context of incomplete blinding to treatment assignment resulting from infusion site symptoms.

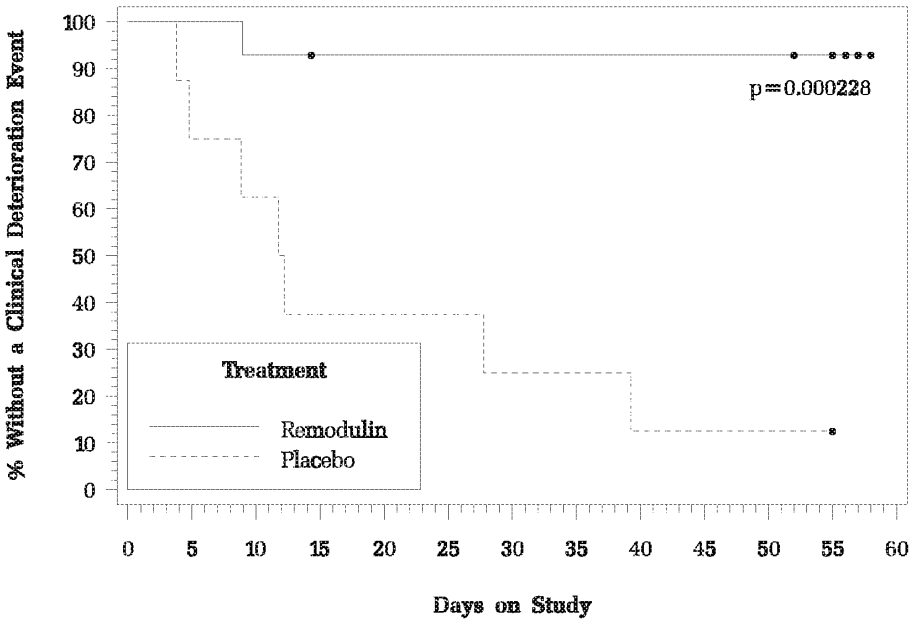
14.2 Flolan-To-Remodulin Transition Study

In an 8-week, multicenter, randomized, double-blind, placebo-controlled study, patients on stable doses of Flolan were randomly withdrawn from Flolan to placebo or Remodulin. Fourteen

Remodulin and 8 placebo patients completed the study. The primary endpoint of the study was the time to clinical deterioration, defined as either an increase in Flolan dose, hospitalization due to PAH, or death. No patients died during the study.

During the study period, Remodulin effectively prevented clinical deterioration in patients transitioning from Flolan therapy compared to placebo (Figure 1). Thirteen of 14 patients in the Remodulin arm were able to transition from Flolan successfully, compared to only 1 of 8 patients in the placebo arm (p=0.0002).

Figure 1: Time to Clinical Deterioration for PAH Patients Transitioned from Flolan to Remodulin or Placebo in an 8-Week Study



16 HOW SUPPLIED / STORAGE AND HANDLING

Remodulin is supplied in 20-mL multidose vials as sterile solutions in water for injection, individually packaged in cartons. Unopened vials of Remodulin are stable until the date indicated when stored at 25°C (77°F), with excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. A single vial of Remodulin should be used for no more than 30 days after the initial introduction into the vial.

Remodulin Injection is supplied as:

Remodulin	Concentration	NDC 66302-xxx-xx
20 mg / 20 mL	1 mg/ mL	101-01
50 mg / 20 mL	2.5 mg/ mL	102-01
100 mg / 20 mL	5 mg/ mL	105-01
200 mg / 20 mL	10 mg/ mL	110-01

Sterile Diluent for Remodulin is supplied separately as:
50 mL vial, carton of 1 (NDC 66302-150-50).

17 PATIENT COUNSELING INFORMATION

Patients receiving Remodulin should be given the following information: Remodulin is infused continuously through a subcutaneous or surgically placed indwelling central venous catheter, via an infusion pump. Patients receiving intravenous infusion should use an infusion set with an in-line filter. Therapy with Remodulin will be needed for prolonged periods, possibly years, and the patient's ability to accept and care for a catheter and to use an infusion pump should be carefully considered. In order to reduce the risk of infection, aseptic technique must be used in the preparation and administration of Remodulin. Additionally, patients should be aware that subsequent disease management may require the initiation of an alternative intravenous prostacyclin therapy, Flolan (epoprostenol sodium).

Copyright 2014 United Therapeutics Corp. All rights reserved.

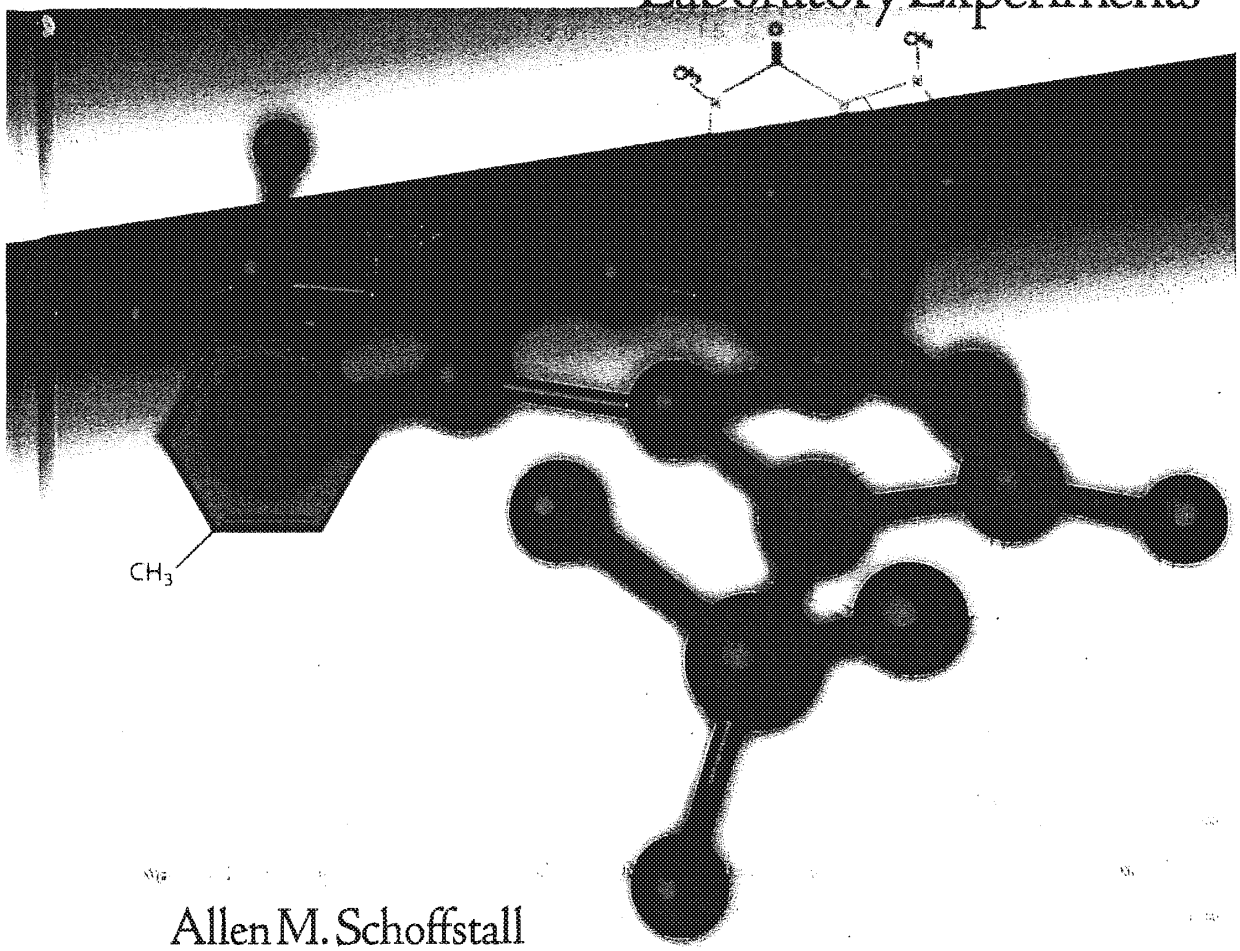
REMODULIN manufactured for:

United Therapeutics Corp.
Research Triangle Park, NC 27709

Microscale and Miniscale

ORGANIC CHEMISTRY

Laboratory Experiments



Allen M. Schoffstall
Barbara A. Gaddis
Melvin L. Druelinger

Second Edition

IPR2020-00770
United Therapeutics EX2007
Page 3302 of 7335

Results and Conclusions for Part B

1. Calculate the percent recovery for the recrystallization process. Explain why it is not 100%.
2. Explain and evaluate the effectiveness of the recrystallization solvent in terms of percent recovery and purity of the recrystallized solid.
3. Suggest other solvents or solvent pairs that might have been used for this recrystallization.

Cleanup & Disposal

Place the solvents used for recrystallization in a container labeled "nonhalogenated organic solvent waste." Aqueous solutions can be washed down the drain with water.

Critical Thinking Questions *(The harder one is marked with a ❖.)*

1. List the main criteria for selecting a recrystallization solvent.
2. When is it necessary to use a solvent-pair recrystallization?
3. Why should the recrystallization solvent have a fairly low boiling point?
4. ❖ Will the following pairs of solvents be suitable for doing a solvent-pair recrystallization? Explain.
   a. ethanol (bp 78.5°C) and water
   b. methylene chloride (bp 40°C) and water
   c. dimethylformamide (bp 153°C) and diethyl ether (bp 37°C)
5. If a solute is soluble in cold solvent, is it necessary to test the solubility of the solute in the same solvent when hot? Explain.
6. Arrange the following solvents in order of increasing polarity: ethanol, ethyl acetate, petroleum ether, toluene, and acetone.
7. Methylene chloride (CH_2Cl_2) is polar, whereas carbon tetrachloride (CCl_4) is nonpolar. Explain.
8. Carbon disulfide (CS_2) is sometimes used as a recrystallization solvent. Will this solvent dissolve polar or nonpolar compounds? Explain.

Experiment 3.5: Separations Based upon Acidity and Basicity

Extraction is a technique in which a solute is transferred from one solvent to another. In this experiment, you will investigate acid-base extraction. You will:

- determine the solubilities of an organic acid, an organic base, and a neutral organic compound.
- design a flow scheme to separate an organic acid, an organic base, and a neutral compound.
- use microscale extraction techniques to separate and isolate each component of a mixture of naphthalene, benzoic acid, and ethyl 4-aminobenzoate.
- use miniscale extraction techniques to separate and isolate a mixture of benzoic acid and ethyl 4-aminobenzoate.

IPR2020-00770
United Therapeutics EX2007
Page 3303 of 7335

Techniques

Technique C	Melting point
Technique F	Vacuum filtration
Technique I	Drying and extraction

Background

A water-insoluble, acidic organic compound such as a carboxylic acid or phenol can be easily separated from neutral and basic organic compounds by conversion to a water-soluble salt.

a water-insoluble carboxylic acid — a water-soluble carboxylate salt

Neutral and basic organic compounds remain in the organic layer. The two layers can then be separated. Addition of HCl to the aqueous layer regenerates the water-insoluble carboxylic acid, which can then be filtered or extracted into an organic solvent:

a water-soluble carboxylate salt — a water-insoluble carboxylic acid

A similar scheme can be used to separate a basic compound, such as a water-insoluble amine, from neutral or acidic organic compounds by conversion of the amine to a water-soluble salt:

a water-insoluble amine — a water-soluble ammonium salt

Neutral compounds and acidic organic compounds remain in the organic solvent, where they can be removed. Addition of sodium hydroxide to the aqueous layer regenerates the amine, which is now insoluble in the aqueous solution. The amine can be filtered or extracted into an organic solvent.

a water-soluble ammonium salt — a water-insoluble amine

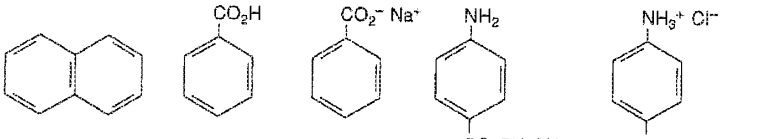
The neutral compound remains in the organic solvent, where it can be recovered by drying the solution to remove traces of water, filtering off the drying agent, and evaporating the solvent.

In this exercise, the solubilities of an organic acid (benzoic acid), an organic base (ethyl 4-aminobenzoate), a neutral compound (naphthalene), and the organic salts (ethyl 4-aminobenzoate hydrochloride and sodium benzoate) will be tested in methylene chloride and water.

From the solubilities, you will construct a flow scheme outlining the separation of naphthalene, benzoic acid, and ethyl 4-aminobenzoate. In Part B, you will use the flow

IPR2020-00770
United Therapeutics EX2007
Page 3304 of 7335

scheme to separate a mixture of naphthalene, benzoic acid, and ethyl 4-aminobenzoate in microscale. In Part C, you will use the flow scheme to separate a mixture of benzoic acid and ethyl 4-aminobenzoate in miniscale.



naphthalene — benzoic acid — sodium benzoate — ethyl 4-amino-benzoate — ethyl 4-amino-benzoate hydrochloride

The instructor may substitute other compounds for those shown here.

Prelab Assignment

1. Read Technique I on the theory and technique of extraction and do all assigned problems.
2. Construct a solubility table similar to Table 3.5-1 in the experimental section.
3. Identify the conjugate acid/conjugate base pairs for the structures above.
4. Write the reaction (if any) and give the products for the reaction of each pair of reagents below. If no reaction occurs, write NR. Indicate whether the product will be water-soluble or water-insoluble.
   a. benzoic acid with NaOH.
   b. sodium benzoate with HCl.
   c. ethyl 4-aminobenzoate with HCl.
   d. ethyl 4-aminobenzoate hydrochloride with NaOH.
   e. naphthalene and NaOH.
   f. ethyl 4-aminobenzoate with NaOH.
5. Determine whether each of the five compounds is predominantly ionically or covalently bonded. Based upon this answer, indicate whether the compound would be expected to be more soluble in water or more soluble in methylene chloride.

Experimental Procedure

Safety First!

Always wear eye protection in the laboratory.

1. Wear eye protection at all times in the laboratory.
2. Wear gloves when handling reagents in this experiment.
3. Methylene chloride is a toxic irritant and a suspected carcinogen. Do not breathe the vapors. Work under the hood or in a well-ventilated area.
4. NaOH and HCl are corrosive and toxic and can cause burns.

Part A: Determination of Solubilities

Obtain 20 small, dry test tubes or a spot plate. Place approximately 10–20 mg of benzoic acid into four of the test tubes or wells; place 10–20-mg of sodium benzoate into four other test tubes or wells. Repeat, using 10–20-mg samples of the other solutes. It is

IPR2020-00770
United Therapeutics EX2007
Page 3305 of 7335

The McGraw-Hill Companies

Higher Education

MICROSCALE AND MINISCALE ORGANIC CHEMISTRY LAB EXPERIMENTS
SECOND EDITION

Published by McGraw-Hill, a business unit of The McGraw-Hill Companies, Inc., 1221 Avenue of the Americas, New York, NY 10020. Copyright © 2004, 2000 by The McGraw-Hill Companies, Inc. All rights reserved. No part of this publication may be reproduced or distributed in any form or by any means, or stored in a database or retrieval system, without the prior written consent of The McGraw-Hill Companies, Inc., including, but not limited to, in any network or other electronic storage or transmission, or broadcast for distance learning.

Some ancillaries, including electronic and print components, may not be available to customers outside the United States.

This book is printed on acid-free paper.

1 2 3 4 5 6 7 8 9 0 VNH/VNH 0 9 8 7 6 5 4 3

ISBN 0–07–242456–7

Publisher: *Kent A. Peterson*
Sponsoring editor: *Thomas D. Timp*
Senior developmental editor: *Shirley R. Oberbroeckling*
Senior marketing manager: *Tamara L. Good-Hodge*
Project manager: *Joyce Watters*
Lead production supervisor: *Sandy Ludovissy*
Senior media project manager: *Stacy A. Patch*
Senior media technology producer: *Jeffry Schmitt*
Senior coordinator of freelance design: *Michelle D. Whitaker*
Cover/interior designer: *Rokusek Design*
Cover image: *Rokusek Design*
Senior photo research coordinator: *Lori Hancock*
Compositor: *Precision Graphics*
Typeface: *10/12 Times Roman*
Printer: *Von Hoffmann Corporation*

"Permission for the publication herein of Sadtler Standard Spectra has been granted, and all rights are reserved, by BIO-RAD Laboratories, Sadtler Division."

"Permission for the publication of Aldrich/ACD Library of FT NMR Spectra has been granted and all rights are reserved by Aldrich Chemical."

All experiments contained in this laboratory manual have been performed safely by students in college laboratories under the supervision of the authors. However, unanticipated and potentially dangerous reactions are possible due to failure to follow proper procedures, incorrect measurement of chemicals, inappropriate use of laboratory equipment, and other reasons. The authors and the publisher hereby disclaim any liability for personal injury or property damage claimed to have resulted from the use of this laboratory manual.

Library of Congress Cataloging-in-Publication Data

Schoffstall, Allen M.
Microscale and miniscale organic chemistry laboratory experiments / Allen M. Schoffstall, Barbara A. Gaddis, Melvin L. Druelinger.—2nd ed.
p. cm.
Includes bibliographical references and index.
ISBN 0–07–242456–7 (acid-free paper)
1. Chemistry, Organic—Laboratory manuals. I. Gaddis, Barbara A. II. Druelinger, Melvin L. III. Title.

QD261 .S34 2004
547.0078—dc21 2003008663
CIP

www.mhhe.com

IPR2020-00770
United Therapeutics EX2007
Page 3306 of 7335

ORGANIC CHEMISTRY

Thomas N. Sorrell
THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

University Science Books
Sausalito, California

IPR2020-00770
United Therapeutics EX2007
Page 3307 of 7335

University Science Books
55D Gate Five Road
Sausalito, CA 94965
Fax: (415) 332-3393
www.uscibooks.com

Production manager: *Susanna Tadlock*
Manuscript editor: *Ann McGuire*
Designer: *Robert Ishi*
Illustrators: *John and Judy Waller*
Compositor: *Compset Inc.*
Printer & binder: *Edwards Brothers, Inc.*

This book is printed on acid-free paper.

Copyright ©1999 by University Science Books

Reproduction or translation of any part of this work beyond that permitted by Section 107 or 108 of the 1976 United States Copyright Act without the permission of the copyright owner is unlawful. Requests for permission or further information should be addressed to the Permissions Department, University Science Books.

Library of Congress Cataloging-in-Publication Data

Sorrell, Thomas N.
Organic chemistry / Thomas N. Sorrell.
p. cm.
Includes bibliographical references (p. –) and index.
ISBN 0-935702-47-4 (hardcover)
1. Chemistry, Organic. I. Title.
QD251.2.S67 1997
547—dc21

98-47383
CIP

Printed in the United States of America
10 9 8 7 6 5 4 3 2 1

IPR2020-00770
United Therapeutics EX2007
Page 3308 of 7335

Closely related to economic concerns are environmental issues. Chapter 13 introduced the notion of the **atom economy** of a reaction (page 620). If a chemist makes a racemic mixture of products and has to carry out a resolution (discussed below), a large amount of byproduct may be generated that has to be disposed of or recycled.

THERE ARE TWO COMMON METHODS FOR OBTAINING OPTICALLY ACTIVE COMPOUNDS, RESOLUTION AND ASYMMETRIC SYNTHESIS

Faced with the need to obtain a chiral substance, a chemist has two choices that have general applicability. A third method is physical separation of enantiomeric forms, a method successfully employed by Louis Pasteur to obtain enantiomeric crystals of tartaric acid salts (page 12 and 176). This method is limited to only a handful of cases, however, so we will not consider it further.

The first general method is by **resolution** of enantiomers. As noted in the introduction to this chapter, enantiomers have *identical* chemical and physical properties but diastereomers have *different* properties. Converting a pair of enantiomers to diastereomers often makes it possible to separate them. Subsequently, the diastereomeric derivatives can be converted back to the desired enantiomerically pure substances.

The other route for making an optically active product is called a **kinetically controlled asymmetric transformation**. These processes have attracted the most interest in recent years because they allow chemists to create enantiomerically enriched products from achiral starting materials by employing a chiral catalyst or reagent. We will look at examples of both catalytic and stoichiometric processes.

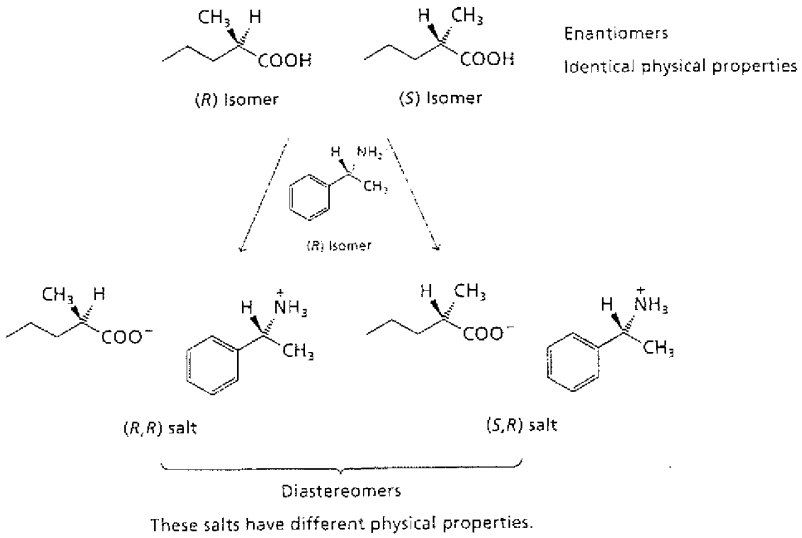
RESOLUTION OF A RACEMATE MAKES USE OF DIASTEREOMERIC FORMS

The most general method for obtaining optically pure compounds from a racemic mixture is based on exploiting differences in chemical and physical properties of diastereomeric derivatives of the mirror-image isomers. In the process that constitutes a classical **resolution**, the racemate is first treated with an optically active reagent, producing a pair of diastereoisomers. These are then separated by crystallization, chromatography, or any other means that makes use of the different physical properties of the derivatives. Once the diastereomeric pair is separated, the pure isomer is treated with a second reagent to regenerate the resolving agent and the original substrate, in its enantiomerically pure form.

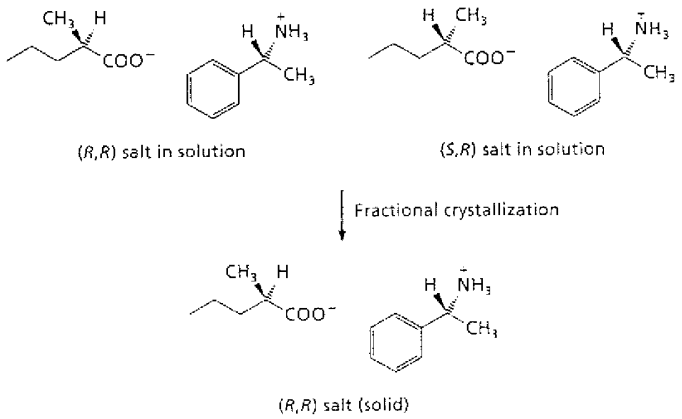
The procedure will be illustrated for the resolution of a carboxylic acid via formation of a salt, a process frequently employed to resolve amino acids. In this example, the resolving agent is α-phenethylamine (1-amino-1-phenylethane), an amine that has a single asymmetric carbon atom.

The carboxylic acid and amine undergo an acid–base reaction, producing the ammonium carboxylate salt. Because only one enantiomer of the amine is added to the racemic mixture of carboxylic acid, *the resulting salt, which comprises two asymmetric centers, is a diastereomeric mixture.*

IPR2020-00770
United Therapeutics EX2007
Page 3309 of 7335

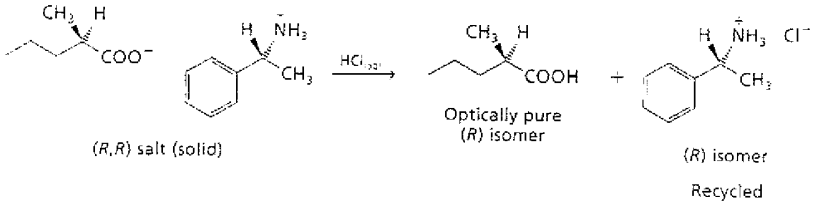


Diastereomeric salts can often be separated by fractional crystallization, taking advantage of their different solubility characteristics.

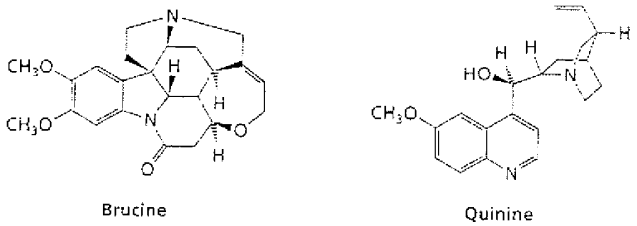


The pure salt is subsequently treated with hydrochloric acid, which regenerates the optically active carboxylic acid and liberates the chloride salt of the amine. The latter can be separated by extraction and recovered by neutralization.

IPR2020-00770
United Therapeutics EX2007
Page 3310 of 7335



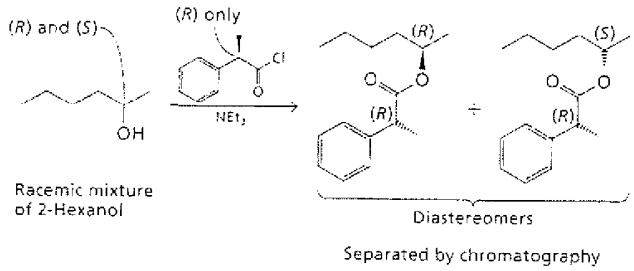
The resolution process illustrated here employs an optically active amine that has a single stereogenic center. In practice, the optically active amine is normally a substance that can be isolated as a pure compound from nature. Many amines used for resolutions are alkaloids such as brucine and quinine, which have multiple stereogenic centers. The salts formed when they are treated with a racemic carboxylic acid are still diastereomers, so they can be separated by fractional crystallization.



EXERCISE 16.1

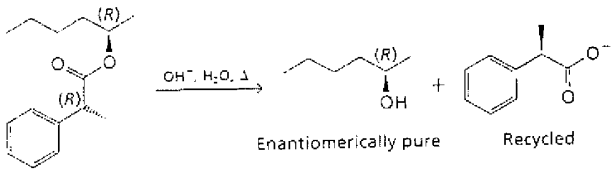
How many stereogenic centers are there in brucine and quinine? Recall that some nitrogen atoms can be chiral (review Chapter 5, page 194).

Another way to carry out the resolution of a racemic compound is to make a *covalent* derivative of the racemate. For example, enantiomeric alcohols can be treated with an optically active acid chloride to produce esters, a reaction that will be described in Chapter 19. These esters are diastereomers and can be separated



IPR2020-00770
United Therapeutics EX2007
Page 3311 of 7335

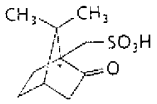
by chromatography, a technique amenable for use with neutral substances. Hydrolysis of the ester after chromatography regenerates the optically active carboxylic acid as its salt and yields each of the optically active alcohols [only recovery of the (*R*)-2-hexanol is illustrated below].



This reaction is discussed in Chapter 19.

EXERCISE 16.2

Amines and sulfonic acids form salts by an acid–base reaction. Show how racemic α-phenethylamine can be resolved using optically active 10-camphorsulfonic acid (shown below).

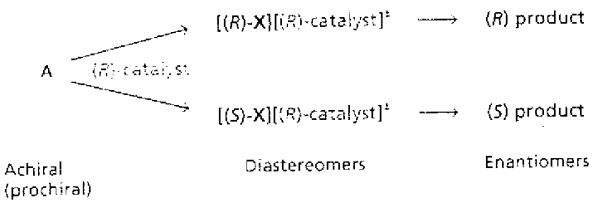


What is the configuration of the carbon atom marked with an asterisk?

A KINETICALLY CONTROLLED ASYMMETRIC TRANSFORMATION RELIES ON DIFFERENCES IN THE TRANSITION-STATE ENERGIES

Apart from a resolution, the only other general method for making an optically active substance is that by which an achiral starting material is transformed into a chiral product. Reactions that accomplish this goal define an **asymmetric synthesis**. Such transformations exploit the use of a chiral species that generates transition states with unequal energies as a result of the spatial interaction of the reactant with the reagent or catalyst.

In the abstract, we can represent an asymmetric reaction by the following scheme in which an achiral substance reacts with a chiral catalyst, generating diastereomeric transition states but enantiomeric products.



IPR2020-00770
United Therapeutics EX2007
Page 3312 of 7335

Laboratory Technique in Organic Chemistry

KENNETH B. WIBERG

Professor of Chemistry
University of Washington

McGRAW-HILL BOOK COMPANY, INC.

1960 New York Toronto London

IPR2020-00770
United Therapeutics EX2007
Page 3313 of 7335

LABORATORY TECHNIQUE IN ORGANIC CHEMISTRY

Copyright © 1960 by the McGraw-Hill Book Company, Inc. Printed in the United States of America. All rights reserved. This book, or parts thereof, may not be reproduced in any form without permission of the publishers. *Library of Congress Catalog Card Number* 59-11950

IV

70095

THE MAPLE PRESS COMPANY, YORK, PA.

IPR2020-00770
United Therapeutics EX2007
Page 3314 of 7335

PREFACE

Although there are a number of monographs available which deal with an aspect of the techniques required in dealing with organic compounds, there has for some time been no book which gives a brief description of most of the important techniques. This book is written in an effort to fill this need and is directed mainly to the advanced undergraduate or beginning graduate student who is about to undertake a program of research work.

Each of the three types of matter, liquids, solids and gases, is considered with respect to both its properties and the methods of purification. It is felt that an understanding of the properties of the substances adds materially to the appreciation of the methods of purification. Methods which involve distribution between two phases are then considered. Finally, the reaction itself is examined in relation to the apparatus and techniques involved.

In organic chemical laboratory technique, the use of the proper apparatus is important. A drawing of a commonly used piece of equipment has generally been provided to accompany the description of each method. These drawings are for the most part derived from the working drawings used in the shops at the University of Washington, and in most cases all important dimensions are given in millimeters.

In writing a book of this type, it is very difficult to give credit to

IPR2020-00770
United Therapeutics EX2007
Page 3315 of 7335

a specific designer for a piece of equipment or to the originator of a technique. The art of laboratory work in organic chemistry has evolved from the experiments and modifications of many technicians, and only rarely can the contribution of an individual be specifically recognized.

Kenneth B. Wiberg

CONTENTS

IPR2020-00770
United Therapeutics EX2007
Page 3316 of 7335

IPR2020-00770
United Therapeutics EX2007
Page 3317 of 7335

ing homogeneity, particularly of natural products. If the material is fractionally crystallized, giving perhaps 8 to 10 fractions from the head fraction to the tail fraction (8 to 10 layers), and if these fractions are compared and found to be identical, it is reasonable to assume that the material is homogeneous.

The alembic shown in Fig. 2-21 is particularly useful in fractional crystallization, since it permits convenient adjustment of the amount of solvent and prevents loss of solvent during the prolonged refluxing sometimes required to bring the material into solution.

Precipitation

In some cases, the most convenient method for the purification of a solid consists in precipitating it from a solution in which it is contained as a derivative. A typical example is the purification of a water-insoluble solid carboxylic acid by dissolving it in sodium hydroxide solution, filtering, and precipitating the compound by the addition of acid. A similar procedure may be used with amines: dissolve the compound in acid and precipitate it with a base. These procedures usually work quite well in that they utilize a chemical reaction to aid in separation from nonacidic or nonbasic impurities.

Another method of precipitation involves precipitating the compound as a derivative and then converting the derivative back to the original compound. An example of this is to dissolve an amine in ether, precipitate it as the hydrochloride by passing in hydrogen chloride, and convert the hydrochloride back to the amine with sodium hydroxide solution. Again, this method is useful because it involves separation through the use of a reaction.

One method of precipitation which is usually relatively unsuccessful involves dissolving the compound in one solvent and precipitating by the addition of another solvent in which it is insoluble. This procedure usually leads to coprecipitation and relatively little purification. If two solvents are to be used, the compound should be recrystallized from a mixture of the two solvents as described in the preceding section.

Distillation

If the compound is relatively impure, crystallization usually entails considerable loss of material, and several recrystallizations are required to effect complete purification. The procedure often may be

IPR2020-00770
United Therapeutics EX2007
Page 3318 of 7335

Organic Process Research & Development 2006, 10, 829–832

Technical Notes

Novel Synthetic Route of a Pivotal Intermediate for the Synthesis of 1β-Methyl Carbapenem Antibiotics

Yuan Yu,[†,‡,§] Wu-Chun Zhou,[‡] Ji Zhang,[†] Mei Zhang,[‡] Da-Yong Xu,[‡] Yun Tang,[‡] Bo-Gang Li,*[,‡,§] and Xiao-Qi Yu*[,†,∥]

Department of Chemistry, Key Laboratory of Green Chemistry and Technology (Ministry of Education), Sichuan University, Chengdu, Sichuan 610064, P.R. China, Chengdu Di-Ao Pharmaceuticals Company, Chengdu 610041, Sichuan, P.R. China, Chengdu Institute of Biology, The Chinese Academy of Science, Chengdu 610041, P.R. China, and State Key Laboratory of Biotherapy, West China Hospital, West China Medical School, Sichuan University, Chengdu, Sichuan 610041, P.R. China

Abstract:

A novel synthetic method using an original and practical procedure for the preparation of the *N*-PNZ protected 2-aminomethylpyrrolidin-4-ylthio-containing side chain of doripenem hydrate (S-4661), a new parenteral 1β-methylcarbapenem antibiotic, is described. *trans*-4-Hydroxy-L-proline was converted through an efficient process to (2*S*,4*S*)-4-acetylthio-2-(*N*-sulfamoyl-4-nitro-benzyloxycarbonyl-aminomethyl)-1-(4-nitrobenzyloxycarbonyl) pyrrolidine with 60−70% overall yield via a two-step sequence. This procedure requires no chromatographic purifications, no cryogenic temperatures, no haloalkane solvent, and shorter operating times and avoids the side reaction brought by acid hydrolysis. Furthermore, the product was obtained as a crystal rather than an oil, which made it to be an advantage for quantization in the pilot-scale manufacture. Several kilograms of the side chain were prepared by using this method.

1. Introduction

Members of the carbapenem family are important among the β-lactam antibiotics for their broad and potent antibacterial activity and their relatively high resistance to most clinically encountered β-lactamases.[1] So far many products, such as imipenem,[2] panipenem,[3] meropenem,[4] biapenem,[5] and ertapenem,[6] have been put into market. The introduction of a 1β-methyl group to the carbapenem skeleton in meropenem, biapenem, and ertapenem enhances metabolic stability to renal dehydropeptidase-1 (DHP-1) and leads to high antibacterial potency.[7] Doripenem hydrate (S-4661, **1**, Shionogi Research Laboratories, Shionogi & Co., Ltd., Osaka, Japan) is a novel parenteral 1β-methylcarbapenem antibiotic.[8] Compound **1** is superior to meropenem against Gram positive bacteria and, meanwhile, is superior to imipenem against Gram negative bacteria. Furthermore, **1** has an antibacterial potency against *Pseudomonas aeruginosa* which is up to twice as strong as that of imipenem or meropenem. With its potent, broad, and well-balanced antibacterial activity against a wide range of both Gram-positive and Gram-negative bacteria, doripenem is now under phase 3 clinical trials for the treatment of serious infections such as pneumonia, pyelonephritis, and respiratory tract infections.

According to the conventional retrosynthetic analysis of a carbapenem, doripenem can be assembled from 4-nitrobenzyl-protected 1β-methylcarbapenem enolphosphate **2**[7,10] and 2-aminomethyl-pyrrolidin-4-ylthio-containing side chain **3** (Scheme 1). SAR studies revealed that the acylation and sulfamoylamination of the side chain pyrrolidine would benefit the enhancement of the antibacterial activity.

Several papers have been published regarding the synthesis of the side chain aminomethylpyrrolidine derivatives,[8,9,11a,11b] among which two are important. In 1996, Iso and co-workers reported the synthesis of *N*-*p*-methoxybenzyl (PMZ)-protected aminomethylpyrrolidine **3a** (R^2 = PMZ) or *N*-BOC-protected aminomethylpyrrolidine **3b** (R^2 =

* Corresponding author. E-mail: xqyu@tfol.com,libg@cib.ac.cn.
† Department of Chemistry, Key Laboratory of Green Chemistry and Technology (Ministry of Education), Sichuan University.
‡ Chengdu Di-Ao Pharmaceuticals Company.
§ Chengdu Institute of Biology, The Chinese Academy of Science.
∥ State Key Laboratory of Biotherapy, Sichuan University.

(1) (a) For a brief history: Sunagawa, M.; Sasaki, A. *Heterocycles* **2001**, *54*, 497−528. (b) Kawamoto, I. *Drugs Future* **1998**, *23*, 181−189. (c) Coulton, S.; Hunt, E. In *Progress in Medicinal Chemistry*; Ellis, G. P., Luscombe, D. K., Eds.; Elsevier Science: New York, 1996; Vol. 33, pp 99−145. (d) Sader, H. S.; Gales, A. C. *Drugs* **2001**, *61*, 553−564. (e) Neu, H. C. Why carbapenems? *Curr. Opin. Infect. Dis.* **1994**, *7*, 3−10.

(2) (a) Leanza, W. J.; Wildonger, K. J.; Miller, T. W.; Christensen, B. G. *J. Med. Chem.* **1979**, *22*, 1435−1436. (b) Kropp, H.; Sundelof, J. G.; Kahan, J. S.; Kahan, F. M.; Birnbaum, *J. Antimicrob. Agents Chemother.* **1980**, *17*, 993−1000. (c) Kahan, F. M.; Kropp, H.; Sundelof, J. G.; Birnbaum, J. *J. Antimicrob. Chemother.* **1983**, *12* (Suppl. D), 1−35.

(3) Miyadera, T.; Sugimura, Y.; Hashomoto, T.; Tanaka, T.; Iino, K.; Shibata, T.; Sugawara, S. *J. Antibiot.* **1983**, *36*, 1034−1039.

(4) Sunagawa, I.; Matsumura, H.; Inoue, T.; Fukasawa, M.; Kato, M. *J. Antibiot.* **1990**, *43*, 519−532.

(5) Hiraishi, T.; Miyata, A.; Hara, T.; Araake, M.; Ogawa, H. *Jpn. J. Antibiot.* **2001**, *54*, 581−595.

(6) Fuchs, P. C.; Barry, A. L.; Brown, S. D. *Antimicrob. Agents Chemother.* **2001**, *45*, 1915−1918 and references therein.

(7) Shih, D. H.; Baker, F.; Cama, L.; Christensen, B. G. *Heterocycles* **1984**, *21*, 29−40.

(8) Iso, Y.; Irie, T.; Nishino, Y.; Motokawa, K.; Nishitani, Y. *J. Antibiot.* **1996**, *49*, 199−209.

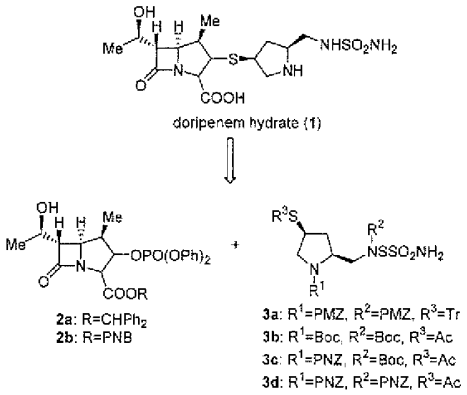
(9) Iso, Y.; Irie, T.; Iwaki, T.; Kii, M.; Sendo, Y.; Motokawa, K.; Nishitani, Y. *J. Antibiot.* **1996**, *49*, 478−484.

(10) Ohtani, M.; Watanabe, F.; Narisada, M. *J. Org. Chem.* **1984**, *49*, 5271−5272.

10.1021/op0600714 CCC: $33.50 © 2006 American Chemical Society
Published on Web 08/29/2006

IPR2020-00770
United Therapeutics EX2007
Page 3319 of 7335

Scheme 1. **Retrosynthetic analysis of a carbapenem**



BOC),[8] after coupling with the diphenylmethyl-protected enolphosphate **2a**, compound **1** was prepared by deprotection with $AlCl_3$-anisole.

Although this route facilitated the SAR studies and led to rapid optimization of the lead derivatives, it had several drawbacks for multikilogram-scale preparation of compound **1**. The two most serious problems resided in the isolation and deprotection steps. Compound **1** was isolated as a foam, which needed further purification on a Diaion HP-20. Later, a modified process was developed, and compound **1** was obtained as a crystalline monohydrate.[9] However, the process still required chromatographic purification, and the yield of compound **1** through the deprotection, purification, and crystallization steps on a pilot scale (49%) was lower than that through the deprotection and purification steps on a bench scale (72%). During the column chromatography and concentration of the eluents, decomposition of the target compound **1** was observed, resulting in a 16% yield decrease due to longer operating times on scale-up. Furthermore, this process included several severe conditions such as cryogenic reaction temperatures (three reactions required −45 ℃), long operation times, and the use of haloalkane solvent (CH_2Cl_2). To reduce the cost of processing time and to make the process more environmentally suitable, Nishino and co-workers[11b] reported *N*-PNZ-protected aminomethylpyrrolidine (R^2 = Boc) **3c**, which was prepared from *trans*-4-hydroxy-L-proline. But the deprotection of the *tert*-butylcarbonyl group by 98% H_2SO_4 results in an oily product at room temperature, and the carbonium ion brought many side reactions, while scavenger usage will increase the producing cost.

To increase the yield and to avoid the chromatographic purification, we developed an improved process. Compound **1** was synthesized from PNB-protected enolphophate **2b** and *N*-[*p*-nitrobenzyloxycarbonyl] (PNZ)-protected aminomethylpyrrolidine **3d**. In this contribution, we describe the preparation of the new pyrrolidine derivative **3d** and its coupling with enolphosphate **2b** (Scheme 2). This process avoided the side reaction brought by deprotection of the *tert*-butoxycarbonyl group and made it easier for purification. Furthermore, the product was obtained as a crystal rather than an oil, which made it an advantage for quantization in the pilot-scale manufacture.

(11) (a) A portion of this study was patented. Nishino, Y.; Yuasa, T.; Komurasaki, T.; Kakinuma, M.; Masui, T.; Kobayashi, M. Patent Application No. JP 2001-140782. (b) Nishino, Y.; Komurasaki, T.; Yuasa, T.; Kakinuma, M.; Izumi, K.; Kobayashi, M.; Fujiie, S.; Gotoh, T.; Masui, Y.; Hajima, M.; Takahira, M.; Okuyama, A.; Kataoka, T. *Org. Process Res. Dev.* **2003**, *7*, 649−654.

2. Experimental Section

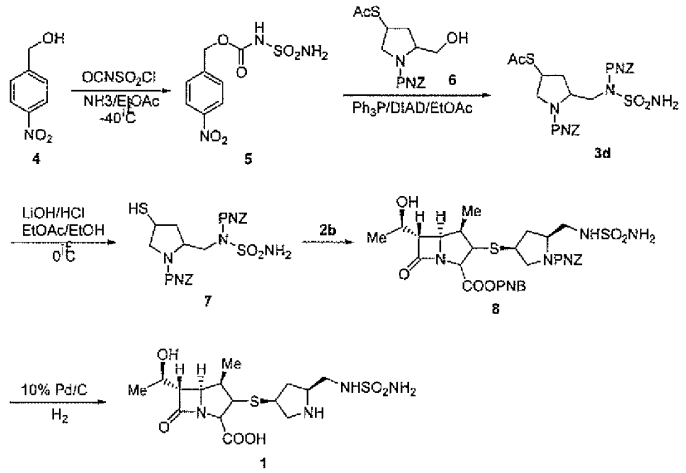
2.1. Materials and Instrumentations. ESI-MS spectral data were measured on a Finnigan LCQ^{DECA} mass spectrometer. ^{1}H NMR and ^{13}C NMR experiments were measured on a Bruker Avance 600 spectrometer. Chemical shifts are reported in ppm (δ scale) using tetramethylsilane as an internal standard. Melting points were determined with a micromelting point apparatus and are uncorrected. All commercially available materials and solvents were used as received without any further purification. 4-Nitrobenzyl (4*R*,5*S*,6*S*)-3-[(diphenylphosphono)oxy]-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3, 2, 0]hept-2-ene-2-carboxylate (**2b**) is commercially available.

2.2. Preparation of the Compounds. 2.2.1. Preparation of the *N*-PNZ-Protected Pyrrolidine Derivative 3d. 2.2.1.a. Preparation of *N*-4-Nitrobenzyloxycarbonyl-sulfonamide (5). To a solution of 4-nitrobenzyl alcohol (38.25 g, 250 mmol) in THF, chlorosulfonyl isocyanate (21.75 mL, 250 mmol) was added dropwise at −40 ℃, and the mixture was stirred at −40 ℃ for 30 min. After cooling the mixture to −60 ℃, gaseous amine was bubbled into the reaction with stirring. After bubbling, the mixture was stirred for 30 min at 15 ℃ and then acidified with 1 N HCl until no more precipitation was generated. The precipitate was collected by filtration and dissolved in EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, and evaporated in a vacuum. The residue was crystallized from EtOAc−hexane to give 55 g of *N*-4-nitrobenzyl sulfonamide as a colorless crystal (80%). Mp: 160−162 ℃ (dec). FT-IR (KBr, cm^{-1}): 3348, 3258, 3223, 1721, 1610, 1473, 1454, 1348, 1260, 1156, 847. ^{1}H NMR (600 MHz, DMSO-d_6) δ 5.29 (2H, s, −O−CH_2−Ar), 7.54 (br, 2H, $-SO_2NH_2$), 7.64 (A_2B_2, 2H, J = 8.7 Hz, −ArH), 8.26 (A_2B_2, 2H, J = 8.7 Hz, −ArH), 11.38 (br, 1H, −CO−NH−SO_2−). ^{13}C NMR (600 MHz, DMSO-d_6) δ 65.6 (−O−CH_2−Ar), 124.1 (o, −Ar−NO_2), 128.8 (m, −Ar−NO_2), 144.3 (p, −Ar−NO_2), 147.6 (−Ar−NO_2 in situ), 152.0 (C=O, PNZ−). ESI-MS: 298 [M + Na]$^-$, 314 [M + K]$^+$. FTICR/MS: Calculated for [$C_8H_9N_2Na_1O_6S_1$], 298.0110; found, 298.0104.

2.2.1.b. Preparation of Acetylthiol-pyrrolidine Derivative (3d). A solution of diisopropyl azodicarboxylate (DIAD, 22 mL, 130 mmol) in EtOAc was added dropwise to a mixture of (2*S*,4*S*)-4-acetylthio-2-hydroxymethyl-1-(4-nitrobenzyl-oxycarbonyl)pyrrolidine (**6**, 35.5 g, 100 mmol), *N*-4-nitrobenzylsulfamide (**5**, 41.25 g, 150 mmol), triphenyl phospine (34.125 g, 130 mmol), and THF (1000 mL) at 0 ℃. The reaction mixture was stirred at 20 ℃ for 2 h. After the reaction was completed, the reaction mixture was concentrated to 200 mL, and 500 mL of anhydrate alcohol were then added. The solution was stored in a refrigerator over-

IPR2020-00770
United Therapeutics EX2007
Page 3320 of 7335

Scheme 2. **Improved method for the preparation of 1**



night and resulted in 54 g of amorphous yellowish powder (88%). FT-IR (KBr, cm^{-1}): 3383, 3082, 2960, 1695, 1607, 1522, 1430, 1395, 1296, 1267, 1181, 1154, 1114, 850. ^1H NMR (600 MHz, $CDCl_3$) δ 1.60 (1H, m, pyrrolidine, H-3β), 2.33 (3H, s, AcS—), 2.59 (dt, 1H, J = 14.0, 8.7 Hz, pyrrolidine, H-3α), 3.17 (dd, 1H, J = 11.9, 6.24 Hz, pyrrolidine H-5β), 3.71 (dd, 1H, J = 14.9 Hz, —CH_2N(PNZ)SO_2—), 3.92 (1H, m, pyrrolidine H-4), 4.10 (dd, 1H, J = 15.3,10.2 Hz, —CH_2N(PNZ)SO_2—), 4.20 (dd, 1H, J = 11.7, 7.5 Hz, pyrrolidine H-5α), 4.52 (1H, m, pyrrolidine H-2α), 5.16 (AB_q, 2H, J = 13.4 Hz, —O—CH_2—Ar), 5.25 (br, 2H, —O—CH_2—Ar), 5.86 (br, 2H, —SO_2NH_2), 7.47 (A_2B_2, m, 2H, J = 8.46 Hz, —$ArNO_2$), 7.51 (A_2B_2, m, 2H, J = 8.46 Hz, —$ArNO_2$), 8.21 (A_2B_2, 2H, o, J = 8.52 Hz, —$ArNO_2$), 8.23 (A_2B_2, 2H, o, J = 8.28 Hz, —$ArNO_2$). ^{13}C NMR (600 MHz, $CDCl_3$) δ 30.5 (Me—, AcS—), 34.7 (pyrrolidine C-3), 39.1 (pyrrolidine C-4), 50.6 (—CH_2NSO_2—), 52.2 (pyrrolidine C-5), 56.7 (pyrrolidine C-2), 66.1 (—OCH_2—Ar), 74.0 (—OCH_2—Ar), 123.9 (o, —$ArNO_2$), 124.0 (o, —$ArNO_2$), 128.0 (m, —$ArNO_2$), 128.5 (m, —$ArNO_2$), 141.7 (p, —$ArNO_2$), 143.1 (p, —$ArNO_2$), 147.8 (—$ArNO_2$, in situ), 148.0 (—$ArNO_2$, in situ), 152.7 (C=O, PNZ—), 155.4 (C=O, PNZ—), 194.6-(C=O, AcS—). ESI-MS: 610.2 $[M - H]^-$. FTICR/MS: Calculated for $[C_{23}H_{25}N_5O_{11}S_2Na]$, 634.0890; found, 634.0884.

2.2.2. Preparation of Doripenem (S-4661). 2.2.2.a. Preparation of Thiol-pyrrolidine Derivative (2*S*,4*S*)-1-*tert*-Nitrobenzyl-oxycarbonyl-2—4*S*)-1-*tert*-nitrobenzyloxycarbonyl-2-(*N*-4-nitrobenzyloxycarbonylbenzyl-*N*-sulfamoulaminomethyl)-4-mercaptopyrrolidine (7). To a solution of 50 g (81.8 mmol) of (2*S*,4*S*)-1-*tert*-nitrobenzyl-2-(*N*-*tert*-nitrobenzylcarbonyl-*N*-aminosulfamide)methyl-4-acetylthiopyrrolidine (**3d**) in 200 mL of THF, 6 g of lithium hydroxide in 20 mL of water were added with an ice bath. After stirring for 2 h, the mixture was acidified with 6 N HCl and gave a sticky solid. The solid was collected by filtration, was dissolved with EtOAc and alcohol, and then stored in a refrigerator overnight. The product was precipitated as a yellowish amorphous powder (32 g, 68.8%). FT-IR (KBr, cm^{-1}): 3381, 2959, 1717, 1607, 1521, 1432, 1393, 1347, 1268, 1181, 1154, 1112, 850. ^1H NMR (600 MHz, $CDCl_3$) δ 1.52 (m, 1H, H-3β of pyrrolidine), 1.83 (d, 1H, J = 6.12 Hz, H of HS—), 2.62 (m, 1H, H-3α of pyrrolidine), 3.13 (dd, 1H, J = 11.64 and 7.68 Hz, H-5β of pyrrolidine), 3.39 (m, 1H, H-4 of pyrrolidine), 3.75 (d, 1H, J = 15.3 Hz, one of —CH_2N(PNZ)SO_2—), 4.10 (dd, 1H, J = 11.64 and 7.26 Hz, H-5α of pyrrolidine), 4.27 (dd, 1H, J = 15.3 and 10.32 Hz, one of —CH_2N(PNZ)SO_2—), 4.48 (m, 1H, H-2α of pyrrolidine), 5.15 (AB_q, 2H, J = 13.74 Hz, —OCH_2—Ar), 5.26 (AB_q, 2H, J = 13.74 Hz, —OCH_2—Ar), 5.84 (br, 2H, —SO_2NH_2), 7.45 (A_2B_2, 2H, J = 8.22 Hz, meta-H of nitrophenyl), 7.51 (A_2B_2, 2H, J = 8.40 Hz, *meta*-H of nitrophenyl), 8.21 (m, 4H, *ortho*-H of nitrophenyl). ^{13}C NMR (600 MHz, $CDCl_3$) δ: 34.5 (pyrrolidine C-3), 39.4 (pyrrolidine C-4), 50.9 (—CH_2N(PNZ)SO_2—), 55.3 (pyrrolidine C-5), 57.2 (pyrrolidine C-2), 66.1 (—OCH_2—Ar), 67.3 (—OCH_2—Ar), 123.9 and 124.0 (nitrophenyl *ortho*-C), 128.0 and 128.5 (nitrophenyl *meta*-C), 141.9 and 143.2 (nitrophenyl *para*-C), 147.8 and 148.0 (nitrophenyl ipso-C), 152.8 and 155.3 (C=O of PNZ—). ESI-MS: 592.1 $[M + Na]^+$, 608.1 $[M + K]^+$. FTICR/MS: Calculated for $[C_{21}H_{23}N_5Na_1O_{10}S_2]$, 592.0784; found, 592.0779.

2.2.2.b. Preparations of 8. To a DMF solution (250 mL) of (1*R*,5*S*,6*S*)-2-diphenoxy-phosphonyloxy-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid-4-nitrobenzyl ester (**7**, 17.82 g, 30 mmol) and the corresponding mercaptopyrrolidine (**2b**, 22 g, 38.66 mmol), diisopropylethylamine (7.23 mL, 42.5 mmol) was added with an ice bath. After stirring for 2 h, the mixture was diluted with 500 mL of EtOAc and washed with 1 N HCl, saturated Na_2CO_3, and saturated brine, dried over anhydrous Na_2SO_4, and evaporated in a vacuum. Toluene was added to deposit the product. After filtration, the product was obtained as a yellowish amorphous powder (27 g, 98.5%). FT-IR (KBr cm^{-1}): 3405, 2969, 1771, 1716, 1607, 1522,1433, 1392, 1347, 1276, 1181, 1141, 1111, 850.^1H NMR (600 MHz, $CDCl_3$) δ 1.26 (d, 3H, J = 7.14 Hz, CH_3— on 4-position), 1.37 (d, 3H, J = 6.18 Hz, CH_3CHOH—), 1.64 (m, 1H, H-3β of pyrrolidine), 2.62 (m, 1H, H-3α of pyrrolidine), 3.27 (m,

IPR2020-00770
United Therapeutics EX2007
Page 3321 of 7335

1H, H-4α), 3.27 (m, 1H, H-6), 3.27 (m, 1H, H-5β of pyrrolidine), 3.73 (m, 1H, one of $-CH_2N(PNZ)SO_2-$), 3.73 (m, 1H, H-4 of pyrrolidine), 4.10 (m, 1H, H-5α of pyrrolidine), 4.25 (m, 1H, H-5), 4.25 (m, 1H, $-CH(OH)\ CH_3$), 4.25 (m, 1H, one of $-CH_2N(PNZ)SO_2-$), 4.54 (m, 1H, H-2α of pyrrolidine), 5.12−5.48 (m, 6H, $-OCH_2-Ar$), 5.85 (br, 2H, $-SO_2NH_2$), 7.47 (m, 4H, *meta*-H of nitrophenyl), 7.63 (A_2B_2, 2H, $J = 8.70$ Hz, *meta*-H of nitrophenyl), 8.16 (A_2B_2, 2H, $J = 8.28$ Hz, *ortho*-H of nitrophenyl), 8.20 (m, 4H, *ortho*-H of nitrophenyl).^{13}C NMR (600 MHz, $CDCl_3$) δ 16.9 (Me— of 4-position), 22.0 (Me— of CH_3CHOH-), 34.7 (pyrrolidine C-3), 40.5 (pyrrolidine C-4), 44.0 (C-4), 50.7 (C of $-CH_2N(PNZ)SO_2-$), 54.0 (pyrrolidine C-5), 56.2 (C-5), 56.8 (pyrrolidine C-2), 59.8 (C-6), 65.5 (—CH— of CH_3CHOH-), 66.2 and 67.4 and 68.4 ($-OCH_2-Ar$), 123.8 and 123.9 and 124.0 (*ortho*-C of nitrophenyl), 125.8 (C-2), 128.3 and 128.4 (*meta*-C of nitrophenyl), 141.8 and 142.6 and 143.0 (*para*-C of nitrophenyl), 147.7 and 147.8 and 148.0 (ipso-C of nitrophenyl), 148.2 (C-3), 152.7 and 155.0 (C=O of PNZ—), 160.0 (C=O of PNB—), 172.4(C=O of C-7). FTICR/MS: Calculated for $[C_{38}H_{39}N_7Na_1O_{16}S_2]$, 936.1792; found, 936.1787.

2.2.2.c. Deprotection and Preparation of Doripenem (S-4661, 1). To a solution (180 mL) of (1*R*,5*S*,6*S*)-2-[(3*S*,5*S*)-1-*p*-nitrobenzyloxycarbonyl-5-(*N*-*p*-nitrobenzyloxycarbonyl-*N*-aminosulfonyl-amide)methylpyrrolidine]-sulfur-6-[(1*R*)-1-hydroxyethyl]-1-methylcarbapen-2-em-3-carboxylic acid-4-nitrobenzyl ester (**8**, 10 g, 10.95 mmol), 120 mL of water and 10 g of 10% Pd/C (contents 54% H_2O) were added, and the reaction mixture stirred under 0.5 mpa H_2 pressure for 4 h and then was filtered to remove the catalyst. Then 4 g of $MgCl_2 \cdot H_2O$ were added followed by partitioning with 300 mL of THF. 2-Propanol was added to the separated aqueous layer, which was then stored in a refrigerator overnight. The product S-4661 was precipitated and collected by filtration and dried in a vacuum as a white powder (2.269 g, 49%). FT-IR(KBr cm^{-1}): 3532, 3391, 3261, 3080, 2949, 2922, 2853, 1713, 1630, 1567, 1455, 1378, 1350, 1321, 1278, 1264, 1162, 1092, 1071, 930, 764. ^{1}H NMR (600 MHz, D_2O) δ 1.11 (d, $J = 7.26$ Hz, 3H), 1.18 (d, $J = 6.48$ Hz, 3H), 1.62−1.67 (m, 1H), 2.60−2.65 (m, 1H), 3.25−3.35 (m, 3H), 3.36 (dd, $J = 2.58$, 6 Hz, 1H), 3.43 (dd, $J = 4.77$, 10.11 Hz, 1H), 3.60 (dd, $J = 6.96$, 12.48 Hz, 1H), 3.8−3.84 (m, 1H), 3.92−3.96 (m, 1H), 4.12−4.16 (m, 2H). ^{13}C NMR (600 MHz, D_2O) δ 15.76, 20.05, 32.67, 39.22, 42.42, 43.06, 52.15, 55.88, 58.08, 59.57, 65.03, 133.69, 138.11, 167.63, 176.60. ESI-MS: 421.1 $[M + H]^+$. FTICR/MS: Calculated for $[C_{15}H_{24}N_4Na_1O_6S_2]$, 443.4940; found, 443.1029. The data are coincident with literature.

3. Conclusions

We developed and described a practical multikilogram scale synthesis of doripenem hydrate (**1**) by deprotection of compound **8**, which was prepared from enolphosphate **2b** and *N*-PNZ protected aminomethylpyrrolidine **3d**. We found effective extraction conditions to remove *p*-toluidine and most other organic impurities using THF/water and $MgCl_2$. The reported process requires no chromatographic purification and affords compound **1** as a sterile crystalline monohydrate in satisfactory yield. This process is practical and efficient. In fact, this process is now under pilot-scaled study to make compound **1** for clinical studies.

Acknowledgment

We acknowledge the useful help from Di-Ao Pharmaceutical Company for its financial support. This work was also financially supported by the National Natural Science Foundation of China (Nos.: 20372051, 20471038), Program for New Century Excellent Talents in University, Specialized Research Fund for the Doctoral Program of Higher Education, and Scientific Fund of Sichuan Province for Outstanding Young Scientist.

Received for review March 31, 2006.

OP0600714

IPR2020-00770
United Therapeutics EX2007
Page 3322 of 7335

United Therapeutics
CORPORATION

PATENT OWNER
UNITED THERAPEUTICS CORPORATION

IPR2016-00006

U.S. Patent No. 8,497,393

November 29, 2016

UT Ex. 2061
SteadyMed v. United Therapeutics
IPR2016-00006

IPR2020-00770
United Therapeutics EX2007
Page 3323 of 7335

Petitioner Bears the Burden of Proving Invalidity

- "In an inter partes review, the burden of persuasion is on the petitioner to prove 'unpatentability by a preponderance of the evidence,' 35 U.S.C. § 316(e), and that burden never shifts to the patentee."
  - *In re Magnum Oil Tools International, Inc.* (Fed. Cir. 2016), citing *Dynamic Drinkware*, 800 F.3d at 1378; Paper No. 48.
- "[T]he petitioner continues to bear the burden of proving unpatentability after institution, and must do so by a preponderance of the evidence at trial."
  - *In re Magnum Oil Tools International, Inc.* (Fed. Cir. 2016); Paper No. 48.
- "[T]he Board has an obligation to assess the question anew after trial based on the totality of the record."
  - *Id.*

IPR2020-00770
United Therapeutics EX2007
Page 3324 of 7335

Prior Art at Issue

- The only prior art treprostinil examples in this IPR are (a) the single example in Moriarty 2004 of treprostinil acid (Ex. 1004, p. 13) and (b) the single example in Phares WO 2005/007081 of diethanolamine salt of treprostinil, form B (Ex. 1005, pp. 87-88).

- Kawakami and Ege do not disclose treprostinil or any prostacyclin derivative and do not disclose how to purify such compounds specifically.

- To the extent Petitioner's evidence shifts burden of production, Patent Owner need only present sufficient evidence to rebut that evidence relied upon by Petitioner.

IPR2020-00770
United Therapeutics EX2007
Page 3325 of 7335

Claim Construction in an IPR Analysis

- "While it is true that, as a general rule, the words of a patent claim are to be given their plain, ordinary and accustomed meaning to one of ordinary skill in the relevant art, *Toro Co. v. White Consol. Indus., Inc.*, 199 F.3d 1295, 1299 (Fed. Cir. 1999), *a court must nevertheless examine the remaining intrinsic evidence to determine whether the patentee has set forth an explicit definition of a term contrary to its ordinary meaning, has disclaimed subject matter, or has otherwise limited the scope of the claims*."
  - *Day Intern., Inc. v. Reeves Brothers, Inc.*, 260 F.3d 1343, 1349 (Fed. Cir. 2001) (emphasis added) (PO Resp. at pp. 13-14).
- The Federal Circuit in *SafeTCare Mfg* incorporated limitations into claim construction where the specification repeatedly indicated that the invention operated by "pushing (as opposed to pulling) forces," and then characterized the "pushing forces" as "an important feature of the present invention."
  - *SafeTCare Mfg., Inc. v.Tele-Made, Inc.*, 497 F.3d 1262, 1269-70 (Fed. Cir. 2007)(PO Resp. at p. 14).

IPR2020-00770
United Therapeutics EX2007
Page 3326 of 7335

Proper Claim Construction Requires Consideration of Impurities Present In The Product

Example 6

Comparison of the Former Process and a Working Example of the Process According to the Present Invention

-continued

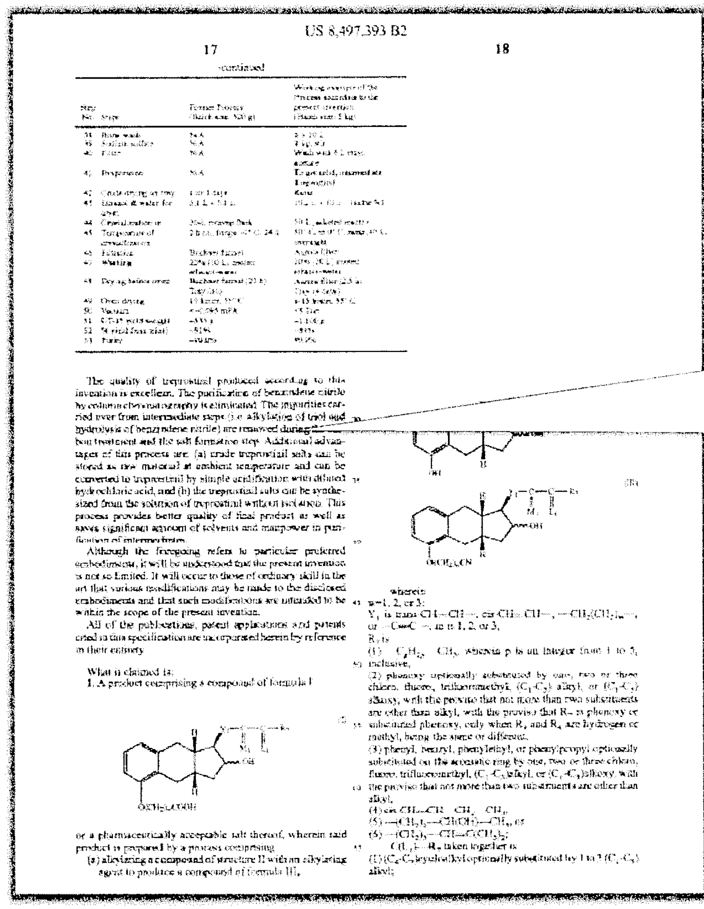
Step No.	Steps	Former Process (Batch size: 500 g)	Working example of the Process according to the present invention (Batch size: 5 kg)
38	Brine wash	N/A	
39	Sodium sulfate	N/A	
40	Filter	N/A	
41	Evaporation	N/A	
42	Crude drying on tray	1 or 3 days	
43	Ethanol & water for cryst.	5.1 L + 5.1 L	
44	Crystallization in	20-L rotavap f	
45	Temperature of crystallization	2 h r.t., fridge	
46	Filtration	Buchner funnel	Auro
47	Washing	20% (10 L) cooled ethanol-water	20% ethan
48	Drying before oven	Buchner funnel (20 h) Tray (no)	Auro Tray
49	Oven drying	15 hours, 55° C.	6-15 h
50	Vacuum	<–0.095 mPA	<5 Tor
51	UT-15 yield weight	~535 g	~1,100
52	% yield from triol)	~91%	~89%
53	Purity	~99.0%	99.9%

Example 6 in the '393 Patent specification indicates the purity of a working example of the invention is 99.9% whereas purity of former Moriarty product was ~99.0%

- Ex. 1001, 17:step 53. (PO Resp. at p. 16)

IPR2020-00770
United Therapeutics EX2007
Page 3327 of 7335

Proper Claim Construction Requires Consideration of Impurities Present In The Product


US 8,497,393 B2

17 18

-continued

- ’393 patent specification further identifies differences in impurities

“impurities carried over from intermediate steps (i.e., alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and salt formation step”

- Ex. 1001, 17:29-32.

Proper Claim Construction Requires Consideration of Impurities Present In The Product

- Prosecution history clarified that impurity profiles were important to the claimed invention
  - "[e]ach of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 . . . is physically different from treprostinil prepared according to the process of 'Moriarty' due to *differences in their impurity profiles*."
    - Ex. 1002 at 344. (emphasis added) (PO Resp. at p. 16)
  - UTC thereafter filed the Walsh Declaration, which demonstrated that the claimed product had a different *impurity profile and higher purity* than a representative batch of Moriarty's product.
    - Ex. 1002 at 347-349. (PO Resp. at p. 16)
  - Claims allowed within eight days of the submission of Walsh's Declaration demonstrating differences in impurities.
    - *Id.* at 354.

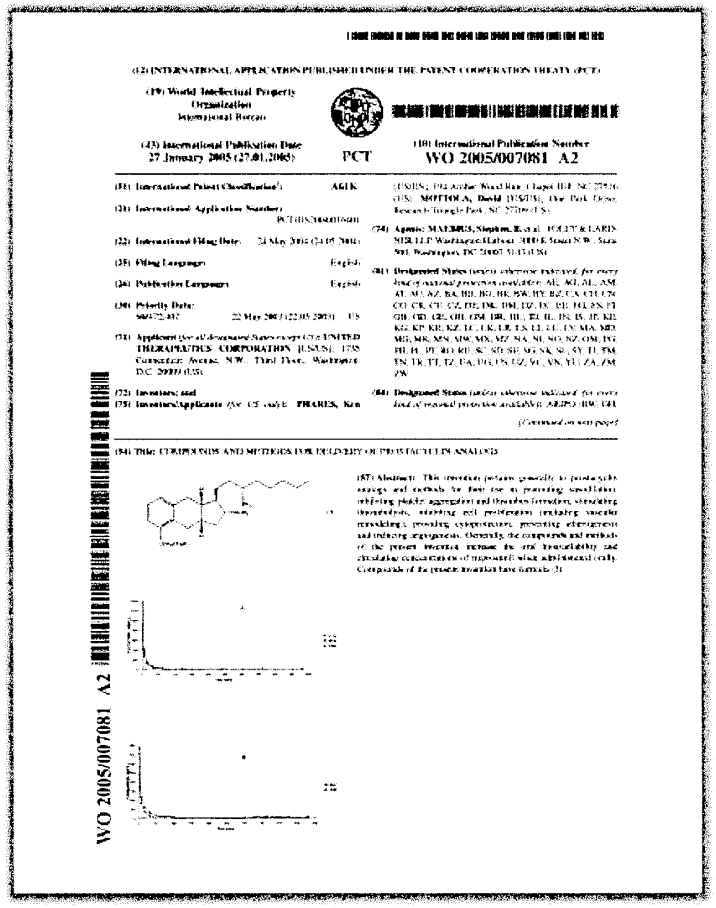
IPR2020-00770
United Therapeutics EX2007
Page 3329 of 7335

Proper Claim Construction Requires Consideration of Impurities Present In The Product

- The '393 patent specifically distinguishes the purification limitation [eliminating purification after step (a) as required in claims 8 & 16] over the prior art. Ex. 1001, Example 6. Moriarty expressly discloses that the compound of formula (VI) from step (a) is purified.
  - Ex. 2020 at ¶104; PO Resp. at p. 32.
- No evidence from Petitioner of the impact of eliminating column purification step from Moriarty 2004 publication; the only direct comparative evidence in the record for claims 8 and 16 is Ex. 6 in '393 patent.
  - Ex. 2020 at ¶104; PO Resp. at p. 32.

IPR2020-00770
United Therapeutics EX2007
Page 3330 of 7335

Phares Does Not Anticipate Any '393 Patent Claim



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau

(43) International Publication Date: 27 January 2005 (27.01.2005)

PCT

(10) International Publication Number: WO 2005/007081 A2

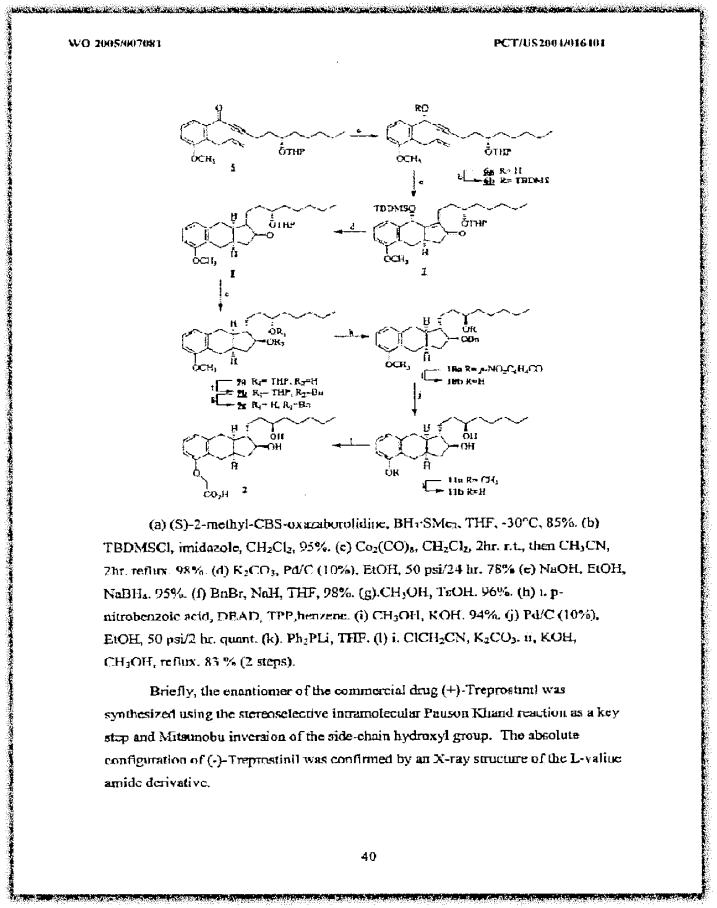
(54) Title: CEREBROSIDS AND METHODS FOR DELIVERY OF PROSTACYCLIN ANALOGS

WO 2005/007081 A2

- Phares was disclosed on the face of the '393 patent
- Phares fails to disclose any detailed synthesis of treprostinil
- Phares fails to disclose any impurity or impurity profile for treprostinil or treprostinil diethanolamine
- Phares fails to disclose any purity level for treprostinil diethanolamine

IPR2020-00770
United Therapeutics EX2007
Page 3331 of 7335

Synthesis Disclosed In Phares Is Not For Treprostinil



WO 2005/007081 PCT/US2004/016401

(a) (S)-2-methyl-CBS-oxazaborolidine, BH_3·SMe$_2$, THF, -30°C, 85%. (b) TBDMSCl, imidazole, CH_2Cl_2, 95%. (c) $Co_2(CO)_8$, CH_2Cl_2, 2hr. r.t., then CH_3CN, 2hr. reflux. 98%. (d) K_2CO_3, Pd/C (10%), EtOH, 50 psi/24 hr. 78% (e) NaOH, EtOH, $NaBH_4$, 95%. (f) BnBr, NaH, THF, 98%. (g) CH_3OH, TsOH. 96%. (h) i. p-nitrobenzoic acid, DBAD, TPP,benzene. (i) CH_3OH, KOH. 94%. (j) Pd/C (10%), EtOH, 50 psi/2 hr. quant. (k). Ph_2PLi, THF. (l) i. $ClCH_2CN$, K_2CO_3. ii, KOH, CH_3OH, reflux. 83 % (2 steps).

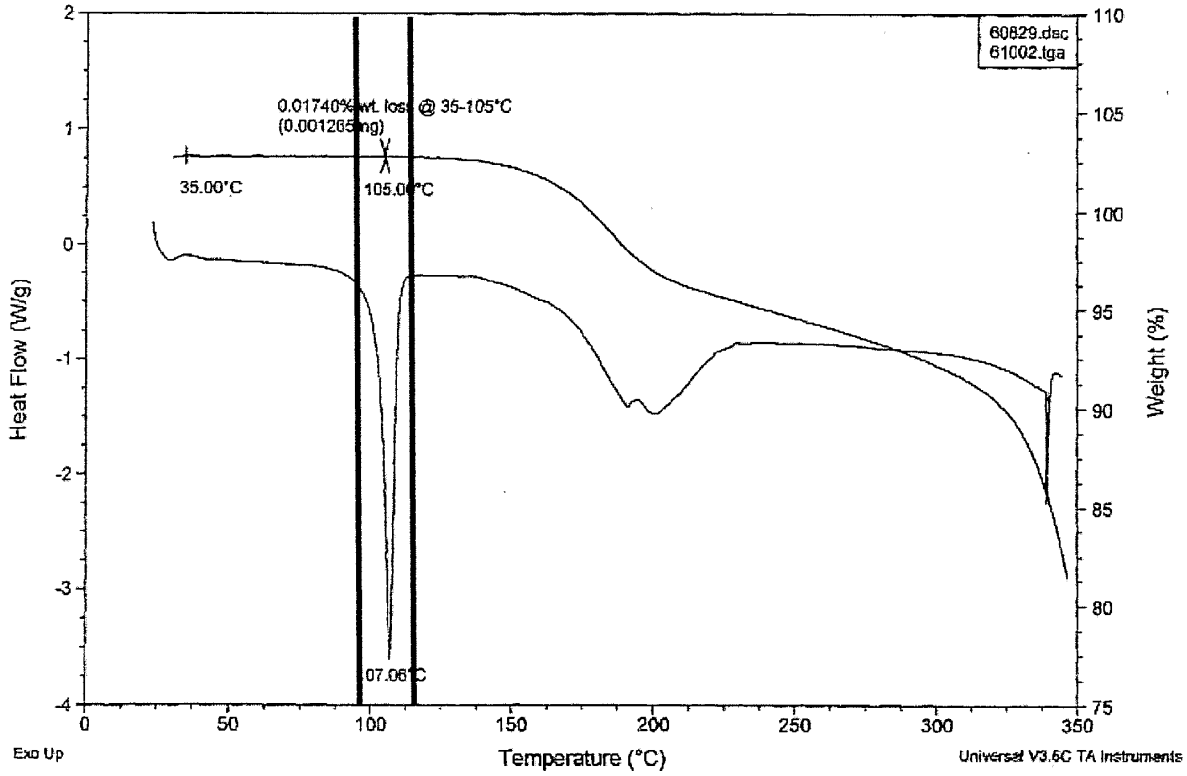
Briefly, the enantiomer of the commercial drug (+)-Treprostinil was synthesized using the stereoselective intramolecular Pauson Khand reaction as a key step and Mitsunobu inversion of the side-chain hydroxyl group. The absolute configuration of (-)-Treprostinil was confirmed by an X-ray structure of the L-valine amide derivative.

40

- Dr. Williams confirmed the synthesis in Phares is for the enantiomer of treprostinil, a different product.
  - Ex. 2059, 264:13-265:18; 265:20-23; Ex. 2020 ¶79
- Phares fails to disclose the source of treprostinil used in single step example making treprostinil diethanolamine.
  - Ex. 1005, p. 24; Ex. 2020, ¶79.
- Only reference to treprostinil synthesis in Phares is to early syntheses resulting in impure substances.
  - Ex. 1005, p. 9; Ex. 2020, ¶78.

IPR2020-00770
United Therapeutics EX2007
Page 3332 of 7335

Phares Fails to Disclose Purity of Treprostinil Diethanolamine



- Dr. Williams confirmed broad approximate 10 degree melting point range from Phares indicated a less pure substance. Ex. 2020, ¶76.

IPR2020-00770
United Therapeutics EX2007
Page 3333 of 7335

Phares Form B Diethanolamine Salt Example Is Not the Same as the '393 Patent Product

Williams' Declaration	Rogers' Declaration
Melting point range is "broad" (¶ 76)	Melting Point range is "narrow" (¶ 87)
Cites to Marti reference (Ex. 2031) (¶ 76)	*NO SUPPORT*
Conclusion: Cannot determine purity from melting point range of Phares (¶ 76)	Conclusion: Phares at least as pure as '393 (¶ 88)

IPR2020-00770
United Therapeutics EX2007
Page 3334 of 7335

Phares Does Not Anticipate Any Claim of the '393 Patent

- Petitioner's expert Dr. Rogers acknowledges Phares form B has a different melting point range than the '393 patent products and "[a]ny difference in their measured melting point, Ts, is due to differing levels of impurities."
  - Ex. 1022, ¶72 and 82
- Phares form B sample made for polymorph screen by a very different process that converts to form B from form A, it is not clear where the specific batch of form B used for analysis came from, and is not a large scale batch.
  - Ex. 2020, ¶73; PO Resp., p. 25.
- Petitioner has failed to show the Phares product is the same as the products disclosed in the '393 patent.
  - PO Resp. at pp. 22-26.

IPR2020-00770
United Therapeutics EX2007
Page 3335 of 7335

Phares and Moriarty Do Not Render the '393 Claims Obvious

JOC*Article*

The Intramolecular Asymmetric Pauson–Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil)

Robert M. Moriarty,*,† Neena Rao,† Livia A. Enache,† Murugaiah S. Reddy,† Hitesh Batra,† Laing Gao,† Raju A. Penmasta,† James P. Staszewski,† Sudersan M. Tuladhar,† Om Prakash,† David Crich,‡ Anna Hirtopeanu,§ and Richard Gilardi||

Department of Chemistry (MC 111), University of Illinois at Chicago, Chicago, Illinois 60607, United Therapeutics Chicago, Illinois 60612, and Institute of Organic Chemistry, C.D. Nenitzescu, and Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, DC 20375

Received June 5, 2003

A general and novel solution to the synthesis of biologically important stable analogues of prostacyclin PGI$_2$, namely benzindene prostacyclins, has been achieved via the stereoselective intramolecular Pauson–Khand cyclization (PKC). This work illustrates for the first time the synthetic utility and reliability of the asymmetric PKC route for synthesis and subsequent manufacture of a complex drug substance on a multikilogram scale. The synthetic route surmounts issues of individual step stereoselectivity and scalability. The key step in the synthesis involves efficient stereoselection effected in the PKC of a benzenetriyne under the agency of the benzyl-OTBDMS group, which serves as a temporary stereodirecting group that is subsequently removed via benzylic hydrogenolysis concomitantly with the catalytic hydrogenation of the enyne PKC product. Thus the benzylic chiral center dictates the subsequent stereochemistry of the stereogenic centers at three carbon atoms (C_9, C_{9a}, and C_1).

Prostacyclin (PGI$_2$) (1) is an important physiological prostanoid and occurs as a major metabolic product from arachidonic acid throughout the vasculature and is produced in the endothelium and in smooth muscles.[1,2] PGI$_2$ is the most potent endogenous vasodilator in both systemic and pulmonary circulation. It exerts effects on vascular smooth muscle cells and inhibits both platelet aggregation and adhesion.[3,4] These biological activities are relevant to a broad range of cardiovascular diseases including congestive heart failure, peripheral vascular disease, myocardial ischemia, and pulmonary hypertension.[5–7] Use of PGI$_2$ as a drug for coronary disease has not been helpful because of the fleeting $t_{1/2}$ of 3 min of this compound (~10 min at pH 7.6 at 25 °C). The ability to inhibit platelet aggregation in plasma samples is lost within 5 min.[8] Application of PGI$_2$ to disease therapy presents a typical drug delivery challenge that is dealt with either mechanically by an appropriate pharmaceutical device or chemically by synthesizing a hydrolytically stable analogue that retains the biological activity. The first option currently is used for the treatment of pulmonary hypertension in which an aqueous solution of PGI$_2$ sodium salt (chemical name, epoprostenol; trade name Flolan) is pumped continuously and intravenously through a catheter permanently placed in the patient's chest via a portable external pump. PGI$_2$ is light sensitive and must be stored between 15 and 25 °C, and the formulation in a buffer solution must be prepared by the patient on a daily basis.[9] The PGI$_2$ is thereby introduced directly

* To whom correspondence should be addressed.
† Department of Chemistry (MC 111), University of Illinois at Chicago, 845 W. Taylor St., Room 4500.
‡ United Therapeutics.
§ NRC/ONR Graduate Fellow.
|| Laboratory for the Structure of Organic Chemistry, C.D. Nenitzescu.
⊥ Naval Research Laboratory.

- Moriarty was disclosed on the face of the '393 patent
- Moriarty fails to disclose steps (c) or (d) from the '393 patent in the synthesis of treprostinil and does not disclose treprostinil diethanolamine
- Moriarty fails to disclose any impurity or impurity profile for treprostinil
- Purity level disclosed in Moriarty cannot be compared to '393 Patent purity

IPR2020-00770
United Therapeutics EX2007
Page 3336 of 7335

Winkler Improperly Compared Purity Levels

- "When purity is determined by comparison of a sample to a reference standard *such as assay purity, one cannot directly compare the purity values of two samples in any meaningful way unless each value was achieved by comparison to the same reference standard*. Neither the Walsh Declaration nor Moriarty identifies a specific reference standard." (emphasis supplied)
  - Ex. 2034, pp. 28-29; Ex. 2035, pp. 5-8; Ex. 2020, ¶ 88; PO Resp., pp. 2, 29

- Moriarty 2004 purity of "99.7%" cannot be compared to Walsh, '393 data or any FDA data in the record.
  - Ex. 1004, p. 13

IPR2020-00770
United Therapeutics EX2007
Page 3337 of 7335

Winkler Improperly Compared Purity Levels

- Winkler mistakenly thought that an "assay" purity in the '393 patent represented HPLC error rate rather than a *relative* purity level compared to a reference standard, which gave rise to his further misunderstanding about the Walsh Declaration, the '393 specification, & Moriarty purity measurements.
  - Ex. 1001, col. 13, l. 2; Ex. 2020 ¶¶ 89-93; PO Resp. at pp. 29-30
- Winkler later acknowledged that assay purity determinations over 100% and FDA purity measurement limits are valid; however, the Institution Decision was based on Winkler's erroneous initial purity conclusions.
  - PO Response at 3; Ex. 2051 at 64:7-9; Paper No. 12 at pp. 8, 17, 19, 48

IPR2020-00770
United Therapeutics EX2007
Page 3338 of 7335

Winkler Improperly Compared Purity Levels

- Dr. Wiliams: "the *level of detection for measuring impurities in these treprostinil samples was somewhere between 0 and 0.05%,* not something in excess of 0.4% as Dr. Winkler erroneously concludes" (emphasis supplied).
  - Ex. 2020, at ¶92; PO Resp. at p. 3
- Dr. Ruffolo: the Certificates of Analysis purity data presented in the Walsh, Ruffolo and Williams Dec.'s is the same data required by FDA in its purity specification for treprostinil *and relied upon by UT to comply with FDA's requirements* .
  - Ex. 2022 at ¶32; Ex. 2020 at ¶94; PO Resp. at pp. 3-4

IPR2020-00770
United Therapeutics EX2007
Page 3339 of 7335

Petitioner Bears the Burden of Proving Invalidity

- Institution Decision was based on Winkler's erroneous initial purity conclusions (Paper No. 12 at pp. 8, 17, 19, & 48)
- '393 comparative data, FDA data submitted in this IPR & Walsh's Declaration should all be credited over Winkler's debunked Declaration/misunderstanding of purity
- When Winkler's mistaken testimony about purity levels is removed, Petitioner has not carried its threshold burden

IPR2020-00770
United Therapeutics EX2007
Page 3340 of 7335

Significant Differences Exist Between Batches Made by the '393 Patent and Moriarty Processes

Moriarty Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	0.9545

'393 Patent Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0004	0.0004	0.0455	0.0643	0.0488	0	0.1208	0.005	0.2944

- Dr. Williams analyzed over 170 batches of treprostinil and treprostinil diethanolamine made by either the Moriarty process or the '393 patent process to analyze impurities and total related substances
  - Ex. 2020, ¶¶94-98

IPR2020-00770
United Therapeutics EX2007
Page 3341 of 7335

Significant Differences Exist Between Batches Made by the '393 Patent and Moriarty Processes

Moriarty Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	0.9545
'393 Patent Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0004	0.0004	0.0455	0.0643	0.0488	0	0.1208	0.005	0.2944

- Greater than 100 fold reduction in 1AU90 and 2AU90 impurities
  - Ex. 2020, ¶¶94-98

IPR2020-00770
United Therapeutics EX2007
Page 3342 of 7335

Significant Differences Exist Between Batches Made by the '393 Patent and Moriarty Processes

Moriarty Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	0.9545

'393 Patent Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0004	0.0004	0.0455	0.0643	0.0488	0	0.1208	0.005	0.2944

- Twenty fold reduction in methyl ester impurity
  - Ex. 2020, ¶¶94-98

IPR2020-00770
United Therapeutics EX2007
Page 3343 of 7335

Significant Differences Exist Between Batches Made by the '393 Patent and Moriarty Processes

Moriarty Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	0.9545

'393 Patent Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0004	0.0004	0.0455	0.0643	0.0488	0	0.1208	0.005	0.2944

- Significant reductions in 750W93, 751W93, and 3AU90 impurities
- 97W86 impurity eliminated in '393 patent process
  - Ex. 2020, ¶¶94-98

IPR2020-00770
United Therapeutics EX2007
Page 3344 of 7335

Significant Differences Exist Between Batches Made by the '393 Patent and Moriarty Processes

Moriarty Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	0.9545
'393 Patent Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0004	0.0004	0.0455	0.0643	0.0488	0	0.1208	0.005	0.2944

- Overall reduction in impurities by approximately 0.7%
  - Ex. 2020, ¶¶94-98

IPR2020-00770
United Therapeutics EX2007
Page 3345 of 7335

Significant Differences Exist Between Batches Made by the '393 Patent and Moriarty Processes

Moriarty Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0473	0.0407	0.2545	0.1646	0.1025	0.0405	0.0889	0.1028	0.9545
'393 Patent Process Impurities (Average Percent Detected)								
1AU90	2AU90	3AU90	750W93	751W93	97W86	ethyl ester	methyl ester	Total Related Substance
0.0004	0.0004	0.0455	0.0643	0.0488	0	0.1208	0.005	0.2944

- Ethyl ester actually increased in '393 patent demonstrating another difference between the '393 and Moriarty batches
  - Ex. 2020, ¶¶94-98

IPR2020-00770
United Therapeutics EX2007
Page 3346 of 7335

'393 Product Has Higher Ethyl Ester Impurities Than Moriarty

- Dr. Williams also found that ethyl ester unexpectedly increased in the '393 product of the batches he reviewed compared to the Moriarty batches he reviewed
  - Ex. 2020, ¶¶94-98; PO Resp. at p. 10
- This point is not challenged by Petitioner
- '393 product is different regardless of claim construction due to higher impurity level of ethyl ester compared to Moriarty

IPR2020-00770
United Therapeutics EX2007
Page 3347 of 7335

Petitioner Challenges Averages But Ignores Other Evidence Supporting Williams Declaration

- "*Looking past the average data*, it is also worth noting that, out of all the batches of treprostinil product made by the '393 patent process which I reviewed, 1AU90 was only detected in a single batch (01A07001) and 2AU90 was also only detected in a single batch (01A07003), and both impurities were only detected at a level of 0.05% or less. Furthermore, batches 01A07001 and 01A07003 were both identified as 'optimization batches' (as distinguished from commercial batches)." (emphasis supplied).
  - Ex. 2020 at ¶ 97, PO Resp. at p. 4

- Dr. Williams relied on these *individual impurity values and trends*, not just calculated averages to support his conclusion that the products are different.

IPR2020-00770
United Therapeutics EX2007
Page 3348 of 7335

Petitioner Challenges Averages But Ignores Other Evidence Supporting Williams Declaration

- "the averages presented in the Process Optimization Report still show significant differences between '393 treprostinil products and the Moriarty treprostinil products. Specifically, Table 2 of the Process Optimization Report shows that on average 97W86 was detectable *in these 96 batches, and that these 96 batches contained higher average levels of 3AU90, 750W93, 751W93, and total impurities as compared to the averages for the '393 treprostinil product*. Ex. 2005 at 7; Appendix B. " (emphasis supplied) .
  - UT Ex. 2005, at 7; Ex. 2020 at footnote 1

- These 96 batches relied upon by Williams were *not used in the other average calculations criticized by Petitioner for including development batches*.

IPR2020-00770
United Therapeutics EX2007
Page 3349 of 7335

Petitioner Objects To Admissibility Of Certain Moriarty Batches But Filed No Motion To Exclude Them

- Petitioner's Reply objects to relevance of certain Moriarty batches, but yet Petitioner filed no Motion to Exclude as to this evidence.
  - Paper No. 52, p. 7.
- However, Petitioner also objected to relevance of the Moriarty batches in its evidentiary objections, in response to which Patent Owner supplemented the record with authenticating Declarations.
  - Ex. 2052; Paper No. 43, p. 11.
- Petitioner cannot maintain its position on lack of relevance after objecting and then failing to move to exclude, depriving Patent Owner of its right to rely on timely served supplemental evidence.

IPR2020-00770
United Therapeutics EX2007
Page 3350 of 7335

[intentionally left blank]

IPR2020-00770
United Therapeutics EX2007
Page 3351 of 7335

[intentionally left blank]

IPR2020-00770
United Therapeutics EX2007
Page 3352 of 7335

Additional Comparative Data in Dr. Williams Declaration Stands Unchallenged By Petitioner and Confirms Dr. Williams Conclusions

Table 2. RELEASE TESTING DATA RANGE FOR UT-15 (TREPROSTINIL) API
SUMMARY 2000 TO 2006 FOR CHICAGO SITE
BATCH SIZE 350 GRAMS TO 1 KILOGRAM
NUMBER OF BATCHES: 96

TEST	SPECIFICATION	MINIMUM	MAXIMUM	AVERAGE
Specific Rotation	Not less than +42.0° and not more than +49.0° at 589 nm and 25 °C, volatiles-free basis	+43.3°	+47.7°	+45.8°
Residue on Ignition	Not more than 0.2%, w/w	0.0 %, w/w	0.2%, w/w	0.0%, w/w
Water (Karl Fischer)	Not more than 2.0%, w/w	0.1 %, w/w	1.8%, w/w	0.4%, w/w
Residual Solvents by Gas Chromatography				
▪ Ethyl Acetate	Not more than 0.5%, w/w	ND	<0.1 %	<0.1%
▪ Ethanol	Not more than 0.5%, w/w	0.0 %	0.2 %	0.1%
▪ Acetic Acid	Not more than 0.5%, w/w	ND	0.2 %	<0.1%
▪ Methanol	Not more than 0.1%, w/w	ND	<0.1 %	<0.1%
Melting Range	Not less than 120.0 °C and not more than 126.0 °C	120.1 °C	125.2 °C	Low:121.6 °C High:122.7 °C
Heavy Metals	Not more than 0.002%	Not more than 0.002%	Not more than 0.002%	Not more than 0.002%
Assay (HPLC)	Not less than 97.0% and not more than 101.0%, w/w, on the volatiles-free basis	98.9 % w/w	100.3 % w/w	99.5 %, w/w
Impurities				
▪ 1AU90	Not more than 0.4%	ND	0.2 %	<0.05 %
▪ 2AU90	Not more than 0.1%	ND	<0.05 %	<0.05 %
▪ 97W86	Not more than 0.2%	ND	0.07 %	<0.05 %
▪ 3AU90	Not more than 1.0%	0.09 %	0.4 %	0.2 %
▪ UT-15 methyl ester	Not more than 0.2%	ND	0.1%	<0.05 %
▪ 98W86		ND	<0.05 %	<0.05 %
▪ UT-15 ethyl ester	Not more than 0.5%	<0.05 %	0.4 %	0.1 %
▪ 750W93	Not more than 0.5%	<0.05 %	0.2 %	0.1 %
▪ 751W93	Not more than 0.3%	<0.05 %	0.3%	0.07 %
▪ Unidentified	Not more than 0.1% AUC each	ND	0.6% (Total)	0.05 %
Total Related Substances	Not more than 3.0%	0.3 %	0.8 %	0.5 %

w/w = weight/weight; ND = not detected; AUC = area under the curve.

- Ex. 2005 at 7; Ex. 2020 at FN 1.

7

UT Ex. 2005
SteadyMed v. United Therapeutics
IPR2016-00006

IPR2020-00770
United Therapeutics EX2007
Page 3353 of 7335

Additional Comparative Data in Dr. Williams Declaration Stands Unchallenged By Petitioner and Confirms Dr. Williams Conclusions

- The averages of impurities presented in the Process Optimization Report analyzing 96 Moriarty batches also show significant differences between '393 treprostinil products and the Moriarty treprostinil products.
  - Ex. 2005 at 7; Ex. 2020 at FN 1.

- These 96 batches contained higher average levels of 3AU90, 750W93, 751W93, and total impurities as compared to the averages for the '393 treprostinil product and lower overall average impurities.
  - Ex. 2005 at 7; Ex. 2020 at FN 1.

IPR2020-00770
United Therapeutics EX2007
Page 3354 of 7335

FDA Expressed a Long-Felt Need For Each Individual Known Impurity To Be Minimized

- Each of the known impurities are "sources of potential adverse toxicities to patients. Impurities, therefore, can only add to the risk assessments, which are often unknown, made by regulatory agencies in the evaluation of new drug products."
  - Ex. 2040 at 3-4 and 5-8; Ex. 2022 at ¶ 36; PO Resp. at p. 7.
- Even trace impurities can pose serious health risks.
  - Ex. 2022 at ¶ 40; PO Resp. at p. 12.
- To FDA, a product is different if it presents a reduced risk profile due to reduced amounts of individual known impurities, even if there is currently no known adverse effect in patients attributable to those impurities.
  - Ex. 2022 at ¶ 36; PO Resp. at pp. 7-8.

IPR2020-00770
United Therapeutics EX2007
Page 3355 of 7335

The '393 Patent Met the Long-Felt Need of Improved Purity

- Patent Owner requested and FDA approved a higher purity specification to reflect the treprostinil product resulting from Patent Owner's switch to the '393 patent steps.
  - Ex. 2006, 2003; PO Resp. at p. 12.

- "[W]hile FDA approval is not determinative of nonobviousness, it can be relevant in evaluating the objective indicia of nonobviousness."
  - *Knoll Pharm. Co., Inc. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); PO Resp. at p. 48.

IPR2020-00770
United Therapeutics EX2007
Page 3356 of 7335

The '393 Patent Met the Long-Felt Need of Improved Purity

- FDA initially rejected UT's requested purity specification change, leading to resubmission with additional evidence.
  - Ex. 2006 at 1; Ex. 2022 at ¶ 66; PO Resp. at pp. 12 and 48.
- "any change in the synthesis or manufacture of the drug substance that may affect its impurity profile and/or the physical, chemical, or biological properties of a drug is considered a *major change*."
  - Ex. 2050 at 17. (emphasis added); Ex. 2022 at ¶72; PO Resp. at p. 12.
- "Because the FDA allowed the drug specification for purity to be changed to reflect the higher level of purity, from a lower level of 97% to 98%, around means of 99% to 100%, respectfully, resulting from the '393 patent process, it is clear that the FDA considered this to represent a major/significant change."
  - Ex. 2022 at ¶72; PO Resp. at p. 12.

IPR2020-00770
United Therapeutics EX2007
Page 3357 of 7335

[intentionally left blank]

IPR2020-00770
United Therapeutics EX2007
Page 3358 of 7335

[intentionally left blank]

IPR2020-00770
United Therapeutics EX2007
Page 3359 of 7335

FDA's Drug Purity Specifications Are Rigorously Analyzed & Commercially Important

- Purity data must be prepared according to detailed FDA guidelines.
  - Ex. 2022, ¶53, citing: Ex. 2006 p. 6, Ex. 2044 pp. 34-35, and Ex. 2035 pp. 8-11
- UT's data had to meet these requirements.
  - Ex. 2022 ¶ 57
- If a Certificate of Analysis for a batch does not meet the FDA's purity specification in any aspect, it cannot be sold for use by patients.
  - Ex. 2022 ¶ 32; PO Resp. p. 12

IPR2020-00770
United Therapeutics EX2007
Page 3360 of 7335

'393 Patent Product Is Structurally Different Regardless Of Batch-To-Batch Variability In Starting Material

- Petitioner has not established that any specific batch of Moriarty treprostinil is not physically changed by performing step (c), and all the evidence suggests that it is.
  - PO Resp. at p. 12
- Petitioner presents no test data of its own.
- The FDA agreed that the evidence presented by the Patent Owner in this IPR warranted a change in purity specification.
  - PO Resp. at p. 12; Ex. 2006 at 4-6; Ex. 2022 at ¶¶66-72.

IPR2020-00770
United Therapeutics EX2007
Page 3361 of 7335

The '393 Patent Product Is Structurally Different Regardless Of Batch-To-Batch Variability In Starting Material

- "The chemical manufacturing steps have not changed during the transfer to [supplier A] and [supplier B] from the process used by UT in Chicago to prepare benzindene triol."
  - Ex. 2006 at 3.
- "There is a release specification for benzindene triol that must be achieved for each lot of benzindene triol before it is released for use by UT to prepare treprostinil. This is the same specification that was used by United Therapeutics in our Chicago facility."
  - *Id.*
- "*In all lots [of benzindene triol from suppliers A, B, C, and D], the total unidentified impurity level (%AUC) decreased from triol [step (a)] to UT-15C intermediate [step (c)].*"
  - *Id.*

IPR2020-00770
United Therapeutics EX2007
Page 3362 of 7335

Winkler Fundamentally Misunderstood Certain Purity Measurements

- The level of detection for measuring impurities in these treprostinil samples was somewhere between 0 and 0.05%, not something in excess of 0.4% as Dr. Winkler erroneously concluded.
  - Ex. 2020 at ¶92; PO Resp. at p. 3.
- The Certificates of Analysis purity data presented in the declarations of Drs. Walsh and Williams is the same data required by FDA in its purity specification for treprostinil and relied upon by UT to comply with FDA's requirements
  - Ex. 2022 at ¶32; Ex. 2020 at ¶94; PO Resp. at pp. 3-4.
- Walsh's Declaration should be credited over Winkler's debunked Declaration/misunderstanding of purity
  - Petitioner did not depose Dr. Walsh, a further reason to credit Dr. Walsh's Declaration over Dr. Winkler

IPR2020-00770
United Therapeutics EX2007
Page 3363 of 7335

Petitioner's Expert Dr. Winkler Fundamentally Misunderstood Certain Purity Measurements

- Dr. Winkler mistakenly thought that an "assay" purity in the '393 patent represented HPLC error rate rather than a *relative* purity level compared to a reference standard, which gave rise to his further misunderstanding about the Walsh Declaration, the '393 specification, & Moriarty purity measurements.
  - Ex. 2020 at ¶¶ 89-93; PO Resp. at pp. 29-30.
- Winkler later acknowledged that assay purity determinations over 100% and FDA purity measurement limits are valid, however, the Institution Decision was based on Dr. Winkler's erroneous initial purity conclusions.
  - PO Response at 3; see also Ex. 2051 at 64:7-9; Paper No. 12 at pp. 8, 17, 19, & 48.

IPR2020-00770
United Therapeutics EX2007
Page 3364 of 7335

Claims 6,10, 15, 21, & 22 Are Not Obvious

- Only instituted ground for claims 6, 10, 15, 21, and 22 is obviousness based on Moriarty, Phares, Kawakami & Ege
  - Institution Decision at 37.
- "the absence of a known or obvious process for making the claimed compounds overcomes any presumption that the compounds are obvious based on close relationships between their structures and those of prior art compounds."
  - *In re Hoeksema*, 399 F.2d 269, 274 (C.C.P.A. 1968); PO Response at p. 45.
- Petitioner fails to provide any motivation or reason a POSA would look to Kawakami or Ege to purify treprostinil or any related prostacyclin.
  - PO Resp. at pp. 34-44.

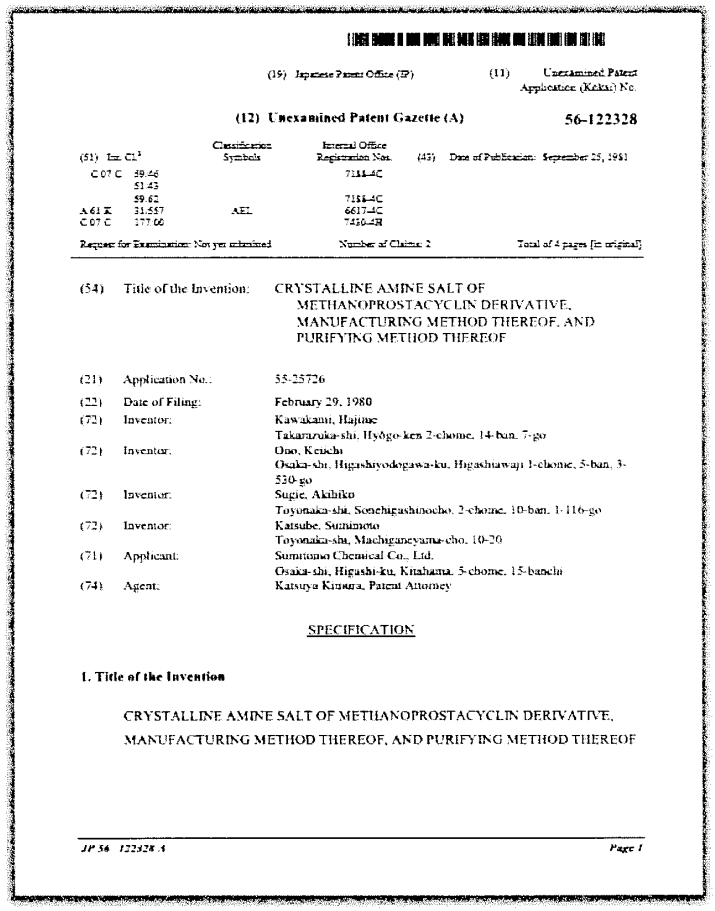
IPR2020-00770
United Therapeutics EX2007
Page 3365 of 7335

No Reasonable Expectation To Further Purify Moriarty By Combining Phares, Ege, & Kawakami

- Petitioner contradicts itself by asserting that Moriarty is already as pure as the '393 product, but yet a POSA would be motivated to apply further purification efforts to Moriarty based on Phares, Ege & Kawakami.
  - Compare Petitioner Reply at 4-6 and 19-20.
- Kawakami relates to use of a *different salt* to purify a *different impurity* present in a *much larger amount* (at least 22.8%) in a *different compound*
  - PO Response at pp. 39-44.
- A POSA would have no reason to turn to Kawakami or Ege given these differences.
  - Ex. 2020 at ¶ 106, PO Response at p. 37.

IPR2020-00770
United Therapeutics EX2007
Page 3366 of 7335

A POSA Would Not Turn to Kawakami



(19) Japanese Patent Office (JP) (11) Unexamined Patent Application (Kokai) No.

(12) Unexamined Patent Gazette (A) **56-122328**

(51) Int. Cl.³	Classification Symbols	Internal Office Registration Nos.	(43) Date of Publication: September 25, 1981
C 07 C 59/46		7184-4C	
51/43			
59/62		7158-4C	
A 61 K 31/557	AEL	6617-4C	
C 07 C 177/00		7430-4H	

Request for Examination: Not yet submitted Number of Claims: 2 Total of 4 pages [in original]

(54) Title of the Invention: CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN DERIVATIVE, MANUFACTURING METHOD THEREOF, AND PURIFYING METHOD THEREOF

(21) Application No.: 55-25726
(22) Date of Filing: February 29, 1980
(72) Inventor: Kawakami, Hajime
Takarazuka-shi, Hyōgo-ken 2-chome, 14-ban, 7-go
(72) Inventor: Ono, Keiichi
Osaka-shi, Higashiyodogawa-ku, Higashiawaji 1-chome, 5-ban, 3-530-go
(72) Inventor: Sugie, Akihiko
Toyonaka-shi, Somehigashinocho, 2-chome, 10-ban, 1-116-go
(72) Inventor: Katsube, Sunimoto
Toyonaka-shi, Machiganeyama-cho, 10-20
(71) Applicant: Sumitomo Chemical Co., Ltd.
Osaka-shi, Higashi-ku, Kitahama, 5-chome, 15-banchi
(74) Agent: Katsuya Kimura, Patent Attorney

SPECIFICATION

1. Title of the Invention

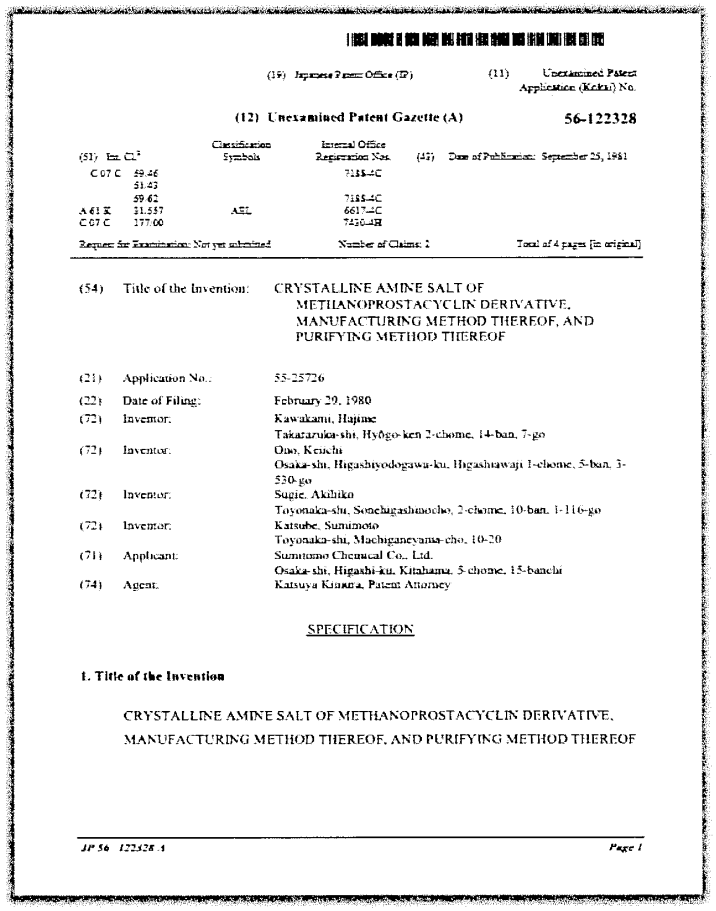
CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN DERIVATIVE, MANUFACTURING METHOD THEREOF, AND PURIFYING METHOD THEREOF

JP 56-122328 A Page 1

- Kawakami uses a different salt to remove a different sort of impurity from a different structure.
- a POSA would have no reason to combine the teachings of Kawakami with Moriarty and Phares in the particular manner of the asserted grounds in the Petition, or a reasonable expectation of success of achieving a more pure treprostinil product by such a combination.
  - Ex. 2020 ¶114; PO Resp. at p. 41.

IPR2020-00770
United Therapeutics EX2007
Page 3367 of 7335

Kawakami Teaches Away From Claim 15



(19) Japanese Patent Office (JP) (11) Unexamined Patent Application (Kokai) No.

(12) Unexamined Patent Gazette (A) 56-122328

(51) Int. Cl.³	Classification Symbols	Internal Office Registration Nos.	(43) Date of Publication: September 25, 1981
C 07 C 59/46		7188-4C	
51/43			
59/62		7188-4C	
A 61 K 31/557	AEL	6617-4C	
C 07 C 177/00		7430-4H	

Request for Examination: Not yet submitted Number of Claims: 2 Total of 4 pages [in original]

(54) Title of the Invention: CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN DERIVATIVE, MANUFACTURING METHOD THEREOF, AND PURIFYING METHOD THEREOF

(21) Application No.: 55-25726
(22) Date of Filing: February 29, 1980
(72) Inventor: Kawakami, Hajime
Takarazuka-shi, Hyôgo-ken 2-chome, 14-ban, 7-go
(72) Inventor: Ono, Kenichi
Osaka-shi, Higashiyodogawa-ku, Higashiawaji 1-chome, 5-ban, 3-520-go
(72) Inventor: Sugie, Akihiko
Toyonaka-shi, Sonehigashinocho, 2-chome, 10-ban, 1-116-go
(72) Inventor: Katsube, Sumimoto
Toyonaka-shi, Machiganeyama-cho, 10-20
(71) Applicant: Sumitomo Chemical Co., Ltd.
Osaka-shi, Higashi-ku, Kitahama, 5-chome, 15-banchi
(74) Agent: Katsuya Kimura, Patent Attorney

SPECIFICATION

1. Title of the Invention

CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN DERIVATIVE, MANUFACTURING METHOD THEREOF, AND PURIFYING METHOD THEREOF

JP 56 122328 A Page 1

- Petition selectively uses Kawakami only for teaching regenerating the acid after salt formation, while ignoring the fact that it suggests using a different salt than what is taught by Phares for the purpose of purifying a much less pure starting material.
  - PO Resp. at p. 41.

IPR2020-00770
United Therapeutics EX2007
Page 3368 of 7335

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner alleged that Williams did not know if 10 data points in his analysis were produced under the Moriarty process.
  - Petitioner's Reply pp. 2 & 6.
- Dr. Williams clarified on redirect that they "were made by the Moriarty process."
  - Ex. 2059, 254-256.

IPR2020-00770
United Therapeutics EX2007
Page 3369 of 7335

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also falsely alleged that the Moriarty batches were "cherry-picked" by including developmental batches with poor results.
  - Petitioner's Reply pp. 2 & 6.
- Dr. Williams clarified that he relied on Dr. Aristoff's selection of Moriarty batches from a separate case, *United Therapeutics v. Sandoz*.
  - Ex. 2059, 94:29-95:9.
- Those same batches were previously used to show how **good** the Moriarty batches were compared to a previous method.

IPR2020-00770
United Therapeutics EX2007
Page 3370 of 7335

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- *In United Therapeutics v. Sandoz, Inc.*, the Court ruled that the same Moriarty batches used by Dr. Williams had fewer amounts of impurities and a lower amount of total related substances over batches made by the prior art.
  - 2014 WL 4259153, C.A. Nos. 12–CV–01617, 13–CV–316 (D.N.J. August, 29, 2014).

- Dr. Williams also clarified that developmental batches for both the Moriarty and '393 patent process were used in his analysis.
  - Ex. 2059, 101:21-102:13.

IPR2020-00770
United Therapeutics EX2007
Page 3371 of 7335

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams "had no explanation for why he included 10 development batches… for his analysis of Moriarty batches, but only 5 development batches… for his analysis of '393-Patent batches".
  - Petitioner's Reply p. 7.

- But Dr. Williams actually testified that "these were all the batches we could find records for".
  - Ex. 2059, 94:25- 95:9

IPR2020-00770
United Therapeutics EX2007
Page 3372 of 7335

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Dr. Williams' testimony stated only that *calculation* was correct, not that it was a "a fair analysis" as claimed in Petitioner's reply.
  - Ex. 2059 p. 219; Petitioner's Reply p. 2

- Petitioner also alleged that Dr. Williams testimony suggested that Steadymed's calculation of 99.7% "should be relied upon." Dr. Williams merely confirmed that calculation was correct using Steadymed's selected numbers.
  - Petitioner's Reply pp. 2-3;

IPR2020-00770
United Therapeutics EX2007
Page 3373 of 7335

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams did not perform calculations on data in Appendices A and B of his declaration, "having relied solely on counsel's work". Dr. Williams actually testified that he "checked the calculation" performed by counsel.
    - Petitioner's Reply pp. 8-9; Ex. 2059, 102:12-20

IPR2020-00770
United Therapeutics EX2007
Page 3374 of 7335

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that the free acid is *less pure* than the diethanoleamine salt, and not more pure as UT represented to the FDA in Exhibit 2006. Dr. Williams could not provide an explanation for this discrepancy, which contradicts the Walsh Declaration. Dr. Williams stated that this wasn't something he considered in forming his opinion, and that he'd need more time to consider it; he simply wasn't able to provide an immediate explanation.
    - Petitioner's Reply p. 12; Ex. 2059, 199:6-18; Ex. 2059, 198:1-199:5, 199:19-21

IPR2020-00770
United Therapeutics EX2007
Page 3375 of 7335

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams concedes that the process in Phares for making treprostinil's (-)-enantiomer carries out the same alkylation step (a) and hydrolysis step (b) in the '393 Patent's claims, thus disclosing these steps for treprostinil. Dr. Williams stated on redirect that it was, in fact, a different step because in Phares you're using and producing the enantiomers, not the specified structures.
  - Petitioner's Reply p. 13; Ex. 2059, 264:15-265:23

IPR2020-00770
United Therapeutics EX2007
Page 3376 of 7335

Petitioner Grossly Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams, who is "not a polymorph expert," contends nevertheless that the melting point of two samples of the same polymorph (crystal form) cannot be compared to determine their relative purities. Dr. Williams' Declaration states that, when different solvents and crystallization conditions are used, you can't directly compare melting points to determine purities, not that melting points can't ever be compared to determine purity, and he reiterated this point at his deposition.
  - Petitioner's Reply p. 14; Ex. 2059, 158:17-18; 156:25-157:2; 159:6-160:12; Ex. 2020 ¶ 75

IPR2020-00770
United Therapeutics EX2007
Page 3377 of 7335

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that, as admitted by Dr. Williams, melting point is one of the most common ways to identify different polymorphs; but the cited portion of Dr. Williams' transcript actually says "Q. Well, why do you think they do that? Why do you think they append a melting point to each polymorph? [Objection] THE WITNESS:· Well, certainly, that's a physical characteristic of an individual solid form."
  - Petitioner's Reply p. 14; Ex. 2059, 158:20-25

IPR2020-00770
United Therapeutics EX2007
Page 3378 of 7335

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams concedes that the same treprostinil diethanolamine salt polymorph—Form B—is presented in the Phares reference and '393 Patent; while Dr. Williams conceded they were both "called" polymorph B, he said he couldn't "be 100 percent certain" they were the same crystal form because the melting points differed.
  - Petitioner's Reply P. 15; Ex. 2059, 168:6-11, 168:12-169:2

IPR2020-00770
United Therapeutics EX2007
Page 3379 of 7335

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that while Dr. Williams relies on his "personal experience" observing different melting points for crystals made with different solvents, he conceded that he knew of no literature to support his opinion; Dr. Williams does base it on his own experience but in the cited testimony states, regarding literature references, "I'm sure I could find it if I was asked to".
    - Petitioner's Reply p. 15; Ex. 2059, 184:22-185:2, 184-185:2

IPR2020-00770
United Therapeutics EX2007
Page 3380 of 7335

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams conceded that the one article he relied upon in his declaration, Ex. 2030, in fact describes different crystal forms having different melting points, and not the same crystal form having different melting points; but Dr. Williams' testimony was actually the opposite: "I'm not sure I can come to that conclusion. And what I did cite from this article is that the conclusion, which I quoted in my Declaration, and it's also based on my experience of crystallizing the same compound on different days from different solvents under slightly different conditions, you can get a different melting point. And it depends on the scale and lots of things."
    - Petitioner's Reply p. 15; Ex. 2059, 180:9-25, 181:17-182:13

IPR2020-00770
United Therapeutics EX2007
Page 3381 of 7335

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that it is now confirmed that UT's Moriarty purity varies by at least 0.6%, and indeed, Dr. Williams conceded he had no reason to disagree with this 0.6% value; but directly before the cited portion, Dr. Williams said that he was "not familiar" with the standard deviation function in Excel because he doesn't use it "in [his] normal course of work."
  - Petitioner's Reply P. 16; Ex. 2059, 218:22-24, 218:15-21

IPR2020-00770
United Therapeutics EX2007
Page 3382 of 7335

Petitioner Mischaracterizes Dr. Williams Testimony Regarding Batch Analysis

- Petitioner also alleged that Dr. Williams' own example of "product" in his own writing—Ex. 2028—uses "product" to mean a product created by nature, and not by a chemical reaction, when it refers to "the natural product from marine sources." But Dr. Williams testimony actually was:

  "Q· · ·All right.· It's not a -- it's not a chemical reaction; this is a biological reaction; correct? A· · ·They're still reactions, so it's the product of, ultimately, chemical-bond formation.· So it's still understood by a person skilled in the art of a product of chemical reactions."

  - Petitioner's Reply p. 22; Ex. 2020, ¶ 63; Ex. 2059, 221:19-25

IPR2020-00770
United Therapeutics EX2007
Page 3383 of 7335

IPR2016-00006
Patent 8,497,393

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of Exhibit 2061 was served on November 23, 2016 via email to the counsel of record for the Petitioner at the following address: Steadymed-IPR@dlapiper.com.

Date: November 23, 2016

/Stephen B. Maebius/
Stephen B. Maebius
Registration No. 35,264
Counsel for Patent Owner

4843-5539-4874.1

Trials@uspto.gov
571-272-7822

Paper No. 28
Entered: May 12, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.,
Petitioner,

v.

UNITED THERAPEUTICS CORPORATION,
Patent Owner.

Case IPR2016-00006
Patent 8,497,393 B2

Before LORA M. GREEN, JONI Y. CHANG, and
JACQUELINE T. HARLOW, *Administrative Patent Judges.*

HARLOW, *Administrative Patent Judge.*

DECISION
Redacted Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Petitioner, SteadyMed LTD ("SteadyMed"), filed a Petition requesting an *inter partes* review of claims 1–22 of U.S. Patent No. 8,497,393 B2 (Ex. 1001, "the '393 patent"). Paper 1 ("Pet."). Patent Owner, United Therapeutics Corporation ("UTC"), filed a Preliminary Response on January 14, 2016. Paper 10[1] ("Prelim. Resp."). We have jurisdiction under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted unless the information presented in the petition "shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

For the reasons set forth below, we institute an *inter partes* review of claims 1–22 of the '393 patent.

A. Related Matters

The '393 patent is asserted in: *United Therapeutics Corp. v. Sandoz, Inc.*, No. 14-cv-05499 (D.N.J.); *United Therapeutics Corp. v. Teva Pharmaceuticals U.S.A., Inc.*, No. 14-cv-05498 (D.N.J.); and *United Therapeutics Corp. v. Watson Laboratories, Inc.*, No. 15-cv-05723 (D.N.J). Pet. 1. SteadyMed is not party to the above identified litigations. *Id.*

[1] Paper 10 is the Unredacted Preliminary Response. Paper 8, filed concurrently with Paper 10, is a redacted version of the Preliminary Response.

IPR2020-00770
United Therapeutics EX2007
Page 3386 of 7335

B. The '393 Patent

The '393 patent, titled "Process to Prepare Treprostinil, the Active Ingredient in Remodulin®," issued July 30, 2013, from U.S. Patent Application No. 13/548,446 ("the '446 application") (Ex. 1002), filed July 13, 2012. Ex. 1001, [54], [45], [21], [22]. The '446 application is a continuation of U.S. Patent Application No. 12/334,731 ("the '731 application") (Ex. 1002), filed on December 15, 2008, now issued as U.S. Patent No. 8,242,305 ("the '305 patent"). Ex. 1001, [63]. The '393 patent claims priority to U.S. Provisional Patent Application No. 61/014,232 (Ex. 2008), filed December 17, 2007. Ex. 1001, [60].

The '393 patent recites 22 product-by-process claims for prostacyclin derivatives, including treprostinil.[2] *Id.* at 17:51–21:16; Pet. 5; Prelim. Resp. 3. The process disclosed by the '393 patent takes advantage of carbon treatment and salt formation steps to remove impurities, eliminating the need for purification by column chromatography. *Id.* at 17:29–32; *see also id.* at 5:41–45 ("purification by column chromatography is eliminated . . . . [T]he salt formation is a much easier operation than column chromatography.").

---

[2] The '305 patent, which issued from the parent to the application for the '393 patent, recites claims to a process for the preparation of prostacyclin derivatives comprising steps similar to those set forth in the product-by-process claims of the '393 patent. *Compare* Ex. 1001, 17:51–21:16, *with* Ex. 2007, 17:39–24:3.

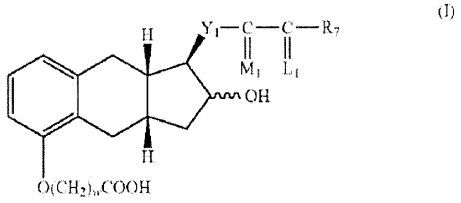
IPR2020-00770
United Therapeutics EX2007
Page 3387 of 7335

The process for forming prostacyclin derivatives described in the '393 patent includes four steps: (a) alkylating a prostacyclin derivative to form an alkylated prostacyclin derivative; (b) hydrolyzing the alkylated prostacyclin derivative with a base to form a prostacyclin acid; (c) contacting the prostacyclin acid with a base to form a prostacyclin carboxylate salt; and (d) optionally reacting the prostacyclin carboxylate salt formed in (c) with an acid to form the desired compound, or pharmaceutically acceptable salt thereof. *Id.* at 1:65–3:19.

C. Illustrative Claim

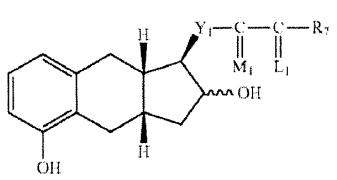
Each of the challenged claims is a product-by-process claim. Of the challenged claims, claims 1 and 9 are independent. Claim 1, reproduced below, is illustrative of the claimed subject matter.

1. A product comprising a compound of formula I

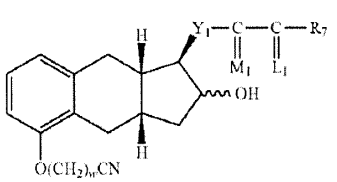


or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising

a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,



(II)

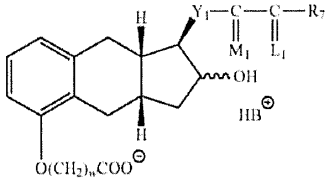


(III)

wherein [recitation of Markush groups for the specified structures],

b) hydrolyzing the product of formula III of step (a) with a base,

c) contacting the product of step (h)[3] with a base B to form a salt of formula I_s.



(I_s)

and

d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula I.

---

[3] We note that the reference to "step (h)," rather than "step (b)," in claim 1 is an apparent typographical error. *See* Ex. 1001, 3:66–67 ("(c) contacting the product of step (b) with a base B to for a salt of formula IV_s"); *see also* Pet. 25; Ex. 1009 ¶ 51.

Ex. 1001, 17:51–19:29. Claim 9 is drawn to a product comprising a specific treprostinil compound within the genus set forth in claim 1, and made by the process recited in claim 1. *Id.* at 19:48–20:46.

D. Prior Art Relied Upon

SteadyMed relies upon the following prior art references (Pet. 4–6):

Phares	WO 2005/007081 A2	Jan. 27, 2005	(Ex. 1005)
Kawakami	JP 56-122328A	Sept. 25, 1981	(Ex. 1006[4])

Moriarty et al., *The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil)*, 69 J. Org. Chem. 1890–1902 (2004) ("Moriarty") (Ex. 1004); and

Seyhan N. Eğe, ORGANIC CHEMISTRY 543–547 (2d ed. 1989) ("Eğe") (Ex. 1008).

E. Asserted Grounds of Unpatentability

SteadyMed asserts the following grounds of unpatentability (Pet. 3–4):

Claims	Basis	Reference(s)
1–5, 7–9, 11–14, and 16–20	§ 102(b)	Phares
1–5, 7–9, 11–14, and 16–20	§ 103(a)	Moriarty and Phares or Kawakami
6, 10, 15, 21, and 22	§ 103(a)	Moriarty, Phares, Kawakami, and Eğe

[4] SteadyMed submitted a certified English translation of Kawakami as Ex. 1007. As discussed in Part II.F below, UTC argues the admissibility of this translation.

II. ANALYSIS

A. 35 U.S.C. § 325(d)

UTC urges the exercise of our discretion under 35 U.S.C. § 325(d) to deny some or all of the grounds of unpatentability presented by SteadyMed because the same, or substantially similar issues were addressed during prosecution. Prelim. Resp. 25–26. UTC states that the Patent Office considered Moriarty alone, and in combination with Phares, during prosecution of the '393 patent. *Id.* at 8–10, 26. UTC also reports that Phares was considered alone, and in combination with Moriarty, during prosecution of U.S. Patent Application No. 13/910,583 ("the '583 application") (Ex. 2010) filed June 5, 2013, which is a continuation of the '446 application. *Id.* at 11–14.

Regarding the patentability of claims 6, 15, 21, and 22, in particular, UTC asserts that Eğe "is nothing more than a first-year organic chemistry textbook," and that SteadyMed "relies on nothing more than conclusory statements in three paragraphs of the [Declaration of Jeffery D. Winkler]" to support its unpatentability arguments. *Id.* at 26. UTC therefore contends that SteadyMed "has provided no evidence of probative value that is any different than what was already before the Patent Office during prosecution." *Id.* at 26–27.

Although it is within our discretion to "reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office" pursuant to 35 U.S.C. § 325(d), we decline to do so here.

IPR2020-00770
United Therapeutics EX2007
Page 3391 of 7335

We note that during prosecution of the '446 application, which issued as the '393 patent, the Examiner rejected the claims as anticipated by Moriarty, but subsequently withdrew that rejection, without elaboration, in response to a declaration filed by David A. Walsh ("Walsh Declaration") (Ex. 1002, 346–350), one of the named inventors of the '393 patent, and the Executive Vice President of Chemical Research and Development at UTC. Ex. 1002, 344, 346–360. Although Phares is listed as a cited reference on the face of the '393 patent (Ex. 1001, [56]), we observe that the Examiner neither relied on, nor otherwise discussed Phares during prosecution of the '446 application (Ex. 1002, 295–296, 327–330, 359). In addition, neither Eğe nor Kawakami was considered during prosecution of the '446 application. *Id.* at 235–359. The grounds of unpatentability asserted in the instant Petition likewise differ from the rejections entered by the Examiner during prosecution of the '731 application, the parent to the '446 application. *See* Ex. 1002, 122–124.

Moreover, as discussed in detail in Part II.B below, the Declaration of Jeffrey D. Winkler ("Winkler Declaration") (Ex. 1009), submitted in support of SteadyMed's Petition, calls into question Dr. Walsh's conclusion that treprostinil prepared according to the process claimed in the '393 patent is "physically different from treprostinil prepared according to the process of 'Moriarty'" (Ex. 1002, 347 (¶ 6)). Ex. 1009 ¶¶ 63–71. In addition, as set forth in Part II.F, we disagree with UTC's characterization of Dr. Winkler's testimony as conclusory. *See, e.g.*, Ex. 1009 ¶¶ 80–90.

We, therefore, decline to exercise our discretion to deny the Petition pursuant to 35 U.S.C. § 325(d). *See Nestle USA, Inc. v. Steuben Foods, Inc.*, Case IPR2014-01235, slip op. at 7 (PTAB Dec. 22, 2014) (Paper 12) ("[W]e conclude that Petitioner's arguments regarding the unpatentability of claims 18–20, which include arguments relating to Biewendt and a combination of references previously not considered and supported by a declaration previously not considered, are persuasive. . ."); *Merial Ltd., v. Virbac*, Case IPR2014-01279, slip op. at 9 (PTAB Jan. 22, 2015) (Paper 13) (noting the different burdens of proof and evidentiary standards applicable to *ex parte* examination and *inter partes review* proceedings).

B. Claim Construction

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable interpretation in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b); *see also In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278–79 (Fed. Cir. 2015) ("Congress implicitly approved the broadest reasonable interpretation standard in enacting the AIA," and "the standard was properly adopted by PTO regulation."), *cert. granted sub nom. Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 890 (2016) (mem.). Under this standard, we may take into account definitions or other explanations provided in the written description of the specification. *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). Any special definition for a claim term must be set forth in the specification with reasonable clarity, deliberateness, and precision. *In re Paulsen*, 30 F.3d

IPR2020-00770
United Therapeutics EX2007
Page 3393 of 7335

1475, 1480 (Fed. Cir. 1994). Only those terms that are in controversy need be construed, and only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

"Product" / "A product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof"

Independent claims 1 and 9 recite the phrase "[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof . . . ." Ex. 1001, 19:48–20:46. In addition, each challenged dependent claim recites the term "product." *Id.* at 17:51–21:16. Because the parties advance similar arguments pertaining to the construction of these terms, we address these terms together.

SteadyMed asserts that the phrase "[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof" should be interpreted to mean "a chemical composition that includes, but is not limited to, a compound of Formula I, or a pharmaceutically acceptable salt thereof, and that may also include other non-mentioned substances (including impurities), additives, or carriers, without limitation as to the types or relative amounts thereof." Pet. 11. SteadyMed contends that because independent claims 1 and 9 recite "[a] product comprising," the claim term "product" should be construed to include "the treprostinil compound along with other substances (including impurities)," i.e., a "chemical composition." *Id.* at 11.

UTC counters that "[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof" should be interpreted as "a substance resulting from a chemical reaction constituted primarily of formula I/IV or a pharmaceutically acceptable salt thereof." Prelim. Resp. 21. As an initial matter, UTC notes that SteadyMed's proposed construction refers only to Formula I, and asserts that SteadyMed "inexplicably read[s] Formula IV out of the term entirely." *Id.* at 22.

UTC further argues that the claims and Specification of the '393 patent use "product" to refer to a substance resulting from a chemical reaction. *Id.* at 17. UTC also contends that the prosecution history for the '393 patent supports its proposed construction because "during prosecution, the Patent Owner and Examiner explicitly discussed the 'product' of the claims as a real world substance that results from employing a specific chemical process, as differentiated from the substance obtained from employing a different chemical process." *Id.* at 18–19. UTC points to chemistry textbooks as buttressing its position that a skilled artisan would understand the claim term "product" as referring to "a substance resulting from a chemical reaction." *Id.* at 19. UTC further reasons that "the 'product' claimed in a product-by-process claim is necessarily a substance that results from the process specified in that claim" (*id.*), and that SteadyMed's proposed construction "contradicts this inherent limitation of the claims" (*id.* at 22).

On this record, and for purposes of this decision, we interpret the phrase "[a] product comprising a compound [of/having] formula [I/IV] or a

IPR2020-00770
United Therapeutics EX2007
Page 3395 of 7335

pharmaceutically acceptable salt thereof," to mean "a product including, but not limited to, a compound [of/having] formula [I/IV] or a pharmaceutically acceptable salt thereof."

The claim term "product," as it is used in the '393 patent, does not require construction because the claimed "product" is defined by the limitations recited in the challenged claims. This is evidenced by independent claims 1 and 9, which recite "[a] product comprising . . . ," and go on to define the essential elements of the claimed product. The transitional term "'comprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997); *see also* Ex. 1001, 4:23–25 (defining "comprising" as "including, but not limited to"). Thus, the open-ended structure of the challenged claims forecloses limitation of the term "product" beyond that achieved by the recited claim elements.

Indeed, neither UTC nor SteadyMed identifies any disclosure in the '393 patent or its prosecution history that necessitates a contrary understanding of the term "product." For example, the portions of the Specification to which UTC points comport with an understanding of "product" as being defined only by the recited claim elements. *See* Ex. 1001, 5:45–46, 7:16–20, 17:37–40. Furthermore, far from disavowing or otherwise limiting claim scope, the portions of the prosecution history identified by UTC are consistent with an understanding that the claimed "product" is defined solely by the recited claim elements. *See* Ex. 1002,

IPR2020-00770
United Therapeutics EX2007
Page 3396 of 7335

315, 328–329, 346–350. We similarly are unpersuaded that the chemistry textbook glossaries to which UTC points (Exs. 2011, 2012, 2014) provide a basis for narrowly interpreting "product" to require that the product result from a chemical reaction.

Regarding the larger claim phrase "[a] product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof," as explained above, we determine that the embedded claim term "comprising" means "including, but not limited to." *See Genentech*, 112 F.3d at 501; *see also* Ex. 1001, 4:23–25. Accordingly, we reject UTC's proposal that claims 1 and 9 be read to require a product "*constituted primarily of* formula I/IV or a pharmaceutically acceptable salt thereof." Prelim. Resp. 21 (emphasis added).

"[A/the] process comprising"

SteadyMed argues that the claim phrase "[a/the] process comprising," which appears in independent claims 1 and 9, should be interpreted as "a process that includes, but is not limited to, the recited process steps, and may include, without limitation, any other non-recited steps." Pet. 12. UTC counters that this claim phrase should be construed to mean "a/the process including but not limited to." Prelim. Resp. 23–24. For the reasons set forth above, we agree with UTC that these claim phases should be interpreted to mean "a/the process including, but not limited to."

IPR2020-00770
United Therapeutics EX2007
Page 3397 of 7335

Product-by-Process Claims

Each of the challenged claims is a product-by-process claim. Ex. 1001, 17:51–21:16; Pet. 5; Prelim. Resp. 3. The general rule when determining patentability of a product-by-process claim is to "focus . . . on the product and not on the process of making it." *Amgen, Inc. v. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1369 (Fed. Cir. 2009). This general rule embodies the long-standing principle that "an old product is not patentable even if it is made by a new process." *Id.* at 1370. An exception applies when process steps recited in the claim impart "structural and functional differences" to the claimed product. *Greenliant Sys., Inc. v. Xicor LLC*, 692 F.3d 1261, 1267–1268 (Fed. Cir. 2012). If the exception applies, the structural and functional differences conveyed by the recited process steps "'are relevant as evidence of no anticipation' although they 'are not explicitly part of the claim.'" *Id.* at 1268 (citing *Amgen*, 580 F.3d at 1370).

SteadyMed contends that the challenged claims do not yield a treprostinil product having structural or functional differences as compared to treprostinil products produced by prior art methods. Pet. 19–22. Specifically, SteadyMed asserts that the Walsh Declaration, relied on by UTC during prosecution as evidencing differences in the treprostinil products of the '393 patent and Moriarty, fails to demonstrate any functional or structural differences between the instantly claimed and prior art treprostinil products. *Id.* SteadyMed relies on the Winkler Declaration (Ex. 1009) to support its position. *Id.*

UTC acknowledges that "at the time of the '393 patent, there existed at least three prior art methods" for making treprostinil. Prelim. Resp. 33. Relying on the Walsh Declaration, UTC asserts that the process steps recited in independent claims 1 and 9 are entitled to patentable weight because they yield a "physically different and improved final product with significantly reduced overall impurities and a distinct and unexpected impurity profile" as compared to treprostinil produced using prior art methods. *Id.* at 3.

The Walsh Declaration compares the impurity profile of treprostinil free acid "prepared according to the process of 'Moriarty'" to the impurity profiles of treprostinil free acid and treprostinil diethanolamine "prepared according to the process specified in claim 1 or [9]" of the '393 patent.[5] Ex. 1002, 347–348 (¶ 6). Dr. Walsh concludes that the treprostinil free acid and treprostinil diethanolamine prepared according to the process of claims 1 and 9 is physically different from the treprostinil diethanolamine prepared according to the process of Moriarty "at least because neither of [the '393 patent products] contains a detectable amount of any of benzindene triol, treprostinil methyl ester, 1AU90 treprostinil stereoisomer and 2AU90 treprostinil stereoisomer, each of which were present in detectable amounts in treprostinil produced according to the process of 'Moriarty'." *Id.* at 349 (¶ 8). In addition, Dr. Walsh provides "data obtained from representative Certificates of Analysis" indicating that treprostinil free acid "prepared

---

[5] Issued claim 9 of the '393 patent is identified as claim 10 in the Walsh Declaration, and other documents in the prosecution history in the '393 patent.

IPR2020-00770
United Therapeutics EX2007
Page 3399 of 7335

according to 'Moriarty'" is 99.4% pure, while the treprostinil free acid and treprostinil diethanolamine "prepared according to the process specified in claim 1 or [9]" are 99.8% pure and 99.9% pure, respectively. *Id.* at 347–348 (¶ 6).

SteadyMed disputes Dr. Walsh's contention that there are physical differences between the treprostinil products of the '393 patent and prior art. Pet. 19–22; *see also* Ex. 1009 ¶¶ 63–71. As an initial matter, SteadyMed points out that the 99.7% treprostinil purity reported by Moriarty (Ex. 1004, 13) is higher than the 99.5% purity recited in claims 2 and 10 of the '393 patent, the only challenged claims that recite a purity level. Pet. 20; *see also* Ex. 1009 ¶ 65. In addition, Dr. Winkler testifies that the limited sample set, consisting of "*only two specific batches* of treprostinil" (Ex. 1009 ¶ 66), and absence of any disclosure concerning the reaction conditions, reagents, and solvents used in carrying out the process of claims 1 and 9 of the '393 patent (*id.* ¶ 67), undermine the veracity of Dr. Walsh's conclusion regarding the purity of these products. *Id.* ¶¶ 66–67. SteadyMed also observes that the statement in the Specification of the '393 patent that in one embodiment the purity of treprostinil is "at least 90.0%, 95.0%, 99.0%, 99.5%" (Ex. 1001, 8:66–67), supports the conclusion that the 99.8% purity purportedly achieved by Dr. Walsh "is based on a particular set of process steps that are not claimed and which must have been found after the filing date." Pet. 20.

Dr. Winkler additionally testifies that the alleged differences in purity between the treprostinil batches described by Dr. Walsh are attributable to

IPR2020-00770
United Therapeutics EX2007
Page 3400 of 7335

experimental error. *Id.* ¶¶ 68–70. Dr. Winkler testifies that "the literature on [High Performance Liquid Chromatography's ("HPLC's")] precision indicates that the 'RSD' or 'relative standard deviation' for a typical instrument is about 1%. (Ex. 1017.)." *Id.* ¶ 70. Dr. Winkler further observes that "[i]n the present case, we can estimate the precision of the equipment the inventors actually used, since the inventors found that Example 4's Batch 1 had an HPLC Assay of 100.4%, which is obviously greater than the 100% value theoretically achievable. (Ex. 1001, col. 13, lines 50-65)." *Id.* Dr. Winkler, thus, concludes that "[t]his deviation between experimental and theoretical shows that the instrument can have variations of at least 0.4%, which is greater than the differences in purity that the inventors offered to support their contention regarding greater purity over the prior art." *Id.* On this record, we credit Dr. Winkler's testimony, as it is consistent with the disclosures of the prior art and the disclosure of the '393 patent itself.

UTC does not challenge SteadyMed's arguments concerning the shortcomings of the Walsh Declaration. Rather, UTC points to correspondence with, and reports submitted to, the Food and Drug Administration ("FDA") relating to the acceptance of a supplemental new drug application for treprostinil. Prelim. Resp. 36–38. UTC contends that these reports show that "the purity of the treprostinil improved close to 100%" for treprostinil prepared as described in claims 1 and 9 of the '393 patent as opposed to the prior process implemented by UTC. Prelim. Resp. 38; *see also* Ex. 2006, 3–4.

IPR2020-00770
United Therapeutics EX2007
Page 3401 of 7335

On the record before us, and for purposes of this decision, we conclude that the process steps recited in the challenged claims do not impart structural or functional differences to the claimed product.

As an initial matter, we observe that the challenged product-by-process claims are drawn to "[a] product comprising a compound" of either formula I or formula IV, or a pharmaceutically acceptable salt of the recited formula. Ex. 1001, 17:51–19:29, 19:48–20:46). "'Comprising' is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." *Genentech*, 112 F.3d at 501. Thus, a product comprising a particular compound must contain that compound, but may additionally include other substances, such as impurities. On this record, therefore, it is unclear how claims 1, 3–9, and 11–22, which claim a product comprising a particular compound, but do not recite limitations concerning the purity profile of that product, could be restricted to a product including the claimed compound, but also having a particular purity profile. In addition, although claims 2 and 10 require a purity of at least 99.5% (Ex. 1001, 19:29–30, 20:47–48), these claims similarly are drawn to a product comprising a compound, and do not specify the type of impurities that may be present in the compound or restrict the amount of any particular impurity that may be present, so long as the product remains at least 99.5% pure.

Furthermore, the evidence presently before us, including UTC's own testing results, suggests that inter-batch variability in impurity profiles,

IPR2020-00770
United Therapeutics EX2007
Page 3402 of 7335

experimental error in impurity measuring equipment, and variations in reagents, solvents, and reaction conditions, rather than the instantly recited process steps, account for any purported improvements in purity reported by UTC. We observe that UTC offers no explanation for the variation between the 99.7% purity reported by Moriarty, and the 99.4% purity Dr. Walsh obtained for treprostinil purportedly prepared according to the process described by Moriarty. Neither does UTC offer reasoning for crediting Dr. Walsh's results over those reported by Moriarty himself. Similarly, UTC neglects Dr. Winker's assessment of the experimental error present, but unaccounted for, in the impurity measurements reported in the Walsh Declaration, and fails to account for the absence of any disclosure regarding the experimental protocols followed by Dr. Walsh, such as the reaction conditions, or the solvents or reagents used, in synthesizing treprostinil according to Moriarty or the '393 patent.

Moreover, the Process Optimization Report (Ex. 2005) proffered by UTC supports the conclusion that the process steps recited in the '393 patent do not produce a treprostinil product that differs, either structurally or functionally, from that produced using prior art methods.

The Process Optimization Report discloses the impurity analyses for five batches of treprostinil identified by UTC as having been prepared using the process recited in the '393 patent. Ex. 2005, 4–6; *see also* Prelim. Resp. 36 ("Ex. 2005 is a Process Optimization Report that provides results

IPR2020-00770
United Therapeutics EX2007
Page 3403 of 7335

for batches resulting from step (d) of claims 1 and 10 in the '393 patent,[6] which was performed on specific batches of the diethanolamine salt intermediate produced by steps (a)-(c) [redacted].").
The Process Optimization Report states that the purity of these batches, as determined by HPLC analysis, ranged from [redacted] to [redacted].[7] Ex. 2005, 6. Additionally, the Process Optimization Report indicates that each of the following impurities were detected by HPLC analysis in one or more of the above referenced treprostinil batches: [redacted]. *Id.*

We also observe that although UTC sought, and obtained from the FDA, modification of the specification for the HPLC assay for treprostinil to require a purity range of 98%–102%, rather than 97%–101%, [redacted] Ex. 2006, 3–4, 6; Ex. 2003. Notably, UTC's specification for treprostinil produced according to the '393 patent permits

---

[6] We note that UTC likely intended to reference independent claim 9 of the '393 patent, rather than dependent claim 10; however our analysis is equally applicable to claim 9 or claim 10.

[7] The reported batch purity values were [redacted] for an average purity of [redacted] Ex. 2005, 6.

IPR2020-00770
United Therapeutics EX2007
Page 3404 of 7335

each of the following impurities: [redacted]. Ex. 2006, 6. The analysis of treprostinil purportedly prepared according to the process of Moriarty, set forth in the Walsh Declaration, reveals that each of the impurities detected in Moriarty treprostinil was present in an amount [redacted] *Compare* Ex.1002, 347, *with* Ex. 2006, 6.

Accordingly, on the record before us, and for purposes of this decision, we conclude that the process steps recited in the challenged claims of '393 patent do not impart structural or functional differences to the claimed product as compared to prior art processes, and therefore, that these process steps do not patentably limit the claimed product. We note, however, that the factual dispute between the parties concerning the existence of any structural or functional differences between treprostinil products produced according to the process recited in the '393 patent and prior art processes, as well as arguments addressing our concerns regarding the relevance of the impurity profile of a product obtained by the recited process to the patentability of claims drawn to a product *comprising* a compound, are appropriate for further development at trial.

C. Principles of Law

To establish anticipation, each and every element in a claim, arranged as recited in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008). "A reference anticipates a claim if it discloses the claimed invention 'such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of the invention.'" *In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995) (emphasis omitted) (quoting *In re LeGrice*, 301 F.2d 929, 936 (CCPA 1962)).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

> When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the

IPR2020-00770
United Therapeutics EX2007
Page 3406 of 7335

> same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida* [*v. Ag Pro, Inc.*, 425 U.S. 273 (1976)] and *Anderson's–Black Rock* [*v. Pavement Salvage Co.*, 396 U.S. 57 (1969)] are illustrative—a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

KSR, 550 U.S. at 417.

The level of ordinary skill in the art is reflected by the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995); *In re Oelrich*, 579 F.2d 86, 91 (CCPA 1978).

D. Anticipation Grounds of Unpatentability Based on Phares

SteadyMed asserts that claims 1–5, 7–9, 11–14, and 16–20 are unpatentable under § 102(b) as anticipated by Phares. Pet. 22–37. Claims 2–5, 7, 8, and 19 depend directly from claim 1, and claims 11–14, 16–18, and 20 depend, directly or indirectly, from claim 9. In support of its assertion, SteadyMed provides detailed explanations as to how Phares discloses each claim limitation (*id.*), and relies upon the Winkler Declaration (Ex. 1009) to support its positions.

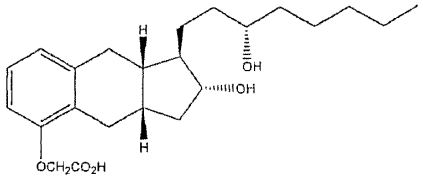
UTC counters that the treprostinil product of Phares is physically different from that produced by the process disclosed in the '393 patent, and, therefore, that the process steps disclosed in the claims of the '393 patent are limiting for purposes of the patentability determination. Prelim. Resp. 33–36. UTC also argues that SteadyMed improperly engages in picking and choosing among distinct embodiments in Phares to piece together an

IPR2020-00770
United Therapeutics EX2007
Page 3407 of 7335

anticipation argument as to the recited process steps. *Id.* at 29–31. UTC further asserts that explicit disclosure of certain claimed process steps is absent from SteadyMed's anticipation analysis, and that SteadyMed fails to show that those limitations are inherently disclosed by Phares. *Id.* at 31–36.

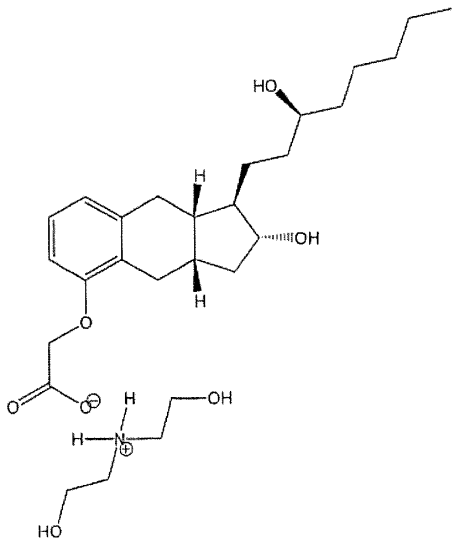
Phares

Phares describes "compounds and methods for inducing prostacyclin-like effects in a subject or patient," including treprostinil and derivatives thereof. Ex. 1005, 10. The chemical structure of treprostinil disclosed by Phares, on page 10 of Exhibit 1005, is reproduced below:



Id. Phares explains that "[t]reprostinil is a chemically stable analog of prostacyclin, and as such is a potent vasodilator and inhibitor of platelet aggregation." *Id.*

Phares further discloses that "[a] preferred embodiment of the present invention is the diethanolamine salt of treprostinil. . . . A particularly preferred embodiment of the present invention is form B of treprostinil diethanolamine." *Id.* at 11. The structure of the diethanolamine salt of treprostinil described by Phares, on page 99 of Exhibit 1005, is reproduced below:

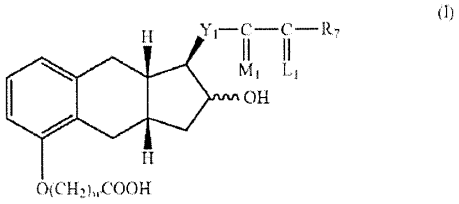


Id. at 99 (claim 49). Phares reports that form B of the diethanolamine salt of treprostinil "appears to be a crystalline material which melts at 107°C." *Id.* at 91.

Phares describes the synthesis of (-)-treprostinil, the enantiomer of treprostinil. Ex. 1005, 41–42. Phares explains that "[e]nantiomers of these compounds . . . can be synthesized using reagents and synthons of enantiomeric chirality of the above reagents." *Id.* at 41. In particular, Phares teaches that "the enantiomer of the commercial drug (+)-Treprostinil was synthesized using the stereoselective intramolecular Pauson Khand reaction as a key step and Mitsunobu inversion of the side-chain hydroxyl group." *Id.* at 42. Phares discloses the following reaction procedure: "i. $ClCH_2CN$, K_2CO_3. ii, KOH, CH_3OH, reflux. 83 % (2 steps)." *Id.*

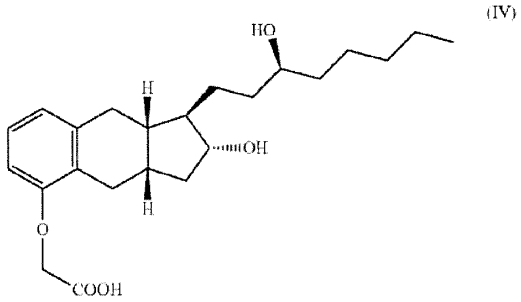
A product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof

Claim 1 of the '393 patent recites "[a] product comprising a compound of formula I



(I)

or a pharmaceutically acceptable salt thereof," and sets forth a series of process steps for obtaining the claimed product. Claim 9 recites "[a] product comprising a compound having formula IV



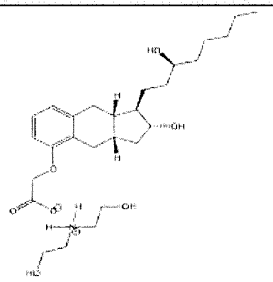
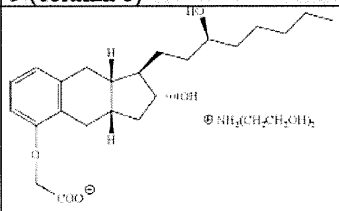
(IV)

or a pharmaceutically acceptable salt thereof," and includes the same process steps for obtaining the claimed product as recited in claim 1. Claim 9 is identical to claim 1, except that it is drawn to a product comprising the specific treprostinil compound, a species of the genus of claim 1. Accordingly, we address these claims together.

SteadyMed contends that "Phares discloses in its Claim 49 the identical, pharmaceutically acceptable treprostinil diethanolamine salt" claimed in the '393 patent. Pet. 26; *see also* Ex. 1005, 24, 85–93, 99

(claim 49); Ex. 1009 ¶¶ 50–53. In support of SteadyMed's position, Dr. Winkler testifies that "[o]ther than a change in formatting, the two structures [for treprostinil diethanolamine salt] from Phares and the '393 Patent are identical." Ex. 1009 ¶ 53.

Paragraph 52 of the Winkler Declaration depicts a side-by-side comparison of the chemical structures disclosed in claim 49 of Phares, and column 8, lines 50–63 of the '393 patent, reproduced below:

Phares (Ex. 1005), Claim 49	'393 Patent (Ex. 1001), Claims 1 & 9 (column 8)
	

Id. ¶ 52. As shown in the figure from paragraph 52 of the Winkler Declaration, the treprostinil diethanolamine salt disclosed by Phares is structurally identical to that disclosed in the '393 patent.

As set forth in Part II.B above, SteadyMed, relying on the Winkler Declaration, further asserts that the process disclosed in claims 1 and 9 of the '393 patent does not result in a treprostinil product that is physically different or unique from treprostinil produced by prior art methods. Pet. 19–22; *see also* Ex. 1009 ¶¶ 63–71. In support of this position, Dr. Winkler testifies that "[i]n both the '393 Patent and Phares (Ex. 1005), treprostinil diethanolamine salt Form B is made . . . . Phares further discloses a melting point of 107° C (Ex. 1005, p. 91 & Fig. 21) for the Form B salt."

Ex. 1009 ¶ 59; *see also* Ex. 1005, 90–93; Pet. 27. Dr. Winkler also testifies that Phares discloses the same procedure as is claimed in the '393 patent, but describes this procedure in reference to the synthesis of the enantiomer of treprostinil. Ex. 1009 ¶¶ 55–57; Ex. 1005, 41–42; Pet. 25–26. Dr. Winkler thus concludes that in "making the most stable crystal form (Form B) and preparing a product that melts at a higher temperature higher than that described in the '393 Patent, Phares necessarily discloses a salt of at least equal purity to the salt in the '393 Patent." Ex. 1009 ¶ 62; *see also id.* ¶ 60 (citing Ex. 1018, 6); Pet. 27–28.

SteadyMed also contends that Phares anticipates the process steps recited in claim 1. Pet. 24–28; Ex. 1005, 24, 41–42, 85–93, 99 (claim 49); Ex. 1009 ¶¶ 44–71.

UTC does not dispute Phares' disclosure of a treprostinil product; rather, as previewed in relation to its claim construction arguments above, UTC contends that the treprostinil product of Phares is "physically different" from that claimed in the '393 patent, and, therefore, not anticipatory. Prelim. Resp. 33–36. UTC argues that as Phares does not disclose which treprostinil starting material is used, it "cannot inherently anticipate the final treprostinil product of the '393 patent because each method would result in a distinct impurity profile." Prelim. Resp. 34. Referring to the Walsh Declaration, UTC further asserts that "even if the Moriarty treprostinil was used for Phares, Petitioner has failed to provide any evidence that the final Phares treprostinil product would necessarily be the same as the products claimed in the '393 patent." *Id.* UTC also asserts that SteadyMed's reliance

IPR2020-00770
United Therapeutics EX2007
Page 3412 of 7335

on the melting point of the treprostinil product of Phares as a proxy for purity is misplaced because "melting point does not disclose any specific impurity level and instead may demonstrate a different form, or polymorph, of treprostinil diethanolamine altogether." *Id.* at 35.

UTC additionally argues that Phares does not disclose the same process for generating treprostinil as recited in claims 1 and 9, and that SteadyMed improperly "cobbles together disclosure from four disparate portions of Phares covering multiple distinct embodiments" to arrive at the claimed invention. Prelim. Resp. 27. Further, UTC asserts that even if SteadyMed were permitted to pick and choose steps from various embodiments of Phares, SteadyMed nevertheless must rely on inherency to prove anticipation because "Phares lacks express disclosure of certain claim elements." *Id.* at 28.

The present record supports SteadyMed's contention that the treprostinil diethanolamine salt taught by Phares is identical in structure to the pharmaceutically acceptable treprostinil diethanolamine salt recited in claims 1 and 9. Pet. 24; *see also* Ex. 1005, 24, 99 (claim 49); Ex. 1009 ¶¶ 52–53. Dr. Winkler testifies that the process for producing treprostinil disclosed by Phares yields the same form (Form B) of treprostinil diethanolamine salt as the process of the '393 patent, and that the treprostinil diethanolamine salt of Phares is at least equal in purity to the treprostinil product of the '393 patent. Ex. 1009 ¶¶ 59–62. Dr. Winkler further testifies that Phares discloses the same process for synthesizing treprostinil as the

IPR2020-00770
United Therapeutics EX2007
Page 3413 of 7335

'393 patent. Ex. 1009 ¶¶ 55–57, 62; Ex. 1005, 41–42; Pet. 25–26. On this record, we credit Dr. Winkler's testimony.

We are not persuaded by UTC's arguments concerning the possibility that treprostinil produced according to Phares might have a different impurity profile than that produced according to the process disclosed in the '393 patent. First, for the reasons set forth in Part II.B above, it is unclear on this record how the use of the transitional phrase "comprising" excludes any impurities that may possibly be produced by the process of Phares. In addition, the present record supports a finding that the impurity profiles for treprostinil diethanolamine salt prepared as described by Phares and that prepared according to the '393 patent are the same. As explained above, Dr. Winkler's testimony regarding the form and melting point of Phares' treprostinil product, is consistent with the conclusion that the products of Phares and the '393 patent are the same.

Furthermore, we note that, as explained in Parts II.A and II.B above, the inter-batch variability in treprostinil impurity profiles, experimental error inherent in impurity measurements, and the variety and extent of impurities permitted in UTC's specification for the manufacture of treprostinil according to the process of the '393 patent, which remained unchanged when UTC migrated from a prior art process to the process of the '393 patent, support the conclusion that the process steps recited in claims 1 and 9 of the '393 patent do not impart any structural or functional differences over prior art treprostinil products.

IPR2020-00770
United Therapeutics EX2007
Page 3414 of 7335

Accordingly, given the evidence before us in this record, we conclude that SteadyMed has established adequately for purposes of this decision that Phares teaches the treprostinil diethanolamine salt product recited in claims 1 and 9. Because we determine, on the record before us, and for purposes of this decision, that the process steps recited in claims 1 and 9 do not impart structural or functional differences to the claimed treprostinil product and are therefore not limiting, we do not address the parties' contentions concerning Phares' anticipation of the recited process steps.

Conclusion

UTC has not raised any additional arguments with regard to the dependent claims other than those addressed above. We have reviewed SteadyMed's evidence, arguments, and claim charts, and conclude that SteadyMed has sufficiently demonstrated that the dependent claims are also anticipated by Phares. Thus, for the foregoing reasons, we conclude that SteadyMed has shown a reasonable likelihood of prevailing on its assertions that claims 1–5, 7–9, 11–14, and 16–20 are anticipated by Phares.

E. Obviousness Grounds of Unpatentability Based on Moriarty and Phares

SteadyMed asserts that claims 1–5, 7–9, 11–14, and 16–20 are unpatentable under § 103(a) as obvious in view of Moriarty and Phares. Pet. 37–52. Claims 2–5, 7, 8, and 19 depend directly from claim 1, and claims 11–14, 16–18, and 20 depend, directly or indirectly, from claim 9. In support of its assertion, SteadyMed provides detailed explanations as to how

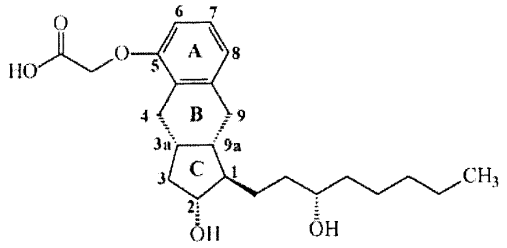
IPR2020-00770
United Therapeutics EX2007
Page 3415 of 7335

the combination of Moriarty and Phares discloses each claim limitation (*id.*), and relies upon the Winkler Declaration (Ex. 1009) to support its positions.

UTC counters that "Phares fails to disclose the synthetic route or purity of the claimed treprostinil product. Moriarty adds nothing to cure these deficiencies." Prelim. Resp. 43. UTC asserts that the process described in the '393 patent "unexpectedly reduced the impurity level in the claimed treprostinil product even more" than Moriarty, and reiterates its position that treprostinil produced according to the process of the '393 patent has "a superior purity profile compared to the prior art." *Id.* at 44.

Moriarty

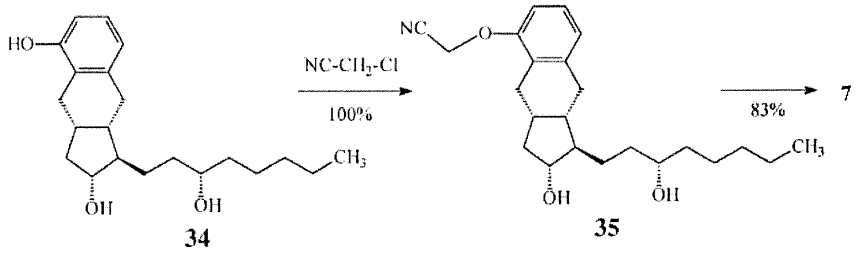
Moriarty describes the synthesis of treprostinil "via the stereoselective intramolecular Pauson-Khand cyclization." Ex. 1004, 1. Formula 7 of Moriarty is reproduced below:



7

Id. at 3. Formula 7 of Moriarty depicts the chemical structure of treprostinil. *Id.*

An excerpt of Scheme 4 of Moriarty is reproduced below:



Id. at 6. The excerpted portion of Scheme 4 of Moriarty illustrates the alkylation Formula 34 to yield Formula 35, and subsequent hydrolysis of Formula 35 with a base (followed by acidification) to yield Formula 7, treprostinil. Ex. 1004, 6, 13.

A product comprising a compound [of/having] formula [I/IV] . . . or a pharmaceutically acceptable salt thereof

SteadyMed contends that Moriarty and Phares respectively disclose treprostinil acid and treprostinil diethanolamine salt, as recited in claims 1 and 9 of the '393 patent. Pet. 22–23, 24, 33, 39, 48; *see also* Ex. 1004, 6, 13; Ex. 1005, 24, 99 (claim 49); Ex. 1009 ¶¶ 74, 76. Furthermore, Dr. Winkler testifies that the combination of Moriarty and Phares "discloses the same process steps and same product of the '393 Patent. For the same reasons discussed above regarding Phares, the purity of the combinations would be of at least equal purity to that claimed in the '393 Patent." Ex. 1009 ¶ 76.

SteadyMed asserts that Moriarty discloses steps (a) and (b) of claims 1 and 9, and that Phares discloses step (c) of these claims. Pet. 43; *see also* Ex. 1004, 6, 13; Ex. 1005, 24; Ex. 1009 ¶ 74. Dr. Winkler testifies

that a relevant skilled artisan would have recognized that the treprostinil acid produced in Moriarty could be purified by contacting it with a base as described by Phares. Ex. 1009 ¶ 74. In addition, as discussed in Part II.D above, Dr. Winkler testifies that Phares "details the same Claim 1 and 9 steps (a) or (b) as were used to make treprostinil in the '117 Patent and Moriarty reference, but applies them to make (-)-treprostinil, the enantiomer of (+)- treprostinil (Ex. 1005, p. 42)." *Id.* ¶55. Dr. Winkler further testifies that a relevant skilled artisan would have had "more than a reasonable expectation of success that the reaction of treprostinil with diethanolamine would be successful" because "Phares (Ex. 1005, p. 24, p. 99, Claim 49) performed the same reaction and it was successful." Ex. 1009 ¶ 80.

UTC reasserts the arguments described above concerning the purity of treprostinil produced according to the process disclosed in the '393 patent. UTC acknowledges that Moriarty itself was an improvement over the prior art, but contends that "the '393 patent unexpectedly reduced the impurity level in the claimed treprostinil product even more." Prelim. Resp. 44. Specifically, UTC contends that "performing step (c) on a product that resulted from steps (a) and (b) provided a product with reduced impurities." *Id.* UTC also reiterates its arguments concerning the Walsh Declaration, and highlights the purported differences in the impurity profile of treprostinil produced according to Moriarty compared to that produced according to the '393 patent.

The present record supports SteadyMed's contention that the treprostinil diethanolamine salt disclosed by the combination of Moriarty

and Phares is identical in structure to the pharmaceutically acceptable treprostinil diethanolamine salt recited in claims 1 and 9. Pet. 41–42; *see also* Ex. 1004, 6, 13; Ex. 1005, 24, 99 (claim 49); Ex. 1009 ¶ 76.

First, as explained in Part II.B above, the present record does not support the conclusion that claims drawn to "[a] product comprising a compound . . ." can be distinguished from prior art products on the basis of differences in the impurity profiles of those products.

Moreover, as explained in detail in Parts II.A, II.B, and II.D above, we determine that the present record supports the contention that the treprostinil product of Moriarty and Phares is the same as that produced according to the steps recited in claims 1 and 9 of '393 patent.

As discussed in Part II.B, the Walsh Declaration fails to disclose the protocols followed in producing the Moriarty and '393 patent treprostinil samples analyzed, and fails to account for the experimental error in Dr. Walsh's impurity measurements. In addition, the inter-batch variability in the types and amounts of impurities observed in treprostinil prepared according to the '393 patent, and the fact that the treprostinil Dr. Walsh prepared according to Moriarty satisfies the FDA purity specification for treprostinil prepared per the '393 patent, lends further support to the conclusion that no structural or functional differences exist between treprostinil produced according to Moriarty, and that produced according to the'393 patent.

Similarly, as discussed in Part II.D, the present record supports a finding that the impurity profile of treprostinil diethanolamine salt prepared

IPR2020-00770
United Therapeutics EX2007
Page 3419 of 7335

as described by Moriarty in combination with Phares is the same as that prepared according to the '393 patent. Dr. Winkler's testimony regarding the form and melting point of Phares' treprostinil product (Ex. 1009 ¶¶ 59–60, 62), as well as his testimony regarding the disclosure by Phares of the same synthesis process as described by Moriarty (Ex. 1009 ¶¶ 55–57), is consistent with the conclusion that treprostinil diethanolamine generated by reacting Formula 7 of Moriarty with a base, as disclosed by Phares, to form a salt of Formula 7 would result in a treprostinil diethanolamine salt of at least equal purity to that disclosed in the '393 patent.

Accordingly, given the evidence before us in this record, we conclude that SteadyMed has established adequately for purposes of this decision that the combination of Moriarty and Phares renders obvious the treprostinil diethanolamine salt product recited in claims 1 and 9. Because we determine, on the record before us, and for purposes of institution, that the process steps recited in claims 1 and 9 do not impart structural or functional differences to the claimed treprostinil product and are therefore not limiting, we need not address the parties' contentions concerning the obviousness of the recited process steps.

Conclusion

UTC has not raised any additional arguments with regard to the dependent claims other than those addressed above. We have reviewed SteadyMed's evidence, arguments, and claim charts, and conclude that SteadyMed has sufficiently demonstrated that the dependent claims are also rendered obvious by the combination of Moriarty and Phares. Thus, for the

foregoing reasons, we conclude that SteadyMed has shown a reasonable likelihood of prevailing on its assertions that claims 1–5, 7–9, 11–14, and 16–20 are obvious in view of Moriarty and Phares.

F. Obviousness Grounds of Unpatentability Based on Moriarty, Phares, Kawakami, and Eğe

SteadyMed asserts that claims 6, 10, 15, 21, and 22 are unpatentable under § 103(a) as obvious in view of Moriarty, Phares or Kawakami, and Eğe. Pet. 37–52. Although SteadyMed nominally identifies this ground of unpatentability as being over "Moriarty (Ex. 1004) with Phares (Ex. 1005) or Kawakami (Exs. 1006 & 1007) and in further combination with Ege (Ex. 1008)" (Pet. 53 (emphasis omitted), as discussed below, SteadyMed explicitly relies on Kawakami in arguing unpatentability in view of Moriarty, Phares, and Eğe. Accordingly, we understand SteadyMed's stated ground of unpatentability as relying on the combination of Moriarty, Phares, Kawakami, and Eğe. Claims 6, 21, and 22 depend, directly or indirectly, from claim 1, and claims 10 and 15 depend directly from claim 9. In support of its assertion, SteadyMed provides detailed explanations as to how the combination of Moriarty, Eğe, Phares, and Kawakami discloses each claim limitation (*id.*), and relies upon the Winkler Declaration (Ex. 1009) to support its positions.

UTC contends that Kawakami should not be considered as evidence of unpatentability because the declaration certifying the accuracy of the translation is deficient. Prelim. Resp. 38–39. UTC also asserts that Eğe is merely a generic introductory chemistry text, and irrelevant to the

IPR2020-00770
United Therapeutics EX2007
Page 3421 of 7335

'393 patent. *Id.* at 47. UTC further argues that SteadyMed has not identified a rationale for, or expectation of success in, combining either Moriarty, Phares, and Eğe, or Moriarty, Kawakami, and Eğe. *Id.* In addition, UTC contends that SteadyMed improperly asserts that the cited combination would inherently result in the claimed product. *Id.* at 54.

Kawakami

Kawakami describes "a crystalline dicyclohexylamine salt of a methanoprostacyclin derivative, a manufacturing method thereof, and a purifying method thereof." Ex. 1007, 3. Kawakami discloses obtaining a dicyclohexylamine salt by "mixing a methanoprostacyclin derivative [I] . . . with dicyclohexylamine in an appropriate solvent." Ex. 1007, 5–6. Kawakami explains that "[t]he dicyclohexylamine salt of the methanoprostacyclin derivative [I] thus obtained generally has fairly high purity, and the purity can be further improved by recrystallization as needed with the use of an appropriate solvent." *Id.* at 6.

Kawakami further teaches that "[t]he dicyclohexylamine salt obtained by the present invention can be easily reverted to a free methanoprostacyclin derivative [I] by conventional methods, and the resulting methanoprostacyclin derivative exhibits excellent crystallinity compared with substances not purified according to the present invention." *Id.*

Eğe

Eğe is an organic chemistry textbook. Ex. 1008, 1. Eğe discloses:

> Carboxylic acids that have low solubility in water, such as benzoic acid, are converted to water-soluble salts by reaction

IPR2020-00770
United Therapeutics EX2007
Page 3422 of 7335

> with aqueous base. Protonation of the carboxylate anion by a strong acid regenerates the water-insoluble acid. These properties of carboxylic acids are useful in separating them from reaction mixtures containing neutral and basic compounds.

Id. at 8 (reference omitted).

Compliance with 37 C.F.R. § 42.63(b)

Kawakami is a Japanese patent application. Ex. 1006. SteadyMed submitted an English translation of Kawakami (Ex. 1007), as well as an affidavit certifying that translation (Ex. 1011) with its Petition.

UTC nevertheless contends that Kawakami should not be considered as evidence of unpatentability because the President of the translation service, rather than the individual who prepared the translation, executed the certification affidavit. Prelim. Resp. 38–39. UTC asserts that certification affidavit is objectionable because the affiant lacks personal knowledge of the relevant facts, the accuracy of the translation cannot be determined, and the translator is shielded from cross-examination. *Id.* at 39.

In view of the record before us, and for purposes of this decision, we decline UTC's invitation to disregard Kawakami. No credible prejudice to UTC has been called to our attention, and none is apparent. An English translation of Kawakami was available to UTC in time to prepare its Preliminary Response.[8] Furthermore, UTC has not identified any error in

[8] It does not appear that UTC has served objections on SteadyMed concerning the adequacy of the English translation of Kawakami or the certifying affidavit.

IPR2020-00770
United Therapeutics EX2007
Page 3423 of 7335

the translation that would call into question its authenticity. Regarding UTC's contention that the accuracy of the translation cannot be determined absent a certification affidavit from the translator himself, we note that the commission of an independent translation would confirm the veracity of the translation submitted by SteadyMed. We also observe that even if the individual personally responsible for generating the English translation of Kawakami had submitted a certification affidavit, UTC would not have had the opportunity to cross-examine him prior to the submission of its Preliminary Response.

Accordingly, on the record before us, and for purposes of this decision, we decline UTC's request that we disregard Kawakami. We observe, however, that the adequacy of the Kawakami translation and certification affidavit may be subject to further challenge during trial.[9]

Rationale to Combine Prior Art Teachings

Building on the rationale for combining Moriarty and Phares discussed in Part II.E above, SteadyMed contends that a relevant skilled

---

[9] Pursuant to 37 C.F.R. § 42.64(b)(1), "[a]ny objection to evidence submitted during a preliminary proceeding must be served within ten business days of the institution of the trial. . . . The objection must identify the grounds for the objection with sufficient particularity to allow correction in the form of supplemental evidence." "The party relying on evidence to which an objection is timely served may respond to the objection by serving supplemental evidence within ten business days of service of the objection." 37 C.F.R. § 42.64(b)(2). Furthermore, "[a] motion to exclude evidence must be filed to preserve any objection. . . . The motion may be filed without prior authorization from the Board." 37 C.F.R. § 42.64(c)

artisan would add further purification steps from Kawakami and Eğe because Kawakami "discloses that the dicyclohexylamine salt of a methanoprostacyclin derivative 'can be easily reverted to the free methanoprostacyclin derivative by *conventional methods*,'" and that the "fairly high purity" of the salt obtained "can be further improved by recrystallization as needed with the use of an appropriate solvent." Pet. 53; *see also* Ex. 1007, 6; Ex. 1009 ¶ 83. Dr. Winkler testifies that, as evidenced by Eğe, a relevant skilled artisan "would understand that one such conventional method for converting the dicyclohexylamine salt of a methanoprostacyclin derivative to the free methanoprostacyclin derivative, or converting the treprostinil diethanolamine salt to treprostinil (*i.e.*, the free acid) is by treating the salt with a strong acid such as HCl or H_2SO_4." Ex. 1009 ¶ 84; *see also* Pet. 53–54.

Dr. Winkler elaborates on this rationale for combining the cited references, testifying that a relevant skilled artisan

> would want to form the treprostinil diethanolamine salt, purify it, and then convert it back to its free form (*i.e.*, treprostinil) in order to obtain excellent crystallinity and increased purity. And Ege (Ex. 1008, p. 8) teaches that one such method for obtaining the free form of treprostinil or any carboxylic acid would be by treatment of the carboxylate salt with a strong acid.

Ex. 1009 ¶ 88; *see also* Ex. 1008, 8; Pet. 54.

UTC does not address the combination of Moriarty, Eğe, Phares, and Kawakami. Instead, UTC addresses Moriarty, Eğe, and Phares as one combination, and Moriarty, Eğe, and Kawakami as an alternative combination. Prelim. Resp. 46–47.

IPR2020-00770
United Therapeutics EX2007
Page 3425 of 7335

As an initial matter, UTC asserts that Eğe is irrelevant to the '393 patent because it does not discuss prostacyclin derivatives or pharmaceutical synthesis. *Id.* at 47. UTC argues that Eğe in fact "would teach away or discourage the use of salt formation for purifying a mixture of compounds that includes other carboxylic-acid containing compounds as impurities." *Id.* at 48.

Regarding the combination of Moriarty, Eğe, and Phares, UTC contends that "even though Phares discloses forming a salt from treprostinil free acid, and Ege generally discusses that carboxylate salt formation was known in the art, there would have been no motivation or expectation of success in using these teachings on the already-formed free acid disclosed in Moriarty." Prelim. Resp. 50. Pertaining to the combination of Moriarty, Eğe, and Kawakami, UTC asserts that SteadyMed "fails to establish that a [relevant skilled artisan] would reasonably expect the teachings of Kawakami to extend to the products in Moriarty." *Id.* at 52.

UTC also argues that Dr. Winkler's testimony regarding the reasons a relevant skilled artisan would want to form treprostinil diethanolamine salt, and treat it with a strong acid to convert it back to its free form (treprostinil) is improperly conclusory. *Id.* at 50, 52.

On the record before us, and for purposes of this decision, we agree that SteadyMed has sufficiently demonstrated that a relevant skilled artisan would have had reason to include the carboxylate salt formation and regeneration of the neutral carboxylic acid with the syntheses of Moriarty and Phares based on the teachings of Kawakami and Eğe.

IPR2020-00770
United Therapeutics EX2007
Page 3426 of 7335

We recognize, but do not find persuasive, UTC's position that Eğe is irrelevant to the synthesis of prostacyclin derivatives, and that it teaches away from the use of salt formation for purifying a mixture of compounds that includes other carboxylic-acid containing compounds as impurities. First, we observe that SteadyMed relies on Eğe not for any teachings specific to prostacyclin derivative synthesis, but rather, to support the contention that the addition of a strong acid to a carboxylate salt to regenerate the neutral carboxylic acid is a conventional purification technique in organic chemistry. Pet. 53–55; Ex. 1009 ¶¶ 86, 88. In particular, Dr. Winkler testifies that the "addition of a strong acid to a carboxylate salt to regenerate the neutral carboxylic acid is a common reaction in organic chemistry and this process is well within the skill of one of ordinary skill in the art (indeed, a process that I teach to my organic chemistry students)" (Ex. 1009 ¶ 85), and that Eğe, an introductory organic chemistry text, "discloses that sodium benzoate (i.e., a carboxylate salt) can be converted back to benzoic acid (i.e., a carboxylic acid) by treatment with the acid HCl" (*id.* ¶ 86). On this record, we credit Dr. Winkler's testimony, as it is consistent with the prior art.

Second, we note that even crediting UTC's position that the use of salt formation would not be effective for purifying treprostinil from its stereoisomers (Prelim. Resp. 47–48), the present record suggests that it would be effective for removing other impurities (Pet. 53–55; Ex. 1009 ¶¶ 86, 88). Moreover, as explained below, the present record, including Kawakami, indicates that treprostinil diethanolamine salt formation followed

IPR2020-00770
United Therapeutics EX2007
Page 3427 of 7335

by regeneration of treprostinil using a strong acid is an effective purification step. Pet. 53–55; *see also* Ex. 1007, 6; Ex. 1008, 8; Ex. 1009 ¶¶ 82–90.

Additionally, we agree with SteadyMed that a relevant skilled artisan would have had reason to combine Moriarty, Phares, Kawakami, and Eğe. Pet. 53–55; Ex. 1009 ¶¶ 82–90. For example, Dr. Winkler testifies that a relevant skilled artisan would want to include a carboxylate salt formation and regeneration of the neutral carboxylic acid as described by Eğe with the syntheses of Moriarty and Phares because Kawakami teaches that "'the dicyclohexylamine salt obtained by the present invention can be easily reverted to a free methanoprostacyclin derivative [I] by conventional methods, and the resulting methanoprostacyclin derivative exhibits excellent crystallinity compared with substances not purified according to the present invention.'" Ex. 1009 ¶ 86; *see also* Ex. 1007, 6; Pet. 53–55. Dr. Winkler additionally testifies that a skilled artisan would be motivated to form treprostinil diethanolamine salt, and treat it with a strong acid to "obtain excellent crystallinity and increased purity" of the final treprostinil product (Ex. 1009 ¶ 88), and that a skilled artisan would have a reasonable expectation of success in performing such reaction because it is "a common reaction in organic chemistry and this process is well within the skill of one of ordinary skill in the art" (*id.* ¶ 90).

On this record, we credit Dr. Winkler's testimony, as it is consistent with the prior art. Moreover, we disagree with UTC that Dr. Winkler's testimony is improperly conclusory. Rather, as illustrated by the excerpts of his testimony referenced above, Dr. Winkler supports his opinions with

IPR2020-00770
United Therapeutics EX2007
Page 3428 of 7335

reference to the cited art, as well as his experience as a chemist and chemistry professor.

Accordingly, on the record before us, we agree that SteadyMed has sufficiently demonstrated that one of ordinary skill in the art would have included the carboxylate salt formation and regeneration of the neutral carboxylic acid of Eğe with the syntheses of Moriarty and Phares based on Kawakami's disclosure that the conversion of salts of prostacyclin derivatives to their free forms by conventional methods increases purity of the final product. *See KSR*, 550 U.S. at 417 ("[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.").

Claims 6, 15, and 21

Claims 6, 15, and 21 each recite the product of either claim 1 or claim 9, subject to additional process steps. For example, claim 6 recites "[t]he product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4." Ex. 1001, 19:39–40. Claim 15 similarly recites "[t]he product of claim 9, wherein the acid in step (d) is HCl." *Id.* at 20:59–60. Claim 21 simply recites "[t]he product of claim 1, wherein step (d) is performed." *Id.* at 21:13.

The present record supports SteadyMed's contention that claims 6, 15, and 21 would have been obvious in view of Moriarty, Eğe, Phares, and

IPR2020-00770
United Therapeutics EX2007
Page 3429 of 7335

Kawakami. Pet. 53–56; Ex. 1009 ¶¶ 82–90. For example, Dr. Winkler testifies that

> the combination of Moriarty (Ex. 1004) and Phares (Ex. 1005) (or Kawakami, Exs. 1006 & 1007) and Ege (Ex. 1008) would disclose . . . treprostinil of at least equal purity to that claimed in the '393 Patent, since the combination of these references discloses the same product and same process of Claims 1 and 9.

Ex. 1009 ¶ 89; *see also* Pet. 54. In addition, as explained above, Dr. Winkler testifies that a skilled artisan would have made the cited combination, with an expectation of success, in order to obtain a treprostinil product of improved purity. Ex. 1009 ¶¶ 88–90; Pet. 54–55. On this record, we credit Dr. Winkler's testimony.

UTC does not offer evidence or argument to suggest that the additional process steps recited in claims 6, 15, and 21 impart structural or functional differences to the claimed product beyond that discussed above in Parts II.B, II.D, and II.E. Rather, UTC contends that SteadyMed has not asserted that the products of claims 6, 15, and 21 would have been obvious in view of the cited art. Prelim. Resp. 54. UTC frames SteadyMed's position as an argument that the recited process steps would have been obvious, and would have inherently resulted in the claimed product. *Id.*

We do not find UTC's contentions persuasive. We observe that claims 6, 15, and 21 differ from their respective independent claims only in that they require the performance of optional step (d) from claims 1 and 9, and in the case of claims 6 and 15, specify the acid to be used in carrying out that process step. Ex. 1001, 19:39–40, 20:59–60. As set forth in detail in Parts II.A, II.B, II.D, and II.E, on the record before us, and for purposes of

IPR2020-00770
United Therapeutics EX2007
Page 3430 of 7335

this decision, we conclude that the process steps recited in the challenged claims, including step (d), do not impart structural or functional differences over prior art treprostinil products.

Furthermore, we disagree with UTC's characterization of SteadyMed's obviousness argument. We note, for example, that under the general rule for the interpretation of product-by-process claims, which we determine applies here, the products of claims 1, 6, and 21 are interpreted to be the same, namely, the product of claim 1. Likewise, the same analysis applies for the products of claims 9 and 15.

Accordingly, given the evidence before us in this record, we conclude that SteadyMed has established adequately for purposes of this decision that the combination of Eğe, Phares, and Kawakami renders obvious the treprostinil products of claims 6, 15, and 21. Because we determine, on the record before us, and for purposes of institution, that the process steps recited in claims 6, 15, and 21 do not impart structural or functional differences to the claimed treprostinil product, we do not address the parties' contentions concerning the obviousness of the recited process steps.

Claim 10

Claim 10 recites "[t]he product of claim 9, wherein the purity of product of step (d) is at least 99.5%." Ex. 1001, 20:47–48. The present record supports SteadyMed's contention that claim 10 is obvious in view of Moriarty, Eğe, Phares, and Kawakami. Pet. 55–56; *see also* Ex. 1009 ¶¶ 82–90. As detailed in Parts II.B, II.D, and II.E, the present record supports SteadyMed's position that Moriarty discloses treprostinil free acid having a

IPR2020-00770
United Therapeutics EX2007
Page 3431 of 7335

purity of 99.7% (Pet. 20; *see also* Ex. 1004, 13; Ex. 1009 ¶ 65), and Phares discloses treprostinil diethanolamine salt of the same form and at least the same purity as that claimed in the '393 patent (Pet. 27–28; Ex. 1005, 88–93; Ex. 1009 ¶¶ 59–62). The present record further supports SteadyMed's contention that even if Dr. Walsh's impurity measurements are credited, the 0.1% difference between the purity of the sample prepared according to Moriarty, and claim 10 is within the expected level experimental error for impurity measurements, and the degree of inter-batch variability in impurity content is such that Dr. Walsh's results are insufficient to support a conclusion of nonobviousness. Pet. 19–22; *see also* Ex. 1009 ¶¶ 63–71.

UTC does not offer evidence or argument to suggest that the additional process step recited in claim 10 imparts structural or functional differences to the claimed product beyond that discussed above in Parts II.A, II.B, II.D, and II.E. Neither does UTC present any additional argument regarding the recited purity requirement beyond those already addressed above. UTC does reassert its position, discussed with regard to claims 6, 15, and 21, that SteadyMed has not asserted that the product of claim 10 would have been obvious in view of the cited art. Prelim. Resp. 54. For the reasons set forth above, however, we do not find this contention persuasive.

Accordingly, given the evidence before us in this record, we conclude that SteadyMed has established adequately for purposes of this decision that the combination of Eğe, Phares, and Kawakami renders obvious the treprostinil product of claim 10. Because we determine, on the record before us, and for purposes of institution, that the process steps recited in claim 10

IPR2020-00770
United Therapeutics EX2007
Page 3432 of 7335

do not impart structural or functional differences to the claimed treprostinil product, we do not address the parties' contentions concerning the obviousness of the recited process steps at this time.

Claim 22

Claim 22 recites "[t]he product of claim 21, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d)." Ex. 1001, 21:14–16. The present record supports SteadyMed's contention that claim 22 is obvious in view of Moriarty, Eğe, Phares, and Kawakami. Pet. 56–57; *see also* Ex. 1009 ¶¶ 82–90. As discussed above in Parts II.D and II.E, the present record supports SteadyMed's position that the cited combination renders obvious a pharmaceutically acceptable treprostinil salt.

UTC does not offer evidence or argument to suggest that the additional process step recited in claim 22 imparts structural or functional differences to the claimed product beyond that discussed above in Parts II.A, II.B, II.D, and II.E. Neither does UTC present any additional argument regarding the recited purity requirement beyond those already addressed above. UTC does reassert its position, discussed with regard to claims 6, 15, and 21, that SteadyMed has not asserted that the product of claim 22 would have been obvious in view of the cited art. Prelim. Resp. 54. For the reasons set forth above, however, we do not find this contention persuasive

Accordingly, given the evidence before us in this record, we conclude that SteadyMed has established adequately for purposes of this decision that the combination of Eğe, Phares, and Kawakami renders obvious the

IPR2020-00770
United Therapeutics EX2007
Page 3433 of 7335

treprostinil products of claim 22. Because we determine, on the record before us, and for purposes of institution, that the process steps recited in claims 22 do not impart structural or functional differences to the claimed treprostinil product, we do not address the parties' contentions concerning the obviousness of the recited process steps at this time.

Conclusion

For the foregoing reasons, we conclude that SteadyMed has shown a reasonable likelihood of prevailing on its assertions that claims 6, 10, 15, 21, and 22 are obvious in view of Moriarty, Eğe, Phares, and Kawakami.

G. Secondary Considerations of Non-Obviousness

UTC contends that objective indicia of non-obviousness, such as purported evidence of long-felt but unmet need, unexpected results, commercial success, and copying support the patentability of the challenged claims of the '393 patent. Prelim. Resp. 55–58.

We conclude that the evidence of secondary considerations currently of record is not sufficient, at this point in the proceeding, to support UTC's contention. As an initial matter, we observe that "secondary considerations are better considered in the context of a trial when the ultimate determination of obviousness is made." *Crocs, Inc. v. Polliwalks, Inc.*, Case IPR2014-00424, slip op. 16 (PTAB Aug. 20, 2014) (Paper 8). In addition, we note that UTC's contentions regarding long-felt need and unexpected results are predicated on UTC's claim that treprostinil made according to the process described in the '393 patent has fewer impurities than treprostinil produced by other methods. However, as explained in Parts II.B, II.D, and

IPR2020-00770
United Therapeutics EX2007
Page 3434 of 7335

II.E above, the present record does not support that contention. We also observe that UTC does not offer evidence of a nexus between the claimed invention and its commercial success. For example, UTC does not offer evidence concerning its relative share of the market for treprostinil products, or demonstrating that its revenues or market share increased after it began manufacturing treprostinil according to the process described in the '393 patent. Finally, we note that the mere existence of litigation concerning the '393 patent alone is insufficient to establish copying. *See Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004) ("Not every competing product that arguably fails within the scope of a patent is evidence of copying. Otherwise every infringement suit would automatically confirm the nonobviousness of the patent.").

H. Other Asserted Grounds of Unpatentability

SteadyMed also asserts the following ground of unpatentability:

Claims	Basis	Reference(s)
1–5, 7–9, 11–14, and 16–20	§ 103(a)	Moriarty and Kawakami

In light of the grounds specifically discussed above, on the basis of which we institute review, we exercise our discretion and decline to consider these other grounds asserted in the Petition. *See* 37 C.F.R. § 42.108(a). We observe that SteadyMed presents the above ground of unpatentability and the obviousness of claims 1–5, 7–9, 11–14, and 16–20 in view of Moriarty and Phares, a ground on which we institute review, in the alternative.

III. CONCLUSION

For the foregoing reasons, we determine that the information presented in the Petition establishes that there is a reasonable likelihood that SteadyMed would prevail in challenging claims 1–22 of the '393 patent. At this juncture, we have not made a final determination with respect to the patentability of the challenged claims, nor with respect to claim construction.

IV. ORDER

For the foregoing reasons, it is

ORDERED that pursuant to 35 U.S.C. § 314(a), an *inter partes* review is hereby instituted for the following grounds of unpatentability:

Claims	Basis	Reference(s)
1–5, 7–9, 11–14, and 16–20	§ 102(b)	Phares
1–5, 7–9, 11–14, and 16–20	§ 103(a)	Moriarty and Phares
6, 10, 15, 21, and 22	§ 103(a)	Moriarty, Phares, Kawakami, and Eğe

FURTHER ORDERED that no other ground of unpatentability asserted in the Petition is authorized for this *inter partes* review; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial; the trial will commence on the entry date of this decision.

IPR2020-00770
United Therapeutics EX2007
Page 3436 of 7335

PETITIONER:

Stuart E. Pollack
Lisa A. Haile
DLA Piper LLP
stuart.pollack@dlapiper.com
lisa.haile@dlapiper.com
steadymed-ipr@dlapiper.com

PATENT OWNER:

Stephen B. Maebius
George Quillin
FOLEY & LARDNER LLP
smaebius@foley.com
gquillin@foley.com

Shaun R. Snader
UNITED THERAPEUTICS CORP.
ssnader@unither.com

Douglas Carsten
Richard Torczon
Robert Delafield
WILSON, SONSINI, GOODRICH & ROSATI
dcarsten@wsgr.com
rtorczon@wsgr.com
bdelafield@wsgr.com

IPR2020-00770
United Therapeutics EX2007
Page 3437 of 7335

Doc Code: PET.AUTO Document Description: Petition automatically granted by EFS-Web	PTO/SB/140 U.S. Patent and Trademark Office Department of Commerce

Electronic Petition Request	**PETITION TO WITHDRAW AN APPLICATION FROM ISSUE AFTER PAYMENT OF THE ISSUE FEE UNDER 37 CFR 1.313(c)**
Application Number	14754932
Filing Date	30-Jun-2015
First Named Inventor	Hitesh Batra
Art Unit	1672
Examiner Name	YEVGENY VALENROD
Attorney Docket Number	080618-1550
Title	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN2

An application may be withdrawn from issue for further action upon petition by the applicant. To request that the Office withdraw an application from issue, applicant must file a petition under this section including the fee set forth in § 1.17(h) and a showing of good and sufficient reasons why withdrawal of the application from issue is necessary.

APPLICANT HEREBY PETITIONS TO WITHDRAW THIS APPLICATION FROM ISSUE UNDER 37 CFR 1.313(c).

A grantable petition requires the following items:
(1) Petition fee; and
(2) One of the following reasons:
(a) Unpatentability of one or more claims, which must be accompanied by an unequivocal statement that one or more claims are unpatentable, an amendment to such claim or claims, and an explanation as to how the amendment causes such claim or claims to be patentable;
(b) Consideration of a request for continued examination in compliance with § 1.114 (for a utility or plant application only); or
(c) Express abandonment of the application. Such express abandonment may be in favor of a continuing application, but not a CPA under 37 CFR 1.53(d).

Petition Fee

○	Small Entity
○	Micro Entity
◉	Regular Undiscounted

Reason for withdrawal from issue

○ One or more claims are unpatentable ◉ Consideration of a request for continued examination (RCE) (List of Required Documents and Fees) ○ Applicant hereby expressly abandons the instant application (any attorney/agent signing for this reason must have power of attorney pursuant to 37 CFR 1.32(b)).
RCE request,submission, and fee. ☐ I certify, in accordance with 37 CFR 1.4(d)(4) that : The RCE request ,submission, and fee have already been filed in the above-identified application on ☒ Are attached.
THIS PORTION MUST BE COMPLETED BY THE SIGNATORY OR SIGNATORIES I certify, in accordance with 37 CFR 1.4(d)(4) that I am: ◉ An attorney or agent registered to practice before the Patent and Trademark Office who has been given power of attorney in this application. ○ An attorney or agent registered to practice before the Patent and Trademark Office, acting in a representative capacity. ○ A sole inventor ○ A joint inventor; I certify that I am authorized to sign this submission on behalf of all of the inventors as evidenced by the power of attorney in the application ○ A joint inventor; all of whom are signing this e-petition

Signature	/Kristel Schorr/
Name	Kristel Schorr
Registration Number	55600

Electronic Patent Application Fee Transmittal

Application Number:	14754932
Filing Date:	30-Jun-2015
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN2
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Kristel Schorr/Karen Strawderman
Attorney Docket Number:	080618-1550

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
PETITION FEE- 37 CFR 1.17(H) (GROUP III)	1464	1	140	140
RCE- 2ND AND SUBSEQUENT REQUEST	1820	1	1700	1700
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1840**

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Decision Date : December 21, 2016

In re Application of :

Hitesh Batra

DECISION ON PETITION
UNDER CFR 1.313(c)(2)

Application No : 14754932

Filed : 30-Jun-2015

Attorney Docket No : 080618-1550

This is an electronic decision on the petition under 37 CFR 1.313(c)(2), filed December 21, 2016 to withdraw the above-identified application from issue after payment of the issue fee.

The petition is **GRANTED.**

The above-identified application is withdrawn from issue for consideration of a submission under 37 CFR 1.114 (request for continued examination). See 37 CFR 1.313(c)(2).

Petitioner is advised that the issue fee paid in this application cannot be refunded. If, however, this application is again allowed, petitioner may request that it be applied towards the issue fee required by the new Notice of Allowance.

Telephone inquiries concerning this decision should be directed to the Patent Electronic Business Center (EBC) at 866-217-9197.

This application file is being referred to Technology Center AU 1672 for processing of the request for continuing examination under 37 CFR 1.114 .

Office of Petitions

Electronic Acknowledgement Receipt	
EFS ID:	27860642
Application Number:	14754932
International Application Number:	
Confirmation Number:	1865
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN2
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Kristel Schorr/Karen Strawderman
Filer Authorized By:	Kristel Schorr
Attorney Docket Number:	080618-1550
Receipt Date:	21-DEC-2016
Filing Date:	30-JUN-2015
Time Stamp:	13:47:22
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$1840
RAM confirmation Number	122216INTEFSW13471500
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	RCETM.pdf	105952 508fd8ae32ef6699395e08d6f7d1ecb542039604	no	4
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	IDS.pdf	384362 fb773e46fda6090eeaf4487a449b69851e84e757	no	6
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
3	Other Reference-Patent/App/Search documents	11-28-2016PetitionerDemonstratives.pdf	12565962 7142b69357b8c2f269caedc971e12d5cef5f9321	no	82
Warnings:					
The page size in the PDF is too large. The pages should be 8.5 x 11 or A4. If this PDF is submitted, the pages will be resized upon entry into the Image File Wrapper and may affect subsequent processing					
Information:					
4	Other Reference-Patent/App/Search documents	11-23-2016PatentOwnerResponseandExhibits.pdf	5048622 85f049c2e11a99e2bc14f25f70b687446d908145	no	1151
Warnings:					
Information:					
5	Other Reference-Patent/App/Search documents	ThirdPtySubmPARTONE.pdf	12232042 62e26c7f469400038e2c93b2291abc94b32886af	no	400
Warnings:					
Information:					

6	Other Reference-Patent/App/Search documents	ThirdPtySubmPARTTWO.pdf	12573947 f17f8c9481a1f3313d75406c88c2144d2975b902	no	422
Warnings:					
Information:					
7	Other Reference-Patent/App/Search documents	SandozInvCont2-5-2015Redacted.pdf	603522 e6a3a54cee4303307b4a54ccb540ddb9c308eb80	no	90
Warnings:					
Information:					
8	Other Reference-Patent/App/Search documents	SandozInvContCharts2-5-2015.pdf	698449 b63f37bd11c3839e30470758af75d70041231fd9	no	189
Warnings:					
Information:					
9	Other Reference-Patent/App/Search documents	ActavisPrelInvCont8-30-2016.pdf	1806962 c4469aba665c0ada06bd1cb9c46c2f66d783d254	no	330
Warnings:					
Information:					
10	Other Reference-Patent/App/Search documents	Treprostinil_-_Ex__G_invalidity_chart_for_the__393_patent_1-12-2015.pdf	304304 6bc080014897a484b8d06175e4d7985d11b1ec92	no	66
Warnings:					
Information:					
11	Other Reference-Patent/App/Search documents	TevaInvCont4-24-2015.pdf	567620 856442f52f1d8f3a02c1a3892acfcb7b123cb0c4	no	94
Warnings:					
Information:					
12	Non Patent Literature	Arumugam.pdf	510030 437a3975900966a808334a109ba44ad67432f70b	no	2
Warnings:					
Information:					

13	Non Patent Literature	Burk.pdf	704672 18b841deda8a39082b82cf4da79b3d470fa0af71	no	4
Warnings:					
Information:					
14	Non Patent Literature	Eliel.pdf	643300 aab21634720bd173fac8b09074dc0e550aba6b99	no	6
Warnings:					
Information:					
15	Non Patent Literature	Harwood.pdf	904588 9ebe079787102934b9284aa2a9f29b4b0240fac7	no	11
Warnings:					
Information:					
16	Non Patent Literature	Jones.pdf	544757 115e7f7ef706251e05ce52a08662401312d12185	no	5
Warnings:					
Information:					
17	Non Patent Literature	Lin.pdf	1300793 77655d6bb757ad96b8b08737c99e80e57bc60ff4	no	8
Warnings:					
Information:					
18	Non Patent Literature	McManus.pdf	745927 43532b7572f451474c2b10cd7cd91bd74c8eb9bc	no	4
Warnings:					
Information:					
19	Non Patent Literature	Monson.pdf	787507 c11a6382504698cca5cdcbbceef885dc8d3b7a98	no	13
Warnings:					
Information:					

20	Non Patent Literature	Ohno.pdf	2055739 01c03319fb6a8140a0c95478a9c1586decff546a	no	16
Warnings:					
Information:					
21	Non Patent Literature	Olmsted.pdf	14163672 c4e45e76ce502d6f097a9ca771ca1911d1bcd175	no	62
Warnings:					
Information:					
22	Non Patent Literature	Pavia.pdf	479524 74f5a68bdb2973f0492dde185e6d40d6ebc0985f	no	3
Warnings:					
Information:					
23	Non Patent Literature	PDR2005.pdf	1176914 83b70e21d08abeaefcfee3c4b70abd631686f6e5	no	5
Warnings:					
Information:					
24	Non Patent Literature	Prisinzano.pdf	754866 aa23db551f329816a2997cfbff0f6bd9e23bc772	no	4
Warnings:					
Information:					
25	Non Patent Literature	Remodulin.pdf	288112 95d1746902a33b23b318865a79fc61e391a21390	no	17
Warnings:					
Information:					
26	Non Patent Literature	Schoffstall.pdf	7105291 e97a314c08d1ec7a795ed31c69ee90fb172b9d76	no	5
Warnings:					
Information:					

27	Non Patent Literature	Sorrell.pdf	560691 9a6f445c1399544cb4cba882cb28bcfc927d498b	no	6
Warnings:					
Information:					
28	Non Patent Literature	Wiberg.pdf	5760043 414bd0a91ea52145029ba4b60477a777fc400b3c	no	6
Warnings:					
Information:					
29	Non Patent Literature	Yu.pdf	689895 9e21b8aced370b80d93c796cfd434a72a159d29f	no	4
Warnings:					
Information:					
30	Other Reference-Patent/App/Search documents	11-23-2016PatentOwnerDemonstratives.pdf	11944838 839a943270b3278a2096b8e53ab34487aac3be0e	no	62
Warnings:					
Information:					
31	Other Reference-Patent/App/Search documents	11-23-2016RedactedDecisiontoInstitute.pdf	2124535 d1f286e1b0f08b79783924384114df8d52f823ed	no	53
Warnings:					
Information:					
32	Petition automatically granted by EFS	petition-request.pdf	31628 c3cdda2387dcd7b37564ae294bb6a95fff83c89b7	no	2
Warnings:					
Information:					
33	Fee Worksheet (SB06)	fee-info.pdf	32537 7e9575e20d85e2b5bc8780b9196423cd5a6f4983	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	100201603	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 02/08/2017

ABOARDLE SALE #00000001 Mailroom Dt: 12/21/2016 190741 14754932
01 FC : 1806 180.00 DA

To: ipdocketing@foley.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 22428

Dec 08, 2016 03:26:17 AM

Dear PAIR Customer:

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 22428 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Disclaimer:
The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
14754932	ISSUE.NTF	12/07/2016	080618-1550

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/754,932	12/27/2016	9527794	080618-1550	1865

22428 7590 12/07/2016

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Hitesh Batra, Herndon, VA;
United Therapeutics Corporation, Silver Spring, MD;
Sudersan M. Tuladhar, Silver Spring, MD;
Raju Penmasta, Herndon, VA;
David A. Walsh, Palmyra, VA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

22428 7590 11/09/2016

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/754,932	06/30/2015	Hitesh Batra	080618-1550	1865

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN2

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	02/09/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
VALENROD, YEVGENY	1672	562-466000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Foley & Lardner LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: United Therapeutics Corporation

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Silver Spring, MD

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☒ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☒ Payment by credit card. Form PTO-2038 is attached.
- ☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 19-0741 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
  NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ☐ Applicant asserting small entity status. See 37 CFR 1.27
  NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ☐ Applicant changing to regular undiscounted fee status.
  NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Stephen B. Maebius/ Date Nov. 10, 2016

Typed or printed name Stephen B. Maebius Registration No. 35264

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

IPR2020-00770
United Therapeutics EX2007
Page 3453 of 7335

Electronic Patent Application Fee Transmittal

Application Number:	14754932
Filing Date:	30-Jun-2015
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN2
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1550

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
UTILITY APPL ISSUE FEE	1501	1	960	960

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**960**

Electronic Acknowledgement Receipt	
EFS ID:	27477347
Application Number:	14754932
International Application Number:	
Confirmation Number:	1865
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN2
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Stephen Bradford Maebius/Karen Strawderman
Filer Authorized By:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1550
Receipt Date:	10-NOV-2016
Filing Date:	30-JUN-2015
Time Stamp:	16:28:21
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	$960
RAM confirmation Number	111416INTEFSW16300500
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	IFTM.pdf	130822 677be73ee4a6d67b68aced156990a512731b397c	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30820 f1daee09d653a0e362b34011f556a756ed4c8cf9	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	161642		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

22428 7590 11/09/2016

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

EXAMINER
VALENROD, YEVGENY

ART UNIT	PAPER NUMBER
1672	

DATE MAILED: 11/09/2016

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/754,932	06/30/2015	Hitesh Batra	080618-1550	1865

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN2

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	02/09/2017

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

IPR2020-00770
United Therapeutics EX2007
Page 3458 of 7335

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

22428 7590 11/09/2016

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/754,932	06/30/2015	Hitesh Batra	080618-1550	1865

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN2

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	02/09/2017

EXAMINER	ART UNIT	CLASS-SUBCLASS
VALENROD, YEVGENY	1672	562-466000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

IPR2020-00770
United Therapeutics EX2007
Page 3459 of 7335

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/754,932	06/30/2015	Hitesh Batra	080618-1550	1865

22428 7590 11/09/2016

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

EXAMINER	
VALENROD, YEVGENY	

ART UNIT	PAPER NUMBER
1672	

DATE MAILED: 11/09/2016

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

IPR2020-00770
United Therapeutics EX2007
Page 3460 of 7335

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 14/754,932	Applicant(s) BATRA ET AL.	
	Examiner YEVGENY VALENROD	Art Unit 1672	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *reply filed on 10/25/16*.
   ☒ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on *7/19/16.*
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1,6 and 8-14*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   Certified copies:
   a) ☐ All b) ☐ Some *c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1672

IPR2020-00770
United Therapeutics EX2007
Page 3462 of 7335

OK TO ENTER: /Y.V/

Atty. Dkt. No. 080618-1550
Appl. No. 14/754,932

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	14/754,932
Filing Date:	6/30/2015
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation Number:	1865

REQUEST FOR RECONSIDERATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This request is submitted in response to the outstanding final Office Action mailed on Oct. 19, 2016.

Remarks begin on page 2 of this document.

IPR2020-00770
United Therapeutics EX2007
Page 3463 of 7335

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14754932	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1672

CPC							
Symbol						**Type**	**Version**
C07C		59	/	72		F	2013-01-01
C07C		51	/	08		I	2013-01-01
C07C		51	/	412		I	2013-01-01
C07C		213	/	08		I	2013-01-01
C07C		51	/	41		I	2013-01-01
A01N		37	/	10		A	2013-01-01
C07C		39	/	12		A	2013-01-01
C07C		39	/	17		A	2013-01-01
C07C		59	/	60		A	2013-01-01
C07C		405	/	0075		I	2013-01-01
			/				
			/				
			/				
			/				
			/				

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
C07C		51	/	08	I	1	1	2013-01-01
C07C		59	/	72	I	1	2	2013-01-01
C07C		51	/	412	I	2	1	2013-01-01
C07C		59	/	72	I	2	2	2013-01-01

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	9	
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672	11/04/2016	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14754932	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1672

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION	
CLASS	SUBCLASS	CLAIMED	NON-CLAIMED
562	466	C 0 7 C 59 / 72 (2006.01.01)	

CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	9	
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672	11/04/2016	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14754932	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1672

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1														
2	6														
3	8														
4	9														
5	10														
6	11														
7	12														
8	13														
9	14														

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 9	
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672 (Primary Examiner)	11/04/2016 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14754932	BATRA ET AL.
	Examiner	Art Unit
	YEVEGENY VALENROD	1672

CPC- SEARCHED		
Symbol	Date	Examiner
C07C 59/72; 51/08; 51/41; 51/412; 213/08; 405/0075	11/4/2016	YV

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
562	466	11/4/2016	YV

SEARCH NOTES		
Search Notes	Date	Examiner
EAST	10/14/2016	YV
Inventor	10/14/2016	YV
C07C 59/72; 51/08; 51/41; 51/412; 213/08; 405/0075	11/4/2016	YV

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
C07C	59/72; 51/08; 51/41; 51/412; 213/08; 405/0075	11/4/2016	YV
562	466	11/4/2016	YV

	/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672

PTO/SB/08 (modified)

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/754932
Date Submitted: October 21, 2016				**Filing Date**	6/30/2015
				First Named Inventor	Hitesh BATRA
(use as many sheets as necessary)				Art Unit	1672
				Examiner Name	Yevgeny Valenrod
Sheet	1	of	1	Attorney Docket Number	080618-1550

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number / Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document / Serial Number-Kind Code[2] (if known)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	D1	Redacted Petitioner's Reply to Patent Owner's Response to Petition filed on September 27, 2016 in *Steadymed Ltd. (Petitioner), v. United Therapeutics Corporation (Patent Owner)*, Case IPR2016-00006, US Patent 8,497,393, with Exhibits 1022-1028.	

Examiner Signature	/YEVGENY VALENROD/	Date Considered	11/04/2016

4847-4472-2491.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /Y.V/

PTO/SB/08 (modified)

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: FEB 29 2016

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	14/754932
Filing Date	6/30/2015
First Named Inventor	Hitesh BATRA
Art Unit	1672
Examiner Name	Yevgeny Valenrod
Attorney Docket Number	080618-1550

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	C1	2001/0038855 A1	11/08/2001	Desjardin et al.	
	C2	2001/0056095 A1	12/27/2001	Mylari	
	C3	4,434,164 A	02/28/1984	Lombardino	
	C4	5,466,713 A	11/14/1995	Blitstein-Willinger et al.	
	C5	5,506,265 A	04/09/1996	Blitstein-Willinger	
	C6	6,706,283 B1	03/16/2004	Appel et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	C7	WO 98/18452 A1	05/07/1998	Shire Laboratories, Inc.		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	C8	BIGHLEY et al., "Salt Forms of Drugs and Absorption," Encyclopedia of Pharmaceutical Technology, Swarbrick et al., Eds., 1995, 13:453-499.	
	C9	SIMONNEAU et al., "Continuous Subcutaneous Infusion of Treprostinil, a Prostacyclin Analogue, in Patients with Pulmonary Arterial Hypertension," Am. J. Respir. Crit. Care Med., 2002, 165:800-804.	

Examiner Signature	/YEVGENY VALENROD/	Date Considered	11/04/2016

4818-3879-5054.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /Y.V/

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14754932	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1672

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/28/2015	09/10/2015	02/04/2016	10/14/2016	11/04/2016				
1	1	✓	=	✓	=	=				
	2	✓	=	✓	-	-				
	3	✓	=	✓	-	-				
	4	✓	-	-	-	-				
	5	✓	-	-	-	-				
2	6	✓	=	✓	=	=				
	7	✓	-	-	-	-				
3	8	✓	=	✓	=	=				
4	9			✓	=	=				
5	10			✓	=	=				
6	11			✓	=	=				
7	12			✓	=	=				
8	13			✓	✓	=				
9	14			✓	✓	=				

IPR2020-00770
United Therapeutics EX2007
Page 3470 of 7335

To: ipdocketing@foley.com,,
From: PAIR_eOfficeAction@uspto.gov
Cc: PAIR_eOfficeAction@uspto.gov
Subject: Private PAIR Correspondence Notification for Customer Number 22428

Nov 09, 2016 03:31:15 AM

Dear PAIR Customer:

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109
UNITED STATES

The following USPTO patent application(s) associated with your Customer Number, 22428 , have new outgoing correspondence. This correspondence is now available for viewing in Private PAIR.

The official date of notification of the outgoing correspondence will be indicated on the form PTOL-90 accompanying the correspondence.

Disclaimer:
The list of documents shown below is provided as a courtesy and is not part of the official file wrapper. The content of the images shown in PAIR is the official record.

Application	Document	Mailroom Date	Attorney Docket No.
14754932	NOA	11/09/2016	080618-1550
	1449	11/09/2016	080618-1550
	1449	11/09/2016	080618-1550

To view your correspondence online or update your email addresses, please visit us anytime at https://sportal.uspto.gov/secure/myportal/privatepair.

If you have any questions, please email the Electronic Business Center (EBC) at EBC@uspto.gov with 'e-Office Action' on the subject line or call 1-866-217-9197 during the following hours:

Monday - Friday 6:00 a.m. to 12:00 a.m.

Thank you for prompt attention to this notice,

UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION INFORMATION RETRIEVAL SYSTEM

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	14/754,932	BATRA ET AL.	

Document Code - DISQ	Internal Document – DO NOT MAIL

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed : 10/21/16	**This patent is subject to a Terminal Disclaimer**	

Approved/Disapproved by:

Felicia D. Roberts

8,242,305

U.S. Patent and Trademark Office

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	14/754,932
Filing Date:	6/30/2015
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation Number:	1865

REQUEST FOR RECONSIDERATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

This request is submitted in response to the outstanding final Office Action mailed on Oct. 19, 2016.

Remarks begin on page 2 of this document.

REMARKS

Applicants respectfully request reconsideration and allowance of the present application.

Status of Claims

No amendments are presented.

Double Patenting

Claims 13-14 have been rejected for non-statutory double patenting as unpatentable over claims 24 and 26 of US Patent No. 8,242,305. Without acquiescing in the grounds of rejection and solely to expedite prosecution, Applicants submit a terminal disclaimer to overcome the rejection.

Concluding Remarks

Applicants believe that the application is in condition for allowance. Favorable reconsideration is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance prosecution.

The Commissioner is hereby authorized to charge any additional fees that may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition

for such extension under 37 C.F.R. § 1.136 and authorize payment of any such extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date Oct. 21, 2016

By /Stephen B. Maebius/

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

PTO/AIA/26 (04-14)
Approved for use through 07/31/2016. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A "PRIOR" PATENT	Docket Number (Optional) 080618-1550

In re Application of: Hitesh BATRA, Sudersan M. TULADHAR, Raju PENMASTA and David A. WALSH

Application No.: 14/754932

Filed: 6/30/2015

For: AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

The applicant, United Therapeutics Corporation, owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 8,242,305 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

expires for failure to pay a maintenance fee;
is held unenforceable;
is found invalid by a court of competent jurisdiction;
is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
has all claims canceled by a reexamination certificate;
is reissued; or
is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☑ The undersigned is an attorney or agent of record. Reg. No. 35,264

/Stephen B. Maebius/ — Signature
10/21/2015 — Date

Stephen B. Maebius — Typed or printed name

Foley & Lardner LLP Attorney — Title
(202) 672-5569 — Telephone Number

☑ Terminal disclaimer fee under 37 CFR 1.20(d) included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

This collection of information is required by 37 CFR 1.321. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Application No.:	14/754932
Filing Date:	6/30/2015
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation No.:	1865

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicant submits herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicant respectfully requests that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith. However, in accordance with MPEP §

IPR2020-00770
United Therapeutics EX2007
Page 3478 of 7335

609.04(a)(I), Applicant hereby states that for items for which the date of publication supplied does not include the month of publication, the year of publication is sufficiently earlier than the effective U.S. filing date and any foreign priority date so that the particular month of publication is not in issue.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(d), before payment of the issue fee.

STATEMENT UNDER 37 CFR §1.97(e)

The undersigned hereby states in accordance with 37 CFR §1.97(e)(2) that no item of information contained in this information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application and, to the knowledge of the undersigned, after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR §1.56(c) more than three months prior to the filing of the information disclosure statement.

FEE

Fees in the amount of $180.00 to cover the fee associated with an information disclosure statement are being paid by credit card via EFS-Web.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this submission under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account Number 19-0741.

Respectfully submitted,

Date October 21, 2016

By /Stephen B. Maebius/

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

IPR2020-00770
United Therapeutics EX2007
Page 3479 of 7335

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	14/754932
Date Submitted: October 21, 2016				**Filing Date**	6/30/2015
(use as many sheets as necessary)				**First Named Inventor**	Hitesh BATRA
				Art Unit	1672
				Examiner Name	Yevgeny Valenrod
Sheet	1	of	1	Attorney Docket Number	080618-1550

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number / Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document / Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document / Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	D1	Redacted Petitioner's Reply to Patent Owner's Response to Petition filed on September 27, 2016 in *Steadymed Ltd. (Petitioner), v. United Therapeutics Corporation (Patent Owner)*, Case IPR2016-00006, US Patent 8,497,393, with Exhibits 1022-1028.	

Examiner Signature		Date Considered	

4847-4472-2491.1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

STEADYMED LTD.

Petitioner,

v.

UNITED THERAPEUTICS CORPORATION

Patent Owner.

Case IPR 2016-00006

Patent No. 8,497,393B2

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE TO PETITION

37 C.F.R. § 42.23

Mail Stop "Patent Board"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

WEST\272027923.2

TABLE OF CONTENTS

Page

Petitioner SteadyMed, Ltd. submits this reply pursuant to 37 C.F.R. § 42.23.

I. SUMMARY OF THE ARGUMENT

As SteadyMed explained in its Petition, purifying by crystallization is taught in undergraduate chemistry courses: it's Organic Chemistry 101. Even Patent Owner United Therapeutics' (UT) expert recognizes this fact:

> Q: How long has crystallization been around as a method of purification?
>
> A: I don't know how long it's been around.
>
> Q: Before 2007?
>
> A: Oh, yes.
>
> Q: Did you learn about it when you were in college at the university?
>
> A: Yes, I did. […]
>
> Q: And when did you go to college?
>
> A: In 1968 I started. In 1968.
>
> ...
>
> Q: ... But how far back does doing that process you just described, how far back does that go?
>
> The Witness: Decades.

(Ex. 2058, 175:19-176:22, 179:11-17).

Even though the purification process claimed in the '393 Patent is so trivial an undergraduate student in the late 1960s would know how to do it, UT maintains that a product made by the '393 Patent process is "materially and functionally" distinct from products of the prior art Moriarty (Ex. 1004) and Phares (Ex. 1005) references. UT relies on 175 measurements showing the average purity of products

IPR2020-00770
United Therapeutics EX2007
Page 3483 of 7335

made by one process included in the '393 Patent's claims is [redacted]. (Resp., 34; Ex. 2020, ¶¶ 94-99.) And it relies on measurements alleged to show that one version of the Moriarty process produced an average purity of 99.0%. (Ex. 2020, ¶ 98.) Except that the 99.0% value is a distortion of this data, that required UT, and its attorneys who actually performed this calculation (Ex. 2059, 79:3-10, 81:2-13, 104:14-20), to select 10 data points from another source to lower the purity results (*id.*, 112:22-113:20).

As confirmed by Dr. Williams (*id.*, 218:3-219:16), a fair analysis of the data without the 10 data points shows that the value of [redacted], reported in [redacted] itself, is consistent with UT's purity measurements for batches made according to the Moriarty process (Ex. 2059, 219:17-20). Data purporting to show a lower purity, including UT's Walsh Declaration, mischaracterizes the Moriarty process' purity.

UT's expert Dr. Williams initially believed UT's counsel's calculations. But Dr. Williams conceded that: (1) he performed no calculations on this data himself; (2) he only "spot-checked" the data that was selected by counsel; and (3) he "did not know" whether the 10 data points were produced under the Moriarty process. (Ex. 2059, 81:2-13; 82:1-11; 103:24-104:20; 112:24-114:2). Accordingly, no weight should be afforded to his declaration, or UT's reliance on his declaration. Dr. Williams agreed that SteadyMed's calculation of [redacted] purity was correctly

IPR2020-00770
United Therapeutics EX2007
Page 3484 of 7335

performed, and should be relied upon (*id.*, 217:11-219:20). This corrected calculation supported what SteadyMed stated in its Petition: that the [redacted] showed that treprostinil made by Moriarty was of similar purity, and similarly, the particular example of treprostinil diethanolamine salt made by Phares was as pure as the examples in the '393 Patent. This calculation confirms that the '393 Patent claims merit cancellation.

UT relies on these now-discredited differences in purity values to argue there was a "long-felt unmet need" for more pure treprostinil. (Resp., 12, 47-48; Ex. 2022, ¶¶ 70-72). But UT's long-felt-need expert Dr. Ruffolo concedes that the claims are not limited to treprostinil, nor treprostinil salt, but include hundreds of thousands of other compounds, for which UT provides no evidence regarding long-felt need or impurities. (Ex. 2059, 71:17-72:17; Ex. 2058, 234:16-235:17.) Except for those claims that are limited to treprostinil alone (only claims 10 and 15), or treprostinil diethanolamine salt (claims 14 and 17), Dr. Ruffolo is not offering an opinion that there is a long-felt need for any other claims. (Ex. 2058, 109:18-121:23.) And even for the products in claims 10, 14, 15, and 17, Dr. Ruffolo concedes that: (1) the FDA requires only a [redacted] purity level, which is *much lower* than any levels produced by the prior art, (Ex. 2058, 159:20-161:7); and, (2) the FDA would allow treprostinil batches produced by the Moriarty process to be sold, (Ex. 2058, 179:23-180:17), since Moriarty products are "highly, highly pure,"(*id.*

IPR2020-00770
United Therapeutics EX2007
Page 3485 of 7335

217:11-218:5). *See also* (Ex. 2059, 151:2-25).

UT devotes much of its Response to argue that the common patent claim terms "product" and "comprising" were improperly construed by the Board, and should not have their usual legally defined meaning. (Resp., 5, 13-15). UT contends these terms should have special meaning in the '393 Patent, although UT's expert concedes that a plain and ordinary meaning should apply, and that the patent and prosecution history contain no language that redefine these terms. (Ex. 2059, 248:24-249:13.) UT cannot show "clear and unambiguous disclaimer" of the plain meaning of these terms.

II. UT MISCHARACTERIZES ITS OWN DATA.

A. UT's Moriarty Batches Have an Average Purity of [redacted].

In its Response and supporting Williams Declaration (Ex. 2020), UT uses Dr. Williams to present the average purity of treprostinil made by the Moriarty prior-art method, in order to contrast it to the '393 Patent product. Specifically, Dr. Williams relied on 56 batch Certificates of Analysis of treprostinil that were allegedly produced under the Moriarty method (*see* Ex. 2020, Appx. A), and contended that the treprostinil product produced by the '393 Patent process had a higher average purity than the Moriarty product ([redacted]% v. 99.05%), and thus "the treprostinil product of the '393 patent has an average purity that is [redacted] higher than that of Moriarty's." (Ex. 2020, ¶ 98; Resp., 4, 34, and 45). But UT's counsel

IPR2020-00770
United Therapeutics EX2007
Page 3486 of 7335

selected batches to include in its calculation, and cherry-picked 10 batches to drive down the average purity value of the Moriarty product from [redacted] to 99.05%. These 10 "development" batches, as UT calls them, come from a separate source, and may not have been produced by the Moriarty method. When instead, the 46 "production" batches made by the Moriarty method, and under the same analytical methods, are examined, the correct conclusion is that the Moriarty method produces the *same product as the product of the '393 Patent*: a product with [redacted] purity, just as Moriarty himself reported in his JOC article (Ex. 1004).

Because Dr. Williams and Dr. Ruffolo relied on UT's counsel's incorrect calculation, UT's experts' opinions on differences between the Moriarty product and the '393 Patent product should be disregarded.

1. UT's Data Sources.

UT attaches three exhibits that contain purity information for treprostinil made under the Moriarty method: Exhibits 2036, 2052, and 2053. (Ex. 2020, Appx. A.) Exhibit 2036 is the main source of this data, and contains 44 Certificates of Analysis from either Magellan Laboratories or Cardinal Health for commercial lots of treprostinil. Exhibit 2053 is UT's NDA Annual Report from 2003, which summarizes Certificates of Analysis and purity information from 32 commercial lots, including 30 lots that were already included in Exhibit 2036, plus two additional lots not included in Exhibit 2036. Thus, Exhibits 2036 and 2053 contain

IPR2020-00770
United Therapeutics EX2007
Page 3487 of 7335

purity data for 46 lots of treprostinil.

Exhibit 2052 is an undated but older document entitled "UT-15 Injection Drug Substance Volume 1.2 Chemistry, Manufacturing and Controls, NDA 21-272," and appears to be a portion of UT's original New Drug Application to sell treprostinil. It contains a summary of purity analyses for 13 lots of treprostinil made by third party companies called "[redacted]" "[redacted]," and "[redacted]" (Ex. 2052, 25-30.) The two [redacted] lots, made in 1986, were not included in UT's Appendix A. "These lots were manufactured by [redacted] using a slightly different route of synthesis." (*id.*, at 25 n.4.) [redacted] was also not included in UT's Appendix A. [redacted], "which was deliberately spiked for use in toxicology studies," (*id.*, at 29 n.2) was included by UT, as were "[redacted], and [redacted] [which] were tested and released using different analytical procedures previously submitted," and for which "the listed specifications do not apply ...," (*id.*, at 25 n.3). The 10 samples selected from the 13 samples in Ex. 2052 were manufactured several years before Moriarty's 2004 Journal of Organic Chemistry article (Ex. 1004). As Dr. Williams confirmed, there is no information provided on what method was used to make these lots, other than the fact that the methods used for many of them were similar to methods [redacted] used in 1986. These 10 data points have purity values far below the values reported in Exhibits 2036 and 2053.

IPR2020-00770
United Therapeutics EX2007
Page 3488 of 7335

2. Are the 10 Batches Even Moriarty Samples?

The dates of manufacture and footnotes recorded in Exhibit 2052 associated with UT's 10 cherry-picked samples make it unlikely that they were representative of treprostinil made by the Moriarty process:

> Q You don't know the details of how all these lots were made?
>
> A No. I haven't seen the detailed batch records of what went into those lots.
>
> Q Okay. So you don't know whether or not these lots were made by the '393 process, the Moriarty process, the older Aristoff process; is that right?
>
> THE WITNESS: Um, you know, I -- I'd have to investigate further. I don't know.
>
> Q Right. You -- you don't know if any of these are from the Moriarty process? At least not the ones on page 25?
>
> A So the Moriarty paper came out in 2003.
>
> ...
>
> A So I don't think it's possible that any of these could have been made by Moriarty process just based on the dates.

(Ex. 2059, 112:20-113:20). While Dr. Williams contends that these 10 samples represent "development" batches included for "fairness" (*id.*, at 81:23-82:7), he had no explanation for why he included 10 development batches out of 56 samples for his analysis of Moriarty batches, but only 5 development batches out of 157 samples for his analysis of '393-Patent batches. (*Id.*, at 270:15-271:6).

IPR2020-00770
United Therapeutics EX2007
Page 3489 of 7335

3. 46 Known Moriarty Samples Average to [redacted].

Once the cherry-picked data points are eliminated, the average purity of the 46 remaining samples increases from 99.05% to [redacted]: *the same purity as the product produced by the '393 Patent process*. SteadyMed prepared an Excel spreadsheet containing these 46 data points (Ex. 1021), and had Dr. Williams review every data point and calculation at his deposition to confirm that the [redacted] number is correct, and consistent with the number reported in Ex. 1004:

> Q: Okay. So now that we've – now that you've checked every single data point and looked at the calculations, you agree with me that this calculation of the purity is fair and accurate?
>
> A: The overall purity. But this does not reflect impurity profile.
>
> Q: Yeah I understand. I'm just talking about the overall – the level of purity.
>
> A: Yes.
>
> […]
>
> Q: Okay. And so it is correct that for the samples from Exhibits 2036 and 20[5]3, the 46 samples, the average level of purity was [redacted] percent for the samples made under the Moriarty process?
>
> A: Yes.
>
> Q: Okay. That [redacted] value, that is consistent with the value that [redacted]?
>
> A: They're the same numbers.

(Ex. 2059, 218:25-219:20). By contrast with Dr. Williams' careful review of SteadyMed's calculation, Dr. Williams did not perform any calculations on UT's

IPR2020-00770
United Therapeutics EX2007
Page 3490 of 7335

data in Appendices A and B, having relied solely on counsel's work. (*id.*, 81:2-13; 82:1-11; 103:24-104:20; 112:24-114:2).

When the science is done properly, UT's data proves that Dr. Moriarty's [redacted] reported value in Ex. 1004 is correct.

4. Any Difference in "Impurity Profiles" is Meaningless.

UT still argues that the exact identity of the impurities generated by each process in the tiny [redacted] set of impurities matters. UT ignores that the '393 Patent claims contain at least hundreds of thousands of compounds (Ex. 2059, 71:17-22), for which none of the impurities have ever been characterized, (*id.*, 72:12-17). And the '393 Patent does not even characterize the impurities of treprostinil (Ex. 2058, 234:16-235:12), which UT maintains as a trade secret requiring a protective order, (Ex. 2058, 93:19-94:24, 233:5-12). As UT's expert Dr. Ruffolo conceded, "I see primarily purities of the parent compound, which is what I believe the invention is related to" and "so I see comparisons between the old process and new process with purities, but – but I don't see, unless I've missed it, I don't see the impurities." (Ex. 2058, 235:6-12.) Secret impurities not identified in the '393 patent for treprostinil, or for hundreds of thousands of other compounds, cannot make the claims patentable.

In any event, neither Dr. Williams nor Dr. Ruffolo opined that the impurity profile of treprostinil mattered:

IPR2020-00770
United Therapeutics EX2007
Page 3491 of 7335

Q: Do ... any of these particular impurities have deleterious biological consequences? [...]

A: I'm not a clinician, so I don't know.

Q: You don't know?

A: I don't know.

(Ex. 2059, 47:4-13; *see also* Ex. 2058, 257:22-258:9.)

Dr. Ruffolo agrees that both the prior-art and '393 Patent treprostinil are "highly, highly pure." (Ex. 2058, 217:24-218:5.) The FDA only requires [redacted] purity for treprostinil, so achieving higher purity is immaterial to the product, (Ex. 2058, 159:20-161:7), and Moriarty-process treprostinil was, and can still be, sold to the public, (Ex. 2058, 179:23-180:17). Where Moriarty and '393-Patent treprostinil have the same purity, as proven by the [redacted]-purity level, there are no functional differences between them, as Dr. Williams conceded. (Ex. 2059, 67:2-15.)

B. The Walsh Declaration Is Questionable.

During prosecution of the '393 Patent, UT relied on the Walsh Declaration, and differentiated the '393 Patent product from Moriarty's product by showing a "representative sample" of Moriarty product containing 0.6% impurities, which was contrasted with '393 Patent treprostinil diethanolamine salt and treprostinil having 0.1% and 0.2% impurities, respectively. (Ex. 1002 at 343-350.). As noted by UT, the '393 Patent claims were allowed after submission of the Walsh Declaration. (Resp., 5).

IPR2020-00770
United Therapeutics EX2007
Page 3492 of 7335

The 46 samples contained in Exhibits 2036 and 2053, and a new exhibit submitted by UT—Exhibit 2006—contradict the Walsh Declaration. As Dr. Winkler observed, the data in the Walsh Declaration was derived from a single sample, and significant batch-to-batch variations in the impurity profile of each batch of treprostinil could affect the results. (Ex. 1009, ¶ 66).

Dr. Winkler's concern is confirmed by UT's results from the 46 batches. For example, Moriarty Batch No. [redacted], dated January 25, 2004, and having a purity of [redacted] which is the [redacted] for these batches, had only [redacted]: [redacted]. (Ex. 2036, 5.) According to Dr. Walsh's June 4, 2013 Declaration, "treprostinil as the free acid prepared according to the process specified in claim 1 or 10 of the present application has only three impurities ...." (Ex. 1002, 348-49.) Moreover, "each of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 of the present application is physically different from treprostinil prepared according to the process of 'Moriarty' at least because neither of them contains a detectable amount of any of benzindene triol, treprostinil methyl ester, 1AU90 treprostinil stereoisomer and 2AU90 treprostinil stereoisomer, each of which were present in detectable amounts in treprostinil produced according to the process of "Moriarty." (Ex. 1002, 349.) Yet Moriarty Batch No. [redacted] did not contain detectable amounts of any of these impurities either, proving that

IPR2020-00770
United Therapeutics EX2007
Page 3493 of 7335

Dr. Walsh could not make his conclusion.

UT told the FDA that treprostinil diethanolamine salt made in accordance with the '393 Patent "[redacted]." (Ex. 2006, 3-6.) Yet these impurities, supposedly removed by carrying out step (d) in the '393 Patent's claims, are not described in the Walsh Declaration, which instead presents "Impurities ... [Total Related Substances]" as 0.2% for the free acid, and 0.1% for the salt, (Ex. 1002, 348), meaning that the free acid is *less pure* than the diethanolamine salt, and not more pure as UT represented to the FDA in Exhibit 2006. Dr. Williams could not provide an explanation for this discrepancy (Ex. 2059, 199:6-18), which contradicts the Walsh Declaration.

III. DR. WILLIAMS' TESTIMONY CONFIRMS THAT PHARES ANTICIPATES CERTAIN '393 PATENT CLAIMS.

Phares (Ex.1005) makes the same treprostinil diethanolamine salt claimed in every claim of the '393 Patent where optional step (d) is not completed, as explained in SteadyMed's Petition and Dr. Winkler's Declaration (Ex. 1009, ¶¶ 44-71.) UT responds by rejecting the Board's claim construction, discussed later in this Reply, and with three factual arguments: (1) that SteadyMed cannot show that Phares used the Moriarty process, claimed in steps (a) and (b) of the '393 Patent's claims; (2) that SteadyMed cannot show that Phares' treprostinil diethanolamine

IPR2020-00770
United Therapeutics EX2007
Page 3494 of 7335

Form B salt has the same purity level as the '393 Patent's Form B salt; and (3) that HPLC Assay Analysis can measure purity better than 0.4%, even though Dr. Winkler pointed out that the error in UT's own equipment is at least 0.4%, (Ex. 1009, ¶ 70).

But Dr. Williams concedes that the process in Phares for making treprostinil's (-)-enantiomer carries out the same alkylation step (a) and hydrolysis step (b) in the '393 Patent's claims, thus disclosing these steps for treprostinil. And the attached Declaration of Robin D. Rogers (Ex. 1022), SteadyMed's polymorph expert, explains why the melting point of treprostinil diethanolamine salt Form B can be compared between the '393 Patent and Phares reference, and that the particular sample in Phares had at least the same purity as the '393 Patent's examples. Finally, UT's own data showed that the average purity of Moriarty samples was [redacted], proving that batch variation is at least [redacted] and UT's representation to the FDA stated that treprostinil purity will be maintained between [redacted], (Ex. 2006), proving a [redacted] variability applies to purity measurements.

A. Phares discloses steps(a) and (b) of the '393 Patent.

"Q. Okay. So what we see here is there's an alkylating step (a) and a hydrolyzing step (b) on page 42 of the Phares reference. A. Yes." (Ex. 2059, 190:16-19). On Phares page 42 (Ex. 1005), as Dr. Williams concedes in this testimony, steps (a) and (b) are carried out on the mirror image version of the

IPR2020-00770
United Therapeutics EX2007
Page 3495 of 7335

compounds described in the '393 Patent claims, and as Dr. Winkler explains, the Phares patent at page 42 states that the enantiomer procedure is the same procedure used to make "the commercial drug (+)-Treprostinil." (Ex. 1009 ¶ 56; Ex. 1005, 42.) Thus, in describing that the process for making both enantiomers uses steps (a) and (b), and explaining that the process for the (-)-enantiomer is merely a variation on the already known (+)-enantiomer process, Phares inherently discloses steps (a) and (b) to create the (+)-enantiomer.

B. Phares' Higher Melting Point Means It is at Least Equally Pure.

Dr. Winkler explained that since the Phares treprostinil diethanolamine salt Form B melted at 107°C, but the same Form B in the '393 Patent melted at around 106.6 °C, the Phares sample was necessarily as pure as the '393 Patent's samples. Dr. Williams, who is "not a polymorph expert," (Ex. 2059, 158:17-18; 156:25-157:2), contends nevertheless that the melting point of two samples of the same polymorph (crystal form) cannot be compared to determine their relative purities. (Ex. 2020 ¶ 75.) According to UT and Dr. Williams, how a polymorph is made, including what solvents are used, can affect its melting point, even if the polymorphs are identical. (Resp., 22-24; Ex. 2020 ¶ 75.)

As set forth in Dr. Rogers' Declaration (Ex. 1022, ¶¶ 49-52) and admitted by Dr. Williams, melting point is one of the most common ways to identify different polymorphs. (Ex. 2059, 158:20-25); *see also* Exs. 1024-1026. Dr. Williams

IPR2020-00770
United Therapeutics EX2007
Page 3496 of 7335

concedes that in the '393 Patent, treprostinil diethanolamine salt is identified as being Form B based solely on its melting point. (Ex. 2059, 170:24-171:3.) And Dr. Williams concedes that the same treprostinil diethanolamine salt polymorph—Form B—is presented in the Phares reference and '393 Patent. (*Id.*, 168:6-11).

While Dr. Williams relies on his "personal experience" observing different melting points for crystals made with different solvents, he conceded that he knew of no literature to support his opinion. (*Id.*, 184:22-185:2.) Dr. Williams conceded that the one article he relied upon in his declaration, Ex. 2030, in fact describes different crystal forms having different melting points, and not the same crystal form having different melting points. (*Id.*, 180:9-25.)

By contrast, Dr. Rogers' Declaration cites several literature sources explaining that melting point uniquely identifies a polymorph. (Ex. 1022, ¶¶ 49-52). Thus, for the same polymorph, if the melting point differs, it is due to impurities contained in the sample having a lower melting point. (*Id.*, ¶ 64.) Dr. Rogers concludes that Phares' higher melting point is necessarily due to higher or at least identical purity. (*Id.*, ¶ 74.) Moreover, the width of the DSC peak in the Phares reference is very narrow, consistent with a very pure material. (*Id.*, ¶ 84.)

C. HPLC Analysis Has Error Bars Too Large to Distinguish the Tiny Differences in Purity Levels UT Relies Upon.

As Dr. Winkler explained, it is not possible to measure treprostinil purity levels better than 0.4%, as shown by UT's own data. (Ex. 1009, ¶ 70.) Now that UT has

IPR2020-00770
United Therapeutics EX2007
Page 3497 of 7335

provided multiple certificates of analysis for treprostinil, it is now confirmed that UT's Moriarty purity varies by at least [redacted], and indeed, Dr. Williams conceded he had no reason to disagree with this [redacted] value. (Ex. 2059, 218:22-24.)

UT's own exhibits confirm that HPLC assay analysis has a wide error range: "[redacted]." (Ex. 2006, 3.) UT's expert Dr. Williams agrees with this statement and that "[redacted]" refers to the HPLC assay for purity. (Ex. 2059, 133:17-25, 134:24-135:4.)

UT discounts that HPLC assay analysis has a wide error range by suggesting that purity should instead be measured by totaling up "total related substances," which are measurements of particular impurities identified in the HPLC analysis. (Resp., 2-3, 29-30.) But as acknowledged by Dr. Williams, some impurities will not be detected in a total-related-substance analysis (Ex. 2059, 140:5-9.). UT's expert Dr. Ruffolo confirmed that in the '393 Patent, all of the analyses are HPLC analyses of the total treprostinil against a reference standard, and not measurements of total related substances. (Ex. 2058, 153:16-154:7.) And both UT experts acknowledged that the FDA uses HPLC assay analysis to evaluate the overall purity of treprostinil, and to decide whether that treprostinil meets a [redacted] purity requirement that would allow it to be sold. (Ex. 2058, 159:20-161:7; Ex.

IPR2020-00770
United Therapeutics EX2007
Page 3498 of 7335

2059, 150:23-151:25.)

UT criticizes Dr. Winkler, falsely stating that Dr. Winkler does not understand HPLC analysis, and does not know anything about the error in UT's HPLC equipment. (Resp., 3, 30.) Dr. Winkler instead testified that there is no information regarding the error in the amount of "[redacted]," an impurity present in UT's treprostinil at about [redacted]. (Ex. 2051, 63:3-14.) The error in the [redacted] measurement is irrelevant to the error in treprostinil purity, especially where treprostinil purity is a number near [redacted] ([redacted]), 1000 times larger than the amount of [redacted]. Regarding error in HPLC Analysis of treprostinil purity, Dr. Winkler was unequivocal at his deposition:

> I think the thing that I am able to conclude from the data that is on page 6 of this, of this letter is that the error in the HPLC assay could be as high as 1 percent in the first column and by my analysis could be as high as 2 percent in the second column.

(Ex. 2051, 88:12-18.)

IV. UT'S EXPERTS CONFIRM THE CLAIMS' OBVIOUSNESS.

A. Moriarty Was Recognized as the Best Method to Make Treprostinil Before the Phares Reference was Published.

UT contends that Phares does not anticipate because it does not disclose the first two steps, steps (a) and (b), which were used in the Moriarty process. As explained above, this contention is wrong. But even if it were true, UT's expert Dr. Williams provided testimony confirming that there was a strong reason to combine

IPR2020-00770
United Therapeutics EX2007
Page 3499 of 7335

Moriarty with Phares: Moriarty was well-known to be the best way to make treprostinil, and would have been the way Dr. Williams' own graduate students would have made the treprostinil in Phares before turning it into its salt.

First, Dr. Williams confirmed that steps (a) and (b) in the '393 Patent claims were disclosed by the Moriarty patent, Ex. 1003. (Ex. 2059, 53:19-54:7). Second, Dr. Williams confirmed that "a person of ordinary skill in the art in 2005 reading the Phares reference, that person would know that the best way to make treprostinil is the Moriarty method ...." (*id.*, 240:2-7). And third, he confirmed that "a typical person of ordinary skill in the art, typical graduate student, they would have found the Moriarty paper and used that technique to make treprostinil in 2005." (*Id.*, 244:10-21.) While UT's expert Dr. Ruffolo disagrees with Dr. Winkler regarding the appropriate level of skill, it is Dr. Ruffolo's opinion that the skill level should be higher than Dr. Winkler's, and that a person of ordinary skill should at least have a Ph.D. (Ex. 2058, 52:2-17.) If a graduate student would use Moriarty, then certainly a Ph.D. would do so. Thus, UT's experts essentially confirm that a person of ordinary skill in the art would combine Moriarty with Phares when making Phares' treprostinil salt.

B. UT's Experts Confirm That Crystallization Through A Salt To Purify Is Organic Chemistry 101.

As shown by UT expert Dr. Ruffolo's testimony, *supra*, the process steps (c) and (d), which crystallize a compound as its salt and then convert the salt back to

IPR2020-00770
United Therapeutics EX2007
Page 3500 of 7335

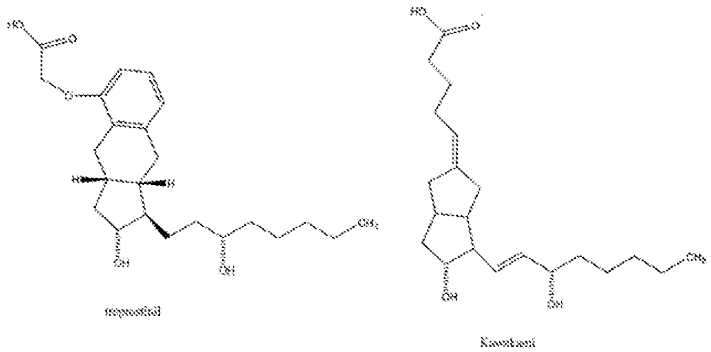
the acid, have been around for "decades," at least as far back as the late 1960s. (Ex. 2058, 175:19-176:22, 179:11-17.) "[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007). UT cannot claim that using this elementary chemistry technique is nonobvious merely because UT applied it to treprostinil.

UT also argues that the particular impurities found in treprostinil, which are said to be stereoisomers, would not have been removed using crystallization. First, there is no teaching in the '393 Patent or the prior art of record regarding what kinds of impurities are present in treprostinil, or, as conceded by UT's experts, of the hundreds of thousands of other compounds included in the claims. (Ex. 2059, 74:18-25; Ex. 2058, 234:16-235:17.) UT maintains the identity of these impurities as a trade secret, necessitating a Protective Order to cover these proceedings so that information on these impurities is not revealed. UT's secret information regarding these impurities' identity cannot be the basis for why a person of ordinary skill in the art would not use crystallization here.

Second, the Kawakami reference, Ex. 1007, used crystallization to separate stereoisomers, as confirmed by Dr. Winkler under UT's counsel's cross-examination. (Ex. 2051, 203:4-204:20.) UT distinguishes Kawakami on grounds

IPR2020-00770
United Therapeutics EX2007
Page 3501 of 7335

that it concerns a different prostacyclin, not treprostinil, and offers chemical drawings making Kawakami's prostacyclin look different from treprostinil. (Resp., 40.) But SteadyMed has generated more fair drawings of these two structures, and Dr. Williams confirmed that these drawings accurately depict the structures. (Ex. 2059, 245:23-247:1). These new drawings are submitted as Ex. 1028:



When properly depicted, treprostinil and Kawakami are similar compounds.

Finally, treprostinil can be made in any purity desired, as Dr. Williams admitted, by prior-art purification processes like chromatography, since "you could repurify and purify anything you want by chromatography to 99.99999 percent if you wanted to." (Ex. 2059, 94:8-12). While Dr. Williams contends that would be an impractical approach in large-scale manufacturing, he concedes that the '393 Patent's claims are not limited to large-scale manufacturing. (*Id.*, 187:18-188:3.) Thus, there was no barrier to making treprostinil of any purity, and while doing so by using crystallization is obvious, a product having any desired purity can be made by any method, so purer treprostinil is obvious.

IPR2020-00770
United Therapeutics EX2007
Page 3502 of 7335

V. THE BOARD CONSTRUED THE CLAIMS CORRECTLY.

UT challenges the Board's construction of the legal terms "comprising" and "product," which is surprising since that the Board generally accepted UT's constructions from UT's Preliminary Response. UT had argued that "comprising" should mean "included but not limited to." (Paper 10, at 23). And the Board agreed. (Paper 12, at 13). Now UT contends that "comprising" should not be given its usual open-ended construction. (Resp., 13.) UT points to the prosecution history as effecting a disclaimer of the usual meaning of "comprising," but "[a] statement in the prosecution history can only amount to disclaimer if the applicant clearly and unambiguously' disavowed claim scope." *Toshiba Corp. v. Imation Corp.*, 681 F. 3d 1358, 1370 (Fed. Cir. 2012). UT points to no statements in the prosecution history regarding the meaning of "comprising," but, argues that since the examiner allowed the claims, he must have construed "comprising" according to UT's non-open construction. (Resp., 16.) If that were a clear and unambiguous disavowal, every Patent Owner could argue that its claims should be construed narrowly enough to make them valid, since the initial examiner allowed them.

UT also objects to the Board's plain and ordinary meaning for the term "product," and contends that "product" should be narrowly construed. But this narrow construction is not supportable, and even UT's expert Dr. Williams conceded that "product" is broadly used in the art, assuming that it is even a term

IPR2020-00770
United Therapeutics EX2007
Page 3503 of 7335

of art and not a legal term. First, Dr. Williams acknowledged that "chemists use the word 'product' in two different contexts, routinely." (Ex. 2059, 248:4-5.) "Product" can mean in chemistry a product and its impurities, or the molecular structure alone. (*Id.*, 248:13-23.) Second, Dr. Williams conceded that the '393 Patent and prosecution history do not provide definitions for "product." (*Id.*, 248:24-249:13.) Third, Dr. Williams' Declaration recognizes that "product" is a term in patent law relating to "product-by-process" claims, (Ex. 2020, ¶ 30), but does not explain why this legal definition should not apply here. Fourth, Dr. Williams' own example of "product" in his own writing—Ex. 2028—uses "product" to mean a product created by nature, and not by a chemical reaction, when it refers to "the natural product from marine sources." (Ex. 2020, ¶ 63.) And fifth, while Dr. Winkler testified that "product" includes the product of a chemical reaction, he testified that "product" was a broad term that encompassed more. (Ex. 2051, 152:21-154:21.)

It is unclear how UT's claim constructions matter. UT seeks a construction limiting the claims by impurity profile, (Resp., 18), but UT cannot articulate how its proposed constructions for "comprising" and "product" effect this result. There is no record evidence showing that the claimed processes and their products have unique impurity profiles, and the '393 Patent lacks information regarding the impurity profiles of treprostinil or its many salts, or for the thousands of compounds in its claims. (Ex. 2059, 71:17-72:17, 74:18-25; Ex. 2058, 234:16-

IPR2020-00770
United Therapeutics EX2007
Page 3504 of 7335

235:17.) The impurity profiles are not unique to each claim, but depend on unclaimed elements like what solvents were used, (Ex. 2058, 239:22-241:14), whether the intermediate products were purified, (Ex. 2058, 239:8-20, Ex. 2059, 69:17-71:9), and what bases, acids, or other reactants that the claims allow were used. Product-by-process claims would have no definite scope under UT's analysis.

VI. NO LONG-FELT NEED FOR THESE CLAIMS' PRODUCTS.

While UT suggests there was a long-felt need for these claims' products, its long-felt-need expert Dr. Ruffolo testified otherwise: "there's nothing I can tell you about the long-felt need for those other compounds [of claim 1]," (Ex. 2058, 65:4-13); or of claim 9 (Ex. 2058, 69:20-70:11); or of claims 12, 13, 16, 17, 21, or 22 (Ex. 2058, 110:17-111:9, 114:16-117:3, 118:2-5; 118:23-119:23, 121:5-23); or of any claim that was not limited to treprostinil and treprostinil diethanolamine salt, (Ex. 2058, 68:14-25). Only claims 10, 14, 15, and 17 are limited to treprostinil or its salt.

Regarding treprostinil or its diethanolamine salt, Dr. Ruffolo conceded that he had no idea if FDA had asked for a change in purity, (*id.*, 45:15-22), nor could he identify anyone who expressed a particular desire for greater purity, (*id.*, 130:16-25.) He also recognized that one could usually purify a drug further by running purification procedures repeatedly, (*id.*, 46:9-18), which Dr. Williams confirmed was true for treprostinil, (Ex. 2059, 94:8-12), and proves that there was no need for

IPR2020-00770
United Therapeutics EX2007
Page 3505 of 7335

the "invention." Dr. Ruffolo also conceded, contrary to UT's arguments, that a change in purity specifications is not a major amendment, (Ex. 2058, 310:5-13), but that the other changes UT applied for—changing starting materials and manufacturing facilities, were major amendments (*id.*, 310:13-18).

Regarding claims 10, 14, 15, and 17, Dr. Ruffolo concedes that: (1) the FDA requires only a [redacted] purity level, which is *much lower* than any levels produced by the prior art, (*id.*,159:20-161:7); (2) the FDA would allow batches of treprostinil produced by the Moriarty process to be sold, (*id.*,179:23-180:17), since Moriarty products are "highly, highly pure," (*id.*, 217:11-218:5); and (3) there is no clinical difference between the prior-art Moriarty product and the '393 Patent product (*id.* 315:15-23). Thus, the FDA expressed no need for a purer product. Moreover, Dr. Ruffolo does not know if UT's products that he relies upon are covered by these claims. (*Id.*, 292:25-293:2.)

Dr. Ruffolo's opinion relies on Dr. Williams' incorrect calculation showing 99.0% purity, but Dr. Ruffolo concedes he did not review that calculation, nor speak to Dr. Williams, and depends entirely on Dr. Williams. (*Id.*, 262:4-263:5.) Since Dr. Williams now concedes that the correctly performed calculation shows a [redacted] purity, (Ex. 2059, 218:3-8), Dr. Ruffolo's opinions should be disregarded.

IPR2020-00770
United Therapeutics EX2007
Page 3506 of 7335

Date: September 27, 2016

Respectfully submitted,

/s Stuart E. Pollack /
Stuart E. Pollack, J.D. Ph.D.
Reg. No. 43,862
DLA Piper LLP (US)

/s Lisa A. Haile /
Lisa A. Haile, J.D., Ph.D.
Reg. No. 38,347
DLA Piper LLP (US)

CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24, the undersigned attorney for Petitioner certifies that the document contains 5,599 words in 14-point Times New Roman font, excluding the parts of the document that are exempted by 37 C.F.R. § 42.24(a)(1), according to the word count tool in Microsoft Word.

Date: September 27, 2016

Respectfully submitted,

/s Stuart E. Pollack /
Stuart E. Pollack, J.D. Ph.D.
Reg. No. 43,862
DLA Piper LLP (US)

/s Lisa A. Haile /
Lisa A. Haile, J.D., Ph.D.
Reg. No. 38,347
DLA Piper LLP (US)

IPR2020-00770
United Therapeutics EX2007
Page 3508 of 7335

CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the attached Petitioner's Reply was served via electronic mail to the following:

Stephen B. Maebius
George Quillin
FOLEY & LARDNER LLP
UT393-IPR@foley.com

Shaun R. Snader
UNITED THERAPEUTICS CORP.
ssnader@unither.com

Douglas Carsten
Richard Torczon
Robert Delafield
WILSON, SONSINI, GOODRICH & ROSATI
dcarsten@wsgr.com
rtorczon@wsgr.com
bdelafield@wsgr.com

Date: September 27, 2016

/s Stuart E. Pollack /
Stuart E. Pollack, J.D., Ph.D.
Reg. No. 43,862
DLA Piper LLP (US)

/s Lisa A. Haile /
Lisa A. Haile, J.D., Ph.D.
Reg. No. 38,347
DLA Piper LLP (US)

IPR2020-00770
United Therapeutics EX2007
Page 3509 of 7335

Paper _____

UNITED STATES PATENT AND TRADEMARK OFFICE

_____

BEFORE THE PATENT TRIAL AND APPEAL BOARD

_____

STEADYMED LTD.

Petitioner,

v.

UNITED THERAPEUTICS CORPORATION

Patent Owner.

Case IPR 2016-00006

Patent No. 8,497,393

_____

DECLARATION OF ROBIN D. ROGERS IN SUPPORT OF PETITIONER'S REPLY

Mail Stop "Patent Board"
Patent Trial and Appeal Board
U.S. Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

TABLE OF CONTENTS

I. OVERVIEW

1. I have been retained by counsel for the Petitioner, SteadyMed Ltd., to offer technical opinions with respect to certain technical matters relating to the *inter partes review* proceedings concerning U.S. Patent No. 8,497,393 ("the '393 Patent") and certain prior art references cited in regard to the '393 Patent.

2. In particular, I have been asked to opine regarding crystal forms of organic molecules, also known as "polymorphs," the melting points of polymorphs, how melting point and purity of polymorphs are related, how differential scanning calorimetry and other analytical techniques are used to analyze polymorphs, and how some of these analytical techniques can be used to compare the purity of two samples.

3. This declaration presents my opinion that the treprostinil diethanolamine Form B polymorph made in the Phares Reference, Ex. 1005, is at least as pure as the same Form B polymorph made in the '393 Patent, Ex. 1001, and is likely purer, based on comparing their melting points.

4. I also opine that the method of making a particular polymorph, such as Form B, and the solvents used, are irrelevant to the properties of the polymorph: two crystals of Form B have the properties of Form B, including melting point and PXRD pattern, regardless of how they were made. Differences present here between two Form B crystals made using different solvents are due to different

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 3

IPR2020-00770
United Therapeutics EX2007
Page 3512 of 7335

impurity profiles and different levels of impurities. In fact, the '393 Patent contains six examples, called Example 3 Batches 1-4 and Example 4 Batches 1 & 2, where the melting points, and thus the impurity level and profile, were each different.

II. QUALIFICATIONS

5. I am currently Canadian Excellence Research Chair in Green Chemistry and Green Chemicals at McGill University, Montreal, Quebec, Canada, a position I started January 1, 2015. Prior to this appointment I served as Distinguished Research Professor in the Department of Chemistry at The University of Alabama, Tuscaloosa, Alabama, USA, where I was Robert Ramsay Chair of Chemistry and the Director of the Center for Green Manufacturing also at The University of Alabama. Since 2009, I have held the title of Honorary Professor in the Institute for Process Engineering at The Chinese Academy of Sciences in Beijing, China. A copy of my curriculum vitae and list of publications is attached as Ex. 1023.

6. I received a B.S. in chemistry (*summa cum laude*) in 1978 and a Ph.D. in chemistry in 1982 from The University of Alabama. During the period 1982–1996, I was successively an assistant, associate, full, and Presidential Research Professor at Northern Illinois University. During the period of 1991–1998, I also held a faculty appointment at the Argonne National Research Laboratory, Argonne, Illinois. In 1996, I became a Professor of Chemistry at The University of

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 4

IPR2020-00770
United Therapeutics EX2007
Page 3513 of 7335

Alabama and, in 1998 I was named Director of The University of Alabama's Center for Green Manufacturing. I was awarded the titles Distinguished Research Professor in 2004 and Robert Ramsay Chair of Chemistry in 2005. From 2007 to 2009, I held a joint appointment as Chair in Green Chemistry in the School of Chemistry & Chemical Engineering and Director of the Queen's University Ionic Liquid Laboratory ("QUILL") at The Queen's University of Belfast, Belfast, Northern Ireland, UK.

7. I am a member of various professional societies, including the American Association for the Advancement of Science (Fellow), American Chemical Society (Fellow), American Crystallographic Association, American Institute of Chemical Engineers, Materials Research Society, American Association of Crystal Growth, and Royal Society of Chemistry (Fellow).

8. In 1989, I joined the Editorial Board of the *Journal of Chemical Crystallography* (then named *Journal of Crystallographic and Spectroscopic Research*). I became Associate Editor of the journal in 1993 and was the Editor from 1996 to 2000. In 1998, I founded the journal *Crystal Engineering* and served as Editor until 1999. In 2000, I was asked by the American Chemical Society ("ACS") to found a new journal called *Crystal Growth & Design*, for which I currently serve as Founding Editor-in-Chief. I also have served or currently serve as editor or on the editorial board of the following journals:

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 5

IPR2020-00770
United Therapeutics EX2007
Page 3514 of 7335

- *Separation Science and Technology*: Associate Editor, 1996-99; Editorial Board, 1999-;
- *Industrial & Engineering Chemistry Research*: Editorial Board, 1999-2001;
- *Journal of Chromatography, B*, Guest Editor, Volume 743 (1 + 2), 2000;
- *Solvent Extraction and Ion Exchange*, Editorial Board, 2002-;
- *Green Chemistry*, International Advisory Board, 2002-;
- *Chemical Communications*, Editorial Advisory Board, 2005-;
- *Accounts of Chemical Research*, Guest Editor (with G. A. Voth), Special Issue on Ionic Liquids, Volume 40(11), 2007
- *ChemSusChem*, International Advisory Board, 2008-;
- *Chemistry Letters*, Advisory Board, 2010-;
- *Australian Journal of Chemistry*, Guest Editor, Research Front on Crystal Engineering, Volume 63(4), 2010;
- *Separation Science & Technology*, Guest Editor (with H. Rodriguez and J. Chen), Special Issue on Ionic Liquids (2012);
- *Chemical Communications* Guest Editor (with D. MacFarlane and S. Zhang), Special Issue on Ionic Liquids (2012);
- *Science China – Chemistry* Guest Editor (with S. Zhang), Special Issue on Ionic Liquids (2012); and

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 6

IPR2020-00770
United Therapeutics EX2007
Page 3515 of 7335

- *Catalysis Today* Guest Editor (with S. Zhang), Special Issue on Ionic Liquids (2012). *Green Chemistry and Sustainable Technology*, Springer, Heidelberg, Germany, Book Series Editor (with L.-N. He, D. Su, P. Tundo, and Z. C. Zhang).
- *Chimica Oggi/Chemistry Today*, Scientific Advisory Board, 2014-
- *Green Energy & Environment*, 2016-

9. In 2002, the ACS asked me to organize and chair a specialty meeting devoted to the topic of polymorphism (*Polymorphism in Crystals: Fundamentals, Prediction, and Industrial Practice*, Tampa, FL, February 23–27, 2003). I was asked to organize and chair follow-up meetings in 2004 (*Polymorphism in Crystals*, Tampa, FL, February 8–11, 2004), in 2006 (*Process Crystallization in the Pharmaceutical and Chemical Industries*, Philadelphia, PA, April 25–27, 2006), and in 2007 (*Crystallization Process Development: Case Studies and Research*, Boston, MA, February 26–27, 2007).

10. In 2010, I was co-founder, co-organizer, and Vice Chair of the first Gordon Research Conference devoted to the topic of Crystal Engineering (Waterville Valley Resort, NH, June 6-11, 2010). I was the organizer and Chair of the second Gordon Research Conference on Crystal Engineering, which was held in June of 2012.

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 7

IPR2020-00770
United Therapeutics EX2007
Page 3516 of 7335

11. I have published more than 760 articles in refereed journals, edited 14 books, and have been named as an inventor on 50 domestic and foreign patents. I have also given over 1,000 presentations before regional, national and international meetings, and over 200 seminars worldwide. In both 2014 and 2015 I have been named to the Thomson Reuters Highly Cited Researchers List, ranking among the top 1% most cited in chemistry.

12. Since 1996, I have had a leadership role in the development of the field of ionic liquids (pure salts liquid at low temperature); probing their fundamental nature while advancing their technological relevance in areas which include crystallization and novel pharmaceutical forms. These efforts have been recognized with several awards including the 2005 Presidential Green Chemistry Challenge Award, the 2011 American Chemical Society Award in Separations Science and Technology, and in recently being elected as a Fellow of the American Association for the Advancement of Science.

13. I use and have used over the past 40 years X-ray diffraction techniques, Differential Scanning Calorimetry ("DSC"), and Thermogravimetric Analysis ("TGA"), among other techniques, in my research efforts. I have also used other spectroscopic techniques to analyze crystalline and amorphous forms, including Infra-red ("IR"), and Raman spectroscopy ("Raman").

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 8

IPR2020-00770
United Therapeutics EX2007
Page 3517 of 7335

14. I have collaborated with organic chemists in industry and in academia as part of a team in the discovery and characterization of novel drug compounds. I have also acted as a consultant in industry in the development of pharmaceutical drug compounds. I have also trained students in organic synthesis and supervised their Ph.D. research. Within my research group, I regularly hire and supervise Ph.D. organic chemists and direct their research in the synthesis and characterization of novel forms of active pharmaceutical ingredients.

15. In my position as Founding Editor-in-Chief of the American Chemical Society journal *Crystal Growth & Design*, I regularly evaluate and judge suitability for publication of numerous manuscripts which utilize and study crystal engineering, polymorphism, and crystal growth and the characterization of solid state materials. Accordingly, I am quite familiar with the academic and scientific standards for experimental work in this field.

16. In 2004, 2005, and 2008, I organized three special issues of *Crystal Growth & Design* dedicated to the phenomenon of polymorphism, and in 2009, I organized a special issue dedicated to pharmaceutical co-crystals. Many of these papers addressed pharmaceutical compounds, hydration, salt selection, and the use of X-ray diffraction.

17. Based on my experience and qualifications, I consider myself an expert in the field of solid-state chemistry including crystal engineering,

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 9

IPR2020-00770
United Therapeutics EX2007
Page 3518 of 7335

crystallization, hydration, solvate formation, and polymorphism, including the isolation and characterization of solvates and hydrates of organic compounds and their applications in pharmaceutical products. Accordingly, I believe that I am more than competent to express the opinions set forth below.

18. Additional details of my education and experience, and a complete list of my publications are set forth in my curriculum vitae, Ex. 1023.

III. MATERIALS CONSIDERED

19. In forming my opinions, I had the materials cited in the Petition, including the '393 Patent (Ex. 1001), Patent Owner's Response, and the Phares Reference (Ex. 1005), the materials cited in this report, Dr. Williams' Declaration (Ex. 2020), Dr. Ruffolo's Declaration (Ex. 2022), Dr. Winkler's Declaration (Ex. 1009), Dr. Williams' and Dr. Ruffolo's deposition transcripts, and have also relied on my own known and my numerous publications listed on my *curriculum vitae* (Ex. 1023).

IV. MY ROLE AND SUMMARY OF MY OPINIONS

20. I am not offering an opinion on the invalidity of the '393 Patent's claims, or commenting on Dr. Winkler's or Dr. Williams' opinions on that ultimate issue.

21. I am offering opinions only on certain scientific questions that are within my expertise, regarding polymorphs, measurement of polymorphs, melting

points of polymorphs, techniques to analyze polymorphs, purity and how melting point relates to purity, and other related issues.

22. I am also offering an opinion about the ability to compare the melting point of samples of a polymorph.

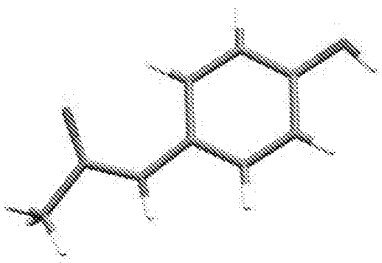
23. I also conclude that a sample of treprostinil diethanolamine salt Form B made by Phares, Ex. 1005, is at least as pure, and likely purer, than samples made and described in columns 12 and 13 of the '393 Patent, Ex. 1001.

V. BACKGROUND

A. Polymorphism

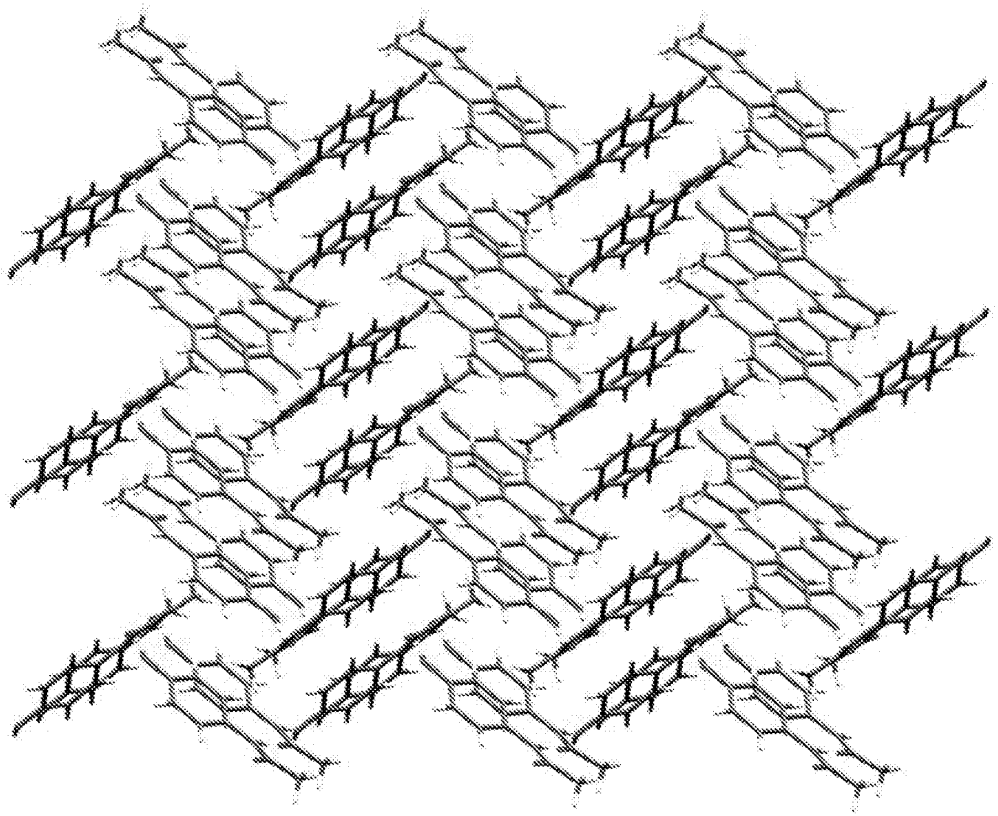
24. Before addressing what a "polymorph" is, it is helpful to begin with a short explanation of what crystals are. Crystals are solids made up of highly organized molecules arranged in a regularly repeating three-dimensional array. These highly organized arrangements of regularly repeating molecules form what are known as crystal lattices.

25. I will explain these concepts using acetaminophen as an example. A single molecule of acetaminophen has the following structure below:



Acetaminophen Molecule

26. When a sample of acetaminophen is crystallized, the molecules in the sample can arrange themselves into a regularly repeating three-dimensional pattern as shown below:

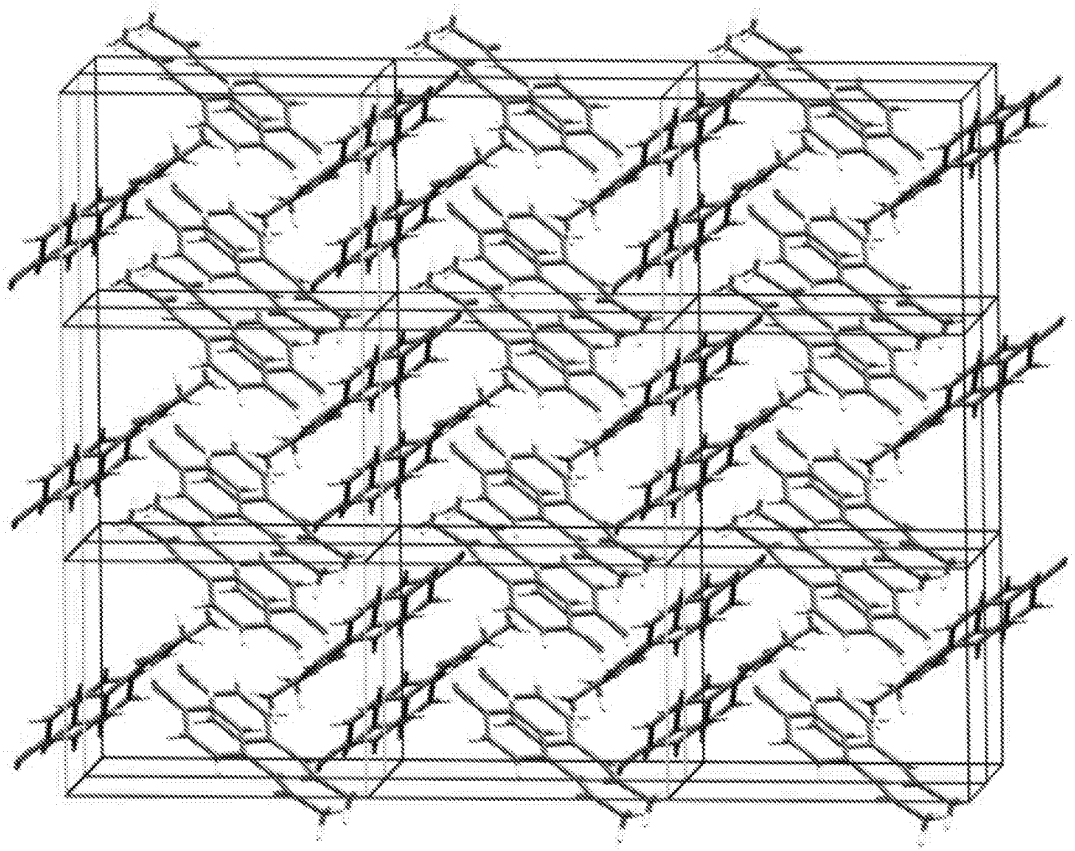


Regularly Repeating 3-D Array of Acetaminophen Molecules

27. This three-dimensional arrangement of molecules is the crystalline lattice, which is like a framework of molecules packed in a regular and repeating manner:

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 12

IPR2020-00770
United Therapeutics EX2007
Page 3521 of 7335

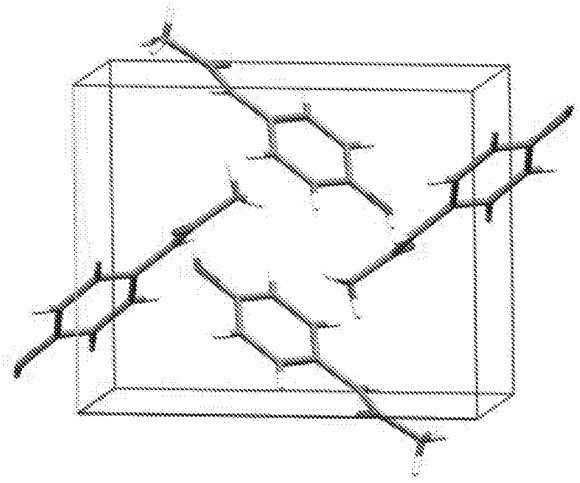


Crystal Lattice of Acetaminophen

28. The smallest repeating unit of the crystalline lattice is known as the unit cell. The crystalline lattice of acetaminophen shown above can also be depicted in terms of the unit cell, shown below.

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 13

IPR2020-00770
United Therapeutics EX2007
Page 3522 of 7335



Acetaminophen Unit Cell

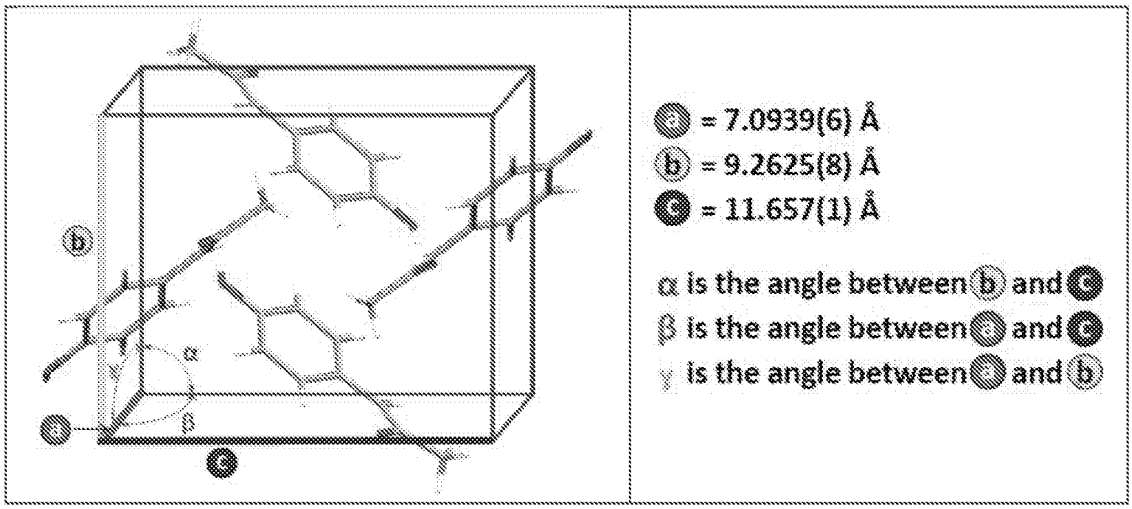
29. As can be seen above, the unit cell is a theoretical construct that aids scientists in studying and characterizing crystals, and does not correspond to the shape of the molecules themselves. The ways in which the molecules of the compound (acetaminophen in my example) arrange themselves in space determine the size and shape of the unit cell. Each unit cell is like a brick and the crystal lattice a three-dimensional brick structure. A crystalline solid therefore can be described by the shape and size of a single unit cell because its three-dimensional crystal structure is simply a lattice of those unit cells repeating in all three dimensions.

30. The unit cell is characterized in terms of three lengths, *a*, *b*, and *c*, and three angles, α, β, and γ. These lengths and angles are known as the unit cell parameters. Different unit cells have different values of *a*, *b*, *c*, α, β, and γ, and

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 14

IPR2020-00770
United Therapeutics EX2007
Page 3523 of 7335

thus have different sizes and shapes. The unit cell parameters for the crystalline acetaminophen in my example are shown below.



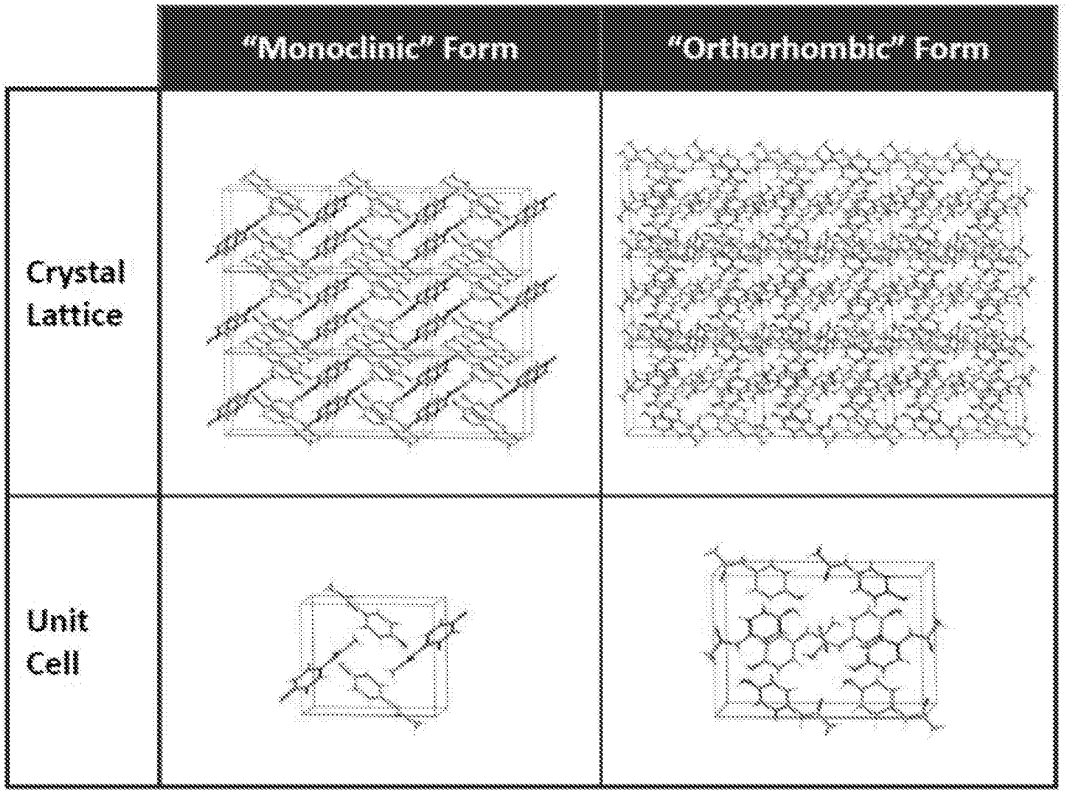
Unit Cell Parameters for Acetaminophen

31. Molecules of a compound may arrange, or "pack" themselves in more than one way, which can give rise to different crystalline structures or "forms." Many substances, including pharmaceutical compounds, can exist in more than one crystal form, each form having a different crystalline lattice and different unit cell. This phenomenon is termed "polymorphism" and the different crystal forms are called "polymorphs." A classic example is that of carbon, where one crystal form is diamond, and another crystal form of the same substance is graphite.

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 15

IPR2020-00770
United Therapeutics EX2007
Page 3524 of 7335

32. Two different crystalline forms of acetaminophen, referred to as "monoclinic" and "orthorhombic" are shown below.[1]



Two Different Crystal Forms of Acetaminophen

33. As shown in this example, the size and shape of the unit cell can differ, depending on how the molecules in the lattice of a particular polymorph are organized. Different polymorphs of pharmaceutical compounds may exhibit

[1] The terms "monoclinic" and "orthorhombic" refer to a specific type of crystal lattice. However, for convenience, forms are often named "Form I," Form II," Form III," etc. without any indication of its physical properties.

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 16

IPR2020-00770
United Therapeutics EX2007
Page 3525 of 7335

different properties, such as crystal shape, melting temperature, solubility, and stability.

B. Characterizing crystals

34. Because each crystal form, or polymorph, has its own unique unit cell and thus three-dimensional lattice, that particular crystal form can be identified by certain characteristics associated with its crystal lattice (and unit cell). For example, different polymorphs "diffract" (*i.e.*, reflect) X-rays differently. Thus, one technique that can be used to identify the crystal structure of a crystalline compound and to distinguish different polymorphs of the same compound is X-ray diffraction ("XRD"), which when carried out on compounds in powder form is called powder X-ray diffraction ("PXRD").[2]

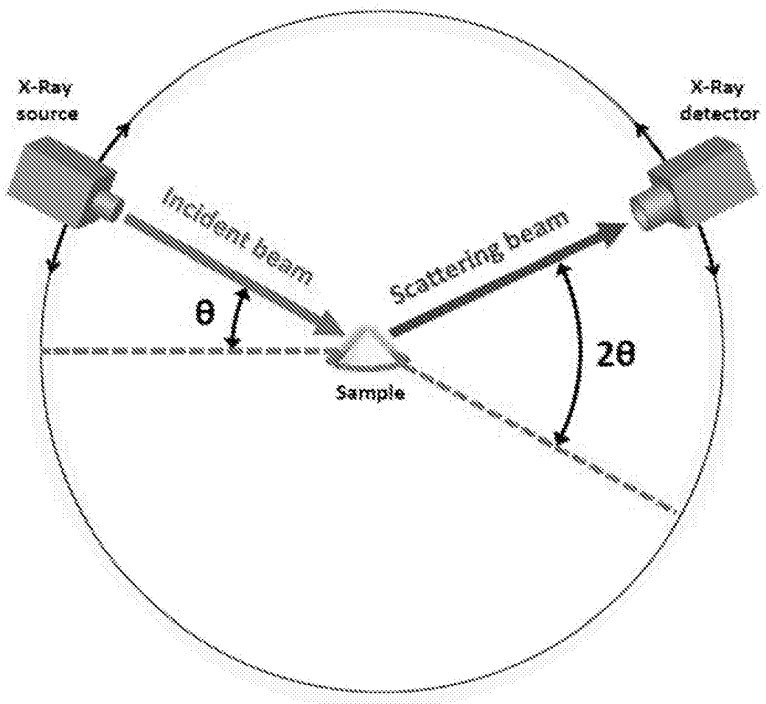
35. The molecules within each unit cell of the crystal lattice will diffract incident radiation, such as X-rays, in a specific pattern due to the orientation of those molecules within the unit cell. Each different crystal form will diffract X-rays at different "scattering angles" (the angle of the incident X-ray beam to the crystal where scattering of the X-rays is observed) and at differing "intensities" (how many X-rays are scattered). The scattering angles (as shown below) are measured and reported as diffraction peaks 2θ ("two theta"), and can also be referred to as the 2θ values or 2θ peaks.

---

[2] PXRD can also be referred to as X-ray powder diffraction, or "XRPD."

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 17

IPR2020-00770
United Therapeutics EX2007
Page 3526 of 7335

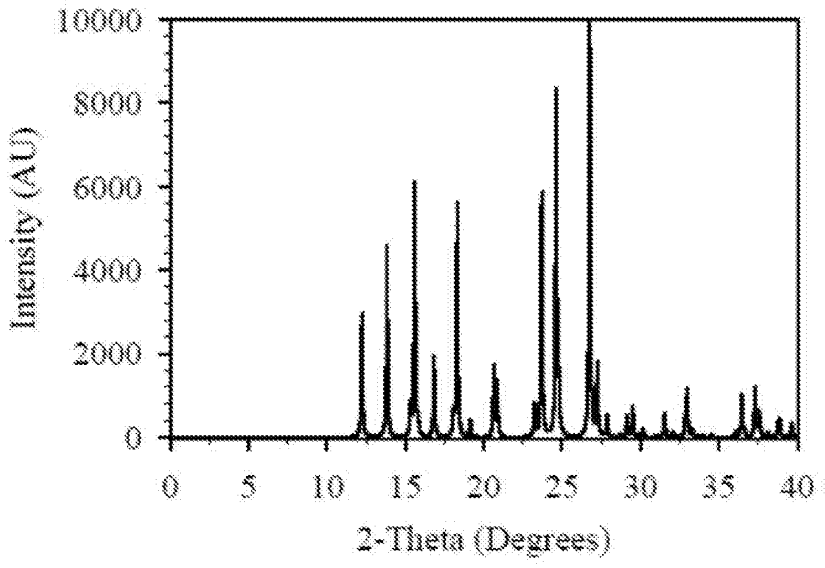


X-Ray Diffraction

36. A given crystalline form of a compound will always diffract X-rays at the same scattering angles. By measuring the scattering angles (2θ) and intensities of X-rays diffracted from a given sample of a polymorph, the 2θ values can be plotted against the differing intensities, as "lines" or "peaks," to produce a specific "X-ray diffraction pattern" for each polymorph. An X-ray diffraction pattern, therefore, can act as a fingerprint for that polymorph. For example, this is the X-ray diffraction pattern for one of the crystalline polymorphs of acetaminophen I discussed above:

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 18

IPR2020-00770
United Therapeutics EX2007
Page 3527 of 7335

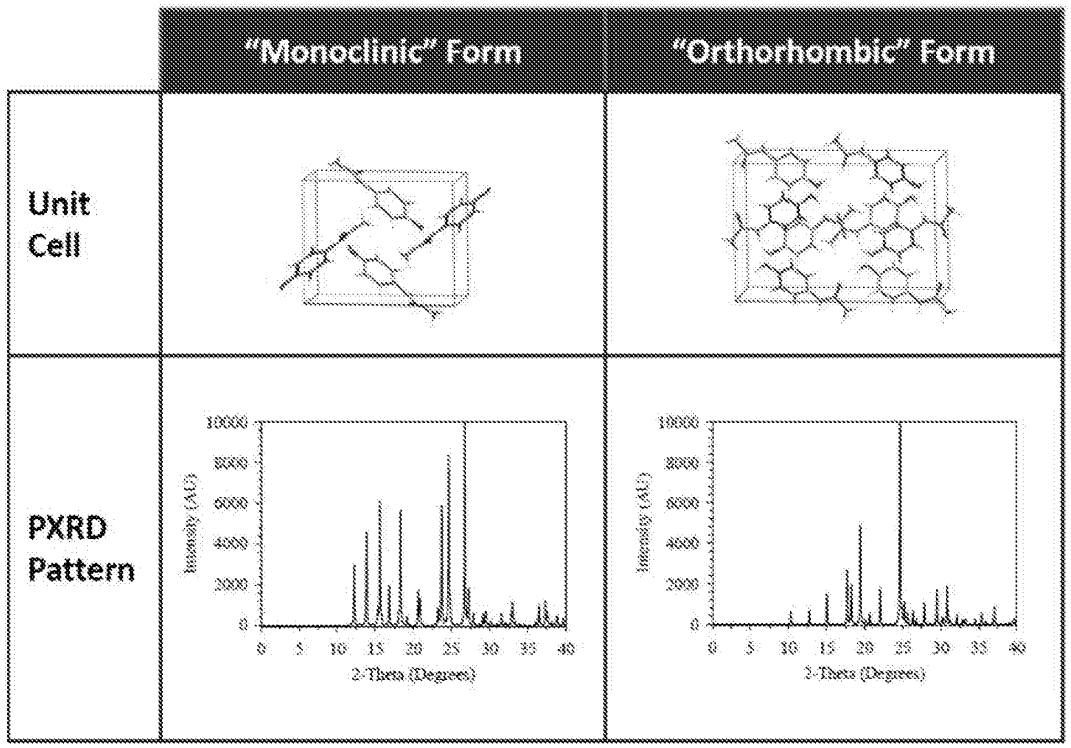


X-Ray Diffraction Pattern of Acetaminophen

37. As discussed above, the X-ray diffraction patterns (or "diffractograms") obtained from PXRD analysis are unique to a particular crystal form. The positions of the diffraction peaks provide information about the size and shape of the unit cell, and the intensities of the peaks provide information as to the contents of the unit cell, *i.e.*, the arrangement of atoms within the unit cell. The intensities of the peaks in a given PXRD pattern can be compared to each other. Different crystal forms yield different diffractograms and the technique can be used to distinguish one form from another, as shown below for two polymorphs of acetamimophen.

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 19

IPR2020-00770
United Therapeutics EX2007
Page 3528 of 7335



X-Ray Diffraction Patterns of Different Crystal Forms of Acetaminophen

C. Identifying crystals

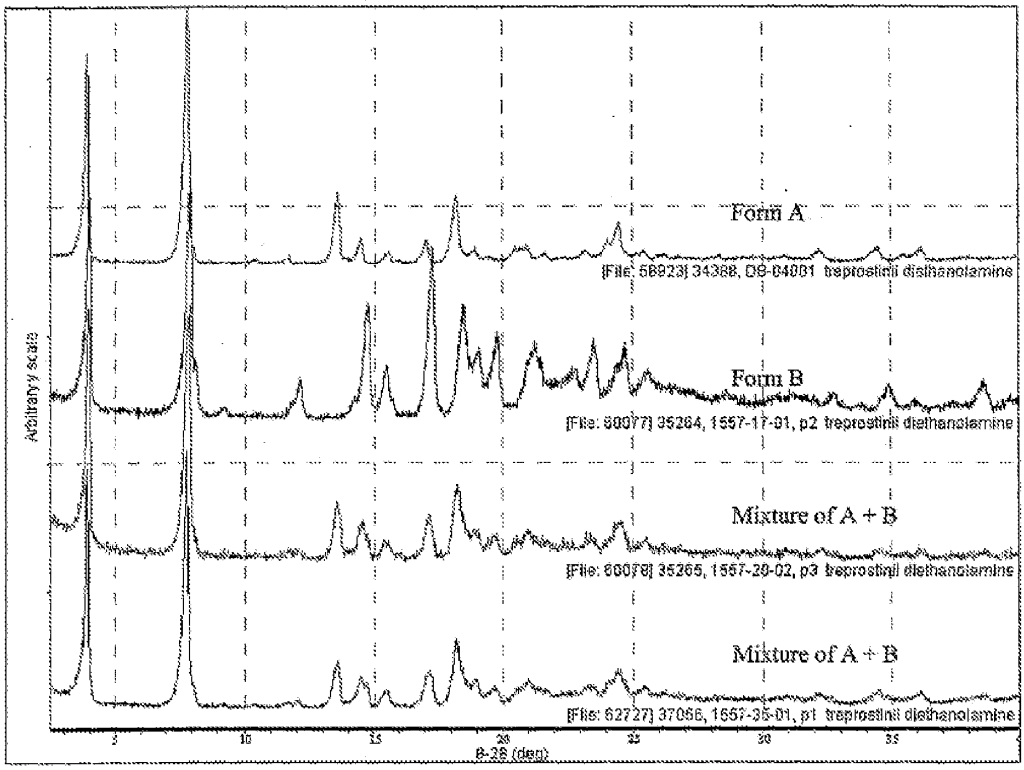
38. Once a reference PXRD pattern has been established for a particular polymorph, an unknown sample can be identified as that polymorph if its PXRD pattern corresponds to that of the reference PXRD pattern.

39. For example, the Phares Reference, Ex. 1005, provides a comparison of the PXRD patterns for treprostinil diethanolamine salt Form A and Form B:

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 20

IPR2020-00770
United Therapeutics EX2007
Page 3529 of 7335

FIGURE 20



(Ex. 1005 at 120.) The technique can accurately distinguish Form B from Form A, and can even be used to quantitatively assess mixtures of Form A and B.

D. Other techniques for characterizing crystals

40. There are other commonly-used analytical techniques besides PXRD for studying or characterizing crystal forms. While PXRD relays information about the inherent structure of a crystal form, and is therefore considered the best method for identifying crystal forms, visual and thermal techniques provide additional information about the physicochemical properties of a sample.

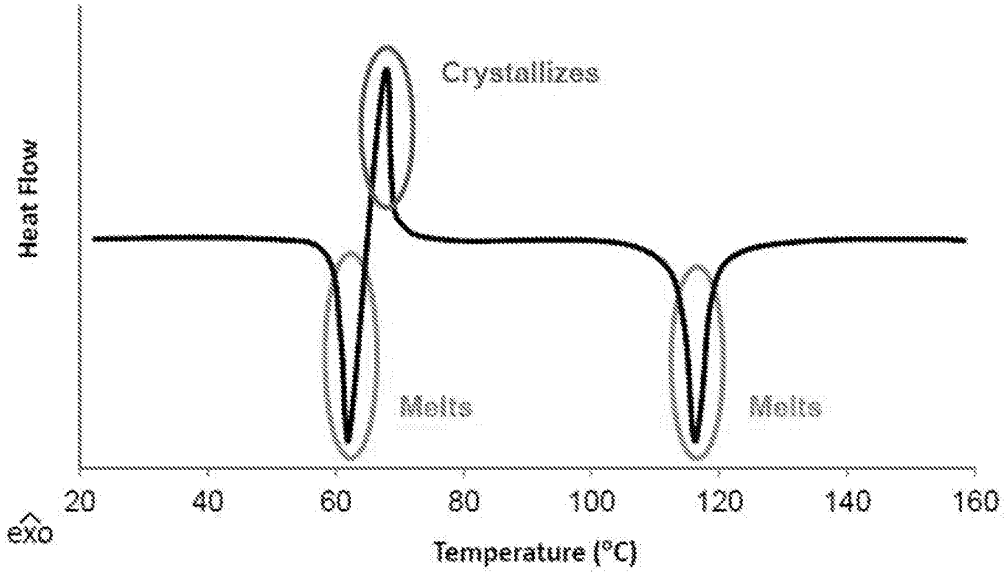
41. Microscopy (visual observation under a microscope) can reveal the morphology (size and shape) of the crystals themselves. In hot-stage microscopy, a sample can be observed as it is heated and/or cooled, which allows one to observe how the sample changes forms (between different crystal forms, or between liquid and solid), and at which temperatures they occur.

42. Thermal analyses provide quantitative information about different crystal forms. A material can go through changes in physical state when it is heated, for example, melt, crystalize, or change crystal forms. Each of these changes in physical state, also called phase transitions, is accompanied by either an absorption (endotherm) or release (exotherm) of heat. When a material melts, it absorbs heat, resulting in an endotherm, and when it crystallizes, it releases heat, resulting in an exotherm.

43. Differential scanning calorimetry (DSC) is a method of analysis that allows scientists to track these changes in physical state of a sample as it is heated, by detecting any endotherms (indicative of melting) and/or exotherms (indicative of crystallizations or changes of form) that occur. For example, in the hypothetical DSC plot below, the sample melts at about 62°C (endothermic event, resulting in a downward pointing peak), immediately recrystallizes (exothermic event, resulting in an upward pointing peak), then melts again at about 118 °C (endothermic event, resulting in a downward pointing peak).

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 22

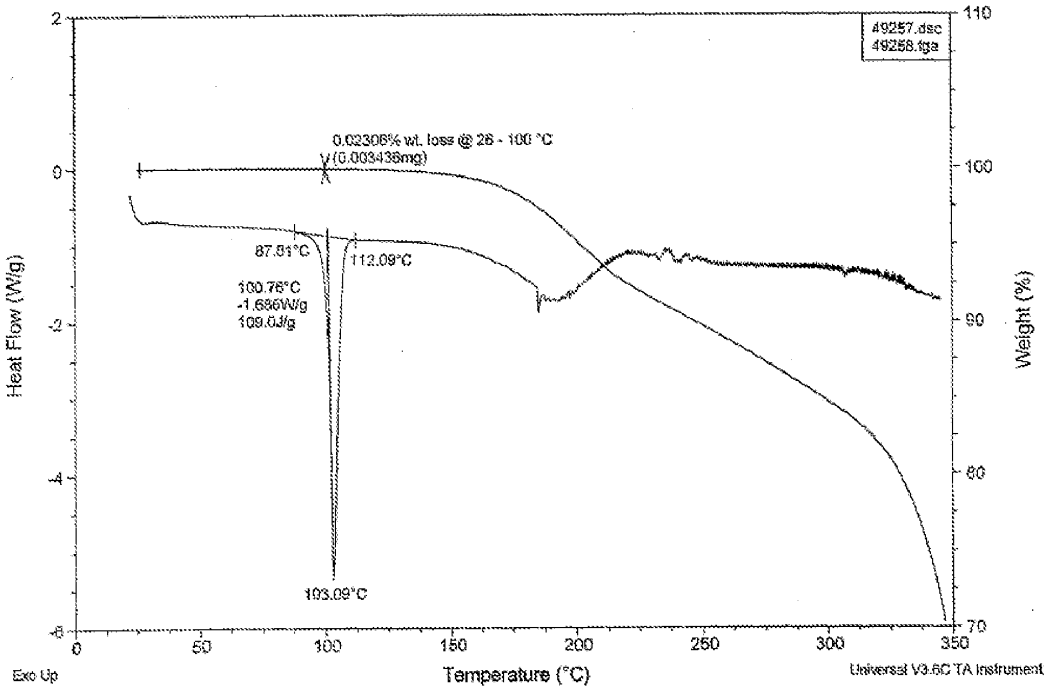
IPR2020-00770
United Therapeutics EX2007
Page 3531 of 7335



Illustrative DSC

44. In the Phares Reference (Ex. 1005) melting point data taken using DSC is used to distinguish and verify the identities of Form A and Form B treprostinil diethanolamine crystals. The melting point data for Form A shows that it melts at 103.09°C.

FIGURE 18



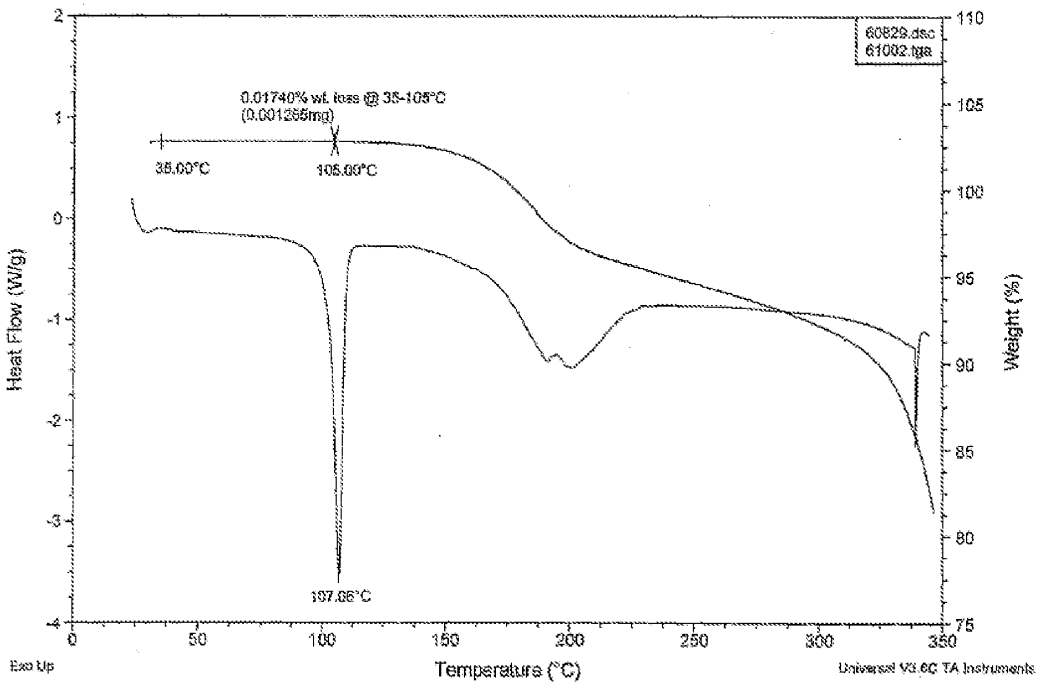
(Ex. 1005 at 118.)

45. Similarly, the melting point of a Form B crystal was also measured in the Phares Reference:

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 24

IPR2020-00770
United Therapeutics EX2007
Page 3533 of 7335

FIGURE 21



(Ex. 1005 at 121.) A computer has automatically marked the position of the melting point for this particular Form B crystal, which is indicated as 107.06°C. And this melting point value is reported in the text as 107°C. (Ex. 1005 at 91.)

46. In fact, the '393 Patent recognizes the importance of melting point in identifying which polymorph is present:

> At this stage, if melting point of the treprostinil diethanolamine salt is more than 104° C., it was considered polymorph B. There

> is no need of recrystallization. If it is less than 104°C. it is recrystallized in EtOH-EtOAc to increase the melting point.

(Ex. 1001 col.12 ll.52-56.)

47. Thermogravimetric analysis, known as "TGA" or "TG," is another technique for analyzing polymorphs, and is also used in the Phares Reference, Ex. 1005. TG can be used to determine if a material is a solvate or hydrate. If, upon heating, the weight of the crystal drops, it may indicate that a solvent has been released, due to conversion of the crystal from a pseudo-polymorph where the solvent (or water in the case of a hydrate) is incorporated in the crystal form, to a real polymorph containing the organic chemical alone.

48. For example, in the Phares Reference, Figures 18 and 21 show, in addition to DSC data, a TGA result, which is the upper curve, whose y-axis is the "Weight (%)" at the right. If there is virtually no weight loss at temperatures at or below the melting event, it means the crystal is not a solvate or hydrate. In the Phares Reference, it was demonstrated that neither Form A nor Form B were solvates or hydrates. (Ex. 1005 at 90 ("The TG data [for Form A] shows no measurable weight loss up to 100 °C, indicating that the material is not solvated."); Ex. 1005 at 91 ("The TG [of Form B] shows minimal weight loss up to 100 °C.".)

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 26

IPR2020-00770
United Therapeutics EX2007
Page 3535 of 7335

E. What role does melting point play in polymorph identification?

49. Melting point is so closely associated with the identity of polymorphs, that it has been proposed that polymorphs be identified by their melting points, instead of by their order of discovery.

50. For example, in Stephen R. Byrn *et al.*, *Solid-State Chemistry of Drugs*, Chapter 10, "Polymorphs," 143-231 (2d ed. 1999), a textbook on crystals of drugs, it states:

> It has been suggested that polymorphs be numbered consecutively in the order of their stability at room temperature or by their melting point.

(Ex. 1024, at 2.) This shows that melting point is so closely identified with the identity of a polymorph that melting point has been proposed as a means of distinguishing and identifying polymorphs.

51. Similarly, in Terence L. Threlfall, "Analysis of Organic Polymorphs: A Review," *Analyst* 120(10): 2435 (1995) it is stated that:

> Arbitrary systems are to be discouraged, but numbering based either on order of melting point or of room temperature stability have been recommended.

(Ex. 1025, at 1.)

52. As yet one more example, in the FDA Guidance for Industry, *ANDAs: Pharmaceutical Solid Polymorphism--Chemistry, Manufacturing, and Controls*

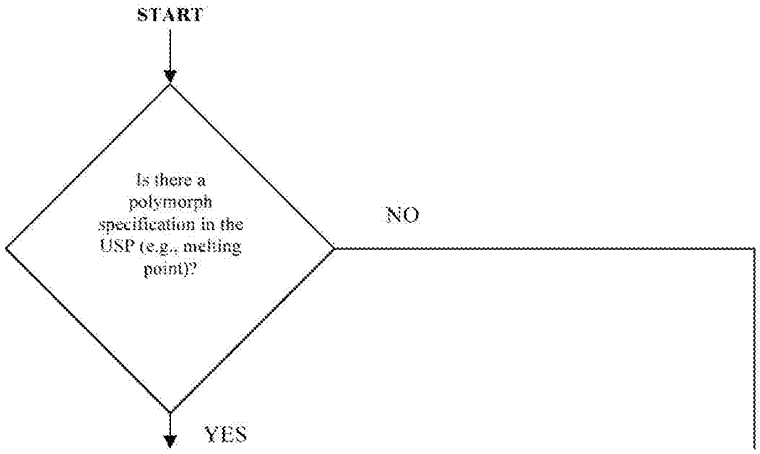
IPR2016-00006
SteadyMed - Exhibit 1022 - Page 27

IPR2020-00770
United Therapeutics EX2007
Page 3536 of 7335

Information, melting point is particularly pointed out as a distinguishing property of polymorphs:

ATTACHMENT 2 – DECISION TREE 2

Decision Tree 2 Setting specifications for polymorphs in drug substances for solid oral and suspension dosage form products.



(Ex. 1026, at 12.)

VI. MELTING POINT AND THE PURITY OF A CRYSTAL

53. As stated in many textbooks, the purity of a crystal can be related to its melting point:

> The method [of differential scanning calorimetry] can also be used as an accurate measure of the melting point and purity of the sample. In fact, the change of melting point is related to the mole fraction of impurities as given by Equation 5.2:

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 28

IPR2020-00770
United Therapeutics EX2007
Page 3537 of 7335

$$T_s = T_0 - \frac{T_o^2 R X_i}{F \Delta H_f} \qquad (5.2)$$

where T_s, is the sample temperature, T_0 is the melting point of the pure compound, R is the gas constant, X_i, is the mole fraction of the impurity, F is the fraction of the solid melted, and ΔH_f is the enthalpy of fusion of the pure compound. According to the equation, a plot of T_s versus $1/F$ should give a straight line whose slope is proportional to X_i (Brittain *et al.*, 1991).

Stephen R. Byrn *et al.*, *Solid-State Chemistry of Drugs*, Chapter 5, "Thermal Methods of Analysis," 81-901 (2d ed. 1999) (Ex. 1027, at 84.)

54. This phenomenon, known as melting-point depression, may be familiar, since it is used to melt ice on the roads in the winter. Salt, which can dissolve in water, is added to roads so that when the water on the road freezes, it contains salt impurities which lower the melting point. The melting point of ice is 0°C (T_0 in the equation above), but it is lower when the ice contains salt as an impurity. Therefore, even if the road temperature is 0°C, the water on the roads will be above the melting point T_s of ice containing salt, and thus, will be a liquid.

55. To simplify, although there is a complex relationship between the amount of impurities (X_i) and the observed melting point (T_s), the melting point will decrease if there are more impurities in the sample from the melting point in a 100% pure sample, which is designated T_0. The decrease will be greater the more impurities there are in the sample.

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 29

IPR2020-00770
United Therapeutics EX2007
Page 3538 of 7335

56. The value T_0 is unique for each polymorph. If I have two crystals that are known from their PXRD patterns to be Form B crystals, then both crystals have the identical T_0 value, regardless of how the crystals were made and what solvents were used to make them.

57. Thus, if the measured melting point of a Form B crystal, T_s, is below 107°C, then the sample contains impurities, in an amount X_i, that is causing a decrease in the observed melting point.

58. As explained in Stephen R. Byrn *et al.*, *Solid-State Chemistry of Drugs*, Chapter 5, "Thermal Methods of Analysis," 81-901 (2d ed. 1999) (Ex. 1027), differential scanning calorimetry or DSC is used to determine the melting point and then the purity of a crystalline sample using Equation 5.2. Another technique, thermal microscopy, is also used for this purpose, and is the technique used in the '393 Patent.

VII. THE CRYSTAL FORMS THAT I HAVE REVIEWED

59. The Phares Reference (Ex. 1005), discussed above, is International Publication No. WO 2005/007081 to Phares, *et al.*, entitled "Compounds and Methods for Delivery of Prostacyclin Analogs," and published January 27, 2005, and is assigned to United Therapeutics. I have been told that there is no dispute that it is prior art to the '393 Patent, but whether it is or not is not relevant to my opinions in this Declaration.

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 30

IPR2020-00770
United Therapeutics EX2007
Page 3539 of 7335

60. The Phares Reference (Ex. 1005) provides a detailed description of the manufacture and characteristics of treprostinil diethanolamine salt, Form A and Form B, using many different solvent systems. It also provides the PXRD patterns, the melting points determined by DSC, the Raman and IR spectra, and the TGA analysis of these crystals.

61. The '393 Patent (Ex. 1001) is also assigned to United Therapeutics. It also describes making treprostinil diethanolamine Form B salt at column 12 and clearly states that Form B is the crystal form that is made. To do so, crystals known to be Form B salt are added to solution, in a process known as seeding. In seeding, by using crystals of a chemical having a known form—here Form B—the same chemical dissolved in that solution will tend to add on to the seed crystal, and thus, will crystallize in accordance with the same crystal pattern, and thus will also form Form B. The '393 Patent authors state that the seed is Form B, which suggests that they must have analyzed its PXRD pattern or had some means to verify this fact.

62. In both the Phares Reference (Ex. 1005) and the '393 Patent (Ex. 1001 col. 12-13), treprostinil diethanolamine salt Form B is made. Phares demonstrated that Form B is the more stable form as compared to Form A. (Ex. 1005 at 88-93). Phares further discloses a Form B melting point for a sample (T_s) determined by DSC of 107° C. (Ex. 1005 at 91 ("Form B appears to be a crystalline material which melts at 107 °C").)

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 31

IPR2020-00770
United Therapeutics EX2007
Page 3540 of 7335

63. The '393 Patent discloses for Form B salt samples having melting point ranges (T_s) determined by thermal microscopy of 104.3-106.3, 105.5-107.2, 104.7-106.6, and 105-108°C, (Ex. 1001 col.12-13, Table,) and 105.0-106.5 and 104.5-105.5°C, (Ex. 1001 col. 13 ll. 50-65).

VIII. NO MATTER HOW FORM B IS MADE, FORM B HAS A SINGLE, DEFINED MELTING POINT

64. No matter how Form B is made, Form B has a single, defined melting point. If impurities are present, the apparent melting point may decrease due to a phenomenon called "melting point depression," but the melting point of a pure substance never changes.

A. Form A Can be Made Using a Number of Different Solvent Systems, But the Result is Still Form A

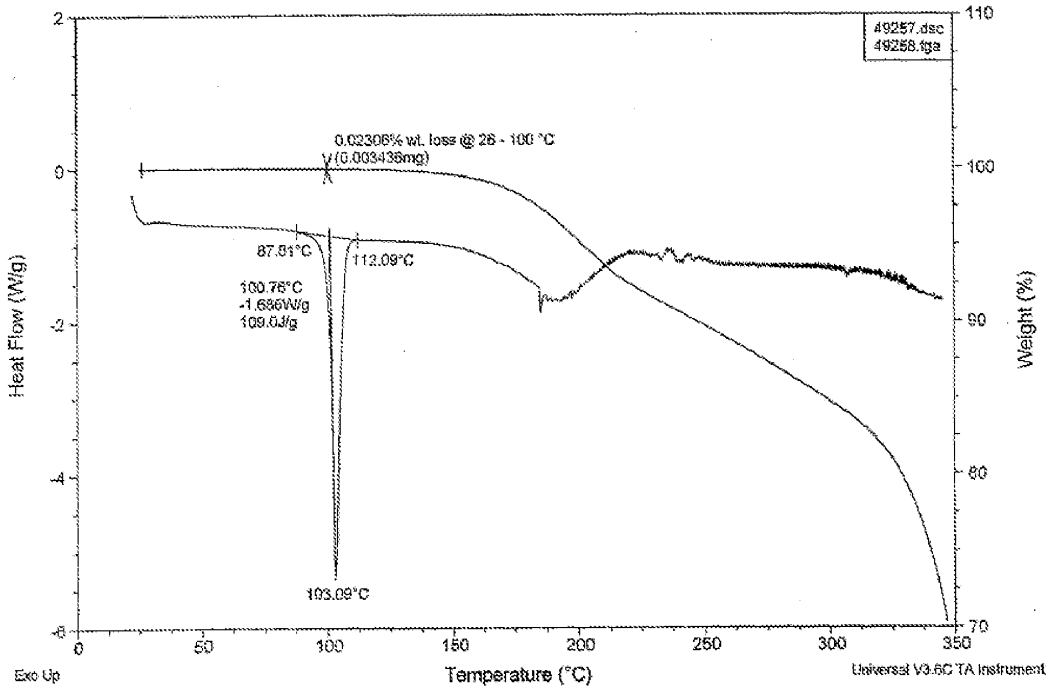
65. As shown in the Phares Reference, Form A can be made using many different solvents, listed in Table 15, including tetrahydrofuran, toluene:IPA, water, and water:ethanol. (Ex. 1005 at 88-89 (Table 15).) Each of these Form A crystals is the same polymorph, and will have the same melting point for the pure material (T_0 in Equation 5.2). The melting point identified in the Phares Reference for Form A is 103°C.

66. The 103°C corresponds to the following DSC thermogram, depicted in Figure 18 of the Phares Reference (Ex. 1005) below, which shows that the 103°C melting point corresponds to the temperature at the peak.

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 32

IPR2020-00770
United Therapeutics EX2007
Page 3541 of 7335

FIGURE 18



67. The Phares Reference states: "[t]he DSC thermogram shows an endotherm at 103°C that is consistent with melting (from hot stage microscopy)." (Ex. 1005, at 90). In other words, DSC and hot-stage microscopy provide the same result.

B. Form B Can be Made Using a Number of Different Solvent Systems, But the Result is Still Form B

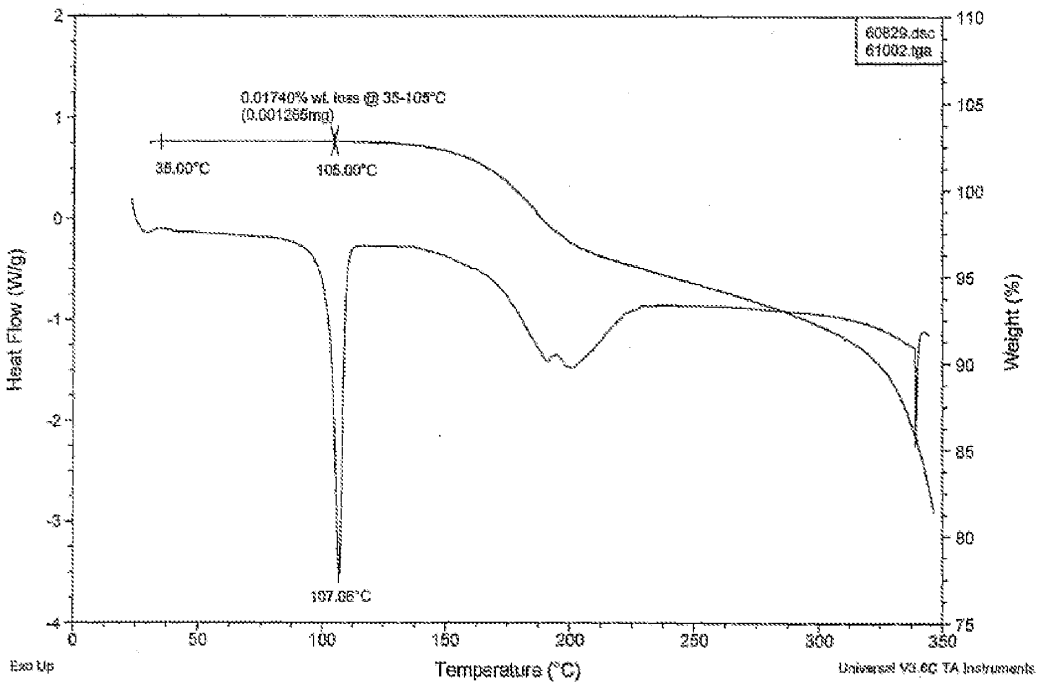
68. As shown in the Phares Reference, Form B can be made using many different solvents, listed in Table 16, including 1,4-dioxane, isopropanol, and toluene. (Ex. 1005 at 89 (Table 16)). Each of these Form B crystals is the same polymorph, and will have the same melting point for the pure material (T_0 in Equation 5.2). The melting point identified in the Phares Reference for Form A is 107°C.

69. The 107°C corresponds to the following DSC thermogram, depicted in Figure 21 of the Phares Reference (Ex. 1005) below, which shows that the 107°C melting point corresponds to the temperature at the peak.

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 34

IPR2020-00770
United Therapeutics EX2007
Page 3543 of 7335

FIGURE 21



70. The Phares Reference states: "[t]he DSC thermogram (Sample ID 1557-17-01) shows a single endotherm at 107°C that is consistent with a melting event (as determined by hotstage microscopy)." (Ex. 1005 at 91). In other words, DSC and hot-stage microscopy provide the same result.

C. The Form B Crystals Made in the Phares Reference Have the At Least the Same Purity as the Form B Crystals Made in the '393 Patent.

71. Since we do not know whether the Form B crystal in the Phares Reference is 100% pure, T_0 (the melting point of 100% pure material) is or exceeds 107°C.

72. As stated above, the observed melting temperature, T_s, for the Form B crystal made in the Phares Reference is 107°C. The '393 Patent reports melting point ranges of 104.3-106.3 °C; 104.7-106.6 °C; 105.0-106.5 °C; and 104.5-105.5 °C. (Ex. 1001, col. 12-13).

73. This comparison of T_s values shows that there is a greater percentage of impurities, X_i, in the '393 Patent Form B batches listed above than in the Phares Reference example. This scientific result is required by Equation 5.2 above, because, for Form B samples, every value in the equation except T_s and X_i is a constant, such that any change in the observed melting temperature, T_s, is necessarily due to a change in impurities, X_i.

74. In conclusion, the higher melting point disclosed in the Phares Reference is consistent with the Form B crystal in the Phares Reference having higher purity than certain of the '393 Patent's Form B crystals, in accordance with Equation 5.2. At the very least, the Phares Reference Form B crystal is at least as pure as any Form B crystal made in the '393 Patent.

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 36

IPR2020-00770
United Therapeutics EX2007
Page 3545 of 7335

D. The *Adhiyaman* reference, Ex. 2030, Does Not Suggest that Form B Crystals Made with Different Solvents Would Have Different Pure Melting Points T_0

75. I understand that United Therapeutics contends that a paper entitled "Crystal modification of dipyridamole using different solvents and crystallization conditions," appearing in *International Journal of Pharmaceutics* 321:27-34 (2006) (Ex. 2030, "Adhiyaman")), supports its contention that two crystals having the same crystal form could have differing T_0 melting point values if made from different solvents. But this paper does not support this conclusion.

76. United Therapeutics argues that, because in the '393 Patent (Ex. 1001 col.12 ll.35-52), treprostinil diethanolamine Form B was made by seeding already-made Form B crystals in a mixed solvent of ethanol and ethanol acetate, while in the Phares Reference (Ex. 1005), treprostinil diethanolamine Form B salt was made by first generating Form A from any of many possible mixed solvents, and then converting Form A to Form B in a second mixed solvent, the two Form Bs could have different T_0 melting point values.

77. As explained above, Form B salt has the same T_0 melting point value, no matter what technique is used to make it.

78. In Adhiyaman, different crystal forms of a drug called "dipyridamole" were made by using three different solvents, including methanol, benzene, and acetonitrile. In each case, the PXRD pattern of the crystals made from each solvent

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 37

IPR2020-00770
United Therapeutics EX2007
Page 3546 of 7335

were different. The differences in PXRD pattern are shown in Figure 3. (Ex. 2030 at 4.)

79. When two crystals have a different PXRD pattern, they are different crystal forms or polymorphs. PXRD patterns are fingerprints for polymorphs.

80. Since each of the crystals generated by using methanol, benzene, and acetonitrile as solvents, in the case of dipyridamole, generate a different crystal form, each crystal form would be expected to have a different T_0 value.

81. By contrast, the crystals generated by United Therapeutics in the '393 Patent and the Phares Reference were both characterized by United Therapeutics as the same crystal form, which United Therapeutics has named Form B.

82. Thus, unlike the case of dipyridamole in Ex. 2030, the crystals being compared in the '393 Patent and Phares Reference are the same crystal form, and thus have the same T_0 pure melting point value. Any difference in their measured melting point, T_s, is due to differing levels of impurities.

E. The Phares Reference Correctly Determined the Melting Point as 107°C, and the Width of the DSC Peak is Narrow

83. I disagree with United Therapeutics' suggestion that the DSC melting point determined in the Phares Reference "shows a broad melting peak with a range of close to 10 degrees which is indicative of a lower purity substance." (Patent Owner's Response, at 23.)

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 38

IPR2020-00770
United Therapeutics EX2007
Page 3547 of 7335

84. The peak in the Phares Reference Figure 21 (Ex. 1005 at 121) is quite narrow and sharp. To determine the 107.06°C melting point, most likely the DSC's on-board computer software was used.

85. According to Figure 21, the figure was generated using software called "Universal V3.6C" from TA Instruments, a leading manufacturer of DSC, TGA, and simultaneous DSC/TGA instruments. I am familiar with this manufacturer's equipment, and I know that this equipment comes with on-board software that automatically calculates melting points for the user.

86. The software is designed to correctly assign the melting point and United Therapeutics itself in the Phares Reference confirmed that the value was consistent with hot-stage microscopy.

87. The width of the peak is actually very narrow. The onset of the melting event is determined by plotting a tangent straight line (as shown by Figure 18 of the Phares Reference) from the left side of the peak. Such a tangent line is not shown in Figure 21, but is shown on Figure 18 for Form A, where it appears at 100.76°C, which is marked by an "X" on the TGA curve. This same "X" is marked in Figure 21 of Phares at 105.00°C, which marks the onset temperature. Thus, the width of the peak is only 2°C, which is quite narrow and typical of a highly pure chemical.

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 39

IPR2020-00770
United Therapeutics EX2007
Page 3548 of 7335

IX. CONCLUSION

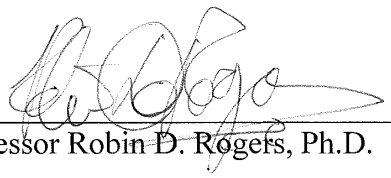
88. In summary, no matter how Form B is made, Form B has a single, defined melting point, and since the Phares Reference (Ex. 1005) discloses the same Form B crystal form as the '393 Patent (Ex. 1001), but a higher melting point than most of the '393 Patent examples, Phares necessarily discloses a salt of at least equal purity to the salt in the '393 Patent, if not higher.

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 40

IPR2020-00770
United Therapeutics EX2007
Page 3549 of 7335

I declare under penalty of perjury that the foregoing is true and correct.

Date: September 27, 2016



Professor Robin D. Rogers, Ph.D.

IPR2016-00006
SteadyMed - Exhibit 1022 - Page 41

IPR2020-00770
United Therapeutics EX2007
Page 3550 of 7335

Dr. Robin D. Rogers
Canada Excellence Research Chair in Green Chemistry and Green Chemicals
Editor, *Crystal Growth & Design*

Department of Chemistry
Otto Maass Chemistry Building
McGill University
801 Sherbrooke St. West
Montreal, QC
Canada H3A 0B8

Email: Robin.Rogers@McGill.ca
URL: http://rdrogers.research.mcgill.ca/
URL (CGD): http://pubs.acs.org/crystal

Date of Birth: March 4, 1957

Schools Attended and Degrees:

1975-1978: The University of Alabama, Tuscaloosa, AL; Chemistry Honors student; B.S. Degree in Chemistry (ACS); Summa Cum Laude.

1978-1982: The University of Alabama, Tuscaloosa, AL; Ph.D. in Inorganic Chemistry; Research Advisor: Professor Jerry L. Atwood.

Positions:

1982-1987:	Assistant Professor, Northern Illinois University, DeKalb, IL, USA
1987-1994:	Associate Professor, Northern Illinois University, DeKalb, IL, USA
1994-1995:	Professor, Northern Illinois University, DeKalb, IL, USA
1995-1996:	Presidential Research Professor, Northern Illinois University, DeKalb, IL, USA
1996-2014:	Professor, The University of Alabama, Tuscaloosa, AL, USA
1998-2014:	Director, The University of Alabama, Center for Green Manufacturing, Tuscaloosa, AL, USA
2004-2014:	Distinguished Research Professor, The University of Alabama, Tuscaloosa, AL, USA
2005-2014:	Robert Ramsay Chair of Chemistry, The University of Alabama, Tuscaloosa, AL, USA
2007-2009:	Chair of Green Chemistry, The Queen's University of Belfast, Belfast, Northern Ireland, United Kingdom
2007-2009:	Director, QUILL Research Centre, The Queen's University of Belfast, Belfast, Northern Ireland, United Kingdom
2015-:	Canada Excellence Research Chair in Green Chemistry and Green Chemicals, McGill University, Montreal, QC, Canada

Adjunct, Honorary, and Visiting:

1982 (summer):	Visiting Assistant Professor, The University of Alabama, Tuscaloosa, AL
1991-1998:	Resident Associate Guest (91-92), Visiting Scientist (92-93), Faculty Appointee (93-97), Guest Appointee (97-98), Argonne National Laboratory, Argonne, IL
1995-1996:	Adjunct Professor, The University of Alabama, Tuscaloosa, AL
1996-1997:	Adjunct Professor, Northern Illinois University, DeKalb, IL
2000 & 2006:	Visiting Professor, Université Louis Pasteur, Strasbourg, France
2004:	Adjunct Professor, Polymer and Fiber Engineering, Auburn University, Auburn, AL
2004:	Adjunct Professor, Department of Biological Sciences, The University of Alabama, Tuscaloosa, AL
2009-:	Honorary Professor, Institute for Process Engineering, Chinese Academy of Sciences, Beijing, China
2010:	Visiting Professor for Senior International Scientists of the Chinese Academy of Sciences, Institute for Process Engineering, Beijing, China
2014:	Adjunct Professor, McGill University, Montreal, QC, Canada
2015-:	Adjunct Professor, The University of Alabama, Tuscaloosa, AL

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 1

IPR2020-00770
United Therapeutics EX2007
Page 3551 of 7335

Memberships and Offices in Societies:

- Phi Beta Kappa; Sigma Xi, American Nuclear Society; American Crystallographic Association; American Institute of Chemical Engineers; Materials Research Society; American Association of Crystal Growth; Fellow of the American Association for the Advancement of Science; Fellow of the Royal Society of Chemistry; Chemical Institute of Canada; National Academy of Inventors.
- American Chemical Society: Rock River Local Section: Chairman Elect (Program Chairman), 1983-84; Chairman, 1984-86; Executive Committee, 1986-87; Secretary-Treasurer, 1988. Separation Science and Technology Subdivision (Industrial and Engineering Chemistry (I&EC)): Program Committee, 1992-2005; Executive Committee, 1993-2006; Vice Chair-Elect, 1993; Chair-Elect, 1994; Chair, 1995; Past-Chair, 1996. Practical Pollution Prevention Subdivision (I&EC): Co-Chair, 1998-99. Green Chemistry & Engineering Subdivision (I&EC): Program Committee, 2000-2006. I&EC Division: Program Committee, 1994-2002; Membership Committee (Academic Chemists Task Force Chair), 1996-2000; Executive Committee, 1995-2006; Program Secretary, 1995-98 ; Chair-Elect, 1998; Chair, 1999; Past-Chair, 2000; Parliamentarian, 2004-2006; I&EC Fellow, 2012. Committee on Science, 2004-06; Fellow of the American Chemical Society, 2009; Committee on Environmental Improvement, Associate 2010-2011; Member 2011-.

Advisory Boards:

- Scientific Advisory Board, EIChroM Industries, Inc., Darien, IL, 1995-2000.
- The University of Alabama College of Arts and Sciences Leadership Board, 1997-2002.
- Technology Review Council, Environmental Technology Demonstration and Commercialization Center (ETDCC), Texas City, TX, 1998-2000.
- Scientific Advisory Board, U.S. Department of Energy Joint Bioenergy Institute, Berkeley, CA, 2010-
- Scientific Advisory Board, Alkermes, Inc., Waltham, MA, 2012.

Editorial Boards and Editorships:

- *Journal of Crystallographic and Spectroscopic Research*: Editorial Board, 1989-93; Associate Editor, 1993
- *Journal of Chemical Crystallography*: Associate Editor, 1994-96; Editor, 1996-2000
- *Separation Science and Technology*: Associate Editor, 1996-99; Editorial Board 1999-
- *Crystal Engineering*: Founding Co-Editor, 1998-99
- *Industrial & Engineering Chemistry Research*: Editorial Board, 1999-2001
- *Journal of Chromatography, B*, Guest Editor, Volume 743 (1 + 2), 2000
- *Crystal Growth & Design*: Founding Editor-in-Chief, 2000-
- *Solvent Extraction and Ion Exchange*, Editorial Board, 2002-
- *Green Chemistry*, Advisory Board, 2002-
- *Chemical Communications*, Advisory Board, 2005-
- *Accounts of Chemical Research*, Guest Editor (with G. A. Voth), Special Issue on Ionic Liquids, Volume 40(11), 2007
- *ChemSusChem*, International Advisory Board, 2008-
- *Chemistry Letters*, Advisory Board, 2010-
- *Australian Journal of Chemistry*, Guest Editor (with K. R. Seddon), Research Front on Crystal Engineering, Volume 63(4), 2010
- *Separation Science & Technology*, Guest Editor (with H. Rodriguez and J. Chen), Special Issue on Ionic Liquids (2012).
- *Chemical Communications* Guest Editor (with D. MacFarlane and S. Zhang), Special Issue on Ionic Liquids (2012).
- *Science China – Chemistry* Guest Editor (with S. Zhang), Special Issue on Ionic Liquids (2012).
- *Catalysis Today* Guest Editor (with S. Zhang), Special Issue on Ionic Liquids (2012).
- *Green Chemistry and Sustainable Technology*, Springer, Heidelberg, Germany, Book Series Editor (with L.-N. He, D. Su, P. Tundo, and Z. C. Zhang).
- *Chimica Oggi/Chemistry Today*, Scientific Advisory Board, 2014-
- *Green Energy & Environment*, Advisory Board, 2016-

National Academy of Sciences Committees:

- National Academy of Sciences Board on Radioactive Waste Management Committee on Long Term Research Needs for High-Level Waste at Department of Energy Sites, 1999-2001.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 2

IPR2020-00770
United Therapeutics EX2007
Page 3552 of 7335

- National Academy of Sciences Board on Radioactive Waste Management Committee on Risk-Based Approaches for Transuranic and High-Level Radioactive Waste, 2003-2005.
- National Academy of Sciences Board on Radioactive Waste Management Committee Development and Implementation of a Cleanup Technology Roadmap, 2007-2009.

Awards:

- Northern Illinois University Outstanding Faculty Advisor - 1993
- Northern Illinois University Presidential Research Professor – 1995
- American Chemical Society Newsmaker Award – 2001 ("ACS Newsmakers honored in Chicago," *Chemical & Engineering News*, September 24, 2001, p 49.)
- The University of Alabama College of Arts & Sciences Leadership Board Fellow – 2002-2005
- The University of Alabama Burnum Distinguished Faculty Award – 2003.
- The University of Alabama Distinguished Research Professor – 2004
- The University of Alabama Robert Ramsay Chair of Chemistry - 2005
- 2005 Presidential Green Chemistry Challenge Award (Academic): "A Platform Strategy Utilizing Ionic Liquids to Dissolve and Process Cellulose for Advanced New Materials," – 2005 (Ritter, S. K. "Green Success," *Chemical & Engineering News*, June 27, 2005, pp 40-43.)
- Fellow of the Royal Society of Chemistry - 2006
- The University of Alabama Frederick Moody Blackmon – Sarah McCorkle Moody Outstanding Professor Award - 2009
- Fellow of the American Chemical Society – 2009
- Chinese Academy of Sciences Visiting Senior Scientist, Institute for Process Engineering, Beijing, China -2010
- American Chemical Society Award in Separations Science and Technology – 2011
- Fellow of the American Chemical Society Division of Industrial & Engineering Chemistry - 2012
- Fellow of the American Association for the Advancement of Science – 2012
- Paul Walden Award in Ionic Liquids, Presented by the German Science Foundation Priority Program on Ionic Liquids (SPP 1191) – 2013
- Thomson Reuters Highly Cited Researchers List 2014, 2015 (ranking among the top 1% most cited in chemistry).

Student Awards:

- Ann E. Visser: American Institute of Chemical Engineers Separations Division Graduate Student Award in Solvent Extraction – 2002
- Richard P. Swatloski: ACS Kenneth G. Hancock Memorial Student Award in Green Chemistry – 2003 ("2003 Hancock Award Honors Student Research," *Chemical & Engineering News*, July 7, 2003, pp 67-68.)

Research Interest:

Utilizing Ionic Liquids and Green Chemistry for Sustainable Technology Through Innovation. Major thrusts include: **Materials:** Advanced polymeric and composite materials from biorenewables; **Separations**: Novel strategies for separation and purification of value added products from biomass; **Energy:** New lubricant technologies and selective separations; **Medicine/Agrochemicals/Nutraceuticals:** Elimination of waste while delivering improved performance and new applications of pharmaceuticals, agrochemicals, and nutraceuticals.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 3

IPR2020-00770
United Therapeutics EX2007
Page 3553 of 7335

Statistics:

A. Refereed Publications: > 760
B. Citations; H-Index: > 35,000; 84
C. Patents: 21 issued (plus numerous foreign equivalents); 26 submitted; 9 licensed
D. Books Edited: 14
E. Non-Refereed Reviews, Reports, and Articles: 75
F. Meetings (Symposia) Organized: 33 (37)
G. Presentations (including students and collaborators) before National and International Meetings: 897
H. Presentations (including students and collaborators) before Regional Meetings: 119
I. Seminars: 227
J. PhD (thesis MS) degrees supervised: 27 (4)

Financial Disclosure:

Dr. Robin D. Rogers has partial ownership of 525 Solutions, Inc., Chitinality LLC, and Iolitec, Inc. in addition to financial interest in patents and patent applications through The University of Alabama.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 4

IPR2020-00770
United Therapeutics EX2007
Page 3554 of 7335

Meetings Organized:

- Chair, *23rd Great Lakes Regional American Chemical Society Meeting*, DeKalb, IL, 1990.
- Conference Chair, *11th International Conference on Partitioning in Aqueous Two-Phase Systems: The Expanding Boundaries of Aqueous Two-Phase Partitioning: Fundamentals and Applications of Environmentally-Benign Polymers in Biological, Industrial and Environmental Processes*, Gulf Shores, AL June 27-July 2, 1999. (Conference URL: http://bama.ua.edu/~rdrogers/aq2phase/11thconf.html.)
- Co-Director (with K. R. Seddon and S. Volkov), NATO Advanced Research Workshop: *Green Industrial Applications of Ionic Liquids*, Crete, Greece, April 12-16, 2000. (Conference URL: http://bama.ua.edu/~rdrogers/NATO.) (Highlighted in Freemantle, M. "Eyes On Ionic Liquids," *Chemical & Engineering News*, May 15, 2000, pp 37-50.)
- Organizer, *Industries of the Future Alabama Symposium: Sustainable Industry through Green Chemistry and Engineering*, Mobile, AL July 27-28, 2000. (Conference URL: http://bama.ua.edu/~rdrogers/IOF/Mobile.)
- Co-Vice Chair (with J. C. Warner), *Gordon Research Conference on Green Chemistry*, Oxford, United Kingdom, September 8-13, 2002.
- Co-Chair (with A. S. Myerson, S. M. Reutzel-Edens, and R. J. Davey), ACS ProSpectives Series: *Polymorphism in Crystals: Fundamentals, Prediction, and Industrial Practice*, Tampa, FL, February 23-27, 2003.
- Co-Chair (with A. S. Myerson, and S. M. Reutzel-Edens), ACS ProSpectives Series: *Polymorphism in Crystals*, Tampa, FL, February 8-11, 2004.
- Organizer, *Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications*, Tuscaloosa, AL, March 23-24, 2004 (Workshop URL: http://www.bama.ua.edu/~rdrogers/ILWorkshop04/).
- Co-Chair (with J. C. Warner), *Gordon Research Conference on Green Chemistry*, Bristol, RI, July 4-9, 2004 (Conference URL: http://bama.ua.edu/~rdrogers/GreenChemistryGRC04).
- U.S. Organizer, NSF Joint China-USA Workshop *Determining the Grand Challenges of Green Chemistry Development and Implementation*, Beijing, China, May 27-31, 2005.
- Organizer, EPA/Green Chemistry Institute Workshop *Incorporating Toxicology into the Design Criteria for New Ionic Liquids Synthesis*, Washington, DC, June 9-10, 2005.
- Program Chair, 2nd International Conference on Green and Sustainable Chemistry; 9th Annual Green Chemistry and Engineering Conference: *Taking Measure of Green Progress: Opportunities to Meet Global Challenges*, Washington, DC, June 20-24, 2005.
- Program Chair, *2005 Rare Earth Research Conference*, Keystone, CO, June 26-30, 2005.
- Co-Organizer (with D. A. Dixon), *Alabama Actinide Day*, April 6, 2005, Tuscaloosa, AL.
- Local Organizer, *Air Force Office of Scientific Research Ionic Liquids Research Workshop*, Tuscaloosa, AL, February 7-8, 2006.
- Organizer, *Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications*, Tuscaloosa, AL, March 23-24, 2006 (Workshop URL: http://www.bama.ua.edu/~rdrogers/ILWorkshop06/).
- Co-Chair (with A. S. Myerson) ACS ProSpectives Series: *Process Crystallization in the Pharmaceutical and Chemical Industries*, Philadelphia, PA, April 25 - 27, 2006.
- Co-Chair (with M. Maase) Intertech Pira Conference *Ionic Liquids: Technical Innovations, Emerging Markets and Applications*, Orlando, FL, December 11-13, 2006.
- Co-Chair (with A. S. Myerson) ACS ProSpectives Series: *Crystallization Process Development: Case Studies & Research*, Boston, MA, February 25-27, 2007.
- Organizing Committee (with K. R. Seddon and J. F. Brennecke), *Biodegradability and Toxicity of Ionic Liquids*, Berlin, Germany, May 6-9, 2007.
- Chair, Intertech Pira Conference *Ionic Liquids: Technical Innovations, Emerging Markets and Applications*, Prague, Czech Republic, October 16-18, 2007.
- Co-Chair (with M. Hong), *5th Chinese National Symposium on Structural Chemistry and Symposium on Chinese Strategy of* Crystal Growth & Design," Fuzhou, China, October 25-31, 2007.
- Conference Chair, *25th Rare Earth Research Conference*, Tuscaloosa, AL, June 22-26, 2008.
- Organizer/Lecturer, *1st Ionic Liquid Workshop Malaysia*, University of Technology PETRONAS, Tronoh, Malaysia, June 30 – July 11, 2008.
- Local Organizing Committee, *15th International Conference on Biopartitioning and Purification*, Brunel University, Uxbridge, UK, June 14-19, 2009.
- Co-Chair (with T. Beyersdorff), Intertech Pira Conference *Ionic Liquids*, Miami Beach, FL, November 18-19, 2009.
- Vice Chair, *Gordon Research Conference on Crystal Engineering*, Waterville Valley, NH, June 6-11, 2010.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 5

IPR2020-00770
United Therapeutics EX2007
Page 3555 of 7335

- Co-Organizer (with G. Desiraju), *Crystal Growth & Design-India Summit* and *Current Trends in Crystal Engineering Research,* Bangalore, India, December 2-3, 2010.
- Conference Chair, *4th Congress on Ionic Liquids*, Washington, DC, June 15-18, 2011.
- Chair, *Gordon Research Conference on Crystal Engineering*, Waterville Valley, NH, June 10-15, 2012.
- Co-Chair (with S. Zhang*), 3rd Asian-Pacific Conference on Ionic Liquids and Green Processes*, APCIL'12, Beijing, China, September 17-19, 2012.
- Theme Organizer, "Chemistry & Global Stewardship" for the 248th ACS National Meeting (2014), San Francisco, CA, August 10-14 2014.
- Chair, *Gordon Research Conference on Ionic Liquids*, Newry, ME, August 17-22, 2014.
- Organizer/Host, 2015 New Journal of Chemistry Symposium *New Directions in Chemistry*, Montreal, QC Canada, June 3, 2015.

Symposia Organized:

- "Aqueous Biphasic Separations: Biomolecules to Metal Ions," (with C. K. Hall) for the 207th ACS National Meeting (1994), San Diego, CA.
- "Lanthanide Coordination Chemistry," for the Rare Earth Research Conference (1996), Duluth, MN.
- "Current Trends in Applied Chemistry: The Industrial/Academic Interface in Separation Science," for the 213th ACS National Meeting (1997), San Francisco, CA.
- "Recent Advances in Metal Ion Separation and Preconcentration," (with M. L. Dietz and A. H. Bond) for the 214th ACS National Meeting (1997), Las Vegas, NV.
- "Crystal Engineering: Functional Solids by Design," (with M. J. Zaworotko) for the Fifth Chemical Congress of North America (1997), Cancún, Mexico.
- "Transactions Symposium: Crystal Engineering," (with M. J. Zaworotko) for the American Crystallographic Association Annual Meeting (1998), Arlington, VA.
- "Nuclear Separations for Radiopharmacy," (with M. L. Dietz and A. H. Bond) for the 216th ACS National Meeting (1998), Boston, MA.
- "Calixarene Molecules for Separations," (with G. Lumetta and A. S. Gopolan) for the 217th ACS National Meeting (1999), Anaheim, CA.
- "Toward Vision 2000: Sustainable Technology for the Future," (with A. Manheim and A. H. Bond) Poster Session for the 217th ACS National Meeting (1999), Anaheim, CA.
- "Synthesis of New Materials by Coordination Chemistry, Self Assembly and Template Formation," (with M. J. Zaworotko) for the 217th ACS National Meeting (1999), Anaheim, CA.
- "Crystal Engineering," Microsymposium 110D (G. R. Desiraju, Chair; M. J. Zaworotko and R. D. Rogers, Co-Chairs) for the XVIIIth International Union of Crystallography Congress and General Assembly (1999), Glasgow, Scotland, UK.
- "Separation Science and Technology Award Honoring E. Philip Horwitz: Solvent Extraction and Ion Exchange in the 21st Century," (with S. Alexandratos) for the 219th ACS National Meeting (2000), San Francisco, CA.
- "Advances in Solvent Selection and Substitution for Extraction," (with M. Overcash) for the 2000 Spring National AIChE Meeting (2000), Atlanta, GA.
- "Crystal Engineering," (with W. T. Pennington) for the 52nd Southeast/56th Southwest Combined Regional Meeting of the ACS (2000), New Orleans, LA.
- "Separation Science: Trends for the New Century," (with S. Alexandratos, A. Jyo, and M. J. Zaworotko) for the 2000 International Chemical Congress of Pacific Basin Societies, Pacifichem 2000 (2000), Honolulu, HI.
- "Green (or Greener) Industrial Applications of Ionic Liquids," (with K. R. Seddon) for the 221st ACS National Meeting (2001), San Diego, CA (URL: http://bama.ua.edu/~rdrogers/sandiego).
- "Crystal Engineering to Crystal Growth: Design and Function," (with A. S. Myerson and K. R. Seddon) for the 223rd ACS National Meeting (2002), Orlando, FL.
- "Ionic Liquids as Green Solvents: Progress and Prospects," (with K. R. Seddon) for the 224th ACS National Meeting (2002), Boston, MA (URL: http://bama.ua.edu/~rdrogers/Boston).
- "Ionic Liquids III: Fundamentals, Progress, Challenges, and Opportunities," (with K. R. Seddon) for the 226th ACS National Meeting (2003), New York, NY (URL: http://bama.ua.edu/~rdrogers/New York).
- "Ionic Liquids in Polymer Systems," (with C. S. Brazel) for the 227th ACS National Meeting (2004), Anaheim, CA (Highlighted in Freemantle, M. "Designer Liquids in Polymer Systems," *Chemical & Engineering News*, May 3, 2004, pp 26-29.)

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 6

IPR2020-00770
United Therapeutics EX2007
Page 3556 of 7335

- "Polymorphism," Microsymposium MS04 (with E. Vlieg) for the XXth International Union of Crystallography Congress and General Assembly (2005), Florence, Italy.
- "Lanthanide-containing Functional Edifices," (with J.-C. Bunzli, H. Tsukube, and J. Takats) for the 2005 International Chemical Congress of Pacific Basin Societies, Pacifichem 2005 (2005), Honolulu, HI.
- "Ionic Liquids: Perspectives on the Present, Visions for the Future" (with J. Davis, Jr., D. MacFarlane, and H. Ohno) for the 2005 International Chemical Congress of Pacific Basin Societies, Pacifichem 2005 (2005), Honolulu, HI.
- "Organic Reactions in Neoteric Media" (with C.-J. Li, T.-H. Chan, D. H. Busch, S. Kobayashi, and P. Jessop) for the 2005 International Chemical Congress of Pacific Basin Societies, Pacifichem 2005 (2005), Honolulu, HI.
- "Ionic Liquids: Not Just Solvents Anymore OR Ionic Liquids: Parallel Futures," (with J. F. Brennecke and K. R. Seddon) for the 231st ACS National Meeting (2006), Atlanta, GA (URL: http://bama.ua.edu/~rdrogers/Atlanta2006/)
- "Green Chemistry and Engineering" (with M. A. Abraham) within the Joint ACS/AIChE Symposium on "Applied Chemistry and Engineering" for the 233rd ACS National Meeting (2007), Chicago, IL.
- "Award in Separations Science and Technology: Symposium in Honor of Allen S. Myerson," for the 235th ACS National Meeting (2008), New Orleans, LA.
- "Ionic Liquids: From Knowledge to Application," (with J. F. Brennecke and K. R. Seddon) for the 236th ACS National Meeting (2008), Philadelphia, PA (URL: http://bama.ua.edu/~rdrogers/Philadelphia2008/).
- "Green Chemistry for a Sustainable World," for the 239th ACS National Meeting (2010), San Francisco, CA.
- "Symposium in Honor of Allan S. Myerson, I&EC Fellow," for the 239th ACS National Meeting (2010), San Francisco, CA.
- "Ionic Liquids in a Sustainable World (#92)" (with D. MacFarlane and H. Ohno) for the 2010 International Chemical Congress of Pacific Basin Societies, Pacifichem 2010 (2010), Honolulu, HI.
- "Ionic Liquids: Science and Applications" (with A. E. Visser and N. J. Bridges) for the 243rd ACS National Meeting (2012), San Diego, CA.
- "Functional Materials and Ionic Liquids (BBB)" (with S. Dai, T. P. Lodge, P. Wasserscheid, and M. Watanabe) for the 2012 Materials Research Society Spring Meeting (2012), San Francisco, CA.
- "Uranium from Seawater" (with S. Dai and B. Hay) for the 244th ACS National Meeting (2012), Philadelphia, PA.
- "Materials Applications of Ionic Liquids (VV)" (with R. E. Del Sesto, S. Dai, and Y. Yoshida) for the 2013 Materials Research Society Spring Meeting (2013), San Francisco, CA.
- "Uranium from Seawater" (with P. F. Britt) for the 249th ACS National Meeting (2015), Denver, CO.
- "Transactions Symposium: Crystallography for Sustainability," (with C. Lind-Kovacs) for the American Crystallographic Association Annual Meeting (2015), Philadelphia, PA.
- "Connecting Ionic Liquids to Societal Issues: Materials, Medicines, Energy, and Water (#113)" (with D. MacFarlane and H. Ohno) for the 2015 International Chemical Congress of Pacific Basin Societies, Pacifichem 2015 (Dec. 14-21, 2015), Honolulu, HI.
- "Pharmaceutical Ionic Liquids: Understanding, Design, and Utilization," for the Molecules, Materials, Medicines (M3) Meeting (May 14-17, 2016), Solomons Island, MD.

Other Professional Activities:

- International Advisory Board member for the 9th International Conference on Partitioning in Aqueous Two-Phase Systems, Zaragoza, Spain, 1995.
- International Advisory Board member for the 6th Conference on Separation of Ionic Solutes, Piestany Spa, Slovakia, 1995.
- International Scientific Committee member for the 10th International Conference on Partitioning in Aqueous Two-Phase Systems, Reading, United Kingdom, 1997.
- Program Committee for the Tenth Symposium on Separations Science and Technology for Energy Applications, Gatlinburg, TN, 1997.
- Program Committee for the Third Department of Energy/Basic Energy Sciences Separations Research Workshop, Savannah, GA, 1999.
- Program Committee for the Eleventh Symposium on Separations Science and Technology for Energy Applications, Gatlinburg, TN, 1999.
- Steering Committee Member for *Chemistry in the 21st Century*, *ACS-2000*, San Francisco, CA, 2000.
- Program Committee for IUPAC CHEMRAWN XIV World Conference, Toward Environmentally Benign Processes and Products, Boulder, CO, 2001.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 7

IPR2020-00770
United Therapeutics EX2007
Page 3557 of 7335

- Program Committee for the Twelfth Symposium on Separations Science and Technology for Energy Applications, Gatlinburg, TN, 2001.
- Chair, Scientific Committee for Bio Partitioning & Purification 2003 Conference, Vancouver, BC, Canada, 2003.
- Instructor, NSF/DOE Pan American Advanced Studies Institute (PASI) on Green Chemistry, Montevideo, Uruguay, 2003.
- International Symposium Committee for the First International Symposium on Process Intensification and Miniturisation, Newcastle upon Tyne, United Kingdom, 2003.
- Program Committee for the Thirteenth Symposium on Separations Science and Technology for Energy Applications, Gatlinburg, TN, 2003.
- Scientific Committee for the International Conference on Materials for Advanced Technologies (ICMAT 2003)/International Union of Materials Research Societies International Conference in Asia (ICA 2003), Singapore, Symposium D: New Materials by Crystal Engineering Design.
- Group of Advisors, LICP Discussions No. 1 - Ionic Liquids: Progress and Prospects, Lanzhou China, 2004.
- Organizing and Scientific Advisory Committee, Canada-US Joint Workshop on Innovative Chemistry in Clean Media, Montreal, Quebec, Canada, 2004.
- International Program Committee, EUCHEM 2004 Molten Salts Conference, Piechowice, Poland, 2004.
- Instructor, ACS-PRF Summer School on Green Chemistry, Pittsburgh, PA, 2004.
- International Advisory Board, 1st International Congress on Ionic Liquids (COIL), Salzburg, Austria, 2005.
- Program Committee for the Fourteenth Symposium on Separations Science and Technology for Energy Applications, Gatlinburg, TN, 2005.
- Advisory Board, Second International Symposium on Green/Sustainable Chemistry, Delhi, India, 2006.
- Organizing Committee 10th Annual Green Chemistry and Engineering Conference: Washington, DC, 2006.
- Scientific Committee, EUCHEM Conference on Molten Salts and Ionic Liquids, Hammamet, Tunisia, 2006.
- International Advisory Committee, International Conference and Exhibition on Green Chemistry, Malaysian Chemical Congress (MCC 2006), Kuala Lumpur, Malaysia, 2006.
- Advisory Committee, DAE-BRNS Biennial Symposium on Emerging Trends in Separation Science and Technology, SESTEC-2006, Mumbai, India, 2006.
- Organizing Committee, 11th Annual Green Chemistry and Engineering Conference, Washington, DC, 2007.
- International Organizing Committee, 2nd International Congress on Ionic Liquids (COIL-2), Yokohama, Japan, 2007.
- Organizing Committee, International Solvent Extraction Conference (ISEC 2008) "Solvent Extraction: Fundamentals to Industrial Applications," Tucson, AZ, 2008.
- International Advisory Board, EUCHEM2008 Conference on Molten Salts and Ionic Liquids, Copenhagen, Denmark, 2008.
- Scientific Advisory Board, Taibah International Chemistry Conference 2009 (TICC-2009), Al-Madinah Al-Munawarah, Saudi Arabia, 2009.
- International Advisory Board for the Joint Conference: The 4th International Conference on Green and Sustainable Chemistry (GSC-4) & the 2nd Asian-Oceanian Conference on Green and Sustainable Chemistry (AOC-2), Beijing, China, 2009.
- International Advisory Committee for the 9th International Workshop on the Crystal Growth of Organic Materials (CGOM9), Singapore, 2010.
- International Advisory Committee for Application of Radiotracers in Chemical, Environmental and Biological Sciences (ARCEBS 10), Kolkata, India, 2010.
- Scientific Committee for 2nd Asian Pacific Conference on Ionic Liquids and Green Processes (APCIL-2), Dalian, China, 2010.
- International Advisory Board for the Green Solvents Conference, Berchtesgaden, Germany, 2010.
- Chair The Rare Earth Research Conference Spedding Award Committee, 2011.
- Technical Committee, International Solvent Extraction Conference (ISEC 2011), Santiago, Chile, 2011.
- International Scientific Committee, 1st International Conference on Ionic Liquids in Separation and Purification Technology, Sitges, Spain, 2011.
- International Advisory Board, EUCHEM2012 Conference on Molten Salts and Ionic Liquids, Newport, South Wales, UK, 2012.
- International Advisory Board, Indo-US Workshop on Green Chemistry for Environments and Sustainable Development, Dehradun, India, March 11-13, 2012.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 8

IPR2020-00770
United Therapeutics EX2007
Page 3558 of 7335

- International Scientific Committee, 3rd Asian-Pacific Conference on Ionic Liquids and Green Processes, APCIL'12, Beijing, China, September 17-19, 2012.
- International Committee, 2nd International Conference on Ionic Liquids in Separation and Purification Technology (ILSEPT), Toronto, Canada, June 29 – July 2, 2014.
- Advisory Board, 7th Green Solvents Conference, Dresden, Germany, October 19-22, 2014.
- International Advisory Board, Collaborative Conference on Crystal Growth, Phuket, Thailand, Nov. 4-7, 2014.
- International Advisory Board, *6th International Congress on Ionic Liquids (COIL-6),* Jeju, Korea, June 16-20, 2015.
- Invited Expert, meeting of the International Council for Science Project "COncepts and termiNology IN Crystal Engineering" (CONvINCE), Como, Italy, August 30, 2015.
- International Advisory Committee, Collaborative Conference on Crystal Growth (3CG 2015), Hong Kong, China, Dec. 14-17, 2015.
- Advisory Board, International Symposium on Ionic Liquids (ISOIL_2016), Mumbai, India, Jan. 21-22, 2016.
- International Advisory Committee, Energy Materials Nanotechnology Meeting on Cellulose (EMN 2016), Taipei, Taiwan, March 8-11, 2016.
- Scientific Advisory Board, EUCHEM2016, Vienna, Austria, July 3-8, 2016.
- Organizing Committee, Molecules, Materials, Medicines (M3), Solomons Island, MD, May 14-17, 2016.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 9

IPR2020-00770
United Therapeutics EX2007
Page 3559 of 7335

Books Edited:

1. *Aqueous Biphasic Separations: Biomolecules to Metal Ions*; Rogers, R. D.; Eiteman, M. A., Eds.; Plenum: New York, 1995; 191 pp.
2. *Metal-Ion Separation and Preconcentration, Progress and Opportunities*; Dietz, M. L.; Bond, A. H.; Rogers, R. D., Eds.; ACS Symposium Series 716, American Chemical Society: Washington, DC, 1999; 418 pp.
3. *Crystal Engineering*, Rogers, R. D.; Zaworotko, M. J., Eds.; Transactions of the American Crystallographic Association, Vol. 33; American Crystallographic Association: Buffalo, NY, 1999; 177 pp.
4. *Calixarenes for Separations*; Lumetta, G.; Rogers, R. D.; Gopalan, A. S., Eds.; ACS Symposium Series 757, American Chemical Society: Washington, DC, 2000; 366 pp.
5. *Ionic Liquids; Industrial Applications to Green Chemistry*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 818; American Chemical Society: Washington, DC, 2002; 474 pp.
6. *Green Industrial Applications of Ionic Liquids*, NATO Science Series II. Mathematics, Physics and Chemistry – Vol. 92, Rogers, R. D.; Seddon, K. R.; Volkov, S. (Eds.); Kluwer: Dordrecht, 2003; 553 pp.
7. *Ionic Liquids as Green Solvents: Progress and Prospects*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 856; American Chemical Society: Washington, DC, 2003; 599 pp.
8. *Ionic Liquids IIIA: Fundamentals, Progress, Challenges, and Opportunities - Properties and Structure*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 901; American Chemical Society: Washington, DC, 2005; 334 pp.
9. *Ionic Liquids IIIB: Fundamentals, Progress, Challenges, and Opportunities - Transformations and Processes*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 902; American Chemical Society: Washington, DC, 2005; 397 pp.
10. *Ionic Liquids in Polymer Systems: Solvents, Additives, and Novel Applications*, Brazel, C. S.; Rogers, R. D. (Eds.); ACS Symposium Series 913; American Chemical Society: Washington, DC, 2005; 206 pp.
11. *Ionic Liquids IV Not Just Solvents Anymore*, Brennecke, J. F.; Rogers, R. D.; Seddon K. R. (Eds.); ACS Symposium Series 975; American Chemical Society: Washington, DC, 2007; 408 pp.
12. *Solvent Extraction: Fundamentals to Industrial Applications - Proceedings of ISEC 2008 International Solvent Extraction Conference, (ISEC 2008)*, Moyer, B. A.; Baron, P.; Chagnes, A.; Cole, P. M.; Cote, G.; Dietz, M. L.; Hatton, T. A.; Horwitz, E. P.; de Ortiz, E. S. P.; Ritcey, G. M.; Robinson, D.; Rogers, R. D.; Sole, K. C.; Tasker, P. A.; Todd, T. A.; Virnig, M. J. (Eds.); Canadian Institute of Mining, Metallurgy and Petroleum: Montréal, 2008; 1661 pp.
13. *Ionic Liquids: From Knowledge to Application*, Plechkova, N. V.; Rogers, R. D.; Seddon K. R. (Eds.); ACS Symposium Series 1030; American Chemical Society: Washington, DC, 2009; 458 pp. ISBN13: 9780841269972; eISBN: 9780841224919; DOI: 10.1021/bk-2009-1030.
14. *Ionic Liquids: Science and Applications*, Visser, A. E.; Bridges, N. J.; Rogers, R. D. (Eds.); ACS Symposium Series 1117; American Chemical Society: Washington, DC, 2012; 313 pp. ISBN 978-0-8412-2763-7; eISBN: 9780841227644; DOI: 10.1021/bk-2012-1117.

Patents:

1. Rogers, R. D.; Horwitz, E. P.; Bond, A. H. "Process for Recovering Pertechnetate Ions from an Aqueous Solution also Containing Other Ions," 2/18/97, U. S. Patent No. 5,603,834.
2. Rogers, R. D.; Horwitz, E. P.; Bond, A. H. "Process for Recovering Chaotropic Ions from an Aqueous Solution also Containing Other Ions," 3/10/99, U. S. Patent No. 5,888,397.
3. Rogers, R. D.; Horwitz, E. P.; Bond, A. H. "Process for Separating and Recovering an Anionic Dye from an Aqueous Solution," 1/13/98, U. S. Patent No. 5,707,525.
4. Mays, J. W.; Bu, L.; Rogers, R. D.; Hong, K.; Zhang, H. "Polymer Formation in Room Temperature Ionic Liquids," 8/2/05, U. S. Patent No. 6,924,341 B2; International Application PCT/US02/10091; International Publication Number WO 02/079269 A1, October 10, 2002.
5. Wu, B.; Reddy, R. G.; Rogers, R. D. "Production, Refining and Recycling of Lightweight and Reactive Metals in Ionic Liquids," 4/19/05, U. S. Patent No. 6,881,321 B2.
6. Holbrey, J. D.; Spear, S. K.; Turner, M. B.; Swatloski, R. P.; Rogers, R. D. "Cellulose Matrix Encapsulation and Method," U.S. Patent No. 6,808,557 B2 (10/26/04); ZA 2005/08446 (04/25/07); EA 009256 (09/12/07); SG 115160 (08/31/07); ZL 200480013560.5 (12/2/09); MX 277934 (08/09/10); KR 10-1064345 (09/05/11); CA 2,519,652 (07/24/12); JP 5213329 (03/08/13).
7. Swatloski, R. P.; Rogers, R. D.; Holbrey, J. D. "Dissolution and processing of cellulose using ionic liquids," U.S. Patent No. 6,824,599 B2 (11/30/04); International Publication Number WO 03/029329 A2 (04/10/03); ZA 2004/2610 (02/23/05); NZ 5,320,076 (01/12/06); ID 0 017 226 (05/4/06); AU 2002347788 (10/26/06); EA 008538 (3/20/07); KR 778793 (11/16/07); ZL 02823875.3 (01/30/08); HK 1076120 (11/28/08); JP 4242768 (01/9/09); MX 26627

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 10

IPR2020-00770
United Therapeutics EX2007
Page 3560 of 7335

(05/11/09); CA 2,462,460 (05/19/09); IL 161124 (06/29/10); EP 1458805 B1 (08/31/11); DE 60240972.1 (08/31/11); PL 206185 (12/14/11); PH 1-2004-500479 (06/29/12); CN ZL200710085298.0 (10/03/12); JP 5148436 (12/07/12); HK1108165 (07/21/13).

8. Swatloski, R. P.; Rogers, R. D.; Holbrey, J. D. "Dissolution and processing of cellulose using ionic liquids," (Divisional Patents), CN ZL200710085298.0 (10/03/12); JP 5148436 (12/07/12); EP 2325246 (11/27/13).
9. Wu, B.; Reddy, R. G.; Holbrey, J. D.; Rogers, R. D. "Ionic Liquid Temperature Sensor," 6/15/04, U. S. Patent No. 6,749,336 B2; International Application PCT/US03/00102; International Publication Number WO 03/058185 A1, July 17, 2003.
10. Holbrey, J. D.; Swatloski, R. P.; Chen, J.; Daly, D. T.; Rogers, R. D. "Polymer Dissolution and Blend Formation In Ionic Liquids." 02/15/11, U. S. Patent No. 7,888,412 B2; PCT Int. Appl. (2005) WO 2005098546 A2; SG 126235 (07/31/07); ZA 2006/08882 (06/25/08); MX 276898 (06/25/10); KR 10-1001533 (12/09/10); AU 2005231083 (03/10/11); NZ 550776 (04/05/11); ID P0028151 (05/02/11); PH 1-2006-501906 (07/22/11); CA 2560680 (11/22/11); EP 1733282 (01/04/12); DE 05729932.3 (01/04/12); JP 5203698 (02/22/13); CN ZL200580016490.3 (08/19/15).
11. Daly, D. T.; Rogers, R. D. "Method of Preparing High Orientation Nanoparticle-Containing Sheets or Films Using Ionic Liquids, and the Sheets or Films Produced Thereby," U.S. Patent No. 7,550,520 B2 (06/23/09); ID P0025079 (02/10/10); SG 137607 (06/30/10).
12. Rogers, R. D.; Daly, D. T.; Turner. M. B.; Spear, S. K.; Holbrey, J. D. "Ionic Liquid Reconstituted Cellulose Composites as Solid Support Matrices." U.S. Patent Application 60/694,902 Filed June 29, 2005; PCT Int. Appl. (2007) WO 2007005388 A3; CN 200680031454.9 (12/21/11); EU 1907470 (04/10/13).
13. Rogers, R. D.; Daly, D. T.; Swatloski, R. P.; Hough, W. L.; Davis Jr., J. H.; Smiglak, M.; Pernak, J.; Spear, S. K. "Multi-Functional Ionic Liquid Compositions for Overcoming Polymorphism and Imparting Improved Properties for Active Pharmaceutical, Biological, Nutritional, and Energetic Ingredients," 7/31/12, U. S. Patent No. 8,232,265; PCT/US2006/039454; WO 2007/044693 A2, April 19, 2007; MX 301158 (07/10/12); CN 200680046195.7 (06/05/13).
14. Rahman, M.; Rodriguez, H.; Sun, N.; Swatloski, R. P.; Daly, D. T.; Rogers, R. D. "Ionic Liquid Systems for the Processing of Biomass, Their Components and/or Derivatives, and Mixtures Thereof," U.S. Patent No. 8,668,807 (03/11/14); PCT Int. Appl. (2009), WO 2009105236 A1 8/27/09.
15. Rogers, R. D.; Daly, D. T.; Swatloski, R. P.; Hough, W. L.; Davis Jr., J. H.; Smiglak, M.; Pernak, J.; Spear, S. K. "Multi-Functional Ionic Liquid Compositions for Overcoming Polymorphism and Imparting Improved Properties for Active Pharmaceutical, Biological, Nutritional, and Energetic Ingredients," 08/12/14, U. S. Patent No. 8,802,596; AU 2012203353 (09/11/14); JP 5713534 (03/20/15).
16. Rogers, R. D.; Myerson, A. S.; Hines, C. C. "Improved Process for the Purification of Aryl Carboxylic Acids," U.S. Patent No. 8,309,760 B2 (11/13/12); PCT/US2008/65348; WO 2008/151034 A1, December 11, 2008.
17. Wu, B.; Reddy, R. G.; Rogers, R. D. "Production, Refining and Recycling of Lightweight and Reactive Metals in Ionic Liquids," 3/28/08, U. S. Patent No. 7,347,920 B2.
18. Spear, Scott K.; Daly, Daniel T.; Frazier, Rachel M.; Rogers, Robin D.; Haque, A. "Conductive composites prepared using ionic liquids," U.S. Patent No. 8,784,691 07/22/14; PCT Int. Appl. (2011), WO 2011011322 A1 1/27/11; U.S. Patent Application US 2012/0241680 A1 09/27/12.
19. DiSalvo, R.; Dykes, H. W. Jr.; Rogers, R. D.; Shamshina, J.; Smiglak, M. "Ionic Liquid Monopropellant Gas Generator," U.S. Patent No. 8,636,860 01/28/14.
20. Daly, D. T.; Rogers, R. D. "Cellulosic Biocomposites as Molecular Scaffolds for Nano-Architectures," US 2012/0122691 A1 05/17/12; U.S. Patent No. 8,883,193 11/11/14.
21. Rogers, R. D.; Myerson, A. S.; Hines, C. C. "Process for Purification of Aryl Carboxylic Acids," U.S. Patent No. 8,859,806 (10/14/14).
22. Frazier, R. M.; Daly, D. T.; Spear, S. K.; Rogers, R. D.; Hough, W. "Organic Photovoltaic-Battery Hybrid Device," (U.S. Application 2012/03818348 A1 12/20/12) U.S. Patent No. 9,073,937 (07/07/15).
23. Qin, Y.; Rogers, R. D.; Daly, D. T. "Process for forming films, fibers, and beads from chitinous biomass," PCT Int. Appl. (2010), WO 2010141470 A2 12/9/10; US 9,096,743 B2 (08/04/15)
24. Rogers, R. D.; Daly, D. T.; MacFarlane, D.; Scott, J. L.; Seddon, K. R.; Gurau, G.; Bica, K.; Turanjanin, J.; Dean, P. M., "Dual Functioning Ionic Liquids and Salts Thereof," PCT Int. Appl. (2010) WO 2010/078300, July 8, 2010; US 2012/0046244 A1 (02/23/12); U.S. Patent No. 9,278,134 (03/08/16).

Patent Applications:

1. Peterson, J. R.; Zjawiony, J. K.; Rogers, R. D. "Synthesis and Optical Resolution of the Taxol Side Chain and Related Compounds," International Application PCT/US1992/009911; International Publication Number WO/1993/010076, May 27, 1993.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 11

IPR2020-00770
United Therapeutics EX2007
Page 3561 of 7335

2. Daly, D. T.; Spear, S. K.; Frazier, R. M.; Hough-Troutman, W. L.; Rogers, R. D. "Substrates for Delivery of Physiologically Active Agents," PCT Int. Appl. (2009) WO 2009/131692 A1 10/29/09.
3. Rahman, M.; Sun, N.; Qin, Y.; Maxim, M. L.; Rogers, R. D. "Ionic Liquid Systems for the Processing of Biomass, Their Components and/or Derivatives, and Mixtures Thereof," PCT Int. Appl. (2010), WO 2010056790 A1 5/20/10.
4. Frazier, R. M.; Daly, D. T.; Spear, S. K.; Rogers, R. D. "Exfoliation of Graphite using Ionic Liquids," U.S. Provisional Patent filed 11/25/08.; PCT Int. Appl. (2010), WO 2010065346 A1 06/10/10.
5. Rogers, R. D.; Rijksen, C.; Daly, D. T.; Caldwell, K.; Caldwell, G.; Hough-Troutman, W. L.; Bica, K., "Compounds Comprising Two or More Biologically Functional Ions and Method of treating Parkinson's Disease," U.S. Provisional Patent filed 12/29/08; PCT Int. Appl. (2010), WO 2010078258 A1 20100708.
6. Qin, Y.; Rogers, R. D.; Daly, D. T.; "Dissolution of Chitinous Biomass with Ionic Liquids and Making Chitin Film/Fiber/Beads from it," U.S. Patent Application 13/375,245 (U.S. national phase of PCT/US2010/036904) 05/10/12.
7. Pernak, J.; Shamshina, J.; Praczyk, T.; Syguda, A.; Janiszewska, D.; Smiglak, M.; Gurau, G.; Daly, D. T.; Rogers, R. D. "Herbicidal Compositions and Methods of Use," PCT Int. Appl. (2012), WO 2012006313 A2 01/12/12.
8. Rogers, R. D.; Holbrey, J. "Ionic liquid solvents of perhalide type for metals for extraction of radioactive metals from mineral ores," PCT Int. Appl. (2010), WO 2010116167 A1 10/14/10.
9. Rogers, R. D.; Holbrey, J.; Rodriquez, H. "Process for the preparation of heterocyclic chalcogenones via reaction of elemental sulfur, selenium, or tellurium with heterocyclic cationic species," PCT Int. Appl. (2010), WO 2010116166 A2 10/14/10.
10. Rogers, R. D.; Holbrey, J.; Rodriquez, H. "Process for removing metals from hydrocarbons," PCT Int. Appl. (2010), WO 2010116165 A2 10/14/10.
11. Daly, D. T.; Rogers, R. D.; Qin, Y. "Compositions Containing Recylable Ionic Liquids for Use in Biomass Processing," U.S. Patent Application US 20130245336 A1 09/27/12.
12. Riisager, A.; Fehrmann, R.; Rodriguez, R.; Bica, K.; Rogers, R. D.; Daly, D. T.; Gurau, G. "Biologically Active Compounds Supported on Solid Carrier such as Silica for Controlled Release and Improved Thermal Stability," PCT Int. Appl. (2011), WO 2011110662 (2011).
13. Rogers, R. D.; Daly, D. T.; Gurau, G. "Methods for dissolving polymers using mixtures of different ionic liquids and compositions comprising the mixtures," PCT Int. Appl. (2011), WO 2011056924 A2 05/12/2011; US Application 2012/0216705 A1 08/30/12.
14. Rogers, R. D.; Cooke, L. "Fungicidal Compositions and Methods of Use," PCT Int. Appl. (2012), WO 2012021825 02/16/12.
15. Riisager, A.; Fehrmann, R.; Rogers, R. D.; Gurau, G. "Enhancing the thermal stability of ionic compounds by immobilization on porous solid support," PCT Int. Appl. (2013), WO 2013030299 A1 03/07/13.
16. Pernak, J.; Shamshina, J.; Praczyk, T.; Syguda, A.; Janiszewska, D.; Smiglak, M.; Gurau, G.; Daly, D. T.; Rogers, R. D. "Herbicidal Compositions and Methods of Use," US Application (13/808,790) filed 1/7/13; published as US 2013/0109572 A1 05/02/13
17. Swatloski, R. P.; Barber, P. S.; Opichka, T.; Bonner, J. R.; Gurau, G.; Griggs, C. S.; Rogers, R. D. "Process for Electrospinning Chitin Fibers from Chitinous Biomass and Fibers and Articles Produced Thereby," PCT Int. Appl. (2014), WO 2014/01856 A1 01/30/14.
18. Rogers, R. D.; Barber, P. S.; Griggs, C. S.; Gurau, G.; Lu, X; Zhang, S. "Coagulation of Chitin from Solutions of Crustacean Shells in Ionic Liquids using Super-Critical CO_2," US Provisional Application No. 61/764,770 (02/14/13); PCT Int. Appl. (2014), WO 2014125438 A1 20140821; US Patent Application US 2015/0368371 (12/24/15).
19. Rogers, R. D.; Gurau, G.; Shamshina, J.; Daly, D. T. "Chitin and Alginate Composite Fibers," US Patent Application US 2016/0082141 (03/24/16). "Chitin and alginate composite fibers for wound dressings," PCT Int. Appl. (2014), WO 2014172703 A1 20141023.
20. Barber, P. S.; Griggs, C. S.; Rogers, R. D. Shamshina, J. L.; Gurau, G. "Chemical pulping of chitinous biomass for chitin" US Application (62/042,392) filed on 08/27/14.
21. McCrary, P. D.; Rogers, R. D. "Hypergolic Salts with Borane Cluster Anions," US Patent Application US 2014/0373984 A1 filed 06/20/14.
22. Wang, H.-T.; Frazier, R. M.; Guo, L.; Quan, H.; McCrary, P. D.; Rogers, R. D. Exfoliation of thermoelectric Materials and Transition Metal Dichalcogenides using Ionic Liquids," US Patent Application US 2015/0004733 A1 filed 06/27/14; Published 01/01/15.
23. Rogers, R. D. "Nucleoside analog salts with improved solubility," PCT Int. Appl. (2014), WO 2014145464 A1 20140918, Filed 03/17/14, Published 09/18/14); US Patent Application US 2016/0002240 (01/07/16).

A. Refereed Publications:

1. Atwood, J. L.; Rogers, R. D.; Kutal, C.; Grutsch, P. A. "X-ray Crystallographic Characterization of the Single Hydrogen Bridge Attachment of the Tetrahydroborate Group in Tris(methyldiphenylphosphine)tetrahydroboratecopper," *J. Chem. Soc., Chem. Comm.* **1977**, 593-594. **DOI:** 10.1039/C3977000593B.
2. Atwood, J. L.; Crissinger, K. D.; Rogers, R. D. "The Synthesis of $M[Al_2(CH_3)_6NO_3]$ ($M^+ = K^+$, Rb^+, Cs^+, NR_4^+) and the Crystal Structures of $K[Al_2(CH_3)_6NO_3]$ and $K[Al(CH_3)_3NO_3]\bullet C_6H_6$," *J. Organomet. Chem.* **1978**, *155*, 1-14.
3. Atwood, J. L.; Hunter, W. E.; Rogers, R. D.; Holton, J.; McMeeking, J.; Pearce, R.; Lappert, M. F. "Neutral and Anionic Silylmethyl Complexes of the Group 3a and Lanthanoid Metals; the X-ray Crystal and Molecular Structure of $[Li(thf)_4][Yb\{CH(SiMe_3)_2\}_3Cl]$ (thf = Tetrahydrofuran)," *J. Chem. Soc., Chem. Comm.* **1978**, 140-142.
4. Atwood, J. L.; Rogers, R. D.; Hunter, W. E.; Bernal, I.; Brunner, H.; Lukas, R.; Schwarz, W. "X-ray Structure of $[(\eta^5\text{-}C_5H_5)W(CO)_2C_{15}H_{15}]$: a Compound Containing Three Unusually Bonded Five-membered Rings," *J. Chem. Soc., Chem. Comm.* **1978**, 451-452.
5. Guzman, E. C.; Wilkinson, G.; Atwood, J. L.; Rogers, R. D.; Hunter, W. E.; Zaworotko, M. J. "Synthesis and Molecular Structures of Chloro(trimethylphosphine)tris(trimethylsilylmethyl)molybdenum(IV) and Di-μ-Chloro-bis[η^2-trimethylsilylmethylcarbonylbis(carbonyl)trimethylphosphinemolybdenum(II)]," *J. Chem. Soc., Chem. Comm.* **1978**, 465-466.
6. Kutal, C.; Grutsch, P.; Atwood, J. L.; Rogers, R. D. "Structural Characterization of the Single Hydrogen Bridge Attachment of the Tetrahydroborate Group in Tris(methyldiphenylphosphine)(tetrahydroborato)copper," *Inorg. Chem.* **1978**, *17*, 3558-3562.
7. Mattia, J.; Humphrey, M. B.; Rogers, R. D.; Atwood, J. L.; Rausch, M. D. "Syntheses and Molecular Structures of Two Metalloindene Complexes: 1,1-Bis(η^5-cyclopentadienyl)-2,3-bis(pentafluorophenyl)benzotitanole and 1,1-Bis(η^5-cyclopentadienyl)-2-trimethylsilyl-3-phenylbenzotitanole," *Inorg. Chem.* **1978**, *17*, 3257-3264.
8. Rogers, R. D.; Atwood, J. L.; Grüning, R. "The Crystal Structure of *N*-Lithiohexamethyldisilazane, $[LiN(SiMe_3)_2]_3$," *J. Organomet. Chem.* **1978**, *157*, 229-237. **DOI:** 10.1016/S0022-328X(00)92291-5
9. Rogers, R. D.; Bynum, R. V.; Atwood, J. L. "Crystal and Molecular Structure of Tetra(cyclopentadienyl)zirconium," *J. Am. Chem. Soc.* **1978**, *100*, 5238-5239. **DOI:** 10.1021/ja00484a069.
10. Atwood, J. L.; Hunter, W. E.; Rogers, R. D.; Carmona-Guzman, E.; Wilkinson, G. "The Crystal Structures of $MoMe_2(\eta^6\text{-}C_6H_6)(PPhMe_2)_2$ and $MoMe_2(\eta^6\text{-}C_6H_5Me)(PPhMe_2)_2$," *J. Chem. Soc., Dalton Trans.* **1979**, 1519-1523. **DOI:** 10.1039/DT9790001519.
11. Rogers, R. D.; Atwood, J. L. "Interaction of Aromatic Hydrocarbons with Organometallic Compounds of the Main Group Elements: VI. Synthesis and Crystal Structure of Cesium Diododimethylaluminate *p*-Xylene Solvate, $Cs[Al(CH_3)_2I_2]\bullet C_6H_4(CH_3)_2$," *J. Cryst. Mol. Struct.* **1979**, *9*, 45-53. **DOI:** 10.1007/BF01370925
12. Rogers, R. D.; Cook, W. J.; Atwood, J. L. "Ferrocenylalanes. 3. Synthesis and Crystal Structure of $(\eta^5\text{-}C_5H_5)Fe[\eta^5\text{-}C_5H_4Al_2(CH_3)_4Cl]$," *Inorg. Chem.* **1979**, *18*, 279-282. **DOI:** 10.1021/ic50192a014
13. Sikora, D. J.; Rausch, M. D.; Rogers, R. D.; Atwood, J. L. "Structure and Reactivity of the First Hafnium Carbonyl, $(\eta^5\text{-}C_5H_5)_2Hf(CO)_2$," *J. Am. Chem. Soc.* **1979**, *101*, 5079-5081. **DOI:** 10.1021/ja00511a056
14. Atwood, J. D.; Janik, T. S.; Atwood, J. L.; Rogers, R. D. "Synthesis of Bis(benzene)tetracarbonyldivanadium, $(C_6H_6)_2V_2(CO)_4$," *Synth. React. Inorg. Met.-Org. Chem.* **1980**, *10*, 397-402. **DOI:** 10.1080/00945718008058251
15. Atwood, J. L.; Rogers, R. D.; Hunter, W. E.; Floriani, C.; Fachinetti, G.; Chiesi-Villa, A. "Crystal and Molecular Structure of Two Early Transition-Metal Dicarbonyldicyclopentadienyl Complexes: $(\eta^5\text{-}C_5H_5)_2Zr(CO)_2$ and $[(\eta^5\text{-}C_5H_5)_2V(CO)_2][B(C_6H_5)_4]$," *Inorg. Chem.* **1980**, *19*, 3812-3817. **DOI:** 10.1021/ic50214a044
16. Bynum, R. V.; Hunter, W. E.; Rogers, R. D.; Atwood, J. L. "Pyrrolyl Complexes of the Early Transition Metals. 1. Synthesis and Crystal Structure of $(\eta^5\text{-}C_5H_5)_2Ti(\eta^1\text{-}NC_4H_4)_2$, $(\eta^5\text{-}C_5H_5)_2Zr(\eta^1\text{-}NC_4H_4)_2$, and $[Na(THF)_6]_2[Zr(\eta^1\text{-}NC_4H_4)_6]$," *Inorg. Chem.* **1980**, *19*, 2368-2374. **DOI:** 10.1021/ic50210a039
17. Carmona, E.; González, F.; Poveda, M. L.; Atwood, J. L.; Rogers, R. D. "Alkyl and Acyl Derivatives of Nickel(II) containing Tertiary Phosphine Ligands," *J. Chem. Soc., Dalton Trans.* **1980**, 2108-2116. **DOI:** 10.1039/DT9800002108
18. Çetinkaya, B.; Gümrükçü, I.; Lappert, M. F.; Atwood, J. L.; Rogers, R. D.; Zaworotko, M. J. "Bivalent Germanium, Tin, and Lead 2,6-Di-*tert*-butylphenoxides and the Crystal and Molecular Structures of $M(OC_6H_2Me\text{-}4\text{-}Bu^t_2\text{-}2,6)_2$ (M = Ge or Sn)," *J. Am. Chem. Soc.* **1980**, *102*, 2088-2089. **DOI:** 10.1021/ja00526a054
19. Daniels, P. H.; Wong, J. L.; Atwood, J. L.; Canada, L. G.; Rogers, R. D. "Unreactive 1-Azadiene and Reactive 2-Azadiene in Diels-Alder Reaction of Pentachloroazacyclopentadienes," *J. Org. Chem.* **1980**, *45*, 435-440. **DOI:** 10.1021/jo01291a011
20. Guzman, E. C.; Wilkinson, G.; Rogers, R. D.; Hunter, W. E.; Zaworotko, M. J.; Atwood, J. L. "Synthesis and Crystal Structures of Chloro(trimethylphosphine)tris(trimethylsilylmethyl)molybdenum(IV) and Di-μ-chloro-bis[bis(carbonyl)trimethylphosphine(1-2-η-trimethylsilylmethylcarbonyl)molybdenum(II)]," *J. Chem. Soc., Dalton Trans.* **1980**, 229-234. **DOI:** 10.1039/DT9800000229
21. Paulson, J. A.; Krost, D. A.; McPherson, G. L.; Rogers, R. D.; Atwood, J. L. "Structural, Spectroscopic, and Theoretical Studies of an Exchange-Coupled Manganese(II)-Copper(II) Dimer," *Inorg. Chem.* **1980**, *19*, 2519-2525. **DOI:** 10.1021/ic50211a007
22. Rogers, R. D.; Bynum, R. V.; Atwood, J. L. "Synthesis and Structure of $(\eta^5\text{-}C_5H_5)_3Gd\bullet OC_4H_8$," *J. Organomet. Chem.* **1980**, *192*, 65-73. **DOI:** 10.1016/S0022-328X(00)93331-X
23. Rogers, R. D.; Hunter, W. E.; Atwood, J. L. "Nature of the Novel $C_{15}H_{15}$ Ligand in $[W(CO)_2(\eta^5\text{-}C_5H_5)(\eta^3\text{-}C_{15}H_{15})]$," *J. Chem. Soc., Dalton Trans.* **1980**, 1032-1035. **DOI:** 10.1039/DT9800001032

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 13

IPR2020-00770
United Therapeutics EX2007
Page 3563 of 7335

24. Rogers, R. D.; Stone, L. B.; Atwood, J. L. "Tetramethylammonium Iodotrimethylaluminate [NMe_4][$AlMe_3I$]," *Cryst. Struct. Comm.* **1980**, *9*, 143-146.
25. Atwood, J. L.; Hrncir, D. C.; Rogers, R. D.; Howard, J. A. K. "Novel Linear Al-H-Al Electron-Deficient Bond in Na[$(CH_3)_3$Al-H-Al$(CH_3)_3$]," *J. Am. Chem. Soc.* **1981**, *103*, 6787.
26. Calderazzo, F.; Vitali, D.; Mavani, I. P.; Marchetti, F.; Bernal, I.; Korp, J. D.; Atwood, J. L.; Rogers, R. D.; Dalton, M. S. "Preparation, Properties, and Crystal and Molecular Structures of Bis(dialkylamine) Complexes of Rhenium(I)," *J. Chem. Soc., Dalton Trans.* **1981**, 2523-2528.
27. Calderazzo, F.; Vitali, D.; Poli, R.; Atwood, J. L.; Rogers, R. D.; Cummings, J. M.; Bernal, I. "Studies on Organometallic Hetero-multiple-bridged Molecules. Part 7. Synthesis and Properties of Dichalcogenide-bridged Complexes of Rhenium(I) and the Crystal and Molecular Structures of the Diphenyl Ditelluride-bridged Complex, [$Re_2Br_2(CO)_6(Te_2Ph_2)$]," *J. Chem. Soc., Dalton Trans.* **1981**, 1004-1009.
28. Carmona, E.; González, F.; Poveda, M. L.; Atwood, J. L.; Rogers, R. D. "Synthesis and Properties of Dialkyl Complexes of Nickel(II). The Crystal Structure of Bis(pyridine)bis(trimethylsilymethyl)nickel(II)," *J. Chem. Soc., Dalton Trans.* **1981**, 777-782.
29. Hrncir, D. C.; Rogers, R. D.; Atwood, J. L. "New Bonding Mode for a Bridging Dioxygen Ligand: Crystal and Molecular Structure of [K•dibenzo-18-crown-6][$Al_2(CH_3)_6O_2$]•1.5C_6H_6," *J. Am. Chem. Soc.* **1981**, *103*, 4277.
30. Liese, W.; Dehnicke, K.; Rogers, R. D.; Shakir, R.; Atwood, J. L. "A Spectroscopic and Crystallographic Study of the [$ReNCl_4$]$^-$ Ion," *J. Chem. Soc., Dalton Trans.* **1981**, 1061-1063.
31. Rogers, R. D.; Atwood, J. L.; Emad, A.; Sikora, D. J.; Rausch, M. D. "The Formation and Molecular Structures of (η^5-$C_5H_5)_3$Y•OC_4H_8 and (η^5-$C_5H_5)_3$La•OC_4H_8," *J. Organomet. Chem.* **1981**, *216*, 383-392.
32. Rogers, R. D.; Atwood, J. L.; Foust, D.; Rausch, M. D. "The Crystal Structure of Vanadocene, (η^5-$C_5H_5)_2$V," *J. Cryst. Mol. Struct.* **1981**, *11*, 183-188.
33. Rogers, R. D.; Bynum, R. V.; Atwood, J. L. "First Authentic Example of a Difference in the Structural Organometallic Chemistry of Zirconium and Hafnium: Crystal and Molecular Structure of (η^5-$C_5H_5)_2$Hf(η^1-$C_5H_5)_2$," *J. Am. Chem. Soc.* **1981**, *103*, 692.
34. Rogers, R. D.; Kalyanaraman, B.; Dalton, M. S.; Smith, W.; Kispert, L. D.; Atwood, J. L. "Crystal Structure of Bromoflouroacetic Acid: A Chiral Molecule," *Journal of Crystal and Molecular Stucture* **1981**, *11*, 105-111.
35. Sikora, D. J.; Rausch, M. D.; Rogers, R. D.; Atwood, J. L. "Formation and Molecular Structure of Bis(η^5-cyclopentadienyl)bis(triflourophosphine)titanium," *J. Am. Chem. Soc.* **1981**, *103*, 982-984.
36. Sikora, D. J.; Rausch, M. D.; Rogers, R. D.; Atwood, J. L. "New Syntheses and Molecular Structures of the Decamethylmetallocene Dicarbonyls (η^5-$C_5Me_5)_2$M$(CO)_2$ (M = Ti, Zr, Hf)," *J. Am. Chem. Soc.* **1981**, *103*, 1265-1267.
37. Atwood, J. L.; Honan, M. B.; Rogers, R. D. "Crystal and Molecular Structure of (η^5-C_5H_5)Ta(η^2-$C_2H_4)Cl_2(PMe_2Ph)_2$, a Sterically Crowded Molecule which Exhibits a Distorted η^5-Coordination Mode of the Cyclopentadienyl Ligand," *J. Crystallogr. Spectrosc. Res.* **1982**, *12*, 205-221.
38. Atwood, J. L.; Hrncir, D. C.; Shakir, R.; Dalton, M. S.; Priester, R. D.; Rogers, R. D. "Reaction of Trimethylaluminum with Crown Ethers. The Synthesis and Structure of (Dibenzo-18-crown-6)bis(trimethylaluminum) and of (15-Crown-5)tetrakis(trimethylaluminum)," *Organometallics* **1982**, *1*, 1021-1025.
39. Carmona, E.; Marín, J. M.; Poveda, M. L.; Atwood, J. L.; Rogers, R. D.; Wilkinson, G. "Bis(dinitrogen)- and Diethylene-molydenum(0) Complexes," *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 441-442.
40. Carmona, E.; Marin, J. M.; Poveda, M. L.; Rogers, R. D.; Atwood, J. L. "Preparation and Properties of Dinitrogen Complexes of Molybdenum and Tungsten with Trimethylphosphine as Coligand. III. Synthesis and Properties of *cis*-[$W(N_2)_2(PMe_3)_4$], *trans*-[$W(C_2H_4)_2(PMe_3)_4$] and [$M(N_2)(PMe_3)_5$] (M = Mo, W). The Crystal and Molecular Structure of [$Mo(N_2)(PMe_3)_5$]," *J. Organomet. Chem.* **1982**, *238*, C63-C66.
41. Foust, D. F.; Rogers, R. D.; Rausch, M. D.; Atwood, J. L. "Photoinduced Reactions of (η^5-$C_5H_5)_2MH_3$ and (η^5-$C_5H_5)_2$M(CO)H (M = Nb, Ta) and the Molecular Structure of (η^5-$C_5H_5)_2$Ta(CO)H," *J. Am. Chem. Soc.* **1982**, *104*, 5646-5650.
42. Jones, R. A.; Stuart, A. L.; Atwood, J. L.; Hunter, W. E.; Rogers, R. D. "Steric Effects of Phosphido Ligands. Synthesis and Crystal Structure of Di-*tert*-butylphosphido-Bridged Dinuclear Metal-Metal Bonded Complexes of Fe(II), Co(I, II), and Ni(I)," *Organometallics* **1982**, *1*, 1721–1723.
43. Rausch, M. D.; Edwards, B. H.; Atwood, J. L.; Rogers, R. D. "Formation and Molecular Structure of (η^4-Tetraphenylcyclobutadiene)dicarbonylnitrosylmanganese," *Organometallics* **1982**, *1*, 1567-1571.
44. Rogers, R. D.; Atwood, J. L.; Rausch, M. D.; Macomber, D. W.; Hart, W. P. "The Formation and Molecular Structure of Acetylcyclopentadienylsodium•tetrahydrofuranate," *J. Organomet. Chem.* **1982**, *238*, 79-85.
45. Rogers, R. D.; Bynum, R. V.; Atwood, J. L. "Synthesis and Crystal Structure of [(η^5-$C_5H_5)_2$HfO]$_3$•C_6H_5Me," *J. Crystallogr. Spectrosc. Res.* **1982**, *12*, 239-244.
46. Zaworotko, M. J.; Rogers, R. D.; Atwood, J. L. "Interaction of Trimethylaluminum and Trimethylgallium with the Acetate Ion. Synthesis and Crystal Structures of [$N(CH_3)_4$][$Al_2(CH_3)_6CH_3COO$] and Rb[$Ga_2(CH_3)_6CH_3COO$]," *Organometallics* **1982**, *1*, 1179-1183.
47. Atwood, J. L.; Bernal, I.; Calderazzo, F.; Canada, L. G.; Poli, R.; Rogers, R. D.; Veracini, C. A.; Vitali, D. "Studies on Organometallic Hetero-Multiple-Bridged Molecules. 8. Preparation and Crystal and Molecular Structures of Diphenyl Dichalcogenide Complexes of Manganese(I). Kinetic, Spectroscopic, and Equilibrium Data: A Quantitative Assessment of the

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 14

IPR2020-00770
United Therapeutics EX2007
Page 3564 of 7335

Solid-State and Solution Properties within Members of Homogeneous Families of Chalcogenide Low-Valent Metal Complexes," *Inorg. Chem.* **1983**, *22*, 1797-1804.
48. Atwood, J. L.; Hrncir, D. C.; Priester, R. D.; Rogers, R. D. "Decomposition of High-Oxygen Content Organoaluminum Compounds. The Formation and Structure of the $[Al_7O_6Me_{16}]^-$ Anion," *Organometallics* **1983**, *2*, 985-989.
49. Atwood, J. L.; Hrncir, D. C.; Rogers, R. D. "The Use of Crown Ethers to Access New $M[Al_2R_6X]$ Species. Synthesis and Crystal Structure of [K•dibenzo-18-crown-6][Al_2Me_6C1]•$2C_6H_6$," *J. Inclusion Phenom.* **1983**, *1*, 199-207.
50. Atwood, J. L.; Priester, R. D.; Rogers, R. D.; Canada, L. G. "Reaction of Trimethylaluminum with Crown Ethers. II. The Synthesis and Crystal Structure of (Dibenzo-18-crown-6)tris(trimethylaluminum) and of (18-Crown-6)tetrakis(trimethylaluminum)," *J. Inclusion Phenom.* **1983**, *1*, 61-69.
51. Carmona, E.; González, F.; Poveda, M. L.; Marin, J. M.; Atwood, J. L.; Rogers, R. D. "Reaction of *cis*-$[Mo(N_2)_2(PMe_3)_4]$ with CO_2. Synthesis and Characterization of Products of Disproportionation and the X-ray Structure of a Tetrametallic Mixed-Valence Mo^{II}-Mo^{V} Carbonate with a Novel Mode of Carbonate Binding," *J. Am. Chem. Soc.* **1983**, *105*, 3365-3366.
52. Carmona, E.; Marin, J. M.; Poveda, M. L.; Atwood, J. L.; Rogers, R. D. "Preparation and Properties of Dinitrogen Trimethylphosphine Complexes of Molybdenum and Tungsten. 4. Synthesis, Chemical Properties, and X-ray Structure of *cis*-$[Mo(N_2)_2(PMe_3)_4]$. The Crystal and Molecular Structures of *trans*-$[Mo(C_2H_4)_2(PMe_3)_4]$ and *trans*, *mer*-$[Mo(C_2H_4)_2(CO)(PMe_3)_3]$," *J. Am. Chem. Soc.* **1983**, *105*, 3014-3022.
53. Carmona, E.; Marín, J. M.; Poveda, M. L.; Atwood, J. L.; Rogers, R. D. "Preparation and Properties of Dinitrogen Trimethylphosphine Complexes of Molybdenum and Tungsten-II. Synthesis and Crystal Structures of $[MCl(N_2)(PMe_3)_4]$(M = Mo, W) and *trans*-$[MoCl_2(PMe_3)_4]$," *Polyhedron* **1983**, *2*, 185-193.
54. Carmona, E.; Marín, J. M.; Poveda, M. L.; Sánchez, L.; Rogers, R. D.; Atwood, J. L. "Synthesis of Chloro(trimethylphosphine)tris(trimethylsilymethyl)tungsten(IV); Synthesis and Molecular Structure of Di-μ-chloro-bis[dicarbonyl(trimethylphosphine)(1-2-η-trimethylsilylmethylcarbonyl)tungsten(II)]," *J. Chem. Soc., Dalton Trans.* **1983**, 1003-1005.
55. Carmona, E.; Sánchez, L.; Poveda, M. L.; Marín, J. M.; Atwood, J. L.; Rogers, R. D. "β-C-H Interaction vs. Dihaptoacyl Coordination in a Molybdenum Acetyl Complex. X-ray Crystal Structure of $[Mo(Ac)(S_2CNMe_2)(CO)(PMe_3)_2]$," *J. Chem. Soc., Chem. Comm.* **1983**, 161-162.
56. Edwards, B. H.; Rogers, R. D.; Sikora, D. J.; Atwood, J. L.; Rausch, M. D. "Formation, Reactivities, and Molecular Structures of Phosphine Derivatives of Titanocene. Isolation and Characterization of a Titanium Monoolefin π Complex," *J. Am. Chem. Soc.* **1983**, *105*, 416-426.
57. Herrmann, W. A.; Plank, J.; Hubbard, J. L.; Kriechbaum, G. W.; Kalcher, W.; Koumbouris, B.; Ihl, G.; Schäfer, A.; Ziegler, M. L.; Pfisterer, H.; Pahl, C.; Atwood, J. L.; Rogers, R. D. "Transition Metal Methylene Complexes, LI. Carbocyclic Carbenes, Carbene Bridges, Small Hydrocarbon Ligands, and Metallacycles: Examples of a General Synthetic Concept," *Z. Naturforsch., B: Chem. Sci.* **1983**, *38b*, 1392-1398.
58. Lappert, M. F.; Slade, M. J.; Singh, A.; Atwood, J. L.; Rogers, R. D.; Shakir, R. "Structure and Reactivity of Sterically Hindered Lithium Amides and Their Diethyl Etherates: Crystal and Molecular Structures of $[Li\{N(SiMe_3)_2\}(OEt_2)]_2$ and $[Li(NCMe_2CH_2CH_2CH_2CMe_2)]_4$," *J. Am. Chem. Soc.* **1983**, *105*, 302-304.
59. Rausch, M. D.; Edwards, B. H.; Rogers, R. D.; Atwood, J. L. "Formation of [(Diphenylphosphino)cyclopentadienyl]thallium and Its Utility in the Synthesis of Heterobimetallic Ti-Mn Complexes: The Molecular Structure of (η^5-Cyclopentadienyl)dicarbonyl{(η^5- cyclopentadienyl)[η^5-(diphenylphosphino)cyclopentadienyl]dichlorotitanium-P}manganese]," *J. Am. Chem. Soc.* **1983**, *105*, 3882-3886.
60. Rogers, R. D.; Atwood, J. L. "The Crystal and Molecular Structure of $SnBr[N(SiMe_3)_2]_3$," *J. Crystallogr. Spectrosc. Res.* **1983**, *13*, 1-7.
61. Atwood, J. L.; McMaster, A. D.; Rogers, R. D.; Stobart, S. R. "Stereochemically Nonrigid Silanes, Germanes, and Stannanes. 12. Crystal and Molecular Structures of Tetrakis(η^1-indenyl) Derivatives of Germanium and Tin: Meso Diastereoisomers with S_4 Symmetry," *Organometallics* **1984**, *3*, 1500-1504.
62. Atwood, J. L.; Rogers, R. D.; Bynum, R. V. "Tris(1,2-dimethoxyethane)lithium μ-Chloro-μ-oxo-bis[chloro(pentamethylcyclopentadienyl)(1-pyrrolyl)zirconate(IV)] Dimethoxyethane Solvate, $[Li(C_4H_{10}O_2)_3][Zr_2Cl_3O(C_4H_4N)_2(C_{10}H_{15})_2]$•$C_4H_{10}O_2$," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1984**, *C40*, 1812-1814.
63. Carmona, E.; Paneque, M.; Poveda, M. L.; Rogers, R. D.; Atwood, J. L. "Further Studies on Organonickel Compounds: The Synthesis of Some New Alkyl-, Acyl- and Cyclopentadienyl- Derivatives and the Crystal Structure of *trans*-$[Ni(CH_2SiMe_3)_2(PMe_3)_2]$," *Polyhedron* **1984**, *3*, 317-323.
64. Carmona, E.; Sánchez, L.; Marín, J. M.; Poveda, M. L.; Atwood, J. L.; Priester, R. D.; Rogers, R. D. "η^2-Acyl Coordination and β-C-H Interaction in Acyl Complexes of Molybdenum. Crystal and Molecular Structures of Mo(η^2-$COCH_2SiMe_3$)$Cl(CO)(PMe_3)_3$ and $Mo(COCH_3)(S_2CNMe_2)(CO)(PMe_3)_2$," *J. Am. Chem. Soc.* **1984**, *106*, 3214-3222.
65. Herrmann, W. A.; Plank, J.; Kriechbaum, G. W.; Ziegler, M. L.; Pfisterer, H.; Atwood, J. L.; Rogers, R. D. "Komplexchemie Reaktiver Organischer Verbindungen XLVII. Synthese, Strukturchemie und Druckcarbonylierung von Metallcarben-Komplexen," *J. Organomet. Chem.* **1984**, *264*, 327-352.
66. Rausch, M. D.; Foust, D. F.; Rogers, R. D.; Atwood, J. L. "The Formation and Molecular Structure of Di-η^5-cyclopentadienyl{2-[(dimethylamino)methyl]phenyl-C,N}yttrium," *J. Organomet. Chem.* **1984**, *265*, 241-248.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 15

IPR2020-00770
United Therapeutics EX2007
Page 3565 of 7335

67. Rogers, R. D.; Atwood, J. L. "The Crystal and Molecular Structure of [K•DB-18-C- 6][$AlMe_3NO_3$]•0.5C_6H_6," *J. Crystallogr. Spectrosc. Res.* **1984**, *14*, 1-11.
68. Rogers, R. D.; Atwood, J. L. "Reaction of K_2SO_4 with $AlMe_3$ and the Crystal Structures of $K_2[Al_4Me_{12}SO_4]$ and $K_2[Al_4Me_{12}SO_4]$•0.5*p*-xylene," *Organometallics* **1984**, *3*, 271-274.
69. Rogers, R. D.; Atwood, J. L.; Albright, T. A.; Lee, W. A.; Rausch, M. D. "Structure of (Biphenylene)- and (Triphenylene)$Cr(CO)_3$. An Analysis of the Bonding of $Cr(CO)_3$ to Bicyclic Polyenes," *Organometallics* **1984**, *3*, 263-270.
70. Rogers, R. D.; Baker, J. C.; Atwood, J. L. "The Crystal Structure of [NBu^n_4][AlI_4]," *J. Crystallogr. Spectrosc. Res.* **1984**, *14*, 333-339.
71. Rogers, R. D.; Bynum, R. V.; Atwood, J. L. "Synthesis and Structure of (η^5-$C_5H_5)_2Hf(\eta^1$-$NC_4H_4)_2$," *J. Crystallogr. Spectrosc. Res.* **1984**, *14*, 21-28.
72. Rogers, R. D.; Bynum, R. V.; Atwood, J. L. "The Crystal Structure of LiBr•$(CH_3OCH_2CH_2OCH_3)_2$," *J. Crystallogr. Spectrosc. Res.* **1984**, *14*, 29-34.
73. Rogers, R. D.; Carmona, E.; Galindo, A.; Atwood, J. L.; Canada, L. G. "Trimethylphosphine Complexes of Molybdenum and Tungsten. The Synthesis and Chemical Properties of $MoCl_4(PMe_3)_3$ and the Crystal and Molecular Structures of $WCl_4(PMe_3)_3$ and $MoO(acac)_2PMe_3$," *J. Organomet. Chem.* **1984**, *277*, 403-415.
74. Rogers, R. D.; Hrncir, D. C. "Structure of (η^5-Cyclopentadienyl)(η^6-tetraphenylborato)iron, [$Fe(C_5H_5)\{B(C_6H_5)_4\}$]," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1984**, *C40*, 1160-1161.
75. Rogers, R. D.; Isci, H.; Mason, W. R. "Structure of Tetra(*n*-butyl)ammonium Tetraiodo-μ,μ'-diiododiplatinate(II), [(n-$C_4H_9)_4N]_2[Pt_2I_6]$," *J. Crystallogr. Spectrosc. Res.* **1984**, *14*, 383-392.
76. Samuel, E.; Rogers, R. D.; Atwood, J. L. "Synthesis and Crystal Structure of [(η^5- C_9H_{11})TiCl(μ-O)]$_4$," *J. Crystallogr. Spectrosc. Res.* **1984**, *14*, 573-579.
77. Solar, J. M.; Rogers, R. D.; Mason, W. R. "Synthesis of Some Alkyl Phosphite Complexes of Platinum and Their Structural and Spectral Characterization," *Inorg. Chem.* **1984**, *23*, 373-377.
78. Wayda, A. L.; Dye, J. L.; Rogers, R. D. "Divalent Lanthanoid Synthesis in Liquid Ammonia. 1. The Synthesis and X-ray Structure of $(C_5Me_5)_2Yb(NH_3)(THF)$," *Organometallics* **1984**, *3*, 1605-1610.
79. Atwood, J. L.; Hunter, W. E.; Rogers, R. D.; Weeks, J. A. "Behavior of M[$Al_2Me_6N_3$] (M = K, Rb, Cs) with Aromatic Solvents and the Crystal Structures of Cs[$Al_2Me_6N_3$] 2*p*-xylene and [K•dibenzo-18-crown-6][$Al_2Me_6N_3$]•1.5(1-methylnaphthalene)," *J. Inclusion Phenom.* **1985**, *3*, 113-123.
80. Carmona, E.; Galindo, A.; Poveda, M. L.; Rogers, R. D. "Synthesis and Properties of *cis*-Bis(dinitrogen)tetrakis(trimethylphosphine)tungsten(0). Crystal and Molecular Structures of [$W(N_2)(PMe_3)_5$] and *trans*-[$W(C_2H_4)_2(PMe_3)_4$]," *Inorg. Chem.* **1985**, *24*, 4033-4039.
81. Kool, L. B.; Rausch, M. D.; Rogers, R. D. "The Formation, Crystal and Molecular Structure of (η^5-Pentamethylcyclopentadienyl)(η^7-cycloheptatrienyl)titanium and (η^5- Pentamethylcyclopentadienyl)(η^8-cyclooctatetraene)titanium," *J. Organomet. Chem.* **1985**, *297*, 289-299.
82. Macomber, D. W.; Rogers, R. D. "Preparation and Reactivity of Mononuclear (η^5-Cyclopentadienyl)cobalt Carbene Complexes," *Organometallics* **1985**, *4*, 1485-1487.
83. Medley, J. H.; Fronczek, F. R.; Ahmad, N.; Day, M. C.; Rogers, R. D.; Kerr, C. R.; Atwood, J. L. "The Crystal Structures of $NaAlR_4$, R = Methyl, Ethyl, and *n*-Propyl," *J. Crystallogr. Spectrosc. Res.* **1985**, *15*, 99-107.
84. Rogers, R. D.; Benning, M. M.; Kurihara, L. K.; Moriarty, K. J.; Rausch, M. D. "The Formation and Crystal and Molecular Structures of (η^5-Pentamethylcyclopentadienyl)(η^5- cyclopentadienyl)dichloro-titanium, -zirconium and -hafnium," *J. Organomet. Chem.* **1985**, *293*, 51-60.
85. Vaughn, J. W.; Rogers, R. D. "Structure of *trans*-difluorobis(1,3- propanediamine)chromium(III) perchlorate, *trans*-[$Cr(N_2C_3H_{10})_2F_2$](ClO_4)," *J. Crystallogr. Spectrosc. Res.* **1985**, *15*, 281-287.
86. Wayda, A. L.; Rogers, R. D. "Synthesis, X-ray Crystal Structures, and Reaction Chemistry of Homoleptic and Heteroleptic Organolanthanoid Complexes Incorporating the [(Dimethylamino)methyl]phenyl Ligand," *Organometallics* **1985**, *4*, 1440-1444.
87. Macomber, D. W.; Rogers, R. D. "The Formation and Molecular Structure of (η^5-C_5H_5)Rh(CO)[C(NMe)CH_2CH_2(NMe)]," *J. Organomet. Chem.* **1986**, *308*, 353-360.
88. Rogers, R. D.; Green, L. M. "A Reinvestigation of the Crystal and Molecular Structure of (18-Crown-6)•2CH_3NO_2: D_{3d} Stabilization Via Methyl Hydrogen-Crown Oxygen 'Hydrogen Bonds'," *J. Inclusion Phenom.* **1986**, *4*, 77-84.
89. Rogers, R. D.; Green, L. M.; Benning, M. M. "Crystal and Molecular Structure of a Dinuclear Uranyl(VI) Chloride, [$UO_2Cl_2(THF)_2]_2$," *Lanthanide Actinide Res.* **1986**, *1*, 185-193.
90. Rogers, R. D.; Kurihara, L. K. "f-Element/Crown Ether Complexes. 1. Synthesis and Structure of [$Y(OH_2)_8$]Cl_3•(15-crown-5)," *Inorg. Chim. Acta* **1986**, *116*, 171-177.
91. Rogers, R. D.; Kurihara, L. K. "Crystal Structures of Dichlorohexaaquayttrium(III) Chloride, [$YCl_2(OH_2)_6$]Cl, and Dichlorohexaaquaerbium(III) Chloride, [$ErCl_2(OH_2)_6$]Cl," *Lanthanide Actinide Res.* **1986**, *1*, 295-306.
92. Rogers, R. D.; Kurihara, L. K. "f-Element/Crown Ether Complexes 2. The Synthesis and Crystal Structure of $Y(NO_3)_3$(12-Crown-4)," *J. Inclusion Phenom.* **1986**, *4*, 351-358.
93. Singh, Y. P.; Rupani, P.; Singh, A.; Rai, A. K.; Mehrotra, R. C.; Rogers, R. D.; Atwood, J. L. "Synthesis and IR, UV, NMR (^{1}H and ^{11}B), and Mass Spectral Studies of New β-Ketoamine Complexes of Boron: Crystal and Molecular Structure of $OC_6H_4OBOC(R)CHC(R')NR$" (R = *p*-ClC_6H_4, R' = C_6H_5, R" = CH_3)," *Inorg. Chem.* **1986**, *25*, 3076-3081.

94. Alt, H. G.; Engelhardt, H. E.; Steinlein, E.; Rogers, R. D. "Acetylenliganden als Bausteine für Carben- und Nitrilliganden. Molekulstrukturen von $C_5H_4Me(CO)_2Mn[C(Me)NH_2]$, $C_5Me_5(CO)_2Mn[C(Me)NH_2]$, $C_5Me_5(CO)_2Mn[C(Me)NMe_2]$ und $C_5Me_5(CO)_2MnNCMe$," *J. Organomet. Chem.* **1987**, *344*, 321-341.
95. Alt, H. G.; Hayen, H. I.; Rogers, R. D. "Preparation and Crystal Structure of the Dinuclear, Asymmetric Dioxo Complex (η^5-C_5Me_5)$(CO)_3$W-W$(O)_2(\eta^5$-$C_5Me_5)$," *J. Chem. Soc., Chem. Comm.* **1987**, 1795-1796.
96. Alt, H. G.; Herrmann, G. S.; Engelhardt, H. E.; Rogers, R. D. "Die Konkurrenz Elecktronischer und Sterischer Substituenteneinflüsse in Metallacyclishen Pentamethylcyclopentadienyl-Alkenylketon-Komplexen des Chroms, Molydäns und Wolframs. Molekulstruktur von $C_5Me_5(CO)_2Cr[HC=CPhC(O)Me]$," *J. Organomet. Chem.* **1987**, *331*, 329-339.
97. Hayen, H. I.; Alt, H. G.; Rogers, R. D. "Darstellung, Charakterisierung und Molekulstruktur des η^2-Acylkomplexes $C_5Me_5(CO)(CF_3COO)_2W[\eta^2$-$C(O)CH_2CH_2COMe]$," *J. Organomet. Chem.* **1987**, *323*, 339-351.
98. Rogers, R. D. "Crystal Structure of Dichlorohexaaquadysprosium(III) Chloride, $[DyCl_2(OH_2)_6]Cl$," *Lanthanide Actinide Res.* **1987**, *2*, 41-48.
99. Rogers, R. D. "f-Element/Crown Ether Complexes. 13. Direct Coordination of 12-Crown-4 to Hydrated Terbium Chloride. Synthesis and Crystal Structure of $[Tb(OH_2)_5$(12-crown- 4)$]Cl_3 \bullet 2H_2O$," *Inorg. Chim. Acta* **1987**, *133*, 175-180.
100. Rogers, R. D. "f-Element/Crown Ether Complexes. 16. Synthesis, Crystallization and Crystal Structure of $[Dy(OH_2)_8]Cl_3 \bullet$18-crown-$6 \bullet 4H_2O$," *Inorg. Chim. Acta* **1987**, *133*, 347-352.
101. Rogers, R. D.; Kurihara, L. K. "f-Element/Crown Ether Complexes. 6. Interaction of Hydrated Lanthanide Chlorides with 15-Crown-5: Crystallization and Structures of $[M(OH_2)_8]Cl_3 \bullet$(15-crown-5) (M = Gd, Lu)," *Inorg. Chim. Acta* **1987**, *130*, 131-137.
102. Rogers, R. D.; Kurihara, L. K. "f-Element/Crown Ether Complexes III: Synthesis and Structural Characterization of $[Y(NO_3)_3(OH_2)_5][NO_3] \bullet 2$(15-*Crown*-5)," *J. Less-Comm. Metals* **1987**, *127*, 199-207.
103. Rogers, R. D.; Kurihara, L. K. "f-Element/Crown Ether Complexes. 7. Low Temperature (-150°C) Structure of $[Y(OH_2)_8]Cl_3 \bullet$(15-crown-5)," *Inorg. Chim. Acta* **1987**, *129*, 277-282.
104. Rogers, R. D.; Kurihara, L. K. "f-Element/Crown Ether Complexes. 4. Synthesis and Crystal and Molecular Structures of $[MCl(OH_2)_2$(18-crown-6)$]Cl_2 \bullet 2(H_2O)$ (M = Sm, Gd, Tb)," *Inorg. Chem.* **1987**, *26*, 1498-1502.
105. Rogers, R. D.; Kurihara, L. K.; Benning, M. M. "f-Element/Crown Ether Complexes, 11. Preparation and Structural Characterization of $[UO_2(OH_2)_5][ClO_4]_2 \bullet 3$(15-crown-5)$\bullet CH_3CN$ and $[UO_2(OH_2)_5][ClO_4]_2 \bullet 2$(18-crown-6)$\bullet 2CH_3CN \bullet H_2O$," *J. Inclusion Phenom.* **1987**, *5*, 645-658.
106. Rogers, R. D.; Kurihara, L. K.; Benning, M. M. "Structure of Thorium Nitrate-1,4,7,10,13,16-Hexaoxacyclooctadecane-Water (1/1/3), $[Th(OH_2)_3(NO_3)_4] \bullet$18-Crown-6 at 123 K," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1987**, *C43*, 1056-1058.
107. Rogers, R. D.; Kurihara, L. K.; Benning, M. M. "f-Element/Crown Ether Complexes. 10. Oxidation of UCl_4 to $[UO_2Cl_4]^{2-}$ in the Presence of Crown Ethers: Structural Characterization of Crown Ether Complexed Ammonium Ions $[(NH_4)$(15-crown-$5)_2]_2[UO_2Cl_4] \bullet 2CH_3CN$, $[(NH_4)$(benzo-15-crown-$5)_2]_2[UCl_6] \bullet 4CH_3CN$, and $[(NH_4)$(dibenzo-18-crown-6)$]_2[UO_2Cl_4] \bullet 2CH_3CN$ and Synthesis of $[Na$(12-crown-$4)_2]_2[UO_2Cl_4] \bullet 2OHMe$ and $[UO_2Cl_2(OH_2)_3] \bullet$18-crown-$6 \bullet H_2O \bullet OHMe$," *Inorg. Chem.* **1987**, *26*, 4346-4352.
108. Rogers, R. D.; Kurihara, L. K.; Richards, P. D. "Crystallization and Structural Characterization of Dibenzo-18-crown-$6 \bullet 2$(MeCN) and Dibenzo-18-crown-$6 \bullet 2(MeNO_2)$; Assignment of Specific C-H$\bullet\bullet\bullet$O Interactions," *J. Chem. Soc., Chem. Comm.* **1987**, 604-606.
109. Rogers, R. D.; Kurihara, L. K.; Voss, E. J. "f-Element/Crown Ether Complexes. 5. Structural Changes in Complexes of Lanthanide Chloride Hydrates with 18-Crown-6 Accompanying Decreases in Ln^{3+} Ionic Radii: Synthesis and Structures of $[M(OH_2)_7(OHMe)][MCl(OH_2)_2$(18-crown-6)$]_2Cl_7 \bullet 2(H_2O)$ (M = Y, Dy)," *Inorg. Chem.* **1987**, *26*, 2360-2365.
110. Rogers, R. D.; Richards, P. D. "Neutral Solvent/Crown Ether Interactions 3. Reorientation of the Hydrogen Bonds in the Low Temperature (-150°C) Structure of 18-Crown-$6 \bullet 2(CH_3NO_2)$," *J. Inclusion Phenom.* **1987**, *5*, 631-638.
111. Rogers, R. D.; Voss, E. J. "f-Element/Crown Ether Complexes. 14. Synthesis and Crystal Structure of $[Lu(OH_2)_8][Na$(12-crown-$4)_2]Cl_4 \bullet 2H_2O$," *Inorg. Chim. Acta* **1987**, *133*, 181-187.
112. Wayda, A. L.; Mukerji, I.; Dye, J. L.; Rogers, R. D. "Divalent Lanthanoid Synthesis in Liquid Ammonia. 2. The Synthesis and X-ray Crystal Structure of $(C_8H_8)Yb(C_5H_5N)_3 \bullet 1/2C_5H_5N$," *Organometallics* **1987**, *6*, 1328-1332.
113. Alt, H. G.; Engelhardt, H. E.; Razavi, A.; Rausch, M. D.; Rogers, R. D. "Pentamethylcyclopentadienyl-, Acetylcyclopentadienyl-, und Indenyl-dicarbonyl-Acetylenkomplexe des Vanadiums. Molekulstruktur von $C_9H_7V(CO)_2PhC_2H$," *Z. Naturforsch., B: Chem. Sci.* **1988**, *43b*, 438-444.
114. Carmona, E.; Muñoz, M. A.; Rogers, R. D. "Synthesis, Characterization, and Properties of the η^2-Acyl Complexes Mo(η^2-$COCH_2CMe_3)X(PMe_3)_4$ (X = Cl, Br)," *Inorg. Chem.* **1988**, *27*, 1598-1601.
115. Macomber, D. W.; Hung, M.-H.; Verma, A. G.; Rogers, R. D. "A New, General Route to (μ-Bis(carbene))ditungsten Complexes: X-ray Crystal Structure of $(CO)_5W\{C(OCH_3)CH_2[CH(CH_2)_3C(CH_2CH=CH_2)]C(OCH_3)\}W(CO)_5$," *Organometallics* **1988**, *7*, 2072-2074.
116. Macomber, D. W.; Liang, M.; Rogers, R. D. "Synthesis and Reactivity of Ditungsten μ-Carbene Complexes: X-ray Crystal Structure of $W_2(CO)_9[\mu$-η^1,η^3-$C(OCH_3)C=CH(CH_2)_5CH_2]$," *Organometallics* **1988**, *7*, 416-422.
117. Macomber, D. W.; Verma, A. G.; Rogers, R. D. "Intermolecular [2+2+2] Cycloaddition Reactions of Alkynes and Alkenes Mediated by Cobalt: X-ray Crystal Structures of Two Isomeric (η^5-Cyclopentadienyl)(η^4-1,3-cyclohexadiene)cobalt Complexes," *Organometallics* **1988**, *7*, 1241-1253.
118. Paquette, L. A.; DeRussy, D. T.; Rogers, R. D. "On Possible Redirection of the Course of Anionic Oxy-Cope Rearrangements,"

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 17

IPR2020-00770
United Therapeutics EX2007
Page 3567 of 7335

Tetrahedron **1988**, *44*, 3139-3148.
119. Paquette, L. A.; Lau, C. J.; Rogers, R. D. "Uni- and Biparticulate Electrophilic Additions to Conjugated Bis(bicyclo[1.1.0]butanes)," *J. Am. Chem. Soc.* **1988**, *110*, 2592-2600.
120. Peterson, J. R.; Do, H. D.; Rogers, R. D. "Anticancer-Agent Development: X-ray Structure of Dimethyl 2,3,4,5-Tetrahydro-3-(3,4-methylenedioxybenzoyl)-2-oxo-5β-(3,4,5-trimethoxyphenyl)-3α,4α-furandicarboxylate," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1988**, *C44*, 1786-1789.
121. Peterson, J. R.; Rogers, R. D.; Do, H. D. "Structure of Dimethyl 2,3,4,5-Tetrahydro-2-oxo-5α-(3,4,5-trimethoxyphenyl)-3α,4β-furancarboxylate," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1988**, *C44*, 1784-1786.
122. Robinson, G. H.; Sangokoya, S. A.; Rogers, R. D. "Synthesis and Molecular Structure of the Optically Active Organoaluminum Dimer (S)-(-)-(S)-(-)-[$(C_6H_5)CH(CH_3)NHAl(CH_3)_2]_2$," *Polyhedron* **1988**, *7*, 2727-2730.
123. Rogers, R. D. "f-Element/Crown Ether Complexes. 26. Crystallization of Two Hydrated Forms of Hydrogen Bonded Complexes of $NdCl_3 \bullet nH_2O$ and 15-crown-5. Crystal Structures of $[Nd(OH_2)_9]Cl_3 \bullet$15-crown-5$\bullet H_2O$ and $[NdCl_2(OH_2)_6]Cl \bullet$15-crown-5," *Inorg. Chim. Acta* **1988**, *149*, 307-314.
124. Rogers, R. D. "f-Element/Crown Ether Complexes 15. Synthesis and Crystal Structure of $[Lu(OH_2)_8]Cl_3 \bullet$1.5(12-crown-4)$\bullet 2H_2O$," *J. Coord. Chem.* **1988**, *16*, 415-424.
125. Rogers, R. D. "Neutral Molecule/Crown Ether Interactions 5. Comparison of the C-H Acidic Interactions of Nitromethane and Acetonitrile with 18-crown-6 and Dibenzo-18-crown-6. Crystal Structures of Dibenzo-18-crown-6$\bullet 2CH_3NO_2$ and Dibenzo-18-crown-6$\bullet 2CH_3CN$," *J. Inclusion Phenom.* **1988**, *6*, 629-645.
126. Rogers, R. D. "Structure of Di[bis(1,4,7,10-tetraoxacyclododecane)sodium] Tetrachlorodioxouranate(VI)-Methanol (1/2), $[Na(12\text{-crown-}4)_2]_2[UO_2Cl_4] \bullet$2MeOH," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1988**, *C44*, 638-641.
127. Rogers, R. D.; Benning, M. M. "Synthesis and Structure of Thorium Chloride-1,4,7,10,13-Pentaoxacyclopentadecane-Water-Methanol-Acetonitrile (1/1/2/2/1), $[ThCl_4(OHMe)_2(OH_2)_2] \bullet$15-Crown-5$\bullet CH_3CN$," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1988**, *C44*, 641-644.
128. Rogers, R. D.; Benning, M. M. "Preparation and Structure of Bis(1,4,7,10,13,16- hexaoxacyclododecaneammonium) Hexachlorouranate(IV)-Acetonitrile (1/2), $[(NH_4)$(18-crown-6)$]_2[UCl_6] \bullet 2CH_3CN$," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1988**, *C44*, 1397-1399.
129. Rogers, R. D.; Etzenhouser, R. D. "Structure of $[LuCl_3$(triethylene glycol)$] \bullet$OHMe," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1988**, *C44*, 1400-1402.
130. Rogers, R. D.; Etzenhouser, R. D. "Structure of $[DyCl_3$(triethylene glycol)$] \bullet$18-crown-6," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1988**, *C44*, 1533-1535.
131. Rogers, R. D.; Kurihara, L. K.; Benning, M. M. "f-Element/Crown Ether Complexes. Part 9. The Role of Solvent Hydrogen Bonding: Synthesis and Crystal Structure of Aquatetrachlorotris(ethanol)thorium(IV)-1,4,7,10,13,16-hexaoxacyclo-octadecane-Water (1/1/1)," *J. Chem. Soc., Dalton Trans.* **1988**, 13-16.
132. Rogers, R. D.; Richards, P. D.; Voss, E. J. "Neutral Solvent/Crown Ether Interactions, 4. Crystallization and Low Temperature (-150 °C) Structural Characterization of 18-crown-6$\bullet 2(CH_3CN)$," *J. Inclusion Phenom.* **1988**, *6*, 65-71.
133. Rogers, R. D.; Rollins, A. N.; Benning, M. M. "f-Element/Crown Ether Complexes. 22. Preparation and Structural Characterization of Lanthanide Chloride Complexes of 12-crown-4," *Inorg. Chem.* **1988**, *27*, 3826-3835.
134. Rogers, R. D.; Shakir, R.; Atwood, J. L.; Macomber, D. W.; Wang, Y.-P.; Rausch, M. D. "The Crystal and Molecular Structures of Formyl-, Cyano-, and Aminocyclopentadienyldicarbonylnitrosylchromium," *J. Crystallogr. Spectrosc. Res.* **1988**, *18*, 767-778.
135. Rogers, R. D.; Teuben, J. H. "The Crystal and Molecular Structures of (η^5- Pentamethylcyclopentadienyl)(η^7-Cyclohepatatrienyl)zirconium and -hafnium," *J. Organomet. Chem.* **1988**, *354*, 169-176.
136. Rogers, R. D.; Voss, E. J. "f-Element/Crown Ether Complexes 12. Synthesis and Crystal Structure of $[Y(NO_3)_3(OH_2)_2$(NCMe)$][Y(NO_3)_3(OH_2)_2$(OHMe)$] \bullet 2$(benzo-15-crown-5)$\bullet$OHMe," *J. Coord. Chem.* **1988**, *16*, 405-414.
137. Rogers, R. D.; Voss, E. J.; Etzenhouser, R. D. "f-Element/Crown Ether Complexes. 17. Synthetic and Structural Survey of Lanthanide Chloride Triethylene Glycol Complexes," *Inorg. Chem.* **1988**, *27*, 533-542.
138. Alt, H. G.; Engelhardt, H. E.; Frister, T.; Rogers, R. D. "Darstellung und Charakterisierung der Isonitril-Hydridkomplexe Cp'$(CO)_2$(CNR)MH (Cp' = η^5-C_5H_5, η^5-C_5Me_5; R = Me, ^{t}Bu; M = Mo, W). Molekülstruktur von $C_5Me_5(CO)_2$(CN^{t}Bu)MoH," *J. Organomet. Chem.* **1989**, *366*, 297-304.
139. Alt, H. G.; Engelhardt, H. E.; Hayen, H. I.; Rogers, R. D. "Umsetzungen des Asymmetrischen, Zweikernigen Dioxokomplexes $C_5Me_5(CO)_3$W-W$(O)_2C_5Me_5$ mit Cl_2, Br_2, I_2, HCl, CF_3COOH, NOCl, NO und Luft. Molekülstruktur von $C_5Me_5W(CO)_2Br_3$," *J. Organomet. Chem.* **1989**, *366*, 287-295.
140. Alt, H. G.; Engelhardt, H. E.; Rogers, R. D. "Die Protonierung von Ylidkomplexen des Mangans mit HBF_4. Die Molekülstruktur von $[C_5H_5(CO)_2MnCH_2CH(PEt_3)]BF_4$," *J. Organomet. Chem.* **1989**, *362*, 117-124.
141. Alt, H. G.; Engelhardt, H. E.; Rogers, R. D.; Abu-Orabi, S. T. "Photoinduzierte Umsetzungen der Komplexe (η^6-$C_6H_3R_3)(CO)_3Cr$ (R = Me, Et) mit den Acetylenen $C_2R'_2$ (R' = H, C_3H_7, $C(OEt)_2H$). Die Molekülstruktur von $(C_6H_3Me_3)(CO)Cr(\mu\text{-}CO)\{\mu\text{-}C_2[C(OEt)_2H]_2\}Cr(CO)_4$," *J. Organomet. Chem.* **1989**, *378*, 33-43.
142. Alt, H. G.; Engelhardt, H. E.; Wrackmeyer, B.; Rogers, R. D. "Die Photoinduzierte Umsetzung der Tricarbonyl-Hydridkomplexe Cp'$W(CO)_3H$ (Cp' = η^5-C_5H_5, η^5-C_5Me_5) mit Methylacetylen und Dimethylacetylen zu η^3-Allyl- und Metallacyclischen Alkenylketon-Komplexen. Molekülstruktur von $C_5Me_5W(CO)_2(\eta^3\text{-}C_3H_5)$," *J. Organomet. Chem.* **1989**, *379*, 289-301.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 18

IPR2020-00770
United Therapeutics EX2007
Page 3568 of 7335

143. Beachley, O. T., Jr.; Spiegel, E. F.; Kopasz, J. P.; Rogers, R. D. "Indium(III) Compounds Containing the Neopentyl Substituent, $In(CH_2CMe_3)_3$, $In(CH_2CMe_3)_2Cl$, $In(CH_2CMe_3)Cl_2$, and $In(CH_2CMe_3)_2CH_3$. Crystal and Molecular Structure of Dichloroneopentylindium(III), an Inorganic Polymer," *Organometallics* **1989**, *8*, 1915-1921.
144. Burford, N.; Spence, R. E. v. H.; Rogers, R. D. "Preparation, Crystal Structures, and Spectroscopic Characterization of Diaminochalcogenophosphonium Cations," *J. Am. Chem. Soc.* **1989**, *111*, 5006-5008.
145. Hall, T. J.; Bachrach, S. M.; Spangler, C. W.; Sapochak, L. S.; Lin, C. T.; Guan, H. W.; Rogers, R. D. "Structure of All-*trans*-1,6-diphenyl- (*A*) and All-*trans*-1,6-bis(*o*-methoxyphenyl)-1,3,5-hexatriene (*B*)," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1989**, *C45*, 1541-1543.
146. Hall, T. J.; Mertz, C. J.; Bachrach, S. M.; Hipple, W. G.; Rogers, R. D. "The Crystal Structure of $UO_2Cl_2(OH_2)(MeCN)_2 \bullet 2MeCN$," *J. Crystallogr. Spectrosc. Res.* **1989**, *19*, 499-505.
147. Heeres, H. J.; Meetsma, A.; Teuben, J. H.; Rogers, R. D. "Mono(pentamethylcyclopentadienyl) Complexes of Cerium(III). Synthesis, Molecular Structure, Thermal Stability, and Reactivity of $(C_5Me_5)CeX_2$ (X = 2,6-Di-*tert*-butylphenoxo, $CH(SiMe_3)_2$, and $N(SiMe_3)_2$) Complexes," *Organometallics* **1989**, *8*, 2637-2646.
148. Heeres, H. J.; Teuben, J. H.; Rogers, R. D. "Novel Monopentamethylcyclopentadienyl Alkoxides of La and Ce; X-ray Crystal Structure of $(C_5Me_5Ce(OCMe_3)_2)_2$," *J. Organomet. Chem.* **1989**, *364*, 87-96.
149. Jaw, H.-R. C.; Savas, M. M.; Rogers, R. D.; Mason, W. R. "Crystal Structures and Solution Electronic Absorption and MCD Spectra for Perchlorate and Halide Salts of Binuclear Gold(I) Complexes Containing Bridging $Me_2PCH_2PMe_2$ (dmpm) or $Me_2PCH_2CH_2PMe_2$ (dmpe) Ligands," *Inorg. Chem.* **1989**, *28*, 1028-1037.
150. Kool, L. B.; Ogasa, M.; Rausch, M. D.; Rogers, R. D. "Synthesis of [η^5-(Diphenylphosphino)cyclopentadienyl][η^7-(diphenylphosphino)cycloheptatrienyl]titanium and Its Utility in the Formation of Heterobimetallic Complexes: The Molecular Structure of Tetracarbonyl{[η^5-(diphenylphosphino)cyclopentadienyl][η^7- (diphenylphosphino)cycloheptatrienyl]titanium-*P*,*P*'}chromium Hemitoluene Solvate," *Organometallics* **1989**, *8*, 1785-1790.
151. Lin, W. O.; da Costa, J. B. N.; Alt, H. G.; Rogers, R. D. "A New System of Ionophores Derived from *o*,*o*'-Biphenyldiol. X-ray Structure of *o*-Hydroxy-biphenyl-*o*'-oxyacetamide," *Z. Naturforsch., B: Chem. Sci.* **1989**, *44b*, 1331-1332.
152. Macomber, D. W.; Madhukar, P.; Rogers, R. D. "Synthesis of [Alkenyl(dimethylamino)carbene]tungsten Complexes using the Peterson Reaction: X-ray Crystal Structure of (*E*)-$(CO)_5W[C(NMe_2)CH{=}CH(\eta\text{-}C_5H_4)Fe(\eta\text{-}C_5H_5)]$," *Organometallics* **1989**, *8*, 1275-1282.
153. Moriarty, K. J.; Rogers, R. D.; Paquette, L. A. "Stereoselective Formation from a (1*S*,5*S*)-(-)-Verbenone-Derived Cyclopentadiene of Dimeric and Mixed Titanium and Zirconium Dichloride Complexes," *Organometallics* **1989**, *8*, 1512-1517.
154. Paquette, L. A.; He, W.; Rogers, R. D. "Comparative Analysis of Molecular-Recognition Levels Attained during Capture of Chiral Cyclopentenyl Organometallics by Conformationally Immobilized Ketonic Systems," *J. Org. Chem.* **1989**, *54*, 2291-2300.
155. Paquette, L. A.; Moriarty, K. J.; McKinney, J. A.; Rogers, R. D. "Analysis of the π-Facial Preference for Complexation of a Camphor-Derived, Enantiomerically Pure Cyclopentadienyl Ligand to $CpMCl_2$ Fragments (M = Ti and Zr)," *Organometallics* **1989**, *8*, 1707-1713.
156. Paquette, L. A.; Moriarty, K. J.; Meunier, P.; Gautheron, B.; Sornay, C.; Rogers, R. D.; Rheingold, A. L. "Stereochemical Course of π-Face Coordination to Isodicyclopentadiene during Formation of Mixed Titanocene and Zirconocene Dichloride Complexes," *Organometallics* **1989**, *8*, 2159-2167.
157. Paquette, L. A.; Moriarty, K. J.; Rogers, R. D. "(1*R*)-(-)-Nopol as the Source of an Optically Pure Fused Cyclopentadienyl Ligand. Stereochemical Course of Complexation to Cyclopentadienyltitanium and -zirconium Dichloride Fragments," *Organometallics* **1989**, *8*, 1506-1511.
158. Paquette, L. A.; O'Doherty, G. A.; Miller, B. L.; Rogers, R. D.; Rheingold, A. L.; Geib, S. L. "Stereochemically Uniform Mode of Iron Carbonyl Complexation to Spirocyclic Isodicyclopentadienes," *Organometallics* **1989**, *8*, 2167-2172.
159. Paquette, L. A.; Vanucci, C.; Rogers, R. D. "Stereochemical Course of Diels-Alder Cycloadditions to Hydroxymethyl-Substituted Plane-Nonsymmetric Cyclopentadienes," *J. Am. Chem. Soc.* **1989**, *111*, 5792-5800.
160. Peterson, J. R.; Do, H. D.; Rogers, R. D. "Platelet Activating Factor Antagonist Design. 2. X-ray Structure of Dimethyl 2,3,4,5-Tetrahydro-5β-(3,4-methylenedioxyphenyl)-2-oxo-3β-(3,4,5-trimethoxybenzoyl)-3α,4α- furandicarboxylate," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1989**, *C45*, 1059-1063.
161. Peterson, J. R.; Do, H. D.; Rogers, R. D. "Anticancer Agent Development. 3. X-ray Structure of Dimethyl 1-Methoxy-6,7-methylenedioxy-4-(3,4,5-trimethoxyphenyl)-*trans*-3,4- dihydronaphthalene-2,3-dicarboxylate," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1989**, *C45*, 1568-1571.
162. Peterson, J. R.; Horsley, D. B.; Brozik, J. A.; Rogers, R. D. "Platelet Activating Factor Antagonist Design. 3. X-ray Crystal Structure and Intermolecular Crystal Lattice Interactions of Methyl *trans*-4-Acetoxymethyl-4,5-dihydro-2,5-bis(3,4-methylenedioxyphenyl)-3- furancarboxylate," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1989**, *C45*, 1164-1167.
163. Peterson, J. R.; Smillie, T. J.; Rogers, R. D. "Platelet Activating Factor Antagonist Design: Structure of Methyl *trans*-5-(3,4-Dimethoxyphenyl)-2,3,4,5-tetrahydro-2-oxo-4-furancarboxylate," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1989**, *C45*, 297-300.
164. Peterson, J. R.; Winter, T. J.; Do, H. D.; Rogers, R. D. "Anticancer Agent Development: X-ray Crystal Structure and Keto-Enol Tautomerism of Dimethyl 1-hydroxy-6,7-methylenedioxy-4- (3',4',5'-trimethoxyphenyl)-*trans*-3,4-dihydronaphthalene-2,3-dicarboxylate," *J. Crystallogr. Spectrosc. Res.* **1989**, *19*, 135-145.
165. Peterson, J. R.; Winter, T. J.; Everson, T. P.; Rogers, R. D. "Novel Manganese(III) Oxidation Chemistry: X-ray Crystal Structure

of 5,7,8-Trimethoxy-1-(2,4,5-trimethoxyphenyl)-1,2-dihydronapthalene," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1989**, *C45*, 132-134.
166. Rausch, M. D.; Tsai, W.-M.; Chambers, J. W.; Rogers, R. D.; Alt, H. G. "Synthetic and X-ray Structural Studies on Pentabenzylcyclopentadienyl Derivatives of Manganese, Rhenium, and Iron," *Organometallics* **1989**, *8*, 816-821.
167. Robinson, G. H.; Sangokoya, S. A.; Pennington, W. T.; Self, M. F.; Rogers, R. D. "Unexpected Conformation of the Hydrogen Chloride Salt of [14]aneN$_4$: An X-ray Structural Examination of [H$_2$[14]aneN$_4$H$_2$]Cl$_4$ and Its Role in Organaluminum Host-Guest Chemistry," *J. Coord. Chem.* **1989**, *19*, 287-294.
168. Rogers, R. D. "Macrocycle Complexation Chemistry. 31. The Crystal Structure of [ThCl$_2$(OH$_2$)$_7$]Cl$_2$•18-crown-6•2H$_2$O," *Lanthanide Actinide Res.* **1989**, *3*, 71-81.
169. Rogers, R. D. "f-Element/Crown Ether Complexes: 21. Conformational Changes in Metal Complexed versus Hydrogen Bonded Benzo-15-crown-5 in the Structure of [Y(OH$_2$)$_3$(NCMe)(benzo-15-crown-5)][ClO$_4$]$_3$•benzo-15-crown-5•CH$_3$CN," *J. Inclusion Phenom. Mol. Recognit. Chem.* **1989**, *7*, 277-287.
170. Rogers, R. D.; Alt, H. G.; Engelhardt, H. E. "Umsetzungen des Acetylenkomplexes (C$_6$H$_3$Me$_3$)(CO)$_2$Cr(C$_2$H$_2$) mit PMe$_3$ und HNMe$_2$. Festkörperstrukturen von (C$_6$H$_3$Me$_3$)(CO)$_2$Cr(PMe$_3$) und (C$_6$H$_3$Me$_3$)(CO)$_2$Cr[C(Me)NMe$_2$]," *J. Organomet. Chem.* **1989**, *366*, 305-312.
171. Rogers, R. D.; Benning, M. M.; Etzenhouser, R. D.; Rollins, A. N. "Novel Unidentate Co-ordination of a Crown Ether and of a Polyethylene Glycol to Uranium(VI)," *J. Chem. Soc., Chem. Comm.* **1989**, 1586-1588.
172. Rogers, R. D.; Teuben, J. H. "Structure of (η^5-C$_5$Me$_5$)(η^8-C$_8$H$_8$)Zr, an Aromatic Mixed Sandwich Complex of Zirconium(III)," *J. Organomet. Chem.* **1989**, *359*, 41-47.
173. Spangler, B. D.; Vaný sek, P.; Hernandez, I. C.; Rogers, R. D. "Structure of Crystal Violet Tetraphenylborate," *J. Crystallogr. Spectrosc. Res.* **1989**, *19*, 589-596.
174. Spangler, C. W.; Hall, T. J.; Saindon, M. L.; Rogers, R. D.; McCoy, R. K.; Birge, R. R.; Fleitz, P. A.; Zhang, C.-F. "The Relationship between Structure and Nonlinear Optical Properties in Donor-Acceptor Polyenes," *Inst. Phys. Conf. Ser.* **1989**, *103*, 233-238.
175. Alt, H. G.; Palackal, S. J.; Rogers, R. D. "Umsetzungen des 1,2-Bis(3-indenyl)ethan-Dianions mit Photochemisch Aktivierten Carbonylkomplexen des Chroms, Molybdäns und Wolframs. Molekülstruktur von C$_9$H$_7$CH$_2$CH$_2$C$_9$H$_7$ und (η^5:η^5-C$_9$H$_6$CH$_2$CH$_2$C$_9$H$_6$)[W(CO)$_3$Me]$_2$," *J. Organomet. Chem.* **1990**, *388*, 105-116.
176. Banks, M. A.; Beachley, O. T., Jr.; Maloney, J. D.; Rogers, R. D. "The Chemistry of Diphenylphosphine Adducts of Tris(neopentyl) and Tris(trimethylsilylmethyl)gallium and -indium Including the Crystal and Molecular Structure of (Me$_3$CCH$_2$)$_3$Ga•P(H)Ph$_2$," *Polyhedron* **1990**, *9*, 335-342.
177. Burford, N.; Royan, B. W.; Spence, R. E. v. H.; Cameron, T. S.; Linden, A.; Rogers, R. D. "Linear Co-ordinative Bonding at Oxygen: A Spectroscopic and Structural Study of Phosphine Oxide-Group 13 Lewis Acid Adducts," *J. Chem. Soc., Dalton Trans.* **1990**, 1521-1528.
178. Burford, N.; Royan, B. W.; Spence, R. E. v. H.; Rogers, R. D. "Nuclear Magnetic Resonance Spectroscopic Characterization and the Crystal and Molecular Structures of Ph$_3$PS•AlCl$_3$ and Ph$_3$PSe•AlCl$_3$: A Classification of the Co-ordinative Bonding Modes of the Phosphine Chalcogenides," *J. Chem. Soc., Dalton Trans.* **1990**, 2111-2117.
179. Burford, N.; Royan, B. W.; Whalen, J. M.; Richardson, J. F.; Rogers, R. D. "Co-ordinatively Unsaturated Group 15 Elements: The Isolation and Crystal Structure of a Novel Dimeric Dithiarsolidinium Cation," *J. Chem. Soc., Chem. Comm.* **1990**, 1273-1275.
180. Burford, N.; Spence, R. E. v. H.; Rogers, R. D. "Chemistry of the Diaminochalcogenophosphinic Chloride-Aluminum Trichloride System: Preparation and Crystal Structures of New Chalcogenophosphonium Cations," *J. Chem. Soc., Dalton Trans.* **1990**, 3611-3619.
181. Burford, N.; Spence, R. E. v. H.; Whalan, J. M.; Rogers, R. D.; Richardson, J. F. "Syntheses and Crystal Structures for the First Two Examples of the Four-Membered PNSiS Heterocycle," *Organometallics* **1990**, *9*, 2854-2856.
182. Lee, B.; Pennington, W. T.; Robinson, G. H.; Rogers, R. D. "Organogallium Chemistry of Macrocyclic Amines. Synthesis and Molecular Structure of [Ga(CH$_3$)$_3$]$_4$[(CH$_3$)$_4$[14]aneN$_4$] and [Ga(CH$_3$)$_2$][14]aneN$_4$[Ga(CH$_3$)$_3$]$_2$," *J. Organomet. Chem.* **1990**, *396*, 269-278.
183. Murray, C. K.; Warner, B. P.; Dragisich, V.; Wulff, W. D.; Rogers, R. D. "Thermal Reactions of Acyloxy and Alkoxy Carbene Complexes with Imines: Metathesis, Acetate Rearrangements, and a New Route to Imino Carbene Complexes via Peterson Type Eliminations," *Organometallics* **1990**, *9*, 3142-3151.
184. Paquette, L. A.; DeRussy, D. T.; Vandenheste, T.; Rogers, R. D. "Comparative Analysis of Diastereoselection Levels Attainable during Controlled Exo and Endo Addition of Chiral Cyclopentenyl Organometallics to Optically Pure and Racemic 1-Vinylnorbornan-2-ones," *J. Am. Chem. Soc.* **1990**, *112*, 5562-5573.
185. Paquette, L. A.; Kesselmayer, M. A.; Rogers, R. D. "Quantitation of Proximity Effects on Rate. A Case Study Involving Dyotropic Hydrogen Migration within *syn*-Sesquinorbornene Disulfones Carrying Central Substituents Having Different Spatial Demands," *J. Am. Chem. Soc.* **1990**, *112*, 284-291.
186. Paquette, L. A.; Liang, S.; Waykole, L.; DeLucca, G.; Jendralla, H.; Rogers, R. D.; Kratz, D.; Gleiter, R. "[4.4.4]Propellahexaene by Triple Shapiro Degradation. Structural and Electronic Properties of This Maximally Unsaturated Hydrocarbon and Consequences of O-Methylation of Its [4.4.4]Propellatrienetrione Precursors," *J. Org. Chem.* **1990**, *55*, 1598-1611.
187. Paquette, L. A.; Pegg, N. A.; Toops, D.; Maynard, G. D.; Rogers, R. D. "[3.3] Sigmatropy within 1-Vinyl-2-alkenyl-7,7-

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 20

IPR2020-00770
United Therapeutics EX2007
Page 3570 of 7335

dimethyl-*exo*-norbornan-2-ols. The First Atropselective Oxyanionic Cope Rearrangement," *J. Am. Chem. Soc.* **1990**, *112*, 277-283.
188. Paquette, L. A.; Teleha, C. A.; Taylor, R. T.; Maynard, G. D.; Rogers, R. D.; Gallucci, J. C.; Springer, J. P. "Boat/Chair Topographic Stereoselection during Anionic Oxy-Cope Rearrangement of 1-Alkenyl-2-cyclopentenyl-*endo*-norbornan-2-ols," *J. Am. Chem. Soc.* **1990**, *112*, 265-277.
189. Peterson, J. R.; Everson, T. P.; Rogers, R. D. "Novel Manganese(III) Oxidation Chemistry: X-ray Crystal Structures of (1α,2α,4β)-1,2-diacetoxy-4-(4-methoxyphenyl)-6-methoxy-1,2,3,4- tetrahydronaphthalene (Compound A) and (1α,2α,4β)-1,2-diacetoxy-4-(2-methoxyphenyl)-8-methoxy-1,2,3,4-tetrahydronaphthalene (Compound B)," *J. Crystallogr. Spectrosc. Res.* **1990**, *20*, 37-45.
190. Peterson, J. R.; Horsley, D. B.; Brozik, J. A.; Rogers, R. D. "Anticancer Agent Development. 4. X-ray Crystal Structure and Intermolecular Crystal Lattice Interactions of Methyl *Trans*-4,5-dihydro-4-acetoxymethyl-5-(3,4,5-trimethoxyphenyl)-2-(3,4-methylenedioxyphenyl)-3- furancarboxylate," *J. Crystallogr. Spectrosc. Res.* **1990**, *20*, 47-52.
191. Peterson, J. R.; Horsley, D. B.; Rogers, R. D. "Platelet-Activating-Factor Antagonist Design. 4. Structure and Intermolecular Crystal Lattice Interactions of *cis*-3,4-Dibenzyl-2-oxo-2,3,4,5-tetrahydrofuran," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1990**, *C46*, 872-875.
192. Peterson, J. R.; Peterson, S.; Baker, J. K.; Rogers, R. D. "Anticancer Agent Development. 5. X-ray Structure and ^{1}H NMR Spectral Analysis of (1α,2α,5α,6α)-2,6-bis(3,4-methylenedioxyphenyl)-3,7-dioxabicyclo[3.3.0]octane-4,8-dione," *J. Crystallogr. Spectrosc. Res.* **1990**, *20*, 327-333.
193. Rausch, M. D.; Spink, W. C.; Conway, B. G.; Rogers, R. D.; Atwood, J. L. "Synthetic and Structural Studies on (η^5:η^5-Fulvalene)bimetallic Compounds Derived from (η^5:η^5-Fulvalene)dithallium," *J. Organomet. Chem.* **1990**, *383*, 227-252.
194. Rogers, R. D.; Alt, H. G.; Maisel, H. E. "Die Molekülstruktur des Carbenartigen Ylidkomplexes $(C_5H_4Me)(CO)_2Mn[CHCH(PEt_3)]$," *J. Organomet. Chem.* **1990**, *381*, 233-238.
195. Rogers, R. D.; Atwood, J. L.; Rausch, M. D.; Macomber, D. W. "Crystal Structures of (η^5-C_5H_4COMe)$M(CO)_3Me$ (M = Mo,W)," *J. Crystallogr. Spectrosc. Res.* **1990**, *20*, 555-560.
196. Rogers, R. D.; Bond, A. H.; Hipple, W. G. "Macrocycle Complexation Chemistry. 33. Preparation of [Ca(12-crown-4)$_2$][UO_2Cl_4] and [$Ca(OH_2)_3$(15-crown-5)][UO_2Cl_4]. Structure of [$Ca(OH_2)_3$(15-crown-5)][UO_2Cl_4]," *J. Crystallogr. Spectrosc. Res.* **1990**, *20*, 611-616.
197. Rogers, R. D.; Nunez, L. "Macrocycle Complexation Chemistry. 29. Synthesis and Crystal Structure of [CuCl(18-thiacrown-6)]$_n$," *J. Coord. Chem.* **1990**, *21*, 111-118.
198. Rogers, R. D.; Nuñez, L. "Macrocycle Complexation Chemistry. 32. Modification of the Lanthanide Ion Coordination Sphere via Electrocrystallization of Hydrated Lanthanide Chloride Complexes of 12-crown-4," *Inorg. Chim. Acta* **1990**, *172*, 173-180.
199. Rogers, R. D.; Park, M.-G.; Kevill, D. N. "Structure of 3-(4-Methoxyphenyl)-4-phenyl-4*H*-1,2,4-triazole," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1990**, *C46*, 2218-2221.
200. Rogers, R. D.; Rollins, A. N. "Macrocycle Complexation Chemistry 30: Comparison of the Crystal Structures of [$La(NO_3)_3$(15-crown-5)] and [$La(NO_3)_3$(monoaza-15-crown-5)]," *J. Crystallogr. Spectrosc. Res.* **1990**, *20*, 389-393.
201. Rogers, R. D.; Rollins, A. N.; Etzenhouser, R. D.; Henry, R. F. "f-Element/Crown Ether Complexes. 27. The Synthesis and Crystal Structure of [$Ce(NO_3)_3(OH_2)$(12-crown-4)]•12-crown-4," *J. Inclusion Phenom. Mol. Recognit. Chem.* **1990**, *8*, 375-382.
202. Rogers, R. D.; Royal, J. D.; Bolton, D. M.; Boeyens, J. C. A.; Allen, C. C. "f-Element/Crown Ether Complexes. 20. Synthesis and Structure of [$Y(NO_3)_3(OH_2)_3$]•1.5(15-crown-5)•Me_2CO," *J. Crystallogr. Spectrosc. Res.* **1990**, *20*, 525-533.
203. Sivik, M. R.; Rogers, R. D.; Paquette, L. A. "Isodicyclopentadienes and Related Molecules LII. Comparative Analysis of the Solid State Structural Features of Bis(η^5-(1*R*,8*R*)- and (η^5-1*R*,8*R*),η^5-(1*S*,8*S*)-7,7,9,9-tetramethyltricyclo[6.1.1.$0^{2,6}$]deca-3,5-dien-2-yl)dichlorotitanium," *J. Organomet. Chem.* **1990**, *397*, 177-185.
204. Wayda, A. L.; Kaplan, M. L.; Lyons, A. M.; Rogers, R. D. "Mixed-Ligand Imidazole Complexes of Organolanthanides," *Polyhedron* **1990**, *9*, 751-756.
205. Alvarez, R.; Atwood, J. L.; Carmona, E.; Pérez, P. J.; Poveda, M. L.; Rogers, R. D. "Formation of Carbonyl-Carbonate Complexes of Molybdenum by Reductive Disproportionation of Carbon Dioxide. X-ray Structure of $Mo_4(\mu_4\text{-}CO_3)(CO)_2(O)_2(\mu_2\text{-}O)_2(\mu_2\text{-}OH)_4(PMe_3)_6$," *Inorg. Chem.* **1991**, *30*, 1493-1499.
206. Beachley, O. T., Jr.; Lees, J. F.; Rogers, R. D. "(Tert-butyl)cyclopentadienylindium(I), In($C_5H_4CMe_3$): Synthesis, Characterization and X-ray Structural Study," *J. Organomet. Chem.* **1991**, *418*, 165-171.
207. Burford, N.; McInnis, J. D.; Schriver, M. J.; Rogers, R. D. "Structure of Bis[bis(trimethylsilyl)methylene]methoxyphosphorane," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1991**, *C47*, 884-885.
208. Carmona, E.; Contreras, L.; Poveda, M. L.; Sánchez, L. J.; Atwood, J. L.; Rogers, R. D. "η^2-Acyl and Methyl Complexes of Tungsten. Crystal and Molecular Structures of W(η^2-C(O)CH_2SiMe_3)Cl(CO)(PMe_3)$_3$ and W(CH_3)(S_2CNMe_2)(CO)$_2$(PMe_3)$_2$," *Organometallics* **1991**, *10*, 61-71.
209. Christie, S.; Dubois, R. H.; Rogers, R. D.; White, P. S.; Zaworotko, M. J. "Air Stable Liquid Clathrates: Solid State Structure and Hydrocarbon Solubility of Organic Cation Triodide Salts," *J. Inclusion Phenom. Mol. Recognit. Chem.* **1991**, *11*, 103-114.
210. Gilbert, T. M.; Rogers, R. D. "Spectroscopic Properties of Conjugated Metal-Carbon Multiple Bonds: Synthesis and Absorption Spectra of the "Dialkylidynes" $(RO)_3W/C\text{-}C/W(OR)_3$ (OR = $OCMe_3$, $OCMe_2CF_3$, $OCMe_2Et$)," *J. Organomet. Chem.* **1991**, *421*, C1-C5.
211. Hufford, C. D.; Badria, F. A.; Abou-Karam, M.; Shier, W. T.; Rogers, R. D. "Preparation, Characterization, and Antiviral

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 21

IPR2020-00770
United Therapeutics EX2007
Page 3571 of 7335

Activity of Microbial Metabolites of Stemodin," *J. Nat. Prod.* **1991**, *54*, 1543-1552.
212. Jürgens, A. R.; McChesney, J. D.; Rogers, R. D. "Synthesis of Hydrophenanthrene Natural Products. Structure of a 17-Nordehydropimarane Derived from Dehydroabietic Acid," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1991**, *C47*, 1675-1678.
213. Macomber, D. W.; Hung, M.-H.; Madhukar, P.; Liang, M.; Rogers, R. D. "Synthesis and Structures of (μ-Bis(carbene))dimetal Complexes of Chromium and Tungsten," *Organometallics* **1991**, *10*, 737-746.
214. Macomber, D. W.; Madhukar, P.; Rogers, R. D. "Unusual Rearrangement of [(α-(Silyl)alkyl)alkoxycarbene]tungsten Complexes: X-ray Crystal Structure of (*E*)-$(CO)_5W[C(N(CH_3)_2)CH_2CH_2CH{=}C(OCH_3)Si(CH_3)_3]$," *Organometallics* **1991**, *10*, 2121-2126.
215. Negri, J. T.; Rogers, R. D.; Paquette, L. A. "Belted Spirocyclic Tetrahydrofurans: A New Class of Preorganized Ionophoric Polyethers. Molecular Structure, Conformation, and Binding to Alkali-Metal Atoms," *J. Am. Chem. Soc.* **1991**, *113*, 5073-5075.
216. Nuñez, L.; Rogers, R. D.; Crabtree, G. W.; Welp, U.; Vandervoort, K.; Umezawa, A.; Fang, Y. "Magnetic and Structural Properties of Fe in Single Crystals of $YBa_2Cu_{3-x}Fe_xO_{7-\delta}$," *Phys. Rev. B: Condensed Matter* **1991**, *44*, 4526-4531.
217. Ogasa, M.; Mallin, D. T.; Macomber, D. W.; Rausch, M. D.; Rogers, R. D.; Rollins, A. N. "Synthetic and Structural Studies on New Vinylcyclopentadienyl Derivatives of Titanium, Iron and Thallium," *J. Organomet. Chem.* **1991**, *405*, 41-52.
218. Ogasa, M.; Rausch, M. D.; Rogers, R. D. "New Heterobimetallic Compounds Derived from [η^5-(Dimethylphosphino)cyclopentadienyl][η^7-(dimethylphosphino)cycloheptatrienyl]titanium," *J. Organomet. Chem.* **1991**, *403*, 279-291.
219. Paquette, L. A.; Combrink, K. D.; Elmore, S. W.; Rogers, R. D. "Impact of Substituent Modifications on the Atropselectivity Characteristics of an Anionic Oxy-Cope Ring Expansion," *J. Am. Chem. Soc.* **1991**, *113*, 1335-1344.
220. Paquette, L. A.; Friedrich, D.; Rogers, R. D. "Alkylaluminum-Catalyzed Claisen Expansion Reactions. Scope and Stereochemistry," *J. Org. Chem.* **1991**, *56*, 3841-3849.
221. Paquette, L. A.; Moorhoff, C. M.; Maynard, G. D.; Hickey, E. R.; Rogers, R. D. "Stereochemical Course of the Base-Promoted Aldol Self-Coupling of Racemic 5-Norbornen-2-one and 2-Norbornanone," *J. Org. Chem.* **1991**, *56*, 2449-2455.
222. Paquette, L. A.; O'Doherty, G. A.; Rogers, R. D. "Intramolecular Reaction Rate Is Not Determined Exclusively by the Distance Separating Reaction Centers. The Kinetic Consequences of Modulated Ground State Strain on Dyotropic Hydrogen Migration in Systems of Very Similar Geometric Disposition," *J. Am. Chem. Soc.* **1991**, *113*, 7761-7762.
223. Peterson, J. R.; Do, H. D.; Rogers, R. D. "Anticancer Agent Development; 6. Application of the Heterocycle Annulation-Rearrangement Strategy in the Synthesis of a Podophyllotoxin Precursor," *Synthesis* **1991**, 275-277.
224. Peterson, J. R.; Do, H. D.; Rogers, R. D. "X-ray Structure and Crystal Lattice Interactions of the Taxol Side-Chain Methyl Ester," *Pharm. Res.* **1991**, *8*, 908-912.
225. Piatak, D. M.; Tang, P.-F. L.; Franciskovich, J.; Rogers, R. D. "Stereochemistry of Erysulfone," *J. Nat. Prod.* **1991**, *54*, 902-904.
226. Rausch, M. D.; Ogasa, M.; Ayers, M. A.; Rogers, R. D.; Rollins, A. N. "Formation and Molecular Structure of Hydridotricarbonyl{[η^5-(diphenylphosphino)cyclopentadienyl][η^7- (diphenylphosphino)cycloheptatrienyl]titanium-*P*,*P*'}manganese: A New Chelated Titanium-Manganese Heterobimetallic Compound," *Organometallics* **1991**, *10*, 2481-2484.
227. Rausch, M. D.; Ogasa, M.; Rogers, R. D.; Rollins, A. N. "Synthetic and Structural Studies on Carboxy, Carbomethoxy, and Trimethylsilyl Derivatives of (η^5-Cyclopentadienyl)(η^7- cycloheptatrienyl)titanium," *Organometallics* **1991**, *10*, 2084-2086.
228. Rogers, R. D.; Benning, M. M. "Macrocycle Complexation Chemistry. 37. The Isolation and Crystallographic Characterization of the U^{4+} and UO_2^{2+} Extraction Complexes $[(H_5O_2)(dicyclohexano\text{-}24\text{-}crown\text{-}8)]_2[UO_2Cl_4]\bullet MeOH$ and $[(H_5O_2)(dicyclohexano\text{-}24\text{-}crown\text{-}8)]_2[UCl_6]\bullet MeOH$," *J. Inclusion Phenom. Mol. Recognit. Chem.* **1991**, *11*, 121-135.
229. Rogers, R. D.; Bond, A. H.; Henry, R. F. "Structure of Ammonium *p*-Toluenesulfonate," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1991**, *C47*, 168-170.
230. Rogers, R. D.; Bond, A. H.; Hipple, W. G.; Rollins, A. N.; Henry, R. F. "Synthesis and Structural Elucidation of Novel Uranyl-Crown Ether Compounds Isolated from Nitric, Hydrochloric, Sulfuric, and Acetic Acids," *Inorg. Chem.* **1991**, *30*, 2671-2679.
231. Rogers, R. D.; Bond, A. H.; Witt, M. M. "Macrocycle Complexation Chemistry 34. Polyethylene Glycol and Glycolate Complexes of Th^{4+}. Preparation and Structural Characterization of $[ThCl_3(pentaethylene\ glycol)]Cl\bullet CH_3CN$ and the $(Th^{4+})_4$ Cluster, $[Th_4Cl_8(O)(tetraethylene\ glycolate)_3]\bullet 3CH_3CN$," *Inorg. Chim. Acta* **1991**, *182*, 9-17.
232. Rogers, R. D.; Etzenhouser, R. D.; Murdoch, J. S.; Reyes, E. "Macrocycle Complexation Chemistry. 35. Survey of the Complexation of the Open Chain 15-Crown-5 Analogue Tetraethylene Glycol with the Lanthanide Chlorides," *Inorg. Chem.* **1991**, *30*, 1445-1455.
233. Rogers, R. D.; Rollins, A. N.; Henry, R. F.; Murdoch, J. S.; Etzenhouser, R. D.; Huggins, S. E.; Nuñez, L. "Direct Comparison of the Preparation and Structural Features of Crown Ether and Polyethylene Glycol Complexes of $NdCl_3\bullet 6H_2O$," *Inorg. Chem.* **1991**, *30*, 4946-4954.
234. Rogers, R. D.; Weitl, F. L.; Kevill, D. N. "Structure of 1-(1-adamantyl)-5-(α-methylvinyl)tetrazole," *J. Crystallogr. Spectrosc. Res.* **1991**, *21*, 661-665.
235. Zaworotko, M. J.; Sturge, K. C.; Nunez, L.; Rogers, R. D. "Sterically Crowded Organometallics. Influence of Complexation upon the Conformation of Hexakis(phenylethyl)benzene," *Organometallics* **1991**, *10*, 1806-1810.
236. Burford, N.; Mason, S.; Spence, R. E. v. H.; Whalen, J. M.; Richardson, J. F.; Rogers, R. D. ""Genuine Heterocycles" from the Acid-Induced Cyclization of (Silylamino)(imino)(chalcogeno)phosphoranes and as a Result of Chloride Ion Abstraction from Bis[bis(trimethylsilyl)amino]thiophosphoryl Chloride," *Organometallics* **1992**, *11*, 2241-2250.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 22

IPR2020-00770
United Therapeutics EX2007
Page 3572 of 7335

237. Burford, N.; Spence, R. E. v. H.; Whalen, J. M.; Richardson, J. F.; Rogers, R. D. "Novel Cyclisations of the Chalcogeno-Phosphoryl Unit and the Formation of Genuine Heterocycles," *Phosphorus, Sulfur, and Silicon* **1992**, *64*, 137-144.
238. Gilbert, T. M.; Landes, A. M.; Rogers, R. D. "Synthesis and Electronic Properties of Triply Bonded Hexakis(fluoroalkoxy)dimolybdenum Complexes. Structure of $Mo_2[OCMe(CF_3)_2]_6$ and Investigation of the Nature of the Frontier Orbitals in Triply Bonded M_2X_6 Compounds," *Inorg. Chem.* **1992**, *31*, 3438-3444.
239. Nuñez, L.; Rogers, R. D. "Crystal Structure of [$PrCl_3$(15-crown-5)] Prepared via Electrocrystallization," *J. Crystallogr. Spectrosc. Res.* **1992**, *22*, 265-269.
240. Paquette, L. A.; Andrews, J. F. P.; Vanucci, C.; Lawhorn, D. E.; Negri, J. T.; Rogers, R. D. "Regio- and Stereochemical Course of the Ring Expansion of Bridged Bicyclic Ketones to Spirocyclic α-Keto Tetrahydrofurans," *J. Org. Chem.* **1992**, *57*, 3956-3965.
241. Paquette, L. A.; Branan, B. M.; Rogers, R. D. "X-ray Crystallographic Study of α-Brominated Diketo Tetraquinanes. Conformational Effects of the Number of Halogens and their Position on Bond Length and Solid-State Conformation," *Tetrahedron* **1992**, *48*, 297-306.
242. Paquette, L. A.; Elmore, S. W.; Combrink, K. D.; Hickey, E. R.; Rogers, R. D. "134. An Enantioselective Approach to the Taxanes: Direct Access to Functionalized *cis*-Tricyclo[9.3.1.$0^{3,8}$]pentadecanes *via* α-Hydroxy Ketone and *Wagner-Meerwein* Rearrangements," *Helv. Chim. Acta* **1992**, *75*, 1755-1771.
243. Paquette, L. A.; Kesselmayer, M. A.; Underiner, G. E.; House, S. D.; Rogers, R. D.; Meerholz, K.; Heinze, J. "Multifaceted Consequences of Holding Two [8] Annulene Rings Face-to-Face. Synthesis, Structural Characteristics, and Reduction Behavior of [2_2](1,5)Cyclooctatetraenophane," *J. Am. Chem. Soc.* **1992**, *114*, 2644-2652.
244. Paquette, L. A.; Negri, J. T.; Rogers, R. D. "Synthesis and Molecular Structure of Belted Spirocyclic Tetrahydrofurans, a New Class of Preorganized Hosts for Cations," *J. Org. Chem.* **1992**, *57*, 3947-3956.
245. Peterson, J. R.; Zjawiony, J. K.; Liu, S.; Hufford, C. D.; Clark, A. M.; Rogers, R. D. "Copyrine Alkaloids: Synthesis, Spectroscopic Characterization, and Antimycotic/Antimycobacterial Activity of A- and B-Ring-Functionalized Sampangines," *J. Med. Chem.* **1992**, *35*, 4069-4077.
246. Rogers, R. D.; Benning, M. M.; Etzenhouser, R. D.; Rollins, A. N. "Synthesis and Structural Characterization of the Monodentate 12-Crown-4 and Hexaethylene Glycol Complexes of Uranium(VI): $[UO_2Cl_2(OH_2)_2$(12-crown-4)]•12-crown-4 and $UO_2Cl_2(OH_2)_2$(hexaethylene glycol)," *J. Coord. Chem.* **1992**, *26*, 299-311.
247. Rogers, R. D.; Bond, A. H. "Crown Ether Complexes of Lead(II) Nitrate. Crystal Structures of the 12-Crown-4, 15-Crown-5, Benzo-15-Crown-5, and 18-Crown-6 Complexes," *Inorg. Chim. Acta* **1992**, *192*, 163-171.
248. Rogers, R. D.; Bond, A. H. "Structure of $[ThCl(OH)(OH_2)_6]_2Cl_4$•18-crown-6•$2H_2O$," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1992**, *C48*, 1199-1201.
249. Rogers, R. D.; Bond, A. H. "Structure of [Ca(triethylene glycol)$_2$]Cl_2•$4H_2O$," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1992**, *C48*, 1782-1785.
250. Rogers, R. D.; Bond, A. H.; Aguinaga, S. "Alcoholysis of $Bi(NO_3)_3$•$5H_2O$ by Polyethylene Glycols. Comparison with Bismuth(III) Nitrate Crown Ether Complexation," *J. Am. Chem. Soc.* **1992**, *114*, 2960-2967.
251. Rogers, R. D.; Bond, A. H.; Aguinaga, S.; Reyes, A. "Complexation Chemistry of Bismuth(III) Halides with Crown Ethers and Polyethylene Glycols. Structural Manifestations of a Stereochemically Active Lone Pair," *J. Am. Chem. Soc.* **1992**, *114*, 2967-2977.
252. Rogers, R. D.; Bond, A. H.; Hipple, W. G. "Synthesis and Crystal Structure of $[UO_2(NO_3)_2(OH_2)_2]$•2(benzo-15-crown-5)," *J. Crystallogr. Spectrosc. Res.* **1992**, *22*, 365-369.
253. Rogers, R. D.; Etzenhouser, R. D.; Murdoch, J. S. "Triethylene Glycol Complexes of the Early Lanthanide(III) Chlorides," *Inorg. Chim. Acta* **1992**, *196*, 73-79.
254. Rogers, R. D.; Henry, R. F. "Crystal Structure of $[CeCl(OH_2)_3$(EG4)]Cl_2•H_2O (EG4 = Tetraglyme)," *J. Crystallogr. Spectrosc. Res.* **1992**, *22*, 361-364.
255. Rogers, R. D.; Henry, R. F. "Structure of $[PrCl_3$(EO4)$]_2$," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1992**, *C48*, 1099-1101.
256. Rogers, R. D.; Henry, R. F.; Rollins, A. N. "Macrocycle Complexation Chemistry. 38. Crystallographic and Ultraviolet/Visible Characterization of Nitrobenzo-15-crown-5, Dinitrobenzo-15-crown-5, and Dinitrodibenzo-18-crown-6•$2CH_3CN$," *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, *13*, 219-232.
257. Rogers, R. D.; Huggins, S. E.; Henry, R. F.; Bond, A. H. "Arene-Substituent Effects in Benzo-15-crown-5 Complexes. The Crystal Structures of 4-Aminobenzo-15-crown-5 and $[KI(OH_2)$(4-nitrobenzo-15-crown-5)$]_2$," *Supramol. Chem.* **1992**, *1*, 59-63.
258. Alt, H. G.; Han, J. S.; Rogers, R. D. "Darstellung und Charakterisierung von Indenyl- und Fluorenylfunktionalisierten Cyclopentadienylcarbonyl-Methylkomplexen des Molybdäns und Wolframs. Molekülstrukturen von (η^5-$C_5H_4CMe_2C_9H_7$)M(CO)$_3$Me (M = Mo,W), (η^5-$C_5H_4CMe_2C_{13}H_9$)M(CO)$_3$Me und (η^5:η^2-$C_5H_4CMe_2C_9H_7$)Mo(CO)$_2$Me," *J. Organomet. Chem.* **1993**, *445*, 115-124.
259. Alt, H. G.; Han, J. S.; Rogers, R. D. "Photoinduzierte Desalkylierungsreaktionen an Indenyl- und Fluorenylfunktionalisierten Cyclopentadienyltricarbonyl-Methylkomplexen des Molybdäns und Wolframs. Molekülstrukturen von (η^5:η^1-$C_5H_4CMe_2C_9H_6$)Mo(CO)$_3$, (η^5:η^1- $C_5H_4CMe_2C_{13}H_8$)W(CO)$_3$, und [(η^5-$C_5H_4(CH_2)_3C_{13}H_9$)W(CO)$_3$]$_2$," *J. Organomet. Chem.* **1993**, *454*, 165-172.
260. Alt, H. G.; Han, J. S.; Rogers, R. D.; Thewalt, U. "Acetylenkomplexe des Wolframs. Molekülstrukturen von (η^5-

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 23

IPR2020-00770
United Therapeutics EX2007
Page 3573 of 7335

$C_5H_4CMe_2C_{13}H_9$)W(CO)(HC$_2$Ph)Me, (η^5:η^1-$C_5H_4CMe_2C_{13}H_8$)W(CO)(C$_2$Ph$_2$) und (η^5-C_5H_5)Cr(CO)(C$_2$H$_2$)NO; ein Vergleich von alkinischen Vier- und Zweielektronenliganden," *J. Organomet. Chem.* **1993**, *459*, 209-217.
261. Beachley, O. T., Jr.; Maloney, J. D.; Rogers, R. D. "Gallium and Indium Compounds Containing Three Different Substituents. Crystal and Molecular Structure of [(Me_3CCH_2)ClGaPPh$_2$]$_3$," *J. Organomet. Chem.* **1993**, *449*, 69-75.
262. Beachley, O. T., Jr.; Maloney, J. D.; Rogers, R. D. "Synthesis of [(Me_3CCH_2)Ga(PPh$_2$)$_2$]$_2$ from [(Me_3CCH_2)ClGaPPh$_2$]$_3$," *Organometallics* **1993**, *12*, 229-232.
263. Burford, N.; Losier, P.; Mason, S.; Royan, B. W.; Spence, R. E. v. H.; Bakshi, P. K.; Borecka, B.; Cameron, T. S.; Richardson, J. F.; Rogers, R. D. "The Stability of *Carbenic* and *Alkenic* Phosphorus Environments," *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *76*, 17-20.
264. Filippou, A. C.; Völkl, C.; Rogers, R. D. "Metal-Centered C-C Coupling of Nitriles with 1- Azaallyl Ligands; Synthesis and Structure of β-Diiminato Complexes of Tungsten," *J. Organomet. Chem.* **1993**, *463*, 135-142.
265. Gilbert, T. M.; Rogers, R. D. "Structure of [W$_2$(μ-C$_2$){OC(CH_3)$_3$}$_6$]: a Dimetallabutadiyne," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1993**, *C49*, 677-680.
266. Hadley, F. J.; Gilbert, T. M.; Rogers, R. D. "Crystal Structures of (η^6-C_7H_8)M(CO)$_3$ (M = Cr, W). Comparisons Among a Homologous Series of Cycloheptatriene Complexes and Experimental Evidence for a Boat Conformation of the Coordinated Ring," *J. Organomet. Chem.* **1993**, *455*, 107-113.
267. Heeres, H. J.; Nijhoff, J.; Teuben, J. H.; Rogers, R. D. "Reversible Carbon-Carbon Bond Formation in Organolanthanide Systems. Preparation and Properties of Lanthanide Acetylides [Cp*$_2$LnC/CR]$_n$ and Their Rearrangement Products [Cp*$_2$Ln]$_2$(μ-η^2:η^2-RC_4R) (Ln = La, Ce, R = alkyl)," *Organometallics* **1993**, *12*, 2609-2617.
268. Horwitz, E. P.; Dietz, M. L.; Diamond, H.; Rogers, R. D.; Leonard, R. A. "Advanced Chemical Separations in Support of the Clean Option Strategy," In *International Conference and Technology Exhibition on Future Nuclear Systems: Emerging Fuel Cycles and Waste Disposal Options Global '93*, American Nuclear Society, Inc.: La Grange Park, IL, 1993; Vol. 1; pp 39-43.
269. Horwitz, E. P.; Dietz, M. L.; Diamond, H.; Rogers, R. D.; Leonard, R. A. "Combined TRU-Sr Extraction/Recovery Process," In *Solvent Extraction in the Process Industries, Proceedings of ISEC '93*; Logsdail, D. H.; Slater, M. J., Eds.; Elsevier: London, 1993; Vol. 3; pp 1805-1812.
270. Hufford, C. D.; Jia, Y.; Croom, E. M., Jr.; Muhammed, I.; Okunade, A. L.; Clark, A. M.; Rogers, R. D. "Antimicrobial Compounds from *Petalostemum purpureum*," *J. Nat. Prod.* **1993**, *56*, 1878-1889.
271. Nuñez, L.; Rogers, R. D. "Utilization of Crown Ether Chemistry to Prepare Bimetallic Compounds: Preparation and Structural Characterization of [Ba(15-crown-5)$_2$][$CuCl_4$]," *J. Coord. Chem.* **1993**, *28*, 347-354.
272. Rogers, R. D.; Alt, H. G. "Crystal Structure of Cr(CO)$_5$($NHMe_2$)," *J. Crystallogr. Spectrosc. Res.* **1993**, *23*, 533-535.
273. Rogers, R. D.; Bauer, C. B. "Crystal Structures of [Gd_6(O)(OH)$_8$(NO_3)$_6$(OH_2)$_{12}$][NO_3]$_2$•2H_2O and [NH_4]$_2$[Yb_6(O)(OH)$_8$(NO_3)$_7$(OH_2)$_{10}$][NO_3]$_3$•H_2O," *J. Crystallogr. Spectrosc. Res.* **1993**, *23*, 537-545.
274. Rogers, R. D.; Bond, A. H.; Aguinaga, S. "Synthesis and Crystallographic Characterization of [Cd(OH_2)$_2$(μ-Br)$_4$(Cd(2-hydroxyethyl sulfide)(μ-Br))$_2$]$_n$," *J. Crystallogr. Spectrosc. Res.* **1993**, *23*, 857-862.
275. Rogers, R. D.; Bond, A. H.; Aguinaga, S.; Reyes, A. "Polyethylene Glycol Complexation of Cd^{2+}. Structures of Triethylene Glycol Complexes of $CdCl_2$, $CdBr_2$ and CdI_2," *Inorg. Chim. Acta* **1993**, *212*, 225-231.
276. Rogers, R. D.; Bond, A. H.; Bauer, C. B. "Aqueous Biphase Systems for Liquid/Liquid Extraction of f-Elements Utilizing Polyethylene Glycols," *Sep. Sci. Technol.* **1993**, *28*, 139-153.
277. Rogers, R. D.; Bond, A. H.; Bauer, C. B. "The Crown Ether Extraction of Group 1 and 2 Cations in Polyethylene Glycol-Based Aqueous Biphasic Systems at High Alkalinity," *Pure Appl. Chem.* **1993**, *65*, 567-572.
278. Rogers, R. D.; Bond, A. H.; Bauer, C. B. "Metal Ion Separations in Polyethylene Glycol-Based Aqueous Biphasic Systems," *Sep. Sci. Technol.* **1993**, *28*, 1091-1126.
279. Rogers, R. D.; Bond, A. H.; Bauer, C. B. "Polyethylene Glycol-Based Aqueous Biphasic Systems for Liquid/Liquid Extraction of Environmentally Toxic Heavy Metals," In *Solvent Extraction in the Process Industries, Proceedings of ISEC '93*; Logsdail, D. H.; Slater, M. J., Eds.; Elsevier: London, 1993; Vol. 3; pp 1641-1648.
280. Rogers, R. D.; Bond, A. H.; Wolff, J. L. "Structural Studies of Polyether Coordination to Mercury(II) Halides: Crown Ether versus Polyethylene Glycol Complexation," *J. Coord. Chem.* **1993**, *29*, 187-207.
281. Rogers, R. D.; Henry, R. F.; Ochrymowycz, L. A.; Toske, S. G. "The Improved Synthesis and Crystal Structure of 20-Thiocrown-4," *J. Inclusion Phenom. Mol. Recognit. Chem.* **1993**, *15*, 145-152.
282. Rogers, R. D.; Macomber, D. W.; Liang, M. "Crystal Structure of a (μ-Bis(carbene))dimetal Complex of Tungsten," *J. Crystallogr. Spectrosc. Res.* **1993**, *23*, 623-628.
283. Rogers, R. D.; Rollins, A. N.; Etzenhouser, R. D.; Voss, E. J.; Bauer, C. B. "Structural Investigation into the Steric Control of Polyether Complexation in the Lanthanide Series: Macrocyclic 18-Crown-6 versus Acyclic Pentaethylene Glycol," *Inorg. Chem.* **1993**, *32*, 3451-3462.
284. Rogers, R. D.; Sivik, M. R.; Paquette, L. A. "Isodicyclopentadienes and Related Molecules LVII. Solid State Structural Studies of the Diastereomeric *exo*- and *endo*-(η^5-Cyclopentadienyl)(η^5-1*S*,8*R*)-9,9-dimethyltricyclo[6.1.1.0^{2,6}]deca-2,5-dienyl)dichlorotitaniums and a Stereopure *exo*-(η^5-Pentamethyl-cyclopentadienyl) Congener," *J. Organomet. Chem.* **1993**, *450*, 125-135.
285. Sangokoya, S. A.; Pennington, W. T.; Byers-Hill, J.; Robinson, G. H.; Rogers, R. D. "Toward Unusual Al-O Compounds. Synthesis and Molecular Structure of [Al_4O(OCH_2CF_3)$_{11}$]$^-$: Structural Characterization of a Novel Al_4O_{12} Cluster," *Organometallics* **1993**, *12*, 2429-2431.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 24

IPR2020-00770
United Therapeutics EX2007
Page 3574 of 7335

286. Donaldson, W. A.; Shang, L.; Rogers, R. D. "Reactivity of Tricarbonyl(pentadienyl)iron(1+) Cations: Preparation of an Optically Pure Tricarbonyl(diene)iron Complex via Second-Order Asymmetric Transformation," *Organometallics* **1994**, *13*, 6-7.
287. Fierro, R.; Rausch, M. D.; Rogers, R. D.; Herberhold, M. "New Sulfur and Selenium Derivatives of (η^5-Cyclopentadienyl)(η^7-cycloheptatrienyl)titanium, and Their Application in the Syntheses of Heterobimetallic Compounds," *J. Organomet. Chem.* **1994**, *472*, 87-95.
288. Gilbert, T. M.; Bond, A. H.; Rogers, R. D. "Structures of a Series of [4-R-C_6H_4-CH(OR')$_2$]Cr(CO)$_3$ Complexes: Evidence Against a Favored Carbonyl Orientation in (*Para*-disubstituted Arene)chromium Tricarbonyl Compounds," *J. Organomet. Chem.* **1994**, *479*, 73-86.
289. Gilbert, T. M.; Hadley, F. J.; Bauer, C. B.; Rogers, R. D. "Organotransition Metal Compounds for Photonics: Syntheses and Structures of a Series of (Nitrostilbene)chromium Tricarbonyl Complexes," *Organometallics* **1994**, *13*, 2024-2034.
290. Gilbert, T. M.; Rogers, R. D. "Structures of Z-(Nitrostilbene)chromium Tricarbonyl Complexes: The Effect of Metal Coordination on the Nonplanarity of the Stilbene System," *J. Chem. Crystallogr.* **1994**, *24*, 315-320.
291. Hasinoff, L.; Takats, J.; Zhang, X. W.; Bond, A. H.; Rogers, R. D. "Application of the Sterically Demanding Hydrotris(3-*tert*-butyl-5-methylpyrazolyl)borate Ligand to Ln(II) Chemistry: Synthesis of a New Class of Mixed-Ligand Yb(II) Complexes," *J. Am. Chem. Soc.* **1994**, *116*, 8833-8834.
292. Ji, Z. P.; Rogers, R. D. "Structure of [La(NO_3)$_3$(OH_2)$_2$(OHMe)(bipy)]•15-crown-5," *J. Chem. Crystallogr.* **1994**, *24*, 415-419.
293. Ji, Z. P.; Rogers, R. D. "The Synthesis and Crystal Structure of [La(OH_2)$_5$(phen)$_2$]Cl_3•4H_2O•phen," *J. Chem. Crystallogr.* **1994**, *24*, 797-800.
294. Khalifa, S. I.; Baker, J. K.; Rogers, R. D.; El-Feraly, F. S.; Hufford, C. D. "Microbial and Mammalian Metabolism Studies of the Semisynthetic Antimalarial, Anhydrodihydroartemisinin," *Pharm. Res.* **1994**, *11*, 990-994.
295. O'Doherty, G. A.; Rogers, R. D.; Paquette, L. A. "Consequences of Modulated Precompression along Reaction Coordinates. Synthesis, Crystallographic Structural Studies, and Rate of Intramolecular Dyotropy in an Extended Series of *syn*-Sesquinorbornene Disulfones," *J. Am. Chem. Soc.* **1994**, *116*, 10883-10894.
296. Okunade, A. L.; Liu, S.; Clark, A. M.; Hufford, C. D.; Rogers, R. D. "Sesquiterpene Lactones from *Peucephyllum schottii*," *Phytochemistry* **1994**, *35*, 191-194.
297. Paquette, L. A.; Branan, B. M.; Friedrich, D.; Edmondson, S. D.; Rogers, R. D. "Analysis of the Conformational Nature, Resolvability, and Thermal Racemization of Hetero 2,3-Dispiro Cyclohexanones. The Weighting of Carbonyl/C-X Stabilization Relative to the Electronic Interaction between the Vicinal Electronegative Substituents," *J. Am. Chem. Soc.* **1994**, *116*, 506-513.
298. Rogers, R. D.; Adrowski, M. J.; Bond, A. H. "Crystal Structure of Pt(S_2COEt)$_2$," *J. Chem. Crystallogr.* **1994**, *24*, 707-710.
299. Rogers, R. D.; Bauer, C. B. "Structure of Diethylenetriammonium Nitrate," *J. Chem. Crystallogr.* **1994**, *24*, 281-283.
300. Rogers, R. D.; Bauer, C. B. "Crystal Structure of Pyridinium Hydrogen Sulfate, [HC_5H_5N][HSO_4]," *J. Chem. Crystallogr.* **1994**, *24*, 285-287.
301. Rogers, R. D.; Bauer, C. B.; Bond, A. H. "Crown Ethers as Actinide Extractants in Acidic Aqueous Biphasic Systems: Partitioning Behavior in Solution and Crystallographic Analyses of the Solid State," *J. Alloys Compd.* **1994**, *213/214*, 305-312.
302. Rogers, R. D.; Jezl, M. L. "Ammonium Heptachlorooxodiantimonate(III), (NH_4)$_3$[Sb_2Cl_7O]," *Acta Crystallogr., Sect. C. Cryst. Struct. Commun.* **1994**, *C50*, 1527-1529.
303. Rogers, R. D.; Jezl, M. L.; Bauer, C. B. "Effects of Polyethylene Glycol on the Coordination Sphere of Strontium in $SrCl_2$ and Sr(NO_3)$_2$ Complexes," *Inorg. Chem.* **1994**, *33*, 5682-5692.
304. Rogers, R. D.; Rollins, A. N. "Primary to Secondary Sphere Coordination of 18-Crown-6 to Lanthanide(III) Nitrates: Structural Analysis of [Pr(NO_3)$_3$(18-crown-6)] and [M(NO_3)$_3$(OH_2)$_3$]•18-crown-6 (M = Y, Eu, Tb-Lu)," *J. Chem. Crystallogr.* **1994**, *24*, 321-329.
305. Rogers, R. D.; Rollins, A. N. "Primary to Secondary Sphere Coordination of 15-Crown-5 to Lanthanide(III) Chlorides: Structural Analysis of [MCl_3(15-crown-5)] (M = La, Ce) and [Er(OH_2)$_8$]Cl_3•15-crown-5," *J. Chem. Crystallogr.* **1994**, *24*, 531-537.
306. Bauer, C. B.; Rogers, R. D.; Nuñez, L.; Ziemer, M. D.; Pleune, T. T.; Vandegrift, G. F.; "Review and Evaluation of Extractants for Strontium Removal Using Magnetically Assisted Chemical Separation," Report ANL-95/26, Argonne National Laboratory: Argonne, IL 1995; 25 pp.
307. Beachley, O. T., Jr.; Maloney, J. D.; Banks, M. A.; Rogers, R. D. "Synthesis and Characterization of a Series of Organoindium Phosphides, Including Molecular Structures of [(Me_3CCH_2)$_2$InPEt_2]$_2$ and [(Me_3CCH_2)$_2$InP(H)(C_6H_{11})]$_3$," *Organometallics* **1995**, *14*, 3448-3454.
308. Black, D. G.; Swenson, D. C.; Jordan, R. F.; Rogers, R. D. "Tetraaza Macrocycles as Ancillary Ligands in Early Metal Alkyl Chemistry. Synthesis and Characterization of Out-of-Plane (Me_4taen)ZrX_2 (X = Alkyl, Benzyl, NMe_2, Cl) and (Me_4taen)ZrX_2($NHMe_2$) (X = Cl, CCPh) Complexes," *Organometallics* **1995**, *14*, 3539-3550.
309. Bowen, D. E.; Jordan, R. F.; Rogers, R. D. "Group 4 Metal Mono-Dicarbollide Piano Stool Complexes. Synthesis, Structure, and Reactivity of (η^5-$C_2B_9H_{11}$)M(NR_2)$_2$(NHR_2) (M = Zr, R = Et; M = Ti, R = Me, Et)," *Organometallics* **1995**, *14*, 3630-3635.
310. Dietz, M. L.; Horwitz, E. P.; Rogers, R. D. "Extraction of Strontium from Acidic Nitrate Media Using a Modified PUREX Solvent," *Solvent Extr. Ion Exch.* **1995**, *13*, 1-17.
311. Feil-Jenkins, J. F.; Nash, K. L.; Rogers, R. D. "Lanthanide Complexes with Tetrahydrofuran-2,3,4,5-tetracarboxylic Acid: The Effect of Ligand Rigidity on Cation Size-Selectivity," *Inorg. Chim. Acta* **1995**, *236*, 67-74.
312. Fu, W.; McDonald, R.; Takats, J.; Bond, A. H.; Rogers, R. D. "Cycloheptatrienyl bridged heterobimetallic complexes: fluxional behavior and X-ray crystal structure of *syn*-(μ^3:η^2-C_7H_7)Fe(CO)$_3$Pd(η^3-C_3H_5)," *Inorg. Chim. Acta* **1995**, *229*, 307-313.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 25

IPR2020-00770
United Therapeutics EX2007
Page 3575 of 7335

313. Galindo, A.; Gutiérrez, E.; Monge, A.; Paneque, M.; Pastor, A.; Pérez, P. J.; Rogers, R. D.; Carmona, E. "Dinitrogen, Butadiene and Related Complexes of Molybdenum. Crystal Structures of $Mo(N_2)(PMe_3)_5$ and $[Mo(\eta^3\text{-}CH_3CHCHCH_2)(\eta^4\text{-}C_4H_6)(PEt_3)_2][BF_4]$," *J. Chem. Soc., Dalton Trans.* **1995**, 3801-3808.
314. Horwitz, E. P.; Dietz, M. L.; Diamond, H.; Rogers, R. D.; Leonard, R. A. "Combined TRUEX-SREX Extraction/Recovery Process," In *Chemical Pretreatment of Nuclear Waste for Disposal*; Schulz, W. W.; Horwitz, E. P., Eds.; Plenum: New York, 1995; pp 81-99.
315. Hufford, C. D.; Khalifa, S. I.; Orabi, K. Y.; Wiggers, F. T.; Kumar, R.; Rogers, R. D.; Campana, C. F. "1α-Hydroxyarteether, a New Microbial Transformation Product," *J. Nat. Prod.* **1995**, *58*, 751-755.
316. Paquette, L. A.; Branan, B. M.; Rogers, R. D. "High-Pressure Diels-Alder Reactions of 1-Oxa[4.4.4]propella-5,7-diene Proceed with Framework Isomerization," *J. Org. Chem.* **1995**, *60*, 1852-1855.
317. Paquette, L. A.; Branan, B. M.; Rogers, R. D.; Bond, A. H.; Lange, H.; Gleiter, R. "Heteroatomic Influences on the π-Facial Selectivity of Diels-Alder Cycloadditions to Dispiro[4.0.4.4]tetradeca-11,13-dienes," *J. Am. Chem. Soc.* **1995**, *117*, 5992-6001.
318. Peterson, J. R.; Zjawiony, J. K.; Clark, A. M.; Hufford, C. D.; Rogers, R. D. "Antifungal Copyrine Alkaloids: Crystal Structure of 3-Methylsampangine," *J. Chem. Crystallogr.* **1995**, *25*, 223-226.
319. Rogers, R. D.; Bauer, C. B.; Bond, A. H. "Novel Polyethylene Glycol-Based Aqueous Biphasic Systems for the Extraction of Strontium and Cesium," *Sep. Sci. Technol.* **1995**, *30*, 1203-1217.
320. Rogers, R. D.; Bond, A. H.; Bauer, C. B.; Zhang, J.; Jezl, M. L.; Roden, D. M.; Rein, S. D.; Chomko, R. R. "Metal Ion Separations in Polyethylene Glycol-Based Aqueous Biphasic Systems," In *Aqueous Biphasic Separations: Biomolecules to Metal Ions*; Rogers, R. D.; Eiteman, M. A., Eds.; Plenum: New York, 1995; pp 1-20.
321. Rogers, R. D.; Bond, A. H.; Bauer, C. B.; Zhang, J.; Rein, S. D.; Chomko, R. R.; Roden, D. M. "Partitioning Behavior of ^{99}Tc and ^{129}I from Simulated Hanford Tank Wastes Using Polyethylene Glycol-Based Aqueous Biphasic Systems," *Solvent Extr. Ion Exch.* **1995**, *13*, 689-713.
322. Rogers, R. D.; Bond, A. H.; Henry, R. F.; Rollins, A. N. "The Effects of Methylene-Substituents in Crown Ether Backbones. Crystal Structures of $[Na(OH_2)$(methylene-16-crown-5)]I, $[Na(NO_2)$(methylene-16-crown-5)]•0.5(H_2O), 3,16-Dimethylene-26-crown-8, $[Na_4I_4$(3,16-dimethylene-26-crown-8)], and $[Na_2(OH_2)_4$(3,16-dimethylene-26-crown-8)]I_2," *Supramol. Chem.* **1995**, *4*, 191-202.
323. Rogers, R. D.; Rollins, A. N. "Mixed Anion Lanthanide(III) Crown Ether Complexes: Crystal Structures of $[LaCl_2(NO_3)$(12-crown-4)]$_2$, $[La(NO_3)(OH_2)_4$(12-crown-4)]Cl_2•CH_3CN and $[LaCl_2(NO_3)$(18-crown-6)]," *Inorg. Chim. Acta* **1995**, *230*, 177-183.
324. Rogers, R. D.; Rollins, A. N.; Gatrone, R. C.; Horwitz, E. P. "Comparison of the Crystal Structure and Molecular Models of N-N-Diisobutyl-2-(octylphenylphosphinyl)acetamide (CMPO)," *J. Chem. Crystallogr.* **1995**, *25*, 43-49.
325. Rogers, R. D.; Song, Y. "Crystal Structure Analyses of Two Crown Ether Complexes of Copper(II) Nitrate: $[Cu(NO_3)_2$(12-crown-4)] and $[Cu(OH_2)_2$(15-crown-5)]$[NO_3]_2$," *J. Coord. Chem.* **1995**, *34*, 149-157.
326. Rogers, R. D.; Song, Y. "The Crystal Structure of a Heterobimetallic Crown Ether Complex: [Na(dibenzo-18-crown-6)]$[FeCl_4]$," *J. Chem. Crystallogr.* **1995**, *25*, 579-582.
327. Rogers, R. D.; Zhang, J.; Bond, A. H.; Bauer, C. B.; Jezl, M. L.; Roden, D. M. "Selective and Quantitative Partitioning of Pertechnetate in Polyethylene Glycol-Based Aqueous Biphasic Systems," *Solvent Extr. Ion Exch.* **1995**, *13*, 665-688.
328. Whitcomb, D. R.; Rogers, R. D. "The Properties, Crystal, and Molecular Structure of Catena-[(μ-actetato-)(μ-phthalazine)silver(I)dihydrate]: $\{[Ag(\mu\text{-}O_2CCH_3)(\mu\text{-PHZ})(H_2O)_2]_2\}_n$," *J. Chem. Crystallogr.* **1995**, *25*, 137-142.
329. Beachley, O. T., Jr.; Banks, M. A.; Kopasz, J. P.; Rogers, R. D. "Main Group Compounds as Amphoteric Ligands to Transition Metals. Synthesis and Molecular Structure of $Cr(CO)_5[PPhCH_2Ga(CH_2CMe_3)_2$•$NMe_3]$," *Organometallics* **1996**, *15*, 5170-5174.
330. Blair, J. T.; Patel, R. C.; Rogers, R. D.; Whitcomb, D. W. "The Molecular Structure of [bis-(2- (Tribromomethylsulfonyl-benzothiazole)-silver(I)-tetrafluroborate•(acetone)] $[Ag\{(C_7H_4NS)SO_2CBr_3\}_2BF_4$•$Me_2CO]$: A Possible Model for Bromine Elimination of Silver Halide Fog Centers," *J. Imaging Sci. Technol.* **1996**, *40*, 117-122.
331. Brechbiel, M. W.; Gansow, O. A.; Pippin, C. G.; Rogers, R. D.; Planalp, R. P. "Preparation of the Novel Chelating Agent *N*-(2-Aminoethyl)-*trans*-1,2-diaminocyclohexane-*N,N′,N″*-pentaacetic Acid (H_5CyDTPA), a Preorganized Analogue of Diethylenetriaminepentaacetic Acid (H_5DTPA), and the Structures of $Bi^{III}(CyDTPA)^{2-}$ and $Bi^{III}(H_2DTPA)$ Complexes," *Inorg. Chem.* **1996**, *35*, 6343-6348.
332. Brogan, J. B.; Bauer, C. B.; Rogers, R. D.; Zercher, C. K. "Selectivity in the Rearrangements of Oxonium Ylides," *Tetrahedron Lett.* **1996**, *37*, 5053-5056.
333. Chen, M. J.; Nuñez, L.; Rathke, J. W.; Rogers, R. D. "Hydrido(1,4,8,11,15,18,22,25-octa-*n*- pentylphthalocyanato)-rhodium Dimers: Single-Crystal X-ray Structure, and the Isomerization of the Four Isomers," *Organometallics* **1996**, *15*, 2338-2344.
334. Cooke, J.; McClung, R. E. D.; Takats, J.; Rogers, R. D. "Synthesis, Characterization, and Dynamic Behavior of $Os_2Pt(CO)_8(PPh_3)_2$: A Trinuclear Osmium-Platinum Cluster with Flexible Metal Framework," *Organometallics* **1996**, *15*, 4459-4468.
335. Fettinger, J. C.; Mattamana, S. P.; Poli, R.; Rogers, R. D. "Accessibility of 17-Electron Structures for Cyclopentadienylchromium(III) Compounds. 1. Experimental Studies on the Dichloride and Dimethyl Compounds," *Organometallics* **1996**, *15*, 4211-4222.
336. Gilbert, T. M.; Bauer, C. B.; Rogers, R. D. "Structures of (η^6-Benzene dimethylacetal)- and (η^6-Benzene diethylacetal)chromium Tricarbonyl: Structural Evidence for the Near-Electroneutrality of the Dialkylacetal Substituent," *J. Chem. Crystallogr.* **1996**, *26*, 355-360.
337. Gilbert, T. M.; Hadley, F. J.; Simmons, M. D.; Bauer, C. B.; Rogers, R. D. "Syntheses and Structures of

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 26

IPR2020-00770
United Therapeutics EX2007
Page 3576 of 7335

Bis(tricarbonylchromium)-Substituted α, ω-Diphenylhexatriene Complexes," *J. Organomet. Chem.* **1996**, *510*, 83-92.
338. Ji, Z. P.; Rogers, R. D. "The Crystal Structure and Supramolecular Chain of $[La(NO_3)_3(OH_2)_2(phen)]$•15-crown-5," *J. Chem. Crystallogr.* **1996**, *26*, 573-577.
339. Johnson, C. P.; Atwood, J. L.; Steed, J. W.; Bauer, C. B.; Rogers, R. D. "Transition Metal Complexes of *p*-Sulfanatocalix[5]arene," *Inorg. Chem.* **1996**, *35*, 2602-2610.
340. Melendez, R. E.; Sharma, C. V. K.; Zaworotko, M. J.; Bauer, C.; Rogers, R. D. "Toward the Design of Porous Organic Solids: Modular Honeycomb Grids Sustained by Anions of Trimesic Acid," *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2213-2215.
341. Paquette, L. A.; Morwick, T. M.; Negri, J. T.; Rogers, R. D. "Addition of 2,3-Dihydro-5-furanyllithium to Diisopropyl Squarate as a Means for the Rapid Generation of Structurally Complex Oxygen-Containing Tetraquinane Networks," *Tetrahedron* **1996**, *52*, 3075-3094.
342. Paquette, L. A.; Stephanian, M.; Branan, B. M.; Edmondson, S. D.; Bauer, C. B.; Rogers, R. D. "Conformational Analysis of Poly(spirotetrahydrofuranyl)cyclohexyl Systems. The Preference of Multiple C-O Bonds for Equatorial Occupancy," *J. Am. Chem. Soc.* **1996**, *118*, 4504-4505.
343. Rogers, R. D. "The Crystal and Molecular Structure of $[\eta^5\text{-}C_5H_3(SiMe_3)_2]_2Yb(THF)$," *J. Organomet. Chem.* **1996**, *512*, 97-100.
344. Rogers, R. D.; Bauer, C. B. "Water Soluble Calixarenes as Possible Metal Ion Extractants in Polyethylene Glycol-Based Aqueous Biphasic Systems," *J. Radioanal. Nucl. Chem.* **1996**, *208*, 153-161.
345. Rogers, R. D.; Bauer, C. B. "Partitioning Behavior of Group 1 and 2 Cations in Polyethylene Glycol-Based Aqueous Biphasic Systems," *J. Chromatogr., B: Biomed. Appl.* **1996**, *680*, 237-242.
346. Rogers, R. D.; Bauer, C. B. "Structural Chemistry of Metal-Crown Ether and Polyethylene Glycol Complexes Excluding Group 1 and 2," In *Comprehensive Supramolecular Chemistry*; Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D.; Vögtle, F., Exec. Eds., Lehn, J. M., Chair. Ed. Bd., Vol. I, *Molecular Recognition: Receptors for Cationic Guests*; Gokel, G. W., Ed.; Pergamon: Exeter, 1996; pp 315-355.
347. Rogers, R. D.; Bond, A. H. "Crown Ether Mediated Cadmium Halide Dimers and Polymers," *Inorg. Chim. Acta* **1996**, *250*, 105-117.
348. Rogers, R. D.; Bond, A. H.; Bauer, C. B.; Griffin, S. T.; Zhang, J. "Polyethylene Glycol-Based Aqueous Biphasic Systems for Extraction and Recovery of Dyes and Metal/Dye Complexes," In: *Value Adding through Solvent Extraction Proceedings of ISEC'96*; Shallcross, D. C.; Paiman, R.; Prvcic, L. M. Eds.; The University of Melbourne: Parkville, Victoria, Australia, 1996; Vol. 2; pp 1537-1542.
349. Rogers, R. D.; Bond, A. H.; Bauer, C. B.; Zhang, J.; Griffin, S. T. "Metal Ion Separations in Polyethylene Glycol-Based Aqueous Biphasic Systems: Correlation of Partitioning Behavior with Available Thermodynamic Hydration Data," *J. Chromatogr., B: Biomed. Appl.* **1996**, *680*, 221-230.
350. Rogers, R. D.; Bond, A. H.; Griffin, S. T.; Horwitz, E. P. "New Technologies for Metal Ion Separations: Aqueous Biphasic Extraction Chromatography (ABEC). Part I. Uptake of Pertechnetate," *Solvent Extr. Ion Exch.* **1996**, *14*, 919-946.
351. Rogers, R. D.; Bond, A. H.; Roden, D. M. "Structural Chemistry of Poly(ethylene glycol) Complexes of Lead(II) Nitrate and Lead(II) Bromide," *Inorg. Chem.* **1996**, *35*, 6964-6973.
352. Rogers, R. D.; Bond, A. H.; Zhang, J.; Bauer, C. B. "Polyethylene Glycol Based-Aqueous Biphasic Systems as Technetium-99m Generators," *Appl. Radiat. Isotop.* **1996**, *47*, 497-499.
353. Rogers, R. D.; Zhang, J. "Effects of Increasing Polymer Hydrophobicity on Distribution Ratios of TcO_4^- in Polyethylene/Polypropylene Glycol-Based Aqueous Biphasic Systems," *J. Chromatogr., B: Biomed. Appl.* **1996**, *680*, 231-236.
354. Schulz, S.; Gillan, E. G.; Ross, J. L.; Rogers, L. M.; Rogers, R. D.; Barron, A. R. "Synthesis of Gallium Chalcogenide Cubanes and Their Use as CVD Precursors for Ga_2E_3 (E = S, Se)," *Organometallics* **1996**, *15*, 4880-4883.
355. Steed, J. W.; Tocher, D. A.; Rogers, R. D. "Ruthenium Mediated Cyclodimerisation of Buta-1,3-diene," *Chem. Commun.* **1996**, 1589-1590.
356. Tsai, W.-M.; Rausch, M. D.; Rogers, R. D. "Improved Synthesis of Pentabenzylcyclopentadiene and Study of the Reaction between Pentabenzylcyclopentadiene and Iron Pentacarbonyl," *Organometallics* **1996**, *15*, 2591-2594.
357. Whitcomb, D. R.; Rogers, R. D. "The Molecular Structure of [*bis*-Triphenylphosphine-silver(I)stearate], $[((C_6H_5)_3P)_2Ag(O_2C(CH_2)_{16}CH_3)]$, Solubilization of Long Alkyl Chain Silver Carboxylates," *J. Chem. Crystallogr.* **1996**, *26*, 99-105.
358. Zhao, H.; Heintz, R. A.; Dunbar, K. R.; Rogers, R. D. "Unprecedented Two-Dimensional Polymers of Mn(II) with $TCNQ^{\bullet}$ (TCNQ = 7,7,8,8-Tetracyanoquinodimethane)," *J. Am. Chem. Soc.* **1996**, *118*, 12844-12845.
359. Zong, K.; Chen, W.; Cava, M. P.; Rogers, R. D. "Synthesis and Properties of Bis(2,5-dimethylpyrrolo[3,4-*d*])tetrathiafulvalenes, a Class of Annelated Tetrathiafulvalene Derivatives with Excellent Donor Properties," *J. Org. Chem.* **1996**, *61*, 8117-8124.
360. Adams, R. D.; McBride, K. T.; Rogers, R. D. "A New Route to Polyselenoether Macrocycles. Catalytic Macrocyclization of 3,3-Dimethylselenatane by $Re_2(CO)_9SeCH_2CMe_2CH_2$," *Organometallics* **1997**, *16*, 3895-3901.
361. Beachley, O. T., Jr.; Maloney, J. P.; Rogers, R. D. "Cyclopentadiene Elimination Reaction as a Route to Bis(neopentyl)gallium Phosphides. Crystal and Molecular Structures of $[(Me_3CCH_2)_2GaPEt_2]_2$ and $[(Me_3CCH_2)_2GaP(C_6H_{11})_2]_2$," *Organometallics* **1997**, *16*, 3267-3272.
362. Black, D. G.; Jordan, R. F.; Rogers, R. D. "Structural Trends in Group 4 Metal Tetraaza Macrocycle Complexes. Molecular Structures of $(Me_4taen)Zr(OtBu)_2$ and $(Me_4taen)Hf(NMe_2)_2$," *Inorg. Chem.* **1997**, *36*, 103-108.
363. Bodige, S. G.; Rogers, R. D.; Blackstock, S. C. "Supramolecular Networks *via* Pyridine *N*-oxide CH•••O Hydrogen Bonding in the Crystal Structures of 2,2'-Dithiobis(pyridine *N*-oxide) and its Complexes with 1,2,4,5-Tetracyanobenzene and Pyromellitic

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 27

IPR2020-00770
United Therapeutics EX2007
Page 3577 of 7335

Dianhydride," *Chem. Commun.* **1997**, 1669-1670.
364. Brogan, J. B.; Zercher, C. K.; Bauer, C. B.; Rogers, R. D. "Study of the Rearrangements of Oxonium Ylides Generated from Ketals," *J. Org. Chem.* **1997**, *62*, 3902-2909.
365. Greer, M. L.; McGee, B. J.; Rogers, R. D.; Blackstock, S. C. "Pyrazinedioxide - Tetracyanoethylene Arrays in the Solid State - New Donor-Acceptor Interactions for Crystal Engineering," *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1864-1866.
366. Hennigar, T. L.; MacQuarrie, D. C.; Losier, P.; Rogers, R. D.; Zaworotko, M. J. "Supramolecular Isomerism in Coordination Polymers: Conformational Freedom of Ligands in $[Co(NO_3)_2(1,2\text{-bis}(4\text{-pyridyl})ethane)_{1.5}]_n$," *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 972-973.
367. Hilfiker, K. A.; Brechbiel, M. W.; Rogers, R. D.; Planalp, R. P. "Tricationic Metal Complexes ($[ML][NO_3]_3$, M = Ga, In) of *N*,*N*',*N*"-Tris(2-pyridylmethyl)-*cis*-1,3,5-triaminocyclohexane: Preparation and Structure," *Inorg. Chem.* **1997**, *36*, 4600-4603.
368. Kim, I.; Nishihara, Y.; Jordan, R. F.; Rogers, R. D.; Rheingold, A. L.; Yap, G. P. A. "Synthesis, Structures, Dynamics, and Olefin Polymerization Behavior of Group 4 Metal $(pyCAr_2O)_2M(NR_2)_2$ Complexes Containing Bidentate Pyridine-Alkoxide Ancillary Ligands," *Organometallics* **1997**, *16*, 3314-3323.
369. Luckay, R.; Cukrowski, I.; Mashishi, J.; Reibenspies, J. H.; Bond, A. H.; Rogers, R. D.; Hancock, R. D. "Synthesis, Stability and Structure of the Complex of Bismuth(III) with the Nitrogen-Donor Macrocycle 1,4,7,10-Tetraazacyclododecane. The Role of the Lone Pair on Bismuth(III) and Lead(II) in Determining Coordination Geometry," *J. Chem. Soc., Dalton Trans.* **1997**, 901-908.
370. McChesney, J. D.; Dou, J.; Sindelar, R. D.; Goins, D. K.; Walker, L. A.; Rogers, R. D. "Tirucallane- Type Triterpenoids: NMR and X-ray Diffraction Analyses of 24-*epi*-Piscidinol A and Piscidinol A," *J. Chem. Crystallogr.* **1997**, *27*, 283-290.
371. Morss, L. R.; Rogers, R. D. "Syntheses and Crystal Structures of $[M(NO_3)_2(tpen)][NO_3]\cdot 3H_2O$ (M = La, Tb), Rare Earth Complexes with Strong M-N Bonds," *Inorg. Chim. Acta* **1997**, *255*, 193-197.
372. Nuñez, L.; Rogers, R. D. "Synthesis and Structural Characterization of $[H_2(diaza\text{-}18\text{-}crown\text{-}6)][CuCl_4]\cdot H_2O$," *J. Chem. Crystallogr.* **1997**, *27*, 5-10.
373. Rogers, R. D.; Bond, A. H. "Crystal Structure of $[Pb(cis\text{-}anti\text{-}cis\text{-}dicyclohexyl\text{-}18\text{-}crown\text{-}6)(OH_2)_2][ClO_4]_2$," *J. Chem. Crystallogr.* **1997**, *27*, 263-267.
374. Rogers, R. D.; Bond, A. H.; Zhang, J.; Horwitz, E. P. "New Technetium-99m Generator Technologies Utilizing Polyethylene Glycol-Based Aqueous Biphasic Systems," *Sep. Sci. Technol.* **1997**, *32*, 867-882.
375. Rogers, R. D.; Griffin, S. T.; Horwitz, E. P.; Diamond, H. "Aqueous Biphasic Extraction Chromatography (ABEC™): Uptake of Pertechnetate from Simulated Hanford Tank Wastes," *Solvent Extr. Ion Exch.* **1997**, *15*, 547-562.
376. Rogers, R. D.; Zhang, J. "New Technologies for Metal Ion Separations *Polyethylene Glycol Based-Aqueous Biphasic Systems and Aqueous Biphasic Extraction Chromatography*," In *Ion Exchange and Solvent Extraction*; Vol. 13, Marinsky, J. A.; Marcus, Y., Eds.; Marcel Dekker: New York, 1997; Ch. 4, pp 141-193.
377. Rogers, R. D.; Zhang, J.; Bauer, C. B. "The Effects of Choice of Anion ($X = Cl^-, SCN^-, NO_3^-$) and Polyethylene Glycol (PEG) Chain Length on the Local and Supramolecular Structures of LnX_3/PEG Complexes," *J. Alloys Compd.* **1997**, *249*, 41-48.
378. Rogers, R. D.; Zhang, J.; Griffin, S. T. "The Effects of Halide Anions on the Partitioning Behavior of Pertechnetate in Polyethylene Glycol-Based Aqueous Biphasic Systems," *Sep. Sci. Technol.* **1997**, *32*, 699-707.
379. Sharma, C. V. K.; Bauer, C. B.; Rogers, R. D.; Zaworotko, M. J. "Interdigitated Supramolecular Laminates," *Chem. Commun.* **1997**, 1559-1560.
380. Simonsen, K. B.; Zong, K.; Rogers, R. D.; Cava, M. P.; Becher, J. "Stable Macrocyclic and Tethered Donor-Acceptor Systems. Intramolecular Bipyridinium and Tetrathiafulvalene Assemblies," *J. Org. Chem.* **1997**, *62*, 679-686.
381. Whitcomb, D. R.; Rogers, R. D. "The Molecular Structure of Catena-[(μ-phthalato)-di-(μ-phthalazine)-di-silver(I)hydrate] $([Ag_2(\mu\text{-}(O_2C)_2C_6H_4)(\mu\text{-}PHZ)_2(H_2O)]_n)$: Carboxylate Control of Side-on versus Stacked Coordination Polymerization," *Inorg. Chim. Acta* **1997**, *256*, 263-267.
382. Whitcomb, D. R.; Rogers, R. D. "Crystal and Molecular Structure of [Ammonia-silver(I)-2-(4-chlorobenzoyl)benzoate]: $[(NH_3)\cdot Ag(C_{14}H_8ClO_3)]$, a Silver Complex Containing Both Linear and Three-Coordinate Silvers," *Polyhedron* **1997**, *16*, 863-868.
383. Bauer, C. B.; Concolino, T. E.; Eglin, J. L.; Rogers, R. D.; Staples, R. J. "Synthesis of Dirhenium Species with Benzamide Ligands *via* Hydrolysis of Benzonitrile," *J. Chem. Soc., Dalton Trans.* **1998**, 2813-2817.
384. Bond, A. H.; Rogers, R. D. "Synthesis and X-ray Crystallographic Characterization of $[Cd(NO_3)_2(15\text{-crown-}5)]$ and $[Cd(NO_3)_2(18\text{-crown-}6)]$," *J. Chem. Crystallogr.* **1998**, *28*, 521-527.
385. Brandon, E. J.; Rogers, R. D.; Burkhart, B. M.; Miller, J. S. "The Structure and Ferrimagnetic Behavior of *meso*-Tetraphenylporphinatomanganese(III) 1,4-Tetrachlorobenzoquinoneide, $[Mn^{III}TPP]^+[QCl_4]^{\bullet-}\cdot PhMe$. Evidence of a Quinoidal Structure for $[QCl_4]^{\bullet-}$," *Chem. Eur. J.* **1998**, *4*, 1938-1943.
386. Bünzli, J.-C. G.; Ihringer, F.; Dumy, P.; Sager, C.; Rogers, R. D. "Structural and Dynamic Properties of Calixarene Bimetallic Complexes: Solution *versus* Solid-State Structure of Dinuclear Complexes of Eu^{III} and Lu^{III} with Substituted Calix[8]arenes," *J. Chem. Soc., Dalton Trans.* **1998**, 497-503.
387. Cannon, R. D.; Jayasooriya, U. A.; Sowrey, F. E.; Tilford, C.; Little, A.; Bourke, J. P.; Rogers, R. D.; Vincent, J. B.; Kearley, G. J. "Concealed Asymmetry in an Exchange-Coupled Trichromium(III) Cluster: Structure and Magnetic Spectrum of $[Cr_3O(OOCPh)_6(py)_3](py)_{0.5}ClO_4$," *Inorg. Chem.* **1998**, *37*, 5675-5677.
388. Huddleston, J. G.; Willauer, H. W., Boaz, K. R.; Rogers, R. D. "Separation and Recovery of Food Coloring Dyes using Aqueous Biphasic Extraction Chromatographic Resins," *J. Chromatogr. B, Biomed. Sci. Appl.* **1998**, *711*, 237-244.
389. Huddleston, J. G.; Willauer, H. W., Swatloski, R. P.; Visser, A. E.; Rogers, R. D. "Room Temperature Ionic Liquids as Novel

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 28

IPR2020-00770
United Therapeutics EX2007
Page 3578 of 7335

Media for 'Clean' Liquid-Liquid Extraction," *Chem. Commun.* **1998**, 1765-1766. (Highlighted in Freemantle, M. "'Green' solution for ionic liquids," *Chemical & Engineering News*, August 24, 1998, p 12; Guterman, L. "Weird mixtures replace toxic solvents," *New Scientist*, September 5, 1998, p 13; WJP "Room-temperature ionic liquids provide a new approach to liquid-liquid extraction of aromatics," *CHEMTECH*, May 1999, p 6. Reported to be the 6th most cited ionic liquids paper by ISI Essential Science Indicators, Special Topics (http://www.esi-topics.com/ionic-liquids/index.html May 2004) with 215 citations at that time. Reported to be the 22nd most cited paper in the 40 year history of *Chemical Communications*; http://www.rsc.org/Publishing/Journals/cc/News/Top40MostCitedArticles.asp September 8, 2005.)

390. Jackson, Y. A.; Rogers, L. M.; Rogers, R. D.; Cava, M. P. "Cycloaddition Products of 3-Oxido-1-phenylpyridinium and 1-Cyanoacenaphthylene," *J. Chem. Soc. Perkin I* **1998**, 1865-1868.
391. Martin, A.; Uhrhammer, R.; Gardner, T. G.; Jordan, R. F.; Rogers, R. D. "Neutral and Cationic Group 4 Metal Compounds Containing Octamethyldibenzotetraazaannulene (Me_8taa^{2-}) Ligands. Synthesis and Reactivity of $(Me_8taa)MX_2$ and $(Me_8taa)MX^+$ Complexes (M = Zr, Hf; X = Cl, hydrocarbyl, NR_2, OR)," *Organometallics* **1998**, *17*, 382-397.
392. Mohanakrishnan, A. K.; Lakskmikantham, M. V.; Cava, M. P.; Rogers, R. D.; Rogers, L. M. "*o*-Quinoid Heterocyclic Compounds: Naphtho[2,3-*c*]thiophene Revisited," *Tetrahedron* **1998**, *54*, 7075-7080.
393. Nash, K. L.; Rogers, R. D.; Ferraro, J.; Zhang, J. "Lanthanide Complexes with 1-Hydroxyethane-1,1-diphosphonic Acid: Solvent Organization and Coordination Geometry in Crystalline and Amorphous Solids," *Inorg. Chim. Acta* **1998**, *269*, 211-223.
394. Paquette, L. A.; Bolin, D. G.; Stephanian, M.; Branan, B. M.; Mallavadhani, U. V.; Tae, J.; Eisenberg, S. W. E.; Rogers, R. D. "Intramolecular Oxymercuration of Stereoisomeric Cyclohexyl-Belted Poly(spirotetrahydrofuranyl) Platforms," *J. Am. Chem. Soc.* **1998**, *120*, 11603-11615.
395. Paquette, L. A.; Rothhaar, R. R.; Isaac, M.; Rogers, L. M.; Rogers, R. D. "Diastereo- and Enantiodifferentiation in Indium-Promoted Allylations of 2,3-Azetidinediones in Water. Definition of Long-Range Stereocontrol Elements on π-Facial Selectivity for β-Lactam Synthesis," *J. Org. Chem.* **1998**, *63*, 5463-5472.
396. Rogers, R. D.; Griffin, S. T. "Partitioning of Mercury in Aqueous Biphasic Systems and on ABEC™ Resins," *J. Chromatogr. B, Biomed. Sci. Appl.* **1998**, *711*, 277-283.
397. Rogers, R. D.; Sharma, C. V. K.; Whitcomb, D. R. "Molecular Tweezers and Pentameric Aggregates: Convergent Hydrogen-Bonded Self-Assembly of 2:1 and 2:3 Cocrystals of Phthalazine:Phthalic Acid," *Crystal Eng. (*Suppl*., Mat. Res. Bull.)* **1998**, *3/4*,255-262.
398. Rogers, R. D.; Willauer, H. D.; Griffin, S. T.; Huddleston, J. G. "Partitioning of Small Organic Molecules in Aqueous Biphasic Systems," *J. Chromatogr. B, Biomed. Sci. Appl.* **1998**, *711*, 255-263.
399. Rogers, R. D.; Zaworotko, M. J. "Whither Crystal Engineering?" In *Crystal Engineering*, Rogers, R. D.; Zaworotko, M. J., Eds.; Transactions of the American Crystallographic Association, Vol. 33; American Crystallographic Association: Buffalo, NY, 1998; pp 1-5.
400. Rogers, R. D.; Zhang, J.; Campbell, D. T. "Crown Ether Complexes of $UO_2(NCS)_2$ and $Th(NCS)_4$: Clues to Solution Behavior or Just Interesting Supramolecular Structures?," *J. Alloys Compd.* **1998**, *271-273*, 133-138.
401. Sharma, C. V. K.; Rogers, R. D. "C-H•••X (X = N,O) Hydrogen Bond-Mediated Assembly of Donors and Acceptors: The Crystal Structures of Phenazine Complexes with 1,4-Dinitrobenzene and TCNQ," *Crystal Eng. (*Suppl*., Mat. Res. Bull.)* **1998**, *1*, 139-145.
402. Sharma, C. V. K.; Rogers, R. D. "Discrete Macrocycles to Infinite Polymeric Frames: Crystal Engineering Studies of Ag(I):Pyrimidine Complexes," *Crystal Eng.* (Suppl., *Mat. Res. Bull.*) **1998**, *1*, 19-38.
403. Sharma, C. V. K.; Griffin, S. T.; Rogers, R. D. "Simple Routes to Supramolecular Squares with Ligand Corners: 1:1 Ag^I:Pyrimidine Cationic Tetranuclear Assemblies," *Chem. Commun.* **1998**, 215-216.
404. Sharma, C. V. K.; Swatloski, R. P.; Rogers, R. D. "4,4'-Dipyridine•$2H_2O$: Complementarity of Hydrogen Bond Donor:Acceptor Ratio," *Crystal Eng. (*Suppl*., Mat. Res. Bull.)* **1998**, *1*, 153-158.
405. Sharma, C. V. K.; Swenson, J. A.; Rogers, R. D. "The Design of Two Dimensional Polymeric Networks: Coordination Complexes of Cadmium Iodide with Bifunctional Ligands," In *Crystal Engineering*, Rogers, R. D.; Zaworotko, M. J., Eds.; Transactions of the American Crystallographic Association, Vol. 33; American Crystallographic Association: Buffalo, NY, 1998; pp 59-66.
406. Uzelmeier, C. E.; Bartley, S. L.; Fourmigué, M.; Rogers, R.; Grandinetti, G.; Dunbar, K. R. "Reaction of Octachlorodirhenate with a Redox-Active Tetrathiafulvalene Phosphine Ligand: Spectroscopic, Magnetic, and Structural Characterization of the Unusual Paramagnetic Salt $[ReCl_2(o\text{-}P2)_2][Re_2Cl_6(o\text{-}P2)]$ (*o*-P2 = *ortho*-$\{P(C_6H_5)_2\}_2(CH_3)_2TTF$)," *Inorg. Chem.* **1998**, *37*, 6706-6713.
407. Wisniewski, K.; Zamojski, A.; Rogers, R. D. "(Phenylthio)acetyliron Complex $[(\eta^5\text{-}C_5H_5)Fe(CO)(PPh_3)COCH_2SPh]$ Configuration of Aldols," *Tetrahedron* **1998**, *54*, 14201-14212.
408. Ye, N.; Rogers, R. D.; Brechbiel, M. W.; Planalp, R. P. "Synthesis and X-ray Crystal Structure of N,N',N''-Tris(2-thienylmethyl)-cis-1,3,5-triaminocyclohexanecopper(II) Dichloride," *Polyhedron* **1998**, *17*, 603-606.
409. Zhang, L.; Cava, M. P.; Rogers, R. D.; Rogers, L. M. "Synthesis of a Wakayin Model Compound: Oxidative Formation of a New Pyrrole Ring in the Indol-3-yl-indoloquinone System," *Tetrahedron Lett.* **1998**, *39*, 7677-7678.
410. Bartsch, R. A.; Hwang, H.-S.; Talanov, V. S.; Talanova, G. G.; Purkiss, D. W.; Rogers, R. D. "New Proton-Ionizable Lariat Ethers with Picrylamino-Type Side Arms and Their Alkali Metal Salts. Synthesis and Structural Studies," *J. Org. Chem.* **1999**, *64*, 5341-5349.
411. Bond, A. H.; Chang, F. W. K.; Thakkar, A. H.; Williamson, J. M.; Gula, M. J.; Harvey, J. T.; Griffin, S. T.; Rogers, R. D.;

Horwitz, E. P. "Design, Synthesis, and Uptake Performance of ABEC® Resins for the Removal of Pertechnetate from Alkaline Radioactive Wastes," *Ind. Eng. Chem. Res.* **1999**,*38*, 1676-1682.
412. Bond, A. H.; Dietz, M. L.; Rogers, R. D. "Progress in Metal Ion Separation and Preconcentration: An Overview," In *Metal-Ion Separation and Preconcentration, Progress and Opportunities*; Dietz, M. L.; Bond, A. H.; Rogers, R. D., Eds.; ACS Symposium Series 716, American Chemical Society: Washington, DC, 1999; pp 2-12.
413. Bond, A. H.; Gula, M. J.; Harvey, J. T.; Duffey, H. M.; Horwitz, E. P.; Griffin, S. T.; Rogers, R. D.; Collins, J. L. "Flowsheet Feasibility Studies Using ABEC® Resins for the Removal of Pertechnetate from Nuclear Wastes," *Ind. Eng. Chem. Res.* **1999**, *38*, 1683-1689.
414. Bryan, J. C.; Delmau, L. H.; Hay, B. P.; Nicholas, J. B.; Rogers, L. M.; Rogers, R. D.; Moyer, B. A. "Cesium Recognition by Supramolecular Assemblies of 2-Benzylphenol and 2-Benzylphenolate," *Structural Chem.* **1999**, *10*, 187-203.
415. Clark, D. L.; Conradson, S. D.; Donohoe, R. J.; Keogh, D. W.; Morris, D. E.; Palmer, P. D.; Rogers, R. D.; Tait, C. D. "Chemical Speciation of the Uranyl Ion under Highly Alkaline Conditions. Synthesis, Structures, and Oxo Ligand Exchange Dynamics," *Inorg. Chem.* **1999**, *38*, 1456-1466.
416. del Mar Conejo, M.; Parry, J. S.; Carmona, E.; Schultz, M.; Brennann, J. G.; Beshouri, S. M.; Andersen, R. A.; Rogers, R. D.; Coles, S.; Hursthouse, M. "Carbon Monoxide and Isocyanide Complexes of Trivalent Uranium Metallocenes," *Chem. Eur. J.* **1999**, *5*, 3000-3009.
417. Gilbert, T. M.; Bauer, C. B.; Bond, A. H.; Rogers, R. D. "Structures of Homoleptic Triply Bonded $M_2(OR)_6$ Compounds where the Alkoxide is Tertiary: The Effect of Steric Bulk and Alkoxide Conformation on Structural Parameters," *Polyhedron.* **1999**, *18*, 1293-1301.
418. Gilbert, T. M.; Bauer, C. B.; Bond, A. H.; Rogers, R. D. "Syntheses and Structures of Metal-Metal Triply Bonded M_2R_6 Compounds: Consideration of Starting Materials, Stability, and Structural Parameters," *Polyhedron* **1999**, *18*, 1303-1310.
419. Gobley, O.; Gentil, S.; Schloss, J. D.; Rogers, R. D.; Gallucci, J. C.; Meunier, P.; Gautheron, B.; Paquette, L. A. "Magnesiation of Isodicyclopentadiene. Formation of Sandwich and Monomeric Complexes and the Stereoselectivity of Their Reactions with Transition Metal Halides," *Organometallics* **1999**, *18*, 2531-2535.
420. Huddleston, J. G.; Griffin, S. T.; Zhang, J.; Willauer, H. D.; Rogers, R. D. "Metal Ion Separations in Aqueous Biphasic Systems and Using Aqueous Biphasic Extraction Chromatography," In *Metal-Ion Separation and Preconcentration, Progress and Opportunities*; Dietz, M. L.; Bond, A. H.; Rogers, R. D., Eds.; ACS Symposium Series 716, American Chemical Society: Washington, DC, 1999; pp 79-100.
421. Huddleston, J. G.; Ingenito, C. C.; Rogers, R. D. "Partitioning Behavior of Porphyrin Dyes in Aqueous Biphasic Systems," *Sep. Sci. Technol.* **1999**, *34*, 1091-1101.
422. Huddleston, J. G.; Willauer, H. D.; Griffin, S. T.; Rogers, R. D. "Aqueous Polymeric Solutions as Environmentally Benign Liquid/Liquid Extraction Media," *Ind. Eng. Chem. Res.* **1999**, *38*, 2523-2539.
423. Nowak, I.; Rogers, L. M.; Rogers, R. D.; Thrashe, J. S. "Toward the Synthesis of Novel Fluorinated Building Blocks: 3,4-difluorothiophene-1,1-dioxide," *J. Fluorine Chem.* **1999**, *93*, 27-31.
424. Nowak, I.; Rogers, L. M.; Rogers, R. D.; Thrasher, J. S. "The Effect of Fluorine on the Diastereoselectivity of the Addition of α-Oxyradicals to 3-Fluoro-2,3-dihydro-1H-λ^6-thiophene-1,1-dione," *J. Fluorine Chem.* **1999**, *93*, 73-81.
425. Paquette, L. A.; Edmondson, S. D.; Monck, N.; Rogers, R. D. "Studies Directed toward the Synthesis of the Unusual Antileukemic Diterpene Jatrophatrione. 2. Functionalization of Advanced Polycyclic Precursors to the 9-Epi and 8,9-Dehydro Congeners," *J. Org. Chem.* **1999**, *64*, 3255-3265.
426. Paquette, L. A.; Tae, J.; Hickey, E. R.; Rogers, R. D. "A Belted Monofacial Ionophore Featuring High Selectivity for Lithium Ion Complexation," *Angew. Chem. Int. Ed.* **1999**, *38*, 1409-1411.
427. Rapko, B. M.; McNamara, B. K.; Rogers, R. D.; Lumetta, G. J.; Hay, B. P. "Coordination Chemistry of Lanthanide Nitrates with *N*,*N*,*N'*,*N'*-Tetramethylsuccinamide," *Inorg. Chem.* **1999**, *38*, 4585-4592.
428. Rogers, R. D. "Chemical Crystallography in Crystal Engineering," In *Crystal Engineering: The Design and Application of Functional Solids*; Seddon, K. R.; Zaworotko, M. J. Eds., NATO ASI Series, Kluwer: Dordrecht. 1999; pp 155-189.
429. Rogers, R. D.; Visser, A. E.; Swatloski, R. P.; Hartman, D. H. "Metal Ion Separations in Room Temperature Ionic Liquids: Potential Replacements for Volatile Organic Diluents," In *Metal Separation Technologies Beyond 2000: Integrating Novel Chemistry with Processing*; Liddell, K. C.; Chaiko, D. J., Eds.; The Minerals, Metals & Materials Society: Warrendale, PA, 1999; pp 139-147.
430. Sharma, C. V. K.; Broker, G. A.; Huddleston, J. G.; Baldwin, J. W.; Metzger, R. M.; Rogers, R. D. "Design Strategies for Solid-State Supramolecular Arrays Containing Both Mixed-Metallated and Freebase Porphyrins," *J. Am. Chem. Soc.* **1999**, *121*, 1137-1144.
431. Sharma, C. V. K.; Rogers, R. D. "'Molecular Chinese Blinds': Self-Organization of Tetranitrato Lanthanide Complexes Into Open, Chiral Hydrogen-Bonded Networks," *Chem. Commun.* **1999**, 83-84.
432. Talinova, G. G.; Elkarim, N. S. A.; Hanes, Jr., R. E.; Hwang, H.-S.; Rogers, R. D.; Bartsch, R. A. "Extraction Selectivities of Crown Ethers for Alkali Metal Cations: Differences between Single-Species and Competitive Solvent Extractions," *Anal. Chem.* **1999**, *71*, 672-677.
433. Talinova, G. G.; Elkarim, N. S. A.; Talanov, V. S.; Hanes, Jr., R. E.; Hwang, H.-S.; Bartsch, R. A.; Rogers, R. D. "The 'Picrate Effect' on Extraction Selectivities of Aromatic Group-Containing Crown Ethers for Alkali Metal Cations," *J. Am. Chem. Soc.* **1999**, *121*, 11281-11290.
434. Visser, A. E.; Griffin, S. T.; Ingenito, C. A.; Hartman, D. H.; Huddleston, J. G.; Rogers, R. D. "Aqueous Biphasic Systems as a

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 30

IPR2020-00770
United Therapeutics EX2007
Page 3580 of 7335

Novel Environmentally-Benign Separations Technology for Metal Ion Removal," In *Metal Separation Technologies Beyond 2000: Integrating Novel Chemistry with Processing*; Liddell, K. C.; Chaiko, D. J., Eds.; The Minerals, Metals & Materials Society: Warrendale, PA, 1999; pp 119-130.

435. Whitcomb, D. R.; Rogers, R. D. "The Crystal and Molecular Structure of the Tetrameric Methyl-2-mercaptobenzimidazole•AgBr (Acetone Solvate) Complex: Mode of Complex Formation between Silver Bromide and Thione Type Photographic Stabilizers," *J. Imaging Sci. Technol.* **1999**, *43*, 498-502.
436. Whitcomb, D. R.; Rogers, R. D. "Chemistry of Photothermographic Imaging Materials. II," *J. Imaging Sci. Technol.* **1999**, *43*, 517-520.
437. Willauer, H. D.; Huddleston, J. G.; Griffin, S. T.; Rogers, R. D. "Partitioning of Aromatic Molecules in Aqueous Biphasic Systems," *Sep. Sci. Technol.* **1999**, *34*, 1069-1090.
438. Yordanov, A. T.; Gansow, O. A.; Brechbiel, M. W.; Rogers, L. M.; Rogers, R. D. "The Preparation and X-ray Crystallographic Characterization of Lead(II) Calix[4]arenesulfonate Complex," *Polyhedron* **1999**, *18*, 1055-1059.
439. Zhao, H.; Heintz, R. A.; Ouyang, X.; Dunbar, K. R.; Campana, C. F.; Rogers, R. D. "Spectroscopic, Thermal, and Magnetic Properties of Metal/TCNQ Polymers with Extensive Supramolecular Interactions bewteen Layers," *Chem. Mater.* **1999**, *11*, 736-746.
440. Zucchi, Z.; Scopelliti, R.; Pittet, P.-A.; Bünzli, J.-C. G.; Rogers, R. D. "Structural and Photophysical Behavior of Lanthanide Complexes with a Tetraazacyclododecane Featuring Carbamoyl Pendant Arms," *J. Chem. Soc., Dalton Trans.* **1999**, 931-938.
441. Adams, R. D.; Perrin, J. L.; Queisser, J. A.; Rogers, R. D. "Synthesis and Structural Characterization of Chiral Thiacrowns: The Crystal and Molecular Structure of (*R,R,R*)-2,6,10-Trimethyl-1,5,9-trithiacyclododecane," *J. Organomet. Chem.* **2000**, *596*, 115-120.
442. Blair, E.; Nikles, J. A.; Nikles, D. E.; Rogers, L. M.; Rogers, R. D.; Stabler, D.; Street, S. C. "Molecular Structure of the Amine-Quinone Model Compound, 2,4-Bis(dimethylamino)-1,4-benzoquinone," *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **2000**, *41*, 317-318.
443. Blais, M. S.; Rogers, R. D.; Rausch, M. D. "Synthesis, Reactions and Structure of Bromo(η^5-diphenylphosphinocyclopentadienyl)nickel(II) Dimer," *J. Organomet. Chem.* **2000**, *593-594*, 142-146.
444. Bond, A. H.; Dietz, M. L.; Rogers, R. D. "Nuclear Separations for Radiopharmacy: The Need for Improved Separations to Meet Future Research and Clinical Demands," *Ind. Eng. Chem. Res.* **2000**, *39*, 3130-3134.
445. Hay, B. P.; Dixon, D. A.; Lumetta, G. J.; Rapko, B. M.; Roundhill, D. M.; Rogers, R. D.; Hutchinson, J. E.; Paine, R. T.; Raymond, K. N. "Architectural Design Criteria for f-Block Metal Ion Sequestering Agents Final Report," Report PNNL-13221, Pacific Northwest National Laboratory: Richland, WA, 2000; 32 pp.
446. Huddleston, J. G.; Griffin, S. T.; Zhang, J.; Willauer, H. D.; Rogers, R. D. "Metal Ion Separations in Aqueous Biphasic Systems and with ABEC™ Resins," In *Aqueous Two-Phase Systems: Methods and Protocols*; Hatti-Kaul, R., Ed.; In *Methods in Biotechnology*, Vol. 11; Walker, J. M., Ed.; Humana Press, Totowa, NJ, 2000, pp 77-94.
447. Huddleston, J. G.; Willauer, H. W.; Rogers, R. D. "Solvatochromic Studies in Polyethylene Glycol-Salt Aqueous Biphasic Systems," *J. Chromatogr. B: Biomed. Sci. Appl.* **2000**, *743*, 137-149.
448. Jensen, M. P.; Beitz, J. V.; Rogers, R. D.; Nash, K. L. "Thermodynamics and Hydration of the Europium Complexes of a Nitrogen Heterocycle Methane-1,1-Diphosphonic Acid," *J. Chem. Soc., Dalton Trans.* **2000**, 3058-3064.
449. Lumetta, G. J.; McNamara, B. K.; Rapko, B. M.; Sell, R. L.; Rogers, R. D.; Broker, G.; Hutchison, J. E. "Synthesis and characterization of mono- and bis-(tetraalkylmalonamide)uranium(VI) complexes," *Inorg. Chim. Acta* **2000**, *309*, 103-108.
450. Paquette, L. A.; Ohmori, N.; Lowinger, T. B.; Rogers, R. D. "Vicinal Tetrahydrofuranyl Substitution of Alkyl Chains. Tetra-, Penta-, and Hexafunctionalized Arrays," *J. Org. Chem.* **2000**, *65*, 4303-4308.
451. Paquette, L. A.; Tae, J.; Hickey, E. R.; Trego, W. E.; Rogers, R. D. "Preorganized ligand arrays based on spirotetrahydrofuranyl motifs. Synthesis of the stereoisomeric 1,8,14-trioxatrispiro[4.1.4.1.4.1]octadecanes and the contrasting conformational features and ionic binding capacities of these belted ionophores," *J. Org. Chem.* **2000**, *65*, 9160-9171.
452. Park, G.; Ye, N.; Rogers, R. D.; Brechbiel, M. W.; Planalp, R. P. "Effect of Metal Size on Coordination Geometry of *N,N',N''*-tris(2-pyridylmethyl)-*cis,cis*-1,3,5-triaminocyclohexane: Synthesis and Structure of $[M^{II}L](ClO_4)_2$ (M = Zn, Cd and Hg)," *Polyhedron* **2000**, *19*, 1155-1161.
453. Rapko, B. M.; McNamara, B. K.; Rogers, R. D.; Broker, G. A.; Lumetta, G. J.; Hay, B. P. "Coordination Chemistry of Lanthanide Triflates and Perchlorates with *N,N,N',N'*-Tetramethylsuccinamide," *Inorg. Chem.* **2000**, *39*, 4858-4867.
454. Rogers, R. D.; Reichert, W. M.; Klingshirn, M. A.; Visser, A. E.; Spear, S. K. "Vision 2020: How Green Chemistry Can Shape the Future of the Sugar Processing Industry," In *Proceedings SPRI 2000 Conference on Sugar Processing Research, April 9-12, 2000, Porto, Portugal*, Godshall, M. A., Ed; Sugar Processing Research Institute, Inc., New Orleans, LA, 2000; pp 20-40.
455. Sharma, C. V. K.; Broker, G. A.; Szulczewski, G. J.; Rogers, R. D. "Self-Assembly of Freebase- and Metalated-Tetrapyridylporphyrins to Modified Gold Surfaces. *Chem. Commun.* **2000**, 1023-1024.
456. Sharma, C. V. K.; Broker, G. A.; Rogers, R. D. "Polymorphous One-Dimensional Tetrapyridylporphyrin Coordination Polymers Which Structurally Mimic Aryl Stacking Interactions," *J. Solid State Chem.* **2000**, *152*, 253-260.
457. Spear, S. K.; Griffin, S. T.; Huddleston, J. G.; Rogers, R. D. "Radiopharmaceutical and Hydrometallurgical Separations of Perrhenate Using Aqueous Biphasic Systems and the Analogous Aqueous Biphasic Extraction Chromatographic Resins," *Ind. Eng. Chem. Res.* **2000**, *39*, 3173-3180.
458. Tae, J.; Rogers, R. D.; Paquette, L. A. "Lithium Ion-Selective Binding Properties of a Conformationally Constrained Tris(spirotetrahydrofuran) Secured to an Inositol Orthoformate Platform," *Org. Lett.* **2000**, *2*, 139-142.

459. Visser, A. E.; Griffin, S. T.; Hartman, D. H.; Rogers, R. D. "Napthol- and Resorcinol-Based Azo Dyes as Metal Ion Complexants in Aqueous Biphasic Systems," *J. Chromatogr. B: Biomed. Sci. Appl.* **2000**, *743*, 107-114.
460. Visser, A. E.; Swatloski, R. P.; Hartman, D. H.; Huddleston, J. G.; Rogers, R. D. "Calixarenes as Ligands in Environmentally-Benign Liquid/Liquid Extraction Media, Aqueous Biphasic Systems and Room Temperature Ionic Liquids," In *Calixarenes for Separations*; Lumetta, G. J.; Rogers, R. D.; Gopalan, A. S., Eds.; ACS Symposium Series 757, American Chemical Society: Washington, DC, 2000; pp 223-236.
461. Visser, A. E.; Swatloski, R. P.; Reichert, W. M.; Griffin, S. T.; Rogers, R. D. "Traditional Extractants in Nontraditional Solvents: Groups 1 and 2 Extraction by Crown Ethers in Room-Temperature Ionic Liquids," *Ind. Eng. Chem. Res.* **2000**, *39*, 3596-3604.
462. Visser, A. E.; Swatloski, R. P.; Rogers, R. D. "pH-Dependent Partitioning in Room Temperature Ionic Liquids Provides a Link to Traditional Solvent Extraction Behavior," *Green Chem.* **2000**, *2*, 1-4.
463. Willauer, H. D.; Huddleston, J. G.; Li, M.; Rogers, R. D. "Investigation of Aqueous Biphasic Systems for the Separations of Lignins from Cellulose in the paper Pulping Process," *J. Chromatogr. B: Biomed. Sci. Appl.* **2000**, *743*, 127-135.
464. Wu, B.; Reddy, R. G.; Rogers, R. D. "Aluminum recycling via near room temperature electrolysis in ionic liquids," In *Int. Symp. Recycl. Met. Eng. Mater., Proc., 4th*; Stewart, D. L., Jr.; Daley, J. C.; Stephens, R. L., Eds.; The Minerals, Metals & Materials Society, Warrendale, PA, 2000, pp 845-856.
465. Huddleston, J. G.; Visser, A. E.; Reichert, W. M.; Broker, G. A.; Willauer, H. D.; Rogers, R. D. "Characterization and Comparison of Hydrophobic and Hydrophilic Room Temperature Ionic Liquids Incorporating the Imidazolium Cation," *Green Chem.* **2001**, *3*, 156-164. (Highlighted in Emsley, J. "Ionic Liquids Poised for a Solvent-Free Atmosphere," *Science Watch* September/October 2003, Vol. 14 No. 5 as the 5th most cited paper in Chemistry for the time period March-April 2003. Among the Top Five most accessed papers for *Green Chem.* May 2004. Reported to be the 11th most cited ionic liquids paper by ISI Essential Science Indicators, Special Topics (http://www.esi-topics.com/ionic-liquids/index.html May 2004) with 123 citations at that time. Reported to be the 5th most accessed article in *Green Chemistry* in 2005 and in 2006.)
466. Kus, P.; Dalley, N. K.; Kuo, X.; Rogers, R. D.; Bartsch, R. A. "X-ray structural investigation of 4-phenyl-, 4-(o-Tolyl)-and 4-(2',4',6'-trimethylphenyl)[2.2]paracyclophanes," *Polish J. Chem.* **2001**, *75*, 1351-1360.
467. Li, M.; Willauer, H. W.; Huddleston, J. G.; Rogers, R. D. "Temperature Effects on Polymer-Based Aqueous Biphasic Extraction Technology in the Paper Pulping Process," *Sep. Sci. Technol.* **2001**, *36*, 835-847.
468. Luo, H.; Eberly, N.; Rogers, R. D.; Brechbiel, M. W. "Syntheses and Characterizations of Metal Complexes Derived from *cis,cis*-1,3,5-Triaminocyclohexane-*N,N',N''*-triacetic Acid," *Inorg. Chem.* **2001**, *40*, 493-498.
469. Luo, H.; Rogers, R. D.; Brechbiel, M. W. „A convenient and selective route to a trans-difunctionalized macrocyclic hexadentate N_4O_2 ligand," *Can. J. Chem.*, **2001**, *79*, 1105-1109.
470. Park, G.; Dadachova, E.; Przyborowska, A.; Lai, S.; Ma, D.; Broker, G.; Rogers, R. D.; Planalp, R. P.; Brechbiel, M. W. "Synthesis of novel 1,3,5-*cis,cis*-triaminocyclohexane ligand based Cu(II) complexes as potential radiopharmaceuticals and correlation of structure and serum stability," *Polyhedron* **2001**, *20*, 3155-3163.
471. Park, G.; Shao, J.; Lu, F. H.; Rogers, R. D.; Chasteen, N. D.; Brechbiel, M. W.; Planalp, R. P. "Copper(II) Complexes of Novel N-Alkylated Derivatives of *cis,cis*-1,3,5-Triaminocyclohexane. 1. Preparation and Structure," *Inorg. Chem.* **2001**, *40*, 4167-4175.
472. Rogers, R. D.; Spear, S. K.; Swatloski, R. P.; Reichert, W. M.; Godshall, M. A.; Johnson, T. P.; Moens, L. "Non-sugar products from sugarcane for the new millennium: green pathways to a carbohydrate-economy?" *Publ. Tech. Pap. Proc. Annu. Meet. Sugar Ind. Technol. (May 6-9, 2001, Taipei, Taiwan)* **2001**, *60*, 291-301.
473. Spear, S. K.; Visser, A. E.; Willauer, H. W.; Swatloski, R. P.; Griffin, S. T.; Huddleston, J. G.; Rogers, R. D. "Green Separations Science & Technology: Replacement of Volatile Organic Compounds in Industrial Scale Liquid-Liquid or Chromatographic Separations," In *Green Engineering*; Anastas, P. T.; Heine, L. G.; Williamson, T. C., Eds.; ACS Symposium Series 766, American Chemical Society: Washington, DC, 2001; pp 206-221.
474. Swatloski, R. P.; Visser, A. E.; Reichert, W. M.; Broker, G. A.; Farina, L. M.; Holbrey, J. D.; Rogers, R. D. "Solvation of 1-butyl-3-methylimidazolium hexafluorophosphate in aqueous ethanol-a green solution for dissolving 'hydrophobic' ionic liquids," *Chem. Commun.* **2001**, 2070-2071. (Highlighted in "'Green' solution for ionic liquids," *Chemical & Engineering News*, October 22, 2001, p 50.)
475. Visser, A. E.; Holbrey, J. D.; Rogers, R. D. "Hydrophobic ionic liquids incorporating N-alkylisoquinolinium cations and their utilization in liquid-liquid separations," *Chem. Commun.* **2001**, 2484-2485.
476. Visser, A. E.; Swatloski, R. P.; Griffin, S. T.; Hartman, D. H.; Rogers, R. D. "Liquid/Liquid Extraction of Metal Ions in Room Temperature Ionic Liquids," *Sep. Sci. Technol.* **2001**, *36*, 785-804.
477. Visser, A. E.; Swatloski, R. P.; Reichert, W. M.; Mayton, R.; Sheff, S.; Wierzbicki, A.; Davis, Jr. J. H.; Rogers, R. D. "Task-Specific Ionic Liquids for the Extraction of Metal Ions from Aqueous Solutions," *Chem. Commun.* **2001**, 135-136. (Highlighted in Beard, J. "What's Wet and Green?," *The Alchemist*, January 26, 2001, URL: http://www.chemweb.com/alchem/2001/news/nw_010126_ionic.html; last accessed January 30, 2001.)
478. Wu, B.; Reddy, R. G.; Rogers, R. D. "Aluminum reduction via near room temperature electrolysis in ionic liquids," *Light Metals (Proceedings of the Technical Sessions Presented by the TMS Aluminum Committee at the 130th TMS Annual Meeting, New Orleans, LA, February 11-15, 2000)* The Minerals, Metals & Materials Society, Warrendale, PA, 2001; pp 237-243.
479. Wu, B.; Reddy, R. G.; Rogers, R. D. "Novel Ionic Liquid Thermal Storage for Solar Thermal Electric Power Systems," *Proceedings of Solar Forum 2001: Solar Energy: The Power to Choose, April 21-25, 2001, Washington, DC* ASME,

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 32

IPR2020-00770
United Therapeutics EX2007
Page 3582 of 7335

Washington, DC, 2001.

480. Amaresh, R. R.; Lakshmikantham, M. V.; Baldwin, J. W.; Cava, M. P.; Metzger, R. M.; Rogers, R. D. "Condensed Thiophenes and Selenophenes: Thionyl Chloride and Selenium Oxychloride as Sulfur and Selenium Transfer Reagents," *J. Org. Chem.* **2002**, *67*, 2453-2458.
481. Broker, G. A.; Klingshirn, M. A.; Rogers, R. D. "Green Chemistry and Lanthanide-Based Crystal Engineering," *J. Alloys Comp.* **2002**, *344*, 123-127.
482. Chong, H.-s.; Ganguly, B.; Broker, G. A.; Rogers, R. D.; Brechbiel, M. W. "Stereoselective and Regioselective Synthesis of Azepane and Azepine Derivatives via Piperidine Ring Expansion," *J. Chem. Soc. Perkin I* **2002**, 2080-2086.
483. Guo, Z.; Li, M.; Willauer, H. D.; Huddleston, J. G.; April, G. C.; Rogers, R. D. "Evaluation of Polymer-Based Aqueous Biphasic Systems as Improvement for the Hardwood Alkaline Pulping Process," *Ind. Eng. Chem. Res.* **2002**, *41*, 2535-2542.
484. Holbrey, J. D.; Reichert, W. M.; Swatloski, R. P.; Broker, G. A.; Pitner, W. R.; Seddon, K. R.; Rogers, R. D. "Efficient, halide free synthesis of new, low cost ionic liquids: Alkylimidazolium salts containing methyl- and ethyl-sulfate anions" *Green Chem.* **2002**, *4*, 407-413.
485. Holbrey, J. D.; Rogers, R. D. "Green Chemistry and Ionic Liquids - Synergies and Ironies," In *Ionic Liquids; Industrial Applications to Green Chemistry*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 818; American Chemical Society: Washington DC, 2002; pp 2-14.
486. Holbrey, J. D.; Rogers, R. D. "Green Industrial Applications of Ionic Liquids: Technology Review," In *Ionic Liquids; Industrial Applications to Green Chemistry*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 818; American Chemical Society: Washington DC, 2002; pp 446-458.
487. Holbrey, J. D.; Shaughnessy, K. H.; Klingshirn, M. A.; Broker, G. A.; Rogers, R. D. "Transition Metal Catalyzed CO/Olefin Co-Polymerization in Room Temperature Ionic Liquids," In *Molten Salts XIII: Proceedings of the International Symposium*, Trulove, P. C.; De long, H. C.; Mantz, R. A.; Stafford, G. R.; Matsunaga, M., Eds.; The Electrochemical Society: Pennington, NJ, 2002; Vol. 2002-19, pp 213-223.
488. Hong, K.; Zhang, H.; Mays, J. W.; Visser, A. E.; Brazel, C. S.; Holbrey, J. D.; Reichert, W. M.; Rogers, R. D. "Conventional free radical polymerization in room temperature ionic liquids: A green approach to Commodity Polymers with Practical Advantages," *Chem. Commun.* **2002**, 1368-1369.
489. Huddleston, J. G.; Broker, G. A.; Willauer, H. D.; Rogers, R. D. "Free-Energy Relationships and Solvatochromatic Properties of 1-Alkyl-3-methylimidazolium Ionic Liquids," In *Ionic Liquids; Industrial Applications to Green Chemistry*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 818; American Chemical Society: Washington DC, 2002; pp 270-288.
490. Huddleston, J. G.; Willauer, H. D.; Rogers, R. D. "The Solvatochromic Properties, α, β, and π^*, of PEG-Salt Aqueous Biphasic Systems," *Phys. Chem. Chem. Phys.* **2002**, *4*, 4065-4070.
491. Katritzky, A. R.; Jain, R.; Lomaka, A.; Petrukhin, R.; Karelson, M.; Visser, A. E.; Rogers, R. D. "Correlation of the Melting Points of Potential Ionic Liquids (Imidazolium Bromides and Benzimidazolium Bromides) Using the CODESSA Program," *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 225-231. [*Erratum: J. Chem. Inf. Mod.* **2005**, *45*, 533-534.]
492. Katritzky, A. R.; Lomaka, A.; Petrukhin, R.; Jain, R.; Karelson, M.; Visser, A. E.; Rogers, R. D. "QSPR Correlation of the Melting Point for Pyridinium Bromides, Potential Ionic Liquids," *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 71-74.
493. Klingshirn, M. A.; Broker, G. A.; Holbrey, J. D.; Shaughnessy, K. H.; Rogers, R. D. "Polar, non-coordinating ionic liquids as solvents for alternating copolymerization of styrene and CO catalyzed by cationic palladium catalysts," *Chem. Commun.* **2002**, 1394-1395.
494. Planalp, R. P.; Przyborowska, A. M.; Ye, N.; Ku, F. H.; Rogers, R. D.; Broker, G. A.; Torti S. V.; Brechbiel, M. W. "Novel Cytotoxic Chelators that Bind Iron(II) Selectively over Zinc(II) under Aqueous Aerobic Conditions," *Biochem. Soc. Trans.* **2002**, *30*, 758-762.
495. Royer, A. C.; Rogers, R. D.; Arrington, D. L.; Street, S. C.; Vincent, J. B. "Spectroscopic studies of the dodecanuclear chromium complex $Cr_{12}O_9(OH)_3(pivalate)_{15}$: confirmation of the presence of twelve Cr(III) centers and the crystal structure of $Cr_{12}O_9(OH)_3(pivalate)_{15}\bullet 2PrOH\bullet 9H_2O$," *Polyhedron* **2002**, *21*, 155-165.
496. Scott, M. P.; Brazel, C. S.; Benton, M. G.; Mays, J. W.; Holbrey, J. D.; Rogers, R. D. "Application of ionic liquids as plasticizers for poly(methyl-methacrylate)," *Chem. Commun.* **2002**, 1370-1371.
497. Scovazzo, P.; Visser, A. E.; Davis, Jr., J. H.; Rogers, R. D.; Koval, C. A.; DuBois, D. L.; Noble, R. D. "Supported Ionic Liquid Membranes (SILMs) and Facilitated Ionic Liquid Membranes (FILMs)," In *Ionic Liquids; Industrial Applications to Green Chemistry*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 818; American Chemical Society: Washington DC, 2002; pp 69-87.
498. Spear, S. K.; Visser, A. E.; Rogers, R. D. "Ionic Liquids: Green Solvents for Carbohydrate Studies," In *Proceedings of the 2002 Sugar Processing Research Conference, Advances in the Chemistry and Processing of Beet and Cane Sugar, March 10-13, 2002, New Orleans, LA;* Godshall, M. A., Ed; Sugar Processing Research Institute, Inc.: New Orleans, LA, 2002; pp 336-340.
499. Swatloski, R. P.; Holbrey, J. D.; Spear, S. K.; Rogers, R. D. "Ionic Liquids for the Dissolution and Regeneration of Cellulose," In *Molten Salts XIII: Proceedings of the International Symposium*, Trulove, P. C.; De long, H. C.; Mantz, R. A.; Stafford, G. R.; Matsunaga, M., Eds.; The Electrochemical Society: Pennington, NJ, 2002; Vol. 2002-19, pp 155-164.
500. Swatloski, R. P.; Spear, S. K.; Holbrey, J. D.; Rogers, R. D. "Dissolution of Cellose with Ionic Liquids," *J. Am. Chem. Soc.* **2002**, *124*, 4974-4975. (Highlighted in "Ionic Liquids Can Dissolve Cellulose," *Chemical & Engineering News*, April 29, 2002, p 24. Reported to be the 18th most cited ionic liquids paper in the previous two-year period by ISI Essential Science Indicators, Special Topics (http://www.esi-topics.com/ionic-liquids/index.html May 2004) with 22 citations at that time.)

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 33

IPR2020-00770
United Therapeutics EX2007
Page 3583 of 7335

501. Swatloski, R. P.; Visser, A. E.; Reichert, W. M.; Broker, G. A.; Farina, L. M.; Holbrey, J. D.; Rogers, R. D. "On the solubilization of water with ethanol in hydrophobic hexafluorophosphate ionic liquids," *Green Chem.* **2002**, *4*, 81-87.
502. Visser, A. E.; Holbrey, J. D.; Rogers, R. D. "Room temperature ionic liquids as alternatives to traditional organic solvents in solvent extraction," In *ISEC 2002, Proceeding of the International Solvent Extraction Conference Cape Town, South Africa 17 to 21 March 200*; Sole, K. C.; Cole, P. M.; Preston, J. S.; Robinson, D. J., Eds.; Chris van Rensburg Publications, Melville, South Africa, 2002; Vol. 1; pp 474-480.
503. Visser, A. E.; Reichert, W. M.; Swatloski, R. P.; Willauer, H. D.; Huddleston, J. G.; Rogers, R. D. "Characterization of Hydrophilic and Hydrophobic Ionic Liquids: Alternatives to Volatile Organic Compounds for Liquid-Liquid Separations," In *Ionic Liquids; Industrial Applications to Green Chemistry*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 818; American Chemical Society: Washington DC, 2002; pp 289-308.
504. Visser, A. E.; Rogers, R. D. "Actinide Chemistry in Novel Solvent Media: Room Temperature Ionic Liquids," In *Molten Salts XIII: Proceedings of the International Symposium*, Trulove, P. C.; De long, H. C.; Mantz, R. A.; Stafford, G. R.; Matsunaga, M., Eds.; The Electrochemical Society: Pennington, NJ, 2002; Vol. 2002-19, pp 516-529.
505. Visser, A. E.; Swatloski, R. P.; Reichert, W. M.; Mayton, R.; Sheff, S. Wierzbicki, A.; Davis, Jr. J. H.; Rogers, R. D. "Task-Specific Ionic Liquids Incorporating Novel Cations for the Coordination and Extraction of Hg^{2+} and Cd^{2+}: Synthesis, Characterization, and Extraction Studies," *Env. Sci. Technol.* **2002**, *36*, 2523-2529.
506. Willauer, H. D.; Huddleston J. G.; Rogers, R. D. "Solute Partitioning in Aqueous Biphasic Systems Composed of Polyethylene Glycol and Salt: The Partitioning of Small Neutral Organic Species," *Ind. Eng. Chem. Res.* **2002**, *41*, 1892-1904.
507. Willauer, H. D.; Huddleston, J. G.; Rogers, R. D. "Solvent Properties of Aqueous Biphasic Systems Composed of Polyethylene Glycol and Salt Characterized by the Free Energy of Transfer of a Methylene Group Between the Phases and by a Linear Solvation Energy Relationship," *Ind. Eng. Chem. Res.* **2002**, *41,* 2591-2601.
508. Yamato, K.; Bartsch, R. A.; Dietz, M. L.; Rogers, R. D. "Improved stereospecific synthesis of the *trans*-isomers of dicyclohexano-18-crown-6 and the solid-state structure of the *trans-syn-trans*-isomer," *Tetrahedron Lett.* **2002**, *43*, 2153-2156.
509. Yamato, K.; Bartsch, R. A.; Dietz, M. L.; Broker, G. A.; Rogers, R. D. "Synthesis of chiral *trans-anti-trans*-isomers of dicyclohexano-18-crown-6 via an enzymatic reaction and the solid-state structure of one enantiomer," *Tetrahedron Lett.* **2002**, *43*, 5805-5808.
510. Zhang, H.; Bu, L.; Li, M.; Hong, K.; Visser, A. E.; Rogers, R. D.; Mays, J. W. "Homopolymerization and Block Copolymer Formation in Room Temperature Ionic Liquids using Conventional Free Radical Initiators," In *Ionic Liquids; Industrial Applications to Green Chemistry*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 818; American Chemical Society: Washington DC, 2002; pp 114-124.
511. Abraham, M. H.; Zissimos, A. M.; Huddleston, J. G.; Willauer, H. D.; Rogers, R. D.; Acree, Jr., W. E. "Some Novel Liquid Partitioning Systems: Water-Ionic Liquids and Aqueous Biphasic Systems," *Ind. Eng. Chem. Res.* **2003**, *42*, 413-418.
512. Aqad, E.; Lakshmikantham, M. V.; Cava, M. P.; Broker, G. A.; Rogers, R. D. "Synthesis of Benzo[*c*]selenophene and Derivatives via New Routes," *Org. Lett.* **2003**, *5*, 2519-2521.
513. Guo, Z.; Huddleston, J. G.; Rogers, R. D.; April, G. C. "Reaction Parameter Effects in Metal-Salt-Catalyzed Aqueous Biphasic Pulping Systems," *Ind. Eng. Chem. Res.* **2003**, *42*, 248-253.
514. Guo, Z.; Li, M.; Willauer, H. D.; Huddleston, J. G.; Rogers, R. D. "PEG-Based Aqueous Biphasic Systems as Improvement for Kraft Hardwood Pulping Process," *Chem. Eng. Commun.* **2003**, *190*, 1155-1169.
515. Gutowski, K. E.; Bridges, N. J.; Cocalia, V. A.; Spear, S. K.; Holbrey, J. D.; Swatloski, R. P.; Davis, J. H., Jr.; Rogers, R. D. "Approaches to Nuclear Separations Using Room Temperature Ionic Liquids," *American Nuclear Society GLOBAL 2003 Winter Meeting Proceedings* **2003**; pp 1604-1608.
516. Gutowski, K. E.; Broker, G. A.; Willauer, H. D.; Huddleston, J. G.; Swatloski, R. P.; Holbrey, J. H. "Controlling the aqueous miscibility of ionic liquids: Aqueous biphasic systems of water-miscible ionic liquids and water-structuring salts for recycle, metathesis, and separations," *J. Am. Chem. Soc.* **2003**, *125*, 6632-6633.
517. Helm, M. L.; Loveday, K. D.; Combs, C. M.; Bentzen, E. L.; VanDerveer, D. G.; Rogers, R. D.; Grant, G. J. "Heavy Metal Complexes of Macrocyclic Thioethers," *J. Chem. Crystallogr.* **2003**, *33* 447-455.
518. Holbrey, J. D.; Reichert, W. M.; Nieuwenhuyzen, M.;Johnson, S.; Seddon, K. R.; Rogers, R. D., "Crystal polymorphism in 1-butyl-3-methylimidazolium halides: supporting ionic liquid formation by inhibition of crystallization," *Chem. Commun.* **2003**, 1636-1637.
519. Holbrey, J. D.; Reichert, W. M.; Nieuwenhuyzen, M.; Sheppard, O.; Hardacre, C.; Rogers, R. D., "Liquid Clathrate Formation in Ionic Liquid/Aromatic Mixtures," *Chem. Commun.* **2003**, 476-477.
520. Holbrey, J. D.; Reichert, W. M.; Reddy, R. G.; Rogers, R. D. "Heat Capacities of Ionic Liquids and Their Applications as Thermal Fluids," In *Ionic Liquids as Green Solvents: Progress and Prospects*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 856; American Chemical Society: Washington DC, 2003; pp 121-133.
521. Holbrey, J. D.; Reichert, W. M.; Tkatchenko, I.; Bouajila, E.; Walter, O.; Tommasi, I.; Rogers, R. D. "1,3-Dimethylimidazolium-2-carboxylate: The Unexpected Synthesis of an Ionic Liquid Precursor and Carbene-CO_2 Adduct," *Chem. Commun.* **2003**, 28-29.
522. Holbrey, J. D.; Rogers, R. D. "Physico-chemical properties of ionic liquids: Melting points and phase diagrams," In *Ionic Liquids in Synthesis*; Wasserscheid, P.; Welton, T., Eds.; Wiley-VCH, Weinheim, **2003**; pp 41-55.
523. Holbrey, J. D.; Turner, M. B.; Rogers, R. D. "Selection of Ionic Liquids for Green Chemical Applications," In *Ionic Liquids as Green Solvents: Progress and Prospects*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 856; American Chemical

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 34

IPR2020-00770
United Therapeutics EX2007
Page 3584 of 7335

Society: Washington DC, 2003; pp 2-12.
524. Holbrey, J. D.; Turner, M. B.; Reichert, W. M.; Rogers, R. D. "New ionic liquids containing an appended hydroxyl functionality from the clean, atom-efficient, one-pot reaction of 1-methylimidazole and acid with propylene oxide," *Green Chem.* **2003**, *5*, 731-736.
525. Holbrey, J. D.; Visser, A. E.; Rogers, R. D. "Physico-chemical properties of ionic liquids: Solubility and solvation in ionic liquids," In *Ionic Liquids in Synthesis*; Wasserscheid, P.; Welton, T., Eds.; Wiley-VCH, Weinheim, 2003; pp 68-81.
526. Holbrey, J. D.; Visser, A. E. Spear, S. K.; Reichert, W. M.; Swatloski, R. P.; Broker, G. A.; Rogers, R. D. "Mercury(II) partitioning from aqueous solutions with a new, hydrophobic ethylene-glycol functionalized bis-imidazolium ionic liquid," *Green Chem.* **2003**, *5*, 129-135.
527. Huddleston, J. G.; Looney, T. K.; Broker, G. A.; Griffin, S. T.; Spear, S. K.; Rogers, R. D. "Comparative Behavior of Poly(ethylene glycol) Hydrogels and Poly(ethylene glycol) Aqueous Biphasic Systems," *Ind. Eng. Chem. Res.* **2003**, *42*, 6088-6095.
528. Huddleston, J. G.; Willauer, H. D.; Rogers, R. D. "Phase Diagram Data for Several PEG + Salt Aqueous Biphasic Systems at 25 ºC," *J. Chem. Eng. Data* **2003**, *48*, 1230-1236.
529. Park, G.; Przyborowska, A. M.; Ye, N.; Tsoupas, N. M.; Bauer, C. B.; Broker, G. A.; Rogers, R. D.; Brechbiel, M. W.; Planalp, R. P. "Steric effects caused by N-alkylation of the tripodal chelator N, N', N''-tris(2-pyridylmethyl)-*cis,cis*-1,3,5-triaminocyclohexane (tachpyr): structural and electronic properties of the Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) complexes," *J. Chem. Soc., Dalton Trans.* **2003**, 318-324.
530. Rajagopal, D.; Lakshmikantham, M. V.; Cava, M. P.; Broker, M. P.; Rogers, R. D. "Synthesis and Transformations of Some New 2,4-Bismethylene-1,3-ditelluretanes," *Tetrahedron Lett.* **2003**, *44*, 2397-2400.
531. Rogers, R. D.; Seddon, K. R. "Ionic Liquids – Solvents of the Future?" *Science* **2003**, *302*, 792-793.
532. Shaughnessy, K. H.; Klingshirn, M. A.; P'Pool, S. J.; Holbrey, J. D.; Rogers, R. D. "Polar, Non-Coordinating Ionic Liquids as Solvents for Coordination Polymerization of Olefins," In *Ionic Liquids as Green Solvents: Progress and Prospects*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 856; American Chemical Society: Washington DC, 2003; pp 300-313.
533. Swatloski, R. P.; Holbrey, J. D.; Rogers, R. D. "Ionic liquids are not always green: hydrolysis of 1-butyl-3-methylimidazolium hexafluorophosphate," *Green Chem.* **2003**, *5*, 361-363.
534. Turner, M. B.; Spear, S. K.; Huddleston, J. G.; Holbrey, J. D.; Rogers, R. D. "Ionic Liquid-Induced Inactivation and Unfolding of Cellulase from *Trichoderma reesei*, *Green Chem.* **2003**, *5*, 443-447. (Also in *Chemical Biology Virtual Journal*, **2003**, Issue 15: http://www.rsc.org/cgi-shell/empower.exe?DB=rsc-cbvjournal&B=F22003&B=F415&ISSNO=15.)
535. Visser, A. E.; Jensen, M. P.; Laszak, I.; Nash, K. L.; Choppin, G. R.; Rogers, R. D. "Uranyl Coordination Environment in Hydrophobic Ionic Liquids: An in Situ Investigation," *Inorg. Chem.* **2003**, *42*, 2197-2199.
536. Visser, A. E.; Rogers, R. D. "Room Temperature Ionic Liquids: New Solvents for f-Element Separations and Associated Solution Chemistry," *J. Solid State Chem.* **2003**, *171*, 109-113.
537. Visser, A. E.; Swatloski, R. P.; Reichert, W. M.; Willauer, H. D.; Huddleston, J. G.; Rogers, R. D. "Room Temperature Ionic Liquids as Replacements for Traditional Organic Solvents and Their Applications Towards "Green Chemistry" in Separation Processes," In *Green Industrial Applications of Ionic Liquids*, Rogers, R. D.; Seddon, K. R.; Volkov, S. (Eds.); Kluwer: Dordrecht, 2003; pp 137-156.
538. Burns, C. J.; Neu, M.; Boukhalfa, H.; Gutowski, K. E.; Bridges, N. J.; Rogers, R. D. "The Actinides," in *Comprehensive Coordination Chemistry-II From Biology to Nanotechnology*, McCleverty, J. A.; Meyer, T. J., Eds., Vol. 3 *Coordination Chemistry of the s, p, and f Metals*, Parkin, G. F. R. Ed.; Elsevier Pergamon: Amsterdam, 2004; pp 189-346.
539. Chen, J.; Spear, S. K.; Huddleston, J. G.; Holbrey, J. D.; Rogers, R. D. "Application of polyethylene glycol-based aqueous biphasic reactive extraction to the oxidation of olefins." *J. Chromatogr. B* **2004**, *807*, 145-149.
540. Chen, J.; Spear, S. K.; Huddleston, J. G.; Holbrey, J. D.; Swatloski, R. P.; Rogers, R. D. "Application of poly(ethylene glycol)-based aqueous biphasic systems as reaction and reactive extraction media," *Ind. Eng. Chem. Res.* **2004**, *43*, 5358-5364.
541. Gilbert, T. M.; Littrell, J. C.; Talley, C. E.; Vance, M. A.; Dallinger, R. F.; Rogers, R. D. "Experimental and Computational Studies of the Metal-Metal Stretching Vibration in $X_3M{\equiv}MX_3$ Compounds (X = Alkoxide, Alkyl, Amide)," *Inorg. Chem.* **2004**, *43*, 1762-1769.
542. Griffin, S. T.; Spear, S. K.; Rogers, R. D. "Effects of speciation on partitioning of iodine in aqueous biphasic systems and onto ABEC® resins," *J. Chromatogr. B* **2004**, *807*, 151-156.
543. Holbrey, J. D.; Reichert, W. M.; Rogers. R. D. "Crystal structures of imidazolium bis(trifluoromethanesulfonyl)imide 'ionic liquid' salts: The first organic salt with a cis-TFSI anion conformation," *J. Chem. Soc., Dalton Trans.* **2004**, 2267-2271.
544. Huddleston, J. G.; Willauer, H. D.; Burney, M. T.; Tate, L. J.; Carruth, A. D.; Rogers, R. D. "Comparison of an Empirical and a Theoretical Linear Solvation Energy Relationship Applied to the Characterization of Solute Distribution in a Poly(ethylene) Glycol-Salt Aqueous Biphasic System," *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 549-558.
545. Katritzky, A. R.; Tämm, K.; Kuanar, M.; Fara, D. C.; Oliferenko, A.; Oliferenko, P.; Huddleston, J. G.; Rogers, R. D. "Aqueous Biphasic Systems. Partitioning of Organic Molecules: a QSPR Treatment," *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 136-142.
546. Klingshirn, M. A.; Spear, S. K.; Subramanian, R.; Holbrey, J. D.; Huddleston, J. G.; Rogers, R. D. "Gellation of ionic liquids using a cross-linked poly(ethylene glycol) gel matrix," *Chem. Mater.* **2004**, *16*, 3091-3097.
547. Luo, H.; Dai, S.; Bonnesen, P. V.; Buchanan, A. C.; Holbrey, J. D.; Bridges, N. J.; Rogers, R. D. "Extraction of Cesium Ions from Aqueous Solutions Using Calix[4]arene-bis(tert-octylbenzo-crown-6) in Ionic Liquids," *Anal. Chem.* **2004**, 76, 3078-3083.
548. Oliferenko, A. A.; Oliferenko, P. V.; Huddleston, J. G.; Rogers, R. D.; Palyulin, V. A.; Zefirov, N. S.; Katritzky, A. R.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 35

IPR2020-00770
United Therapeutics EX2007
Page 3585 of 7335

"Theoretical Scales of Hydrogen Bond Acidity and Basicity for Application in QSAR/QSPR Studies and Drug Design. Partitioning of Aliphatic Compounds," *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 1042-1055.

549. Spear, S. K.; Holbrey, J. D.; Rogers, R. D. "Liquid Clathrates," In *Encyclopedia of Supramolecular Chemistry*, Atwood, J. L.; Steed, J. W. (Eds.); Marcel Dekker: New York, 2004; pp 804-808.
550. Swatloski, R. P.; Holbrey, J. D.; Memon, S. B.; Caldwell, G. A.; Caldwell, K. A.; Rogers, R. D. "Using *Caenorhabditis elegans* to probe toxicity of 1-alkyl-3-methylimidazolium chloride based ionic liquids," *Chem. Commun.* **2004**, 668-669.
551. Turner, M. B.; Holbrey, J. D.; Spear, S. K.; Rogers, R. D. "Production of bioactive cellulose films reconstituted from ionic liquids," *Biomacromolecules* **2004**, *5*, 1379-1384.
552. Wang, W.; Shen, G.; Swatloski, R. P.; Farag, R.; Broughton, Jr., R. M.; Rogers, R. D. "Cellulose Fibers Extruded from Ionic Liquids," In *Proceedings of the International Nonwovens Technical Conference, Toronto Canada, September 20-23, 2004*, INDA, Association of the Nonwoven Fabrics Industry: Cary, NC, 2004.
553. Ye, N.; Park, G.; Przyborowska, A. M.; Sloan, P. E.; Clifford, T.; Bauer, C. B.; Broker, G. A.; Rogers, R. D.; Ma, R.; Torti, S. V.; Brechbiel, M. W.; Planalp, R. P., "Nickel(II), copper(II) and zinc(II) binding properties and cytotoxicity of tripodal, hexadentate tris(ethylenediamine)– analogue chelators," *Dalton Trans.* **2004**, 1304-1311. (Among the Top Ten accessed papers for *Dalton Trans.* June 2004.)
554. Chen, J.; Spear, S. K.; Huddleston, J. G.; Rogers, R. D. "Polyethylene glycol and solutions of polyethylene glycol as green reaction media," *Green Chem.* **2005**, *7*, 64-82. [This was the cover article for this issue of *Green Chemistry*. Reported to be the 10th most accessed article in *Green Chemistry* in 2006.]
555. Childers, M. L.; Su, F.; Przyborowska, A. M.; Bishwokarma, B.; Park, G.; Brechbiel, M. W.; Torti, S. V.; Torti, F. M.; Broker, G.; Alexander, J. S.; Rogers, R. D.; Ruhlandt-Senge, K.; Planalp, R. P. "Pyridine-ring alkylation of cytotoxic *N, N', N''*-tris(2-pyridylmethyl)-*cis,cis*-1,3,5-triaminocyclohexane chelators: Structural and electronic properties of the Mn^{II}, Fe^{II}, Ni^{II}, Cu^{II} and Zn^{II} complexes," *Eur. J. Inorg. Chem.* **2005**, *19*, 3971-3982.
556. Clapp, L. A.; Siddons, C. J.; Whitehead, J. R.; VanDerveer, D. J.; Rogers, R. D.; Griffin, S. T.; Jones, S. B.; Hancock, R. D. "Factors Controlling Metal-Ion Selectivity in the Binding Sites of Calcium-Binding Proteins. The Metal Binding Properties of Amide Donors. A Crystallographic and Thermodynamic Study," *Inorg. Chem.* **2005**, *44*, 8495-8502.
557. Cocalia, V. A.; Holbrey, J. D.; Gutowski, K. E.; Bridges, N. J.; Rogers; R. D. "Separations of Metal Ions Using Ionic Liquids: The Challenges of Multiple Mechanisms," In *Proceedings of the International Solvent Extraction Conference, Solvent Extraction for Sustainable Development (ISEC 2005) Beijing, China 19-23 September 2005*; China Academic Journal Electronic Publishing House; Beijing, 2005; pp 39-46.
558. Cocalia, V. A.; Jensen, M. P.; Holbrey, J. D.; Spear, S. K.; Rogers, R. D. "Identical Extraction Behavior and Coordination of Trivalent and Hexavalent f-Element Cations Using Ionic Liquid and Molecular Solvents," *Dalton Trans.* **2005**, 1966-1971.
559. DeVasher, R. B.; Spruell, J. M.; Dixon, D. A.; Broker, G. A.; Griffin, S. T.; Rogers, R. D.; Shaughnessy, K. H. "Experimental and Computational Study of Steric and Electrnic Effects n the Coordination of Bulky, Water-Soluble Alkylphosphines to Palladium under Reducing Conditions: Correlation to Catalytic Activity," *Organometallics* **2005**, *245*, 962-971.
560. Elshani, S.; Wai, C. M.; Shreeve, J. M.; Rogers, R. D.; Bartsch, R. A. "Synthesis of Proton-Ionizable Acyclic, Macrocyclic and Macrobicyclic Compounds Containing One or Two Triazole Groups," *J. Heterocyclic Chem.* **2005**, *42*, 621-629.
561. Fox, P. A.; Griffin, S. T.; Reichert, W. M.; Salter, E. A.; Smith, A. B.; Tickell, M. D.; Wicker, B. F.; Cioffi, E. A.; Davis, Jr. J. H.; Rogers, R. D.; Wierzbicki, A. "Exploiting isolobal relationships to create new ionic liquids: Novel room-temperature ionic liquids based upon (*N*-alkylimidazole)(amine)BH_2^+ "boronium" ions," *Chem. Commun.* **2005**, 3679-3681.
562. Gutowski, K. E.; Holbrey, J. D.; Rogers, R. D.; Dixon, D. A. "Prediction of the Formation and Stabilities of Energetic Salts and Ionic Liquids Based on ab Initio Electronic Structure Calculations," *J. Chem. Phys. B* **2005**, *109*, 23196-23208.
563. Gutowski, K. E.; Bridges, N. J.; Cocalia, V. A.; Spear, S. K.; Visser, A. E.; Holbrey, J. D.; Davis, Jr., J. H.; Rogers, R. D. "Ionic Liquid Technologies for Utilization in Nuclear-Based Separations," In *Ionic Liquids IIIB: Fundamentals, Progress, Challenges, and Opportunities - Transformations and Processes*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 902; American Chemical Society: Washington DC, 2005; pp 33-48.
564. Haque, A.; Daly, D. T.; Rogers, R. D.; Mobley, C.; Swatloski, R. P. "Effects of MAPP as Coupling Agent on the Performance of Cellulose/Polypropylene Laminated Composites," In *Proceedings of the 3rd International Conference on Eco-Composites*, Royal Institute of Technology, Stockholm, Sweden, June 20-21, 2005.
565. Holbrey, J. D.; Chen, J.; Turner, M. B.; Swatloski, R. P.; Spear, S. K.; Rogers, R. D., "Applying Ionic Liquids for Controlled Processing of Polymer Materials," In *Ionic Liquids in Polymer Systems: Solvents, Additives, and Novel Applications*, Brazel, C. S.; Rogers, R. D. (Eds.); ACS Symposium Series 913; American Chemical Society: Washington DC, 2005; pp 71-87.
566. Katritzky, A. R.; Singh, S.; Kirichenko, K.; Holbrey, J. D.; Smiglak, M.; Reichert, W. M.; Rogers, R. D. "1-Butyl-3-methylimidazolium 3,5-dinitro-1,2,4-triazolate: A novel ionic liquid containing a rigid, planar energetic anion," *Chem. Commun.* **2005**, 868-870. (Among the Top Five most accessed papers for *Chem. Commun.* February 2005.)
567. Klingshirn, M. A.; Rogers, R. D.; Shaughnessy, K. H., "Palladium-catalyzed hydroesterification of styrene derivatives in the presence of ionic liquids," *J. Organomet. Chem.* **2005**, *690*, 3620-3626.
568. Klingshirn, M. A.; Spear, S. K.; Holbrey, J. D.; Huddleston, J. G.; Rogers, R. D. "Synthesis, Characterization, and Application of Cross-Linked Poly(ethylene glycol) Networks Used for Gelation of Ionic Liquids," In *Ionic Liquids in Polymer Systems: Solvents, Additives, and Novel Applications*, Brazel, C. S.; Rogers, R. D. (Eds.); ACS Symposium Series 913; American Chemical Society: Washington DC, 2005; pp 149-162.
569. Klingshirn, M. A.; Spear, S. K.; Holbrey, J. D.; Rogers, R. D. "Ionic liquids as solvent and solvent additives for the synthesis of

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 36

IPR2020-00770
United Therapeutics EX2007
Page 3586 of 7335

sol-gel materials," *J. Mater. Chem.* **2005**, *15*, 5174-5180.

570. Mobley, C.; Ramasetty, A.; Haque, A.; Poplin, J. H.; Daly, D. T.; Rogers, R. D. "Affordable Bio-polymer Matrix Composites for Lightweight Automotive Components," In *Proceedings of the Sixth Annual Global Automotive Conference*, Western Kentucky University, Bowling Green, KY, April 6-8, 2005.
571. Moody, M. L.; Willauer, H. D.; Griffin, S. T.; Huddleston, J. G.; Rogers, R. D. "Solvent Property Characterization of Poly(ethylene glycol)/Dextran Aqueous Biphasic Systems Using the Free Energy of Transfer of a Methylene Group and a Linear Solvation Energy Relationship," *Ind. Eng. Chem. Res.* **2005**, *44*, 3749-3760.
572. Moulthrop, J. S.; Swatloski, R. P.; Moyna, G.; Rogers, R. D. "High-resolution ^{13}C NMR studies of cellulose and cellulose oligomers in ionic liquid solutions," *Chem. Commun.* **2005**, 1557-1559.
573. P'Pool, S. J.; Klingshirn, M. A.; Rogers, R. D.; Shaughnessy, K. H. "Kinetic Study of the Oxidative Addition of Methyl Iodide to Vaska's Complex in Ionic Liquids," *J. Organomet. Chem.* **2005**, *690*, 3522-3528.
574. Sliger, M. D.; Broker, G. A.; Griffin, S. T.; Rogers, R. D.; Shaughnessy, K. H. "Di-*t*-butyl(ferrocenylphosphine: Air-Stability, Structural Characterization, Coordination Chemistry, and Applications to Palladium-Catalyzed Cross-Coupling Reactions," *J. Organomet. Chem.* **2005**, *690*, 1478-1486.
575. Sliger, M. D.; P'Pool, S. J.; Traylor, R. K.; McNeill III, J.; Young, S. H.; Hoffman, N. W.; Klingshirn, M. A.; Rogers, R. D.; Shaughnessy, K. H. "Promoting Effect of Ionic Liquids on Ligand Substitution Reactions," *J. Organomet. Chem.* **2005**, *690*, 3540-3545.
576. Turner, M. B.; Holbrey, J. D; Spear, S. K.; Pusey, M. L.; Rogers, R. D. "Effects of Oxygen-Containing Functional Groups on Protein Stability in Ionic Liquid Solutions," In *Ionic Liquids IIIB: Fundamentals, Progress, Challenges, and Opportunities - Transformations and Processes*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 902; American Chemical Society: Washington DC, 2005; pp 233-243.
577. Turner, M. B.; Spear, S. K.; Holbrey, J. D.; Daly, D. T.; Rogers, R. D. "Ionic liquid-reconstituted cellulose composites as solid support matrices for biocatalyst immobilization," *Biomacromolecules* **2005**, *6*, 2497-2502.
578. Broughton, R.; Wang, W.; Shen, G.; Farag, R.; Swatloski, R. P.; Rogers, R. D. "Keynote Address: New Solvent for Cellulose Extrusion," In *Proceedings Beltwide Cotton Conferences,* National Cotton Council: Memphis, TN, 2005, pp 3291/1-3291/5 (ISSN: 1059-2644).
579. Cocalia, V. A.; Gutowski, K. E.; Rogers, R. D. **"**The coordination chemistry of actinides in ionic liquids: A review of experiment and simulation," *Coord. Chem. Rev.* **2006**, *250*, 755-764.
580. Cocalia, V. A.; Holbrey, J. D.; Gutowski, K. E.; Bridges, N. J.; Rogers; R. D. "Separations of Metal Ions Using Ionic Liquids: The Challenges of Multiple Mechanisms," *Tsinghua Sci. Technol.* **2006**, *11*, 188-193.
581. Cocalia, V. A.; Holbrey, J. D.; Spear, S. K.; Jensen, M. P.; Rogers, R. D. "Partitioning of Transuranic Metal Ions to Ionic Liquids Containing the Ionizable Complexant Cyanex-272," In *Molten Salts XIV: Proceedings of the International Symposium*, Trulove, P. C.; De long, H. C.; Mantz, R. A.; Stafford, G. R.; Matsunaga, M., Eds.; The Electrochemical Society: Pennington, NJ, 2006; Vol. PV 2004-24; pp 779-789.
582. Drab, D. M.; Smiglak, M.; Rogers, R. D. "Should the Concepts of Green Chemistry be Restrictive or Prescriptive? The Greener Synthesis of High-Performance, Energetic Ionic Liquid Materials" *Chimica Oggi/CHEMISTRY TODAY* **2006**, *24*, 27-30.
583. Fort, D. A.; Swatloski, R. P.; Moyna, P.; Rogers, R. D.; Moyna, G. "Use of Ionic Liquids in the Study of Fruit Ripening by High-Resolution ^{13}C NMR Spectroscopy: 'Green' Solvents Meet Green Bananas," *Chem Commun.* **2006**, 714-716. (Highlighted as a Hot Article by *Chem. Commun.* January 16, 2006, URL: http://www.rsc.org/Publishing/Journals/cc/index.asp; last accessed January 19, 2006; Highlighted in Ritter, S. "Ionic liquids go bananas," *Chemical & Engineering News*, February 6, 2006, p. 48; Listed as a 'Top Ten' accessed article by *Chem. Commun.* for the month of January 2006 at http://www.rsc.org/chemcomm; Highlighted in Lavender, R. "Following the ripening of bananas," *Chemical Science* (an RSC web supplement) February 23, 2006 at URL: http://www.rsc.org/Publishing/ChemScience/Volume/2006/03/ripening_of_bananas.asp; last accessed April 17, 2006.)
584. Griffin, S. T.; Dilip, M.; Spear, S. K.; Huddleston, J. G.; Rogers, R. D. "The Opposite Effect of Temperature on Polyethylene Glycol-Based Aqueous Biphasic Systems versus Aqueous Biphasic Extraction Chromatographic Resins," *J. Chromatogr. B* **2006**, *844*, 23-31.
585. Gutowski, K. E.; Bridges, N. J.; Rogers, R. D. "Actinide Structural Chemistry," In *The Chemistry of the Actinide and Transactinide Elements*, 3rd Edition. Morss, L. R.; Edelstein, N.; Fuger, J.; Katz, J. K., Eds., Springer: Dordrecht, 2006; Vol. 4 pp 2380-2523.
586. Gutowski, K. E.; Rogers, R. D.; Dixon, D. A. "Accurate Thermochemical Properties for Energetic Materials Applications. I. Heats of Formation of Nitrogen-Containing Heterocycles and Energetic Precursor Molecules from Electronic Structure Theory," *J. Chem. Phys. A* **2006**, *110*, 11890-11897.
587. Haque, A.; Mobley, C.; Daly, D. T.; Rogers, R. D.; Swatloski, R. P.; Ramasetty, A. "Effects of MAPP as coupling agent on the performance of regenerated cellulose film reinforced polypropylene composites," *Proceedings of the American Society for Composites, Technical Conference* **2006**, *21st*, 272/1-272/15.
588. Hines, C. C.; Reichert, W. M.; Griffin, S. T.; Bond, A. H.; Snowwhite, P. E.; Rogers, R. D. "Exploring Control of Cadmium Halide Coordination Polymers via Control of Cadmium(II) Coordination Sites Utilizing Short Multidentate Ligands," *J. Mol. Struct.* **2006**, *796*, 76-85.
589. Holbrey, J. D.; Reichert, W. M.; Smiglak, M.; Spear, S. K.; Yang, H.; Manju, K.; Kirichenko, K.; Katritzky, A. R.; Thrasher, J. S.; Sun, L. Y.; Rogers, R. D. "Stability and Thermal Decomposition of Quaternary and Protonated Imidazolium Nitrate and

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 37

IPR2020-00770
United Therapeutics EX2007
Page 3587 of 7335

Picrate Salts," In *Molten Salts XIV: Proceedings of the International Symposium*, Trulove, P. C.; De long, H. C.; Mantz, R. A.; Stafford, G. R.; Matsunaga, M., Eds.; The Electrochemical Society: Pennington, NJ, 2006; Vol. PV 2004-24; pp 396-406.

590. Holbrey, J. D.; Vigour, K. B.; Reichert, W. M.; Rogers, R. D. "The structure of $[Co(H\text{-}tptz)Cl_3]\cdot H_2O$ (tptz = 2,4,6-tri(2-pyridyl)-1,3,5-triazine) prepared by crystallization from the ionic liquid, *N*-butyl-*N*-methyl-pyrrolidinium *bis*(trifluoromethanesulfonyl)imide," *J. Chem. Crystallogr.* **2006**, *36*, 799-804.
591. Katritzky, A. R.; Yang, H.; Zhang, D.; Kirichenko, K.; Smiglak, M.; Holbrey, J. D.; Reichert, W. M.; Rogers, R. D. "Strategies Toward the Design of Energetic Ionic Liquids: Nitro- and Nitrile-substituted *N*,*N'*-Dialkylimidazolium Salts," *New. J. Chem.* **2006**, *30*, 349-358.
592. Katritzky, A. R.; Singh, S.; Kirichenko, K.; Smiglak, M.; Holbrey, J. D.; Reichert, W. M.; Spear, S. K.; Rogers, R. D. "In search of ionic liquids incorporating azolate anions," *Chem. Eur. J.* **2006**, *12*, 4630-4641.
593. Moore, L. R.; Cooks S. M.; Anderson, M. S.; Schanz, H.-J.; Griffin,S. T.; Rogers, R. D.; Kirk, M. C.; Shaughnessy, K. H. "Synthesis and Characterization of Water-Soluble Silver and Palladium Imidazol-2-ylidene Complexes with Noncoordinating Anionic Substituents," *Organometallics* **2006**, *25*, 5151-5158.
594. Parks, B. W.; Gilbertson, R. D.; Hutchison, J. E.; Rather Healey, E.; Weakley, T. J. R.; Rapko, B. M.; Hay, B. P.; Sinkov, S. I.; Broker, G. A.; Rogers, R. D. "Solution and Structural Investigations of Ligand Preorganization in Trivalent Lanthanide Complexes of Bicyclic Malonamides," *Inorg. Chem.* **2006**, *45*, 1498-1507.
595. Pernak, J.; Smiglak, M.; Griffin, S. T.; Hough, W. L.; Wilson, T. B.; Pernak, A.; Zabielska-Matejuk, J.; Fojutowski, A.; Kita, K.; Rogers, R. D. "Long alkyl chain quaternary ammonium-based ionic liquids and potential applications," *Green Chem.* **2006**, *8*, 798-806.
596. Reichert, W. M.; Holbrey, J. D.; Vigour, K. B.; Morgan, T. D.; Broker, G. A.; Rogers, R. D. "Approaches to Crystallization From Ionic Liquids: Complex Solvents-Complex Results, or, a Strategy for Controlled Formation of New Supramolecular Architectures?" *Chem Commun.* **2006**, 4767-4779 (Invited Feature Article).
597. Remsing, R. C.; Swatloski, R. P.; Rogers, R. D.; Moyna, G. "Mechanism of cellulose dissolution in the ionic liquid 1-n-butyl-3-methylimidazolium chloride: a ^{13}C and $^{35/37}Cl$ NMR relaxation study on model systems," *Chem. Commun.* **2006**, 1271-1273.
598. Smiglak, M.; Reichert, W. M.; Holbrey, J. D.; Wilkes, J. S.; Sun, L.; Thrasher, J. S.; Kirichenko, K.; Singh, S.; Katritzky, A. R.; Rogers, R. D. "Combustible Ionic Liquids by Design: Is Laboratory Safety Another Ionic Liquid Myth?" *Chem. Commun.* **2006**, 2554-2556. (Highlighted as a Hot Article by *Chem. Commun.* June 5, 2006, URL: http://www.rsc.org/Publishing/Journals/cc/index.asp; last accessed June 6, 2006); Highlighted in *Chemical Science* (an RSC web supplement), June 20, 2006, URL: http://www.rsc.org/Publishing/ChemScience/Volume/2006/07/ionic_combustible.asp; last accessed April 14, 2007.)
599. Swatloski, R. P.; Holbrey, J. D.; Weston, J. L.; Rogers, R. D. "Preparation of magnetic cellulosic composites using ionic liquids," *Chimica Oggi/CHEMISTRY TODAY* **2006**, *24*, 31-35.
600. Bridges, N. J.; Gutowski, K. E.; Rogers, R. D. "Investigation of aqueous biphasic systems formed from solutions of chaotropic salts with kosmotropic salts (salt-salt ABS)," *Green Chem.* **2007**, *9*,177-183.
601. Bridges, N. J.; Hines, C. C.; Smiglak, M.; Rogers, R. D. "An Intermediate for the Clean Synthesis of Ionic Liquids: Isolation and Crystal Structure of 1,3-Dimethylimidazolium Hydrogen Carbonate Monohydrate," *Chem. Eur. J.* **2007**,*13*, 5207-5212.
602. Cantorias, M. V.; Howell, R. C.; Todaro, L.; Cyr, J. E.; Berndorff, D.; Rogers, R. D.; Francesconi, L. C., "MO Tripeptide Diastereomers (M = $^{99/99m}Tc$, Re): Models to Identify the Structure of ^{99m}Tc Peptide Targeted Radiopharmaceuticals," *Inorg. Chem.* **2007**, *46*, 7326-7340.
603. Cocalia, V. A.; Rogers, R. D. "Ionic Liquid Impregnated Resins in Solid-Liquid Separations," *ECS Transactions* **2007**, *3*, 123-134.
604. Cordes, D. B.; Sharma, C. V. K.; Rogers, R. D. "Enantiomorphic Helical Coordination Polymers of $\{[M(pyrimidine)(OH_2)_4][SiF_6]\cdot H_2O\}_\infty$, (M = Co^{2+} , Cu^{2+}, Zn^{2+})," *Cryst. Growth Des.* **2007**, *7*, 1943-1945.
605. Fort, D. A.; Remsing, R. C.; Swatloski, R. P.; Moyna, P.; Moyna, G.; Rogers, R. D. "Can ionic liquids dissolve wood? Processing and analysis of lignocellulosic materials with 1-*n*-butyl-3-methylimidazolium chloride," *Green Chem.* **2007**, *9*, 63-69.
606. Gutowski, K. R.; Cocalia, V. A.; Griffin, S. T.; Bridges, N. J.; Dixon, D. A.; Rogers, R. D. "Interactions of 1-Methylimidazole with $UO_2(CH_3CO_2)_2$ and $UO_2(NO_3)_2$: Structural, Spectroscopic, and Theoretical Evidence for Imidazole Binding to the Uranyl Ion," *J. Am. Chem. Soc.* **2007** *129*, 526-536.
607. Gutowski, K. E.; Rogers, R. D.; Dixon, D. A. "Accurate Thermochemical Properties for Energetic Materials Applications. II. Heats of Formation of Imidazolium-, 1,2,4-Triazolium-, and Tetrazolium-Based Energetic Salts from Isodesmic and Lattice Energy Calculations" *J. Phys. Chem. B* , **2007**, *111*, 4788-4800.
608. Hines, C. C.; Bauer, C. B.; Rogers, R. D. "Lanthanide Polyether Complexation Chemistry: The Interaction of Hydrated Lanthanide(III) Nitrate Salts with an Acyclic 18-crown-6 Analog, Pentaethylene Glycol," *New J. Chem.* **2007**, *31*, 762-769.
609. Hough, W. L.; Rogers, R. D., "Ionic Liquids Then and Now: From Solvents to Materials to Active Pharmaceutical Ingredients," *Bull. Chem. Soc. Jpn.* **2007**, *80*, 2262-2269.
610. Hough, W. H.; Smiglak, M.; Rodríguez, H.; Swatloski, R. P.; Spear, S. K.; Daly, D. T.; Pernak, J.; Grisel, J. E.; Carliss, R. D.; Soutullo, M. D.; Davis, Jr., J. H.; Rogers, R. D. "The Third Evolution of Ionic Liquids: Active Pharmaceutical Ingredients," *New J. Chem.* **2007**, *31*, 1429-1436. (August Cover Article. Highlighted in Parker, D. "The Third Age of Ionic Liquids?" *Chemistry World*, August 2007, *4*, p 30 and *Chem. Sci.* **2007**, *4*, C59. Also in *Chemical Biology Virtual Journal*, **2007**, Issue 15: http://www.rsc.org/cgi-shell/empower.exe?DB=rsc-cbvjournal&B=F22003&B=F415&ISSNO=15.)

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 38

IPR2020-00770
United Therapeutics EX2007
Page 3588 of 7335

611. Pernak, J.; Feder-Kubis, J.; Cieniecka-Rosłonkiewicz, A.; Fischmeister, C.; Griffin, S. T.; Rogers, R. D. "Synthesis and Properties of Chiral Imidazolium Ionic Liquids with a (*1R,2S,5R*)-(–)-Menthoxymethyl Substituent," *New. J. Chem.* **2007**, *31*, 879-892. [Erratum: *New. J. Chem.* **2007**, *31*, 1022.]
612. Pernak, J.; Syguda, A.; Mirska, I.; Pernak, A.; Nawrot, J.; Prądzyńska, A.; Griffin, S. T.; Rogers, R. D. "Choline-Derivative-Based Ionic Liquids,"*Chem. Eur. J.* **2007**, *13*, 6817-6827.
613. Poplin, J. H.; Rudkevich, D. M.; Swatloski, R. P.; Rogers, R. D. "Development of Ionic Liquid Membranes for NO_x Gas Detection and Storage Utilizing Calix[4]Arenes," *ECS Transactions* **2007**, *3*, 105-108.
614. Poplin, J. H.; Swatloski, R. P.; Holbrey, J. D.; Spear, S. K.; Metlen, A.; Grätzel, M.; Nazeeruddin, M. K.; Rogers, R. D. "Sensor Technologies Based on a Cellulose Support," *Chem. Commun.* **2007**, 2025-2027.
615. Pusey, M. L.; Paley, M. S.; Turner, M. B.; Rogers, R. D. "Protein Crystallization Using Room Temperature Ionic Liquids," *Cryst. Growth Des.* **2007**, *7*, 787-793.
616. Reichert, W. M.; Holbrey, J. D.; Swatloski, R. P.; Gutowski, K. E.; Visser, A. E.; Nieuwenhuyzen, M.; Seddon, K. R.; Rogers, R. D. "Solid-state analysis of low-melting 1,3-dialkylimidazolium hexafluorophosphate salts (ionic liquids) by combined X-ray crystallographic and computational analyses," *Cryst. Growth Des.* **2007**, *7*, 1106-1114.
617. Rogers, R. D. "Reflections on Ionic Liquids," Nature **2007**, *447*, 917-918.
618. Smiglak, M.; Holbrey, J. D.; Griffin, S. T.; Reichert, W. M.; Swatloski, R. P.; Katritzky, A. R.; Yang, H.; Zhang, D.; Kirichenko, K.; Rogers, R. D. "Ionic Liquids *via* reaction of the zwitterionic 1,3-dimethylimidazolium-2-carboxylate with protic acids. Overcoming synthetic limitations and establishing new halide free protocols for the formation of ILs" *Green Chem.* **2007**, *9*, 90-98.
619. Smiglak, M.; Metlen, A.; Rogers, R. D. "The Second Evolution of Ionic Liquids: From Solvents and Separations to Advanced Materials - Energetic Examples from the Ionic Liquid Cookbook," *Acc. Chem. Res.* **2007**, *40*, 1182-1192.
620. Spear, S. K.; Griffin, S. T.; Granger, K. S.; Huddleston, J. G.; Rogers, R. D. "Renewable Plant-Based Soybean Oil Methyl Esters as Alternatives to Organic Solvents," *Green Chem.* **2007**, *9*, 1008–1015.
621. Sun, N.; Swatloski, R. P.; Maxim, M. L.; Broughton, Jr., R. M.; Spear, S. K.; Daly, D. T.; Haque, A.; Harland, A. G.; Rogers, R. D. "Cellulose Fibers Prepared from Direct Dissolution of Cellulose in Ionic Liquids," *Proceedings of the 4th International Conference of Textile Research Division NRC, Cairo, Egypt, April 14-17, 2007; Textile Processing : State of the Art & Future Developments* **2007**, *4*, 139-143.
622. Visser, A. E.; Huddleston, J. G.; Holbrey, J. D.; Reichert, W. M.; Swatloski, R. P.; Rogers, R. D. "Hydrophobic *n*-Alkyl-*N*-Isoquinolinium Salts: Ionic Liquids and Low melting Solids," In *Ionic Liquids IV Not Just Solvents Anymore*, Brennecke, J. F.; Rogers, R. D.; Seddon K. R. (Eds.); ACS Symposium Series 975; American Chemical Society: Washington DC, 2007; pp 362-380.
623. Whitcomb, D. R.; Swatloski, R. P.; Rogers, R. D. "Mode of complex formation between thiones and silver ion within a photothermographic formulation: The crystal and molecular structure of hexa-(silver-5-methyl-2-mercaptobenzimidazole THF)," *J. Imaging Sci. Technol.* **2007**, *51*, 547-551.
624. Bagheri, M.; Rodríguez, H.; Swatloski, R. P.; Spear S. K.; Daly, D. T.; Rogers, R. D. "Ionic liquid-based preparation of cellulose-dendrimer films as solid supports for enzyme immobilization," *Biomacromolecules* **2008**, *9*, 381-387.
625. Bailey, M. M.; Townsend, M. B.; Jernigan, P. L.; Sturdivant, J.; Hough-Troutman, W. L.; Rasco, J. F.; Swatloski, R. P.; Rogers, R. D.; Hood, R. D., "Developmental toxicity assessment of the ionic liquid 1-butyl-3-methylimidazolium chloride in CD-1 mice," *Green Chem.* **2008**, *10*, 1213-1217.
626. Bridges, N. J.; Rogers, R. D. "Can Kosmotropic Salt/Chaotropic Ionic Liquid (Salt/Salt Aqueous Biphasic Systems) be Used to Remove Pertechnetate from Complex Salt Waste?" *Sep. Sci. Technol.* **2008**, *43*, 1083-1090.
627. Cocalia, V. A.; Visser, A. E.; Rogers, R. D.; Holbrey, J. D. "Solubility and solvation in ionic liquids," In *Ionic Liquids in Synthesis, Second Edition*; Wasserscheid, P.; Welton, T., Eds.; Wiley-VCH, Weinheim, 2008; Vol. 1, pp 89-102.
628. Dilip, M.; Griffin, S. T.; Spear, S. K.; Rijksen, C.; Rodríguez, H.; Rogers, R. D. "Dual Nature of Polyethylene Glycol-Based Aqueous Biphasic Extraction Chromatographic (ABEC) Resins: Uptakes of Perchlorate versus Mercury(II)," *Ind. Eng. Chem. Res.* **2008**, *47*, 7390-7396.
629. Gurau, G.; Cocalia, V. A.; Rogers, R. D. "Separations, Coordination, And Solvation In Ionic Liquids; What Is There That Is Unique?" In *Solvent Extraction: Fundamentals to Industrial Applications - Proceedings of ISEC 2008 International Solvent Extraction Conference, (ISEC 2008)*, Moyer, B. A.; Baron, P.; Chagnes, A.; Cole, P. M.; Cote, G.; Dietz, M. L.; Hatton, T. A.; Horwitz, E. P.; de Ortiz, E. S. P.; Ritcey, G. M.; Robinson, D.; Rogers, R. D.; Sole, K. C.; Tasker, P. A.; Todd, T. A.; Virnig, M. J. (Eds.); Canadian Institute of Mining, Metallurgy and Petroleum: Montréal, 2008; Vol. 2; pp 1263-1270.
630. Hines, C. C.; Cocalia, V. A.; Rogers, R. D. "Using Ionic Liquids to Trap Unique Coordination Environments: Polymorphic Solvates of $ErCl_3(OH_2)_4 \cdot 2([C_2mim]Cl)$," *Chem. Commun.* **2008**, 226-228.
631. Hines, C. C.; Cordes, D. B.; Griffin, S. T.; Watts, S. I.; Cocalia, V. A.; Rogers, R. D. "Flexible Coordination Environments of Lanthanide Complexes Grown from Chloride-based Ionic Liquids," *New J. Chem.* **2008**, *32*, 872-877.
632. Hines, J. H.; Wanigasekara, E.; Rudkevich, D. M.; Rogers, R. D. "Calix[4]arenes immobilized in a cellulose-based platform for entrapment and detection of NO_x gases," *J. Mater. Chem.* **2008**, *18*, 4050-4055.
633. Holbrey, J. D.; Rogers, R. D. "Physicochemical properties of ionic liquids: Melting points and phase diagrams," In *Ionic Liquids in Synthesis, Second Edition*; Wasserscheid, P.; Welton, T., Eds.; Wiley-VCH, Weinheim, 2008; Vol. 1, pp 57-72.
634. Remsing, R. C.; Hernandez, G.; Swatloski, R. P.; Massefski, W. W.; Rogers, R. D.; Moyna, G. "Solvation of Carbohydrates in *N*,*N*'-Dialkylimidazolium Ionic Liquids: A Multinuclear NMR Spectroscopy Study," *J. Phys. Chem. B,* **2008**, *112*, 11071-11078.

635. Rodríguez, H.; Williams, M.; Wilkes, J. S.; Rogers, R. D. "Ionic Liquids for Liquid-in-Glass Thermometers", *Green Chem.*, **2008**, *10*, 501-507. (Highlighted in "Pegg, S. "Designer thermometers rise to new levels," *Chemical Technology* **2008** *5*; http://www.rsc.org/Publishing/ChemTech/Volume/2008/05/designer_thermometers.asp last accessed March 25, 2008.)
636. Rijksen, C.; Rogers, R. D. "A solventless route to 1-ethyl-3-methylimidazolium fluoride hydrofluoride, [C_2mim][F]·xHF," *J. Org. Chem.* **2008**, *73*, 5582-5584.
637. Smiglak, M.; Bridges, N. J.; Dilip, M.; Rogers, R. D. "Direct, atom efficient, and halide-free syntheses of azolium azolate energetic ionic liquids and their eutectic mixtures, and method for determining eutectic composition," *Chem. Eur. J.* **2008**, *14*, 11314-11319.
638. Sun, N.; Swatloski, R. P.; Maxim, M. L.; Rahman, M.; Harland, A. G.; Haque, A.; Spear, S. K.; Daly, D. T.; Rogers, R. D. "Magnetite-Embedded Cellulose Fibers Prepared from Ionic Liquid," *J. Mater. Chem.* **2008**, *18*, 283-290.
639. Cordes, D. B.; Smiglak, M.; Hines, C. C.; Bridges, N. J.; Dilip, M.; Srinivasan, G.; Metlen, A.; Rogers, R. D. "Ionic Liquid-Based Routes to Conversion or Reuse of Recycled Ammonium Perchlorate," *Chem. Eur. J.* **2009**, 15, 13441-13448.
640. Haque, R; Spear, S. K.; Daly, D. T.; Rogers R. D.; Vemuganti, S.; Haque, A. " Electrical and Mechanical Properties of Polypyrrole-Cellulose Fiber Composites Synthesized Via a Novel Chemical Processing Route," Technical Proceedings of the 17th International Conference on Composite Materials, Edinburgh, Scotland, 27-31 July, 2009.
641. Hough-Troutman, W. L.; Smiglak, M.; Griffin, S. T.; Reichert, W. M.; Mirska, I.; Jodynis-Liebert, J.; Adamska, T.; Nawrot, J.; Stasiewicz, M.; Rogers, R. D.; Pernak, J. "Ionic Liquids with Dual Biological Function: Sweet and Anti-microbial, Hydrophobic Quaternary Ammonium-based Salts," *New J. Chem.* **2009**, *33*, 26-33.
642. Rodríguez, H.; Francisco, M.; Rahman, M.; Sun, N.; Rogers, R. D. "Biphasic liquid mixtures of ionic liquids and polyethylene glycols," *Phys. Chem. Chem. Phys.* **2009**, *11*, 10916-10922.
643. Rodríguez, H.; Gurau, G.; Rogers, R. D. "Ionic liquids: growth of a field through the eyes of the I&EC division," In *Innovations in Industrial and Engineering Chemistry: A Century of Achievements and Prospects for the New Millenium*, Flank, W. H.; Abraham, M. A.; Matthews, M. A. (Eds.); ACS Symposium Series 1000; American Chemical Society: Washington DC, 2009; pp 389-400.
644. Shamery, T. L.; Huddleston, J. G.; Chen, J.; Spear, S. K.; Rogers, R. D. "Aqueous Biphasic Systems for Liquid-Liquid Separations," in *Experiments in Green and Sustainable Chemistry*, Roesky, H. W.; Kennepohl, D. K. (Eds.); Wiley-VCH: Weinheim, 2009; pp 92-96.
645. Sun, N.; Rahman, M.; Qin, Y.; Maxim, M. L.; Rodríguez, H.; Rogers, R. D. "Complete dissolution and partial delignification of wood in the ionic liquid 1-ethyl-3-methylimidazolium acetate," *Green Chem.* **2009**, *11*, 646-655.
646. Abai, M.; Holbrey, J. D.; Rogers, R. D.; Srinivasan, G. "Ionic liquid *S*-alkylthiouronium salts," *New J. Chem.* **2010**, *34*, 1981-1993.
647. Bailey, M.; Jernigan, P.; Henson, M. B.; Sturdivant, J.; Rasco, J.; Lovich, A. N.; Lockard, J. E.; Hough, W.; Di Bona, K. R.; Bearid, J.; Shernill, J.; Swatloski, R. P; Rogers, R. D.; Hood, R., "A Comparison of the Effects of Prenatal Exposure of CD-1 Mice to Three Imidazolium-Based Ionic Liquids," *Birth Def. Res. B Develop. Reprod. Tox.* **2010**, *89*, 233-238.
648. Bica, K.; Rijksen, C.; Nieuwenhuyzen, M.; Rogers, R. D. "In Search of Pure Liquid Salt Forms of Aspirin: Ionic Liquid Approaches with Acetylsalicylic Acid and Salicylic Acid," *Phys. Chem. Chem. Phys.* **2010**, *12*, 2011-2017. DOI: 10.1039/b923855g.
649. Bica, K.; Rogers, R. D. "Confused Ionic Liquid Ions – A "Liquification" and Dosage Strategy for Pharmaceutically Active Salts," *Chem. Commun.* **2010**, *46*, 1215-1217. DOI: 10.1039/b925147b. (Designated a *Chem. Commun.* Hot Article 02/18/10.)
650. Cocalia, V.; Smiglak, M.; Kelley, S. P.; Shamshina, J. L.; Gurau, G.; Rogers, R. D. "Crystallization of uranyl salts from dialkylimidazolium ionic liquids or their precursors," *Eur. J. Inorg. Chem.* **2010,** 2760-2767. DOI: 10.1002/ejic.201000162.
651. Dilip, M.; Griffin, S. T.; Spear, S. K.; Rodríguez, H.; Rijksen, C.; Rogers, R. D. "Comparison of Temperature Effects on the Salting-Out of Polyethylene Glycol versus Polyethylene Oxide-Polypropylene Oxide Random Copolymer," *Ind. Eng. Chem. Res.* **2010**, *49*, 2371-2379.
652. Drab, D. M.; Shamshina, J. L.; Smiglak, M.; Hines, C. C.; Cordes, D. B.; Rogers, R. D. "A general design platform for ionic liquid ions based on bridged multi-heterocycles with flexible symmetry and charge", *Chem. Commun.* **2010**, *46*, 3544-3546. DOI: 10.1039/c002861d.
653. Forton, M. S.; Sims, J. D.; Askins, R. E.; Stevenson, W. H.; Shamshina, J.; Smiglak, M.; Rogers, R. D.; Barrow, R. "An Ionic Liquid-Based Next Generation Double Base Propellant Stabilizer," In Proceedings of the 46th AIAA/ASME/SAE/ASEE Joint Propulsion Conference & Exhibit, 25-28 July 2010, Nashville, TN; American Institute of Aeronautics and Astronautics, Inc.: Reston, VA; AIAA 2010-6587; pp 1-8.
654. Hanes, Jr., R. E.; Ellingsworth, E. E.; Griffin, S. T.; Rogers, R. D.; Bartsch, R. A. "Polybenzocrown ethers: synthesis by cesium-assisted cyclization and solid-state structures," *ARKIVOC*, **2010**, *vii*, 217-237.
655. Hill, L. L.; Crowell, J. L.; Tutwiler, S. L.; Massie, N. L.; Hines, C. C.; Griffin, S. T.; Rogers, R. D.; Shaughnessy, K. H. "Synthesis and X-ray Structure Determination of Highly Active Pd(II), Pd(I), and Pd(0) Complexes of Di(*tert*-butyl)neopentylphosphine (DTBNpP) in the Arylation of Amines and Ketones," *J. Org. Chem.* **2010**, *75*, 6477-6488.
656. Holbrey, J. D.; Rogers, R. D.; Shukla, S. S.; Wilfred, C. D. "Optimised microwave-assisted synthesis of methylcarbonate salts: a convenient methodology to prepare intermediates for ionic liquid libraries," *Green Chem.* **2010**, *12*, 407-413.
657. Li, W.; Sun, N.; Rogers, R. D. "How can we improve the dissolution and recovery of biopolymers from biomass in ionic liquids specifically for biofuels applications?" In *Preprints of Symposia - American Chemical Society, Division of Fuel Chemistry* **2010**, *55*, 103.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 40

IPR2020-00770
United Therapeutics EX2007
Page 3590 of 7335

658. Maxim, M. L.; Sun, N.; Swatloski, R. P.; Rahman, M.; Harland, A. G.; Haque, A.; Spear, S. K.; Daly, D. T.; Rogers, R. D. "Properties of Cellulose/TiO_2 Fibers Processed from Ionic Liquids," In *Cellulose Solvents; For Analysis, Shaping and Chemical Modification*; Liebert, T. F.; Heinze, T. J.; Edgar, K. J., Eds.; ACS Symposium Series 1033, American Chemical Society: Washington, DC 2010; pp 261-274.
659. Nadeem, S.; Munawar, M. A.; Ahmad, S.; Smiglak, M.; Drab, D. M.; Malik, K. I.; Amjad, R.; Ashraf, C. M.; Rogers, R. D. "Solvent-free synthesis of benzothiazole-based quaternary ammonium salts: Precursors to Ionic Liquids," *ARKIVOC* **2010**, *vii*, 19-37.
660. Qin, Y.; Lu, X.; Sun, N.; Rogers, R. D. "Dissolution or Extraction of Crustacean Shells Using Ionic Liquids to Obtain High Molecular Weight Purified Chitin and Direct Production of Chitin Films and Fibers," *Green Chem.* **2010**, *12*, 968-971. **DOI:** 10.1039/c003583a
661. Rodríguez, H.; Rogers, R. D. "Liquid mixtures of ionic liquids and polymers as solvent systems," *Fluid Phase Equil.* **2010**, *294*, 7-14. DOI:10.1016/j.fluid.2009.12.036.
662. Rogers, R. D. "The fields of crystal engineering and ionic liquids are actually quite similar," *Aust. J. Chem.* **2010**, *63*, 533-534. DOI: 10.1071/CH10099
663. Shamshina, J. L.; Smiglak, M.; Drab, D. M.; Parker, T. G.; Dykes, Jr., H. W. H.; Di Salvo, R.; Reich, A. J.; Rogers, R. D. "Catalytic ignition of ionic liquids for propellant applications," *Chem. Commun.* **2010**, *46*, 8965-8967. DOI: 10.1039/C0CC02162H.
664. Smiglak, M.; Hines, C. C.; Rogers, R. D. "New hydrogen carbonate precursors for efficient and byproduct-free syntheses of ionic liquids based on 1,2,3-trimethylimidazolium and N,N-dimethylpyrrolidinium cores," *Green Chem.* **2010**, *12*, 491-501.
665. Smiglak, M.; Hines, C. C.; Wilson, T. B.; Singh, S.; Vincek, A. S.; Kirichenko, K.; Katritzky, A. R.; Rogers, R. D. "Ionic Liquids Based on Azolate Anions," *Chem. Eur. J.* **2010**, *16*, 1572-1584. (VIP designated paper)
666. Stoimenovski, J.; MacFarlane, D. R.; Bica, K.; Rogers, R. D. "Crystalline vs. Ionic Liquid Salt Forms of Active Pharmaceutical Ingredients: A Position Paper," *Pharm. Res.* **2010**, *27*, 521-526. DOI: 10.1007/s11095-009-0030-0
667. Sun, N.; Jiang, X.; Li, W.; Lu, X.; Rogers, R. D. "Wood Pulping Using Ionic Liquids," In *Research Progress in Paper Industry and Biorefinery - Proceedings of 4th International Symposium on Emerging Technologies of Pulping and Papermaking 2010 (4th ISETPP 2010)*, Sun, R.; Fu, S., Eds.; South China University of Technology Press, Guangzhou, 2010; pp 6-9.
668. Sun, N.; Jiang, X.; Maxim, M. L.; Rogers, R. D. "Wood Delignification Using Polyoxometalates in Ionic Liquid" In *Preprints of Symposia - American Chemical Society, Division of Fuel Chemistry* 2010, *55*, 487-488.
669. Bica, K; Cooke, L. R.; Nugent, P.; Rijksen, C.; Rogers, R. D. "Toxic on Purpose: Ionic Liquid Fungicides as Combinatorial Crop Protecting Agents," *Green Chem.* **2011**, *13*, 2344-2346. DOI: 10.1039/C1GC15170C.
670. Bica, K.; Gaertner, P.; Rogers, R. D. "Ionic Liquids and Fragrances – Direct Isolation of Orange Essential Oil," *Green Chem.* **2011**, *13*, 1997-1999. DOI: 10.1039/c1gc15237h.
671. Bica, K.; Shamshina, J.; Hough. W. L.; MacFarlane, D. R.; Rogers, R. D. "Liquid Forms of Pharmaceutical Co-crystals: Exploring the Boundaries of Salt Formation," *Chem. Commun.* **2011**, *47*, 2267-2269. DOI: 10.1039/C0CC04485G
672. Choi, S. Y.; Rodríguez, H.; Mirjafari, A.; Gilpin, D. F.; McGrath, S.; Malcolm, K. R.; Tunney, M. M.; Rogers, R. D.; McNally, T. "Dual functional ionic liquids as plasticisers and antimicrobial agents for medical polymers," *Green Chem.* **2011**, *13*, 1527-1535. DOI: 10.1039/C1GC15132K.
673. Drab, D. M.; Smiglak, M.; Shamshina, J. L.; Kelley, S. P.; Schneider, S.; Hawkins, T. W.; Rogers, R. D. "Synthesis of *N*-cyanoalkyl-functionalized imidazolium nitrate and dicyanamide ionic liquids with a comparison of their thermal properties for energetic applications," *New J. Chem.* **2011**, *35*, 1701-1717. DOI:10.1039/C0NJ00889C
674. Gurau, G.; Rodríguez, H.; Kelley, S. P.; Janiczek, P.; Kalb, R. S.; Rogers, R. D. "Demonstration of Chemisorption of Carbon Dioxide in 1,3-Dialkylimidazolium Acetate Ionic Liquids," *Angew. Chem. Int. Ed. Engl.* **2011**, *50*, 12024-12026.
675. Li, W.; Sun, N.; Stoner, B.; Jiang, X.; Lu, X.; Rogers, R. D. "Rapid Dissolution of Lignocellulosic Biomass in Ionic Liquids Using Temperatures above the Glass Transition of Lignin," *Green Chem.* **2011**, *13*, 2038-2047. DOI: 10.1039/C1GC15522A.
676. Maiti, A.; Rogers, R. D. "A Correlation-Based Predictor for Pair-Association in Ionic Liquids," *Phys. Chem. Chem. Phys.* **2011,** *13*, 12138-12145. DOI: 10.1039/C1CP21018A.
677. Pogodina, N. V.; Metwalli, E.; Müller-Buschbaum, P.; Wendler, K.; Lungwitz, R.; Spange, S.; Shamshina, J. L.; Rogers, R. D.; Friedrich, Ch. "Peculiar Behavior of Azolium Azolate Energetic Ionic Liquids," *J. Phys. Chem. Lett.* **2011**, *2*, 2571-2576. DOI: 10.1021/jz201175v.
678. Rodríguez, H.; Gurau, G.; Holbrey, J. D.; Rogers, R. D. "Reaction of elemental chalcogens with imidazolium acetates to yield imidazole-2-chalcogenones: direct evidence for ionic liquids as proto-carbenes," *Chem. Commun.*, **2011**, *47*, 3222-3224. DOI: 10.1039/C0CC05223J.
679. Schoedel, A.; Wojtas, L.; Kelley, S. P.; Rogers, R. D.; Eddaoudi, M.; Zaworotko, M. J. "Network Diversity *via* Decoration of Trigonal Prismatic Nodes: Two-Step Crystal Engineering of Cationic Metal-Organic Materials," *Angew. Chem. Int. Ed. Engl.* **2011**, *50*, 11421-11424.
680. Sun, N.; Li, W.; Stoner, B.; Jiang, X.; Lu, X.; Rogers, R. D. "Composite Fibers Spun directly from Solutions of Raw Lignocellulosic Biomass Dissolved in Ionic Liquids," *Green Chem.* **2011**, *13*, 1158-1161. DOI: 10.1039/C1GC15033B.
681. Sun, N.; Jiang, X.; Maxim, M. L.; Metlen, A.; Rogers, R. D. "Use of Polyoxometalate Catalysts in Ionic Liquids to Enhance the Dissolution and Delignification of Woody Biomass," *ChemSusChem* **2011**, *4*, 65-73. DOI: 10.1002/cssc.201000272.
682. Sun, N.; Rodríguez, H.; Rahman, M.; Rogers, R. D. "Where are ionic liquid strategies most suited in the pursuit of chemicals and energy from lignocellulosic biomass?" *Chem. Commun.* **2011**, *47*, 1405-1421. DOI: 10.1039/C0CC03990J.

683. Zhang, X. W.; Maunder, G. H.; Gießmann, S.; MacDonald, R.; Ferguson, M. J.; Bond, A. H.; Rogers, R. D.; Sella, A.; Takats, J. "Stable heteroleptic complexes of divalent lanthanides with bulky pyrazolylborate ligands – iodides, hydrocarbyls and triethylborohydrides," *Dalton Trans.* **2011**, *40*, 195-210. DOI: 10.1039/C0DT00162G.
684. Aitipamula, S.; Banerjee, R.; Bansal, A. K.; Biradha, K.; Cheney, M. L.; Choudhury, A. R.; Desiraju, G. R.; Dikundwar, A. G.; Dubey, R.; Duggirala, N.; Ghogale, P. P; Ghosh, S.; Goswami, P. K.; Goud, N. R.; Jetti, R. R. K. R.; Karpinski, P.; Kaushik, P.; Kumar, D.; Kumar, V.; Moulton, B.; Mukherjee, A.; Mukherjee, G.; Myerson, A. S.; Puri, V.; Ramanan, A.; Rajamannar, T.; Reddy, C. M.: Rodriguez-Hornedo, N.; Rogers, R. D.; Guru Row, T. N.; Sanphui, P.; Shan, N.; Shete, G.; Singh, A.; Changquan, C. S.; Swift, J. A.; Thaimattam, R.; Thakur, T. S.; Thaper, R. K.; Thomas, S. P.; Tothadi, S.; Vangala, V. R.; Vishweshwar, P.; Weyna, D. R.; Zaworotko, M. J."Polymorphs, Salts, and Cocrystals: What's in a Name?" *Cryst. Growth Des.* **2012,** *12* 2147-2152. DOI: 10.1021/cg3002948. [Author List Correction Published *Cryst. Growth Des.* **2012**, *12*, 4290-4291. DOI: 10.1021/cg300704b.
685. Azubuike, C. P.; Rodríguez, H.; Okhamafe, A. O.; Rogers, R. D. "Physicochemical properties of maize cob cellulose powders reconstituted from ionic liquid solution," *Cellulose* **2012**, *19*, 425-433. DOI 10.1007/s10570-011-9631-y.
686. Barber, P. S.; Kelley, S. P.; Rogers, R. D. "Highly selective extraction of the uranyl ion with hydrophobic amidoximefunctionalized ionic liquids via η^2 coordination," *RSC Adv.* **2012**, *2*, 8526-8530. DOI: 10.1039/c2ra21344c.
687. Bica, K.; Rodríguez, H.; Gurau, G.; Cojocaru, O. A.; Riisager, A.; Fehrmann, R.; Rogers, R. D. "Pharmaceutically Active Ionic Liquids with Solids Handling, Enhanced Thermal Stability, and Fast Release," *Chem. Commun.* **2012**, *48*, 5422-5424. DOI: 10.1039/C2CC30959A
688. Drab, D. M.; Kelley, S. P.; Shamshina, J. L.; Smiglak, M.; Cojocaru, O. A.; Gurau, G.; Rogers, R. D. "Reactivity of *N*-cyanoalkyl-substituted imidazolium halide salts by simple elution through an azide anion exchange resin," *Sci. China Chem.* **2012**, *55*, 1683-1687. DOI: 10.1007/s11426-012-4664-0
689. Drab, D. M.; Shamshina, J. L.; Smiglak, M.; Cojocaru, O. A.; Kelley, S. P.; Rogers, R. D. "Zinc-assisted synthesis of imidazolium-tetrazolate bi-heterocyclic zwitterions with variable alkyl bridge length," *Sci. China Chem.* **2012**, *55*, 1620-1626. DOI: 10.1007/s11426-012-4676-9
690. Freire, M. G.; Pereira, J. F. B.; Francisco, M.; Rodríguez, H.; Rebelo, L. P. N.; Rogers, R. D.; Coutinho, J. A. P. "Insight into the Interactions that Control the Phase Behaviour of Novel Aqueous Biphasic Systems Composed of Polyethylene Glycol Polymers and Ionic Liquids," *Chem. Eur. J.* **2012**, *18*, 1831-1839. DOI: 10.1002/chem.201101780.
691. Gurau, G.; Wang, H.; Qiao, Y.; Lu, X.; Zhang, S.; Rogers, R. D. "Chlorine-free alternatives to the synthesis of ionic liquids for biomass processing" *Pure Appl. Chem.* **2012**, *84*, 745-754. DOI: 10.1351/PAC-CON-11-11-10.
692. Gurau, G.; Kelley, S. P.; Di Bona, K. R.; Smiglak, M.; Rogers, R. D. "Anhydrous Caffeine Hydrochloride and Its Hydration," *Cryst. Growth Des.* **2012**, *12*, 4658-4662. DOI: 10.1021/cg300878j.
693. McMahon, B. W.; Perez, J. P. L.; Schneider, S.; Boatz, J.; Hawkins, T.; McCrary, P. D.; Beasley, P. A.; Rogers, R. D.; Anderson, S. L. "Dual ligand passivation and homogeneous media ball milling: novel approaches for both the synthesis and capping of air-stable aluminum nanoparticles," In *Preprints of Symposia - American Chemical Society, Division of Fuel Chemistry* **2012**, *57*, 965-967.
694. Maiti, A.; Kumar, A.; Rogers, R. D. "Water-clustering in hygroscopic ionic liquids-an implicit solvent analysis," *Phys. Chem. Chem. Phys.* **2012,** *14*, 5139-5146. DOI: 10.1039/c2cp00010e.
695. Mallick, B.; Metlen, A.; Nieuwenhuyzen, M.; Rogers, R. D.; Mudring, A.-V. "Mercuric Ionic Liquids: $[C_n mim][HgX_3]$, Where n = 3, 4 and X = Cl, Br," *Inorg. Chem.* **2012**, *52*, 193-200. DOI: 10.1021/ic201415d.
696. Maxim, M. L.; Sun, N.; Wang, H.; Sterner, J. R.; Haque, A.; Rogers, R. D. "Reinforced magnetic cellulose fiber from ionic liquid solution," *Nanomaterials and Energy* **2012**, *1*, 225-236. DOI: 10.1680/nme.12.00010.
697. Maxim, M. L.; White, J. F.; Block, L. E.; Gurau, G.; Rogers, R. D. "Advanced Biopolymer Composite Materials from Ionic Liquid Solutions," In *Ionic Liquids: Science and Applications*, Visser, A. E.; Bridges, N. J.; Rogers, R. D. (Eds.); ACS Symposium Series 1117; American Chemical Society: Washington, DC, 2012; pp 167-188.
698. McCrary, P. D.; Beasley, P. A.; Alaniz, S. A.; Griggs, C. S.; Frazier, R. M.; Rogers, R. D. "Graphene and Graphene Oxide Can 'Lubricate' Ionic Liquids based on Specific Surface Interactions Leading to Improved Low Temperature Hypergolic Performance," *Angew. Chem. Int. Ed.* **2012**, *51*, 9784-9787.
699. McCrary, P. D.; Beasley, P. A.; Cojocaru, O. A.; Schneider, S.; Hawkins, T. W.; Perez, J. P.; McMahon, B. W.; Pfeil, M.; Boatz, J. A.; Anderson, S. L.; Son, S. F.; Rogers, R. D. "Hypergolic Ionic Liquids to Mill, Suspend, and Ignite Boron Nanoparticles," *Chem. Commun.* **2012**, *48*, 4311-4313. DOI: 10.1039/C2CC30957B.
700. McCrary, P. D.; Beasley, P. A.; Kelley, S. P.; Schneider, S.; Hawkins, T. W.; Perez, J. P. L.; McMahon, B. W.; Pfeil, M.; Boatz, J. A.; Anderson, S. L.; Son, S. F.; Rogers, R. D. "Tuning azolium azolate ionic liquids to promote surface interactions with Titanium nanoparticles leading to increased passivation and colloidal stability," *Phys. Chem. Chem. Phys.* **2012**, *14*, 13194-13198. DOI: 10.1039/C2CP42510F.
701. Perez, J. Paulo L.; McMahon, B. W.; Schnieder, S.; Boatz, J.; Hawkins, T.; McCrary, P. D.; Beasley, P. A.; Rogers, R. D.; Son, S.; Anderson, S. L. "Synthesis of air-stable, unoxidized, boron nanoparticles using ball milling technique," In *Preprints of Symposia - American Chemical Society, Division of Fuel Chemistry* **2012**, *57*, 955-956.
702. Smiglak, M.; Hines, C. C.; Reichert, W. M.; Vincek,A. S.; Katritzky, A. R.; Thrasher, J. S.; Sun, L. Y.; McCrary, P. D.; Beasley, P. A.; Kelley, S. P.; Rogers, R. D. "Synthesis, limitations, and thermal properties of energetically-substituted, protonated imidazolium picrate and nitrate salts and further comparison with their methylated analogs," *New J. Chem.* **2012**, *36*, 702-722. DOI: 10.1039/C1NJ20677J.

703. Trivedi, T. J.; Srivastava, D. N.; Rogers, R. D.; Kumar, A. "Agarose processing in protic and mixed protic–aprotic ionic liquids: dissolution, regeneration and high conductivity, high strength ionogels," *Green Chem.* **2012**, *14*, 2831-2839. DOI: 10.1039/C2GC35906E.
704. Wang, H.; Gurau, G.; Rogers, R. D. "Ionic liquid processing of cellulose," *Chem. Soc. Rev.* **2012**, *41*, 1519-1537. DOI: 10.1039/c2cs15311d.
705. Wang, H.; Zhou, X. S., Gurau, G.; Rogers, R. D. "The role of ionic liquids in the pharmaceutical manufacturing processes," in *Green Techniques for Organic Synthesis and Medicinal Chemistry*, Zhang, W.; Cue, B. W., Jr. (Eds.), Wiley-VCH: Weinheim, 2012; Ch. 17, pp 469-496. ISBN 9780470711514.
706. Zhao, Y.; Liu, X.; Lu, X.; Zhang, S.; Wang, J.; Wang, H.; Gurau, G.; Rogers, R. D.; Su, L.; Li, H. "The Behavior of Ionic Liquids under High Pressure: A Molecular Dynamics Simulation," *J. Phys. Chem. B*, **2012**, *116*, 10876-10884. DOI: 10.1021/jp3070568
707. Barber, P. S.; Griggs, C. S.; Bonner, J. R.; Rogers, R. D. "Electrospinning of chitin nanofibers directly from an ionic liquid extract of shrimp shells" *Green Chem.*, **2013**, *15*, 601-607. DOI: 10.1039/C2GC36582K.
708. Barber, P. S.; Griggs, C. S.; Gurau, G.; Liu, Z.; Li, S.; Li, Z.; Lu, X.; Zhang, S.; Rogers, R. D. "Coagulation of Chitin and Cellulose from 1-Ethyl-3-methylimidazolium Acetate Ionic-Liquid Solutions Using Carbon Dioxide," *Angew. Chem. Int. Ed.* **2013**, *52*, 12350-12353. DOI: 10.1002/anie.201304604.
709. Barber, P. S.; Shamshina, Julia L.; Rogers, R. D.; "A 'Green' Industrial Revolution: Using Chitin towards Transformative Technologies" *Pure Appl. Chem.* **2013**, *85*, 1693-1701. DOI: 10.1351/PAC-CON-12-10-14.
710. Cojocaru, O. A.; Bica, K.; Gurau, G.; Narita, A.; McCrary, P. D.; Shamshina, J. S.; Barber, P. S.; Rogers, R. D. "Prodrug ionic liquids: functionalizing neutral active pharmaceutical ingredients to take advantage of the ionic liquid form," *Med. Chem. Commun.* **2013**, *4*, 559-563. DOI: 10.1021/cg400686e.
711. Cojocaru, O. A.; Kelley, S. P.; Gurau, G.; Rogers, R. D. "Procainium acetate versus procainium acetate dihydrate: Irreversible crystallization of a room-temperature active pharmaceutical ingredient-ionic liquid upon hydration," *Cryst. Growth Des.* **2013**, *13*, 3290−3293. DOI: 10.1021/cg400686e.
712. Cojocaru, O. A.; Shamshina, J. L.; Gurau, G.; Syguda, A.; Praczyk, T.; Pernak, J.; Rogers, R. D. "Ionic liquid forms of the herbicide dicamba with reduced volatility and increased efficacy," *Green Chem.* **2013**, *15*, 2110-2120. DOI: 10.1039/C3GC37143C.
713. Cojocaru, O. A.; Shamshina, J. L.; Rogers, R. D. "Review/Preview: Prodrug ionic liquids," *Chimica Oggi/Chemistry Today*, **2013**, *31*, 24-29.
714. Freire, M. G.; Pereira, J. F. B.; Francisco, M.; Rodríguez, H. ; L. P. N.; Rogers, R. D.; Coutinho, J. A. P. "Insight into the Interactions That Control the Phase Behaviour of New Aqueous Biphasic Systems Composed of Polyethylene Glycol Polymers and Ionic Liquids," *Chem. Eur. J.* **2012**, *18*, 1831-1839.
715. Kelley, S. P.; Narita, A.; Holbrey, J. D.; Green, K. D.; Reichert, W. M.; Rogers, R. D. "Understanding the Effects of Ionicity in Salts, Solvates, Co-Crystals, Ionic Co-Crystals, and Ionic Liquids, Rather than Nomenclature, Is Critical to Understanding Their Behavior," *Cryst. Growth Des.* **2013**, *13*, 965-975. DOI: 10.1021/cg4000439.
716. Lu, W.; Barber, P. S.; Kelley, S. P.; Rogers, R. D. "Coordination and extraction of mercury(II) with an ionic liquid-based thione extractant," *Dalton Trans.* **2013**, *42*, 12908-12916. DOI: 10.1039/C3DT50410G.
717. Mateyawa, S.; Xie, D. F.; Truss, R. W.; Halley, P. J.; Nicholson, T. M.; Shamshina, J. L.; Rogers, R. D.; Boehm, M. W.; McNally, T. "Effect of the ionic liquid 1-ethyl-3-methylimidazolium acetate on the phase transition of starch: Dissolution or gelatinization?" *Carbohydrate Polymers* **2013**, *94*, 520-530. DOI: 10.1016/j.carbpol.2013.01.024.
718. McCrary, P. D.; Beasley, P. A.; Gurau, G.; Narita, A.; Barber, P. S.; Cojocaru, A.; Rogers, R. D. "Drug specific, tuning of an ionic liquid's hydrophilic–lipophilic balance to improve water solubility of poorly soluble active pharmaceutical ingredients," *New J. Chem.* **2013**, *37*, 2196-2202. DOI: 10.1039/c3nj00454f.
719. McCrary, P. D.; Rogers, R. D. "1-Ethyl-3-methylimidazolium Hexafluorophosphate: From Ionic Liquid Prototype to Antitype," *Chem. Commun.* **2013**, *49*, 6011-6014. DOI: 10.1039/C3CC42175A.
720. McNeil, S. K.; Kelley, S. P.; Beg, C.; Cook, H. Rogers, R. D.; Nikles, D. E. "Cocrystals of 10-methylphenthiazine and 1,3-dinitrobenzene: Implications for optical sensing of TNT-based explosives," *ACS Appl. Mater. Interfaces*, **2013**, *5*, 7647-7653. DOI: 10.1021/am401961s.
721. Metlen, A.; Mallick, B.; Murphy, R. W.; Mudring, A.-V.; Rogers, R. D. "Phosphonium Chloromercurate Room Temperature Ionic Liquids of Variable Composition," *Inorg. Chem.* **2013**, *52*, 13997-14009. DOI: 10.1021/ic401676r.
722. Pereira, J. F. B.; Rebelo, L. P. N.; Rogers, R. D.; Coutinho, J. A. P.; Freire, M. G. "Combining ionic liquids and polyethylene glycols to boost the hydrophobic-hydrophilic range of aqueous biphasic systems," *Phys. Chem. Chem. Phys.* **2013,** *15*, 19580-19583. DOI: 10.1039/C3CP53701C.
723. Pereira, J. F. B.; L. P. N.; Rogers, R. D.; Coutinho, J. A. P.; Freire, M. G. "Washing-out" Ionic Liquid from Polyethylene Glycol to form Aqueous Biphasic Systems," *Phys. Chem. Chem. Phys.* **2013**, *16*, 2271-2274. DOI: 10.1039/C3CP54047B.
724. Perez, J. P. P.; McMahon, B. W.; Schneider, S.; Boatz, J. A.; Hawkins, T. W.; McCrary, P. D.; Beasley, P. A.; Rogers, R. D.; Anderson, S. L. "Exploring the structure of nitrogen-rich ionic liquids and their binding to the surface of oxide-free boron nanoparticles," *J. Phys. Chem. C* **2013**, *117*, 5693-5707. DOI: 10.1021/jp3100409.
725. Raders, S. M.; Moore, J. N.; Parks, J. K.; Miller, A. D.; Leißing, T. M.; Kelley, S. P.; Rogers, R. D.; Shaughnessy, K. H. "Trineopentylphosphine: A Conformationally Flexible Ligand for the Coupling of Sterically Demanding Substrates in the Buchwald-Hartwig Amination and Suzuki-Miyaura Reaction." *J. Org. Chem.* **2013**, *78*, 4649-4664. DOI: 10.1021/jo400435z.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 43

IPR2020-00770
United Therapeutics EX2007
Page 3593 of 7335

726. Shamshina, J. S.; Barber, P. S.; Rogers, R. D. "Ionic Liquids in Drug Delivery" *Expert Opin. Drug Deliv.* **2013**, *10*, 1367-1381. DOI: 10.1517/17425247.2013.808185.
727. Smiglak, M.; Hines, C. C.; Reichert, W. M.; Shamshina, J. L.; Beasley, P. A.; McCrary, P. D.; Kelley, S. P.; Rogers, R. D. "Azolium azolates from reactions of neutral azoles with 1,3-diemethyl-imidazolium-2-carboxylate, 1,2,3-trimethyl-imidazolium hydrogen carbonate, and N,N dimethyl-pyrrolidinium hydrogen carbonate," *New J. Chem.* **2013**, *37*, 1461-1469. DOI: 10.1039/C3NJ00147D.
728. Wang, H.; Gurau, G.; Kelley, S. P.; Myerson, A. S.; Rogers, R. D. "Hydrophobic *vs.* hydrophilic ionic liquid separations strategies in support of continuous pharmaceutical manufacturing" *RSC Advances*, **2013**, *3*, 10019-10026. DOI: 10.1039/C3RA41082J.
729. Wang, H.; Maxim, M. L.; Gurau, G.; Rogers, R. D. "Microwave-assisted dissolution and delignification of wood in 1-ethyl-3-methylimidazolium acetate" *Bioresour. Technol.* **2013**, *136*, 739-742. DOI: 10.1016/j.biortech.2013.03.064.
730. Barber, P. S.; Kelley, S. P.; Griggs, C. S.; Wallace, S.; Rogers, R. D. "Surface Modification of Ionic Liquid-Spun Chitin Fibers for the Extraction of Uranium from Seawater: Seeking the Strength of Chitin and the Chemical Functionality of Chitosan," *Green Chem.* **2014**, *16*, 1828-1836. DOI: 10.1039/c4gc00092g.
731. Chatel, G.; Pereira, J. F. B.; Debetti, V.; Wang, H.; Rogers, R. D. "Mixing Ionic Liquids – "Simple Mixtures" or "Double Salts"?" *Green Chem.* **2014**, *16*, 2051-2083. DOI: 10.1039/C3GC41389F.
732. Chatel, G.; Rogers, R. D. "Review: Oxidation of Lignin Using Ionic Liquids-An Innovative Strategy To Produce Renewable Chemicals," *ACS Sustainable Chem. Eng.* **2014**, *2*, 322–339. DOI: 10.1021/sc4004086.
733. Cheng, F.; Wang, H.; Chatel, G.; Gurau, G.; Rogers R. D. "Facile Pulping of Lignocellulosic Biomass Using Choline Acetate," *Bioresour. Technol.* **2014**, *164*, 394-401. DOI: 10.1016/j.biortech.2014.05.016.
734. Choi, S. Y.; Rodríguez, H.; Nimal Gunaratne, H. Q.; Puga, A. V.; Gilpin, D. ; McGrath, S.; Vyle, J. S.; Tunney, M. M.; Rogers, R. D.; McNally, T. "Dual functional ionic liquids as antimicrobials and plasticisers for medical grade PVCs," *RSC Adv.* **2014**, *4*, 8567-8581. DOI: 10.1039/c3ra46425c.
735. Cojocaru, O. A.; Siriwardana, A.; Gurau, G.; Rogers, R. D. "Pharmaceutically active supported ionic liquid phases," In *Supported Ionic Liquids – Fundamentals and Applications*, Fehrmann, R., Riisager, A., Haumann, M., Eds.; Wiley-VCH: Weinheim, Germany, 2014; Chapter 19; pp 387-406. ISBN: 978-3-527-32429-3.
736. Griggs, C. S.; Barber, P. S.; Kelley, S. P.; Moser, R. D.; Seiter, J. M.; Thomas, C. C.; Coleman, J. G.; Medina, V. F.; Rogers, R. D. "Biomimetic Mineralization of Uranium by Metabolically-Inactive Shrimp Shell." *Cryst. Growth. Des.* **2014**, *14*, 6172-6176. DOI: 10.1021/cg5015576.
737. Kelley, S. P.; Barber, P. S.; Mullins, P. H. K.; Rogers, R. D. "Structural clues to UO_2^{2+}/VO_2^{+}competition in seawater extraction using amidoxime-based extractants," *Chem. Commun.* **2014**, *50*, 12504-12507. DOI: 10.1039/c4cc06370h.
738. McCrary, P. D.; Barber, P. S.; Kelley, S. P.; Rogers, R. D. "Nonaborane and Decaborane Cluster Anions Can Enhance the Ignition Delay in Hypergolic Ionic Liquids and Induce Hypergolicity in Molecular Solvents," *Inorg. Chem.* **2014**, *53*, 4770-4776. DOI: 10.1021/ic500622f.
739. McCrary, P. D.; Chatel, G.; Alaniz, S. A.; Cojocaru, O. A.; Beasley, P. A.; Flores, L. A.; Kelley, S. P.; Barber, P. S.; Rogers, R. D. "Evaluating Ionic Liquids as Hypergolic Fuels: Determining Reactivity from Molecular Structure," *Energy Fuels* **2014**, *28*, 3460-3473. DOI: 10.1021/ef500264z.
740. Pereira, J. F. B.; Flores, L. A.; Wang, H.; Rogers, R. D. "Benzene Solubility in Ionic Liquids: Working Toward an Understanding of Liquid Clathrate Formation" *Chem. Eur. J.* **2014**, *20*, 15482-15492. DOI: 10.1002/chem.201404253.
741. Pereira, J. F. B.; Kurnia, K. A.; Cojocaru, O. A. ; Gurau, G.; Rebelo, L. P. N.; Rogers, R. D.; Freire, M. G.; Coutinho, J. A. P. "Molecular interactions in aqueous biphasic systems composed of polyethylene glycol and crystalline *vs.* liquid cholinium-based salts," *Phys. Chem. Chem. Phys.* **2014**, *16*, 5723-5731. DOI: 10.1039/C3CP54907K.
742. Perez, J. P. L.; McMahon, B. W.; Yu, J.; Schneider, S.; Boatz, J. A.; Hawkins, T. W.; McCrary, P. D.; Flores, L. A.; Rogers, R. D.; Anderson, S. L. "Boron Nanoparticles with High Hydrogen Loading: Mechanism for B-H Binding and Potential for Improved Combustibility and Specific Impulse," *ACS Appl. Mat. Interfaces* **2014**, *6*, 8513-8525. DOI: 10.1021/am501384m.
743. Pernak, J.; Niemczak, M.; Giszter, R.; Shamshina, J.; Gurau, G.; Cojocaru, O. A.; Praczyk, T.; Marcinkowska, K.; Rogers, R. D. Glyphosate-Based Herbicidal Ionic Liquids with Increased Efficacy. *ACS Sustainable Chem. Eng.* **2014**, *2*, 2845-2851. DOI: 10.1021/sc500612y.
744. Raders, S. M.; Jones, J. M.; Semmes, J. G.; Kelley, S. P; Rogers, R. D.; Shaughnessy, K. H. "Di-*tert*-butylneopentylphosphine (DTBNpP): An efficient ligand in the palladium-catalyzed α-arylation of ketones," *Eur. J. Org. Chem.* **2014**, 7395-7404. DOI: 10.1002/ejoc.201402474.
745. Shamshina, J. L.; Gurau, G.; Block, L. E.; Hansen, L, Dingee, C.; Walters, A.; Rogers, R. D. "Chitin-Calcium Alginate Composite Fibers for Wound Care Dressings Spun from Ionic Liquid Solution," *J. Mater. Chem. B* **2014**, *2*, 3924-3936. DOI: 10.1039/C4TB00329B.
746. Shamshina, J. L.; Rogers, R. D. "Overcoming the problems of solid state drug formulations with ionic liquids: When opinions crystallize is progress lost?" *Therapeutic Delivery* **2014**, *5*, 489-491. DOI: 10.4155/tde.14.28.
747. Smiglak, M.; Pringle, J. M.; Han, L.; Zhang, S.; Gao, H.; MacFarlane, D. R.; Rogers, R. D. "Ionic Liquids for energy, materials, and medicine," *Chem. Commun.* **2014**, *50* (66), 9228–9250. DOI: 10.1039/c4cc02021a.
748. Tome, L. I. N.; Pereira, J. F. B.; Rogers, R. D.; Freire, M. G.; Gomes, J. R. B.; Coutinho, J. A. P. "Evidence for the Interactions Occurring Between Ionic Liquids and Tetraethylene Glycol in Binary Mixtures and Aqueous Biphasic Systems," *J Phys. Chem. B* **2014**, *118*, 4615-4629. DOI: 10.1021/jp501718w.

749. Tome, L. I. N.; Pereira, J. F. B.; Rogers, R. D.; Freire, M. G.; Gomes, J. R. B.; Coutinho, J. A. P. "'Washing-out' ionic liquids from polyethylene glycol to form aqueous biphasic systems," *Phys.Chem.Chem.Phys.* **2014**, *16*, 2271-2274. DOI: 10.1039/c3cp54047b.
750. Wang, H.; Block, L. E.; Rogers, R. D. "Catalytic conversion of biomass in ionic liquids" in *Catalysis in Ionic Liquids: From Catalysts Synthesis to Application*; Hardacre, C.; Parvulescu, V. (Eds.) Series 15; Royal Society of Chemistry: Cambridge, 2014; pp 1-19.
751. Wang, H.; Gurau, G.; Pingali, S. V.; O'Neill, H. M.; Evans, B. R.; Urban, V. S.; Heller, W. T.; Rogers, R. D. "Physical insight into switchgrass dissolution in the ionic liquid 1-ethyl-3-methylimidazolium acetate" *ACS Sustainable Chem. Eng.* **2014**, *2*, 1264-1269. DOI: 10.1021/sc500088w
752. Wang, H.; Gurau, G.; Rogers, R. D. "Dissolution of biomass using ionic liquids," in *Structures and Interactions of Ionic Liquids*, Zhang, S.; Wang, l.; Lu X.; Zhou, Q., Eds., Springer-Verlag: Berlin Heidelberg, 2014; Ch. 3 pp 79-106; Structure and Bonding 151. DOI: 10.1007/978-3-642-38619-0_3.
753. Wang, H.; Gurau, G.; Shamshina, J. L.; Cojocaru, O. A.; Janikowski, J.; MacFarlane, D. R.; Davis, J. H. Jr.; Rogers, R. D "Simultaneous Membrane Transport of Two Active Pharmaceutical Ingredients by Charge Assisted Hydrogen Bond Complex Formation," *Chem. Sci.* **2014**, *5*, 3449-3456. DOI: 10.1039/c4sc01036a.
754. Wang, H.; Pereira, J. F. B.; Myerson, A. S.; Rogers, R. D. "Double Salt Ionic Liquids Prepared by Mixing Partially Miscible Ionic Liquids: Tuning the Solubility of Lipophilic Molecules," *ECS Trans.* **2014**, *64*, 33-44. DOI:10.1149/06404.0033ecst
755. Xie, F.; Flanagan, B.; Li, M.; Sangwan, P.; Truss, R.; Halley, P.; Strounina, E.; Whittaker, A.; Gidley, M.; Dean, K.; Shamshina, J.; Rogers, R. D. McNally, T. "Characteristics of starch-based films plasticised by glycerol and by the ionic liquid 1-ethyl-3-methylimidazolium acetate: a comparative study," *Carbohydrate Polymers* **2014**, *111*, 841–848. DOI: 10.1016/j.carbpol.2014.05.058.
756. Dilip, M.; Bridges, N. J.; Rodriguez, H.; Pereira, J. F. B.; Rogers, R. D. "Effect of Temperature on Salt-Salt Aqueous Biphasic Systems: Manifestations of Upper Critical Solution Temperature," *J. Solution Chem.* **2015**, *44*, 454-468. DOI: 10.1007/s10953-014-0278-9
757. Kelley, S. P.; Rogers, R. D. "A Practical Overview of Organic Synthesis in Ionic Liquids," *Aldrichim. Acta* **2015**, *48*, e1-e2; http://www.sigmaaldrich.com/content/dam/sigma-aldrich/docs/Aldrich/Brochure/1/acta-48-1.pdf (Last accessed March 20, 2015).
758. Kelley, S. P.; Rogers, R. D. "Isolation of Uranyl Dicyanamide Complexes from N-Donor Ionic Liquids," *Inorg. Chem.* **2015**, *54*, 10323-10334. DOI: 10.1021/acs.inorgchem.5b01699.
759. Kelley, S. P.; Nuss, J. S.; Rogers, R. D. "Nonstoichiometric, Protic Azolium Azolate Ionic Liquids Provide Unique Environments for N-Donor Coordination Chemistry," *Chem.-Eur. J.* **2015**, *21*, 17196-17199. DOI: 10.1002/chem.201503914.
760. Ludwig, T.; Guo, L.; McCrary, P.; Zhang, Z.; Gordon, H.; Quan, H.; Stanton, M.; Frazier, R.; Rogers, R. D.; Wang, H.-T.; Turner, C. H. "Mechanism of Bismuth Telluride Exfoliation in an Ionic Liquid Solvent," *Langmuir* **2015**, *31*, 3644-3652. DOI: 10.1021/acs.langmuir.5b00239.
761. Meany, J. E., Kelley, S. P., Metzger, R. M., Rogers, R. D.; Woski, S. A. "4,4'-Dibromo-2',5'-dimethoxy-[1,1'-biphenyl]-2,5-dione (BrHBQBr)," *Acta Crystallogr. E* **2015**, *E71*, 1454-1456. DOI: 10.1107/S2056989015020472.
762. Moore, J. N.; Laskay, N. M.; Duque, K. S.; Kelley, S. P.; Rogers, R. D. "Synthesis of 4-sulfonatobenzylphosphines and their application in aqueous-phase palladium-catalyzed cross coupling." *J. Organomet. Chem.* **2015**, *777*, 16-24. DOI: 10.106/j.jorganchem.2014.11.011.
763. Pereira, J. F. B.; Kurnia, K. A.; Freire, M. G.; Coutinho, J. A. P.; Rogers, R. D. "Controlling the Formation of Ionic-Liquid-based Aqueous Biphasic Systems by Changing the Hydrogen Bonding Ability of Polyethylene Glycol End Groups," *ChemPhysChem* **2015**, *16*, 2219-2225. DOI: 10.1002/cphc.201500146.
764. Pernak, J.; Niemczak, M.; Shamshina, J.; Gurau, G.; Głowacki, G.; Praczyk, T.; Marcinkowska, K.; Rogers, R. D. "Metsulfuron-Methyl-Based Herbicidal Ionic Liquids," *J. Agric. Food Chem.* **2015**, *63*, 3357-3366. DOI: 10.1021/jf505782p.
765. Shadid, M.; Gurau, G.; Shamshina, J. L.; Chuang, B.-C.; Hailu, S.; Guan, E.; Chowdhury, S. K.; Wu, J.-T.; Rizvi, S. A. A.; Griffin, R. J.; Rogers, R. D. "Sulfasalazine in ionic liquid form with improved solubility and exposure," *MedChemComm* **2015**, *6*, 1837-1841. DOI: 10.1039/c5md00290g.
766. Shamshina, J. L.; Kelley, S. P.; Gurau, G.; Rogers, R. D. "Develop ionic liquid drugs," *Nature* **2015**, *528*, 188-189. DOI: 10.1038/528188a.
767. Tadros, A. M.; Rokyo, M. M.; Kelley, S. P.; Belmore, K.; Rogers, R. D.; Vincent, J. B. "Aminopyridine complexes of Cr(III) basic carboxylates as potential polymer precursors: Synthesis, characterization, and crystal structure of $[Cr_3O(propionate)_6(X\text{-aminopyridine})_3]^+$ (X = 3 or 4)," *Polyhedron* **2015**, *100*, 17-27. DOI: 10.1016/j.poly.2015.07.007.
768. Wang, H.; Kelley, S. P.; Brantley III, J. W.; Chatel, G.; Shamshina, J.; Pereira, J. F. B.; Debbeti, V.; Myerson, A. S.; Rogers, R. D. "Ionic fluids containing both strongly and weakly interacting ions of the same charge have unique ionic and chemical environments as a function of ion concentration," *ChemPhysChem* **2015**, *16*, 993-1002. DOI: 10.1002/cphc.201402894.
769. Weber, Cameron C.; Kulkarni, Samir A.; Kunov-Kruse, Andreas J.; Rogers, Robin D.; Myerson, Allan S. "The use of cooling crystallization in an ionic liquid system for the purification of pharmaceuticals," *Cryst. Growth Des.* **2015**, *15*, 4946-4951. DOI: 10.1021/acs.cgd.5b00855.
770. Weber, C. C.; Kunov-Kruse, A. J.; Rogers R. D.; Myerson, A. S. "Manipulation of ionic liquid anion-solute-antisolvent interactions for the purification of acetaminophen," *Chem. Commun.* **2015**, *51*, 4294-4297. DOI: 10.1039/C5CC00198F.

771. Xie, F.; Flanagan, B. M.; Li, M.; Truss, R. W.; Halley, P. J.; Gidley, M. J.; McNally, T.; Shamshina, J. L.; Rogers, R. D. "Characteristics of starch-based films with different amylose contents plasticised by 1-ethyl-3-methylimidazolium acetate," *Carbohydrate Polymers* **2015**, *122*, 160-168. DOI: 10.1016/j.carbpol.2014.12.072.
772. Yao, W.; Kelley, S. P.; Rogers, R. D.; Vaid, T. P. "Electrical conductivity in two mixed-valence liquids," *Phys. Chem. Chem. Phys.* **2015**, *17*, 14107-14114. DOI: 10.1039/C5CP01172H.
773. Zhang, B.; Chen, L.; Xie, F.; Li, X.; Truss, R. W.; Halley, P. J.; Shamshina, J. L.; Rogers, R. D.; McNally, T. "Understanding the structural disorganization of starch in water–ionic liquid solutions," *Phys. Chem. Chem. Phys.* **2015**, *17*, 13860-13871. DOI: 10.1039/C5CP01176K.
774. Berton, P.; Kelley, S. P.; Rogers, R. D. "Stripping uranium from seawater-loaded sorbents with the ionic liquid hydroxylammonium acetate in acetic acid for efficient reuse," *Ind. Eng. Chem. Res.* **2016**, *Advance Article*. DOI: 10.1021/acs.iecr.5b03996.
775. Kelley, S. P.; Nuss, J. S.; Rogers, R. D. "Using crystal structures of ionic compounds to explore complexation and extraction of rare earth elements in ionic liquids," in *Applications of Ionic Liquids on Rare Earth Green Separation and Utilization*; Chen, J., Ed.; Springer: Heidelberg, 2016; pp 21-42.
776. Meany, J. E.; Kelley, S. P.; Rogers, R. D.; Woski, S. A. "4'-Bromo-2,5-dihydoxy-2',5'-dimethoxy-[1,1'-biphenyl]-3,4-dicarbonitrile," *Acta Cryst. Sect. E: Struct. Commun.* **2016**, *submitted.*
777. Shen, X.; Shamshina, J. L.; Berton, P.; Bandomir, J.; Wang, H.; Gurau, G.; Rogers, R. D. "Comparison of hydrogels prepared with ionic-liquid-isolated vs commercial chitin and cellulose," *ACS Sustainable Chem. Eng.*, **2016**, 4, 471-480. DOI: 10.1021/acssuschemeng.5b01400.
778. Shen, X.; Shamshina, J. L.; Berton, P.; Gurau, G.; Rogers, R. D. "Hydrogels based on cellulose and chitin: fabrication, properties, and applications," *Green Chem.* **2016**, *18*, 53-75. DOI: 10.1039/C5GC02396C.
779. Zhang, B.; Xie, F.; Zhang, T.; Chen, L.; Li, X.; Truss, R. W.; Halley, P. J.; Shamshina, J. L.; McNally, T.; Rogers, R. D. "Different characteristic effects of ageing on starch-based films plasticised by 1-ethyl-3-methylimidazolium acetate and by glycerol," *Carbohydrate Polymers* **2016**, *146*, 67-79.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 46

IPR2020-00770
United Therapeutics EX2007
Page 3596 of 7335

B. Non-Refereed Reviews, Reports, Articles, and Extended Abstracts:

1. Rogers, R. D. "Actinide Elements," In *The Encyclopedia of Physical Science and Technology*; 1st ed.; Meyers, R. A., Ed.; Academic Press: Orlando, FL, 1987; Vol. 1; 190-217.
2. Rogers, R. D. Book Review of "Studies in Surface Science and Catalysis. Volume 45. Transition Metal Oxides: Surface Chemistry and Catalysis," *J. Am. Chem. Soc.* **1990**, *112*, 6454.
3. Rogers, R. D.; Rogers, L. M. "Lanthanides and Actinides. Annual Survey Covering the Year 1983," *J. Organomet. Chem.* **1990**, *380*, 51-76.
4. Rogers, R. D.; Rogers, L. M. "Lanthanides and Actinides. Annual Survey Covering the Years 1984-1986," *J. Organomet. Chem.* **1991**, *416*, 201-290.
5. Rogers, R. D. "Actinide Elements," In *The Encyclopedia of Physical Science and Technology*; 2nd ed.; Meyer, R. A., Ed.; Academic Press: Orlando, FL, 1992; Vol. 1; pp 228-256.
6. Rogers, R. D.; Rogers, L. M. "Lanthanides and Actinides. Annual Survey Covering the Years 1987-1989," *J. Organomet. Chem.* **1992**, *442*, 83-224.
7. Rogers, R. D.; Rogers, L. M. "Lanthanides and Actinides. Annual Survey Covering the Year 1990," *J. Organomet. Chem.* **1992**, *442*, 225-269.
8. Rogers, R. D.; Rogers, L. M. "Lanthanides and Actinides. Annual Survey Covering the Year 1991," *J. Organomet. Chem.* **1993**, *457*, 41-62.
9. Rogers, R. D.; Eiteman, M. A. "Preface," In *Aqueous Biphasic Separations: Biomolecules to Metal Ions*; Rogers, R. D.; Eiteman, M. A., Eds.; Plenum: New York, 1995; p v.
10. Rogers, R. D. "Crystal Engineering - ACA Transactions Symposium - July 1998," In *American Crystallographic Association Newsletter*, ACA: Buffalo, NY, Summer 1998.
11. Sharma, C. V. K.; Rogers, R. D. "Perspectives of Crystal Engineering," *Materials Today* **1998**, *1(3)*, 27-30.
12. Bond, A. H.; Dietz, M. L.; Rogers, R. D. "Preface," In *Metal-Ion Separation and Preconcentration, Progress and Opportunities*; Dietz, M. L.; Bond, A. H.; Rogers, R. D., Eds.; ACS Symposium Series 716, American Chemical Society: Washington, DC, 1999; pp XI-XII.
13. Huddleston, J. G.; Willauer, H. D.; Griffin, S. T.; Visser, A. E.; Rogers, R. D. "Green Separation Science & Technology: Using Environmentally Benign Polymers to Replace VOCs in Industrial Scale Liquid/Liquid Separations," In *Green Chemistry and Engineering Conference Proceedings: Implementing Vision 2020 for the Environment, (1997); Global Perspectives, (1998)*; American Chemical Society: Washington, DC, 1999; pp 225-228.
14. Rogers, R. D.; Griffin, S. T.; Willauer, H. D.; Nicol, J. A. "Clean Solvent Extraction Using Polyethylene Glycol-Based Aqueous Biphasic Systems," In *Green Chemistry and Engineering Conference Proceedings: Implementing Vision 2020 for the Environment, (1997); Global Perspectives, (1998)*; American Chemical Society: Washington, DC, 1999; pp 149-151.
15. Lumetta, G. J.; Rogers, R. D.; Gopalan, A. S. "Preface," In *Calixarenes for Separations*; Lumetta, G. J.; Rogers, R. D.; Gopalan, A. S., Eds.; ACS Symposium Series 757, American Chemical Society: Washington, DC, 2000; pp IX-X.
16. Rogers, R.D. "Preface," *J. Chromatogr., B: Biomed. Sci. Appl.* **2000**, *743*, 1.
17. Rogers, R. D. "Green Industrial Applications of Ionic Liquids – A NATO Advanced Research Workshop, Crete, Greece (12-16 April 2000)," *Green Chemistry* **2000**, *2*, G94-G96.
18. Visser, A. E.; Swatloski, R. P.; Reichert, W. M.; Willauer, H. D.; Huddleston, J. G.; Rogers, R. D. "Chemical and Physical Characteristics of Room Temperature Ionic Liquids and the Associated Implications for their Use as Solvent Alternatives," In *Proceedings of GreenChem2000, 4th Annual Green Chemistry and Engineering Conference, Sustainable Technologies: From Research to Industrial Implementation,* American Chemical Society, Washington, DC, 2000; pp 50-52.
19. *Research Needs for High-Level Waste Stored in Tanks and Bins at U.S. Department of Energy Sites, Environmental Management Science Program*, Committee on Long-Term Research Needs for Radioactive High-Level Waste at Department of Energy Sites, Board on Radioactive Waste Management Division on Earth and Life Studies, National Research Council of the National Academies, National Academy Press, Washington, DC, 2001; 134 pp. (Written by Committee)
20. Rogers, R. D. "Editorial," *Cryst. Growth Des.* **2001**, *1*, 1-2.
21. Rogers, R. D. "Editorial," *Cryst. Growth Des.* **2002**, *2*, 1-2.
22. Rogers, R. D. "Editorial – Best New Journal," *Cryst. Growth Des.* **2002**, *2*, 161.
23. Huddleston, J. G.; Moody, M. L.; Willauer, H. D.; Broker, G. D.; Rogers, R. D. "Predicting the Performance of Alternative Solvents Through the Use of Free Energy Relationships," In *Proceedings of GreenChem2002, 6th Annual Green Chemistry and Engineering Conference, Meeting Global Challenges through Economics and Environmental Innovations,* American Chemical Society, Washington, DC, 2002; pp 59-62.
24. Holbrey, J. D.; Shaughnessy, K. H.; Rogers, R. D. "Polymerization and Polymers in Room Temperature Ionic Liquids," In *Proceedings of GreenChem2002, 6th Annual Green Chemistry and Engineering Conference, Meeting Global Challenges through Economics and Environmental Innovations,* American Chemical Society, Washington, DC, 2002; pp 62-64.
25. Rogers, R. D.; Holbrey, J. D.; Spear, S. K.; Swatloski, R. P. "Ionic Liquids: A Look at the Dissolution of Cellulose," In *Proceedings of GreenChem2002, 6th Annual Green Chemistry and Engineering Conference, Meeting Global Challenges through Economics and Environmental Innovations,* American Chemical Society, Washington, DC, 2002; pp 39-40.
26. Rogers, R. D.; Seddon, K. R. "Preface," In *Ionic Liquids; Industrial Applications to Green Chemistry*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 818; American Chemical Society: Washington DC, 2002; pp XIII-XIV.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 47

IPR2020-00770
United Therapeutics EX2007
Page 3597 of 7335

27. Swatloski, R. P.; Holbrey, J. D.; Spear, S. K.; Rogers, R. D. "Ionic Liquids as Green Solvents for Regeneration/Engineering of Cellulose Based Products," In *Proceedings of GreenChem2002, 6th Annual Green Chemistry and Engineering Conference, Meeting Global Challenges through Economics and Environmental Innovations,* American Chemical Society, Washington, DC, 2002; pp 151-152.
28. Rogers, R. D. "Editorial," *Cryst. Growth Des.* **2003**, *3*, 1-2.
29. Rogers, R. D. "Editorial: Introduction: Polymorphism in Crystals," *Cryst. Growth Des.* **2003**, *3*, 867.
30. Rogers, R. D.; Seddon, K. R. "Preface," In *Ionic Liquids as Green Solvents: Progress and Prospects*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 856; American Chemical Society: Washington DC, 2003; pp XIII-XVI.
31. Rogers, R. D.; Seddon, K. R.; Volkov, S. "Preface," In *Green Industrial Applications of Ionic Liquids*, Rogers, R. D.; Seddon, K. R.; Volkov, S. (Eds.); Kluwer: Dordrecht, 2003; pp XI-XVII.
32. Holbrey, J. D.; Chen, J.; Turner, M. B.; Swatloski, R. P.; Spear, S. K.; Rogers, R. D. "Applying ionic liquid solvent characteristics for controlled processing of polymer materials," *Polymer Preprints* (American Chemical Society, Division of Polymer Chemistry) **2004**, *45*, 297-298.
33. Klingshirn, M. A.; Spear, S. K.; Subramanian, R.; Holbrey, J. D.; Rogers, R. D. "Synthesis, characterization, and application of ionic liquid-poly(ethylene) glycol gel matrices," *Polymer Preprints* (American Chemical Society, Division of Polymer Chemistry) **2004**, *45*, 307-308.
34. Shaughnessy, K. H.; P'Pool, S. J.; Klingshirn, M. A.; Rogers, R. D. "Coordination polymerization of alkenes in ionic liquid solvents," *Polymer Preprints* (American Chemical Society, Division of Polymer Chemistry) **2004**, *45*, 317-318.
35. Rogers, R. D. "Editorial: *Crystal Growth & Design* on an Upward Track," *Cryst. Growth Des.* **2004**, *4*, 1.
36. Rogers, R. D. "Robin D. Rogers," *Green Chem.* **2004**, *6*, G17-G19.
37. Rogers, R. D.; Gutowski, K. E.; Griffin, S. T.; Holbrey, J. D. "Aqueous biphasic systems based on salting-out polyethylene glycol or ionic liquid solutions: strategies for actinide or fission product separations. Preprints of Extended Abstracts presented at the ACS National Meeting, American Chemical Society, Division of Environmental Chemistry **2004**, *44*, 403-407.
38. Rogers, R. D. "Editorial: Polymorphism in Crystals-A Special Issue of *Crystal Growth & Design*," *Cryst. Growth Des.* **2004**, *4*, 1085.
39. *Risk and Decisions About Disposition of Transuranic and High-Level Radioactive Waste*, Committee on Risk-Based Approaches for Disposition of Transuranic and High-Level Radioactive Waste, National Research Council of the National Academies, The National Academies Press, Washington, DC, 2005; 215 pp. (Written by Committee)
40. Rogers, R. D. "Editorial: *Crystal Growth & Design* on an Upward Track," *Cryst. Growth Des.* **2005**, *5*, 1.
41. Turner, M. B.; Holbrey, J. D.; Spear, S. K.; Rogers, R. D. "Ionic Liquids," In *2005 Yearbook of Science & Technology*, McGraw-Hill: New York, 2005; pp 158-160.
42. Rogers, R. D. "Editorial: *A Tribute to the Life and Career of J. Michael McBride*," *Cryst. Growth Des.* **2005**, *5*, 2021.
43. Rogers, R. D.; Seddon, K. R. "Preface," In *Ionic Liquids IIIA: Fundamentals, Progress, Challenges, and Opportunities – Properties and Structure*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 902; American Chemical Society: Washington DC, 2005 pp xiii-xiv and In *Ionic Liquids IIIB: Fundamentals, Progress, Challenges, and Opportunities - Transformations and Processes*, Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 902; American Chemical Society: Washington DC, 2005 pp xiii-xiv.
44. Vlieg, E.; Rogers, D. R. "Polymorphism," (A report on the name microsymposium at the XX Congress and General Assembly of the IUCr (2005)), International Union of Crystallography Newsletter **2005**, *13*, 15 and 18.
45. Rogers, R. D. "Preface: China - A Growing Ionic Liquids Community," In *Ionic Liquids: From Fundamentals to Applications*, Zhang, S. (Ed.); ScienceP: Beijing, China, 2006.
46. Rogers, R. D. "Editorial: Authors Lead *Crystal Growth & Design* to Monthly Issues and Higher Impact!" *Cryst. Growth Des.* **2006**, *6*, 1.
47. Rogers, R. D. "First China-USA Green Chemistry Workshop," *Green Chem.* **2006**, *8*, 126-127.
48. Rogers, R. D.; Seddon, K. R. "A Response to an Old-Fashioned Thought Cop," *Anal. Chem.* **2006**, *78*, 3480-3481.
49. Rogers, R. D. "Editorial: Higher Impact, Higher Immediacy, Growth, and Outreach," *Cryst. Growth Des.* **2007**, *7*, 1.
50. Brennecke, J. F.; Rogers, R. D.; Seddon, K. R. "Preface," In *Ionic Liquids IV: Not Just Solvents Anymore*, Brennecke, J. F.; Rogers, R. D.; Seddon, K. R. (Eds.); ACS Symposium Series 975; American Chemical Society: Washington DC, 2007; pp xi-xiii.
51. Rogers, R. D.; Voth, G. A. "Guest Editorial: Ionic Liquids," *Acc. Chem. Res.* **2007**, *40*, 1077-1078.
52. Gurau, G.; Rogers, R. D. "Ionic Liquids: Green Solvents or Advanced Materials?" *Materials World* **2007**, *15*(12), 25-27.
53. Rogers, R. D., "Ionic Liquids: Green Miracles, Toxic Solvents, or New Drugs?," Center for Advanced Bioseparation Technology Newsletter, December 2007.
54. Rogers, R. D. "Editorial: Expanding Horizons," *Cryst. Growth Des.* **2008**, *8*, 1.
55. Rogers, R. D. "Is a Lower Risk 'Green' Industrial revolution in our Future?" *Risk Policy Report*; Inside EPA; Washington, DC; April 1, 2008, *15*, pp 11-12.
56. Kunle, O. O.; Fortunak, J.; Rogers, R. D. "Workshop in Green Chemistry Production of Essential Medicines in Developing Countries," *Green Chem.* **2008**, *10*, 823-824.
57. Rodríguez, H.; Bica, K.; Rogers, R. D. "(Editorial) Ionic Liquid Technology: A Potential New Platform for the Pharmaceutical Industry," *Trop. J. Pharm. Res.* **2008**, *7*, 1011-1012.
58. Rogers, R. D. "Journal Club: A Chemist Believes that an Ionic Liquid is the Place for a Noxious Gas," *Nature* **2008**, *454*, 555.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 48

IPR2020-00770
United Therapeutics EX2007
Page 3598 of 7335

59. Rogers, R. D. "Editorial: *Crystal Growth & Design* in India," *Cryst. Growth Des.* **2009**, *9*, 1639.
60. *Advice on the Department of Energy's Cleanup Technology Roadmap: Gaps and Bridges*, Nuclear and Radiation Studies Board Division of Earth and Life Sciences Committee on Development and Implementation of a Cleanup Technology Roadmap, National Research Council of the National Academies, The National Academies Press, Washington, DC, 2009; 271 pp. (Written by Committee)
61. Rogers, R. D. "Editorial: *Crystal Growth & Design's* First Virtual Special Issue," *Cryst. Growth Des.* **2009**, *9*, 4207.
62. Rogers, R. D. "Preface," In *Ionic Liquids and Green Chemistry*, Zhang, S; Xu, C.; Lu, X.; Zhou, Q. (Eds.); Science Press: Beijing, China, 2009.
63. Rogers, R. D. "Preface, Twenty-Fifth Rare Earth Research Conference," *J. Alloys Comp.* **2009**, *488*, 491.
64. Plechkova, N. V.; Rogers, R. D.; Seddon K. R. "Preface" In *Ionic Liquids: From Knowledge to Application*, Plechkova, N. V.; Rogers, R. D.; Seddon K. R. (Eds.); ACS Symposium Series 1030; American Chemical Society: Washington, DC, 2009; pp xi-xii. DOI: 10.1021/bk-2009-1030.pr001.
65. Rogers, R. D. "10th Anniversary Anticipation," *Cryst. Growth Des.* **2010**, *10*, 1-2.
66. Rogers, R. D. "When Giants Cooperate instead of Collide," *Cryst. Growth Des.* **2010**, *10*, 4671.
67. Rogers, R. D. "A Look at Ionic Liquids," *Chemical & Engineering News*, November 29, 2010, pp 38-39.
68. Rogers, R. D. "Ten Years of Experience: How can we put it to good use?," *Cryst. Growth Des.* **2011**, *11*, 1-3.
69. Brennecke, J. F.; Schatz, G. C.; Rogers, R. D. "Ionic Liquids Virtual Special Issue," *Cryst. Growth Des.* **2011**, *11*, 625-626.
70. Rogers, R. D. "Halogen Bonding: Weak Interactions Result in Strong Opinions," *Cryst. Growth Des.* **2011**, *11*, 4721-4722.
71. Rogers, R. D. "*Crystal Growth & Design* Around the World in 2012," *Cryst. Growth Des.* **2012**, *12*, 1-2.
72. Chen, J.; Rodríguez, H.; Rogers, R. D. "Editorial: SS&T Special Issue on Ionic Liquids for Separations," *Sep. Sci. Technol.* **2012**, *47*, 167-168.
73. Rogers, R. D.; Zhang, S.; Wang, J. "Preface" An International Look at Ionic Liquids," *Sci. China Chem.* **2012**, *55*, 1475-1477. DOI: 10.1007/s11426-012-4718-3
74. Zhang, S.; Ng, F. T. T.; Rogers, R. D. "Preface," *Catalysis Today* **2013**, *200*, 1.
75. Visser, A. E.; Bridges, N. J.; Rogers, R. D. "Preface" In *Ionic Liquids: Science and Applications*, Visser, A. E.; Bridges, N. J.; Rogers, R. D. (Eds.); ACS Symposium Series 1117; American Chemical Society: Washington, DC, 2012; pp ix-x. DOI: 10.1021/bk-2012-1117.pr001.
76. Lind-Kovacs, C.; Rogers, R. D. "TR: The Transactions symposium: Crystallography for Sustainability," ACA Reflexions, ACA – Structure Matters; American Crystallographic Association: Buffalo, NY, 2015, No. 3 Fall; pp 20-21.
77. Rogers, R. D. "Eliminating the Need for Chemistry," *Chemical & Engineering News*, December 7/14, 2015, pp 42-43.
78. Rogers, R. D. "Recognizing, Catalyzing, and Embracing Change," *Cryst. Growth Des.* **2016**, *16*, 1-2. DOI: 10.1021/acs.cgd.5b01801.

C. Presentations before National and International Meetings and Workshops:

1. R. D. Rogers, W. E. Hunter, M. Zaworotko, and J. L. Atwood, "Structural Characterization of the Mo-C Sigma Bond in a Series of Related Organometallic Compounds," Presented by R. D. Rogers before the American Crystallographic Association Winter Meeting (1978), Norman, OK, Abstract E3.
2. J. L. Atwood, R. D. Rogers, and W. E. Hunter, "The Nature of the Cyclopentadienyl Ligand in $(C_5H_5)_4W(CO)_2$," Presented by J. L. Atwood before the American Crystallographic Association Winter Meeting (1978), Norman, OK, Abstract PA3.
3. J. L. Atwood, W. E. Hunter, R. D. Rogers, and R. V. Bynum, "A Comparison of Metal-Carbon Sigma and Pi Bonds in the Closely Related Series of Compounds CpZrRR'," Presented by J. L. Atwood before the 176th ACS National Meeting (1978), Miami Beach, FL, Abstract INOR 031.
4. R. D. Rogers and J. L. Atwood, "The Synthesis and Crystal Structure of $Cs[Al_2Me_6N_3]$•2 p-Xylene," Presented by R. D. Rogers before the 176th ACS National Meeting (1978), Miami Beach, FL, Abstract INOR 032.
5. R. D. Rogers, W. E. Hunter, M. J. Zaworotko, and J. L. Atwood, "Structural Characterization of Organometallic Compounds Containing a Novel Bulky Alkoxide Ligand," Presented by R. D. Rogers before the 177th ACS National Meeting (1979), Honolulu, HA, Abstract INOR 052.
6. J. L. Atwood, R. Shakir, M. J. Zaworotko, R. D. Rogers, and E. A. Lewis, "Synthesis, Crystal Structure, and Solution Behavior of $K[Al_2(CH_3)_6SCN]$," Presented by J. L. Atwood before the 177th ACS National Meeting (1979), Honolulu, HA, Abstract INOR 070.
7. R. D. Rogers, R. V. Bynum, and J. L. Atwood, "The Synthesis and Crystal Structure of $(\eta^5\text{-}C_5H_5)_3Gd$•$OC_4H_8$," Presented by R. D. Rogers before the American Crystallographic Association Winter Meeting (1979), Honolulu, HA, Abstract L7.
8. J. L. Atwood, R. V. Bynum, R. D. Rogers, and W. E. Hunter, "The Reaction of Dichlorodicyclopentadienylzirconium(IV) with Pyrrolylsodium: Synthesis and Structure of $(\eta^5\text{-}C_5H_5)_2Ti(\eta^1\text{-}NC_4H_4)_2$, $(\eta^5\text{-}C_5H_5)_2Zr(\eta^1\text{-}NC_4H_4)_2$, and $[Na(THF)_6]_2[Zr(\eta^1\text{-}NC_4H_4)_6]$," Presented by J. L. Atwood before the IXth International Conference on Organometallic Chemistry (1979), Dijon, France, Abstract C46.
9. E. A. Lewis, R. D. Rogers, and J. L. Atwood, "Heats of Solution and of Liquid Clathrate Formation for some Alkali Metal Tri-Alkyl Aluminum Azide Complexes," Presented by E. A. Lewis before the 34th Annual Calorimetry Conference (1979), Kent, OH, Abstract Program Booklet.
10. R. D. Rogers and J. L. Atwood, "Bonding Modes of the $N(SiMe_3)_2$ Ligands: The Crystal and Molecular Structure of $SnBr[N(SiMe_3)_2]_3$," Presented by R. D. Rogers before the American Crystallographic Association Summer Meeting (1979), Boston, MA, Abstract M10.
11. R. V. Bynum, R. D. Rogers, and J. L Atwood, "A Major Difference in the Structural Chemistry of Zirconium and Hafnium: The Crystal Structure of Tetra(cyclopentadienyl)hafnium," Presented by R. V. Bynum before the American Crystallographic Association Winter Meeting (1980), Eufala, AL, Abstract PB3.
12. R. D. Rogers and J. L. Atwood, "The Effect of the Pentamethylcyclopentadienyl Ligand on the Titanium-Carbonyl Bond in $(\eta^5\text{-}C_5Me_5)_2Ti(CO)_2$," Presented by R. D. Rogers before the American Crystallographic Association Winter Meeting (1980), Eufala, AL, Abstract I3.
13. R. D. Rogers, E. A. Lewis, and J. L. Atwood, "Calorimetric Investigations into Liquid Clathrate Behavior," Presented by R. D. Rogers before the 179th ACS National Meeting (1980), Houston, TX, Abstract PHYS 185.
14. R. D. Rogers, J. L. Atwood, and E. A. Lewis, "Thermodynamic Studies Into the Behavior of the First Air-Stable Liquid Clathrates," Presented by R. D. Rogers before the 35th Annual Calorimetry Conference (1980), Eufala, AL, Abstract page 40.
15. S. R. Stobart, A. D. McMaster, J. L. Atwood, and R. D. Rogers, "Tetra(Indenyl)Tin: A Stereochemically Significant Molecule," Presented by S. R. Stobart before the 3rd International Conference on the Organometallic and Coordination Chemistry of Germanium, Tin and Lead (1980), Dortmund, West Germany, Abstract.
16. J. L. Atwood and R. D. Rogers, "The Incorporation of Aromatic Molecules Into Solid-State Organoaluminum Structures," Presented by J. L. Atwood before the International Symposium on Clathrate Compounds and Molecular Inclusion Phenomena, (1980), Jachranka-Warsaw, Poland, Abstract page 51.
17. R. V. Bynum, R. D. Rogers, W. E. Hunter, and J. L. Atwood, "Novel Pyrrolyl Complexes of Group IVB Metals," Presented by R. D. Rogers before the Second Congress of the North American Continent (1980), Las Vegas, NV, Abstract INOR 139.
18. R. D. Rogers, L. G. Canada, and J. L. Atwood, "The Crystal and Molecular Structure of $Mn_2Br_2(CO)_6Te_2Ph_2$," Presented by R. D. Rogers before the American Crystallographic Association Winter Meeting (1981), College Station, TX, Abstract PA15.
19. R. D. Rogers and J. L. Atwood, "Structural Studies of Group IV-B Metallocence Carbonyl and Phosphine Complexes," Presented by R. D. Rogers before the 181st ACS National Meeting (1981), Atlanta, GA, Abstract INOR 063.
20. E. Carmona, J. Marin, M. L. Poveda, R. D. Rogers, and J. L. Atwood, "Synthesis and Crystal Structure of Molybdenum and Tungsten Dihaptoacyl and Related Compounds," Presented by E. Carmona before the Xth International Conference on Organometallic Chemistry (1981), Toronto, Canada, Abstract 2E37.
21. J. L. Atwood, R. D. Rogers, M. J. Zaworotko, W. E. Hunter, and D. C. Hrncir, "New Type of Electron-Deficient Bond in the Anion $[Me_3Al\text{-}H\text{-}AlMe_3]^-$," Presented by J. L. Atwood before the Xth International Conference on Organometallic Chemistry (1981), Toronto, Canada, Abstract 1B01.
22. R. D. Rogers, D. C. Hrncir, and J. L. Atwood, "Structural Investigations of Liquid Clathrate Parent Complexes: The Crystal and Molecular Structures of $K_2[Al_4Me_{16}SO_4]$, $K_2[Al_4Me_{12}SO_4]$•0.5 p-$Me_2C_6H_4$, and $K[Al_7O_6C_{16}H_{48}]$•C_6H_6," Presented by R. D.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 50

IPR2020-00770
United Therapeutics EX2007
Page 3600 of 7335

Rogers before the XIIth International Congress and General Assembly of the International Union of Crystallography (1981), Ottawa, Canada, Abstract 09.3-01; *Acta Crystallogr., Sect. A*, A37, C217 (1981).
23. J. L. Atwood, R. D. Rogers, D. C. Hrncir, M. J. Zaworotko, and W. E. Hunter, "Classification Scheme for Aromatic 'Solvates' in Ionic Organometallic Compounds," Presented by J. L. Atwood before the XIIth International Congress and General Assembly of the International Union of Crystallography (1981), Ottawa, Canada, Abstract 04.1-09; *Acta Crystallogr., Sect. A*, A37, C83 (1981).
24. R. D. Rogers, R. Priester, D. C. Hrncir, and J. L. Atwood, "Synthesis and Structure of the $[Al_7O_6C_{16}H_{48}]^-$ Anion in $K[Al_7O_6C_{16}H_{48}]\bullet C_6H_6$ and $Cs[Al_7O_6C_{16}H_{48}]\bullet 3C_6H_5Me$," Presented by R. D. Rogers before the 182nd ACS National Meeting (1981), New York, NY, Abstract INOR 222.
25. R. D. Rogers, J. L. Atwood, D. F. Foust, and M. D. Rausch, "Formation and Structure of $Cp_2Y(C_6H_4\text{-}o\text{-}CH_2NMe_2)$," Presented by R. D. Rogers before the Sixteenth Rare Earth Research Conference (1983), Tallahassee, FL, Abstract A1; *J. Less-Comm. Metals*, 94, 402 (1983).
26. C. M. Means, N. C. Means, H.-M. Zhang, W. E. Hunter, R. D. Rogers, and J. L. Atwood, "New High-Oxygen Content Organoaluminum Compounds. Synthesis, Structure, and Decomposition Pathways," Presented by N. C. Means before the 187th ACS National Meeting (1984), St. Louis, MO, Abstract INOR 019.
27. R. D. Rogers, "Structural Characterization of New Pentamethylcyclopentadienyl Derivatives of Group IVB," Presented by R. D. Rogers before the 187th ACS National Meeting (1984), St. Louis, MO, Abstract INOR 271.
28. A. L. Wayda, J. L. Dye, and R. D. Rogers, "Divalent Lanthanoid Synthesis in Liquid Ammonia," Presented by A. L. Wayda before the XXIIIrd International Conference on Coordination Chemistry (1984), Boulder, CO, Abstract.
29. R. D. Rogers and A. L. Wayda, "X-ray Structural Investigations of Organolanthanoids," Presented by R. D. Rogers before the NATO Advanced Study Institute on Fundamental and Technological Aspects of Organo-f-Element Chemistry (1984), Acquafredda di Maratea, Italy, Abstract page P12.
30. L. K. Kurihara and R. D. Rogers, "Lanthanide Crown Ether Complexes," Presented by L. K. Kurihara before the 190th ACS National Meeting (1985), Chicago, IL, Abstract INOR 213.
31. M. M. Benning and R. D. Rogers, "Monosubstituted Cyclopentadienyl Ligands in f-Element Chemistry," Presented by M. M. Benning before the 190th ACS National Meeting (1985), Chicago, IL, Abstract INOR 212.
32. D. W. Macomber, M.-H. Hung and R. D. Rogers, "Preparation, Reactivity, and Structure of Mononuclear η^5-Cyclopentadienyl Cobalt Carbene Complexes," Presented by D. W. Macomber before the 190th ACS National Meeting (1985), Chicago, IL, Abstract INOR 137.
33. R. D. Rogers and D. W. Macomber, "Structural Chemistry of Cobalt and Rhodium Carbene Complexes," Presented by R. D. Rogers before the 190th ACS National Meeting (1985), Chicago, IL, Abstract INOR 214.
34. A. L. Wayda, R. D. Rogers, M. P. Andrews, I. Mukerji, S. H. Bertz and G. Dabbagh, "Lanthanoid Metals in Unusual Coordination Environments: Implications for Organic, Organometallic and Inorganic Chemistry," Presented by A. L. Wayda before the Seventeenth Rare Earth Research Conference (1986), Hamilton, Ontario, Canada, Abstract G.3; *J. Less-Comm. Metals*, 126, 416 (1987).
35. R. D. Rogers, A. L. Wayda, I. Mukerji and J. L. Dye, "Divalent Lanthanoid Synthesis in Liquid Ammonia. 3. The Synthesis and X-ray Crystal Structure of $(C_8H_8)Yb(C_5H_5N)_3\bullet 1/2\ C_5H_5N$," Presented by R. D. Rogers before the Seventeenth Rare Earth Research Conference (1986), Hamilton, Ontario, Canada, Abstract G.6; *J. Less-Comm. Metals*, 126, 418 (1987).
36. R. D. Rogers and L. K. Kurihara, "Solvent Interactions in f-Element/Crown Ether Complexation Chemistry: Synthesis and Structure of (Dibenzo-18-crown-6)$\bullet 2(CH_3CN)$," Presented by R. D. Rogers before the Seventeenth Rare Earth Research Conference (1986), Hamilton, Ontario, Canada, Abstract C(III).5; *J. Less-Comm. Metals*, 127, 268 (1987).
37. L. K. Kurihara and R. D. Rogers, "Crown Ether Complexes of Hydrated f-Element Salts," Presented by L. K. Kurihara before the Seventeenth Rare Earth Research Conference (1986), Hamilton, Ontario, Canada, Abstract C(III).6.
38. M. M. Benning, L. K. Kurihara and R. D. Rogers, "The Synthesis and Crystal Structure of $[UO_2Cl_4][(OH_3)$(Dibenzo-18-crown-6)$]_2\bullet 2CH_3OH$," Presented by M. M. Benning before the Seventeenth Rare Earth Research Conference (1986), Hamilton, Ontario, Canada, Abstract C:(III).7; *J. Less-Comm. Metals*, 127, 269 (1987).
39. A. Verma, D. W. Macomber and R. D. Rogers, "Intermolecular [2+2+2] Cycloadditions of Alkynes and Alkenes Mediated by (η^5-Cyclopentadienyl)cobalt Complexes," Presented by A. Verma before the 192nd ACS National Meeting (1986), Anaheim, CA, Abstract INOR 266.
40. L. B. Kool, M. D. Rausch, and R. D. Rogers, "Dual Ring Phosphination of a Titanium Mixed-Sandwich: A New Route to Heterobimetallic Derivatives," Presented by L. B. Kool before the 193rd ACS National Meeting (1987), Denver, CO, Abstract INORG 250.
41. M. Liang, D. W. Macomber, and R. D. Rogers, "Synthesis and Reactivity of a,b-Unsaturated Tungsten Carbene Complexes: X-ray Crystal Structure of $(CO)_5W[C(OCH_3)(\eta^5\text{-}CH{=}CH_2)]W(CO)_5$," Presented by M. Liang before the 193rd ACS National Meeting (1987), Denver, CO, Abstract INORG 222.
42. E. J. Voss and R. D. Rogers, "Neutral Solvent/Crown Ether Interactions. Crystallization and Structural Characterization of Dibenzo-18-crown-6$\bullet 2(CH_3CN)$ and Dibenzo-18-crown-6$\bullet 2(CH_3NO_2)$, Assignment of Specific C-H···O Interactions," Presented by E. J. Voss before the 193rd ACS National Meeting (1987), Denver, CO, Abstract INORG 179.
43. M. M. Benning and R. D. Rogers, "f-Element/Crown Ether Complexes. Hydrogen Bonding in Actinide Complexes of Crown Ethers," Presented by M. M. Benning before the 193rd ACS National Meeting (1987), Denver, CO, Abstract INORG 180.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 51

IPR2020-00770
United Therapeutics EX2007
Page 3601 of 7335

44. R. D. Rogers, "f-Element/Crown Ether Complexes. Synthetic and Structural Chemistry of Crown Ether Complexes of 4f and 5f Metal Chlorides," Presented by R. D. Rogers before the 193rd ACS National Meeting (1987), Denver, CO, Abstract INORG 316.
45. M. M. Benning and R. D. Rogers, "f-Element/Crown Ether Complexes. Crown Conformations in Hydrogen Bonded Complexes of Hydrated Actinide Salts," Presented by M. M. Benning before the XIVth International Congress and General Assembly of the International Union of Crystallography (1987), Perth, Australia, Abstract 09.4-13.
46. R. D. Rogers, "f-Element/Crown Ether Complexes. Structural Effects of Solvent and Water of Hydration Hydrogen Bonding," Presented by R. D. Rogers before the XIVth International Congress and General Assembly of the International Union of Crystallography (1987), Perth, Australia, Abstract 09.4-12.
47. L. Nunez, G. Crabtree, J. Z. Liu, A. Umazawa, H. Claus, and R. D. Rogers, "Structural and Magnetic Characterization of Single Crystals of $YBa_2Cu_3O_{7-\square}$," Presented by L. Nunez before the 195th ACS National Meeting and 3rd Chemical Congress of North America (1988), Toronto, Canada, Abstract INOR 152.
48. A. N. Rollins and R. D. Rogers, "f-Element/Crown Ether Complexes. Synthetic and Structural Survey of 12-crown-4 Complexes of Hydrated Lanthanide Chlorides," Presented by A. N. Rollins before the 195th ACS National Meeting and 3rd Chemical Congress of North America (1988), Toronto, Canada, Abstract INOR 155.
49. R. D. Etzenhouser and R. D. Rogers, "Precipitation and Structural Characterization of Tetraethylene Glycol Complexes of Hydrated Lanthanide Chlorides, Comparison with Triethylene Glycol," Presented by R. D. Etzenhouser before the 195th ACS National Meeting and 3rd Chemical Congress of North America (1988), Toronto, Canada, Abstract INOR 154.
50. M. M. Benning and R. D. Rogers, "f-Element/Crown Ether Complexes. Thia-Crown Ether Interactions with Actinide Chlorides, Comparison with Crown Ether Results," Presented by M. M. Benning before the 195th ACS National Meeting and 3rd Chemical Congress of North America (1988), Toronto, Canada, Abstract INOR 521.
51. R. D. Rogers, "f-Element/Crown Ether Complexes. The Role of Water in Complexing 12-Crown-4, 15-Crown-5, Benzo-15-Crown-5, 18-Crown-6, and Dibenzo-18-crown-6 to Hydrated Lanthanide Chlorides," Presented by R. D. Rogers before the 195th ACS National Meeting and 3rd Chemical Congress of North America (1988), Toronto, Canada, Abstract INOR 520.
52. R. F. Henry and R. D. Rogers, "Mixed Donor 18-Membered Macrocyclic Complexes of Hydrated f-Element Salts," Presented by R. F. Henry before the Eighteenth Rare Earth Research Conference (1988), Lake Geneva, WI, Abstract P4.45.
53. L. Nunez, R. D. Rogers, G. Crabtree, J. Z. Lui, and H. Claus, "Structure and Magnetic Characterization of Single Crystals of $YBa_2Cu_3O_{7-\square}$. Effects of Annealing," Presented by L. Nunez before the Eighteenth Rare Earth Research Conference (1988), Lake Geneva, WI, Abstract P6.9.
54. A. N. Rollins and R. D. Rogers, "f-Element/Crown Ether Complexes. Preparation and Structural Characterization of Mixed Anion (NO_3^-,Cl^-) Complexes of Lanthanum(III) and Crown Ethers," Presented by A. N. Rollins before the Eighteenth Rare Earth Research Conference (1988), Lake Geneva, WI, Abstract P4.43.
55. R. D. Etzenhouser and R. D. Rogers, "Precipitation and Structural Characterization of Pentaethylene Glycol and Hexaethylene Glycol Complexes of Hydrated Lanthanide Chlorides, Comparison with Tetraethylene Glycol," Presented by R. D. Etzenhouser before the Eighteenth Rare Earth Research Conference (1988), Lake Geneva, WI, Abstract P4.44.
56. R. D. Rogers, "f-Element/Crown Ether Complexation. Crown Ethers and Glycols as Variably Dentate Donors for Uranyl(VI) Chloride," Presented by R. D. Rogers before the Eighteenth Rare Earth Research Conference (1988), Lake Geneva, WI, Abstract P4.48.
57. R. Henry and R. D. Rogers, "Synthesis of an 18 Membered, Mixed Donor, Macrocyclic Lanthanide Complex," Presented by R. Henry at the Fifth International Symposium on Inclusion Phenomena and Molecular Recognition (1988), Orange Beach, AL, Abstract D43.
58. A. N. Rollins and R. D. Rogers, "f-Element/Crown Ether Complexes: Effects of Anion Concentration on Complexation of Dibenzo-18-Crown-6, 18-Crown-6, 15-Crown-5, and 12-Crown-4 with Hydrated Lanthanide Chloride Salts," Presented by A. N. Rollins at the Fifth International Symposium on Inclusion Phenomena and Molecular Recognition (1988), Orange Beach, AL, Abstract D44.
59. R. D. Etzenhouser and R. D. Rogers, "Tying Up the Ln(III) Coordination Sphere One Site at a Time: Tri-, Tetra-, Penta- and Hexaethylene Glycol Complexes of Hydrated Lanthanide Chloride Salts," Presented by R. D. Etzenhouser at the Fifth International Symposium on Inclusion Phenomena and Molecular Recognition (1988), Orange Beach, AL, Abstract D45.
60. R. D. Rogers, "f-Element Crown Ether Complexes: Two Crystal Structures Containing Dicyclohexyl-24-Crown-8 Complexed to Na^+ and $H_5O_2^+$," Presented by R. D. Rogers at the Fifth International Symposium on Inclusion Phenomena and Molecular Recognition (1988), Orange Beach, AL, Abstract D20.
61. D. W. Macomber, M. H. Hung, M. Liang, P. Madhukar, A. G. Verma and R. D. Rogers, "Synthesis, Reactivity, and Structures of (□-Bis(Carbene))Dimetallic Complexes of Chromium and Tungsten," Presented by D. W. Macomber before the 197th ACS National Meeting (1989), Dallas, TX, Abstract INOR 173.
62. A. H. Bond and R. D. Rogers, "f-Element/Crown Ether Complexes. The Reactions of Uranyl Sulfate with Crown Ethers in Sulfuric Acid," Presented by A. H. Bond before the 197th ACS National Meeting (1989), Dallas, TX, Abstract INOR 212.
63. W. G. Hipple and R. D. Rogers, "f-Element/Crown Ether Complexes. Higher Order Hydronium Ion Crown Ether Complexes Stabilized by $[UO_2Cl_4]^{2-}$ Anions. Crystal Structure of $[(H_5O_2)(H_9O_4)(Benzo\text{-}15\text{-}Crown\text{-}5)_2][UO_2Cl_4]$," Presented by W. G. Hipple before the 197th ACS National Meeting (1989), Dallas, TX, Abstract INOR 210.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 52

IPR2020-00770
United Therapeutics EX2007
Page 3602 of 7335

64. A. N. Rollins and R. D. Rogers, "f-Element/Crown Ether Complexes. A Comparison of the Crystal Structures of $La(NO_3)_3$(15-Crown-5), $Eu(NO_3)_3$(15-Crown-5)[1], and $La(NO_3)_3$(Monoaza-15-Crown-5)[2]," Presented by A. N. Rollins before the 197th ACS National Meeting (1989), Dallas, TX, Abstract INOR 211.
65. R. D. Etzenhouser and R. D. Rogers, "f-Element/Crown Ether Complexes. Supramolecular Structures of the Intricate Hydrogen Bonding Networks in Hydrated Lanthanide Chloride Polyethylene Glycol Complexes," Presented by R. D. Etzenhouser before the 197th ACS National Meeting (1989), Dallas, TX, Abstract CHED 113.
66. R. D. Rogers, "f-Element/Crown Ether Complexes. Supramolecular Structures of the Intricate Hydrogen Bonding Networks in Hydrated Lanthanide Chloride Crown Ether Complexes," Presented by R. D. Rogers before the 197th ACS National Meeting (1989), Dallas, TX, Abstract CHED 112.
67. M. A. Banks, O. T. Beachley, Jr., H. J. Gysling, H. R. Luss, J. D. Maloney, and R. D. Rogers, "Neopentylgallium Compounds which Incorporate Group 15 and Group 16 Lewis Bases," Presented by M. A. Banks before the 197th ACS National Meeting (1989), Dallas, TX, Abstract INOR 376.
68. C. W. Spangler, T. J. Hall, M. L. Saindon, R. D. Rogers, R. K. McCoy, R. R. Birge, P. A. Fleitz, and C.-F. Zhang, "The Relationship Between Structure and Nonlinear Optical Properties in Donor-Acceptor Polyenes," Presented by C. W. Spangler before the International Conference on Materials for Non-Linear and Electro-Optics (1989), Cambridge, United Kingdom, Abstract.
69. M. Ogasa, M. D. Rausch, and R. D. Rogers, "Synthesis of Ring-Phosphinated Titanium(II) Mixed Sandwich Compounds (η^5-$C_5H_4PR_2$)Ti(η^7-$C_7H_6PR_2$) (R=CH_3, C_6H_5) and Their Conversion to Heterobimetallic Compounds," Presented by M. Ogasa before the 198th ACS National Meeting (1989), Miami, FL, Abstract INOR 380.
70. D. N. Kevill, M.-G. Park, and R. D. Rogers, "Studies of the Reactions of Diarylimidoyl Chlorides with Diazomethyllithium," Presented by D. N. Kevill before the International Symposium on Nitrogen-Rings and -Chains (1990), Frankfurt, Federal Republic of Germany.
71. L. Nuñez, B. Veal, G. W. Crabtree, W. K. Kwok, H. Claus, R. R. Rogers, and A. P. Paulikas, "Powder X-ray Diffraction Study on $YBa_2(Cu_{3-x}Fe_x)O_{7-\square}$," Presented by L. Nuñez before the APS National Meeting (1989).
72. A. H. Bond and R. D. Rogers, "Macrocyclic Complexation Chemistry of the Environmentally Toxic Metals," Presented by A. H. Bond before the 199th ACS National Meeting (1990), Boston, MA, Abstract INOR 282.
73. L. Nuñez and R. D. Rogers, "Solution Precursors to New Materials Via Macrocyclic Complexation Chemistry," Presented by L. Nuñez before the 199th ACS National Meeting (1990), Boston, MA, Abstract INOR 281.
74. A. N. Rollins and R. D. Rogers, "Macrocyclic Chemistry of the Lanthanides and Actinides," Presented by A. N. Rollins before the 199th ACS National Meeting (1990), Boston, MA, Abstrct INOR 280.
75. R. D. Rogers, "Macrocyclic Complexation Chemistry: Uranyl Salts and Crown Ethers in Acidic Media," Presented by R. D. Rogers before the 199th ACS National Meeting (1990), Boston, MA, INOR 279.
76. W. M. Tsai, M. D. Rausch and R. D. Rogers, "Synthetic and Structural Studies on Pentabenzylcyclopentadienyliron Dicarbonyl Derivatives," Presented by W. M. Tsai before the 199th ACS National Meeting (1990), Boston, MA, Abstract INOR 291.
77. R. J. Strittmatter, B. E. Bursten, L. F. Rhodes, D. E. Morris, and R. D. Rogers, "Readily-Accessible Oxidation of d^0 Organozirconium Compounds: The Electronic Structure of (η^5-$C_5H_5)_3ZrX$ Compounds," Presented by R. J. Strittmatter before the 199th ACS National Meeting (1990), Boston, MA, Abstract INOR 313.
78. G. H. Robinson, B. Lee and R. D. Rogers, "The Interaction of Trimethylgallium with Macrocyclic Amines," Presented by G. H. Robinson before the 199th ACS National Meeting (1990), Boston, MA, Abstract INORG 152.
79. R. D. Rogers, "Macrocycle Complexation Chemistry of Lanthanide Chlorides. Can You Guess Structure from Elemental Data?" Presented by R. D. Rogers before the 73rd Canadian Chemical Congress (1990), Halifax, Nova Scotia, Canada, Abstract 617.
80. A. N. Rollins and R. D. Rogers, "Macrocycle Complexation Chemistry. Direct Comparison of Lanthanide Complexation with 18-Crown-6 and Pentaethylene Glycol," Presented by A. N. Rollins before the 73rd Canadian Chemical Congress (1990), Halifax, Nova Scotia, Canada, Abstract 631.
81. R. F. Henry and R. D. Rogers, "Macrocycle Complexation Chemistry of Lanthanides with Sulfur Donors," Presented by R. F. Henry before the 73rd Canadian Chemical Congress (1990), Halifax, Nova Scotia, Canada, Abstract 630.
82. A. H. Bond and R. D. Rogers, "Structural Comparison of Hard Donor Crown Ether and Polyethylene Glycol Complexes of Pb^{2+} and Bi^{3+}," Presented by A. H. Bond before the 73rd Canadian Chemical Congress (1990), Halifax, Nova Scotia, Canada, Abstract 632.
83. M. D. Rausch, W.-M. Tsai, and M. Ogasa, "Synthetic and Structural Studies on Pentabenzylcyclopentadienyl and Titanium-Containing Heterobimetallic Compounds," Presented by M. D. Rausch before the 73rd Canadian Chemical Congress (1990), Halifax, Nova Scotia, Canada, Abstract 607.
84. K. C. Sturge, R. D. Rogers, and M. J. Zaworotko, "Sterically Crowded Iron(II) Mixed Sandwich Complexes," Presented by K. C. Sturge before the 73rd Canadian Chemical Congress (1990), Halifax, Nova Scotia, Canada, Abstract 559.
85. N. Burford, B. W. Royan, R. E. V. H. Spence, T. S. Cameron, A. Linden, and R. D. Rogers, "Novel Acceptor Features for the Heavier Elements of Group 13 Allowing a Reclassification of the Coordinative Bonding Modes of Phosphine Chalcogenides," Presented by N. Burford before the 73rd Canadian Chemical Congress (1990), Halifax, Nova Scotia, Canada, Abstract 592.
86. S. Christie, M. J. Zaworotko and R. D. Rogers, "2-Oxybenzoate Aluminum Complexes," Presented by S. Christie before the 73rd Canadian Chemical Congress (1990), Halifax, Nova Scotia, Canada, Abstract 629.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 53

IPR2020-00770
United Therapeutics EX2007
Page 3603 of 7335

87. N. Burford, R. E. V. H. Spence, T. S. Cameron, B. Borecka, R. D. Rogers, and J. F. Richardson, "The Reactions of Group 13 Acids with Diaminothiophosphoryl Chlorides," Presented by R. E. V. H. Spence before the 73rd Canadian Chemical Congress (1990), Halifax, Nova Scotia, Canada, Abstract 661.
88. J. R. Peterson, H. D. Do and R. D. Rogers, "Chemical and Biological Investigations of Anticancer Lignan Lactones," Presented by J. R. Peterson and H. D. Do before the 22nd National Medicinal Chemistry Symposium (1990), Austin, TX.
89. A. H. Bond and R. D. Rogers, "Polyethylene Glycols as Ionizable Complexing Agents of Bi^{3+}," Presented by A. H. Bond before the 201st ACS National Meeting (1991), Atlanta, GA, Abstract INOR 039.
90. L. Nunez, R. D. Rogers, G. W. Crabtree, U. Welp, A. Umezawa, K. Vandervoort, and Y. Fang, "Magnetic and Superconducting Properties of $YBa_2Cu_{3-x}Fe_xO_{7-\delta}$ Single Crystals," Presented by L. Nunez before the 201st ACS National Meeting (1991), Atlanta, GA, Abstract INOR 038.
91. A. N. Rollins and R. D. Rogers, "Electrocrystallization of Lanthanide Polyether Complexes," Presented by A. N. Rollins before the 201st ACS National Meeting (1991), Atlanta, GA, Abstract INOR 136.
92. R. D. Rogers, "Crown Ether vs. Polyethylene Glycol Complexation of $NdCl_3$. A Structural Study of Why the Chelate Effect is Greater than the Macrocyclic Effect in f-Element Extractions," Presented by R. D. Rogers before the 201st ACS National Meeting (1991), Atlanta, GA, Abstract INOR 135.
93. A. H. Bond and R. D. Rogers, "The Influence of Cd Halide Polymer Formation on Cd Polyether Structures," Presented by A. H. Bond before the American Crystallographic Association Meeting (1991), Toledo, OH, Abstract PJ06.
94. R. D. Rogers, "The Effect of Decreasing Ionic Size on the Primary Coordination Sphere of Hydrated Lanthanide Chloride Polyether Complexes," Presented by R. D. Rogers before the American Crystallographic Association Meeting (1991), Toledo, OH, Abstract C14.
95. E. P. Horwitz, M. L. Dietz, and R. Rogers, "A Combined Transuranic-Strontium-Technetium Extraction/Recovery Process," Presented by E. P. Horwitz before the 15th Actinide Separations Conference (1991), Charleston, SC, Abstract book page 27.
96. R. C. Gatrone, M. L. Dietz, A. H. Bond, R. D. Rogers, and E. P. Horwitz, "The Influence of Isomerization of Crown Ethers on the Extraction of Strontium and Potassium from Nitrate Media," Presented by R. C. Gatrone before the 7th Symposium on Separation Science and Technology for Energy Applications (1991), Knoxville, TN, Abstract book page 21.
97. R. D. Rogers, A. H. Bond, and C. B. Bauer, "Aqueous Biphase Systems for Liquid/Liquid Extraction of f-Elements Utilizing Polyethylene and Polypropylene Glycols," Presented by R. D. Rogers before the 7th Symposium on Separation Science and Technology for Energy Applications (1991), Knoxville, TN, Abstract book page 60.
98. E. P. Horwitz, M. L. Dietz, R. Chiarizia, H. Diamond, and R. Rogers, "Recent Advances in Solvent Extraction and Extraction Chromatography for Processing Radioactive Waste," Presented by E. P. Horwitz before the 7th Symposium on Separation Science and Technology for Energy Applications (1991), Knoxville, TN, Abstract book page 95.
99. C. B. Bauer and R. D. Rogers, "Liquid/Liquid Extraction of the f-Elements Utilizing Aqueous Biphase Systems," Presented by C. B. Bauer before the 203rd ACS National Meeting (1992), San Francisco, CA, Abstract I&EC 10.
100. A. H. Bond and R. D. Rogers, "Extraction of Pb^{2+} Using Aqueous Polyethylene Glycol Biphasic Systems," Presented by A. H. Bond before the 203rd ACS National Meeting (1992), San Francisco, CA, Abstract I&EC 009.
101. A. N. Rollins and R. D. Rogers, "Comparison of the Crystal Structure and Molecular Models of CMPO," Presented by A. N. Rollins before the 203rd ACS National Meeting (1992), San Francisco, CA, Abstract I&EC 008.
102. A. H. Bond and R. D. Rogers, "Polyethylene Glycol Complexation of Pb^{2+}," Presented by A. H. Bond before the 203rd ACS National Meeting (1992), San Francisco, CA, Abstract INOR 528.
103. C. B. Bauer and R. D. Rogers, "A Structural Comparison Between the Complexes of Tetraethylene Glycol with Lanthanide(III) Chlorides and Nitrates," Presented by C. B. Bauer before the 203rd ACS National Meeting (1992), San Francisco, CA, Abstract INOR 527.
104. R. D. Rogers, A. H. Bond, and C. B. Bauer, "Aqueous Biphasic Systems for Liquid/Liquid Extraction of Environmentally Toxic Heavy Metals," Presented by R. D. Rogers before the 203rd ACS National Meeting (1992), San Francisco, CA, Abstract I&EC 088. (Invited Symposium Presentation.)
105. T. M. Gilbert and R. D. Rogers, "Metathesis Chemistry of $Mo_2Cl_2(DME)_2$: Synthesis and X-ray Diffraction Studies of $Mo_2(OR_F)_6$ (Mo=Mo) Complexes," Presented by T. M. Gilbert before the 203rd ACS National Meeting (1992), San Francisco, CA, Abstract INOR 464.
106. T. M. Gilbert and R. D. Rogers, "Synthesis and Absorption Spectra of the "Dialkylidynes" $(RO)_3W/C\text{-}C/W(OR)_3$ (OR = $OCMe_3$, $OCMe_2CF_3$, $OCMe_2Et$): Excited State Transition Metal-Carbon p Conjugation," Presented by T. M. Gilbert before the 203rd ACS National Meeting (1992), San Francisco, CA, Abstract INOR 308.
107. R. D. Rogers, C. B. Bauer, and A. H. Bond, "Aqueous Biphasic Polyethylene Glycol/Salt Systems for Actinide Ion Separation and Extraction," Presented by R. D. Rogers before the 16th Annual Actinide Separations Conference (1992), Estes Park, CO, Abstract book page 32.
108. M. L. Dietz, E. P. Horwitz, and R. D. Rogers, "A Combined Transuranic-Strontium Extraction/Recovery Process," Presented by M. L. Dietz before the 16th Actinide Separations Conference (1992), Estes Park, CO, Abstract book page 33.
109. E. P. Horwitz, M. L. Dietz, and R. D. Rogers, "A Combined Transuranic-Strontium Extraction/Recovery Process," Presented by E. P. Horwitz before the 204th ACS National Meeting (1992), Washington, DC, Abstract I&EC 108.
110. A. H. Bond and R. D. Rogers, "Structural Analyses of Crown Ether and Polyethylene Glycol Complexes of Cd^{2+}, Hg^{2+}, and Pb^{2+}," Presented by A. H. Bond before the XVII International Symposium on Macrocyclic Chemistry (1992), Provo, UT, Abstract P13.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 54

IPR2020-00770
United Therapeutics EX2007
Page 3604 of 7335

111. C. B. Bauer and R. D. Rogers, "Structural Analyses of Crown Ether and Polyethylene Glycol Complexes of Lanthanide(III) Ions," Presented by C. B. Bauer before the XVII International Symposium on Macrocyclic Chemistry (1992), Provo, UT, Abstract P7.
112. M. L. Dietz, E. P. Horwitz, R. C. Gatrone, A. H. Bond, and R. D. Rogers, "The Influence of Isomerization on the Extraction of Strontium and Potassium from Nitrate Media by Dicyclohexyl-18-Crown-6," Presented by M. L. Dietz before the XVII International Symposium on Macrocyclic Chemistry (1992), Provo, UT, Abstract P30.
113. R. D. Rogers, A. H. Bond, and C. B. Bauer, "The Crown Ether Extraction of Group 1 and 2 Cations in Polyethylene Glycol-Based Aqueous Biphasic Systems at High Alkalinity," Presented by R. D. Rogers before the XVII International Symposium on Macrocyclic Chemistry (1992), Provo, UT, Abstract IS19. (Invited Symposium Presentation.)
114. J. R. Peterson, J. K. Zjawiony, and R. D. Rogers, "A New Synthesis and Optical Resolution of the Taxol Side Chain," Presented by J. R. Peterson before the 2nd National Cancer Institute Workshop on Taxol and Taxus (1992), Alexandria, VA, Poster E-6.
115. A. N. Rollins and R. D. Rogers, "Conformation Analysis of 18-Crown-6 in Complexes with Hydrated Lanthanide Chlorides," Presented by A. N. Rollins before the 205th ACS National Meeting (1993), Denver, CO, Abstract INOR 289.
116. A. H. Bond and R. D. Rogers, "Structural Studies of Aza-18-Crown-6 Complexes of $HgCl_2$, $HgBr_2$, and HgI_2," Presented by A. H. Bond before the 205th ACS National Meeting (1993), Denver, CO, Abstract INOR 286.
117. C. B. Bauer and R. D. Rogers, "Inner Sphere Versus Outer Sphere Coordination of Hexaethylene Glycol in Complexes of Lanthanide(III) Chlorides and Nitrates," Presented by C. B. Bauer before the 205th ACS National Meeting (1993), Denver, CO, Abstract INOR 069.
118. M. L. Jezl, T. S. Forbes, T. Amaro, and R. D. Rogers, "Polyethylene Glycol Complexes of $Sr(NO_3)_2$," Presented by M. L. Jezl before the 205th ACS National Meeting (1993), Denver, CO, Abstract INOR 401.
119. T. M. Gilbert, F. J. Hadley, and R. D. Rogers, "Synthesis, Structure and Nonlinear Optical Properties of a,w-Diphenyl Polyenes Coordinated to Transition Metal Centers," Presented by T. M. Gilbert before the 205th ACS National Meeting (1993), Denver, CO, Abstract INOR 588.
120. A. H. Bond and R. D. Rogers, "Partitioning of Cd^{2+} in Polyethylene Glycol Based Aqueous Biphasic Systems," Presented by A. H. Bond before the 205th ACS National Meeting (1993), Denver, CO, Abstract I&EC 025.
121. C. B. Bauer and R. D. Rogers, "The Extraction of Group 1 and 2 Cations in Aqueous Biphasic Systems," Presented by C. B. Bauer before the 205th ACS National Meeting (1993), Denver, CO, Abstract I&EC 026.
122. R. D. Rogers, A. H. Bond, C. B. Bauer, M. L. Jezl, and A. N. Rollins, "Is Metal Cation Recognition Possible with Acyclic Crown Ether Analogs? An Analysis of the Metal Directed Coordination Modes of Polyethylene Glycols," Presented by R. D. Rogers before the 205th ACS National Meeting (1993), Denver, CO, Abstract I&EC 108.
123. A. H. Bond and R. D. Rogers, "Crystallographic Challenges in the Structural Characterization of Aza-18-Crown-6 Versus 18-Crown-6 Metal Complexes," Presented by A. H. Bond before the American Crystallographic Association Meeting (1993), Albuquerque, NM, Abstract PE01.
124. C. B. Bauer and R. D. Rogers, "Supramolecular Structural Variations in Pentaethylene Glycol Complexes of Lanthanide(III) Nitrates Resulting from Variable Hydrogen Bonding Environments," Presented by C. B. Bauer before the American Crystallographic Association Meeting (1993), Albuquerque, NM, Abstract PD07.
125. R. D. Rogers, "Polyethylene Glycol Complexes of f-Element Salts: Structural Clues to Complexation Behavior," Presented by R. D. Rogers before the American Crystallographic Association Meeting (1993), Albuquerque, NM, Abstract Z003. (Invited Symposium Presentation.)
126. E. P. Horwitz, M. L. Dietz, H. Diamond, R. D. Rogers, and R. A. Leonard, "Advanced Chemical Separations in Support of the Clean Option Strategy," Presented by E. P. Horwitz before the 17th Actinide Separations Conference (1993), Pasco, WA, Abstract book page 52.
127. A. H. Bond and R. D. Rogers, "Crystallographic Investigation of 15-Crown-5 Complexes of CdX_2 (X = Cl, Br, I, NO_3)," Presented by A. H. Bond before the XVIth Congress and General Assembly of the International Union of Crystallography/IUCr XVI Meeting (1993), Beijing, China, Abstract PS-07.01.17.
128. R. D. Rogers, "How Metal Ion Character Controls the Coordination Mode of Polyethylene Glycol," Presented by R. D. Rogers before the XVIth Congress and General Assembly of the International Union of Crystallography/IUCr XVI Meeting (1993), Beijing, China, Abstract OPS-07.01.9.
129. D. M. Roden, A. H. Bond, and R. D. Rogers, "Structural Studies of Substituted Crown Ether Complexes of Bismuth(III) Halides," Presented by D. M. Roden before the 206th ACS National Meeting (1993), Chicago, IL, Abstract INOR 187.
130. Y. Song and R. D. Rogers, "Polyethylene Glycol-Based Aqueous Biphasic Systems for the Extraction of Transition Metal Ions," Presented by Y. Song before the 206th ACS National Meeting (1993), Chicago, IL, Abstract INOR 133.
131. C. B. Bauer and R. D. Rogers, "Anion Directed Coordination in Lanthanide(III) Complexes of Polyethylene Glycols," Presented by C. B. Bauer before the 206th ACS National Meeting (1993), Chicago, IL, Abstract INOR 110.
132. T. M. Gilbert and R. D. Rogers, "Spectroscopic and Structural Investigation of the Nature of the Frontier Orbitals in Hexa(alkoxy)- and Hexa(fluoroalkoxy)ditungsten Compounds $W_2[OCMe_x(CF_3)_{3-x}]$ (x = 1-3)," Presented by T. M. Gilbert before the 206th ACS National Meeting (1993), Chicago, IL, Abstract INOR 355.
133. T. M. Gilbert and R. D. Rogers, "Nonlinear Optical Properties of Substituted Stilbenes Coordinated to (Tricarbonyl)chromium Fragments," Presented by T. M. Gilbert before the 206th ACS National Meeting (1993), Chicago, IL, Abstract INOR 356.

134. E. P. Horwitz, M. L. Dietz, H. Diamond, R. D. Rogers, and R. A. Leonard, "Combined TRU-Sr Extraction/Recovery Process," Presented by M. L. Dietz. Proceedings International Solvent Extraction Conference/ISEC '93, York, England, Vol. 3, pp. 1805-1812, D. H. Logsdail and M. J. Slater (eds.), Elsevier, London (1993).
135. R. D. Rogers, A. H. Bond, and C. B. Bauer, "Polyethylene Glycol-Based Aqueous Biphasic Systems for Liquid/Liquid Extraction of Environmentally Toxic Heavy Metals," Presented by R. D. Rogers. Proceedings International Solvent Extraction Conference/ISEC '93, York, England, Vol. 3, pp. 1641-1648, D. H. Logsdail and M. J. Slater (eds.), Elsevier, London (1993).
136. E. P. Horwitz, M. L. Dietz, H. Diamond, R. D. Rogers, and R. A. Leonard, "Advanced Chemical Separations in Support of the Clean Option Strategy," Presented by E. P. Horwitz before the Global '93 Conference on Future Nuclear Systems: Emerging Fuel Cycles and Waste Disposal Options (1993), Seattle, WA.
137. R. D. Rogers, C. B. Bauer, and A. H. Bond, "Crown Ethers as Actinide Extractants in Acidic Aqueous Biphasic Systems: Partitioning Behavior in Solution and Crystallographic Analyses of the Solid State," Presented by R. D. Rogers before the Actinides-93 International Conference (1993), Santa Fe, NM, Abstract 77. (Invited Symposium Presentation.)
138. R. D. Rogers, A. H. Bond, and C. B. Bauer, "Novel Polyethylene Glycol-Based Aqueous Biphasic Systems for the Extraction of Strontium and Cesium," Presented by R. D. Rogers before the 8th Symposium on Separation Science and Technology for Energy Applications (1993), Gatlinburg, TN, Abstract book page 18.
139. L. Nunez, G. F. Vandegrift, and R. D. Rogers, "In Situ Magnetically Assisted Chemical Separation," Presented by L. Nunez before the 8th Symposium on Separation Science and Technology for Energy Applications (1993), Gatlinburg, TN, Abstract book page 40.
140. D. J. Chaiko and R. D. Rogers, "Aqueous Biphasic Systems for Radioactive Waste Pretreatment," Presented by D. J. Chaiko before the Efficient Separations and Processing Integrated Program (ESPIP) Technical Information Exchange Meeting (1994), Dallas, TX, Abstract book page 17.
141. E. P. Horwitz, M. L. Dietz, H. Diamond, R. D. Rogers, and R. A. Leonard, "Advanced Chemical Separations in Support of the Clean Option," Presented by P. Horwitz before the Efficient Separations and Processing Integrated Program (ESPIP) Technical Information Exchange Meeting (1994), Dallas, TX, Abstract book page 39.
142. F. E. Putnam, A. H. Bond, and R. D. Rogers, "Triethylene Glycol Dimethyl Ether Complexes of CdX_2 (X = C1, Br, I)," Presented by F. E. Putnam before the 207th ACS National Meeting (1994), San Diego, CA, Abstract INOR 347.
143. D. M. Roden, A. H. Bond, and R. D. Rogers, "Structural Studies of Tetra-, Penta- and Hexaethylene Glycol Complexes of Lead Nitrate," Presented by D. M. Roden before the 207th ACS National Meeting (1994), San Diego, CA, Abstract INOR 346.
144. C. B. Bauer and R. D. Rogers, "Structural Analyses of Group 2 Metal/Polyethylene Glycol Complexes," Presented by C. B. Bauer before the 207th ACS National Meeting (1994), San Diego, CA, Abstract INOR 472.
145. A. H. Bond and R. D. Rogers, "Crystallographic Analysis of the Stereochemically Active Lone Pair in Bismuth(III) Halide-Polyethylene Glycol Complexes," Presented by A. H. Bond before the 207th ACS National Meeting (1994), San Diego, CA, Abstract INOR 471.
146. D. M. Roden, Y. Song, M. L. Jezl, C. B. Bauer, A. H. Bond, and R. D. Rogers, "Pertechnetate Partitioning in Polyethylene Glycol-Based Aqueous Biphasic Systems: Applications from Nuclear Medicine to Nuclear Waste," Presented by D. M. Roden before the 207th ACS National Meeting (1994), San Diego, CA, Abstract I&EC 052.
147. Y. Song and R. D. Rogers, "The Investigation of Polymer-Salt Based Aqueous Biphasic Systems for the Separation of Metal Ions," Presented by Y. Song before the 207th ACS National Meeting (1994), San Diego, CA, Abstract I&EC 054.
148. A. H. Bond, D. M. Roden, F. E. Putnam, and R. D. Rogers, "Uptake of Metal Ions by DiphonixJ Resin From NaCl and $CaC1_2$ Solutions," Presented by A. H. Bond before the 207th ACS National Meeting (1994), San Diego, CA, Abstract I&EC 037.
149. A. H. Bond and R. D. Rogers, "The Partitioning of Heavy Metal Halides in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by A. H. Bond before the 207th ACS National Meeting (1994), San Diego, CA, Abstract I&EC 019.
150. C. B. Bauer and R. D. Rogers, "The Design of Metal Ion Specific Extractants for Use in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by C. B. Bauer before the 207th ACS National Meeting (1994), San Diego, CA, Abstract I&EC 064.
151. R. D. Rogers, S. D. Rein, C. B. Bauer, J. Zhang, and A. H. Bond, "The Partitioning Behavior of TcO_4^- and I^- in Polyethylene Glycol-Based Aqueous Biphasic Systems Prepared from Simulated Liquid Radioactive Hanford Tank Wastes," Presented by R. D. Rogers before the 207th ACS National Meeting (1994), San Diego, CA, Abstract I&EC 057.
152. R. D. Rogers, A. H. Bond, C. B. Bauer, and Y. Song, "Metal Ion Separations in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by R. D. Rogers before the 207th ACS National Meeting (1994), San Diego, CA, Abstract I&EC 003. (Invited Symposium Presentation.)
153. C. B. Bauer and R. D. Rogers, "Pseudo-Cyclic Behavior of Acyclic Polyether Ligands in Complexes with Lanthanide(III) Ions," Presented by C. B. Bauer before the XIX International Symposium on Macrocyclic Chemistry (1994), Lawrence, KS, Abstract A3.
154. A. H. Bond, D. M. Roden, and R. D. Rogers, "Mono- and Dicyclohexyl Substituted Crown Ether Complexes of Bismuth(III)," Presented by A. H. Bond before the XIX International Symposium on Macrocyclic Chemistry (1994), Lawrence, KS, Abstract A5.
155. R. D. Rogers and A. H. Bond, "Structural Analysis of cis-syn-cis-4,5'-Ditertbutyl-dicyclohexyl-18-crown-6 and cis-anti-cis-4,5'-Ditertbutyl-dicyclohexyl-18-crown-6•$2CH_3CN$: Comparison with Unsubstituted Dicyclohexyl-18-crown-6," Presented by R. D. Rogers before the XIX International Symposium on Macrocyclic Chemistry (1994), Lawrence, KS, Abstract ST7.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 56

IPR2020-00770
United Therapeutics EX2007
Page 3606 of 7335

156. A. H. Bond, F. E. Putnam, and R. D. Rogers, "Structural Variations in Complexes of Cadmium Halides with Triethylene Glycol and its Dimethyl Ether Derivative," Presented by A. H. Bond before the American Crystallographic Meeting (1994), Atlanta, GA, Abstract PIC16.
157. C. B. Bauer and R. D. Rogers, "Structural Comparison of Lanthanide(III) Nitrate Complexes with Tetraethylene Glycol and Tetraethylene Glycol Dimethyl Ether Ligands," Presented by C. B. Bauer before the American Crystallographic Meeting (1994), Atlanta, GA, Abstract PIC17.
158. L. R. Morss and R. D. Rogers, "Synthesis and Crystal Structure of an f-Element Complex with Strong M-N Bonds," Presented by L. R. Morss before the 208th ACS National Meeting (1994), Washington, DC, Abstract I&EC 021.
159. A. H. Bond, R. D. Rogers, and F. E. Putnam, "Structural Characterization of Five Donor Cyclic and Acyclic Polyether Complexes of Cadmium Halides," Presented by A. H. Bond before the 208th ACS National Meeting (1994), Washington, DC, Abstract INOR 151.
160. C. B. Bauer and R. D. Rogers, "Structural Investigation of Lanthanide(III) Nitrates Complexed With Triethylene Glycol Ligands," Presented by C. B. Bauer before the 208th ACS National Meeting (1994), Washington, DC, Abstract INOR 150.
161. A. H. Bond and R. D. Rogers, "Bromide and Iodide Partitioning in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by A. H. Bond before the 208th ACS National Meeting (1994), Washington, DC, Abstract I&EC 016.
162. C. B. Bauer and R. D. Rogers, "Separation of Group 1 and 2 Cations in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by C. B. Bauer before the 208th ACS National Meeting (1994), Washington, DC, Abstract I&EC 015.
163. R. D. Rogers, A. H. Bond, C. B. Bauer, Y. Song, J. Zhang, and R. R. Chomko, "Polyethylene Glycol-Based Aqueous Biphasic Systems: Inexpensive, Nontoxic Alternatives for Hanford Tank Remediation," Presented by R. D. Rogers before the 208th ACS National Meeting (1994), Washington, DC, Abstract I&EC 017.
164. R. D. Rogers, "The Division of Industrial and Engineering Chemistry's Separation Science and Technology Subdivision: The Place for Separations Scientists," Presented by R. D. Rogers before the 208th ACS National Meeting (1994), Washington, DC, Abstract I&EC 010.
165. J. Zhang and R. D. Rogers, "Pertechnetate/Molybdate Separation Using Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by J. Zhang before the 209th ACS National Meeting (1995), Anaheim, CA, Abstract I&EC 023.
166. C. B. Bauer and R. D. Rogers, "Cation and Anion Influence on the Partitioning of Group 1 and 2 Metals in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by C. B. Bauer before the 209th ACS National Meeting (1995), Anaheim, CA, Abstract I&EC 022.
167. A. H. Bond and R. D. Rogers, "Polyethylene Glycol-Based Aqueous Biphasic Partitioning Behavior of Monovalent Anions," Presented by A. H. Bond before the 209th ACS National Meeting (1995), Anaheim, CA, Abstract I&EC 021.
168. R. D. Rogers, A. H. Bond, and C. B. Bauer, "Extraction and Recovery of Dyes and Metal/Dye Complexes with Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by R. D. Rogers before the 209th ACS National Meeting (1995), Anaheim, CA, Abstract I&EC 020.
169. R. D. Rogers, "The Division of Industrial and Engineering Chemistry's Separation Science and Technology Subdivision: The Place for Separations Scientists," Presented by R. D. Rogers before the 209th ACS National Meeting (1995), Anaheim, CA, Abstract I&EC 019.
170. C. B. Bauer and R. D. Rogers, "Water Soluble Calixarenes as Possible Metal Ion Extractants in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by C. B. Bauer before the 6th Conference on Separation of Ionic Solutes/SIS'95 (1995), Piestany Spa, Slovakia, Abstract book page 41.
171. R. D. Rogers, "Metal Ion Separations in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by R. D. Rogers before the 6th Conference on Separation of Ionic Solutes/SIS'95 (1995), Piestany Spa, Slovakia, Abstract book page 24. (Invited Symposium Presentation.)
172. J. Zhang and R. D. Rogers, "Effects of Increasing Polymer Hydrophobicity on Distribution Ratios of TcO_4^- in Polyethylene/Polypropylene Glycol-Based Aqueous Biphasic Systems," Presented by J. Zhang before the 9th International Conference on Partitioning in Aqueous Two-Phase Systems: Advances in the Uses of Polymers in Cell Biology, Biotechnology and Environmental Sciences (1995), Zaragoza, Spain, Abstract book.
173. C. B. Bauer and R. D. Rogers, " Partitioning Behavior of Group 1 and 2 Cations in Aqueous Biphasic Systems: The Development of Predictive Models Based on Thermodynamic and System Composition Data," Presented by C. B. Bauer before the 9th International Conference on Partitioning in Aqueous Two-Phase Systems: Advances in the Uses of Polymers in Cell Biology, Biotechnology and Environmental Sciences (1995), Zaragoza, Spain, Abstract book.
174. R. D. Rogers, A. H. Bond, C. B. Bauer, and J. Zhang, "Metal Ion Separations in Polyethylene Glycol-Based Aqueous Biphasic Systems: Correlation of Partitioning Behavior with Available Thermodynamic Hydration Data," Presented by R. D. Rogers before the 9th International Conference on Partitioning in Aqueous Two-Phase Systems: Advances in the Uses of Polymers in Cell Biology, Biotechnology and Environmental Sciences (1995), Zaragoza, Spain, Abstract book. (Invited Symposium Presentation.)
175. R. D. Rogers, A. H. Bond, C. B. Bauer, J. Zhang, and S. T. Griffin, "Metal Ion Separations in Polyethylene Glycol-Based Aqueous Biphasic Systems: The Outlook for Commercial Applications," Presented by R. D. Rogers before the 9th International Conference on Partitioning in Aqueous Two-Phase Systems: Advances in the Uses of Polymers in Cell Biology, Biotechnology and Environmental Sciences (1995), Zaragoza, Spain, Abstract book. (Invited Symposium Presentation.)

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 57

IPR2020-00770
United Therapeutics EX2007
Page 3607 of 7335

176. T. M. Gilbert, A. H. Bond, C. B. Bauer, and R. D. Rogers, "Structural Aspects of Triply Bonded Homoleptic Hexa(tertiaryalkoxide)dimolybdenum and ditungsten Compounds," Presented by T. M. Gilbert before the 210th ACS National Meeting (1995), Chicago, IL, Abstract INOR 200.
177. T. M. Gilbert, M. D. Simmons, F. J. Hadley, C. B. Bauer, and R. D. Rogers, "Syntheses and Structures of Substituted a,w-Diphenylhexatrienes Coordinated to (Tricarbonyl)chromium Fragments," Presented by T. M. Gilbert before the 210th ACS National Meeting (1995), Chicago, IL, Abstract INOR 201.
178. R. D. Rogers, "The Division of Industrial and Engineering Chemistry's Separation Science and Technology Subdivision: The Place for Separations Scientists," Presented by R. D. Rogers before the 210th ACS National Meeting (1995), Chicago, IL, Abstract I&EC 025.
179. J. Zhang and R. D. Rogers, "Structural Investigations of Lanthanum(III) Isothiocyanate Complexes with Polyethylene Glycol," Presented by J. Zhang before the 210th ACS National Meeting (1995), Chicago, IL, Abstract INOR 505.
180. J. Zhang and R. D. Rogers, "Structural Investigations of Lanthanide(III) Hydroxyethane-1,1-diphosphonic Acid (HEDPA) Complexes," Presented by J. Zhang before the 210th ACS National Meeting (1995), Chicago, IL, Abstract I&EC 026.
181. J. Zhang and R. D. Rogers, "Predicting Distribution Ratios of Pertechnetate in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by J. Zhang before the 210th ACS National Meeting (1995), Chicago, IL, Abstract I&EC 027.
182. E. Wodziak, J. Zhang, and R. D. Rogers, "Investigation of the Salting-Out of Polyethylene Glycol-2000 in Aqueous Biphasic Systems," Presented by E. Wodziak before the 210th ACS National Meeting (1995), Chicago, IL, Abstract I&EC 028.
183. H. McIlwraith, J. Zhang, and R. D. Rogers, "Structural Studies of Lanthanide(III) 1,2-Ethylene-diphosphonic Acid Complexes," Presented by H. McIlwraith before the 210th ACS National Meeting (1995), Chicago, IL, Abstract I&EC 029.
184. J. Zhang, S. T. Griffin, and R. D. Rogers, "The Effects of Halide Anions on the Partitioning Behavior of Pertechnetate in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by J. Zhang before the 9th Symposium on Separation Science and Technology for Energy Applications (1995), Gatlinburg, TN, Abstract book page 61.
185. R. D. Rogers, A. H. Bond, and E. P. Horwitz, "New Technetium-99m Generator Technologies Utilizing Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by R. D. Rogers before the 9th Symposium on Separation Science and Technology for Energy Applications (1995), Gatlinburg, TN, Abstract book page 17.
186. R. D. Rogers, A. H. Bond, J. Zhang, and C. B. Bauer, "Polyethylene Glycol-Based Aqueous Biphasic Systems: A Potential ^{99m}Tc Generator Technology," Presented by R. D. Rogers before the International Chemical Congress of Pacific Basin Societies/Pacifichem'95 (1995) Honolulu, HA, Abstract INOR 1137.
187. M. T. Tran, R. P. Planalp, C. B. Bauer, and R. D. Rogers, "Titanium and Vanadium Complexes of Tripropoxideamine Derivative Ligand, $N(CH_2C(CH_3)_2O\text{-})_3$," Presented by R. P. Planalp before the 211th ACS National Meeting (1996), New Orleans, LA, Abstract INOR 438.
188. N. M. Tsoupas, N. Ye, R. P. Planalp, C. B. Bauer, R. D. Rogers, and M. W. Brechbiel, "Metal Complexes of Novel Hexadentate Ligands Based on the cis-1,3,5-Triaminocyclohexane Framework: Synthesis, Structure and Stability under Biological Conditions", Presented by R. P. Planalp before the 211th ACS National Meeting (1996), New Orleans, LA, Abstract INOR 559.
189. M. W. Brechbiel, N. M. Tsoupas, N. Ye, R. P. Planalp, C. B. Bauer, and R. D. Rogers, "Facile Synthesis of cis,cis-1,3,5-Triaminocyclohexane and Its use in Synthesis of Novel Hexadentate Chelating Agents as Radiopharmaceuticals," Presented by M. W. Brechbiel before the 211th ACS National Meeting (1996), New Orleans, LA, Abstract ORGN 236.
190. J. Zhang, S. T. Griffin, and R. D. Rogers, "Partitioning Behavior of Iodide in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by J. Zhang before the 211th ACS National Meeting (1996), New Orleans, LA, Abstract I&EC 040.
191. S. T. Griffin, J. Zhang, and R. D. Rogers, "Partitioning Behavior of Iodide with Aqueous Biphasic Extraction Chromatographic (ABEC) Resins," Presented by S. T. Griffin before the 211th ACS National Meeting (1996), New Orleans, LA, Abstract I&EC 041.
192. E. Wodziak, J. Zhang, and R. D. Rogers, "Modified Polyethylene Glycols (PEGs) as Potential Extractants for use in PEG-Based Aqueous Biphasic Systems," Presented by E. Wodziak before the 211th ACS National Meeting (1996), New Orleans, LA, Abstract I&EC 042.
193. R. D. Rogers, S. T. Griffin, J. Zhang, E. P. Horwitz, M. J. Gula, and F. Chang, "Polyethylene Glycol-Based ABEC Resins for the Selective Removal of Technetium from Hanford Tank Wastes," Presented by R. D. Rogers before the 211th ACS National Meeting (1996), New Orleans, LA, Abstract I&EC 184.
194. R. D. Rogers, A. H. Bond, C. B. Bauer, S. T. Griffin, and J. Zhang "Polyethylene Glycol-Based Aqueous Biphasic Systems for Extraction and Recovery of Dyes and Metal/Dye Complexes," Presented by R. D. Rogers before the International Solvent Extraction Conference/ISEC'96 (1996), Melbourne, Australia. *Value Adding through Solvent Extraction Proceedings of ISEC'96*; D. C. Shallcross, R. Paiman, and L. M. Prvcic, Eds.; The University of Melbourne: Parkville, Victoria, Australia, 1996; Vol. 2; pp 1537-1542.
195. D. R. Whitcomb, W. C. Frank, R. D. Rogers, B. P. Tolochkoc, S. V. Chernovc, S. G. Nikitenkod, "Silver Coordination Chemistry in Photothermographic Imaging Systems," Presented by D. R. Whitcomb before the Imaging Science and Technology Conference (1996), Minneapolis, MN, Abstract.
196. J. Zhang and R. D. Rogers, "Structural Investigation of Polyethylene Glycol/Neodymium(III) Isothiocyanate Complexes," Presented by J. Zhang before the Rare Earth Research Conference (1996), Duluth, MN, Abstract PC-7.
197. R. D. Rogers, J. Zhang, and C. B. Bauer, "The Affects of Choice of Anion ($X = Cl^-, Br^-, SCN^-, NO_3^-$) and Polyethylene Glycol Chain Length on the Local and Supramolecular Structures of LnX_3/PEG Complexes," Presented by R. D. Rogers before the Rare Earth Research Conference (1996), Duluth, MN, Abstract IC-5. (Invited Symposium Presentation.)

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 58

IPR2020-00770
United Therapeutics EX2007
Page 3608 of 7335

198. R. D. Rogers, "ABEC™ Resins for Removal of TcO_4^- from Hanford Tank Wastes," Presented by R. D. Rogers before the 20th Actinide Separation Conference (1996), Itasca, IL, no abstract.
199. R. D. Rogers, A. H. Bond, and C. B. Bauer, "New Separations Technologies for TcO_4^-: Applications from Nuclear Medicine to Nuclear Waste," Presented by R. D. Rogers, before the 212th ACS National Meeting (1996), Orlando, FL, Abstract I&EC 008.
200. R. D. Rogers, "Chemical Crystallography in Crystal Engineering," Presented by R. D. Rogers at the NATO ASI *Crystal Engineering: The Design and Application of Functional Solids* (1996), Digby, Nova Scotia, Canada. (Invited Lecture.)
201. L. M. Rogers and R. D. Rogers, "How the New CCD Area Detector for Small Molecule Crystallography will Advance Crystal Engineering," Presented by L. M. Rogers at the NATO ASI *Crystal Engineering: The Design and Application of Functional Solids* (1996), Digby, Nova Scotia, Canada.
202. J. He, L. C. Francesconi, S. Saluja, and R. Rogers, "Synthesis and Characterization of the Indium(III) Complex of a Novel Aminothiol (N_3S_2) Ligand, " Presented by L. C. Francesconi, before the 213th ACS National Meeting (1997), San Francisco, CA, Abstract INOR 027.
203. J. Bartis, L. C. Francesconi, M. Dankova, R. Rogers, and V. G. Young, Jr., "Stoichiometric and Structural Studies of Lanthanide Complexes of $[a\text{-}2\text{-}P_2W_{17}O_{61}]^{10-}$ Complexes," Presented by J. Bartis, before the 213th ACS National Meeting (1997), San Francisco, CA, Abstract INOR 839.
204. R. D. Rogers, M. L. Dietz, E. P. Horwitz, and A. H. Bond, "Ligand Design for Ion Separations: Crystal Structures of Substituted Dicyclohexyl-18-crown-6 Isomers," Presented by R. D. Rogers, before the 213th ACS National Meeting (1997), San Francisco, CA, Abstract I&EC 004. (Invited Symposium Presentation.)
205. R. P. Swatloski, S. T. Griffin, L. M. Rogers, and R. D. Rogers, "4,4'-Dipyridyl as a Synthon for the Design and Synthesis of Porous Solids," Presented by R. P. Swatloski, before the 213th ACS National Meeting (1997), San Francisco, CA, Abstract I&EC 053.
206. S. T. Griffin and R. D. Rogers, "A Direct Comparison of Metal Ion Partitioning in Liquid/Liquid PEG-Based ABS and Retention on ABEC™ Resin. How Good is the Analogy?," Presented by S. T. Griffin, before the 213th ACS National Meeting (1997), San Francisco, CA, Abstract I&EC 054.
207. J. A. Nicol, H. D. Willauer, S. T. Griffin, and R. D. Rogers, "Partitioning of Dyes and Metal/Dye Complexes in Aqueous Biphasic Systems," Presented by H. D. Willauer, before the 213th ACS National Meeting (1997), San Francisco, CA, Abstract I&EC 055.
208. R. D. Rogers, S. T. Griffin, E. P. Horwitz, A. H. Bond, M. J. Gula, and F. Chang, "ABEC™ Resins: From Aqueous Biphasic Novelties to Selective Aqueous Biphasic Extraction Chromatographic Resins for Metal Ions," Presented by R. D. Rogers, before the 213th ACS National Meeting (1997), San Francisco, CA, Abstract I&EC 104. (Invited Symposium Presentation.)
209. A. H. Bond, M. J. Gula, F. Chang, R. D. Rogers, and E. P. Horwitz, "Eichrom's ABEC Resins: Alkaline Radioactive Waste Treatment, Radiopharmaceutical, and Potential Hydrometallurgical Applications," Presented by A. H. Bond, before the 213th ACS National Meeting (1997), San Francisco, CA, Abstract I&EC 105.
210. R. D. Rogers and L. M. Rogers, "The SMART System at The University of Alabama: Experiences, Reflections, and Data," Presented by R. D. Rogers, before the Siemens Area Detector Users Group Meeting 'SADUG97' (1997), Athens, GA, Abstract book. (Invited Presentation.)
211. R. D. Rogers, S. T. Griffin, H. D. Willauer, and J. A. Nicol, "Clean Solvent Extraction Using Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by R. D. Rogers before the 1997 Green Chemistry and Engineering Conference, 'Implementing Vision 2020 for the Environment' (1997), Washington, DC, Abstract book p. 23. (Invited Presentation.)
212. R. D. Rogers, S. T. Griffin, H. Willauer, J. Zhang, and J. G. Huddleston, "Utilization of Aqueous Polymers for 'Clean' Separations Technologies," Presented by R. D. Rogers before the Gordon Conference on Reactive Polymers, Ion Exchange, and Adsorption (1997), New England College, Henniker, NH.
213. J. G. Huddleston, H. Willauer, and R. D. Rogers, "Separations and Recovery of Food Coloring Dyes Using ABEC™ Resins," Presented by J. G. Huddleston before the 10th International Conference on Partitioning in Aqueous Two-Phase Systems (1997), Reading, United Kingdom, Abstract book.
214. S. T. Griffin and R. D. Rogers, "Partitioning of Mercury and Thallium in Aqueous Biphasic Systems and on ABEC™ Resins," Presented by S. T. Griffin before the 10th International Conference on Partitioning in Aqueous Two-Phase Systems (1997), Reading, United Kingdom, Abstract book.
215. H. D. Willauer, S. T. Griffin, and R. D. Rogers, "Partitioning of Small Organic Molecules in Aqueous Biphasic Systems," Presented by H. D. Willauer before the 10th International Conference on Partitioning in Aqueous Two-Phase Systems (1997), Reading, United Kingdom, Abstract book.
216. R. D. Rogers, "Potential Applications of Aqueous Biphasic Systems for the Reduction of Industrial Pollution," Presented by R. D. Rogers before the 10th International Conference on Partitioning in Aqueous Two-Phase Systems (1997), Reading, United Kingdom, Abstract book. (Invited Presentation.)
217. D. L. Clark, S. D. Conradson, D. W. Keogh, M. P. Neu, P. D. Palmer, R. D. Rogers, W. Runde, B. L. Scott, and C. D. Tait "Coordination Chemistry of Actinide Ions (U, Np, Pu) Under Highly Alkaline Conditions," Presented by D. L. Clark before the 1997 Plutonium Futures - The Science Conference (1997), Santa Fe, NM.
218. D. L. Clark, S. D. Conradson, D. W. Keogh, M. P. Neu, P. D. Palmer, R. D. Rogers, W. Runde, B. L. Scott, and C. D. Tait "Coordination Chemistry of Actinide Ions Under Highly Alkaline Conditions," Presented by D. L. Clark before the 214th ACS National Meeting (1997), Las Vegas, NV, Abstract GEOC 064.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 59

IPR2020-00770
United Therapeutics EX2007
Page 3609 of 7335

219. E. J. Brandon, J. S. Miller, R. D. Rogers, and B. M. Burkhart "A New Bulk Magnet Based on the Semiquinone Anion: Structure and Ferrimagnetic Behavior of [MnTPP][Chloroanil]•PhMe," Presented by E. J. Brandon before the 214th ACS National Meeting (1997), Las Vegas, NV, Abstract INOR 276.
220. R. A. Bartsch, G. G. Talinova, H.-S. Hwang, V. S. Talanov, R. D. Rogers, and D. W. Purkiss "New Chromogenic Lariat Ethers for Selective Alkali Metal Cation Extraction," Presented by G. G. Talanova before the 214th ACS National Meeting (1997), Las Vegas, NV, Abstract I&EC 035.
221. J. Zhang, J. G. Huddleston, and R. D. Rogers "Simple Methods for the Prediction of Pertechnetate Distribution in Aqueous Biphasic Systems Based on Polyethylene Glycol," Presented by J. G. Huddleston before the 214th ACS National Meeting (1997), Las Vegas, NV, Abstract I&EC 009.
222. S. T. Griffin and R. D. Rogers "Partitioning of Mercury in Aqueous Biphasic Systems and Uptake on ABEC Resins," Presented by S. T. Griffin before the 214th ACS National Meeting (1997), Las Vegas, NV, Abstract I&EC 008.
223. J. G. Huddleston, H. D. Willauer, K. R. Boaz, and R. D. Rogers "Extraction of Metal Complexed Dyes Utilizing Aqueous Biphasic Systems and Aqueous Biphasic Extraction Chromatography, " Presented by J. G. Huddleston before the 214th ACS National Meeting (1997), Las Vegas, NV, Abstract I&EC 094.
224. R. D. Rogers, S. T. Griffin, J. Zhang, and J. G. Huddleston "New Technologies for Metal Ion Separations: Aqueous Biphasic Systems and Aqueous Biphasic Extraction Chromatographic Resins," Presented by R. D. Rogers before the 214th ACS National Meeting (1997), Las Vegas, NV, Abstract I&EC 023. (Invited Symposium Presentation.)
225. R. D. Rogers, S. T. Griffin, J. Zhang, E. P. Horwitz, A. H. Bond, F. Chang, and M. J. Gula "Separation of Pertechnetate and Iodide from Alkaline Supernate Waste using ABEC™ Resins," Presented by R. D. Rogers before the 214th ACS National Meeting (1997), Las Vegas, NV, Abstract I&EC 138.
226. G. Zucchi, P.-A. Pittet, J.-C. G. Bünzli, and R. D. Rogers, "Lanthanide Complexes with Functionalized Tetraaza Macrocyclic Ligands: Luminescence Studies and Structural Aspect," Presented by G. Zucchi before the International Conference on f Elements, ICFE3 (1997), Paris, France, Abstract.
227. F. Ihringer, J.-C. G. Bünzli, R. D. Rogers, P. Dumy, and C. Sager, "Solid State and Solution Structure of Dinuclear Lanthanide Complexes with Calix[8]arenes," Presented by F. Ihringer before the International Conference on f Elements, ICFE3 (1997), Paris, France, Abstract.
228. D. T. Campbell and R. D. Rogers, "Hydroxy-Crown Ether Complexes of Uranium and Thorium," Presented by D. T. Campbell before the Actinides '97 International Conference (1997), Baden-Baden, Germany, Abstract T3-P5.
229. S. T. Griffin and R. D. Rogers, "Separation of Actinides from Caustic Solution Using Aqueous Biphasic Systems," Presented by S. T. Griffin before the before the Actinides '97 International Conference (1997), Baden-Baden, Germany, Abstract TA-A4.
230. W. Runde, D. L. Clark, S. D. Conradson, D. W. Keogh, M. P. Neu, P. D. Palmer, B. L. Scott, S. D. Reilly, R. D. Rogers, and C. D. Tait " Coordination Chemistry of Actinyl Chloride Complexes in Aqueous Solutions," Presented by W. Runde before the Actinides '97 International Conference (1997), Baden-Baden, Germany, Abstract T3-P19.
231. D. L. Clark, S. D. Conradson, D. W. Keogh, M. P. Neu, P. D. Palmer, R. D. Rogers, W. Runde, B. L. Scott, and C. D. Tait "Coordination Chemistry of Actinide Ions (U, Np, Pu) Under Highly Alkaline Conditions," Presented by D. L. Clark before the Actinides '97 International Conference (1997), Baden-Baden, Germany, Abstract T3-A1.
232. R. D. Rogers, J. Zhang, and D. T. Campbell, "Structural Characterization of Crown Ether Complexes of $UO_2(NCS)_2$ and $Th(NCS)_4$," Presented by R. D. Rogers before the Actinides '97 International Conference (1997), Baden-Baden, Germany, Abstract T3-A6.
233. A. H. Bond, J. T. Harvey, M. J. Gula, F. Chang, J. M. Williamson, R. D. Rogers, and E. P. Horwitz, "Scale-up Synthesis and Performance Assessment of ABEC Resins for the Removal of Technetium and Iodine from Alkaline Radioactive Wastes," Presented by A. H. Bond before the Tenth Symposium on Separation Science and Technology for Energy Applications (1997), Gatlinburg, TN, Abstract book p. 18.
234. R. P. Swatloski, S. T. Griffin, and R. D. Rogers, "Perrhenate/Tungstate Separations in Aqueous Biphasic Systems," Presented by R. P. Swatloski before the Tenth Symposium on Separation Science and Technology for Energy Applications (1997), Gatlinburg, TN, Abstract book p. 50.
235. H. D. Willauer, S. T. Griffin, J. G. Huddleston, and R. D. Rogers, "Partitioning of Aromatic Molecules in Aqueous Biphasic Systems," Presented by H. D. Willauer before the Tenth Symposium on Separation Science and Technology for Energy Applications (1997), Gatlinburg, TN, Abstract book p. 50.
236. S. T. Griffin, A. H. Bond, and R. D. Rogers, "Separation of Heavy Main Group Metal Ions from Sulfate Media Using Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by S. T. Griffin before the Tenth Symposium on Separation Science and Technology for Energy Applications (1997), Gatlinburg, TN, Abstract book p. 80.
237. J. G. Huddleston and R. D. Rogers, "Partitioning Behavior of Porphyrins in Aqueous Biphasic Systems," Presented by J. G. Huddleston before the Tenth Symposium on Separation Science and Technology for Energy Applications (1997), Gatlinburg, TN, Abstract book p. 49.
238. R. D. Rogers and S. T. Griffin, "Separation of Actinides from Caustic Solution Using Aqueous Biphasic Systems," Presented by R. D. Rogers before the Tenth Symposium on Separation Science and Technology for Energy Applications (1997), Gatlinburg, TN, Abstract book p. 20. (Invited Symposium Presentation.)
239. L. M. Rogers, C. V. K. Sharma, and R. D. Rogers "One-Dimensional Polymers and Two-Dimensional Grids Formed by Lanthanide/Ethanediphosphonic Acid Complexation," Presented by L. M. Rogers before the Fifth Chemical Congress of North America (1997), Cancún, Mexico, Abstract 1090.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 60

IPR2020-00770
United Therapeutics EX2007
Page 3610 of 7335

240. R. P. Swatloski, C. V. K. Sharma, and R. D. Rogers "The Design of Two-Dimensional Networks in Cadmium Halide Complexes," Presented by R. P. Swatloski before the Fifth Chemical Congress of North America (1997), Cancún, Mexico, Abstract 1091.
241. C. V. K. Sharma and R. D. Rogers "Crystal Engineering of Pyrimidine Metal Complexes," Presented by C. V. K. Sharma before the Fifth Chemical Congress of North America (1997), Cancún, Mexico, Abstract 1506.
242. R. D. Rogers, C. V. K. Sharma, R. P. Swatloski, and L. M. Rogers "Coordination Chemistry to Crystal Engineering," Presented by R. D. Rogers before the Fifth Chemical Congress of North America (1997), Cancún, Mexico, Abstract 163. (Invited Symposium Presentation.)
243. G. Broker, K. Sharma, and R. D. Rogers "Crystal Engineering: Synthesis and Characterization of Porphrine Metal Complexes," Presented by G. Broker before the 215th ACS National Meeting (1998), Dallas, TX, Abstract CHED 468.
244. L. M. Rogers and R. D. Rogers "Putting Lanthanide Ions in the Crystal Engineer's Tool Box," Presented by L. M. Rogers before the 215th ACS National Meeting (1998), Dallas, TX, Abstract INOR 302.
245. R. P. Swatloski, C. V. K. Sharma, and R. D. Rogers "Toward the Design of Porous Networks: Crystal Structures of Porphyrin-Metal Halide Complexes," Presented by R. P. Swatloski before the 215th ACS National Meeting (1998), Dallas, TX, Abstract INOR 303.
246. C. V. K. Sharma and R. D. Rogers "Crystal Engineering: Coordination and Hydrogen Bonding in Cocrystals of Lanthanide Complexes," Presented by C. V. K. Sharma before the 215th ACS National Meeting (1998), Dallas, TX, Abstract INOR 304.
247. A. E. Visser, S. T. Griffin, and R. D. Rogers "Sulfonic Acid Dyes as Radionuclide Complexants in Aqueous Biphasic Systems," Presented by A. E. Visser before the 215th ACS National Meeting (1998), Dallas, TX, Abstract I&EC 037.
248. H. D. Willauer, J. G. Huddleston, S. T. Griffin, A. D. Carruth, and R. D. Rogers "The Partitioning of Small Organic Molecules in Aqueous Biphasic Systems and on ABEC Resins," Presented by H. D. Willauer before the 215th ACS National Meeting (1998), Dallas, TX, Abstract I&EC 036.
249. J. G. Huddleston, H. D. Willauer, J. F. Herrington, A. D. Carruth, S. T. Griffin, and R. D. Rogers "Extraction of Organic Molecules Utilizing Aqueous Biphasic Systems and the Physicochemical Properties of the Phases," Presented by J. G. Huddleston before the 215th ACS National Meeting (1998), Dallas, TX, Abstract I&EC 035.
250. R. D. Rogers, J. G. Huddleston, S. T. Griffin. H. D. Willauer, and A. E. Visser "Utilizing Surfactants to Control Partitioning of Solutes in Polyethylene Glycol-Based Aqueous Biphasic Systems," Presented by R. D. Rogers before the 215th ACS National Meeting (1998), Dallas, TX, Abstract I&EC 016. (Invited Symposium Presentation.)
251. R. D. Rogers and D. E. Nikles, "The University of Alabama Center for Green Manufacturing," Presented by R. D. Rogers before the 2nd Annual Green Chemistry & Engineering Conference: Global Perspectives, (1998), Washington, DC, Abstract book page 11.
252. R. D. Rogers, J. G. Huddleston, H. D. Willauer, S. T. Griffin, and A. E. Visser, "Green Separation Science & Technology: Can Environmentally Benign Polymers Replace VOCs in Industrial Scale Liquid/Liquid Separations?," Presented by R. D. Rogers before the 2nd Annual Green Chemistry & Engineering Conference: Global Perspectives, (1998), Washington, DC, Abstract book page 20.
253. R. D. Rogers, "Crystal Engineering of Ordered Porphyrin Arrays," Presented by R. D. Rogers before the Fourth Department of Energy/Basic Energy Sciences Conference on Homogeneous Catalysis and Organometallic Chemistry (1998), Baltimore, MD, Abstract book p. 95.
254. R. D. Rogers, C. V. K. Sharma, G. A. Broker, R. P. Swatloski, and L. M. Rogers, "Crystal Engineering of Porous Solids using Coordination Polymers," Presented by R. D. Rogers before the American Crystallographic Association Annual Meeting (1998), Arlington, VA, Abstract TR.00.05. (Invited Transactions Symposium Presentation.)
255. L. M. Rogers, C. V. K. Sharma, and R. D. Rogers, "Lanthanide Ions as Part of the Crystal Engineer's Tool Box," Presented by L. M. Rogers before the American Crystallographic Association Annual Meeting (1998), Arlington, VA, Abstract P348.
256. G. G. Talanova, R. A. Bartsch, N. S. A. Elkarim, R. E. Haynes, Jr., V. S. Talanov, and R. D. Rogers, "Effect of the picrate anion on the selectivity of aromatic-containing crown ethers in alkali metal cation binding," Presented by G. G. Talanova before the 216th ACS National Meeting (1998), Boston, MA, Abstract INOR 008.
257. G. Park, R. D. Rogers, M. W. Brechbiel, and R. P. Planalp, "Structural and Steric Effect Study of Metal Complexes of Novel Hexadentate Ligands Derived from *cis*-1,3,5-Triaminocyclohexane Framework," Presented by G. Park before the 216th ACS National Meeting (1998), Boston, MA, Abstract INOR 645.
258. R. P. Swatloski, C. V. K. Sharma, G. A. Broker, L. M. Rogers, and R. D. Rogers, "The Crystal Engineer's Tool Box: Coordination Polymers for Design of Porous Solids," Presented by R. P. Swatloski before the 216th ACS National Meeting (1998), Boston, MA, Abstract INOR 500.
259. S. T. Griffin and R. D. Rogers, "Aqueous Biphasic Extraction Chromatographic Resins: New Technologies for Low Specific Activity-Molybdenum-99/Technetium-99m Separations," Presented by S. T. Griffin before the 216th ACS National Meeting (1998), Boston, MA, Abstract I&EC 006.
260. R. D. Rogers, R. P. Swatloski, and S. T. Griffin, "Aqueous Biphasic Extraction Chromatographic Resins for Separation of Rhenium-188 from Tungsten-188," Presented by R. D. Rogers before the 216th ACS National Meeting (1998), Boston, MA, Abstract I&EC 012. (Invited Symposium Presentation.)
261. R. D. Rogers, J. G. Huddleston, and S. T. Griffin, "Aqueous Biphasic Extraction Chromatographic Resins as Tunable Affinity Adsorbents: Definitions and Applications in Pollution Prevention," Presented by R. D. Rogers before the 1998 Annual Meeting of the American Institute of Chemical Engineers (1998), Miami Beach, FL, Abstract. (Invited Symposium Presentation.)

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 61

IPR2020-00770
United Therapeutics EX2007
Page 3611 of 7335

262. R. D. Rogers, C. V. K. Sharma, and G. A. Broker, "Crystal Engineering of Ordered Porphyrin Arrays," Presented by R. D. Rogers before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract INOR 046. (Invited Symposium Presentation.)
263. D. W. Keogh, D. L. Clark, S. D. Conradson, R. J. Donohoe, David E. Morris, M. P. Neu, P. D. Palmer, R. D. Rogers, W. Runde, B. L. Scott, and C. D. Tait, "Structure and Reactivity of Penta- and Hexa-Valent Actinide Ions (U, Np, Pu) Under Highly Alkaline Conditions," Presented by D. W. Keogh before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract NUCL 167.
264. B. M. Rapko, B. K. McNamara, G. J. Lumetta, B. P. Hay, R. D. Rogers, and G. Broker, "Coordination Chemistry of Tetraalkyldiamides with f-Block Metal Salts," Presented by B. M. Rapko before the 217th ACS National Meeting (1999), Anaheim, CA, Abstracts INOR 368.
265. D. L. Clark, D. W. Keogh, S. D. Conradson, R. J. Donohoe, D. E. Morris, M. P. Neu, P. D Palmer, R. D. Rogers, W. Runde, B. L. Scott, and C. D. Tait, "Coordination Chemistry of Hexa- and Hepta-Valent Actinide Ions (U, Np, Pu) Under Alkaline Conditions," Presented by D. L. Clark before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract INOR 066.
266. D. L. Clark, D. W. Keogh, S. D. Conradson, L. A. Morales, M. P. Neu, P. D. Palmer, R. D. Rogers, W. Runde, B. L. Scott, and C. D. Tait, "Structural Trends in Actinyl(V, VI) Ions of U, Np, and Pu," Presented by D. L. Clark before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract NUCL 042.
267. J. M. Duffey, M. J. Gula, J. T. Harvey, E. P. Horwitz, A. H. Bond, S. T. Griffin, R. D. Rogers, and J. L. Collins, "A Flowsheet for the Separation, Concentration, and Immobilization of Pertechnetate Ion from Alkaline Wastes Using ABEC Resins," Presented by J. M. Duffey before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract I&EC 044.
268. G. A. Broker, C. V. K. Sharma, B. T. Pyevich, J. A. Swenson, G. J. Szulczewski, and R. D. Rogers, "Hydrogen-Bonded Supramolecular Assembly of Tetrapyridylporphyrins on a Gold Surface," Presented by G. A. Broker before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract INOR 542.
269. G. A. Broker, C. V. K. Sharma, and R. D. Rogers, "Inclusion Properties of Crystal Engineered Tetrapyridylporphyrin Coordination Complexes," Presented by G. A. Broker before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract INOR 543.
270. A. E. Visser, R. P. Swatloski, J. G. Huddleston, and R. D. Rogers, "Room Temperature Ionic Liquids as Alternatives to Organic Solvents in Liquid/Liquid Extraction of Metal Ions," Presented by A. E. Visser before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract I&EC 040.
271. A. E. Visser, D. H. Hartman, J. G. Huddleston, and R. D. Rogers, "Room Temperature Ionic Liquids for Liquid/Liquid Extraction of Dyes from Aqueous Media" Presented by A. E. Visser before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract I&EC 041.
272. R. P. Swatloski, A. E. Visser, J. G. Huddleston, and R. D. Rogers, "Room Temperature Ionic Liquids as Alternatives to Organic Solvents in Liquid/Liquid Extraction of Dilute Organic Contaminants," Presented by R. P. Swatloski before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract I&EC 042.
273. H. W. Willauer, J. G. Huddleston, and R. D. Rogers, "Modeling Partitioning Behavior in Aqueous Biphasic Systems," Presented by H. W. Willauer before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract I&EC 043.
274. R. D. Rogers, A. E. Visser, R. P. Swatloski, D. H. Hartman, and S. T. Griffin, "Environmentally Benign Liquid/Liquid Extraction Media for Metal Ion Separations: Aqueous Biphasic Systems and Room Temperature Ionic Liquids," Presented by R. D. Rogers before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract I&EC 109. (Invited Symposium Presentation.)
275. R. D. Rogers, S. T. Griffin, and A. E. Visser, "The Effects of Plutonium Speciation on Partitioning in Polyethylene Glycol-Based Aqueous Biphasic Systems and ABEC Resins," Presented by R. D. Rogers before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract NUCL 049. (Invited Symposium Presentation.)
276. A. E. Visser, D. H. Hartman, S. T. Griffin, and R. D. Rogers, "Calixarenes as Ligands in Environmentally-Benign Liquid/Liquid Extraction Media," Presented by R. D. Rogers before the 217th ACS National Meeting (1999), Anaheim, CA, Abstract I&EC 226. (Invited Symposium Presentation.)
277. Rogers, R. D. "Polymer-Based, Environmentally-Benign Liquid/Liquid Extraction Media for Separations," presented by R. D. Rogers before the Third DOE/BES Separations Workshop (1999), Savannah, GA, Abstract.
278. R. D. Rogers, A. E. Visser, and S. T. Griffin, "Using Environmentally Benign Liquid/Liquid Extraction Media for Metal Ion Separations: Aqueous Biphasic Systems and Room temperature Ionic Liquids," Presented by R. D. Rogers before the United Engineering Foundation, Inc. Conference *Metal Separation Technologies Beyond 2000: Integrating Novel Chemistry with Processing* (1999), Abstract.
279. A. E. Visser, R. P. Swatloski, D. H. Hartman, and R. D. Rogers, "Room Temperature Ionic Liquids as Replacements for Volatile Organic Solvents in Liquid/Liquid Separations," Presented by A. E. Visser before the United Engineering Foundation, Inc. Conference *Metal Separation Technologies Beyond 2000: Integrating Novel Chemistry with Processing* (1999), Abstract.
280. J. G. Huddleston, H. D. Willauer, S. K. Spear, K. D. Smith, and R. D. Rogers, "Polymer-Based Aqueous Biphasic Extraction Technology in the Paper Pulping Process," Presented by J. G. Huddleston before the 3rd Annual Green Chemistry and Engineering Conference: Moving Toward Industrial Ecology (1999), Washington, DC, Abstract book page 44.
281. R. D. Rogers, A. E. Visser, R. P. Swatloski, H. D. Willauer, and J. G. Huddleston, "Room Temperature Ionic Liquids As Alternatives To Organic Solvents In Liquid/Liquid Extraction," Presented by R. D. Rogers before the 3rd Annual Green Chemistry and Engineering Conference: Moving Toward Industrial Ecology (1999), Washington, DC, Abstract book page 5. (Invited Symposium Presentation.)

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 62

IPR2020-00770
United Therapeutics EX2007
Page 3612 of 7335

282. J. G. Huddleston, J. W. Baldwin, R. M. Metzger, and R. D. Rogers, "Solvatochromic Studies in Polyethylene Glycol/Salt Aqueous Biphasic Systems," Presented by J. G. Huddleston before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 1.
283. H. D. Willauer, J. G. Huddleston, and R. D. Rogers, "Modeling the Partitioning Behavior of Small Organic Molecules in Aqueous Biphasic Systems," Presented by H. D. Willauer before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 6.
284. A. D. Carruth, H. D. Willauer, S. K. Spear, J. G. Huddleston, and R. D. Rogers, "The Use of Quantum Mechanical Models (AMSOL) to Predict the Distribution of Organic Molecules in Aqueous Biphasic Systems," Presented by A. D. Carruth before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 18.
285. K. D. Smith, S. K. Spear, and R. D. Rogers, "Aqueous Biphasic Systems: Influences of Polymer Molecular Weight on System Behavior," Presented by K. D. Smith before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 35.
286. H. D. Willauer, A. P. Kassangottuwar, J. G. Huddleston, J. M. Wiest, G. C. April, and R. D. Rogers, "Aqueous Biphasic Systems for the Separation of Lignins from Cellulose in the Paper Pulping Process," Presented by H. D. Willauer before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 55.
287. G. A. Broker, S. K. Spear, J. G. Huddleston, and R. D. Rogers, "Coordination vs. Hydration of Metal Ions with PEG Polymers as a Function of Polymer Length," Presented by G. A. Broker before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 62.
288. D. Boochee, L. Dunklin, R. Lee, J. G. Huddleston, H. D. Willauer, and R. D. Rogers, "Summer Undergraduate Research Program (SURP) at The University of Alabama: Synthesis and Characterization of Room Temperature Ionic Liquids and Phase Diagrams for Polyethylene Glycol/Salt Mixtures," Presented by L. Dunklin and R. Lee before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 64.
289. Rogers, R. D.; H. D. Willauer, S. T. Griffin, J. G. Huddleston, "Aqueous Polymeric Solutions as Environmentally-Benign Solvent Extraction Media," Presented by R. D. Rogers before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 86.
290. M. J. Gula, M. Langer, R. Rogers, and A. Bond, "Separation, Concentration and Immobilization of Technetium from Alkaline Supernate Waste with Eichrom's ABEC® resin," Presented by M. Langer before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 87.
291. S. T. Griffin, S. K. Spear, and R. D. Rogers, "Partitioning of Iodide in Aqueous Biphasic Systems and Uptake on ABEC® Resins," Presented by S. T. Griffin before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 88.
292. S. K. Spear, S. T. Griffin, and R. D. Rogers, "A New Rhenium-188 Generator Technology Using Polyethylene Glycol-Based Aqueous Biphasic Extraction Chromatographic Resins," Presented by S. K. Spear before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 89.
293. A. E. Visser, S. T. Griffin, D. H. Hartman, and R. D. Rogers, "Napthol and Resorcinol-Based Azo Dyes as Metal Ion Complexants in Aqueous Biphasic Systems," Presented by A. E. Visser before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 90.
294. M. Li, Z.-Q. Zhu, J. G. Huddleston, and R. D. Rogers, "Partitioning of Erythromycin by Temperature-Induced Aqueous Two-Phase System," Presented by M. Li before the 11th International Conference on Partitioning in Aqueous Two-Phase Systems (1999), Gulf Shores, AL, Abstract 94.
295. L. M. Rogers, G. A. Broker, and R. D. Rogers, "Lanthanide Ions as Part of the Crystal Engineer's Tool Box," Presented by L. M. Rogers before the XVIIth International Union of Crystallography Congress & General Assembly (1999), Glasgow, Scotland, Abstract P11.OD.012.
296. R. D. Rogers, G. A. Broker, C. V. K. Sharma, B. T. Pyevich, J. A. Swenson, and G. J. Szulczewski, "Application of Crystal-Engineered Tetrapyridylporphyrin Complexes to Hydrogen-Bonded Supramolecular Assembly on a Gold Surface," Presented by R. D. Rogers before the XVIIth International Union of Crystallography Congress & General Assembly (1999), Glasgow, Scotland, Abstract P11.OD.005.
297. M. P. Neu, D. L. Clark, S. D. Conradson, R. J. Donohoe, J. C. Gordon, D. W. Keogh, D. E. Morris, R. D. Rogers, B. L. Scott, and C. D. Tait, "Structure and Stability of Actinides (U, Np, Pu) under Strongly Alkaline Radioactive Waste Tank Conditions," Presented by M. P. Neu before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract NUCL 088.
298. R. P. Planalp, G. Park, R. D. Rogers, and M. W. Brechbiel, "Synthesis and Characterization of Dicationic Metal Complexes of tachpyr and tach-6-mepyr Ligands Derived from the *cis*-1,3,5-Triaminocyclohexane Framework," Presented by G. Park before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract INOR 516.
299. D. R. Whitcomb and R. D. Rogers, "Taking Advantage of the Ag-O Supramolecular Synthon: Reprise of an Old Coordination Linkage," Presented by D. R. Whitcomb before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract INOR 508.
300. R. D. Rogers, G. A. Broker, C. V. K. Sharma, "Polymorphous One-Dimensional Tetrapyridylporphyrin-Coordination Polymers Structurally Mimic Aryl-Stacking Interactions," Presented by G. A. Broker before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract INOR 463.
301. S. J. Cooke, N. Jackson, and R. Rogers, "Why You Should be in the Division of Industrial & Engineering Chemistry," Presented by S. J. Cooke before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract I&EC 010.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 63

IPR2020-00770
United Therapeutics EX2007
Page 3613 of 7335

302. R. D. Rogers, A. D. Carruth H. D. Willauer, S. K. Spear, and J. G. Huddleston, "Quantum Mechanical Models (AMSOL) for the Prediction of the Distribution of Organic Molecules in Aqueous Biphasic Systems," Presented by K. D. Smith before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract I&EC 016.
303. R. D. Rogers, K. D. Smith, and S. K. Spear, "Aqueous Biphasic Systems: Effect of Temperature on Partitioning," Presented by K. D. Smith before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract I&EC 017.
304. R. D. Rogers, H. D. Willauer, and J. G. Huddleston, Effects of Temperature on the Partitioning of Solutes in PEG/Salt Aqueous Biphasic Systems," Presented by H. D. Willauer before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract I&EC 018.
305. R. D. Rogers, J. G. Huddleston, H. D. Willauer, "Aqueous Polymers for the Extraction of Lignin During Alkaline Pulping," Presented by J. G. Huddleston before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract I&EC 019.
306. R. D. Rogers, S. T. Griffin, and S. K. Spear, "Partitioning of Iodide in Aqueous Biphasic Systems and Uptake on ABEC Resins," Presented by S. T. Griffin before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract I&EC 020.
307. R. D. Rogers, S. K. Spear, K. D. Smith, and J. G. Huddleston, "Aqueous Biphasic Systems Using Polyethylene Glycol/Ammonium Carbamate," Presented by S. K. Spear before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract I&EC 021.
308. R. D. Rogers, R. P. Swatloski, and A. E. Visser, "Liquid-Liquid Extraction of Organics in Room-Temperature Ionic Liquids: Cationic Effects," Presented by R. P. Swatloski before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract I&EC 022.
309. R. D. Rogers, A. E. Visser, R. P. Swatloski, and S. T. Griffin, "Anionic Extractants for Partitioning Metal Ions to Room-Temperature Ionic Liquids," Presented by A. E. Visser before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract I&EC 023.
310. R. D. Rogers, G. A. Broker, and S. K. Spear, "Uptake of Metal Ions by Crystal-Engineered Tetrapyridylporphyrin Coordination Polymers," Presented by G. A. Broker before the 218th ACS National Meeting (1999), New Orleans, LA, Abstract I&EC 27.
311. R. D. Rogers, "Green/Sustainable Separation Science and Technology," Presented by R. D. Rogers at Industry Central, 218th ACS National Meeting (1999), New Orleans, LA (Invited Presentation, No Abstract).
312. R. D. Rogers, A. E. Visser, R. P. Swatloski, and J. G. Huddleston, "Room Temperature Ionic Liquids as Alternatives to Organic Solvents," Presented by R. D. Rogers to the Tenth Annual International Workshop on Solvent Substitution and the Elimination of Toxic Substances and Emissions (1999), Scottsdale, AZ. (Invited Presentation.)
313. K. D. Smith, S. K. Spear, and R. D. Rogers, "Aqueous Biphasic Systems: Polyethylene Glycol Compared with Polyethylene/Polypropylene Glycol Random Copolymer in Biphasic Systems," Presented by K. D. Smith before the Eleventh Symposium on Separation Science and Technology for Energy Applications (1999), Gatlinburg, TN, Abstract book p. 52.
314. S. K. Spear, K. D. Smith, J. G. Huddleston, and R. D. Rogers, "Polyethylene Glycol/Ammonium Carbamate Aqueous Biphasic Systems," Presented by S. K. Spear before the Eleventh Symposium on Separation Science and Technology for Energy Applications (1999), Gatlinburg, TN, Abstract book p. 53.
315. H. D. Willauer, J. G. Huddleston, S. Spear, and R. D. Rogers, "Modeling Partitioning Behavior of Organic Solutes in Aqueous Biphasic Systems," Presented by H. D. Willauer before the Eleventh Symposium on Separation Science and Technology for Energy Applications (1999), Gatlinburg, TN, Abstract book p. 58.
316. J. G. Huddleston, H. D. Willauer, S. K. Spear, K. D. Smith, and R. D. Rogers, "Polymer-Based Aqueous Biphasic Extraction Technology for Reaction Engineering of the Alkaline Paper Pulping Process," Presented by J. G. Huddleston before the Eleventh Symposium on Separation Science and Technology for Energy Applications (1999), Gatlinburg, TN, Abstract book p. 73.
317. A. E. Visser, R. P. Swatloski, H. D. Willauer, D. H. Hartman, J. G. Huddleston, and R. D. Rogers, "Room-Temperature Ionic Liquids as Solvents for Liquid/Liquid Extraction of Organic Molecules and Metal Ions," Presented by A. E. Visser before the Eleventh Symposium on Separation Science and Technology for Energy Applications (1999), Gatlinburg, TN, Abstract book p. 79.
318. S. T. Griffin, S. K. Spear, and R. D. Rogers, "Mercury Uptake from Solutions of Low Salt Concentration Using ABEC™ Resins," Presented by S. T. Griffin before the Eleventh Symposium on Separation Science and Technology for Energy Applications (1999), Gatlinburg, TN, Abstract book p. 82.
319. R. D. Rogers, A. E. Visser, R. P. Swatloski, H. D. Willauer, D. H. Hartman, and J. G. Huddleston, "Room-Temperature Ionic Liquids as Alternatives to Organic Solvents in Liquid/Liquid Extraction," Presented by R. D. Rogers before the Eleventh Symposium on Separation Science and Technology for Energy Applications (1999), Gatlinburg, TN, Abstract book p. 18.
320. R. D. Rogers, "Green Manufacturing: Changing the Way Students Think about Manufacturing Processes and the Environment," presented by R. D. Rogers before the 15th Annual NSF EPSCoR Conference (1999), Orange Beach, AL, No Abstract, Proceedings, page 6. (Invited Presentation.)
321. R. D. Rogers, "Ionic Liquids as Alternatives to Organic Solvents," presented by R. D. Rogers before the United Engineering Foundation, Inc. Conference *Clean Products and Processes II* (1999), Abstract. (Invited Presentation).
322. A. H. Bond, R. D. Rogers, M. J. Gula, E. P. Horwitz, J. T. Harvey, and J. L. Collins, "Flowsheet Development for the Separation and Immobilization of Pertechnetate from Alkaline Radioactive Wastes," presented by A. H. Bond before the Materials Research Society Fall Meeting (1999), Boston, MA, Abstract.
323. J. G. Huddleston, H. D. Willauer, S. K. Griffin, S. S. Spear, and R. D. Rogers, "Wholly Aqueous Solvent Extraction Systems: properties and Applications, Presented by J. G. Huddleston before the 2000 Spring AIChE National Meeting (2000), Atlanta,

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 64

IPR2020-00770
United Therapeutics EX2007
Page 3614 of 7335

GA, Paper 14b, Membrane and Extraction Science and Technologies for Environmental Applications Topical Conference Proceedings, D. Bhattacharyya and J. S. Kanel, Eds.; AIChE, New York, 2000; pp 192-196.

324. R. D. Rogers, A. E. Visser, R. P. Swatloski, H. D. Willauer, and J. G. Huddleston, Room Temperature Ionic Liquids as Alternatives to Organic Solvents in Liquid/Liquid Extraction, Presented by R. D. Rogers before the 2000 Spring AIChE National Meeting (2000), Atlanta, GA, Paper 14e, Membrane and Extraction Science and Technologies for Environmental Applications Topical Conference Proceedings, D. Bhattacharyya and J. S. Kanel, Eds.; AIChE, New York, 2000; pp 200-204.
325. R. D. Rogers, A. E. Visser, R. P. Swatloski, and D. H. Hartman "Room-Temperature Ionic Liquids as Alternatives to Volatile Organic Solvents in Liquid/Liquid Extraction," Presented by A. E. Visser before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract I&EC 003.
326. A. Waterfeld, J. S. Thrasher, J. F. Sullivan, R. D. Rogers, and J. L. Howell "Synthesis, Structure, and Chemistry of the Bistrifluoromethylated Version of Meldrum's Acid," Presented by A. Waterfeld before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract FLUO 007.
327. R. D. Rogers, A. E. Visser, J. G. Huddleston, R. P. Swatloski, G. A. Broker, and H. D. Willauer, "Green Chemistry and Engineering in Separations Science," Presented by R. D. Rogers before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract I&EC 025. (Invited Symposium Presentation.)
328. H. Luo, R. D. Rogers, and M. W. Brechbiel, "Synthesis of Difunctionalized Macrocyclic Chelates Based on Cyclam and Cyclen," Presented by H. Luo before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract INOR 175.
329. E. Blair, J. A. Nikles, D. E. Nikles, L. M. Rogers, R. D. Rogers, D. Stabler, and S. C. Street, "Molecular Structure of the Amine-Quinone Model Compound, 2,4-Bis(Dimethylamino)-1,4-Benzoquinone," Presented by E. Blair before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract POLY 192.
330. B. M. Rapko, G. J. Lumetta, B K. McNamara, B. P. Hay, R. D. Rogers, and G. Broker, "Coordination Chemistry of Tetraalkyldiamides with f-Block Metal Salts," Presented by B. M. Rapko before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract I&EC 050.
331. R. D. Rogers, A. E. Visser, W. M. Reichert, and R. P. Swatloski, "Investigation of Room-Temperature Ionic Liquids via X-Ray Crystallographic Characterization of Low-Melting Analogs," Presented by R. P. Swatloski before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract I&EC 084.
332. W. M. Reichert, A. E. Visser, R. P. Swatloski, and R. D. Rogers, "Synthesis and Characterization of Novel Room-Temperature Ionic Liquids," Presented by W. M. Reichert before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract I&EC 085.
333. R. D. Rogers, A. E. Visser, R. P. Swatloski, and S. T. Griffin, "Crown Ethers as Extractants for Group 1 and 2 Metal Ions in Room-Temperature Ionic Liquids," Presented by A. E. Visser before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract I&EC 086.
334. R. D. Rogers, "Development of ABEC resins: A Study of Academic/National Laboratory/Industry Cooperation," Presented by R. D. Rogers before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract I&EC 164. (Invited Symposium Presentation.)
335. R. D. Rogers, and G. A. Broker, "Toward Understanding Weak Intermolecular Forces: Crystal Engineering of Porous Solids," Presented by R. D. Rogers before the 219th ACS National Meeting (2000), San Francisco, CA, Abstract I&EC 155. (Invited Symposium Presentation.)
336. R. D. Rogers, "Vision 2020: How Green Chemistry Can Shape the Future of the Sugar Processing Industry," Presented by R. D. Rogers Before the SPRI 2000 Conference on Sugar Processing Research (2000), Porto, Portugal, Abstract Book. (Invited Plenary Presentation).
337. R. D. Rogers, "Ionic Liquids as Solvent Replacements in Industrial-Scale Separations – Opportunities and Challenges," Presented by R. D. Rogers before the NATO Advanced Research Workshop, Green Industrial Applications of Ionic Liquids (2000), Crete, Greece, Abstract Book (Invited Presentation).
338. R. D. Rogers, A. Visser, W. M. Reichert, and R. P. Swatloski, "Investigation of Room-Temperature Ionic Liquids via X-ray Crystallographic Characterization of Low Melting Analogs," Presented by R. P. Swatloski before the NATO Advanced Research Workshop, Green Industrial Applications of Ionic Liquids (2000), Crete, Greece, Abstract Book.
339. A. E. Visser, R. P. Swatloski, S. T. Griffin, and R. D. Rogers, "Crown Ethers as Extractants for Group I and II Metal Ions in Room-Temperature Ionic Liquids," Presented by A. E. Visser before the NATO Advanced Research Workshop, Green Industrial Applications of Ionic Liquids (2000), Crete, Greece, Abstract Book.
340. J. G. Huddleston, H. D. Willauer, M. Li, and R. D. Rogers, "The Solution Properties of Aqueous Biphasic Systems," Presented by J. G. Huddleston before the Fourteenth Symposium on Thermophysical Properties (2000), Boulder, CO, Abstract book page 97.
341. R. D. Rogers, J. G. Huddleston, A. E. Visser, and R. P. Swatloski, "Linear Free Energy Relationships to Describe Solute Partitioning in Room Temperature Ionic Liquids," Presented by R. D. Rogers before the Fourteenth Symposium on Thermophysical Properties (2000), Boulder, CO, Abstract book page 97.
342. A. E. Visser, R. P. Swatloski, W. M. Reichert, R. D. Rogers, "Chemical and Physical Characteristics of Room-Temperature Ionic Liquids and the Associated Implications for Their Use as Solvent Alternatives," Presented by R. D. Rogers before the 4th Annual Green Chemistry and Engineering Conference: Sustainable Technologies: From Research to Industrial Implementation (2000), Washington, DC, Abstract book page 11.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 65

IPR2020-00770
United Therapeutics EX2007
Page 3615 of 7335

343. H. D. Willauer, J. G. Huddleston, M. Li, and R. D. Rogers, "Aqueous Biphasic Systems as Green Alternatives to Chemical Pulping in the Alkaline Paper Pulping Process," Presented by H. D. Willauer before the 4th Annual Green Chemistry and Engineering Conference: Sustainable Technologies: From Research to Industrial Implementation (2000), Washington, DC, Abstract book page 38.
344. R. D. Rogers, "Ionic Liquids as Alternative Reaction Media: Challenges and Opportunities," Presented by R. D. Rogers before the Gordon Research Conference on Green Chemistry (2000), New London, CT (Invited Presentation).
345. R. D. Rogers, "Ionic Liquids as Alternatives to Organic Solvents for Liquid Extraction," Presented by R. D. Rogers before the Gordon Research Conference on Separation and Purification (2000), New London, NH (Invited Presentation).
346. A. E. Visser and R. D. Rogers, "Room Temperature Ionic Liquids as Solvents for Liquid/Liquid Extraction of Organic Molecules and Metal Ions," Presented by A. E. Visser before the Gordon Research Conference on Separation and Purification (2000), New London, NH.
347. H. W. Willauer and R. D. Rogers, "Development of Predictive Tools for Partitioning in Aqueous Biphasic Systems," Presented by H. W. Willauer before the Gordon Research Conference on Separation and Purification (2000), New London, NH.
348. H. Luo, N. Eberly, R. D. Rogers, and M. W. Brechbiel, "*cis,cis*-1,3,5-Triaminocyclohexane-*N,N'*,*N''*-Triacetic Acid (H_3tachta) and Its Metal Complexes," Presented by H. Luo before the 220th ACS National Meeting (2000), Washington, DC, Abstract INOR 387.
349. A. E. Visser, R. P. Swatloski, W. M. Reichert, and R. D. Rogers, "Chemical and Physical Characteristics of Room-Temperature Ionic Liquids and the Associated Implications for Their Use as Solvent Alternatives," Presented by A. E. Visser before the 220th ACS National Meeting (2000), Washington, DC, Abstract I&EC 014.
350. R. P. Swatloski, A. E. Visser, W. M. Reichert, and R. D. Rogers, "Crystallographic Characterization of Solid-State Analogs of Room-Temperature Ionic Liquid Solvents," Presented by R. P. Swatloski before the 220th ACS National Meeting (2000), Washington, DC, Abstract I&EC 041.
351. W. M. Reichert, A. E. Visser, R. P. Swatloski, and R. D. Rogers, "Ionic Composition as a Variable to Fine Tune the Physical Properties of Room-Temperature Ionic Liquids," Presented by W. M. Reichert before the 220th ACS National Meeting (2000), Washington, DC, Abstract I&EC 042.
352. R. D. Rogers, A. E. Visser, R. P. Swatloski, and W. M. Reichert, "Liquid/Liquid Extraction of Actinides in Room-Temperature Ionic Liquids," Presented by A. E. Visser before the 220th ACS National Meeting (2000), Washington, DC, Abstract I&EC 043.
353. H. D. Willauer, J. G. Huddleston, M. Li, Z. Guo, G. C. April, R. D. Rogers, "Polymer-Based Aqueous Biphasic Systems for Reaction Engineering of the Kraft Pulping Process," Presented by H. D. Willauer before the 220th ACS National Meeting (2000), Washington, DC, Abstract I&EC 180.
354. R. D. Rogers, A. E. Visser, R. P. Swatloski, and W. M. Reichert, "Room-Temperature Ionic Liquids as Designer Solvents: Manipulation of Solvent Properties through Simple Variation in Ionic Composition," Presented by R. D. Rogers before the 220th ACS National Meeting (2000), Washington, DC, Abstract I&EC 018 (Invited Symposium Presentation).
355. R. D. Rogers, "University of Alabama's Center for Green Manufacturing," Presented by R.D. Rogers before the 22nd Annual Meeting of the Council for Chemical Research (2000), New Orleans, LA.
356. R. D. Rogers, "Alabama Institute of Manufacturing Excellence," Presented by R.D. Rogers before the 22nd Annual Meeting of the Council for Chemical Research (2000), New Orleans, LA
357. B. Wu, R. G. Reddy, and R. D. Rogers, "Aluminum Recycling via Room Temperature Electrolysis in Ionic Liquids," Presented by B. Wu before the TMS Fall Extraction & Process Metallurgy Meeting: New Technologies for the Next Millennium (2000), Pittsburgh, PA, Program booklet p 12.
358. Z. Guo, M. Li, H. D. Willauer, J. G. Huddleston, R. D. Rogers, and G. C. April, "Polymer-Based Aqueous Biphasic Systems as Improvement for Kraft Hardwood Pulping Process," Presented by Z. Guo before the 2000 Fall AIChE National Meeting (2000), Los Angeles, CA.
359. E. Dadachova, C. Park, H. Luo, N. Eberly, R. Rogers, C. Paik, and M. Brechbiel, "Characterization of $^{67}Ga^{3+}$ Complex with *cis, cis*-1,3,5-Triamino-Cyclohexane-*N,N',N''*-Triacetic Acid," Presented by E. Dadachova before the 2000 International Chemical Congress of Pacific Basin Societies, Pacifichem 2000 (2000), Honolulu, HI, Abstract MEDI 69.
360. R. D. Rogers, A. E. Visser, R. P. Swatloski, and W. M. Reichert, "Chemical and Physical Characteristics of Room-Temperature Ionic Liquids (and Solid-State Analogs): Implications for Their Use as Solvent Alternatives," Presented by R. D. Rogers before the 2000 International Chemical Congress of Pacific Basin Societies, Pacifichem 2000 (2000), Honolulu, HI, Abstract ANYL 281.
361. B. Wu, R. G. Reddy, and R. D. Rogers, "Aluminum Recycling via Room Temperature Electrolysis in Ionic Liquids," Presented by B. Wu before the 2001 TMS Annual Meeting (2001), New Orleans, LA, Abstract Program booklet.
362. R. D. Rogers, "Green Chemistry and Ionic Liquids: Synergies and Ironies," Presented by R. D. Rogers before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 001. (Invited Plenary Presentation)
363. W. M. Reichert, A. E. Visser, R. P. Swatloski, R. D. Rogers, and M. Koel, "Characterization of Solute-Solvent Properties in Ionic Liquids by Gas Chromatography," Presented by W. M. Reichert before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 024.
364. P. Scovazzo, A. E. Visser, J. H. Davis, Jr., R. D. Rogers, C. Koval, and R. D. Noble, "Supported Ionic Liquid Membranes and Facilitated Ionic Liquid Membranes," Presented by P. Scovazzo before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 028.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 66

IPR2020-00770
United Therapeutics EX2007
Page 3616 of 7335

365. R. D. Rogers, A. E. Visser, W. M. Reichert, and R. P. Swatloski, "Comparative Study of the Chemical and Physical Properties of Hydrophobic vs. Hydrophilic Ionic Liquids," Presented by A. E. Visser before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 049.
366. R. P. Swatloski, A. E. Visser, W. M. Reichert, and R. D. Rogers, "Characteristics of Room-Temperature Ionic Liquids in Various Water/Ethanol Solutions," Presented by R. P. Swatloski before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 050.
367. J. G. Huddleston, H. D. Willauer, and R. D. Rogers, "Free-Energy Relationships and Solvatochromic Properties of Aqueous Solvent Systems Based on Poly(Ethylene Glycol)," Presented by J. G. Huddleston before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 051.
368. W. M. Reichert, A. E. Visser, R. P. Swatloski, S. K. Spear, and R. D. Rogers, "Solubilization and Derivatization of Chitin In Room-Temperature Ionic Liquids," Presented by W. M. Reichert before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 052.
369. S. K. Spear, G. A. Broker, M. A. Klingshirn, L. Moens, M. A. Godshall, T. P. Johnson, and R. D. Rogers, "Solubility of Mono- and Disaccharides in Ionic Liquids," Presented by S. K. Spear before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 053.
370. P. Scovazzo, A. E. Visser, J. H. Davis, Jr., R. D. Rogers, C. Koval, and R. D. Noble, "Supported Ionic Liquid Membranes and Facilitated Ionic Liquid Membranes," Presented by P. Scovazzo before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 054.
371. R. D. Rogers, A. E. Visser, R. P. Swatloski, S. T. Griffin, and W. M. Reichert, "Applications of Room-Temperature Ionic Liquids: Actinide Separations," Presented by A. E. Visser before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 192.
372. B. Wu, R. G. Reddy, and R. D. Rogers, "Potential Applications of Ionic Liquids in Aluminum Industries," Presented by B. Wu before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 196.
373. J. G. Huddleston, G. A. Broker, H. D. Willauer, A. E. Visser, W. M. Reichert, and R. D. Rogers, "Free-Energy Relationships and Solvatochromic Properties of Room-Temperature Ionic Liquids Based on Methylimidazolium Cations," Presented by J. G. Huddleston before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 278.
374. R. D. Rogers, M. A. Godshall, T. P. Johnson, L. Moens, and S. K. Spear, "Green Chemistry, the Carbohydrate Economy, and Ionic Liquids: Compatible Goals, Compatible Chemistries?" Presented by R. D. Rogers before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 347.
375. S. K. Spear, W. M. Reichert, R. P. Swatloski, and R. D. Rogers, "Ionic Liquids as Benign Solvents for Extraction Of Astaxanthin and Solubilitization of Chitin," Presented by S. K. Spear before the 221st ACS National Meeting (2001), San Diego, CA, Abstract I&EC 412.
376. G. J. Lumetta, B. K. McNamara, B. M. Rapko, R. D. Rogers, G. A. Broker, and J. E. Hutchison, "Extraction of Uranium(VI) with Malonamides: What's Really Going On?" Presented by G. J. Lumetta before the 221st ACS National Meeting (2001), San Diego, CA, Abstract INOR 686.
377. J. G. Huddleston, H. D. Willauer, and R. D. Rogers, "Aqueous Biphasic Systems: Linear Free Energy Relationships and Solvatochromic Parameters," Presented by J. G. Huddleston before the DOE Office of Basic Energy Sciences Separations and Analysis Program Contractor's Meeting (2001), San Diego, CA, Abstract book.
378. J. G. Huddleston, H. D. Willauer, S. T. Griffin, and R. D. Rogers, "Aqueous Biphasic Systems: Solute Partitioning and the Physical Nature of the Phases," Presented by R. D. Rogers before the DOE Office of Basic Energy Sciences Separations and Analysis Program Contractor's Meeting (2001), San Diego, CA, Abstract book.
379. R. D. Rogers, J. G. Huddleston, S. K. Spear, A. E. Visser, R. P. Swatloski, and W. M. Reichert, "Green Chemistry and Ionic Liquids: Synergies and Ironies," Presented by R. D. Rogers before the 2001 Spring National Meeting of AIChE (2001), Houston, TX, Abstract 12b. (Invited Symposium Presentation)
380. Z. Guo, H. D. Willauer, J. G. Huddleston, R. D. Rogers, and G. C. April, "Polymer-Based Aqueous Biphasic Systems as Alternatives for Kraft Pulping Process," Presented by Z. Guo before the 2001 Spring National Meeting of AIChE (2001), Houston, TX, Abstract 99g.
381. Z. Guo, J. G. Huddleston, R. D. Rogers, and G. C. April, "Delignification of Hardwood in Aqueous Biphasic Systems with Metal Salts as Catalysts," Presented by Z. Guo before the 2001 Fall National Meeting of AIChE (2001), Reno, NV, Abstract.
382. B. Wu, R. G. Reddy, and R. D. Rogers, "Novel Ionic Liquid Thermal Storage for Solar Thermal Electric Power Systems," Presented by B. Wu before the Solar Forum 2001: Solar Energy: The Power to Choose (2001), Washington, DC, Abstract.
383. R. D. Rogers; S. K. Spear; R. P. Swatloski; W. M. Reichert; M. A. Godshall; T. P. Johnson; L. Moens "Non-Sugar Products from Sugarcane for the New Millennium: Green Pathways to a Carbohydrate Economy?" Presented by R. D. Rogers before the 60th Annual International Sugar Industry Technologists Meeting (2001), Taipei, Taiwan. (Invited Keynote Speaker)
384. R. D. Rogers, S. K. Spear, R. P. Swatloski, W. M. Reichert, M. A. Godshall, T. P. Johnson, and L. Moens, "Green Chemistry, the Carbohydrate Economy, and Ionic Liquids: Compatible Goals, Compatible Chemistries?" Presented by R. D. Rogers before IUPAC CHEMRAWN XIV World Conference, Toward Environmentally Benign Processes and Products (2001), Boulder, CO, Abstract Book.
385. R. D. Rogers, "Scientific journals, a conversation with top editors of science journals," Presented by R. D. Rogers as part of a Panel Discussion before the Image and Meaning Conference (2001), Cambridge, MA, no abstract (Invited Panel Participant).

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 67

IPR2020-00770
United Therapeutics EX2007
Page 3617 of 7335

386. J. G. Huddleston, M. Li, Z. Guo, H. D. Willauer, G. C. April, and R. D. Rogers, "Polymer-Based Aqueous Biphasic Systems Applied to the Alkaline Pulping Process," Presented by J. G. Huddleston before the 5th Annual Green Chemistry and Engineering Conference (2001), Washington, DC, Abstract Book p 3.
387. R. D. Rogers, S. K. Spear, M. A. Godshall, T. P. Johnson, and L. Moens, "Green Chemistry, the Carbohydrate Economy, and Ionic Liquids: Compatible Goals, Compatible Chemistries?" Presented by R. D. Rogers before the 5th Annual Green Chemistry and Engineering Conference (2001), Washington, DC, Abstract Book p 9.
388. A. E. Visser, R. P. Swatloski, W. M. Reichert, and R. D. Rogers, "Chemical and Physical Characteristics of Room Temperature Ionic Liquids and the Associated Implications for their Use as Solvent Alternatives," Presented by A. E. Visser before the 5th Annual Green Chemistry and Engineering Conference (2001), Washington, DC, Abstract Book p 38.
389. R. P. Swatloski, A. E. Visser, W. M. Reichert, and R. D. Rogers, "Crystallographic Investigation of Room-Temperature Ionic Liquids via X-ray Crystallography – Characterization of Low-Melting Analogs," Presented by R. P. Swatloski before the 5th Annual Green Chemistry and Engineering Conference (2001), Washington, DC, Abstract Book p 39.
390. R. D. Rogers, A. E. Visser, and S. T. Griffin, "Extraction of complex metal anions in non-VOC solvents: Room-temperature ionic liquids and aqueous biphasic systems," Presented by R. D. Rogers before the 222nd ACS National Meeting (2001), Chicago, IL, Abstract I&EC 007.
391. R. D. Rogers, H. A. Betts, R. P. Swatloski, A. E. Visser, and W. M. Reichert, "Synthesis and characterization of 1-alkol-3-methylimidazolium bromide ionic liquids," Presented by H. A. Betts before the 222nd ACS National Meeting (2001), Chicago, IL, Abstract I&EC 020.
392. R. D. Rogers, M. A. Klingshirn, G. A. Broker, J. D. Holbrey, and K. H. Shaughnessy, "Palladium catalyzed CO/alkene copolymerization in room temperature ionic liquids," Presented by M. A. Klingshirn before the 222nd ACS National Meeting (2001), Chicago, IL, Abstract I&EC 021.
393. R. P. Swatloski, A. E. Visser, W. M. Reichert, and R. D. Rogers, "Phase behavior of room-temperature ionic liquids in various water/alcohol solutions," Presented by R. P. Swatloski before the 222nd ACS National Meeting (2001), Chicago, IL, Abstract I&EC 022.
394. R. D. Rogers, G. A. Broker, M. A. Klingshirn, and J. D. Holbrey, "Solubility determination of organic and inorganic compounds in hydrophilic room-temperature ionic liquids," Presented by G. A. Broker before the 222nd ACS National Meeting (2001), Chicago, IL, Abstract I&EC 023.
395. R. D. Rogers and G. A. Broker, "Crystal engineering of coordination polymers containing molecular recognition sites," Presented by G. A. Broker before the 222nd ACS National Meeting (2001), Chicago, IL, Abstract I&EC 024.
396. W. M. Reichert, A. E. Visser, R. P. Swatloski, S. K. Spear, and R. D. Rogers, "Derivatization of chitin in room-temperature ionic liquids," Presented by W. M. Reichert before the 222nd ACS National Meeting (2001), Chicago, IL, Abstract I&EC 025.
397. A. E. Visser, R. P. Swatloski, W. M. Reichert, and R. D. Rogers, "Anionic extractants for metal ion partitioning in room-temperature ionic liquids," Presented by A. E. Visser before the 222nd ACS National Meeting (2001), Chicago, IL, Abstract I&EC 026.
398. R. D. Rogers, G. A. Broker, and M. A. Klingshirn, "Crystal Engineering Using Lanthanide Ions as Nodes in Coordination and Hydrogen Bonded Networks," Presented by R. D. Rogers before the Rare Earths' – 2001 Brazil Conference (2001), Campos do Jordão, Brazil, Abstract IL-12. (Invited Lecture Presentation)
399. G. A. Broker, J. G. Huddleston, J. D. Holbrey, and R. D. Rogers, "Biphasic Systems Formed by Water-Miscible Room-Temperature Ionic Liquids in the Presence of Aqueous Salt Solutions," Presented by G. A. Broker before the Twelfth Symposium on Separations Science and Technology for Energy Applications (2001), Gatlinburg, TN, Abstract Book p 37.
400. G. A. Broker, J. G. Huddleston, H. D. Willauer, and R. D. Rogers, "Solvatochromatic Properties and Linear Solvent Energy Relationships of Room-Temperature Ionic Liquids," Presented by G. A. Broker before the Twelfth Symposium on Separations Science and Technology for Energy Applications (2001), Gatlinburg, TN, Abstract Book p 38.
401. J. G. Huddleston, H. D. Willauer, Z. Guo, G. C. April, and R. D. Rogers, "Aqueous Biphasic Systems in High Temperature Reactive Extraction: Experiences with the Alkaline Pulping of Wood for Paper and Biomass Production," Presented by J. G. Huddleston before the Twelfth Symposium on Separations Science and Technology for Energy Applications (2001), Gatlinburg, TN, Abstract Book p 46.
402. M. A. Klingshirn, J. D. Holbrey, and R. D. Rogers, "The Use of Room Temperature Ionic Liquids for the Extraction of Metal Ions from Non-Aqueous Solvents," Presented by M. A. Klingshirn before the Twelfth Symposium on Separations Science and Technology for Energy Applications (2001), Gatlinburg, TN, Abstract Book p 48.
403. R. D. Rogers, J. D. Holbrey, J. G. Huddleston, G. A Broker, A. E. Visser, R. P. Swatloski, and W. M. Reichert, "Chemical and Physical Characteristics of Room-Temperature Ionic Liquids (and Solid-State Analogs): Implications for Their Use as 'Green' Solvent Alternatives," Presented by R. D. Rogers before the Twelfth Symposium on Separations Science and Technology for Energy Applications (2001), Gatlinburg, TN, Abstract Book p 61.
404. H. D. Willauer, J. G. Huddleston, and R. D. Rogers, "Solvent Properties of PEG-Salt Aqueous Biphasic Systems (ABS) Based on Linear Free Energy Relationships and Solvatochromic Parameters," Presented by H. D. Willauer before the Twelfth Symposium on Separations Science and Technology for Energy Applications (2001), Gatlinburg, TN, Abstract Book p 68.
405. S. K. Spear, J. G. Huddleston, and R. D. Rogers, "Activity of Laccase Immobilized in a PEG Gel Matrix," Presented by S. K. Spear before the Twelfth Symposium on Separations Science and Technology for Energy Applications (2001), Gatlinburg, TN, Abstract Book p 79.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 68

IPR2020-00770
United Therapeutics EX2007
Page 3618 of 7335

406. J. G. Huddleston, H. D. Willauer, S. T. Griffin, and R. D. Rogers, "Solute Partitioning and Phase Behavior in Aqueous Biphasic Systems," Presented by J. G. Huddleston before the Twelfth Symposium on Separations Science and Technology for Energy Applications (2001), Gatlinburg, TN, Abstract Book p 82.
407. A. E. Visser, R. P. Swatloski, W. M. Reichert, and R. D. Rogers, "Actinide Separations in Room-Temperature Ionic Liquids," Presented by A. E. Visser before the Twelfth Symposium on Separations Science and Technology for Energy Applications (2001), Gatlinburg, TN, Abstract Book p 88.
408. R. D. Rogers, J. D. Holbrey, R. P. Swatloski, and W. M. Reichert, "Reverse Crystal Engineering: Can We Use the Concepts Learned to Make New Room Temperature Ionic Liquids for Applications as Green Solvent Alternatives?" presented by R. D. Rogers before the 59th Pittsburgh Diffraction Conference (2001), Covington, KY, Abstract Book. (Invited Symposium Presentation)
409. M. G. Benton, M. P. Scott, J. D. Holbrey, R. D. Rogers, and C. S. Brazel "A New Class of Plasticizing Agents: Room Temperature Ionic Liquids in Poly (Methyl Methacrylate) and Polystyrene," Presented by C. S. Brazel before the 2001 Fall National Meeting of AIChE (2001), Reno, NV, Abstract 118b.
410. J. D. Holbrey, A. E. Visser, and R. D. Rogers, "A New Class of Solvents for TRU Dissolution and Separation: Ionic Liquids," Presented by J. D. Holbrey before the Department of Energy Environmental Management Science Program High Level Waste Kick-Off Meeting (November 7-9, 2001), Richland, WA, no abstract.
411. R. D. Rogers, A. E. Visser, and J. H. Davis, Jr., "Actinide Separations Utilizing Room Temperature Ionic Liquids," Presented by A. E. Visser at the Actinides-2001 International Conference (2001), Hayama, Japan, Abstract 4O10.
412. A. E. Visser, M. P. Jensen, K. L. Nash, and R. D. Rogers, "Investigation of Actinide Complexation and Solvation in Room Temperature Ionic Liquids," Presented by A. E. Visser at the Actinides-2001 International Conference (2001), Hayama, Japan, Abstract 2O15.
413. R. D. Rogers, A. E. Visser, J. H. Davis, Jr., C. Koval, D. L. DuBois, P. Scovazzo, and R. D. Noble, "Designing or Choosing Ionic Liquids for Utilization in Supported Ionic Liquid Membranes and Facilitated Ionic Liquid Membranes," Presented by R. D. Rogers before the 2002 Spring National Meeting of AIChE (2002), New Orleans, LA, Abstract 9e. (Invited Symposium Presentation)
414. S. K. Spear and R. D. Rogers, "Ionic Liquids: Green Solvents for Carbohydrate Studies," Presented by S. K. Spear before SPRI 2002, Conference on Sugar Processing Research (2002), New Orleans, LA, Abstract Book.
415. A. E. Visser, J. D. Holbrey, and R. D. Rogers, "Room temperature ionic liquids as alternatives to traditional organic solvents in solvent extraction," Presented by R. D. Rogers before the 16th International Solvent Extraction Conference, ISEC 2002 (2002), Cape Town, South Africa, Abstract Book p 11. (Invited Plenary Presentation)
416. R. P. Planalp, A. M. Przyborowska, G. Park, N. Ye, F. H. Lu, R. D. Rogers, G. A. Broker, S. V. Torti, and M. W. Brechbiel, "Novel cytotoxic chelators that bind iron(II) selectively over zinc(II) under aqueous aerobic conditions," Presented by R. P. Planalp before the Biometals 2002: 3rd International Biometals Symposium (2002), London, United Kingdom, Abstract S38.
417. R. P. Planalp, K. A. Deal, G. Park, J. Shao, F. H. Lu, N. D. Chasteen, R. D. Rogers, and M. W. Brechbiel, "Metal-promoted phosphate diester hydrolysis by novel Cu(II) complexes of tris(N-alkylated) *cis,cis*-1,3,5-triaminocyclohexane," Presented by R. P. Planalp before the Biometals 2002: 3rd International Biometals Symposium (2002), London, United Kingdom, Abstract E5.
418. R. P. Planalp, S. Lai, G. Lu, A. M. Przyborowska, G. Park, R. D. Rogers, G. A. Broker, M. W. Brechbiel, S. V. Torti, and R. Ma, "Structure, reactivity and cytotoxicity of tripodal chelators and complexes: the effects of heterocyclic donor groups and enforced coordination geometry on Fe(II) complexation by potential antitumor agents," Presented by R. P. Planalp before the Biometals 2002: 3rd International Biometals Symposium (2002), London, United Kingdom, Abstract E4.
419. R. P. Swatloski, A. E. Visser, J. H. Davis, Jr., and R. D. Rogers, "Actinides in room temperature ionic liquids; old elements - new solvents," Presented by R. P. Swatloski before the 223rd ACS National Meeting (2002), Orlando, FL, Abstract NUCL 132.
420. R. D. Rogers, A. E. Visser, J. H. Davis, Jr., C. Koval, D. L. DuBois, P. Scovazzo, and R. D. Noble, "Choosing ionic liquids for supported ionic liquid membranes," Presented by R. D. Rogers before the 223rd ACS National Meeting (2002), Orlando, FL, Abstract I&EC 128. (Invited Symposium Presentation)
421. Z. Guo, J. G. Huddleston, R. D. Rogers, and G. C. April, "Polyethylene glycol effects in aqueous biphasic systems delignification," Presented by Z. Guo before the 223rd ACS National Meeting (2002), Orlando, FL, Abstract CELL 062.
422. R. D. Rogers and J. D. Holbrey, "Challenges and Opportunities in the Use of Ionic Liquids: Focus on Separations and Recycle," Presented by R. D. Rogers before the Challenges of Novel Technologies in Molecular Chemistry Conference (2002), Rennes, France, Abstract Book. (Invited Keynote Presentation)
423. J. D. Holbrey, K. H. Shaughnessy, M. A. Klingshirn, G. A. Broker, and R. D. Rogers, "Transition Metal Catalyzed CO/Olefin Co-Polymerization in Room Temperature Ionic Liquids," Presented by J. D. Holbrey before the Thirteenth International Symposium on Molten Salts, part of the 201st National Meeting of the Electrochemical Society (2002), Philadelphia, PA, Abstract 1400.
424. R. P. Swatloski, J. D. Holbrey, S. K. Spear, and R. D. Rogers, "Ionic Liquids for the Dissolution and Regeneration of Cellulose," Presented by R. P. Swatloski before the Thirteenth International Symposium on Molten Salts, part of the 201st National Meeting of the Electrochemical Society (2002), Philadelphia, PA, Abstract 1394.
425. R. D. Rogers and A. E. Visser, "Actinide Chemistry in Novel Solvent Media: Room Temperature Ionic Liquids," Presented by R. D. Rogers before the Thirteenth International Symposium on Molten Salts, part of the 201st National Meeting of the Electrochemical Society (2002), Philadelphia, PA, Abstract 1446. (Invited Presentation)

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 69

IPR2020-00770
United Therapeutics EX2007
Page 3619 of 7335

426. R. D. Rogers and W. M. Reichert, "Polymorphic 1-butyl-3-methylimidazolium chloride: In search of clues to make ionic salts, ionic liquids," Presented by R. D. Rogers before the American Crystallographic Association Annual Meeting (2002), San Antonio, TX, Abstract 08.04.21. (Invited Presentation)
427. R. D. Rogers, J. D. Holbrey, S. K. Spear, and R. P., Swatloski, "Ionic Liquids—A Look at the Dissolution of Cellulose," Presented by R. D. Rogers before the 6th Annual Green Chemistry and Engineering Conference (2002), Washington, DC, Abstract Book p 17.
428. J. G. Huddleston, H. D. Willauer, G. D. Broker, S. K. Spear, J. D. Holbrey, and R. D. Rogers, "Predicting the Performance of Alternative Solvents Through the Use of Free Energy Relationships," Presented by J. G. Huddleston before the 6th Annual Green Chemistry and Engineering Conference (2002), Washington, DC, Abstract Book p 19.
429. J. D. Holbrey and R. D. Rogers, "Polymerization and Polymers in Room Temperature Ionic Liquids," Presented by J. D. Holbrey before the 6th Annual Green Chemistry and Engineering Conference (2002), Washington, DC, Abstract Book p 20.
430. R. P. Swatloski, J. D. Holbrey, S. K. Spear, and R. D. Rogers, "Ionic Liquids as Green Solvents for Regeneration/Engineering of Cellulose Based Products," Presented by R. P. Swatloski before the 6th Annual Green Chemistry and Engineering Conference (2002), Washington, DC, Abstract Book p 43.
431. R. D. Rogers and A. E. Visser, "Room Temperature Ionic Liquids: New Solvents for f-element Separations and Associated Solution Chemistry," Presented by R. D. Rogers before the 23rd Rare Earth Research Conference (2002), Davis, CA, Abstract OSE-1-05.
432. R. D. Rogers and J. D. Holbrey, "Ionic Liquids: What are They? Are They Useful? And the Case of the Missing Data," Presented by R. D. Rogers before the 57th Annual Calorimetry Conference CALCON 2002 (2002), New Brunswick, NJ, Abstract 47. (Invited Plenary Presentation)
433. J. D. Holbrey, W. M. Reichert, S. K. Spear, R. P. Swatloski, M. B. Turner, A. E. Visser, and R. D. Rogers, "Getting started with Ionic Liquids: An experience-based tutorial on synthesis and handling," Presented by J. D. Holbrey, W. M. Reichert, S. K. Spear, R. P. Swatloski, M. B. Turner, A. E. Visser, and R. D. Rogers before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 1.
434. J. D. Holbrey and R. D. Rogers, "Clean synthesis of 1,3-dialkylimidazolium ionic liquids," Presented by J. D. Holbrey before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 012.
435. J. D. Holbrey, W. M. Reichert, R. G. Reddy, and R. D. Rogers, "Specific heat capacities of common ionic liquids: an examination of the potential for using ionic liquids as thermal fluids," Presented by J. D. Holbrey before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 070.
436. R. P. Swatloski, S. K. Spear, J. D. Holbrey, and R. D. Rogers, "Ionic Liquids: new solvents for non-derivitized cellulose dissolution," Presented by R. P. Swatloski before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 076.
437. W. M. Reichert, J. D. Holbrey, and R. D. Rogers, "Insight into the solvent properties of ionic liquids: a comparative study of solute partitioning in organic/ionic liquid biphasic systems," Presented by W. M. Reichert before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 087.
438. A. E. Visser, M. P. Jensen, K. L. Nash, and R. D. Rogers, "An investigation of actinide and fission product extraction in room temperature ionic liquids: Liquid/liquid separations and in-situ solution analysis," Presented by A. E. Visser before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 088.
439. S. K. Spear, W. M. Reichert, and R. D. Rogers, "Liquid-liquid extraction from ionic liquids using renewable plant-based soybean oil methyl ester as alternatives to organic solvents," Presented by S. K. Spear before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 091.
440. K. H. Shaughnessy, M. A. Klingshirn, S. J. P'Pool, J. D. Holbrey, and R. D. Rogers, "Metal-catalyzed olefin polymerization in polar, non-coordinating ionic liquids," Presented by K. H. Shaughnessy before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 121.
441. A. E. Visser, J. G. Huddleston, J. D. Holbrey, and R. D. Rogers, "Hydrophobic *n*-alkyl-isoquinolinium ionic liquids: characterization, solvent properties, and use in separations," Presented by A. E. Visser before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 021.
442. W. M. Reichert, J. D. Holbrey, and R. D. Rogers, "Comparative solid state analyses of polymorphic 1-butyl-3-methylimidazolium halide ionic liquids," Presented by W. M. Reichert before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 022.
443. M. B. Turner, S. K. Spear, J. G. Huddleston, and R. D. Rogers, "Cellulase activity in an ionic liquid," Presented by M. B. Turner before the 224th ACS National Meeting (2002), Boston, MA, Abstract I&EC 023.
444. K. Yamato, R. A. Bartsch, M. L. Dietz, and R. D. Rogers, "Stereospecific syntheses of the *trans-trans* and the *cis-trans*-isomers of dicyclohexano-18-crown-6," Presented by K. Yamato before the 224th ACS National Meeting (2002), Boston, MA, Abstract ORGN 032.
445. K. H. Shaughnessy, S. J. P'Pool, M. A. Klingshirn, J. D. Holbrey, and R. D. Rogers, "Polar noncoordinating ionic liquids as solvents for late transition metal-catalyzed olefin polymerization," Presented by K. H. Shaughnessy before the 224th ACS National Meeting (2002), Boston, MA, Abstract INOR 524.
446. H.-s. Chong, G. Bishwajit, G. A. Broker, R. D. Rogers, and M. W. Brechbeil, "Stereoselective and regioselective synthesis of azepane and azepine derivatives via piperidine ring expansion," Presented by H.-s. Chong before the 224th ACS National Meeting (2002), Boston, MA, Abstract ORGN 508.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 70

IPR2020-00770
United Therapeutics EX2007
Page 3620 of 7335

447. M. G. Benton, J. D. Holbrey, R. D. Rogers, J. W. Mays, and C. S. Brazel, "Ionic Liquids as Environmentally-Benign Solvents for Synthesis of PMMA in [bmim][PF_6]: Kinetic, Thermal and Mechanical Analysis," Presented by C. S. Brazel before the 2002 AIChE Annual Meeting (2002), Indianapolis, IN, Abstract Book 233h.
448. R. D. Rogers, "Ionic Liquids: What are They? Are They Useful? And the Case of the Missing Data," Presented by R. D. Rogers before the 41st Eastern Analytical Symposium & Exposition (2002), Somerset, NJ, Abstract and Program Booklet page 21 (Invited Symposium Presentation).
449. J. D. Holbrey, W. M. Reichert, R. K. Reddy, and R. D. Rogers, "Specific Heat Capacities of Common Room Temperature Ionic Liquids: An Examination of the Potential for Using Ionic Liquids as Thermal Fluids," Presented by J. D. Holbrey before EUCHEM 2002, Molten Salts Conference (2002), Oxford, United Kingdom, Abstract K7. (Keynote Lecture)
450. R. D. Rogers and J. D. Holbrey, "Challenges and Opportunities in the Use of Ionic Liquids: Separations, Extractions, and the Choice of Ionic Liquid," Presented by R. D. Rogers before EUCHEM 2002, Molten Salts Conference (2002), Oxford, United Kingdom, Abstract K15. (Keynote Lecture)
451. J. D. Holbrey and R. D. Rogers, "Clean Synthesis of Ionic Liquids," Presented by J. D. Holbrey before the Gordon Research Conference on Green Chemistry (2002), Oxford, United Kingdom, No abstract.
452. R. P. Swatloski, S. K. Spear, J. D. Holbrey, and R. D. Rogers, "Green solvents for the dissolution and regeneration of cellulose--A look at ionic liquids," Presented by R. P. Swatloski before the Gordon Research Conference on Green Chemistry (2002), Oxford, United Kingdom, No abstract.
453. W. M. Reichert, J. D. Holbrey, J. G. Huddleston, and R. D. Rogers, "Insight into the Solvent Properties of Ionic Liquids: A Comparative Study of Organic Solute Partitioning in Liquid/Liquid Systems," Presented by W. M. Reichert before the Gordon Research Conference on Green Chemistry (2002), Oxford, United Kingdom, No abstract.
454. R. D. Rogers and J. D. Holbrey, "Challenges and Opportunities in the Use of Ionic Liquids: Separations, Extractions, and the Choice of Ionic Liquid," Presented by J. D. Holbrey at Green Solvents for Catalysis - Environmentally Benign Reaction Media (2002), Bruchsal, Germany, Abstract Book p 17.
455. J. D. Holbrey, K. H. Shaughnessy, M. A. Klingshirn, G. A. Broker, and R. D. Rogers, "Transition Metal Catalysed CO/Olefin Co-polymerisation in Room Temperature Ionic Liquids," Presented by J. D. Holbrey at Green Solvents for Catalysis - Environmentally Benign Reaction Media (2002), Bruchsal, Germany, Abstract Book p 69.
456. R. D. Rogers, "Overview of State-of-the-Art in Ionic Liquids Research," Presented by R. D. Rogers at the Air Force Office of Scientific Research/Air Force Propulsion Laboratory Workshop on Energetic Ionic Liquids" (2002), Dulles, VA, No Abstract. (Invited Plenary Presentation)
457. R. P. Swatloski, S. K. Spear, J. D. Holbrey, and R. D. Rogers, "Ionic liquids as green solvents for the dissolution and regeneration of cellulose," Presented by R. P. Swatloski before the 225th ACS National Meeting (2003), New Orleans, LA, Abstract CELL 131.
458. R. P. Swatloski, J. D. Holbrey, S. K. Spear, and R. D. Rogers, "Properties of regenerated cellulose from ionic liquids," Presented by R. P. Swatloski before the 225th ACS National Meeting (2003), New Orleans, LA, Abstract I&EC 167.
459. S. J. P'Pool, M. A. Klingshirn, J. D. Holbrey, R. D. Rogers, and K. H. Shaughnessy, "Polar, non-coordinating ionic liquids as solvents for coordination polymerization of olefins," Presented by S. J. P'Pool before the 225th ACS National Meeting (2003), New Orleans, LA, Abstract ORGN 057.
460. W. M. Reichert, J. D. Holbrey, M. Nieuwenhuyzen, O. Sheppard, C. Hardacre, and R. D. Rogers, "Liquid clathrate formation in ionic liquids and its effects on the solvent properties," Presented by W. M. Reichert before the 225th ACS National Meeting (2003), New Orleans, LA, Abstract I&EC 168.
461. R. D. Rogers, "Challenges and Opportunities in the Use of Ionic Liquids: Separations, Extractions, and the Choice of Ionic Liquid," Presented by R. D. Rogers to Science in Industry, Fine Chemicals Group Meeting "Chemical Solutions with Ionic Liquids" (2003), London, United Kingdom. (Invited Presentation)
462. R. D. Rogers, "Fundamentals of Solute Partitioning in Aqueous Biphasic Systems," Presented by R. D. Rogers before the Department of Energy Basic Energy Sciences Heavy Elements and Separations Contractors Meeting (2003), Santa Fe, NM, Abstract P6-6.
463. R. D. Rogers, "Aqueous Biphasic Systems: Novel Delivery Systems and Novel Applications," Presented by R. D. Rogers before the Department of Energy Basic Energy Sciences Heavy Elements and Separations Contractors Meeting (2003), Santa Fe, NM, Abstract P6-7.
464. R. D. Rogers, "A New Class of Solvents for TRU Dissolution and Separation: Ionic Liquids," Presented by R. D. Rogers before the Department of Energy Environmental Management Sciences Program Principal Investigators Workshop (2003), Richland, WA, no abstract.
465. R. D. Rogers, J. D. Holbrey, S. K. Spear, K. E. Gutowski, N. J. Bridges, V. A. Cocalia, and R. P. Swatloski, "Application of Ionic Liquid Technologies to Nuclear Separations," Presented by R. D. Rogers before the 27th Actinide Separations Conference (2003), Lemont, IL, Abstract Book p 12.
466. V. A. Cocalia, N. J. Bridges, S. T. Griffin, S. K. Spear, and R. D. Rogers, "Uranyl Extraction using Cyanex-272 in 1-Decyl-3-methylimidazolium Bis(trifluoromethanesulfonyl)imide," Presented by V. A. Cocalia before the 27th Actinide Separations Conference (2003), Lemont, IL, Abstract Book p 36.
467. J. D. Holbrey, W. M. Reichert, M. B. Turner, K. Green, and R. D. Rogers, "Development of Ionic Liquids Containing Environmentally Acceptable and Sustainable Components," Presented by J. D. Holbrey before the Seventh Annual Green Chemistry and Engineering Conference (2003), Washington, DC, Abstract 8.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 71

IPR2020-00770
United Therapeutics EX2007
Page 3621 of 7335

468. R. P. Swatloski, J. D. Holbrey, S. K. Spear, R. B. Moore, and R. D. Rogers, "Greener Dissolution of Cellulose: Can Ionic Liquids Compete with *N*-Methyl-morpholine-*N*-oxide in the Lyocell Process?" Presented by R. P. Swatloski before the Seventh Annual Green Chemistry and Engineering Conference (2003), Washington, DC, Abstract 10.
469. K. E. Gutowski, J. G. Huddleston, G. A. Broker, H. D. Willauer, R. P. Swatloski, and R. D. Rogers, "Controlling the Aqueous Miscibility of Hydrophilic Ionic Liquids by Addition of Water-Structuring Salts: Novel Aqueous Biphasic Systems for Separations and Recycle," Presented by K. E. Gutowski before the Seventh Annual Green Chemistry and Engineering Conference (2003), Washington, DC, Abstract 32.
470. C. R. Lea, I. A. Miller, D. M. Brown, R. P. Swatloski, and R. D. Rogers, "X-ray Crystallography of Novel Ionic Liquids Based on *N*-Akylmorpholinium Salts," Presented by D. M. Brown before the Seventh Annual Green Chemistry and Engineering Conference (2003), Washington, DC, Abstract 34.
471. M. B. Turner, S. K. Spear, R. P. Swatloski, J. D. Holbrey, and R. D. Rogers, "Entrapment and Activity of Biomolecules in Cellulose Films Regenerated from Ionic Liquids," Presented by M. B. Turner before the Seventh Annual Green Chemistry and Engineering Conference (2003), Washington, DC, Abstract 40.
472. W. M. Reichert, J. D. Holbrey, J. G. Huddleston, and R. D. Rogers, "Solvent Properties and Liquid Clathrate Behavior of Ionic Liquids Determined by Partitioning Experiments and Linear Solvent Energy Relationships," Presented by W. M. Reichert before the Seventh Annual Green Chemistry and Engineering Conference (2003), Washington, DC, Abstract 75.
473. M. A. Klingshirn, J. D. Holbrey, S. K. Spear, and R. D. Rogers, "Investigation of the Properties of Poly(ethylene Glycol) Hydrogels Doped with Ionic Liquids," Presented by M. A. Klingshirn before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 45.
474. J. G. Huddleston, S. K. Spear, and R. D. Rogers, "The Aqueous Solution Behavior of Poly(ethyleneglycol) Hydrogels," Presented by J. G. Huddleston before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 48.
475. S. K. Spear, M. B. Turner, J. G. Huddleston, and R. D. Rogers, "Poly(ethylene glycol) Hydrogel for Laccase Immobilization," Presented by S. K. Spear before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 51.
476. J. Chen, S. K. Spear, J. G. Huddleston, and R. D. Rogers, "Polyethylene Glycol Aqueous Solutions as Green Reaction Medium," Presented by J. Chen before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 52.
477. S. T. Griffin, S. K. Spear, J. G. Huddleston, and R. D. Rogers, "A Comparison of the Effect of Temperature on the Uptake of TcO4- in PEG Based ABS and onto ABEC Resins," Presented by S. T. Griffin before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 52.
478. S. T. Griffin, S. K. Spear, J. G. Huddleston, and R. D. Rogers, "Partitioning of Iodide in Aqueous Biphasic Systems and onto ABEC® Resins," Presented by S. T. Griffin before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 59.
479. S. K. Spear, S. T. Griffin, J. G. Huddleston, and R. D. Rogers, "Partitioning Studies of Small Molecules in Ammonium Carbamate/Polyethylene Glycol Aqueous Biphasic Systems," Presented by S. K. Spear before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 59.
480. J. Chen, S. K. Spear, J. G. Huddleston, and R. D. Rogers, "Polyethylene Glycol Aqueous Solutions as Green Reaction Medium," Presented by J. Chen before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 60.
481. J. G. Huddleston, H. D. Willauer, S. T. Griffin, S. K. Spear, and R. D. Rogers, "Free Energy Relationships and Solvent Properties of PEG-Salt Aqueous Biphasic Systems," Presented by J. G. Huddleston before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 60.
482. J. G. Huddleston, Z. Guo, H. D. Willauer, M. Li, S. K. Spear, and R. D. Rogers, "Aqueous Biphasic Systems Applied to the Delignification of Cellulosics ? Experiences with the Paper Pulping Process," Presented by J. G. Huddleston before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 60.
483. S. T. Griffin, S. K. Spear, and R. D. Rogers, "Removal of Mercury from Tap Water and Groundwater Using Aqueous Biphasic Extraction Chromatographic Resin," Presented by S. T. Griffin before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 60.
484. M. A. Klingshirn, S. K. Spear, J. D. Holbrey, and R. D. Rogers, "Synthesis and Characterization of a Poly(ethylene Glycol) - Silica Sol Composite," Presented by M. A. Klingshirn before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 61.
485. M. L. Moody, H. D. Willauer, J. G. Huddleston, and R. D. Rogers, "Characterization studies of PEG/Dextran Aqueous Biphasic Systems Involving Linear Solvation Energy Relationship, pH, and Temperature," Presented by M. L. Moody before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 61.
486. M. L. Moody, J. G. Huddleston, and R. D. Rogers, "Use of Linear Solvation Energy Relationships in Studies of PEG/Organic Biphasic Systems," Presented by M. L. Moody before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 61.
487. R. D. Rogers, J. G. Huddleston, J. D. Holbrey, S. K. Spear, and M. B. Turner, "Ionic Liquids in Separations: What Are They? Are They Useful? and How Do They Compare to Aqueous Biphasic Systems?" Presented by R. D. Rogers before the 12th International Conference on Biopartitioning and Purification (2003), Vancouver, British Columbia, Canada, Abstract Book p 51.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 72

IPR2020-00770
United Therapeutics EX2007
Page 3622 of 7335

488. R. D. Rogers, "Challenges and Opportunities in the Use of Ionic Liquids: Separations, Reactions, and the Choice of Ionic Liquid and/or Process," Presented by J. G. Huddleston before the 1st International Symposium on Process Intensification & Miniaturisation (PIM-1 2003), Newcastle upon Tyne, United Kingdom, Abstract Book. (Invited Keynote Lecture).
489. R. D. Rogers, "How to Talk to the Public About What You Do," Communications Clinic at the 226th ACS National Meeting (2003), New York, NY. (Invited Panel Participant).
490. R. D. Rogers, J. D. Holbrey, S. K. Spear, K. E. Gutowski, N. J. Bridges, V. A. Cocalia, and R. P. Swatloski, Application of ionic liquid technologies to nuclear separations," Presented by R. D. Rogers before the 226th ACS National Meeting (2003), New York, NY, Abstract NUCL 092. (Invited Presentation).
491. M. B. Turner, S. K. Spear, R. P. Swatloski, J. D. Holbrey, and R. D. Rogers "Cellulose films regenerated from ILs and their role as scaffolding for enzyme attachment via glutaraldehyde," Presented by M. B. Turner before the 226th ACS National Meeting (2003), New York, NY, Abstract I&EC 190.
492. W. M. Reichert, J. D. Holbrey, and R. D. Rogers, "Relationships between solid-state ion-ion and hydrogen-bonding interactions and liquid properties in ionic liquid forming salts," Presented by W. M. Reichert before the 226th ACS National Meeting (2003), New York, NY, Abstract I&EC 132.
493. K. E. Gutowski, G. A. Broker, N. J. Bridges, J. G. Huddleston, H. D. Willauer, J. D. Holbrey, and R. D. Rogers, "Formation of aqueous biphasic systems with hydrophilic ionic liquids via the addition of water-structuring salts: applications to nuclear tank wastes," Presented by K. E. Gutowski before the 226th ACS National Meeting (2003), New York, NY, Abstract I&EC 131.
494. J. D. Holbrey, M. B. Turner, W. M. Reichert, and R. D. Rogers, "Synthesis, characterization, and applications of new hydroxyl-appended ionic liquids," Presented by J. D. Holbrey before the 226th ACS National Meeting (2003), New York, NY, Abstract I&EC 130.
495. R. P. Swatloski, R. D. Rogers, C. R. Lea, I. A. Miller, and D. M. Brown, "X-Ray crystallography of novel ionic liquids based on N-alkylmorpholinium salts," Presented by R. P. Swatloski before the 226th ACS National Meeting (2003), New York, NY, Abstract I&EC 129.
496. J. D. Holbrey, W. M. Reichert, M. B. Turner, K. Green, and R. D. Rogers, "Development of Ionic Liquids containing environmentally acceptable and sustainable components," Presented by J. D. Holbrey before the 226th ACS National Meeting (2003), New York, NY, Abstract I&EC 128.
497. R. P. Swatloski, J. D. Holbrey, S. K. Spear, and R. D. Rogers, "Ionic liquids as green solvents: Engineering new bio-based materials," Presented by R. P. Swatloski before the 226th ACS National Meeting (2003), New York, NY, Abstract I&EC 090.
498. W. M. Reichert, J. G. Huddleston, J. D. Holbrey, and R. D. Rogers, "Abraham solvent parameters for ionic liquid/organic two-phase systems," Presented by W. M. Reichert before the 226th ACS National Meeting (2003), New York, NY, Abstract I&EC 070.
499. R. D. Rogers, J. D. Holbrey, S. K. Spear, K. E. Gutowski, and R. P. Swatloski, "CMPO-impregnated cellulosic materials from ionic liquids for f-element separations," Presented by R. D. Rogers before the 226th ACS National Meeting (2003), New York, NY, Abstract I&EC 045. (Invited Presentation.)
500. J. D. Holbrey, R. P. Swatloski, W. M. Reichert, J. F. Brennecke, K. R. Seddon, U. Hakala, M. Deetlefs, M. Nieuwenhuyzen, T. Welton, P. Mawdsley, J. Vallance, O. Sheppard, R. D. Rogers," Getting started with Ionic Liquids: An experience-based tutorial," Presented by all authors before the 226th ACS National Meeting (2003), New York, NY, Abstract I&EC 033.
501. A. M. Przyborowska, G. A. Broker, R. D. Rogers, M. W. Brechbiel, and R. P. Planalp, "Electronic properties and structures of novel Cu(II) complexes of hexadentate aminopyridyl ligands and their alkylated derivatives," Presented by A. M. Przyborowska before the 226th ACS National Meeting (2003), New York, NY, Abstract INOR 486.
502. R. P. Planalp, G. Lu, A. M. Przyborowska, M. W. Brechbiel, S-j. Lai, G. Park, G. A. Broker, R. D. Rogers, R. Ma, and S. V. Torti, "The metal-complexation properties of tripodal hexadentate chelators: Effects of heterocycle donor arms, tripod framework and imine formation on Fe(II) chelation and cytotoxicity," Presented by R. P. Planalp before the 226th ACS National Meeting (2003), New York, NY, Abstract INOR 058.
503. R. D. Rogers, "Utilizing Neoteric Solvent Systems to Explore New Decontamination Technologies," Presented by R. D. Rogers before the Radionuclide Decontamination Science and Technology Workshop (2003), Los Alamos, NM. (Invited Presentation).
504. K. E. Gutowski, N. J. Bridges, V. A. Cocalia, S. K. Spear, J. D. Holbrey, J. H. Davis, Jr., and R. D. Rogers, "Approaches to Nuclear Separations Using Room Temperature Ionic Liquids," Presented by K. E. Gutowski before Global 2003 "Atoms for Prosperity: Updating Eisenhower's Global Vision for Nuclear Energy," part of the 2003 ANS/ENS International Winter Meeting (2003), New Orleans, LA. (Invited Presentation).
505. R. D. Rogers, "Greener Industry: A Growing Trend," Panel Discussion and Invited Speaker before the Society of Women Engineers National Conference (2003), Birmingham, AL, Program Book, page 34 (Invited Presentation).
506. R. D. Rogers, "Alternative Separations in Support of DOE's Mission," Presented by R. D. Rogers before the Thirteenth Symposium on Separations Science and Technology for Energy Applications (2003), Gatlinburg, TN, Abstract Book p 18. (Invited Plenary Presentation).
507. N. J. Bridges, V. A. Cocalia, A. E.Visser, J. H. Davis, Jr., J. Holbrey, and R. D. Rogers, "Task Specific Ionic Liquids for Recovery of Actinides from Aqueous Acid Media," Presented by N. J. Bridges before the Thirteenth Symposium on Separations Science and Technology for Energy Applications (2003), Gatlinburg, TN, Abstract Book p 36-37.
508. K. E. Gutowski, S. K. Spear, and R. D. Rogers, "Use of Ionic Liquids in the Removal Actinides from Nitric Acid Media by HOPO-Type Extractants," Presented by K. E. Gutowski before the Thirteenth Symposium on Separations Science and Technology for Energy Applications (2003), Gatlinburg, TN, Abstract Book p 43.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 73

IPR2020-00770
United Therapeutics EX2007
Page 3623 of 7335

509. R. D. Rogers, J. D. Holbrey, S. K. Spear, K. E. Gutowski, and R. P. Swatloski, "CMPO-Impregnated Cellulosic Materials from Ionic Liquids for Actinide Separations," Presented by R. D. Rogers before the Thirteenth Symposium on Separations Science and Technology for Energy Applications (2003), Gatlinburg, TN, Abstract Book p 52.
510. K. E. Gutowski, G. A. Broker, H. D. Willauer, J. G. Huddleston, R. P. Swatloski, J. D. Holbrey, and R. D. Rogers, "Controlling the Aqueous Miscibility of Hydrophilic Ionic Liquids via the Addition of Water-Structuring Salts," Presented by K. E. Gutowski before the Thirteenth Symposium on Separations Science and Technology for Energy Applications (2003), Gatlinburg, TN, Abstract Book p 68.
511. N. J. Bridges and R. D. Rogers, "Comparative Studies of Cyanex-923® in Ionic Liquids Versus Traditional Organic Solvents," Presented by N. J. Bridges before the Thirteenth Symposium on Separations Science and Technology for Energy Applications (2003), Gatlinburg, TN, Abstract Book p 79.
512. V. A. Cocalia, N. J. Bridges, S. T. Griffin, S. K. Spear, and R. D. Rogers, "Actinide Partitioning using the Traditional Extractant Cyanex-272 in a Room Temperature Ionic Liquid as a Novel Medium for Liquid/Liquid Extraction," Presented by V. A. Cocalia before the Thirteenth Symposium on Separations Science and Technology for Energy Applications (2003), Gatlinburg, TN, Abstract Book p 80.
513. R. D. Rogers, "Alternative Solvents," Presented by R. D. Rogers before the Indo-US Science and Technology Forum Workshop on Green Chemistry (2003), Delhi, India. (Invited Delegate/Workshop Instructor).
514. J. D. Warner and R. D. Rogers, "Crystal Engineering and Non Covalent Derivatization," Presented by J. D. Warner and R. D. Rogers before the Indo-US Science and Technology Forum Workshop on Green Chemistry (2003), Delhi, India. (Invited Delegate/Workshop Instructor).
515. R. D. Rogers and D. L. Hjeresen, "International Issues," Presented by R. D. Rogers and D. L. Hjeresen before the Indo-US Science and Technology Forum Workshop on Green Chemistry (2003), Delhi, India. (Invited Delegate/Workshop Instructor).
516. R. D. Rogers, G. A. Broker, K. E. Gutowski, and N. J. Bridges, "Crystal Engineering Using Lanthanide Ions as Nodes," Presented by R. D. Rogers before the International Conference on Materials for Advanced Technologies (ICMAT 2003)/International Union of Materials Research Societies International Conference in Asia (ICA 2003), Singapore, Abstract D-4-1-I. (Invited Symposium Presentation).
517. R. D. Rogers, "Green Chemistry and Applications of Ionic Liquids as Solvents: Synergies and Ironies," Presented by R. D. Rogers before the LICP Discussions No. 1 Workshop - Ionic Liquids: Progress and Prospects (2004), Lanzhou China, Abstract book pp 9-19. (Invited Keynote Presentation).
518. R. D Rogers, J. D Holbrey, S. K Spear, W. M. Reichert, M. R Smiglac, H. Yang, K. Manju, and A. R Katritzky, "Energetic ionic liquids: Fundamental studies relating target structures and key physical properties," Presented by R. D. Rogers to the AFOSR Contractor's Review on Ionic Liquids Research (2004), Tampa, FL.
519. R. D. Rogers, "Green Chemistry," Presented by R. D. Rogers before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2004), Tuscaloosa, AL.
520. R. D. Rogers, "Liquid/Liquid Separations," Presented by R. D. Rogers before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2004), Tuscaloosa, AL.
521. M. A. Klingshirn, S. K. Spear, R. Subramanian, J. D. Holbrey, and R. D. Rogers, "Synthesis, characterization, and applications of ionic liquid-poly(ethylene) glycol gel matrices," Presented by M. A. Klingshirn before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract POLY 638.
522. J. D. Holbrey, J. Chen; M. B. Turner, R. P. Swatloski, S. K. Spear, and R. D. Rogers, "Applying ionic liquid solvent characteristics for controlled processing of polymer materials," Presented by J. D. Holbrey before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract POLY 607.
523. K. H. Shaughnessy, S. J. P'Pool, M. A. Klingshirn, and R. D. Rogers, "Coordination polymerization of alkenes in ionic liquid solvents," Presented by K. H. Shaughnessy before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract POLY 600.
524. M. A. Klingshirn, S. J. P'Pool, K. H. Shaughnessy, and R. D. Rogers, "Palladium-catalyzed hydroesterification of styrene in ionic liquids," Presented by M. A. Klingshirn before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract INOR 770.
525. R. P. Planalp, N. Ye, G. Park, A. M. Przyborowska, P. E. Sloan, T. Clifford, C. B. Bauer, G. A. Broker, R. D. Rogers, R. Ma, S. V. Torti, and M. W. Brechbiel, "Nickel(II), copper(II) and zinc(II) binding properties and cytotoxicity of tripodal, hexadentate tris(ethylenediamine)-analogue chelators," Presented by R. P. Planalp before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract INOR 107.
526. W. M. Reichert, J. D. Holbrey, S. T. Griffin, V. A. Cocalia, N. J. Bridges, J. Chambers, and R. D. Rogers, "Task specific ionic liquids that incorporate poly (ethylene glycols) functionality for the extraction of metal ions," Presented by W. M. Reichert before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract I&EC 228.
527. R. D. Rogers, N. J. Bridges, J. D. Holbrey, H. Luo, S. Dai, and P. V. Bonnesen, "The role of ion exchange vs. solvent extraction processes in metal ion partitioning in ionic liquid/aqueous systems: cesium extractions with calix[4]arene-bis(tert-octylbenzo-crown-6) in imidazolium bistrifylimide ionic liquids," Presented by R. D. Rogers before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract I&EC-227. (Invited Presentation)
528. G. J. Lumetta, B. K. McNamara, L. A. Snow, D. W. Wester, R. D. Rogers, and N. J. Bridges, "Characterization of the coordinative modes of alkyl-substituted Klaui ligand," Presented by G. J. Lumetta before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract I&EC 222.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 74

IPR2020-00770
United Therapeutics EX2007
Page 3624 of 7335

529. R. D. Rogers, K. E. Gutowski, S. T. Griffin, and J. D. Holbrey, "Aqueous biphasic systems based on salting-out polyethylene glycol or ionic liquid solutions: Strategies for actinide or fission product separations," Presented by R. D. Rogers before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract ENVR 033. (Invited Presentation)
530. T. L. Shamery, S. K. Spear, and R. D. Rogers, "How the RET experience at The University of Alabama was incorporated into the high school teaching experience," Presented by T. L. Shamery before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract CHED 090.
531. R. D. Rogers, J. D. Holbrey, S. K. Spear, and M. B. Turner, "Ionic liquids as green solvents: Engineering bioactive cellulose materials," Presented by R. D. Rogers before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract CELL 198. (Invited Presentation)
532. R. P. Swatloski, S. K. Spear, J. D. Holbrey, and R. D. Rogers, "Utilization of biorenewable resources: Bio-based materials from ionic liquids," Presented by R. P. Swatloski before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract CELL 046.
533. J. H. Poplin, R. P. Swatloski, J. D. Holbrey, S. K. Spear, and R. D. Rogers, "Cellulose-supported colorimetric sensors for mercury ion detection," Presented by M. A. Klingshirn before the 227th ACS National Meeting (2004), Anaheim, CA, Abstract CELL 024.
534. R. P. Swatloski, J. D. Holbrey, S. K. Spear, and R. D. Rogers, "Ionic Liquids Enabling Sustainable Technologies for New Advanced Materials," Presented by R. P. Swatloski before the Spring National AIChE Meeting (2004), New Orleans, LA. (Invited presentation)
535. R. D. Rogers, "Investigation of Ionic Liquids as Environmentally Benign Solvents," Presented by R. D. Rogers to the U. S. EPA National Center for Environmental Research EPA and NSF Technology for a Sustainable Environment (TSE) Grantees Meeting (2004), Arlington, VA. No Abstract.
536. R. D. Rogers, "Ionic Liquids: Solvents for Green Chemistry or Advanced Technological Fluids?" Presented by R. D. Rogers before the Canada-US Joint Workshop on Innovative Chemistry in Clean Media (2004), Montreal, Quebec, Canada. (Invited presentation)
537. R. D. Rogers, "Toxicology of Nanoparticles and Analysis and Modeling of Nanoparticles Solution Properties for Physico-Chemical Characterization and Risk Assessment," Presented by R. D. Rogers before the Center for Nanoscale Materials Workshop for EPSCoR Faculty and Students (2004), Argonne, IL. (Invited presentation)
538. R. D. Rogers, "Prospective on the 2005 Conference 'Taking Measure of Green Progress: Opportunities to Meet Global Challenges,'" Presented by R. D. Rogers before the 8th Annual Green Chemistry and Engineering Conference: 'Green Chemistry and Engineering: The Business Imperative for Sustainability' (2004), Washington, DC, no abstract.
539. R. D. Rogers, S. T. Griffin, G. A. Broker, W. M. Reichert, J. H. Poplin, R. P. Swatloski, and J. D. Holbrey, "Supramolecular Chemistry in Alternative Solvents: Are Nonvolatile Ionic Liquids Effective Crystallization Solvents or Fodder for Co-Crystals?," Presented by R. D. Rogers before the American Crystallographic Association Annual Meeting (2004), Chicago, IL, Abstract TR.01.18. (Invited Presentation)
540. M. A. Klingshirn, R. D. Rogers, and K. H. Shaughnessy "Palladium-Catalyzed Hydroesterification of Styrene in the Presence of Ionic Liquids," Presented by M. Klingshirn before the ACS-PRF Summer School on Green Chemistry (2004), Pittsburgh, PA, Program Booklet 1-12.
541. M. B. Turner, J. D. Holbrey, S. K. Spear, and R. D. Rogers, "Entrapment of Biologically Active Macromolecules in Cellulosic Films Reconstituted from Ionic Liquids," Presented by M. Turner before the ACS-PRF Summer School on Green Chemistry (2004), Pittsburgh, PA, Program Booklet 1-20.
542. J. S. Moulthrop, R. P. Swatloski, R. D. Rogers, and G. Moyna "High-resolution ^{13}C NMR studies of amylose and cellulose oligomers in 1-butyl-3-methylimidazolium chloride solutions," Presented by J. S. Moulthrop before the 228th ACS National Meeting (2004), Philadelphia, PA, Abstract CARB 063.
543. R. D. Rogers, W. M. Reichert, and J. D. Holbrey "Ionic Liquids and Hydrogen Bonding: Understanding the Solvent Characteristics of Ionic Liquids through Study of Crystal Structures and Solvation Parameters," Presented by R. D. Rogers before the 228th ACS National Meeting (2004), Philadelphia, PA, Abstract ORGN 542. (Invited symposium presentation)
544. R. P. Planalp, N. Ye, G. Park, A. M. Przyborowska, P. E. Sloan, T. Clifford, C. B. Bauer, R. D. Rogers, R. Ma. S. V. Torti, and M. W. Brechbiel "Nickel(II), copper(II) and zinc(II) binding properties and cytotoxicity of tripodal, hexadentate tris(ethylenediamine)–analogue chelators," Presented by R. P. Planalp before the 228th ACS National Meeting (2004), Philadelphia, PA, Abstract INOR 424.
545. R. D. Rogers, W. M. Reichert, J. D. Holbrey, and G. A. Broker "Approaches to Crystallization: Techniques for Controlling the Formation of Materials and their Application to Industry," Presented by R. D. Rogers before the Crystallisation and Particle Science Workshop – Bridging the Gap between Research and Industrial Application (2004), Singapore, Abstract. (Invited Workshop Lecture)
546. S. V. Volkov and R. D. Rogers, ""Green" Route of Chemistry Development. Problems and Perspectives," Presented by S. Volkov before the XVIth Ukrainian Conference on Inorganic Chemistry (2004), Uzhhorod, Ukraine.
547. R. D. Rogers, "Supramolecular Chemistry in Alternative Solvents: Are Nonvolatile Ionic Liquids Effective Crystallization Solvents or Fodder for Co-Crystals?," Presented by R. D. Rogers before the Gordon Research Conference on Organic Structures & Properties (2004), Les Diablerets, Switzerland (Invited Presentation).
548. W. Wang, G. Shen, R. P. Swatloski, R. Farag, R. M. Broughton, Jr., and R. D. Rogers, "Cellulose Fibers Extruded from Ionic Liquids," Presented by R. M. Broughton, Jr. before the International Nonwovens Technical Conference (2004), Toronto Canada.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 75

IPR2020-00770
United Therapeutics EX2007
Page 3625 of 7335

549. R. D. Rogers, "Green Chemistry and Applications of Ionic Liquids as Solvents: Enabling Sustainable Technologies for New Advanced Materials," Presented by R. D. Rogers before the Proctor & Gamble Ionic Liquids Symposium (2004), Proctor & Gamble, Cincinnati, OH on 11/10/04. (Invited Workshop Lecture)
550. R. D. Rogers, "A New Class of Solvents for TRU Dissolution and Separation: Ionic Liquids," Presented by R. D. Rogers before the DOE Environmental Management Science Program High Level Waste Workshop (2005), SREL Conference Center, Aiken, SC on 1/29/05; no abstract, Program Booklet.
551. H. Luo, S. Dai, P. V. Bonnesen, A. C. Buchanan, III, R. D. Rogers, J. D. Holbrey, and C. L. Hussey, "Novel Fission-Product Separations Based on Room Temperature Ionic Liquids," Presented by S. Dai before the DOE Environmental Management Science Program High Level Waste Workshop (2005), SREL Conference Center, Aiken, SC on 1/29/05; no abstract, Program Booklet.
552. W. Wang, G. Shen, R. P. Swatloski, R. Farag, R. M. Broughton, Jr., and R. D. Rogers "A New Solvent for Cellulose Extrusion," Presented by R. M. Broughton, Jr. before the Cotton Beltwide Conferences (2005), New Orleans, LA.
553. R. D. Rogers, "Solvent Strength of Ionic Liquids," Presented by R. D. Rogers before the Council for Chemical Research 10th NIChE Conference: Ionic Liquids – Background, State-of-the-Art, and Applications (2005), February 21-22, 2005, University of Notre Dame, South Bend, IN; no abstract. (Invited Workshop Lecturer)
554. R. D. Rogers, "Liquid-Liquid Separations with Ionic Liquids," Presented by R. D. Rogers before the Council for Chemical Research 10th NIChE Conference: Ionic Liquids – Background, State-of-the-Art, and Applications (2005), February 21-22, 2005, University of Notre Dame, South Bend, IN; no abstract. (Invited Workshop Lecturer)
555. R. D. Rogers, "Polymer Chemistry of Ionic Liquids," Presented by R. D. Rogers before the Council for Chemical Research 10th NIChE Conference: Ionic Liquids – Background, State-of-the-Art, and Applications (2005), February 21-22, 2005, University of Notre Dame, South Bend, IN; no abstract. (Invited Workshop Lecturer)
556. R. D. Rogers, "Advanced Materials Utilizing ILs as Enabling Solvents," Presented by R. D. Rogers before the Council for Chemical Research 10th NIChE Conference: *Ionic Liquids – Background, State-of-the-Art, and Applications* (2005), February 21-22, 2005, University of Notre Dame, South Bend, IN; no abstract. (Invited Workshop Lecturer)
557. R. P. Planalp, M. Childers, D. P. Kennedy, A. Lindell, G. Broker, R. D. Rogers, M. W. Brechbiel, R. Ma, F. M. Torti, and S. V. Torti, "Polyamino-heterocycle chelating agents with cytotoxic activity in tumor cells: Structure-activity relationship of imidazole, thiazole and pyridyl donor groups," Presented by R. P. Planalp before the 229th ACS National Meeting (2005), San Diego, CA, Abstract MEDI-501.
558. R. D. Rogers, "DE-FG02-96ER14673 - Alternative (Potentially Green) Separations Media: Aqueous Biphasic and Related Systems - Extending the Frontier," Presented by R. D. Rogers before the Department of Energy Basic Energy Sciences Separations Program, Heavy Elements Program Contractor's Meeting (2005), Rockville, MD; Abstract O6-1.
559. C. Mobley, A. Ramasetty, A. Haque, J. H. Poplin, D. T. Daly, and R. D. Rogers, "Affordable Bio-polymer Matrix Composites for Lightweight Automotive Components," Presented by A. Haque at the Sixth Annual Global Automotive Conference (2005), Western Kentucky University, Bowling Green, KY.
560. R. D. Rogers, "Designer Ionic Liquids Enabling Sustainable Technologies," Presented by R. D. Rogers at the NSF Joint China-USA Workshop *Determining the Grand Challenges of Green Chemistry Development and Implementation* (2005), May 27-31, 2005, Beijing, China; Abstract Book (Co-Organizer).
561. R. D. Rogers, V. A. Cocalia, K. E. Gutowski, N. J. Bridges, J. D. Holbrey, "Separations Using Ionic Liquids: The Challenges of Multiple Mechanisms," Presented by R. D. Rogers at the 1st International Congress on Ionic Liquids (COIL) (2005), Salzburg, Austria; Abstract Book p 28. (Plenary Lecture).
562. J. G. Huddleston, J. Chen, S. K. Spear, R. D. Rogers, "The Role of PEG-based Solvents in Green Chemistry," Presented by J. G. Huddleston before the International Conference on Biopartitioning and Purification, BPP 2005 (2005), The Netherlands, Abstract Book p 7.
563. R. P. Planalp, D. P. Kennedy, M. L. Childers, M. W. Brechbiel, R. Ma, G. A. Broker, R. D. Rogers, F. M. Torti, and S. V. Torti, "Polyamino-heterocycle chelating agents with cytotoxic activity in tumor cells: structure-activity relationship of metal-binding geometry and metal donor groups," Presented by R. P. Planalp before the First Congress of the International BioIron Society (2005), Prague, Czech Republic, Paper P281.
564. R. D. Rogers, D. T. Daly, J. D. Holbrey, J. G. Huddleston, J. H. Poplin, S. K. Spear, R. P. Swatloski, M. B. Turner, and R. L. Wells, "A Platform Strategy Using Ionic Liquids to Dissolve and Process Cellulose for Advanced New Materials," Presented by R. D. Rogers before the joint meeting of the 2nd International Conference on Green and Sustainable Chemistry and the 9th Annual Green Chemistry and Engineering Conference – Taking Measure of Green Progress: Opportunities to Meet Global Challenges (2005), Washington, DC; Abstract 1. (Presidential Green Chemistry Challenge Award Presentation)
565. S. T. Griffin, M. Dilip, S. K. Spear, and R. D. Rogers, "Comparison of the Effect of Temperature in Aqueous Biphasic Systems (ABS) and Aqueous Biphasic Extraction Chromatographic Resins (ABEC®)," Presented by M. Dilip before the joint meeting of the 2nd International Conference on Green and Sustainable Chemistry and the 9th Annual Green Chemistry and Engineering Conference – Taking Measure of Green Progress: Opportunities to Meet Global Challenges (2005), Washington, DC; Abstract 81.
566. M. Dilip, S. T. Griffin, S. K. Spear, and R. D. Rogers, "Towards Greener Environmental Remediation: Use of Aqueous Biphasic Extraction Chromatographic Resins (ABEC®) for Perchlorate Removal," Presented by M. Dilip before the joint meeting of the 2nd International Conference on Green and Sustainable Chemistry and the 9th Annual Green Chemistry and Engineering

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 76

IPR2020-00770
United Therapeutics EX2007
Page 3626 of 7335

Conference – Taking Measure of Green Progress: Opportunities to Meet Global Challenges (2005), Washington, DC; Abstract 82.

567. R. P. Swatloski, J. H. Poplin, D. T. Daly, A. Haque, C. Mobley, and R. D. Rogers, "Functional Bio-polymer Matrix Composites via Ionic Liquid Solution Routes," Presented by R. P. Swatloski before the joint meeting of the 2nd International Conference on Green and Sustainable Chemistry and the 9th Annual Green Chemistry and Engineering Conference – Taking Measure of Green Progress: Opportunities to Meet Global Challenges (2005), Washington, DC; Abstract 264.
568. V. A. Cocalia, M. P. Jensen, J. D. Holbrey, and R. D. Rogers, "The Challenges of Using Ionic Liquids as a New Media for Metal Ion Separations," Presented by V. A. Cocalia before the 24th Rare Earth Research Conference (2005), Keystone, CO; Abstract D-5, p 27.
569. D. A. Dixon, K. Gutowski, R. Rogers, S. Li, N. Shah, P. Keenum, W. deJong, T. L. Windus, and A. Felmy, "Computational Approaches to Lanthanide and Actinide Chemistry for Environmental Remediation," Presented by D. A. Dixon before the 24th Rare Earth Research Conference (2005), Keystone, CO; Abstract F-5, p 37.
570. N. J. Bridges, K. E. Gutowski, S. K. Spear, and R. D. Rogers, "Partitioning Studies of Pertechnetate Salts in Aqueous Biphasic Systems Formed by Contact of Ionic Liquids Solutions with Solutions of Kosmotropic Salts," Presented by N. J. Bridges before the 24th Rare Earth Research Conference (2005), Keystone, CO; Abstract P3-01, p 118.
571. A. Haque, D. T. Daly, R. D. Rogers, C. Mobley, and R. P. Swatloski, "Effects of MAPP as Coupling Agent on the Performance of Cellulose/Polypropylene Laminated Composites," Presented by A. Haque at the 3rd International Conference on Eco-Composites (2005), Royal Institute of Technology, Stockholm, Sweden.
572. R. D. Rogers, "Designer Ionic Liquids Enabling Sustainable Technologies," Presented by R. D. Rogers at the Japan IL workshop July 15, 2005; Abstract. (Invited Presentation).
573. R. D. Rogers and V. Cocalia, "Separations Using Ionic Liquids: Multiple Uses/Multiple Mechanisms," Presented by R. D. Rogers at the 7th International Symposium on Molten Salts Chemistry & Technology (2005), Toulouse, France; Abstract - Proceedings Vol. II, p 1003.
574. R. D. Rogers, "Designer Ionic Liquids Enabling Sustainable Technologies," Presented by R. D. Rogers at the 7th International Symposium on Molten Salts Chemistry & Technology (2005), Toulouse, France; Abstract - Proceedings Vol. I, p 59. (Invited Plenary Presentation)
575. R. D. Rogers, J. D. Holbrey, and S. K. Spear, "Green Chemistry and Applications of Ionic Liquids: Enabling Sustainable Technologies for Advanced New Materials," Presented by R. D. Rogers before the European Congress on Advanced Materials and Processes, EUROMAT 2005 (2005), Prague, Czech Republic; Abstract Symposium D52. (Keynote Lecture)
576. V. A. Cocalia, J. D. Holbrey, K. E. Gutowski, N. J. Bridges, and R. D. Rogers, "Separations of Metal Ions Using Ionic Liquids: The Challenges of Multiple Mechanisms," Presented by R. D. Rogers before the International Solvent Extraction Conference "Solvent Extraction for Sustainable Development" ISEC 2005 (2005), Beijing, China; Abstract A111. (Keynote Lecture)
577. R. D. Rogers, "Applications of Green Chemistry in a Recycling Economy," Presented by R. D. Rogers before the 7th World Congress on Recovery, Recycling and Re-integration (2005), Beijing, China; Abstract Book Page II. (Plenary Lecture)
578. R. D. Rogers, N. J. Bridges, J. G. Huddleston, K. E. Gutowski, and S. K. Spear, "Salt/Salt Aqueous Biphasic Systems Formed by Solutions of Ionic Liquids and Kosmotropic Salts," Presented by R. D. Rogers before the Fourteenth Symposium on Separations Science and Technology for Energy Applications (2005), Gatlinburg, TN, Abstract Book p 37. (Invited Presentation).
579. N. J. Bridges, J. G. Huddleston, S. K. Spear, and R. D. Rogers, "Utilization of Salt/Salt Aqueous Biphasic Systems Formed by Solutions of Ionic Liquids and Kosmotropic Salts for the Extraction of Fission Products," Presented by N. J. Bridges before the Fourteenth Symposium on Separations Science and Technology for Energy Applications (2005), Gatlinburg, TN, Abstract Book p 15.
580. V. A. Cocalia, S. K. Spear, and R. D. Rogers, "$^{99}TcO_4^-$ Extraction from Aqueous Media by XAD-7 Resin Coated with CYPHOS IL101 and CYPHOS IL104 Ionic Liquids," Presented by V. A. Cocalia before the Fourteenth Symposium on Separations Science and Technology for Energy Applications (2005), Gatlinburg, TN, Abstract Book p 16.
581. K. E. Gutowski, R. D. Rogers, and D. A. Dixon, "DFT Studies of the Complexation Behavior of Phosphates and Silicates with Actinide and Fission Product Cations," Presented by K. E. Gutowski before the Fourteenth Symposium on Separations Science and Technology for Energy Applications (2005), Gatlinburg, TN, Abstract Book p 20.
582. S. T. Griffin, S. K. Spear, W. M. Reichert, and R. D. Rogers, "Liquid-Liquid Extractions Using Renewable Plant-Based Soybean Oil as Alternatives to Organic Solvents," Presented by S. T. Griffin before the Fourteenth Symposium on Separations Science and Technology for Energy Applications (2005), Gatlinburg, TN, Abstract Book p 31.
583. J. H. Davis, Jr., R. D. Rogers, S. Griffin, M. Tickell, and P. Fox, "Task-Specific Ionic Liquids (TSIL) for Separations Applications," Presented J. H. Davis, Jr. before the Fourteenth Symposium on Separations Science and Technology for Energy Applications (2005), Gatlinburg, TN, Abstract Book p 39.
584. R. D. Rogers, "Designer Ionic Liquids Enabling Sustainable Technologies," Presented by R. D. Rogers before the 6th Inha ERC International Symposium "Application of Ionic Liquids in Chemical Engineering" (2005), Incheon, Korea, Abstract book p 6. (Invited Keynote Speaker).
585. R. D. Rogers, "Green (or Not) Ionic Liquids to Access Biorenewable Polymer Materials," Presented by R. D. Rogers before the Joint US-Japan Workshop on Sustainable Chemical Synthesis (2005), Honolulu, HI (Invited Speaker).
586. R. D. Rogers, C. Mobely, R. P. Swatloski, J. H. Poplin, D. T. Daly, and A. Haque, "Cellulose-based composites prepared from ionic liquids: Affordable materials for industrial applications," Presented by R. D. Rogers before the 2005 International

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 77

IPR2020-00770
United Therapeutics EX2007
Page 3627 of 7335

Chemical Congress of Pacific Basin Societies, Pacifichem 2005 (2005), Honolulu, HI, Abstract AGRO 391. (Invited Presentation)

587. R. M. Broughton, G. Shen, J. Lee, U. Cho, R. Swatloski, and R. D. Rogers, "Extrusion of composite fibers and films," Presented by R. M. Broughton before the 2005 International Chemical Congress of Pacific Basin Societies, Pacifichem 2005 (2005), Honolulu, HI, Abstract ENVR 883. (Invited Presentation)
588. R. D. Rogers, R. P. Swatloski, S. K. Spear, and D. T. Daly, "Designer ionic liquids enabling sustainable technologies," Presented by R. D. Rogers before the 2005 International Chemical Congress of Pacific Basin Societies, Pacifichem 2005 (2005), Honolulu, HI, Abstract ENVR 894. (Invited Presentation)
589. R. D. Rogers, R. P. Swatloski, J. H. Poplin, V. A. Cocalia, and N. J. Bridges, "Cellulosic materials containing lanthanide complexes: ionic liquid routes to new materials," Presented by R. D. Rogers before the 2005 International Chemical Congress of Pacific Basin Societies, Pacifichem 2005 (2005), Honolulu, HI, Abstract INOR 803. (Invited Presentation)
590. A. Wierzbicki, J. Davis, R. D. Rogers, E. A. Salter, M. Reichert, S. Griffin, E. A. Cioffi, P. A. Fox, B. Wicker, A. Smith, M. Tickell, "Boron, but not boring: Boronium ions and their use in ionic liquids," Presented by A. Wierzbicki before the 2005 International Chemical Congress of Pacific Basin Societies, Pacifichem 2005 (2005), Honolulu, HI, Abstract ENVI 769.
591. R. D. Rogers, M. Smiglak, D. W. Drab, W. M. Reichert, K. E. Gutowski, T. Wilson, A Vincek, D. Zhang, H. Fang, K. Kirischenko, S. Singh, and A. R. Katritzky, "Energetic Ionic Liquids: Fundamental Studies Relating Target Structures and Key Physical Properties," Presented by R. D. Rogers before Air Force Office of Scientific Research Ionic Liquids Research Workshop (2006), Tuscaloosa, AL.
592. A Vincek, D. Zhang, H. Fang, K. Kirischenko, S. Singh, A. R. Katritzky, J. D. Holbrey, , M. Smiglak, W. M. Reichert, S. K. Spear, and R. D. Rogers, "In search of Energetic Ionic Liquids," Presented by K. Kirischenko before Air Force Office of Scientific Research Ionic Liquids Research Workshop (2006), Tuscaloosa, AL.
593. R. D. Rogers, "Designer Ionic Liquids Enabling Sustainable Technologies," Presented by R. D. Rogers, before the Chemical Engineering Students Society VII International Chemical Engineering Congress (2006), Monterrey, Mexico. (Invited Plenary Presentation)
594. C. C. Hines, W. M. Reichert, S. T. Griffin, T. Morgan, and R. D. Rogers, "Ionic liquids as solvents for metal-ligand complexation," Presented by C. C. Hines before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
595. M. Dilip, N. J. Bridges, and R. D. Rogers, "Influence of Temperature on Phase Diagrams and Partitioning of Alcohols in Salt/Salt ABS," Presented by M. Dilip before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
596. J. H. Poplin, R. Swatloski, J. Holbrey, S. Spear, and R. Rogers, "Development of Cellulose Based Dip-and-Read Test Strips for Hg^{2+} Detection," Presented by J. H. Poplin before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
597. M. Smiglak, D. M. Drab, T. Wilson, W. M. Reichert, R. D. Rogers, H. Yang, D. Zhang, K. Kirichenko, and A. R. Katritzky, "Strategies Toward the Design of Energetic Ionic Liquids: Nitro- and Nitrile Substituted Imidazolium Salts," Presented by M. Smiglak before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
598. M. Smiglak, D. M. Drab, T. Wilson, W. M. Reichert, R. D. Rogers, H. Yang, D. Zhang, K. Kirichenko, and A. R. Katritzky, "Strategies Toward the Design of Energetic Ionic Liquids: Azolate-Based Salts," Presented by M. Smiglak before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
599. M. Smiglak, W. M. Reichert, S. T. Griffin, J. D. Holbrey, R. D. Rogers, K. Kirichenko, D. Zhang, and A. R. Katritzky, "Ionic liquids via reaction of the zwitterion 1,3-dimethylimidazolium-2-carboxylate with protic acids," Presented by M. Smiglak before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
600. M. Smiglak, W. M. Reichert, J. D. Holbrey, L. Sun, J. S. Thrasher, R. D. Rogers, and J. S. Wilkes, "Combustible ionic liquids by design: Destroying another ionic liquid myth," Presented by M. Smiglak before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
601. K. E. Gutowski, J. D. Holbrey, D. A. Dixon, and R. D. Rogers, "Prediction of the Formation and Stabilities of Energetic Salts and Ionic Liquids Based on Ab Initio Electronic Structure Calculations," Presented by K. E. Gutowski before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
602. N. J. Bridges and R. D. Rogers, "Fundamental Studies of Chaotropic Salts (e.g., Ionic Liquids) and Kosmotropic Salts in the Formation of Salt/Salt Aqueous Biphasic Systems," Presented by N. J. Bridges before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
603. V. A. Cocalia, S. T. Griffin, and R. D. Rogers, "Ionic Liquids in Actinide Chemistry," Presented by V. A. Cocalia before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
604. W. L. Hough, T. Wilson, M. Smiglak, J. Pernak, S. K. Spear, J. H. Davis, Jr., and R. D. Rogers, "Ionic Liquids: The Next Generation of Sweeteners," Presented by W. L. Hough before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL.
605. R. D. Rogers, "ILs as Technical Materials, Literature, and Choice," Presented before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL. (Organizer).
606. R. D. Rogers, "Separations and Energetic Materials," Presented before the Ionic Liquids Workshop: Background, State-of-the-Art, and Academic/Industrial Applications (2006), Tuscaloosa, AL. (Organizer).

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 78

IPR2020-00770
United Therapeutics EX2007
Page 3628 of 7335

607. M. Smiglak, W. M. Reichert, J. D. Holbrey, J. S. Wilkes, L. Sun, J. S. Thrasher, and R. D. Rogers, "Combustible ionic liquids by design: Destroying another ionic liquid myth," Presented by M. Smiglak before the 231st ACS National Meeting (2006), Atlanta, GA, Abstract I&EC 103.
608. M. Smiglak, W. M. Reichert, S. T. Griffin, J. D. Holbrey, R. D. Rogers**,** K. Kirichenko, D. Zhang, and A. R. Katritzky, "Ionic liquids via reaction of the zwitterion 1,3-dimethylimidazolium-2-carboxylate with protic acids," Presented by M. Smiglak before the 231st ACS National Meeting (2006), Atlanta, GA, Abstract I&EC 104.
609. C. C. Hines, W. M. Reichert, S. T. Griffin, and R. D. Rogers**,** "Ionic liquid mediated metal-ligand complexation," Presented by C. C. Hines before the 231st ACS National Meeting (2006), Atlanta, GA, Abstract I&EC 105.
610. W. Hough, T. Wilson, M. Smiglak, J. Pernak, S. K. Spear, J. H. Davis Jr., and R. D. Rogers**,** "Ionic liquids: The next generation of sweeteners," Presented by W. Hough before the 231st ACS National Meeting (2006), Atlanta, GA, Abstract I&EC 106.
611. R. C. Remsing, D. A. Fort, R. P. Swatloski, P. Moyna, R. D. Rogers**,** and G. Moyna, "Use of ionic liquids for the processing and analysis of lignocellulosic materials," Presented by G. Moyna before the 231st ACS National Meeting (2006), Atlanta, GA, Abstract I&EC 151.
612. R. P. Swatloski, R. M. Broughton, G. Moyna, D. T. Daly, S. K. Spear, and R. D. Rogers, "How understanding the ionic liquid/cellulose dissolution mechanism can guide the generation of advanced cellulose-based materials," Presented by R. P. Swatloski before the 231st ACS National Meeting (2006), Atlanta, GA, Abstract I&EC 204.
613. J. H. Davis Jr., A. Smith, M. Tickell, R. D. Rogers, W. M. Reichert, S. T. Griffin, A. Wierzbicki, and E. A. Salter, "Boronium ion based ionic liquids: Surprises abound," Presented by J. H. Davis, Jr. before the 231st ACS National Meeting (2006), Atlanta, GA, Abstract I&EC 220.
614. R. C. Remsing, D. A. Fort, R. P. Swatloski, P. Moyna, R. D. Rogers, and G. Moyna, "Green solvents gone bananas: Use of ionic liquids for the processing and analysis of biomass," Presented by G. Moyna before the 231st ACS National Meeting (2006), Atlanta, GA, Abstract I&EC 244.
615. J. H. Davis Jr., M. Tickell, R. D. Rogers, W. M. Reichert, and S. T. Griffin, "New task-specific ionic liquids incorporating amine groups and their use for reactive capture," Presented by J. H. Davis, Jr. before the 231st ACS National Meeting (2006), Atlanta, GA, Abstract I&EC 280.
616. R. D. Rogers, "Designer Ionic Liquids Enabling Sustainable Technologies," Presented by R. D. Rogers before the 2nd Australian Symposium on Ionic Liquids (2006), Melbourne, Australia, Abstract Book. (Invited Plenary Speaker).
617. R. D. Rogers and W. M. Reichert, "Approaches to crystallization from ionic liquids: complex solvents-complex results – or – A strategy for controlled formation of new supramolecular architectures?" Presented by R. D. Rogers before the 89th Canadian Chemical Congress (2006), Halifax, Nova Scotia, Canada, Abstract 0338. (Invited Symposium Presentation)
618. J. Fortunak, F. Ohwoavworhua, O. Kunle, R. P. Swatloski, and R. D. Rogers, "Valuable products from Nigerian elephant sawgrass," Presented by J. Fortunak before the 10th Annual Green Chemistry and Engineering Conference (2006), Washington, D.C.
619. D. G. Whitten, L. V. Interrante, P. V. Kamat, and R. D. Rogers, "The Peer Review Process," Panel Presentation at the Institute of Chemistry of the Chinese Academy of Science Workshop on the Frontiers of Molecular Sciences & Symposium on Scholarly Publishing for Celebrating the 50th Anniversary of the Foundation of ICCAS (2006), Beijing, China, Abstract. (Invited Presentation)
620. R. D. Rogers, L. V. Interrante, P. V. Kamat, and D. G. Whitten, "Getting Involved in the Scientific Publishing Process; What Does it Take?," Panel Presentation (Led by R. D. Rogers) at the Institute of Chemistry of the Chinese Academy of Science Workshop on the Frontiers of Molecular Sciences & Symposium on Scholarly Publishing for Celebrating the 50th Anniversary of the Foundation of ICCAS (2006), Beijing, China, Abstract. (Invited Presentation)
621. L. V. Interrante, P. V. Kamat, R. D. Rogers, and D. G. Whitten, "What Constitutes Publishable Science," Panel Presentation at the Institute of Chemistry of the Chinese Academy of Science Workshop on the Frontiers of Molecular Sciences & Symposium on Scholarly Publishing for Celebrating the 50th Anniversary of the Foundation of ICCAS (2006), Beijing, China, Abstract. (Invited Presentation)
622. R. D. Rogers, "Green Chemistry and Applications of Ionic Liquids as Crystallization Solvents: Complex Solvents-Complex Results – or – A Strategy for Controlled Formation of New Supramolecular Architectures?," Presented by R. D. Rogers before the Institute of Chemistry of the Chinese Academy of Science Workshop on the Frontiers of Molecular Sciences & Symposium on Scholarly Publishing for Celebrating the 50th Anniversary of the Foundation of ICCAS (2006), Beijing, China, Abstract. (Invited Presentation)
623. D. G. Whitten, L. V. Interrante, P. V. Kamat, and R. D. Rogers, "The Peer Review Process," Panel Presentation at the 25th Chinese Chemical Society Congress (2006), Changchun, China, Abstract 20-I-002. (Invited Presentation)
624. R. D. Rogers, L. V. Interrante, P. V. Kamat, and D. G. Whitten, "Getting Involved in the Scientific Publishing Process; What Does it Take?," Panel Presentation (Lead by R. D. Rogers) at the Panel Presentation at the 25th Chinese Chemical Society Congress (2006), Changchun, China, Abstract 20-I-001. (Invited Presentation)
625. L. V. Interrante, P. V. Kamat, R. D. Rogers, and D. G. Whitten, "What Constitutes Publishable Science," Panel Presentation at the Panel Presentation at the 25th Chinese Chemical Society Congress (2006), Changchun, China, Abstract 20-I-003. (Invited Presentation)
626. R. D. Rogers, "Green Chemistry and Applications of Ionic Liquids as Crystallization Solvents: Complex Solvents-Complex Results – or – A Strategy for Controlled Formation of New Supramolecular Architectures?," Presented by R. D. Rogers before the 25th Chinese Chemical Society Congress (2006), Changchun, China, Abstract 01-I-004. (Invited Presentation)

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 79

IPR2020-00770
United Therapeutics EX2007
Page 3629 of 7335

627. A. Haque, C. Mobeley, D. T. Daly, R. D. Rogers, R. P. Swatloski, and A. Ramasetty, "Effects of MAPP as Coupling Agent on the performance of Regenerated Cellulose Film Reinforced Polypropylene Composites," Presented by A. Haque before the American Society for Composites 21st Annual Technical Conference (2006), Dearborn, MI.
628. J. Fortunak, F. Ohwoavworhua, O. Kunle, and R. D. Rogers, "Valuable products from Nigerian elephant sawgrass," Presented by J. Fortunak before the 10th Annual Green Chemistry & Engineering Conference 'Designing for a Sustainable Future' (2006), Washington, DC, Abstract 145.
629. C. C. Hines, M. Smiglak, W. M. Reichert, S. T. Griffin, and R. D. Rogers, "Crystal engineering utilizing ionic liquids," Presented by C. C. Hines before the 232nd ACS National Meeting (2006), San Francisco, CA, Abstract PHYS 552.
630. R. P. Planalp, G. Lu, D. P. Kennedy, M. W. Brechbiel, R. D. Rogers, R. Ma, F. M. Torti, and S. V. Torti, "The metal-complexation properties of cytotoxic tripodal hexadentate chelators: Effects of heterocycle donor arms on Fe(II) chelation and fibroblast IC50 value," Presented by R. P. Planalp before the 232nd ACS National Meeting (2006), San Francisco, CA, Abstract MEDI 260.
631. M. Smiglak, C. C. Hines, T. Wilson, W. M. Reichert, S. T. Griffin, R. D. Rogers, K. Kirichenko, S. Singh, and A. Vincek, "Ionic liquids based on azole anions," Presented by M. Smiglak before the 232nd ACS National Meeting (2006), San Francisco, CA, Abstract PHYS 555.
632. M. Smiglak, D. M. Drab., C. C. Hines, W. M. Reichert, R. D. Rogers, K. Kirichenko, and A. Vincek, "Halide free synthesis of energetic azolium azolate salts," Presented by M. Smiglak before the 232nd ACS National Meeting (2006), San Francisco, CA, Abstract PHYS 522.
633. W. M. Reichert, J. D. Holbrey, K. B. Vigour, T. D. Morgan, G. A. Broker, S. T. Griffin, C. C. Hines, and R. D. Rogers, "Stepping stones and stumbling blocks for the utilization of ionic liquids as crystallization solvents," Presented by W. M. Reichert before the 232nd ACS National Meeting (2006), San Francisco, CA, Abstract PHYS 098.
634. N. J. Bridges, and R. D. Rogers "Investigation into ion-pairing of 1-butyl-3-methylimidazolium chloride in aqueous media," Presented by N. J. Bridges before the 232nd ACS National Meeting (2006), San Francisco, CA, Abstract PHYS 059.
635. N. J. Bridges, M. Smiglak, and R.D. Rogers "Synthesis of hydrogen carbonate ionic liquids through the Krapcho reaction," Presented by N. J. Bridges before the 232nd ACS National Meeting (2006), San Francisco, CA, Abstract I&EC 082.
636. R. D. Rogers and W. M. Reichert, "Approaches To Crystallization From Ionic Liquids: Complex Solvents-Complex Results – Or – A Strategy For Controlled Formation Of New Supramolecular Architectures," Presented by R. D. Rogers before the EUCHEM Conferences on Molten Salts and Ionic Liquids (2006), Hammamet, Tunisia, Abstract Book p 82.
637. R. D. Rogers, "Green Chemistry and Applications of Ionic Liquids as Solvents: Enabling Sustainable Technologies for New Advanced Materials," Presented by R. D. Rogers before XVI Congresso Brasileiro de Engenharia Química - COBEQ (2006), Santos, Brazil, Abstract Book p 12. (Invited Plenary Presentation)
638. R. D. Rogers, V. A. Cocalia, L. Nunez "Crystallization of Actinide Complexes from Ionic Liquids", Presented by R. D. Rogers before the 15th International Symposium on Molten Salts part of the 2006 Joint International Meeting (210th Meeting of the Electrochemical Society Meeting/XXI Congreso de la Sociedad Mexicana de Electroquímica (2006), Cancun, Mexico, Abstract 1989.
639. C. C. Hines, W. M. Reichert, S. T. Griffin, and R. D. Rogers, "Crystallization of new and interesting crystal structures in ionic liquids: Complex systems with complex results," Presented by C. C. Hines before the 15th International Symposium on Molten Salts part of the 2006 Joint International Meeting (210th Meeting of the Electrochemical Society Meeting/XXI Congreso de la Sociedad Mexicana de Electroquímica (2006), Cancun, Mexico, Abstract 2021.
640. M. Smiglak, M. Dilip, N. J. Bridges, W. M. Reichert, and R. D. Rogers, "Formation of ionic liquid eutectic mixtures as a tool for melting point depression." Poster presented by M. Smiglak before the 15th International Symposium on Molten Salts part of the 2006 Joint International Meeting (210th Meeting of the Electrochemical Society Meeting/XXI Congreso de la Sociedad Mexicana de Electroquímica (2006), Cancun, Mexico, Abstract 70 and 2022.
641. J. H. Poplin, D. Rudkevich, R. P. Swatloski, and R. D. Rogers, "Development of Liquid Membranes for NO_x Gas Detection and Storage Utilizing Calix[4]Arenes in Ionic Liquids," Presented by J. H. Poplin before the 15th International Symposium on Molten Salts part of the 2006 Joint International Meeting (210th Meeting of the Electrochemical Society Meeting/XXI Congreso de la Sociedad Mexicana de Electroquímica (2006), Cancun, Mexico, Abstract 83.
642. R. P. Swatloski, R. P. Broughton, N. Sun, M. Maxim, D. T. Daly, S. K. Spear, and R. D. Rogers, "A Look at Ionic Liquid Generated Cellulose and Modified Cellulose Fibers," Presented by R. P. Swatloski before the 15th International Symposium on Molten Salts part of the 2006 Joint International Meeting (210th Meeting of the Electrochemical Society Meeting/XXI Congreso de la Sociedad Mexicana de Electroquímica (2006), Cancun, Mexico, Abstract 1970.
643. R. D. Rogers, "What are Ionic Liquids," Presented by R. D. Rogers before the Intertech Pira Conference *Ionic Liquids: Technical Innovations, Emerging Markets and Applications* (2006), Orlando, FL, Abstract Book. (Co-Chair of the meeting)
644. R. D. Rogers, "Have You Considered the Unique Potential of Ionic Liquids as Crystallization Solvents?" Presented by R. D. Rogers before the ACS ProSpectives Series: *Crystallization Process Development: Case Studies & Research* (2007), Boston, MA.
645. R.D. Rogers and M. A. Abraham, "A 'Green' Industrial Revolution is in Our Future," Presented by R. D. Rogers and M. A. Abraham before the 233rd ACS National Meeting (2007), Chicago, IL, Abstract I&EC 046. (Invited Presentation)
646. J. H. Poplin, D. M. Rudkevich, and R. D. Rogers, "New Platforms for Immobilization of Calixarenes for Gas-Sensing and Trapping," Presented by R. D. Rogers before the 233rd ACS National Meeting (2007), Chicago, IL, Abstract I&EC 042. (Invited Presentation)

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 80

IPR2020-00770
United Therapeutics EX2007
Page 3630 of 7335

647. R.D. Rogers, N. J. Bridges, V. A. Cocalia, and K. E. Gutowski, "Separations, coordination, and solvation of f-elements in ionic liquids," Presented by R. D. Rogers before the 233rd ACS National Meeting (2007), Chicago, IL, Abstract NUCL 066. (Invited Presentation)
648. Sun, N.; Swatloski, R. P.; Maxim, M. L.; Broughton, Jr., R. M.; Spear, S. K.; Daly, D. T.; Haque, A.; Harland, A. G.; Rogers, R. D. "Cellulose Fibers Prepared from Direct Dissolution of Cellulose in Ionic Liquids," 4th International Conference of Textile Research Division National Research Centre, Cairo, Egypt; Textile Processing: State of the Art & Future Developments (2007), Abstract Page 16. Invited presentation, not presented due to illness.
649. R. D. Rogers, "The Evolution of Ionic Liquids: From Solvents to Materials to??? (and the New Business Opportunities that Follow)," Presented by R. D. Rogers before the Queen's University Ionic Liquid Laboratory 'Ionic Liquid Week' (2007), Belfast, Northern Ireland. (Invited Presentation)
650. R. D. Rogers, D. M. Drab, and M. Smiglak, "Ionic Liquids as a Unique and Versitile Platform for the Synthesis and Delivery of Energetic Materials," Presented by R. D. Rogers before the 54th Joint Army-Navy-NASA_Air Force (JANNAF) Propulsion Meeting (2007), Denver, CO, Program Booklet page 62.
651. R. D. Rogers "A Green Industrial Revolution is in Our Future," Presented by R. D. Rogers before the Licensing Executives Society Spring Meeting (2007), Atlanta, GA.
652. R. D. Rogers, "A 'Green' Industrial Revolution is in Our Future: Are Ionic Liquids Pointing the Way?," Presented by R. D. Rogers before the 11th Annual Green Chemistry and Engineering Conference: "From Small Steps to Giant Leaps – Breakthrough Innovations for Sustainability" (2007), Washington, DC; Abstract 15. (Invited Plenary Presentation)
653. R. D. Rogers, "Task-Specific Ionic Liquids: What Does this Term Really Mean," Presented by R. D. Rogers before the International Symposium on Task-Specific Ionic Liquids (2007), Keio University, Yokohama, Japan, Abstract p 2. (Invited Presentation)
654. S. Schneider, T. Hawkins, M. Rosander, R. Rogers, D. Drab, M. Smiglak, and A. Vij "From Halides to Azides – Novel Ionic Liquid Azides as Energetic Materials," Presented by S. Schneider before the 2nd International Congress on Ionic Liquids (COIL-2) (2007), Yokohama, Japan, Abstract 2P03-43.
655. C. Rijksen, M. Rahman, Y. Qin, N. Sun, M. Maxim, and R. D. Rogers, "Biomass: Dissolution, Separation, and Applications Enabled by Ionic Liquids," Presented by C. Rijksen before the 2nd International Congress on Ionic Liquids (COIL-2) (2007), Yokohama, Japan, Abstract 1P04-055.
656. M. Smiglak, C. C. Hines, N. J. Bridges, D. M. Drab, and R. D. Rogers, "New Precursors for the Halide Free Synthesis of Ionic Liquids Utilizing the Chemistry of Dimethylcarbonate," Presented by M. Smiglak before the 2nd International Congress on Ionic Liquids (COIL-2) (2007), Yokohama, Japan, Abstract 1P03-047.
657. M. Smiglak, C. C. Hines, D. M. Drab, and R. D. Rogers "Novel Energetic Ionic Liquid Materials Composed Solely of C, H, N, and O," Presented by M. Smiglak before the 2nd International Congress on Ionic Liquids (COIL-2) (2007), Yokohama, Japan, Abstract 2P06-066.
658. A. Metlen, C. Rijksen, W. L. Hough, M. Smiglak, H. Rodríguez, R. P. Swatloski, S. K. Spear, D. T. Daly, J. Pernak, J. E. Grisel, R. D. Carliss, M. D. Soutullo, J. H. Davis, Jr., and R. D. Rogers, "Ionic Liquids as Active Pharmaceutical Ingredients Exemplified by Lidocaine Docusate," Presented by A. Metlen before the 2nd International Congress on Ionic Liquids (COIL-2) (2007), Yokohama, Japan, Abstract 1P09-094.
659. D. R. MacFarlane, P. M. Dean, J. Turanjanin, J. L. Scott, W. L. Hough, M. Smiglak, H. Rodríguez, R. P. Swatloski, S. K. Spear, D. T. Daly, J. Pernak, J. E. Grisel, R. D. Carliss, M. D. Soutullo, J. H. Davis, Jr., and R. D. Rogers, "'Drug'" Ionic Liquids - A New Phase for the Pharmaceutical World," Presented by D. R. MacFarlane before the 2nd International Congress on Ionic Liquids (COIL-2) (2007), Yokohama, Japan, Abstract PL9.
660. R. D. Rogers, M. Smiglak, W. L. Hough, A. Metlen, H. Rodríguez, R. P. Swatloski, S. K. Spear, D. T. Daly, J. Pernak, J. E. Grisel, R. D. Carliss, M. D. Soutullo, J. H. Davis, Jr., J. L. Scott, D. R. MacFarlane, "The Evolution of Ionic Liquids - From Solvents and Separations to Advanced Materials to Pharmaceuticals: Energetic and API Examples from the Ionic Liquid Cookbook," Presented by R. D. Rogers before the 2nd International Congress on Ionic Liquids (COIL-2) (2007), Yokohama, Japan, Abstract LMA1. (Invited Lecture)
661. R. D. Rogers, "The Third Evolution of Ionic Liquids: Physical to Chemical to Biological Properties," Presented by R. D. Rogers before the International Symposium on Ionic Liquids and Life Sciences (2007), Yokohama, Japan. (Invited Keynote Lecture)
662. R. D. Rogers, M. Rahman, N. Sun, M. L. Maxim, G. Moyna, and P. Moyna, "Utilizing Ionic Liquids for Access to and Modification of Bio-renewable Polymers," Presented by A. Metlen (R. Rogers was delayed by air travel difficulties) before Europacat VIII (2007), Turku, Finland, Abstract K12-2. (Invited (Rogers) Keynote Address)
663. R. D. Rogers, "What are Ionic Liquids (ILs)?," Presented by R. D. Rogers before the Intertech Pira Conference *Ionic Liquids: Technical Innovations, Emerging Markets and Applications* (2007), Prague, Czech Republic, Abstract Book. (Invited Talk and Chair of the meeting)
664. R. D. Rogers, "Approaches to Crystallization From Ionic Liquids: Complex Solvents-Complex Results – or – A Strategy for Controlled Formation of New Supramolecular Architectures?" Presented before the 5th Chinese National Symposium on Structural Chemistry and Symposium on Chinese Strategy of *Crystal Growth & Design* (2007), Fuzhou, China, Abstract PL-03. (Invite Plenary Presentation)
665. R. D. Rogers, "Getting Involved in the Scientific Publishing Process with *Crystal Growth & Design*: What Does It Take?" Presented before the 5th Chinese National Symposium on Structural Chemistry and Symposium on Chinese Strategy of *Crystal Growth & Design* (2007), Fuzhou, China, Abstract PL-10. (Invite Plenary Presentation)

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 81

IPR2020-00770
United Therapeutics EX2007
Page 3631 of 7335

666. R. D. Rogers, "Separations, coordination, and solvation of f-elements in ionic liquids," Presented by R. D. Rogers before the 59th Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy (2008), New Orleans, LA, Abstract 300-3. (Invited Symposium Presentation)
667. R. D. Rogers, "Green Chemistry and the New Transformational Platform Technologies Needed to Meet the Goals of Sustainability," Presented by R. D. Rogers before the Workshop in Green Chemistry Production of Essential Medicines in Developing Countries (2008), Abuja, Nigeria, No Abstract. (Invited Presentation)
668. R. D. Rogers, "Cracking Hydrocarbons: Direct Dissolution and Processing of Cellulosic and Related Biomass with Ionic Liquids Leading to New Materials," Presented by R. D. Rogers before the Workshop in Green Chemistry Production of Essential Medicines in Developing Countries (2008), Abuja, Nigeria, No Abstract. (Invited Presentation.
669. R. D. Rogers, M. Rahman, Y. Qin, N. Sun, M. L. Maxim, S. K. Spear, S. K. Mroczynski, and D. T. Daly, "New or Enhanced Materials from Biomass Utilizing the Unique Property Sets of Ionic Liquids," Presented by R. D. Rogers before the Materials Research Society Spring Meeting (2008), San Francisco, CA, Abstract Q1.1. (Invited Presentation)
670. N. Sun, R. P. Swatloski, M. L. Maxim, M. Rahman, A. G. Harland, A. Haque, S. K. Spear, D. T. Daly, and R. D. Rogers, "Cellulose Composite Fibers Prepared from Ionic Liquid-Based Solution," Presented by N. Sun before the 235th ACS meeting (2008), New Orleans, LA, Abstract CELL 285.
671. R. D. Rogers, M. Dilip, N. J. Bridges, M. Smiglak, D. B. Cordes, and K. Materna, "Utilization of hydrophilic ionic liquids in separations: Understanding and taming complexity," Presented by R. D. Rogers before the 235th ACS meeting (2008), New Orleans, LA, Abstract I&EC 078 (Invited Presentation).
672. R. D. Rogers, M. Rahman, Y. Qin, N. Sun, and M. L. Maxim, "Dissolution and processing of cellulosic and related biomass with ionic liquids: Fundamentals and applications," Presented by R. D. Rogers before the 235th ACS meeting (2008), New Orleans, LA, Abstract CELL 164 (Invited Presentation).
673. R. D. Rogers, "The Evolution of Ionic Liquids - From Solvents and Separations to Advanced Materials and Pharmaceuticals: Examples from the Ionic Liquid Cookbook," Presented by R. D. Rogers before Current Status of Ionic Liquid Technology in Chemical Engineering Symposium; part of the Spring National Meeting of the Korean Institute of Chemical Engineering (2008), Jeju Island, Korea, Abstract C-2 p 82. (Invited presentation)
674. R. D. Rogers, "Ionic Liquids Beyond Solvents: Unprecedented Opportunities to Fine Tune Physical, Chemical, and Biological Properties," Presented by R. D. Rogers before the Gordon Research Conference on Organic Structures & Properties: Molecular Design & Supramolecular Assemblies (2008), Lucca (Barga), Italy, no abstract. (Invited Presentation)
675. R. D. Rogers, "The Nature of Ionic Liquids: Are they Green Solvent Replacements or Tunable Crystallization Agents for Proteins?" Presented by R. D. Rogers before the 12th International Conference on the Crystallization of Biological Macromolecules (2008), Cancun, Mexico, Abstract Book Page 23. (Invited Keynote Lecture)
676. R. M. Frazier, W. L. Hough-Troutman, D. T. Daly, and Robin D. Rogers, "Microencapsulation of Active Nutraceutical Ingredients for Controlled Delivery," Presented by R. M. Frazier before Particles 2008, Particle Synthesis, Characterization, and Particle-Based Advanced Materials (2008), Orlando, Florida. Abstract B1.18.
677. R. D. Rogers, "The Evolution of Ionic Liquids - From Solvents and Separations to Advanced Materials and Pharmaceuticals: Examples from the Ionic Liquid Cookbook, Presented by R. D. Rogers before the 3rd Australian Symposium on Ionic Liquids (2008), Melbourne, Australia, Abstract Book. (Invited presentation)
678. M. Smiglak and R. D. Rogers, "Protocols for halide free synthesis of ionic liquids via hydrogen carbonate precursors: Design of Ionic Liquid Energetic Materials," Presented by M. Smiglak before the 3rd Australian Symposium on Ionic Liquids (2008), Melbourne, Australia, Abstract Book.
679. W. Hough-Troutman, M. Smiglak, J. Pernak, D. T. Daly, and R. D. Rogers, "Ionic Liquids for Application in the Food Industry," Presented by W. L. Hough-Troutman before the 3rd Australian Symposium on Ionic Liquids (2008), Melbourne, Australia, Abstract Book.
680. R. D. Rogers, "The Evolution of Ionic Liquids – From Solvents and Separations to Advanced Materials and Pharmaceuticals: Examples from the Ionic Liquid Cookbook," Presented by R. D. Rogers before the Danish Chemical Society Kemisk Forenings Årsmøde (2008), Odense, Denmark, Abstract. (Invited Plenary Presentation)
681. R. D. Rogers, "Separation & Bioprocessing with Ionic Liquids," Presented by R. D. Rogers at the 1st Ionic Liquid Workshop "Ionic Liquid: The Future Solvent for Oil and Gas Industries" (2008), Glenmarie, Malaysia. (Invited Keynote Lecture)
682. R. D. Rogers, "Ionic Liquid Patents and Technology Development," Presented by R. D. Rogers at the 1st Ionic Liquid Workshop "Ionic Liquid: The Future Solvent for Oil and Gas Industries" (2008), Glenmarie, Malaysia. (Invited Keynote Lecture)
683. R. D. Rogers, Marcin Smiglak, and David M. Drab "A Modular 'Ionic Liquid' Platform for the Custom Design of Energetic Materials," Presented by R. D. Rogers at the Energetic Ionic Liquids Workshop (2008), Colorado Springs, CO; no abstract. (Invited Presentation)
684. R. D. Rogers, "Approaches to the Understanding and Utilization of Unique Ionic Liquid Properties: Physical (Solvents), Chemical (Energetic Materials), and Biological (Pharmaceuticals)," Presented by R. D. Rogers before the 20th International Conference on Chemical Thermodynamics (2008), Warsaw, Poland, Abstract IL-In-1, p 181. (Invited Lecture)
685. R. D. Rogers, "How I&EC supports innovative technologies for a sustainable future and those who will develop them," Presented by R. D. Rogers before the 236th ACS National Meeting (2008), Philadelphia, PA, Abstract PRES 005. (Invited Presentation)
686. R. D. Rogers, "Ionic liquids: Growth of a field through the eyes of the I&EC division," Presented by R. D. Rogers before the 236th ACS National Meeting (2008), Philadelphia, PA, Abstract I&EC 079. (Invited Presentation)

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 82

IPR2020-00770
United Therapeutics EX2007
Page 3632 of 7335

687. D. R. MacFarlane, J. L. Scott, and R. D. Rogers, "Drug" ionic liquids: A new phase for the pharmaceutical world," Presented D. R. MacFarlane before the 236th ACS National Meeting (2008), Philadelphia, PA, Abstract ORGN 302.
688. M. Smiglak and R. D. Rogers, "Protocols for halide free synthesis of ionic liquids via hydrogen carbonate precursors," Presented by M. Smiglak before the 236th ACS National Meeting (2008), Philadelphia, PA, Abstract I&EC 200.
689. R. D. Rogers, "From crystalline salts to ionic liquids and back again: In the hunt for novel separations," Presented by R. D. Rogers before the 236th ACS National Meeting (2008), Philadelphia, PA, Abstract I&EC 003. (Invited Presentation)
690. W. L. Hough-Troutman, M. Smiglak, J. Pernak, D. T. Daly, and R. D. Rogers, "Sweetener and antibacterial ionic liquids," Presented by W. L. Hough-Troutman before the 236th ACS National Meeting (2008), Philadelphia, PA, Abstract I&EC 183.
691. J. L. Scott, D. R. MacFarlane, P. Dean, J. Turanjanin, and R. D. Rogers, "An anticrystal engineering approach to functional ionic liquids," Presented by J. L. Scott before the 236th ACS National Meeting (2008), Philadelphia, PA, Abstract I&EC 178.
692. G. Gurau, K. Rogers, and R. D. Rogers, "Caffeine ionic liquids – dream or reality?" Presented by G. Gurau before the 236th ACS National Meeting (2008), Philadelphia, PA, Abstract I&EC 111.
693. R. D. Rogers, "What are Ionic Liquids?" Presented by R. D. Rogers at the Intensive Seminar of the Crystallization Technical Group of the Association of Powder Process Industry and Engineering (APPIE) (2008), Tokyo, Japan, Abstract Booklet. (Invited Plenary Lecture)
694. G. Gurau, V. Cocalia, and R. D. Rogers, "Separations, Coordination, and Solvation in Ionic Liquids: What is There That is Unique? Presented by R. D. Rogers at the International Solvent Extraction Conference: Solvent Extraction - Fundamentals to Industrial Applications (2008), Tucson, AZ, Abstract 266. (Invited Keynote Presentation)
695. R. D. Rogers, "Ionic Liquids and Solvent Extraction," Presented by R. D. Rogers in the Solvent Extraction Short Course at the International Solvent Extraction Conference: Solvent Extraction - Fundamentals to Industrial Applications (2008), Tucson, AZ. (Invited Instructor)
696. R. D. Rogers, J. Chen, H. L. Yang, and D. Q. Li, "Preliminary Investigation of the Kinetics of the Separation of Yttrium(III) Using Cyanex 923 and Ionic Liquids," Presented by R. D. Rogers at the International Solvent Extraction Conference: Solvent Extraction - Fundamentals to Industrial Applications (2008), Tucson, AZ, Abstract 87.
697. R. D. Rogers, "Ionic liquids for the dissolution of biomass: Where can this lead?" Presented by R. D. Rogers before the Green Solvents – Progress in Science and Application conference (2008), Friedrichshafen, Germany, Abstract Book, p 25 (Invited Keynote Presentation)
698. M. Dilip, S. T. Griffin, S. K. Spear, H. Rodríguez, and R. D. Rogers, "Aqueous biphasic extraction chromatographic (ABEC) resins based on polyethylene glycol as an alternative for the removal of perchlorate from aqueous media" Presented by H. Rodríguez before the Green Solvents – Progress in Science and Application conference (2008), Friedrichshafen, Germany, Abstract Book, p 109.
699. M. Francisco, H. Rodríguez, M. Rahman, and R. D. Rogers, "Liquid-liquid equilibria of mixtures of polyethylene glycol and ionic liquid: biphasic systems for high temperature applications" Presented by H. Rodríguez before the Green Solvents – Progress in Science and Application conference (2008), Friedrichshafen, Germany, Abstract Book, p 112.
700. R. D. Rogers, Invited Panelist at the Royal Institution of Great Britain Event "The Best President for Science" (2008), London, United Kingdom. (Invited Lecture).
701. R. D. Rogers, "Approaches to the Understanding and Utilization of Unique Ionic Liquid Properties: Physical (Solvents), Chemical (Energetic Materials), and Biological (Pharmaceuticals)," Presented by R. D. Rogers before the International Bunsen Discussion Meeting "Influence of Ionic Liquids on chemical and physicochemical reactions" (2008), Clausthal, Germany, Abstract Book p 63. (Invited Plenary).
702. R. D. Rogers, "At the Intersection of Cocrystals and Ionic Liquids," Presented by R. D. Rogers before the Indo-US Bilateral Workshop on Pharmaceutical Co-Crystals and Polymorphs (2009), Mysore, India, Abstract Book p 22. (Invited Lecture).
703. R. D. Rogers, "Getting Involved in the Scientific Publishing Process with *Crystal Growth & Design*: What Does it Take?," Presented by R. D. Rogers) at the 38th National Seminar on Crystallography (2009), Mysore, India, Abstract-Supplement to Abstract Book. (Invited Special Presentation)
704. R. D. Rogers, K. R. Seddon, M. Smiglak, and D. F. Wassell, "Ionic Liquids: Tailoring Unique, Multiply Redundant Liquids for Space Applications," Presented by R. D. Rogers before the Space, Propulsion & Energy Sciences International Forum (SPESIF-2009), Huntsville, AL Abstract Book Section W4.1.1.2.
705. R. D. Rogers, "From Green Chemistry to a 'Green' Industrial Revolution: Are Ionic Liquids Pointing the Way?," Presented by R. D. Rogers before the 237th ACS National Meeting (2009), Salt Lake City, UT, Abstract YCC 011. (Invited Presentation)
706. R. D. Rogers, S. Mroczynski, S. K. Spear, M. Rahman, N. Sun, and D. T. Daly "Utilizing the Unique Properties of Ionic Liquids to Prepare Advanced Composite Fibers," Presented by R. D. Rogers before the 6th International Conference of Textile Research Division National Research Centre, Cairo, Egypt; Textile Processing : State of the Art & Future Developments (2009), Cairo, Egypt, Abstract Book Page 9 (4/5/09). (Invited Plenary Presentation)
707. R. D. Rogers, "Ionic Liquids as Active Pharmaceutical Ingredients," Presented by R. D. Rogers before Molecules, Materials, Medicines (M3-2009) an International Conference on the Role of Materials Science and Engineering in Drug Development (2009), Santa Barbara, CA. (Invited Presentation)
708. R. D. Rogers, K. Bica, G. Gurau, M. Smiglak, H. Rodríguez, and J. Shamshina, "Ionic Liquids at the Intersections," Presented by R. D. Rogers before the 3rd International Congress on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Oral 41. (Invited Plenary Presentation)
709. K. Bica and R. D. Rogers, "Confused Ions in Ionic Liquids Pharmaceutically Active Ionic Liquids composed of Oligomers,"

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 83

IPR2020-00770
United Therapeutics EX2007
Page 3633 of 7335

Presented by K. Bica before the 3rd International Congress on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Poster 52.

710. H. Rodríguez, M. Francisco, and R. D. Rogers, "Polymer/Ionic Liquid Aqueous Biphasic Systems," Presented by H. Rodríguez before the 3rd International Congress on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Poster 158.
711. H. Rodríguez, and R. D. Rogers, "Biphasic, Non-Volatile, Liquid Mixtures of Polyethylene Glycols or Polypropylene Glycols with Hydrophilic Imidazolium Ionic Liquids," Presented by H. Rodríguez before the 3rd International Congress on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Poster 157.
712. M. F. Taha, G. Srinivasan, J. D. Holbrey, and R. D. Rogers, "Standard reduction potentials ionic liquids containing polyhalide anions ($[XY_2]^-$, where X and Y are Cl, Br, I)," Presented by M. F. Taha before the 3rd Conference on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Poster 100.
713. G. Gurau and R. D. Rogers, "At the Intersection of Cocrystals and Ionic Liquids", Presented by G. Gurau before the 3rd Congress on Ionic Liquid (COIL-3) (2009), Cairns, Australia, Abstract Poster 211.
714. M. Abai, G. Srinivasan, Y. Zou, J. D. Holbrey, R. D. Rogers, "Ionic Liquid Thiouronium Salts," Presented by M. Abai before the 3rd Conference on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Poster 323.
715. C. D. Wilfred, S. Shukla, J. D. Holbrey, R. D. Rogers, "Microwave optimized synthesis of N-butyl-N-methylpyrrolidinium methylcarbonate; a functional precursor to the diversity synthesis of ionic liquids," Presented by J. D. Holbrey before the 3rd Conference on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Poster 324.
716. W. L. Hough-Troutman, J. Shamshina, M. Smiglak, and R. D. Rogers, "The Synthesis and Characterization of Caine Ionic Liquids," Presented by W. L. Hough-Troutman before the 3rd International Congress on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Poster 325.
717. M. Huszár, A. Varga, A. Metlen, A. Horváth, T. Vántus, H. Rodríguez, M. Idei, G. Kéri, and R. D. Rogers, "Analytical and biological study of a new hydroxiquinoline-based library," Presented by M. Huszár and A. Varga before the 3rd International Congress on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Poster 326.
718. A. Metlen, R. D. Rogers, "Syntheses and characterization of dithiocarbamate salts and ionic liquids," Presented by A. Metlen before the 3rd Conference on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Poster 340.
719. A.-F. Ngomisk and R. D. Rogers, "From ferrofluids to magnetic ionic liquids: New smart fluids in separation process," Presented by A.-F. Ngomisk before the 3rd Conference on Ionic Liquids (COIL-3) (2009), Cairns, Australia, Abstract Poster 343.
720. R. D. Rogers, "Ionic Liquid Cracking of Biomass: Beyond Cellulose to Biorefineries," Presented by R. D. Rogers before the joint 9º Encontro Nacional de Química Física/1st Iberian Meeting on Ionic Liquids (2009), Aveiro, Portugal, Abstract Book p 4. (Invited Plenary Presentation)
721. R. D. Rogers, "Separations using Ionic Liquids; What is there that is unique?," Presented by R. D. Rogers before the 15th International Conference on Biopartitioning and Purification (2009), Uxbridge, UK, Abstract K-8. (Invited Keynote Presentation)
722. A. N. Lovich, J. E. Lockhard, R. L. White, M. M. Bailey, J. F. Rasco, M. B. Henson, P. L. Jernigan, J. Sturdivant, R. P. Swatloski, R. D. Rogers, and R. D. Hood, "A Comparison of the Effects of Prenatal Exposure of CD-1 Mice to Three Imidazolium-based Ionic Liquids," Teratology Society, Presented by M. M. Bailey before the 49th Annual Meeting of the Teratology Society (2009), Rio Grande, Puerto Rico, Abstract P31 (*Birth Defects Research (Part A)* **2009**, *85*, 431.
723. W. L. Hough-Troutman, C. Troutman, M. Smiglak, J. Shamshina, D. Daly, and R. Rogers, "PDH Technologies, Inc. experience in raising funds in a university environment," Presented by W. L. Hough-Troutman before the before the 238th ACS National Meeting (2009), Washington, DC, Abstract BMGT 010.
724. R. D. Rogers and N. Sun, "Ionic Liquid Cracking of Biomass: Beyond Cellulose to Biorefineries," Presented by R. D. Rogers before the Joint Conference: The 4th International Conference on Green and Sustainable Chemistry (GSC-4) & the 2nd Asian-Oceanian Conference on Green and Sustainable Chemistry (AOC-2) (2009), Beijing, China, Abstract PL-8; p. 9. (Invited Plenary Speaker)
725. R. D. Rogers, "Aspects of the Application of Ionic Liquids in the Separations of f-Elements: Coordination and Solvation," Presented by R. D. Rogers before the 7th International Conference on f-Elements ,ICfE-7 (2009), Cologne, Germany, Abstract P12. (Invited Plenary Speaker)
726. R. D. Rogers and N. Sun, "Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose," Presented by R. D. Rogers before the Sixteenth Symposium on Separation Science and Technology for Energy Applications (2009), Gatlinburg, TN, Abstract Book p. 30. (Invited Speaker)
727. H. Rodríguez, M. Francisco, M. Rahman, and R. D. Rogers, "Biphasic liquid mixtures of imidazolium-based chloride ionic liquids and polyethylene glycols," Presented by H. Rodríguez before the 24th European Symposium on Applied Thermodynamics (ESAT-24) (2009), Santiago de Compostela, Spain, Abstract Book, p. 144.
728. R. D. Rogers, "The Hidden Commercial Opportunities for Ionic Liquids" Presented by R. D. Rogers before the Intertech Pira Conference *Ionic Liquids* (2009), Miami Beach, FL, Abstract on cd. (Invited Talk and Co-Chair of the meeting)
729. R. D. Rogers and N. Sun, "Ionic Liquid Cracking of Biomass: Beyond Cellulose to Biorefineries," Presented by R. D. Rogers before Society of Environmental Toxicology and Chemistry (SETAC) North America 30th Annual Meeting (2009), New Orleans, LA, Abstract 431; p. 100. (Invited Speaker)
730. P. E. Clark, R. Boyle, J. Ku, B. Beaman, R. D. Rogers, M. Smiglak, S. Nagihara, G. Knowles, M. Bradley, M. B. Milam, "Geothermal System Designs for Lunar Surface Environment Science Activities," Presented by P. E. Clark before the Annual Meeting of the Lunar Exploration Analysis Group (LEAG 2009) (2009), Houston, TX.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 84

IPR2020-00770
United Therapeutics EX2007
Page 3634 of 7335

731. R. D. Rogers, "What are the greatest challenges for increasing the contribution of green chemistry to the larger scientific community, i.e. what is holding green chemistry back?" Panel Presentation by R. D. Rogers at the National Academies/National Research Council Green Chemistry and Sustainability Project Initiation Meeting (2009), Washington, DC, No Abstract.
732. R. D. Rogers, "Crystallization Process in Ionic Liquids," Presented by R. D. Rogers before the Symposium on Green Process for Particle Production (2010), Kyoto, Japan; Abstract Book pp 7-11. (Invited Keynote Lecture)
733. M. Smiglak, G. T. Parker, R. D. Rogers, "Thermal conductivities of ionic liquid-regolith mixtures: Improving heat transfer for innovative thermal and power systems at the Lunar surface," Presented by M. Smiglak before SPESIF-2010 Space, Propulsion & Energy Sciences International Forum, Johns Hopkins University Applied Physics Laboratory, Laurel, MD, February 23-26, 2010, Abstract 068.
734. R. D. Rogers, "Ionic Liquids: Are the applications of ionic liquids as materials more important than the use of ionic liquids as solvents?" Presented by R. D. Rogers before EUCHEM 2010 Conference on Molten Salts and Ionic Liquids (2010), Bamberg, Germany, Abstract Book p 89. (Invited Keynote Lecture)
735. K. Bica, P. Gaertner, and R. D. Rogers, "Ionic Liquids and Fragrances: Isolation of Essential Oils from Biomass," Presented by K. Bica before EUCHEM 2010 Conference on Molten Salts and Ionic Liquids (2010), Bamberg, Germany, Abstract LMP 47, Abstract Book p 343.
736. B. Stoner, N. Sun, and R. D. Rogers, "Dissolution and regeneration of wood in [C_2mim]OAc and formation of wood composite fibers," Presented by B. Stoner before the 239th ACS National Meeting (2010), San Francisco, CA, Abstract CHED 725.
737. N. Sun, X. Jiang, M. L. Maxim, R. D. Rogers, "Wood delignification using polyoxometalates in ionic liquid," Presented by R. D. Rogers before the 239th ACS National Meeting (2010), San Francisco, CA, Abstract FUEL 014. (Invited Speaker)
738. M. Smiglak, G. Gurau, D. M. Drab, J. L. Shamshina, S. P. Kelley, V. Cocalia, S. T. Griffin, A.-V. Mudring, and R. D. Rogers, "Crystallization of actinides from ionic liquids," Presented by R. D. Rogers before the 239th ACS National Meeting (2010), San Francisco, CA, Abstract NUCL 016. (Invited Speaker)
739. G. Gurau and R. D. Rogers, "Importance of benchmarking Green Chemistry," Presented by R. D. Rogers before the 239th ACS National Meeting (2010), San Francisco, CA, Abstract CINF 026. (Invited Speaker)
740. R. D. Rogers, "Ionic Liquids Laboratory to Commercialization," Presented by R. D. Rogers before the Home for Foreign Experts – Meeting of the Chinese Academy of Sciences Senior International Scientists and Young Fellows (2010), Beijing, China; No Abstract. (Invited Plenary presentation).
741. B. J. Herring, A. L. Logsdon, A. N. Lovich, J. E. Lockard, E. R. Janzen, J. F. Rasco, K. R. Di Bona, R. D. Hood, R. P. Swatloski, R. D. Rogers, and M. M. Bailey, "Anion Influence on the Toxicity of Short-Chain Imidazolium-Based Ionic Liquids in CD-1 Mice," Presented by B. J. Herring before the 50th Annual Meeting of the Teratology Society (2010), Louisville, KY, Abstract P41 (*Birth Defects Research (Part A)* **2010**, *88*, 392).
742. W. Li, N. Sun, B. Stoner, X. Lu, and R. D. Rogers, "How can we improve the dissolution and recovery of biopolymers from biomass in ionic liquids specifically for biofuels applications?" Presented by R. D. Rogers before the 240th ACS National Meeting (2010), Boston, MA, Abstract FUEL 061. (Invited Plenary Speaker)
743. R. D. Rogers, G. Gurau, and D. T. Daly, "Open innovation and the faculty entrepreneur: opportunities and perils," Presented by R. D. Rogers before the 240th ACS National Meeting (2010), Boston, MA, Abstract BMGT 037. (Invited Speaker)
744. R. D. Rogers and Ning Sun, "Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose," Presented by R. D. Rogers before the 2nd Asia Pacific Conference on Ionic Liquids and Green Processes (2010) (APCIL-2), Dalian, China, Abstract Book page 27. (Invited Plenary Presentation)
745. R. D. Rogers, "Developing Ionic Liquid Know-How for the Design of Modular Functionality, Versatile Platforms, and New Synthetic Methodologies for Energetic Materials, Presented by R. D. Rogers before the AFOSR Review for Organic Materials Chemistry and Molecular Design and Synthesis (2010), National Harbor, MD, Abstract.
746. *R. D. Rogers, "How can we improve the dissolution and recovery of biopolymers from biomass in ionic liquids specifically for biofuels applications?" Presented by R. D. Rogers before Frontiers in Biorefining: Biobased Products from Renewable Carbon (2010), St. Simons Island, GA, Abstract Book p 11. (Invited Speaker)*
747. N. Sun, X. Jiang, W. Li, X. Lu, and R. D. Rogers, "Wood Pulping Using Ionic Liquids," Presented by G. Gurau substituting for R. D. Rogers before the 4th International Symposium on Emerging Technologies of Pulping and Papermaking, 4th ISETPP (2010), Guangzhou, China, Abstract. (Invited Plenary Lecture)
748. R. D. Rogers, N. Sun, and Y. Qin, "The unique ability of ionic liquids to dissolve raw biopolymers such as cellulose and chitin, provides an opportunity to develop analytical techniques for molecular weight determination," Presented by R. D. Rogers before the 2010 International Chemical Congress of Pacific Basin Societies, Pacifichem 2010 (2010), Honolulu, HI, Abstract ANYL 870. (Invited Presentation)
749. R. D. Rogers, M. Smiglak, and J. Shamshina, "Azolium azolate ionic liquids from reactions of neutral azoles with 1,3-diemthylimidazolium-2-carboxylate, 1,2,3-trimethylimidazolium hydrogen carbonate, and *N,N*-dimethylpyrrolidinium hydrogen carbonate," Presented by R. D. Rogers before the 2010 International Chemical Congress of Pacific Basin Societies, Pacifichem 2010 (2010), Honolulu, HI, Abstract ENVI 237. (Invited Presentation)
750. R. D. Rogers, "Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose," Presented by R. D. Rogers to the 1st Japanese Symposium on Ionic Liquids (2011), Tottori, Japan, Abstract Book PL-01 pp 1-2. (Invited Plenary Presentation)

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 85

IPR2020-00770
United Therapeutics EX2007
Page 3635 of 7335

751. R. D. Rogers, "Where are ionic liquids strategies most suited in the pursuit of chemicals and energy from lignocellulosic biomass?" Presented by R. D. Rogers before the 2nd Annual Next Generation Bio-Based Chemicals Summit, Bringing Together the Value Chain for Drop-In and New Chemicals (2011), San Diego, CA, Published Presentation. (Invited Keynote Presentation)
752. N. Pogodina, E. Metwalli, P. Müller-Buschbaum, J. Shamshina, R. D. Rogers, and C. Friedrich, "Structure and Dynamics of Azolium-Azolate Ionic Liquids," Presented by N. Pogodina before the DFG-SPP 1191 Priority Program Spring 2011 meeting (Potsdam, Germany); Abstract.
753. S. P. Kelley, T. G. Parker, and R. D. Rogers, "Actinide chemistry in ionic liquids," Presented by Steven Kelley before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract I&EC 029.
754. S. P. Kelley, T. G. Parker, and R. D. Rogers, "Actinide complexes with *N*-donors from ionic liquids," Presented by Steven Kelley before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract NUCL 057.
755. P. D. McCrary, M. Smiglak, S. K. Spear, N. S. Bates, D. T. Daly, and R. D. Rogers, "Release of Ionic Liquid-Active Pharmaceutical Ingredients from Biopolymeric Beads," Presented by P. D. McCrary before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract I&EC 106.
756. G. Gurau and R. D. Rogers, "Ionic liquids as active pharmaceutical ingredients (IL-APIs) – the challenges of commercialization," Presented by G. Gurau before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract I&EC 119.
757. J. Shamshina, M. Smiglak, D. M. Drab, and R. D. Rogers, "Energetic Ionic Liquids," Presented by J. Shamshina before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract I&EC 107.
758. D. Daly, R. Rogers, and Y. Qin, "Amine-CO_2: Tunable Approach for Ionic Liquid Supported Biomass Production and IL Recovery," Presented by D. Daly before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract I&EC 117.
759. J. R. Canada, P. D. McCrary, G. Gurau, and R. D. Rogers, "Building a Career in Chemistry: The Importance of Undergraduate Research," Presented by J. R. Canada before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract I&EC 120.
760. C. Sharma, C. Hines, and R. D. Rogers, "Temperature Controlled Release of Nicotine from its Metal Complexes," Presented by C. Sharma before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract I&EC 028.
761. H. Rodríguez, S. Lago, M. Francisco, M. J. Earle, J. H. Holbrey, K. R. Seddon, R. D. Rogers, A. Soto, and A. Acre, "Ionic Liquids for Improved Liquid-Liquid Extraction Processes," Presented by H. Rodríguez before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract I&EC 101.
762. M. Francisco, H. Rodríguez, N. Sun, M. Rahman, J. F. Pereira, M. G. Freire, L. P. Rebelo, J. A. Coutinho, and R. D. Rogers, "Biphasic Liquid-Liquid Systems Based on Ionic Liquids and Polyethylene Glycols," Presented by M. Francisco before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract I&EC 103.
763. R. D. Rogers, "Award Address (ACS Award in Separations Science & Technology): Ionic Liquids form There to Here," Presented by R. D. Rogers before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract I&EC 148. (Invited Award Address)
764. R. D. Rogers, "An Editor's Perspective on Contentious Issues Arising During Peer Review," Presented by R. D. Rogers before the 241st ACS National Meeting (2011), Anaheim, CA, Abstract CHED 1236. (Invited Presentation)
765. P. D. McCrary, P. A. Beasley, R. D. Rogers, T. W. Hawkins, S. Schneider, J. P. Perez, B. W. McMahon, S. L. Anderson, and S. Son "Loading Metal Nanoparticles in Energetic Ionic Liquids," Presented by P. D. McCrary before the Air Force Office of Scientific Research Molecular Dynamics Contractors Meeting (May 15-17, 2011), Pasadena, CA, Abstract.
766. R. D. Rogers, "Developing Ionic Liquid Know-How for the Design of Modular Functionality, Versatile Platforms, and New Synthetic Methodologies for Energetic Materials," Presented by R. D. Rogers before the Air Force Office of Scientific Research Molecular Dynamics Contractors Meeting (May 15-17, 2011), Pasadena, CA, Abstract.
767. R. D. Rogers, "Crystallographic Publication in the American Chemical Society Journal *Crystal Growth & Design*: An Editor's Perspective (*so pay attention!*)," Presented by R. D. Rogers before the American Crystallographic Association 2011 Annual Meeting (May 28 – June 2, 2011), New Orleans, LA Abstract 08.04.6. (Invited presentation)
768. J. F. B. Pereira, M. G. Freire, M. Francisco, H. Rodríguez, L. P. N. Rebelo, R. D. Rogers, and J. A. P. Coutinho, "Aqueous Biphasic Systems Composed of Polyethylene Glycols and Ionic Liquids and their Ability to Extract Biomolecules," Presented by M. G. Freire before the **2nd Iberian Meeting on Ionic Liquids** (2nd IMIL) (2011), Santiago de Compostela and A Coruña, Galicia, Spain, Abstract.
769. H. Wang, G. Gurau, M. L. Maxim and R. D. Rogers, "Microwave-assisted dissolution and delignification of wood using 1-ethyl-3-methylimidazolium acetate ([emim]OAc)", Presented by H. Wang before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, DC, Abstract 368.
770. A. Narita, Parker D McCrary, John R Canada and R. D. Rogers, "Synthesis of ionic liquids consisting of FDA approved compounds", Presented by A. Narita before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, DC, Abstract 256.
771. G. Gurau, H. Rodríguez, S. P. Kelley, and R. D. Rogers, "Looking at the reactivity of 1-ethyl-3-methylimidazolium acetate with CO_2 and biomass from crystal structures: Will chemistry explain the controversies?", Presented by G. Gurau before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, DC, Abstract 310.
772. S. P. Kelley, E. S. Stoner, T. G. Parker, R. D. Rogers, "Ionic Liquids and Actinides: Unique Environments for f-Element Chemistry", Presented by S. P. Kelley before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, D.C., Abstract 86.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 86

IPR2020-00770
United Therapeutics EX2007
Page 3636 of 7335

773. P. D. McCrary, P. A. Beasley, T. W. Hawkins, S. Schneider, J. Paulo Perez, B. W. McMahon, S. L. Anderson, S. Son and R. D. Rogers, "Loading Metal Nanoparticles in Energetic Ionic Liquids", Presented by P. D. McCrary before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, D. C., Abstract 213.
774. E. Stoner, S. Kelley, and R.D. Rogers, "Role of ionic liquids in the future of the thorium based nuclear fuel cycle", Presented by E. Stoner before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington DC, Abstract 333.
775. P. A. Beasley, P. D. McCrary, and R. D. Rogers, "New Generation of Energetic Materials based on Novel Asymmetric Multi-heterocyclic Architectures", Presented by P. A. Beasley before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, DC, Abstract 93.
776. J. R. Canada, P. D. McCrary, P. A. Beasley, A. Narita, R. D. Rogers, "Ionic Liquids Comprised of Biologically Active Amines", Presented by J. R. Canada before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, D. C., Abstract 75.
777. J. Shamshina, H. W. H. Dykes, A. J. Reich, R. DiSalvo, M. Smiglak, and R. D. Rogers, "Catalytic ignition of ionic liquids for propellant applications," Presented by J. Shamshina before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, D. C., Abstract 11.
778. M. G. Freire, J. F. B. Pereira, M. Francisco, H. Rodríguez, L. P. N. Rebelo, R. D. Rogers, and J. A. P. Coutinho, "Novel aqueous biphasic systems composed of ionic liquids and polyethylene glycols: Phase diagrams and extraction ability," Presented by M. G. Freire before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, D. C., Abstract 17.
779. S. Y. Choi, H. Rodríguez, A. Mirjafari, D. F Gilpin, S. McGrath, K. R Malcolm, M. M Tunney, R. D Rogers, and Tony McNally, "Dual functional ionic liquids as plasticisers and antimicrobial agents for medical polymers, Presented by H. Rodríguez before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, D. C., Abstract 201.
780. R. M. Frazier, D. T. Daly, W. L. Hough, S. K. Spear, and R. D. Rogers, "New Ionic Liquids for Active Layers in Photovoltaics," Presented by R. M. Frazier before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, D. C., Abstract 436.
781. N. V Pogodina, E. Metwalli, P. Müller-Buschbaum, G. Dlubek, J. Shamshina, R. D Rogers, and C. Friedrich, "Molecular structure and dynamics of Azolium-Azolate ionic liquids," Presented by N. V. Pogodina before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, D. C., Abstract 54.
782. C. P Azubuike, H. Rodríguez, A. O Okhamafe, and Robin D Rogers, "Physicochemical properties of maize cob cellulose powders reconstituted from ionic liquid solution," Presented by H. Rodríguez before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, D. C., Abstract 71.
783. O. A. Cojocaru, J. L. Shamshina, J. P. Edgeworth, G. Gurau, R. S. Ruoff, and R. D. Rogers, "Improved Electrical Energy Storage with Electrochemical Double Layer Capacitance Basedon Novel Carbon Electrodes," Presented by O. A. Cojocaru before the 4th Congress on Ionic Liquids (COIL-4) (June 15-18, 2011), Washington, D. C., Abstract 160.
784. R. D. Rogers, "Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose," Presented by R. D. Rogers to the Joint Bioenergy Institute/Energy Biosciences Institute Workshop Lignin, Characterization, Extraction, & Adding Value (July 18-19, 2011), Emeryville, CA, No Abstract. (Invited Presentation)
785. R. D. Rogers, "Crystallographic Publication in the American Chemical Society Journal *Crystal Growth & Design* and Contentious Issues arising During Peer Review: An Editor's Perspective," Presented by R. D. Rogers before the 8th National Conference on Inorganic Chemistry (July 26-28, 2011), Harbin, China, Abstract 26M-PL-003. (Invited Plenary Presentation).
786. R. D. Rogers, "Crystallographic Publication in the American Chemical Society Journal *Crystal Growth & Design* and Contentious Issues arising During Peer Review: An Editor's Perspective (*so pay attention!*)," Presented by R. D. Rogers before the IUCr 2011 Satellite Workshop Categorizing Halogen Bonding and other Noncovalent Interactions Involving Halogen Atoms (Aug. 20-21, 2011), Sigüenza, Spain, Abstract Book p 49. (Invited Plenary). (http://www.iucr2011madrid.es/images/stories/pdf/Book_of_abstracts.pdf).
787. D. T. Daly, R. D. Rogers, and G. Gurau, "Disruptive technology for biomass processing using ionic liquids," Presented by D. T. Daly before the 242nd ACS National Meeting (Aug. 28 – Sept. 1, 2011), Denver, CO, Abstract BMGT 015.
788. J. F. B. Pereira, M. G. Freire, M. Francisco, H. Rodríguez, L. P. N. Rebelo, R. D. Rogers, and J. A. P. Coutinho, "Biomolecules Separation using Aqueous Biphasic Systems Composed of Polyethylene Glycols and Ionic Liquids," Presented by J. F. B. Pereira before IL SEPT (Sept. 4-7, 2011), Sitges, Spain, Abstract K09.
789. R. D. Rogers "Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose," Presented by R. D. Rogers before the 6th Asian Pacific Chemical Engineering Symposium, APCRE11 (Sept. 18-21, 2011), Beijing, China, Abstract Book p 1. (Invited Plenary Speaker)
790. P. S. Barber, S. P. Kelley, and R. D. Rogers, "Design and Coordination of f-elements with Amidoxime-Functionalized Ionic Liquids," Presented by P. S. Barber before the 17th Symposium on Separation Science and Technology for Energy Applications (Oct. 23–27, 2011), Gatlinburg, TN, Abstract 621.
791. S. P. Kelley, E. L. Stoner, and R. D. Rogers, "N-Donor Ionic Liquids as Unique Environments for f-Element Chemistry," Presented by S. P. Kelley before the 17th Symposium on Separation Science and Technology for Energy Applications (Oct. 23–27, 2011), Gatlinburg, TN, Abstract 617.
792. C. S. Griggs, S. L. Larson, J. H. Ballard, P. S. Barber, and R. D. Rogers, "Optimization and Evaluation of Uranium Sorptive Bio-materials," Presented by C. S. Griggs before the 17th Symposium on Separation Science and Technology for Energy Applications (Oct. 23–27, 2011), Gatlinburg, TN, Abstract 113.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 87

IPR2020-00770
United Therapeutics EX2007
Page 3637 of 7335

793. E. L. Stoner, S. P. Kelley, and R. D. Rogers, "Application of Ionic Liquids for Separations in the Thorium Nuclear Fuel Cycle," Presented by E. L. Stoner before the 17th Symposium on Separation Science and Technology for Energy Applications (Oct. 23–27, 2011), Gatlinburg, TN, Abstract 618.
794. J. F. B. Pereira, M. G. Freire, H. Rodríguez, L. P. N. Rebelo, R. D. Rogers, and J. A. P. Coutinho "Insights into the Interactions that Control the Phase Behaviour of Novel Aqueous Biphasic Systems Composed of Polyethylene Glycols and Ionic Liquids," Presented by J. F. B. Pereira before MicroBiotec'11 (December 1-3, 2011), Braga, Portugal.
795. R. D. Rogers, "Preparation of High Purity, High Molecular Weight Chitin Nanofibers from Direct Extraction from Shrimp Shells with ILs for Use as an Adsorbate for Uranium from Seawater," Presented by R. D. Rogers before the DOE-NE Fuel Resources FY 12 Working Group Meeting (January 5–6, 2012), Oak Ridge, TN (No Abstract).
796. R. D. Rogers, "How an Understanding of Solid State Interactions can be Used to Prevent Solidification; the Case for Pure Pharmaceutical Liquid Salts and Cocrystals," Indo-US Bilateral Meeting on the Evolving Role of Solid State Chemistry in the Pharmaceutical Science (February 2-4, 2012), Manesar, India, Abstract Book pp 38-39. (not presented due to illness)
797. R. D. Rogers, "Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction and Separation of Lignin, Cellulose, and Hemicellulose," Presented by R. D. Rogers before the Indo-US Workshop on Green Chemistry for Environments and Sustainable Development (March 11-13, 2012), Dehradun, India, Abstract PL-2 p 7. (Plenary Speaker)
798. D. T. Daly, R. M. Frazier, Y. Qin, S. K. Spear, W. L. Hough, and R. D. Rogers, "Ionic liquids: A platform for innovation," Presented by R. M. Frazier before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract I&EC 261.
799. R. D. Rogers, O. A. Cojocaru, A. Siriwardana, H. Holding, K. Bica, H. Rodriguez, G. Gurau, A. Riisager, and R. Fehrmann, "Ionic liquid active pharmaceutical ingredients loaded on silica: Solids handling for liquid pharmaceutical forms," Presented by R. D. Rogers before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract I&EC 093. (Invited Award Presentation)
800. G. Gurau and R. D. Rogers, "Ionic liquids and shrimp shell waste – emerging technologies for the manufacture of nanochitin materials," Presented by G. Gurau before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract I&EC 117.
801. H. Wang, G. Gurau, and R. D. Rogers, "Membrane transport of active pharmaceutical ingredient-based ionic liquids," Presented by H. Wang before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract I&EC 292.
802. O. A. Cojocaru, G. Gurau, D. T. Daly, J. Pernak, and R. D. Rogers, "Improved Efficacy and Delivery of Herbicides in Ionic Liquid Form," Presented by O. A. Cojocaru before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract I&EC 324.
803. P. A. Beasley, O. A. Cojocaru, P. D. McCrary, and R. D. Rogers, "Energetic Ionic Liquid 'Liquid Clathrates'," Presented by P. A. Beasley before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract I&EC 008.
804. P. D. McCrary, P. A. Beasley, O. A. Cojocaru, T. W. Hawkins, S. Schneider, J. Paulo Perez, B. W. McMahon, S. L. Anderson, S. F. Son, and R. D. Rogers, "Nanoparticles in Hypergolic and Energetic Ionic Liquids," Presented by P. D. McCrary before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract I&EC 007.
805. G. W. Drake, P. D. McCrary, P. A. Beasley, and R. D. Rogers, "Evaluating Energetic Ionic Liquids as Hypergolic Fuels," Presented by P. D. McCrary and Preston A. Beasley before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract I&EC 003.
806. J. R. Canada, O. A. Cojocaru, Gabriela Gurau, Juliusz Pernak, and R. D. Rogers, "Using Herbicidal Ionic Liquids to Reduce the Impact on the Environment," Presented by O. A. Cojocaru before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract I&EC 325.
807. J. R. Canada, R. Rogers, K. E. Peterman, G. P. Foy, "COP 17: Spreading the Word," Presented by K. E. Peterman before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract SOCED 006.
808. G. Gurau, D. T. Daly, and R. D. Rogers, "Ionic liquid (IL) base drugs for the $1.2B pain management sector: New disruptive directions in pain management," Presented by G. Gurau before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract COMSCI 008.
809. B. W. McMahon, J. L. Perez, S, L. Anderson, S, Schneider, J. Boatz, T. Hawkins, P. D. McCray, P. A. Beasley, R. D. Rogers, and S. Son, "Dual ligand passivation and homogeneous media ball milling: Novel approaches for both the synthesis and capping of air-stable aluminum nanoparticles," Presented by B. W. McMahon before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract FUEL 367.
810. J. L. Perez, B. W. McMahon, S, L. Anderson, S, Schneider, J. Boatz, T. Hawkins, P. D. McCray, P. A. Beasley, and R. D. Rogers "Synthesis of air-stable, unoxidized boron nanoparticles using ball milling technique," Presented by J. L. Perez before the 243rd ACS National Meeting (March 25-29, 2012), San Diego, CA, Abstract FUEL 369.
811. R. D. Rogers, P. S. Barber, C. S. Griggs, E. L. Stoner, and S. P. Kelley, "Ionic Liquids for Extraction and Functionalization of Uranium Selective Chitin Sorbents," Presented by G. Gurau before the 2012 Materials Research Society Spring Meeting & Exhibit (April 9-13, 2012), San Francisco, CA, Abstract BBB 6.3. (Invited Speaker)
812. H. Wang, A. Kumar, G. Gurau, and R. D. Rogers, "Extraction of Sandalwood Oil from Sandalwood using Ionic Liquids," Presented by H. Wang before the 2012 Materials Research Society Spring Meeting & Exhibit (April 9-13, 2012), San Francisco, CA, Abstract BBB 4.8. (Invited Speaker)
813. G. Gurau and R. D. Rogers, "Nanochitin Materials from Shrimp Shell Waste – Manufacturing Challenges in an Ionic Liquid Process," Presented by G. Gurau before the 2012 Materials Research Society Spring Meeting & Exhibit (April 9-13, 2012), San Francisco, CA, Abstract BBB 3.6. (Invited Speaker)

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 88

IPR2020-00770
United Therapeutics EX2007
Page 3638 of 7335

814. R. D. Rogers, "Do you really understand all there is to know about Ionic Liquids?" Presented by R. D. Rogers before M3 Molecules Materials Medicines: An International Conference on the Role of Materials Science and Engineering in Drug Development (May 19-22, 2012), Banff, Alberta, Canada, Abstract. (Invited Keynote Address)
815. P. D. McCrary, P. A. Beasley, O. A. Cojocaru, S. P. Kelley, S. A. Alaniz, T. W. Hawkins, S. Schneider, J. A. Boatz, J. P. L. Perez, B. W. McMahon, S. L. Anderson, M. Pfeil, S. F. Son, and R. D. Rogers. "Controlling the Properties of Energetic Ionic Liquids (EILs) by Stabilizing Reactive Nanomaterials," Presented by P. D. McCrary before the AFOSR Contractors' Meeting (May 22-24, 2012), Arlington, VA, Abstract.
816. P. A. Beasley, P. D. McCrary, O. A. Cojocaru, T. W. Hawkins, S. Schneider, and R. D. Rogers, "Energetic Ionic Liquid "Liquid Clathrates"," Presented by P. A. Beasley before the AFOSR Contractors' Meeting (May 22-24, 2012), Arlington, VA, Abstract.
817. G. Gurau, H. Wang, and R. D. Rogers, "Polymorphs, Salts, and Cocrystals of Active Pharmaceutical Ingredients and the FDA Proposed Classifications: What will they think of Ionic Liquid Forms?," Presented by G. Gurau before the Gordon Research Conference on Crystal Engineering (June 10-15, 2012), Waterville Valley Resort, NH, Abstract 34.
818. S. P. Kelley, A. Narita, H. Wang, O. A. Cojocaru, G. Gurau, and R. D. Rogers "Ionic Liquids, Ionic Cocrystals, and Salts: Structural Consequences of Proton Sharing via Strong Hydrogen Bonds," Presented by S. P. Kelley before the Gordon Research Conference on Crystal Engineering (June 10-15, 2012), Waterville Valley Resort, NH, Abstract 41.
819. R. D. Rogers, "Science, service, and the ACS: Becoming an ACS Fellow from the I&EC Division," Presented by R. D. Rogers before the 244th ACS National Meeting (August 19-23, 2012), Philadelphia, PA, Abstract I&EC 043. (Invited Presentation)
820. C. S. Griggs, P. S. Barber, S. P. Kelley, G. Gurau, and R. D. Rogers, "Electrospun chitin nanofibers for uranyl absorbant materials," Presented by C. S. Griggs before the 244th ACS National Meeting (August 19-23, 2012), Philadelphia, PA, Abstract I&EC 058.
821. P. S. Barber, S. P. Kelley, C. S. Griggs, and R. D. Rogers, "Amidoxime functionalized materials for the selective extraction of the uranium," Presented by P. S. Barber before the 244th ACS National Meeting (August 19-23, 2012), Philadelphia, PA, Abstract I&EC 054.
822. R. D. Rogers, P. S. Barber, C. S. Griggs, S. P. Kelley, and G. Gurau, "Extraction of uranium with regenerated chitin from the dissolution of shrimp shells in ionic liquid," Presented by R. D. Rogers before the 244th ACS National Meeting (August 19-23, 2012), Philadelphia, PA, Abstract I&EC 106.
823. S. P. Kelley and R. D. Rogers, "Application of Unusual Metal Speciation in ILs to f-Element Separations," Presented by S. P. Kelley before the 244th ACS National Meeting (August 19-23, 2012), Philadelphia, PA, Abstract I&EC 105.
824. R. D. Rogers, "Ionic liquids and strategic metals: Challenges and opportunities," Presented by R. D. Rogers before the 244th ACS National Meeting (August 19-23, 2012), Philadelphia, PA, Abstract ANYL 189. (Invited Presentation)
825. J. F. B. Pereira, Teresa Mourão, O. A. Cojocaru, G. Gurau, L. P. N. Rebelo, R. D. Rogers, J. A. P. Coutinho, and M. G. Freire, "Biodegradable and biocompatible aqueous biphasic systems composed of polymers and choline-based ionic liquids," Presented by J. F. B. Pereira before the 4th International IUPAC Conference on Green Chemistry (August 25-29, 2012), Foz do Iguaçu/PR, Brazil, Abstract Book p 74.
826. R. D. Rogers, "Unique Roles for Ionic Liquids in a Biorefinery: Extraction, Separation, and Processing of Lignin, Cellulose, Hemicellulose, and Chitin," Presented by R. D. Rogers before the 4th International IUPAC Conference on Green Chemistry (August 25-29, 2012), Foz do Iguaçu/PR, Brazil, Abstract Book p 11. (Invited Plenary Speaker).
827. R. D. Rogers, "Solvents, Separations, and Renewables," A Short Course presented by R. D. Rogers before the 4th International IUPAC Conference on Green Chemistry (August 25-29, 2012), Foz do Iguaçu/PR, Brazil, Abstract Book p xi. (Invited Course Instructor).
828. H. Wang, A. Myerson, and R. D. Rogers, "Separations utilizing hydrophobic vs. hydrophilic ionic liquids in support of continuous pharmaceutical manufacturing," Presented by H. Wang before the 3rd Asian-Pacific Conference on Ionic Liquids and Green Processes, APCIL'12 (Sept. 17-19, 2012), Beijing, China, Abstract E-12, p. 128.
829. G. Gurau, C. S. Griggs, P. S. Barber, and R. D. Rogers, "Shell Fish and Ionic Liquids – Turning Waste into Advance Materials," Presented by G. Gurau before the 3rd Asian-Pacific Conference on Ionic Liquids and Green Processes, APCIL'12 (Sept. 17-19, 2012), Beijing, China, Abstract G-13, p. 176.
830. P. D. McCrary, P. A. Beasley, and R. D. Rogers, "Ionic Liquids as 'Practical' Energetic Materials," Presented by P. D. McCrary before the 3rd Asian-Pacific Conference on Ionic Liquids and Green Processes, APCIL'12 (Sept. 17-19, 2012), Beijing, China, Abstract G-03, p. 166.
831. R. D. Rogers and G. Gurau, "Unique Roles for Ionic Liquids in a Biorefinery: Extraction, Separation, and Processing of Lignin, Cellulose, Hemicellulose, and Chitin," Presented by R. D. Rogers before the 3rd Asian-Pacific Conference on Ionic Liquids and Green Processes, APCIL'12 (Sept. 17-19, 2012), Beijing, China, Abstract P-01, p. 1. (Invited Plenary Speaker).
832. R. D. Rogers and G. Gurau, "Extraction and Manufacturing of Nanochitin Materials from Shrimp Shell Waste Using Ionic Liquids," 15th International Biotechnology Symposium and Exposition (IBS 2012), "Innovative Biotechnology for a Green World and Beyond" (Sept. 16-21, 2012), Daegu, South Korea, Abstract cd O-S8-0086. (Invited Speaker).
833. S. Mateyawa, P. Halley, R. Truss, F. Xie, T. Nicholson, T. McNally, and R. Rogers, Starch polymer nanocomposite systems: use of ionic liquids and nanofillers," Presented by S. Mateyawa before the 13th International Symposium on Biopolymers (ISBP 2012, October 7-10, 2012), Cairns, Australia, Abstract http://isbp2012.com.au/symposium-abstracts/.
834. R. D. Rogers, "What can ionic liquids, the antithesis of solid crystalline materials, teach us about controlling the form of active pharmaceutical ingredients? Crystals, cocrystals, and salts," Presented by R. D. Rogers before the Indian Institute of Technology Bombay – American Chemical Society Symposium (Oct. 1-2, 2012), Mumbai, India, Abstract. (Invited Lecture)

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 89

IPR2020-00770
United Therapeutics EX2007
Page 3639 of 7335

835. R. D. Rogers, "What can ionic liquids, the antithesis of solid crystalline materials, teach us about controlling the form of active pharmaceutical ingredients? Crystals, cocrystals, and salts," Presented by R. D. Rogers before the National Chemical Laboratory - American Chemical Society On Campus Symposium (Oct. 10, 2012), Pune, India, Abstract. (Invited Lecture)
836. R. D. Rogers, "What can ionic liquids, the antithesis of solid crystalline materials, teach us about controlling the form of active pharmaceutical ingredients? Crystals, cocrystals, and salts," Presented by R. D. Rogers before the Indian Association for the Cultivation of Science - American Chemical Society On Campus Symposium (Oct. 12, 2012), Calcutta, India, Abstract. (Invited Lecture)
837. R. D. Rogers, "How can the liquid state help us master the solid state? A study of Ionic Liquids in the pharmaceutical sector," Presented by R. D. Rogers before the 6th National Symposium on Structural Chemistry (6th NSSC; Oct. 22-25, 2012), Suzhou, China, Abstract KL-01. (Invited Keynote Lecture)
838. R. D. Rogers, "Unique Roles for Ionic Liquids in a Biorefinery: Extraction, Separation, and Processing of Lignin, Cellulose, Hemicellulose, and Chitin" Presented by R. D. Rogers before the CSIRO Cutting Edge 2012 Symposium on Biological and Chemical Conversion of Renewables to Fuels and Chemicals (Nov. 13-15, 2012), Parkville, Australia, Abstract D2. (Invited Lecture).
839. R. D. Rogers, "Developing Ionic Liquid Know-How for the Design of Modular Functionality, Versatile Platforms, and New Synthetic Methodologies for Energetic Materials," Presented by R. D. Rogers before the Air Force Office of Scientific Research Molecular Dynamics Contractors Meeting (December 3-4, 2012), Pasadena, CA, Abstract .
840. R. D. Rogers and P. D. McCrary, "The Development of Advanced Liquid Composite Materials by Controlling Stabilization of Nanoparticles in Ionic Liquids," Presented by R. D. Rogers before the 2013 Materials Research Society Spring Meeting & Exhibit (April 1-5, 2013), San Francisco, CA, Abstract VV2.07.
841. P. D. McCrary, G. P. Foy, K. E. Peterman, and R. D. Rogers, "Youth Involvement at the 18th Conference of Parties and the Need for Climate Science Literacy," Presented by P. D. McCrary before the 245th ACS National Meeting (April 7-11, 2013), New Orleans, LA, Abstract CHED 506.
842. P. D. McCrary, S. A. Alaniz, and R. D. Rogers. "Controlling the Properties of Energetic Ionic Liquids through the Incorporation of Reactive Nanomaterials," Presented by P. D. McCrary before the 245th ACS National Meeting (April 7-11, 2013), New Orleans, LA, Abstract I&EC 116.
843. S. K. McNeil, S. P. Kelley, C. Beg, H. W. Cook, R. D. Rogers, and D. E. Nikles. "Co-crystals of 1,3-dinitrobenzene and 10-methylphonothiazine: Implications for detecting explosives," Presented by S. K. McNeil before the 245th ACS National Meeting (April 7-11, 2013), New Orleans, LA, Abstract I&EC 133.
844. R. D. Rogers, "What happens when co-crystals don't crystallize?" Presented by R. D. Rogers before the CPI Conference CRYSTALLIZATION (April 16-17, 2013), Mumbai, India. (Invited Lecture)
845. O. A. Cojocaru, J. Shamshina, K. Bica, G. Gurau, A. Narita, P. D. McCrary, P. S. Barber, and R. D. Rogers, "Prodrug ionic liquids: functionalizing neutral active pharmaceutical ingredients to take advantage of the ionic liquid form," Presented by J. Shamshina before the 5th Congress on Ionic Liquids, COIL-5 (April 21-25, 2013), Algarve, Portugal, Abstract P342. Poster
846. K. R. Di Bona, D. Yancey, S. Rizvi, M. Gray, G. Gurau, J. L. Shamshina, J. F. Rasco, and R. D. Rogers, "Transdermal Pharmacokinetic Studies of Ionic Liquids Composed Entirely of Active Pharmaceutical Ingredients," Presented by K. R. Di Bona before the 5th Congress on Ionic Liquids, COIL-5 (April 21-25, 2013), Algarve, Portugal, Abstract P339.
847. G. Gurau, L. E. Block, J. Shamshina, and R. D. Rogers, "Wound dressings through an ionic liquid process – filling a gap in the wound care sector" Presented by G. Gurau before the 5th Congress on Ionic Liquids, COIL-5 (April 21-25, 2013), Algarve, Portugal, Abstract OP3.
848. P. D. McCrary, P. A. Beasley, G. Gurau, P. S. Barber, and R. D. Rogers, "Drug specific, tuning of an ionic liquid's hydrophilic-lipophilic balance to improve water solubility of poorly soluble pharmaceutical ingredients," Presented by P. D. McCrary before the 5th Congress on Ionic Liquids, COIL-5 (April 21-25, 2013), Algarve, Portugal, Abstract P104.
849. P. D. McCrary, G. P. Foy, K. E. Peterman, and R. D. Rogers, "Youth Involvement at the 18th Conference of Parties and the Need for Climate Science Literacy," Presented by P. D. McCrary before the 5th Congress on Ionic Liquids, COIL-5 (April 21-25, 2013), Algarve, Portugal, Abstract P105.
850. P. D. McCrary, S. A. Alaniz, and R. D. Rogers, "Controlling the Properties of Energetic Ionic Liquids through the Incorporation of Reactive Nanomaterials," Presented by P. D. McCrary before the 5th Congress on Ionic Liquids, COIL-5 (April 21-25, 2013), Algarve, Portugal, Abstract F36/P291.
851. P. S. Barber, C. S. Griggs, S. P. Kelley, S. Wallace, R. D. Rogers, "Using an Ionic Liquid Platform for the Development of Materials for the Extraction of Uranium from Seawater," Presented by P. S. Barber before the 5th Congress on Ionic Liquids, COIL-5 (April 21-25, 2013), Algarve, Portugal, Abstract F43/P81.
852. J. F. B. Pereira, L. P. N. Rebelo, R. D. Rogers, J. A. P. Coutinho, and M. G. Freire, "Combining ionic liquids and polyethylene glycols to boost the hydrophobic-hydrophilic range of aqueous biphasic systems," Presented by J. F. B. Pereira before the 5th Congress on Ionic Liquids, COIL-5 (April 21-25, 2013), Algarve, Portugal, Abstract P65
853. J. Shamshina, P. D. McCrary, O. A. Cojocaru, G. Gurau, and R. D. Rogers, "Formation of pure liquid salt forms from active pharmaceutical ingredients to establish new drug delivery systems with superior properties," Presented by J. Shamshina before the 5th Congress on Ionic Liquids, COIL-5 (April 21-25, 2013), Algarve, Portugal, Abstract P85.
854. R. D. Rogers and S. P. Kelley, Liquid Engineering to Crystal Engineering: How Ionic Liquids Can Help Us Master the Pharmaceutical Solid State," Abstract Only no Presentation to Past, Present, and Future of Crystallography@Politecnico di

Milano, from Small Molecules to Macromolecules and Supramolecular Structures (June 6-7, 2013), Milan, Italy, Abstract Book p 11. (Invited)

855. R. D. Rogers, "Unique Roles for Ionic Liquids in a Biorefinery: Extraction, Separation, and Processing of Lignin, Cellulose, Hemicellulose, and Chitin," Presented by R. D. Rogers before INORG2013 Conference (June 30 – July 4, 2013), Durban, South Africa, Abstract GS3, http://www.ic2013.ukzn.ac.za/. (Invited Plenary Speaker).
856. R. D. Rogers, "Basics of Scholarly Publishing: Peer Review - What It Is, How It Works, and Why It Matters!" Presented by R. D. Rogers before the University of KwaZulu-Natal - American Chemical Society On Campus Symposium (July 5, 2013), Durban, South Africa. (Invited).
857. R. D. Rogers, "Basics of Scholarly Publishing: Peer Review - What It Is, How It Works, and Why It Matters!" Presented by R. D. Rogers before the Wits University - American Chemical Society On Campus Symposium (July 8, 2013), Johannesburg, South Africa. (Invited).
858. R. D. Rogers, "Past, Present, and Future Ghosts in Submission, Review, and Archiving of Crystallographic Data in the American Chemical Society Journal *Crystal Growth & Design*," Presented by R. D. Rogers before the American Crystallographic Annual Meeting (July 20-24, 2013), Honolulu, HI, Abstract 13.10.04. (Invited)
859. O. A. Cojocaru and R. D. Rogers, "Ionic liquid forms of active pharmaceutical ingredients in drug delivery," Presented by O. A. Cojocaru before the 246th ACS National Meeting (September 8-12, 2013), Indianapolis, IN, Abstract AEI 066.
860. R. D. Rogers and G. Gurau, "Novel chitin fibers for wound care," Presented by D. T. Daly before the 246th ACS National Meeting (September 8-12, 2013), Indianapolis, IN, Abstract SCHB 019.
861. Z. Tywabi, B. Sithole, N. Deenadayalu, and R. D. Rogers, Structural changes in South African eucalyptus bleached dissolving pulp after dissolution in ionic liquid and co-solvent mixtures evidenced by FTIR and P'XRD, presented by Z. Tywabi before the Technical Association of the Pulp and Paper Industry of South Africa (TAPPSA) National Conference & Exhibition (October 22-23, 2013), Durban, South Africa.
862. M. Shadid, G. Gurau, B.-C. Chuang, M. Liao, S. Chowdhury, J.-T. Wu, S. A. A. Rizvi, R. D. Rogers, and R. J. Griffin, "Investigating the ADME properties of an ionic liquid salt form of sulfasalzine, a novel approach to improve drug exposure," Presented by M. Shadid before the 10th International Meeting of the International Society for the Study of Xenobiotics (September 30 – October 3, 2013), Toronto, Ontario, Canada, Abstract P127.
863. R. D. Rogers, "Advanced Materials from Renewable Polymers: Why Are We Still Using Synthetics?" Presented by R. D. Rogers before the 2013 CAS – TWAS Symposium on Green Technology (SGT2013; October 20–23, 2013; http://www.sgt2013.com/dct/page/1), Beijing, China, P-01, no abstract. (Plenary Speaker)
864. R. D. Rogers, (Walden Award Lecture) "Liquid Engineering to Crystal Engineering: How Ionic Liquids Can Help Us Master the Pharmaceutical Solid State," Presented by R. D. Rogers to COST Meeting, EXIL – Exchange on Ionic Liquids (November 24-26, 2013), Dresden, Germany, Abstract. (Invited Award Lecture)
865. R. D. Rogers, "Advanced Materials from Renewable Polymers: Why Are We Still Using Synthetics?" Presented by R. D. Rogers to the 65th Detmold Starch Convention, Detmold, Germany, Abstract 4.11. (Invited)
866. J. P. L. Perez, B. W. McMahon, J. Yu, S. Schneider, J. A. Boatz, T. W. Hawkins, P. D. McCrary, L. A. Flores, R. D. Rogers, and S. L. Anderson, "Synthesis and characterization of surface-functionalized aluminum and boron nanoparticles in hypergolic ionic liquid propellants," presented by S. L. Anderson before the Air Force Molecular Dynamics meeting (May 19-21, 2014), Arlington, VA.
867. R. D. Rogers, "Ideality vs. Reality of Green Chemistry in the Development of Advanced Materials from Renewable Polymers," Presented by R. D. Rogers before the 2014 CAS - TWAS Symposium on Advanced Engineering Science for Sustainable Development (AES 2014; May 28-30, 2014), Beijing, China, Abstract P-01. (Plenary Speaker)
868. R. D. Rogers, "Crystal Engineering to Liquid Engineering: Salts, cocrystals, deep eutectics, crystals, liquids…It's about the interactions and effects!" Presented by R. D. Rogers before the International Union of Pure and Applied Chemistry/International Council for Science Workshop on Crystal Engineering at the 1st International Symposium on Halogen Bonding (ISXB-1; June 18-22, 2014), Porto Cesareo, Italy, Abstract CE2. (Plenary Speaker)
869. H. Wang and R. D. Rogers, "Double salt ionic liquids: Expanding the range and tuneability of separations media," Presented by R. D. Rogers before the 2nd International Conference on Ionic Liquids in Separation and Purification Technology (ILSEPT; June 29 – July 2, 2014), Toronto, Canada, Abstract PL2 (Plenary Presentation).
870. C. C. Weber, A. J. Kunov-Kruse1, R. D. Rogers, and A. S. Myerson, "Manipulating hydrogen bond complexes in ionic liquids to facilitate the purification of pharmaceuticals," Presented by C. C. Weber before the 2nd International Conference on Ionic Liquids in Separation and Purification Technology (ILSEPT; June 29 – July 2, 2014), Toronto, Canada, Abstract O02.4.
871. M. G. Freire, A. M. Ferreira, A. M. Fernandes, R. D. Rogers, and J. A. P. Coutinho, "pH-triggered reversible aqueous biphasic systems composed of ionic liquids," Presented by M. G. Freire before the 2nd International Conference on Ionic Liquids in Separation and Purification Technology (ILSEPT; June 29 – July 2, 2014), Toronto, Canada, Abstract O13.1.
872. J. F. B. Pereira, K. A. Kurnia, O. A. Cojocaru, G. Gurau, L. P. N. Rebelo, M. G. Freire, J. A. P. Coutinho, and R. D. Rogers, "Are crystalline cholinium salts really different from liquid cholinium salts in the formation of aqueous biphasic systems with polyethylene glycol?" Presented by J. F. B. Pereira before the 2nd International Conference on Ionic Liquids in Separation and Purification Technology (ILSEPT; June 29 – July 2, 2014), Toronto, Canada, Abstract O15.1.
873. S. Nemser, P. R. Campos, D. Campos, S. Majumdar, R. D. Rogers, G. Gurau, B. A. Simmons, S. Singh, and J. Sun, "Dehydration of ionic liquids by pervaporation with perfluorinated membranes," Presented by S. Nemser before the 2nd

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 91

IPR2020-00770
United Therapeutics EX2007
Page 3641 of 7335

International Conference on Ionic Liquids in Separation and Purification Technology (ILSEPT; June 29 – July 2, 2014), Toronto, Canada, Abstract O17.1.

874. J. A. P. Coutinho, L. I. N. Tomé, M. G. Freire, J. R. Gomes, J. F. B. Pereira, and R. D. Rogers, "'Washing-out' polyethylene glycol-ionic liquid mixtures to form aqueous biphasic systems," Presented by J. A. P. Coutinho before the 2nd International Conference on Ionic Liquids in Separation and Purification Technology (ILSEPT; June 29 – July 2, 2014), Toronto, Canada, Abstract P010.
875. F. A. e Silva, J. F. B. Pereira, R. D. Rogers, A. M. S. Silva, J. A. P. Coutinho, and M. G. Freire, "When do quaternary ammonium halides behave as ionic liquids in the formation of aqueous biphasic systems?" Presented by J. F. B. Pereira before the 2nd International Conference on Ionic Liquids in Separation and Purification Technology (ILSEPT; June 29 – July 2, 2014), Toronto, Canada, Abstract PO44.
876. J. F. B. Pereira, L. A. Flores, H. Wang, and R. D. Rogers, "Ionic liquid-benzene mixtures: The key to understanding liquid clathrate formation," Presented by J. F. B. Pereira before the 2nd International Conference on Ionic Liquids in Separation and Purification Technology (ILSEPT; June 29 – July 2, 2014), Toronto, Canada, Abstract P074.
877. R. D. Rogers, "Processing of Lignocellulosic Biomass Using Ionic Liquids," Presented by R. D. Rogers before the Hybrid Processing for Biorenewable Fuels & Chemicals Production Symposium (July 10-11, 2014), Denver, CO, No Abstract (Invited Speaker).
878. R. D. Rogers, "Using Ionic Liquids for the Development of Renewable Biopolymer-Based Adsorbents for the Extraction of Uranium from Seawater and Testing Under Marine Conditions," Presented by R. D. Rogers before the DOE-NE Fuel Resources FY 14 Working Group Meeting (July 28-29, 2014), Sequim, WA (No Abstract).
879. G. Gurau, J. L. Shamshina, and R. D. Rogers, "High Throughput Electrospinning of Uranium Selective Chitin Adsorbents – A Sustainable Ionic Liquid Technology," Presented by G. Gurau before Gordon Research Conference on Ionic Liquids: Solvents, Materials, or Medicines?, (August 17-22, 2014), Sunday River Resort, Newry, ME, Abstract 23.
880. J. L. Shamshina, G. Gurau, L. E. Block, L. K. Hansen, C. Dingee, A. Walters, and R. D. Rogers, "Chitin-Calcium Alginate Composite Fibers for Wound Care Dressings Spun from an Ionic Liquid," presented by J. L. Shamshina before Gordon Research Conference on Ionic Liquids: Solvents, Materials, or Medicines?, (August 17-22, 2014), Sunday River Resort, Newry, ME, Abstract 48.
881. S. Yerkimbekova, J. L.Shamshina, G. Gurau, A. Zazybin, V. Yu1, and R. D. Rogers, "Ionic Liquids as Electrolytes," Presented by S. Yerkimbekova before Gordon Research Conference on Ionic Liquids: Solvents, Materials, or Medicines?, (August 17-22, 2014), Sunday River Resort, Newry, ME, Abstract 64.
882. F. Cheng, H. Wang, and R. D. Rogers, "Enhancement of Dissolution and Delignification of Woody Biomass in Ionic Liquids in the Presence of Polyoxometalate and Oxygen," Presented by F. Cheng before Gordon Research Conference on Ionic Liquids: Solvents, Materials, or Medicines?, (August 17-22, 2014), Sunday River Resort, Newry, ME, Abstract 10.
883. O. A. Cojocaru, J. Shamshina, J. Pernak, and R. D. Rogers, "Herbicidal Ionic Liquids with Reduced Volatility and Increased Efficacy," Presented by J. Shamshina before Gordon Research Conference on Ionic Liquids: Solvents, Materials, or Medicines?, (August 17-22, 2014), Sunday River Resort, Newry, ME, Abstract 70.
884. H. Wang, A. S. Myerson, and R. D. Rogers, "Finely Tunable Solvent Properties of Ionic Fluids Containing More Than Two Ions," Presented by H. Wang before Gordon Research Conference on Ionic Liquids: Solvents, Materials, or Medicines?, (August 17-22, 2014), Sunday River Resort, Newry, ME, Abstract 60.
885. S. P. Kelley, J. S. Nuss, and R. D. Rogers, "Forcing unusual Coordination with ionic Liquids designed for f-Element Coordination Chemistry," Presented by S. P. Kelley before Gordon Research Conference on Ionic Liquids: Solvents, Materials, or Medicines?, (August 17-22, 2014), Sunday River Resort, Newry, ME, Abstract 28.
886. L. Flores, J. Pereira, H. Wang, P. McCrary, and R. D. Rogers, "Ionic Liquid Mixtures with benzene: A Greater Understanding of Liquid Clathrates," Presented by L. Flores before Gordon Research Conference on Ionic Liquids: Solvents, Materials, or Medicines? (August 17-22, 2014), Sunday River Resort, Newry, ME, Abstract 15.
887. H. Wang, J. Pereira, A. Myerson, and R. D. Rogers, "Double Salt Ionic Liquids Prepared by Mixing Partially Miscible Ionic Liquids: Tuning the Solubility of Lipophilic Molecules," Presented by R. D. Rogers before the 19th International Symposium on Molten Salts part of the 2014 ECS and SMEQ Joint International Meeting of the 226th Meeting of the Electrochemical Society Meeting and the XXIX Congreso de la Sociedad Mexicana de Electroquímica (October 5-9, 2014), Cancun, Mexico, Abstract H6.1419. (Invited Keynote Presentation)
888. R. D. Rogers and K. Boykin, "Green Chemistry and Advanced Materials from Renewable Polymers: Education, Research, and Entrepreneurship to Motivate the Next Generation of Scientists," Presented by R. D. Rogers before the Joint 31st Latin American Chemistry Congress (Congreso Latinoamericano de Química; CLAQ-2014) and XXVII Peruvian Chemistry Congress (October 14-17, 2014), Lima, Peru, Abstract. (Invited Plenary Presentation)
889. S. Nemser, D. Campos, P. R. Campos, J. Bowser, S. Majumdar, B. A. Simmons, S. Singh, J. Sun, J. Shi, R. D. Rogers, G. Gurau, and F. Cheng, "Perfluorinated Membranes for the Dehydration of Ionic Liquids for Processing Biomass," Presented by S. Nemser before the 2014 AIChE Annual Meeting (November 16-21, 2014), Atlanta, GA, Abstract 637b.
890. R. D. Rogers, "Ideality vs. Reality of Green Chemistry in the Development of Advanced Materials from Renewable Polymers," Presented by R. D. Rogers before the Semi-Annual Meeting of the Innovative Green Wood Fibre Products Network (Nov. 18-20, 2014), Esterel, QC, Canada, Abstract book. (Keynote Speaker)

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 92

IPR2020-00770
United Therapeutics EX2007
Page 3642 of 7335

891. R. D. Rogers, "Using Ionic Liquids for the Development of Renewable Biopolymer-Based Adsorbents for the Extraction of Uranium from Seawater and Testing Under Marine Conditions," Presented by R. D. Rogers before the DOE-NE Fuel Resources FY 15 Working Group Meeting (January 12-13, 2015), Oak Ridge, TN (No Abstract).
892. R. D. Rogers, H. Wang, and S. P. Kelley, "Double salt ionic liquids with unique chemical environments for separations." Presented by R. D. Rogers before the 249th National Meeting of the American Chemical Society (March 22-26, 2015), Denver, CO, Abstract I&EC 1.
893. J. L. Shamshina, G. Gurau, S. P. Kelley, and R. D. Rogers, "Uranium-from-seawater sorbents from fishing industry waste – cost reduction through solvent recycle." Presented by J. L. Shamshina before the 249th National Meeting of the American Chemical Society (March 22-26, 2015), Denver, CO, Abstract I&EC 50.
894. G. Gurau, J. L. Shamshina, S. P. Kelley, and R. D. Rogers, "Uranium-from-seawater sorbents from industry waste – from batch to continuous production." Presented by G. Gurau before the 249th National Meeting of the American Chemical Society (March 22-26, 2015), Denver, CO, Abstract I&EC 30.
895. S. P. Kelley, J. L. Shamshina, G. Gurau, and R. D. Rogers, "Dual functional sorbents for coextraction of aqueous copper and uranium." Presented by S. P. Kelley before the 249th National Meeting of the American Chemical Society (March 22-26, 2015), Denver, CO, Abstract I&EC 48.
896. R. D. Rogers, S. P. Kelley, G. Gurau, G., and J. L. Shamshina, "Nanofiber chitin mats for coextraction of value added metals from seawater: Improving the economics of uranium recovery." Presented by R. D. Rogers before the 249th National Meeting of the American Chemical Society (March 22-26, 2015), Denver, CO, Abstract I&EC 15.
897. J. Bandomir, S. P. Kelley, J. L. Shamshina, G. Gurau, and R. D. Rogers, "Homogeneous blending of chitin with biopolymers for advanced biodegradable sorbents for uranium extraction from seawater." Presented by J. Bandomir before the 249th National Meeting of the American Chemical Society (March 22-26, 2015), Denver, CO, Abstract I&EC 47.
898. R. D. Rogers and S. P. Kelley, "A practical overview of organic synthesis in ionic liquids." Presented by R. D. Rogers before the 249th National Meeting of the American Chemical Society (March 22-26, 2015), Denver, CO, Abstract ORGN 307.
899. R. D. Rogers, "Green Chemistry and Advanced Materials from Renewable Polymers: Education, Research, and Entrepreneurship to Motivate the Next Generation of Scientists," Presented by R. D. Rogers before the 5th Annual Meeting of the Canada Excellence Research Chairs (April 13-14, 2015), Waterloo, ON, Canada.
900. R. D. Rogers, "Innovation is the Gateway to the Biomass Biorefinery and Ultimately A sustainable Bio-based Economy," Presented by R. D. Rogers before the L'Oréal Satellite Symposium at the 3rd International Symposium on Green Chemistry (ISGC 2015), May 3-7, 2015, La Rochelle France (Invited).
901. R. D. Rogers, "Are Alternative Solvent Systems such as Ionic Liquids Green or not Based on Toxicity, Chemical or Energy Use, or Utilization? (Hint: It Depends)," Presented by R. D. Rogers before the 3rd International Symposium on Green Chemistry (ISGC 2015), May 3-7, 2015, La Rochelle, France, Abstract PL9. (Invited Plenary Presentation)
902. R. D. Rogers, and H. Wang, "Ionic Fluids Containing Both Strongly and Weakly Interacting Ions of the Same Charge Have Unique Ionic and Thus Chemical Environments As a Function of Ion Concentration," Presented by R. D. Rogers before the 227th ECS Meeting (May 24-28, 2015), Chicago, IL, Abstract M04-2158. (Invited Keynote presentation)
903. R. D. Rogers, "Green chemistry and advanced materials from renewable polymers: education, research, and entrepreneurship to motivate the next generation of scientists," Presented by R. D. Rogers before the 98th Canadian Chemistry Conference and Exhibition (June 13-17, 2015), Ottawa, ON, Abstract 1177 PL2. (Invited Plenary Presentation).
904. R. D. Rogers, "Is 'Sustainability' a new paradigm for the future chemical industry? Cross border perspectives and what we need to train the next generation to face," Presented by R. D. Rogers before the 98th Canadian Chemistry Conference and Exhibition (June 13-17, 2015) CIC Chair's Event: CIC/CGCEN Business Innovation Session, Ottawa, ON, Abstract. (Invited Presentation).
905. H. Passos, T. B. V. Dinis, A. M. Fernandes, R. D. Rogers, M. G. Freire, and J. A. P. Coutinho, "Ionic liquids as phase-forming components of aqueous multiphasic systems," Presented by H. Passos before the 6th International Congress on Ionic Liquids (COIL-6; Jun. 16-20, 2015), Jeju City, South Korea, Abstract S28.
906. M. Ferreira, R. D. Rogers, M. G. Freire, and J. A. P. Coutinho, "pH reversible aqueous biphasic systems," presented by A. M. Ferreira before the 6th International Congress on Ionic Liquids (COIL-6; Jun. 16-20, 2015), Jeju City, South Korea, Abstract S42.
907. M. Ferreira, R. D. Rogers, M. G. Freire, and J. A. P. Coutinho, "pH-Driven Reversible Aqueous Biphasic Systems Composed of Ionic Liquids," Presented by J. A. P. Coutinho before the Nineteenth Symposium on Thermophysical Properties (June 21-26, 2015), Boulder, CO, Abstract 2385.
908. F. B. Pereira, V. C. Santos-Ebinuma, A. Pessoa, R. D. Rogers, S. P. M. Ventura, M. G. Freire, and J. A. P. Coutinho, "Facing the Complexity of Bioproducts' Purification using PEG-IL-based Aqueous Biphasic Systems: From Antibiotics to L-Asparaginase," Presented by J. F. B. Pereira before the Iberoamerican Meeting on Ionic Liquids - IMIL 2015 (July 2-3 July, 2015), Madrid, Spain, Abstract P13.
909. R. D. Rogers, "Using Ionic Liquids for the Development of Renewable Biopolymer-Based Adsorbents for the Extraction of Uranium from Seawater and Testing Under Marine Conditions," Presented by R. D. Rogers before the DOE-NE Fuel Resources Summer 2015 Working Group Meeting (August 6-7, 2015), College Park, MD (No Abstract).
910. R. M. Hanes, J. L. Shamshina, G. Gurau, T. Di Nardo, P. Berton, S. P. Kelley, and R. D. Rogers, "Uranium-from-Seawater Sorbents from Fishing Industry Waste – Pilot Testing and Financial Analysis," Presented by R. M. Hanes before the DOE-NE Fuel Resources Summer 2015 Working Group Meeting (August 6-7, 2015), College Park, MD (No Abstract).

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 93

IPR2020-00770
United Therapeutics EX2007
Page 3643 of 7335

911. R. D. Rogers and S. P. Kelley, "Covalent, Supramolecular…. Ionic? Using Ionic Liquids to Demonstrate Manipulation of the Ionic Bond; an Underutilized Tool in Crystal Engineering," Presented by R. D. Rogers before the 2nd International Council for Science/International Union of Pure and Applied Chemistry Workshop on Crystal Engineering, (August 30-September 1, 2015), Como, Italy, Abstract Book p. 43. (Invited Expert)
912. R. D. Rogers, "Does the Nature of the Bonding in Double Salt Ionic Liquids "Prove" A Difference Between Ionic Liquids and Molecular Liquids?" Presented by R. D. Rogers before the Joint European Molecular Liquids Group/Japanese Molecular Liquids Group Annual Meeting "Molecular Liquids Meet Ionic Liquids, From Fundamentals to Applications," (Sept. 6-10, 2015), Rostock, Germany, Abstract Book OL p. 16. (Invited Opening Lecture)
913. R. D. Rogers, "Basics of Scholarly Publishing: Peer Review - What It Is, How It Works, and Why It Matters!" Presented by R. D. Rogers to the American Chemical Society On Campus Symposium at the University of Toronto (September 24, 2015), Toronto, ON, Canada, No Abstract (Invited).
914. R. D. Rogers, "Basics of Scholarly Publishing: Peer Review - What It Is, How It Works, and Why It Matters!" Presented by R. D. Rogers to the American Chemical Society On Campus Symposium at York University (September 25, 2015), Toronto, ON, Canada, No Abstract (Invited).
915. R. D. Rogers, "Green Chemistry and Sustainable Technology through Innovation," Presented by R. D. Rogers before the Seminar on Exploitation of Residue Generated by Agribusiness Activity Organized by The Centre of Piscicultural Technological Development at Surcolombiano-Acuapez and Corporación Universitaria del Huila-CORHUILA (November 30, 2015), Neiva, Colombia, No Abstract (Invited Opening Lecture – presented via Skype).
916. R. D. Rogers, "ACS *Crystal Growth & Design*: Founding a journal in the cusp of electronic publishing and open access," Presented by R. D. Rogers before the 2015 International Chemical Congress of Pacific Basin Societies, Pacifichem 2015 (Dec. 15-20, 2015), Honolulu, HI, Abstract SCTY 063. (Invited Presentation)
917. G. Gurau, J. L. Shamshina, N. Abdul Faruk Khan, S. P. Kelley, P. Berton, and R. D. Rogers, "Sustainable materials for energy harvesting – how shrimp shell waste and ionic liquids can make an impact on today's society," Presented by G. Gurau before the 2015 International Chemical Congress of Pacific Basin Societies, Pacifichem 2015 (Dec. 15-20, 2015), Honolulu, HI, Abstract SCTY 335.
918. R. D. Rogers, "Green chemistry and advanced materials from renewable polymers: Education, research, and entrepreneurship to motivate the next generation of scientists," Presented by R. D. Rogers before the 2015 International Chemical Congress of Pacific Basin Societies, Pacifichem 2015 (Dec. 15-20, 2015), Honolulu, HI, Abstract SCTY 385. (Invited Presentation)
919. R. D. Rogers, "Using Ionic Liquids for the Development of Renewable Biopolymer-Based Adsorbents for the Extraction of Uranium from Seawater and Testing Under Marine Conditions," Presented by R. D. Rogers before the DOE-NE Fuel Resources Winter 2016 Working Group Meeting (January 14-15, 2016), Oak Ridge National Lab, TN (No Abstract).
920. R. D. Rogers, "Understanding the Interactions of Seawater Ions with Amidoxime through X-Ray Crystallography," Presented by R. D. Rogers before the DOE-NE Fuel Resources Winter 2016 Working Group Meeting (January 14-15, 2016), Oak Ridge National Lab, TN (No Abstract).
921. R. M. Hanes, J. L. Shamshina, Ezinne Achinivu, and R. D. Rogers, "Uranium-from-Seawater Sorbents from Fishing Industry Waste – Pilot Testing and Financial Analysis," Presented by R. M. Hanes before the DOE-NE Fuel Resources Winter 2016 Working Group Meeting (January 14-15, 2016), Oak Ridge National Lab, TN (No Abstract).
922. R. D. Rogers, "What is an Appropriate Academic Business Model to Drive Commercialization of Sustainable Ionic Liquids-Based Technologies?" Presented by R. D. Rogers before the International Symposium on Ionic Liquids (ISOIL_2016; Jan. 21-22, 2016), Mumbai, India, Abstract. (Invited Keynote Presentation)
923. R. D. Rogers, "Why is the Sugar Industry letting 'Big Corn' Drive the Biorefinery? Innovation is the Gateway to the Biomass Biorefinery and Ultimately A sustainable Bio-based Economy," Presented by R. D. Rogers Before the Sugar Processing Research Institute 2016 Conference on The Science and Technology of a Sustainable Sugar Industry (Feb. 21-25, 2016), Walnut Creek, CA, Abstract Book. (Invited Plenary Presentation).
924. S. P. Kelley, G. P. Rachiero, J. Wang, and R. D. Rogers, "Imidazole-2-thiones as liquid sorbents of Hg(0): Thermal behavior, redox chemistry, and loading on solid supports," Presented by R. D. Rogers before the 251st National Meeting of the American Chemical Society (March 13-17, 2016), San Diego, CA, Abstract ENVR 093.
925. J. L. Shamshina, G. Gurau, and R. D. Rogers, "Translational research: From academia to industry. Following the pathway of George Washington Carver," Presented by R. D. Rogers before the 251st National Meeting of the American Chemical Society (March 13-17, 2016), San Diego, CA, Abstract I&EC 054.
926. P. Berton, G. Gurau, J. L. Shamshina, and R. D. Rogers, "In search of green chemistry and sustainability: Polymeric materials based on renewable polymers," Presented by R. D. Rogers before the 251st National Meeting of the American Chemical Society (March 13-17, 2016), San Diego, CA, Abstract I&EC 109.
927. T. Di Nardo, and R. D. Rogers, "Unlocking the true power of ionic liquids: highly functional, environmentally compatible biopolymer platform," Presented by R. D. Rogers before the 1st Middle-Eastern Materials Science Conference (March 22-23, 2016), Abu Dhabi, United Arab Emirates, Abstract. (Invited)
928. R. D. Rogers, "What is an Appropriate Academic Business Model to Drive Commercialization of Sustainable Technology?" Presented by R. D. Rogers before the CIC/SCI Canada Green, Clean and Sustainable Chemistry Seminar: Innovation Through Collaboration (April 7, 2016), Toronto, ON, Canada. (Invited)
929. R. D. Rogers, "Green Quest: Resourceful Approaches to Resources," Presented by R. D. Rogers before the 6th Annual Meeting of the Canada Excellence Research Chairs (April 11-12, 2016), Ottawa, ON, Canada.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 94

IPR2020-00770
United Therapeutics EX2007
Page 3644 of 7335

930. R. D. Rogers, “What is an Appropriate Academic Business Model to Drive Commercialization of Sustainable Technology?” Presented by R. D. Rogers before GreenWin’s International Conference on Green Chemistry and White Biotechnology (May 12-13, 2016), Gembloux, Belgium, Abstract. (Invited Plenary)
931. R. D. Rogers, “Green chemistry and advanced materials from renewable polymers: Education, research, and entrepreneurship to motivate the next generation of scientists,” Presented by video by R. D. Rogers before the (May 18-20, 2016), Buenos Aires, Argentina, Abstract. (Invited Plenary Presentation)
932. P. Berton and R. D. Rogers, “Millions of new ionic liquids are hiding in plain sight: Understanding the nature of the bonding in double salt ionic liquids (aka ionic liquid mixtures),” Presented by R. D. Rogers before the Pacific Rim Meeting on Electrochemical and Solid-State Science (October 2-7, 2016), Honolulu, HI, Abstract. (Invited)
933. R. D. Rogers, “Innovation is the Gateway to the Biomass Biorefinery and Ultimately A sustainable Bio-based Economy," Presented by R. D. Rogers before the Workshop on Insights and Strategies Towards a Bio-Based Economy (November 22-25, 2016), Montevideo, Uruguay.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 95

IPR2020-00770
United Therapeutics EX2007
Page 3645 of 7335

D. Presentations before Regional Meetings:

1. R. D. Rogers and J. L. Atwood, "The Crystal Structure of $Cu[P(C_6H_5)_2CH_3]_3BH_4$," Presented by R. D. Rogers before the Southeast Regional American Chemical Society Student Affiliate Meeting (1977), University, AL, Abstract 20.
2. R. D. Rogers, W. E. Hunter, and J. L. Atwood, "The Crystal and Molecular Structure of $Mo[CH_2Si(CH_3)_3]_3[P(CH_3)_3]Cl$," Presented by R. D. Rogers before the 29th Southeast Regional ACS Meeting (1977), Tampa, FL, Abstract 348.
3. W. E. Hunter, R. D. Rogers, and J. L. Atwood, "The Lanthanide-Carbon Sigma Bond in $Li[Yb\{CH(SiMe_3)_3\}_3C1]$," Presented by W. E. Hunter before the 29th Southeast Regional ACS Meeting (1977), Tampa, FL, Abstract 350.
4. R. D. Rogers, J. L. Atwood, and R. Gruning, "Synthesis and X-ray Structure Determination of N-Lithiohexamethyldisilazane - Bulky Ligand Effects," Presented by R. D. Rogers before the Annual Meeting of the Alabama Academy of Science (1978), Montgomery, AL, Abstract.
5. P. A. Grutsch, C. Kutal, J. L. Atwood, and R. D. Rogers, "Structure of a Copper(I) Compound Containing the Tetrahydroborate Group," Presented by P. A. Grutsch before the 30th Southeast Regional ACS Meeting (1978), Savannah, GA, Abstract 139.
6. R. D. Rogers, W. J. Cook, and J. L. Atwood, "The Synthesis and Crystal Structure of $(\eta^5\text{-}C_5H_5)Fe[\eta^5\text{-}C_5H_4Al_2(CH_3)_4Cl]$," Presented by R. D. Rogers before the 30th Southeast Regional ACS Meeting (1978), Savannah, GA, Abstract 171.
7. R. D. Rogers, W. E. Hunter, and J. L Atwood, "Crystallographic Examination of the Zirconium-Carbonyl Bond in $(\eta^5\text{-}C_5H_5)_2Zr(CO)_2$," Presented by R. D. Rogers before the 31st Southeast Regional ACS Meeting (1979), Roanoke, VA, Abstract 185.
8. M. S. Dalton, R. D. Rogers, and J. L. Atwood, "X-ray Crystal Structure of $ReBr(CO)_3(Me_2NH)_2$," Presented by M. S. Dalton before the 31st Southeast Regional ACS Meeting (1979), Roanoke, VA, Abstract 188.
9. E. A. Lewis, R. Rogers, and J. L. Atwood, "Thermodynamic Studies of Liquid Clathrate Formation and Coal Liquefaction with Liquid Clathrates," Presented by E. A. Lewis before the 31st Southeast Regional ACS Meeting (1979), Roanoke, VA, Abstract 331.
10. M. S. Dalton, R. D. Rogers, L. D. Kispert, and J. L. Atwood, "The Crystal and Molecular Structure of Bromoflouroacetic Acid, A Chiral Hydrogen Bonded Dimer," Presented by M. S. Dalton before the Annual Meeting of the Alabama Academy of Science (1980), Birmingham, AL, Abstract *Journal of the Alabama Academy of Science*, 51(3), 199 (1980).
11. L. G. Canada, R. D. Rogers, and J. L. Atwood, "The Application of X-ray Crystallography to the Pesticide Aldrin and Related Compounds," Presented by L. G. Canada before the Annual Meeting of the Alabama Academy of Science (1980), Birmingham, AL, Abstract *Journal of the Alabama Academy of Science*, 51(3), 196 (1980).
12. R. D. Rogers and J. L. Atwood, "A Comparison of Mo-Ligand (η^2-) Bonding in $MoCl(\eta^2\text{-}COCH_2SiMe_3)(CO)(PMe_3)_3$ and $Mo(\eta^2\text{-}C_2H_4)_2(PMe_3)_4$," Presented by R. D. Rogers before the 28th Southeast/32nd Southwest Regional ACS Meeting (1980), New Orleans, LA, Abstract 232.
13. F. R. Anderson, R. D. Rogers, and J. L. Atwood, "Crystal and Molecular Structure of 7-Aminothiozolo[5,4-d]pyrimidine-6-oxide," Presented by F. R. Anderson before the 32nd Southeast/28th Southwest Regional ACS Meeting (1980), New Orleans, LA, Abstract 303.
14. L. G. Canada, R. D. Rogers, and J. L. Atwood, "Crystal and Molecular Structure of $Mn_2(CO)_6Br_2Te_2Ph_2$," Presented by L. G. Canada before the Annual Meeting of the Alabama Academy of Science (1981), Auburn, AL, Abstract.
15. R. D. Rogers, C. R. Kerr, M. J. Zaworotko, and J. L. Atwood, "Decomposition of High-Oxygen Content Organoaluminum Compounds: Identification and Characterization of Products," Presented by R. D. Rogers before the 37th Southwest Regional ACS Meeting (1981), San Antonio, TX, Abstract 96.
16. L. G. Canada, R. Priester, R. D. Rogers, and J. L. Atwood, "Complexes of Crown Ethers with Aluminum Alkyls," Presented by L. G. Canada before the 34th Southeast Regional ACS Meeting (1982), Birmingham, AL, Abstract 280.
17. R. D. Rogers, "Crystal and Molecular Structures of Formyl-, Cyano-, and Amino-Cyclopentadienyldicarbonylnitrosylchromium," Presented by R. D. Rogers before the 3rd Joint Great Lakes and Central Regional ACS Meeting (1984), Kalamazoo, MI, Abstract 208.
18. L. K. Kurihara and R. D. Rogers, "Crown Ether Complexation of f-Elements," Presented by L. K. Kurihara before the 19th Great Lakes Regional ACS Meeting (1985), Lafayette, IN, Abstract 191.
19. M. M. Benning and R. D. Rogers, "Crystal and Molecular Structures of (η^5-Pentamethylcyclopentadienyl)(η^5-cyclopentadienyl)dichlorotitanium, -zirconium and -hafnium," Presented by M. M. Benning before the 19th Great Lakes Regional ACS Meeting (1985), Lafayette, IN, Abstract 193.
20. R. D. Rogers, "Structural Chemistry of Mixed Sandwich Compounds: $(\eta^5\text{-}C_5Me_5)(\eta^8\text{-}C_8H_8)Ti$ and $(\eta^5\text{-}C_5Me_5)(\eta^7\text{-}C_7H_7)Ti$," Presented by R. D. Rogers before the 19th Great Lakes Regional ACS Meeting (1985), Lafayette, IN, Abstract 192.
21. E. J. Voss and R. D. Rogers, "X-ray Structure of $(\eta^5, \eta^5\text{-}C_{10}H_8)[Rh(CO)_2]_2$," Presented by E. J. Voss before the Thirty-Seventh Annual Undergraduate Research Symposium (1986), Abbott Park, IL, Abstract.
22. R. D. Rogers and L. K. Kurihara, "f-Element/Crown Ether Complexation-Structural Effects of Hydrogen Bonding," Presented by R. D. Rogers before the 20th Great Lakes Regional ACS Meeting (1986), Milwaukee, WI, Abstract 201.
23. L. K. Kurihara and R. D. Rogers, "f-Element/Crown Ether Complexation- Synthesis and Structures," Presented by L. K. Kurihara before the 20th Great Lakes Regional ACS Meeting (1986), Milwaukee, WI, Abstract 200.
24. M. M. Benning and R. D. Rogers, "Crystal Structures of $(\eta^5\text{-}C_5Me_5)M(\eta^7\text{-}C_7H_7)$ (M=Zr, Hf) and $(\eta^5\text{-}C_5Me_5)Zr(\eta^8\text{-}C_8H_8)$," Presented by M. M. Benning before the 20th Great Lakes Regional ACS Meeting (1986), Milwaukee, WI, Abstract 199.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 96

IPR2020-00770
United Therapeutics EX2007
Page 3646 of 7335

25. E. J. Voss and R. D. Rogers, "f-Element/Crown Ether Complexes. The Exclusion of H_2O from the Metal Ion's Coordination Sphere," Presented by E. J. Voss before the 21st Great Lakes Regional ACS Meeting; Thirty-Eighth Annual Undergraduate Research Symposium (1987), Chicago, IL, Abstract.
26. M. M. Benning and R. D. Rogers, "f-Element/Crown Ether Complexes. Synthetic and Structural Survey of UCl_4 Complexes of Common Crown Ethers," Presented by M. M. Benning before the 21st Great Lakes Regional ACS Meeting (1987), Chicago, IL, Abstract 215.
27. R. D. Rogers, "f-Element/Crown Ether Complexes. Structural Effects of Anion Concentration," Presented by R. D. Rogers before the 21st Great Lakes Regional ACS Meeting (1987), Chicago, IL, Abstract 216.
28. A. H. Bond and R. D. Rogers, "Macrocycle Complexation Chemistry. Complexation and Structural Characterization of Biochemically Toxic Metals," Presented by A. H. Bond before the 22nd Great Lakes Regional ACS Meeting (1989), Duluth, MN, Abstract 031.
29. L. Nunez and R. D. Rogers, "Macrocycle Complexation Chemistry. The Crystal Structure of A Cu(I) Thiacrown Polymer, $[CuCl(18\text{-thiacrown-}6)]_n$," Presented by L. Nunez before the 22nd Great Lakes Regional ACS Meeting (1989), Duluth, MN, Abstract 054.
30. R. F. Henry and R. D. Rogers, "Acyclic Mixed Donor Crown Ether Analogs. Synthesis and Characterization of Lanthanide Complexes of Polyethylene Glycols Containing Sulfur," Presented by R. F. Henry before the 22nd Great Lakes Regional ACS Meeting (1989), Duluth, MN, Abstract 053.
31. R. D. Rogers, "The Effects of Anion Concentration on Crystallization of Lanthanide Chloride Polyethylene Glycol Complexes," Presented by R. D. Rogers before the 22nd Great Lakes Regional ACS Meeting (1989), Duluth, MN, Abstract 052.
32. A. H. Bond and R. D. Rogers, "Macrocycle Complexation Chemistry. 12-crown-4, 15-crown-5, and 18-crown-6 Complexes of Biochemically Toxic Metals," Presented by A. H. Bond before the 40th Annual Undergraduate Symposium (1989, Chicago Section ACS), Libertyville, IL, Abstract.
33. M. M. Witt and R. D. Rogers, "Macrocycle Complexation Chemistry. Six Donor (Pentaethylene Glycol) and Seven Donor (Hexaethylene Glycol) Acyclic Crown Ether Analogs as Dehydrating Agents for Lanthanoid Salts?" Presented by M. M. Witt before the 40th Annual Undergraduate Symposium (1989, Chicago Section ACS), Libertyville, IL, Abstract.
34. H. D. Do, J. R. Peterson, and R. D. Rogers, "Synthetic Approaches Toward Anticancer Lignan Lactones," Presented by H. D. Do before the 23rd Great Lakes Regional ACS Meeting (1990), DeKalb, IL, Abstract 185.
35. T. J. Smillie, J. R. Peterson, R. D. Rogers, and T. P. Conway, "Lignan Derivatives as Potential Platelet Activating Factor Antagonists," Presented by T. J. Smillie before the 23rd Great Lakes Regional ACS Meeting (1990), DeKalb, IL, Abstract 244.
36. A. N. Rollins and R. D. Rogers, "Macrocycle Complexation Chemistry. Structural Effects of Changing Anion and Anion Concentration in Complexes of Lanthanide(III) Ions and Crown Ethers," Presented by A. N. Rollins before the 23rd Great Lakes Regional ACS Meeting (1990), DeKalb, IL, Abstract 139.
37. L. Nunez and R. D. Rogers, "Modification of the Lanthanide Ion Coordination Sphere Via Electrocrystallization of Hydrated Lanthanide Chloride Complexes of 12-Crown-4," Presented by L. Nunez before the 23rd Great Lakes Regional ACS Meeting (1990), DeKalb, IL, Abstract 122.
38. R. F. Henry and R. D. Rogers, "Wrapping the Lanthanide Ion Coordination Sphere. A Study of Polyethylene Glycol Complexes with Four to Eight Donor Atoms," Presented by R. F. Henry before the 23rd Great Lakes Regional ACS Meeting (1990), DeKalb, IL, Abstract 130.
39. A. H. Bond and R. D. Rogers, "Crystallographic Studies of Potential Macrocyclic Extractants for Cd," Presented by A. H. Bond before the 23rd Great Lakes Regional ACS Meeting (1990), DeKalb, IL, Abstract 138.
40. J. Wolff, A. H. Bond, and R. D. Rogers, "Macrocyclic Complexation Chemistry. Four, Five, Six and Seven Donor Polyethylene Glycols as Acyclic Crown Ether-Like Complexing Agents of Mercury," Presented by J. Wolff before the 23rd Great Lakes Regional ACS Meeting (1990), DeKalb, IL, Abstract 236.
41. K. C. Sturge, R. D. Rogers, and M. J. Zaworotko, "Reactivity of Iron(II) Mixed Sandwich Complexes Towards Nucleophiles," Presented by K. C. Sturge before the 23rd Great Lakes Regional ACS Meeting (1990), DeKalb, IL, Abstract 110.
42. S. Christie, M. J. Zaworotko, and R. D. Rogers, "Synthesis and Characterization of Oxybenzoate Metal Complexes," Presented by S. Christie before the 23rd Great Lakes Regional ACS Meeting (1990), DeKalb, IL, Abstract 235.
43. T. J. Smillie, J. R. Peterson, R. D. Rogers, and T. P. Conway, "Lignan Derivatives as Potential Platelet Activating Factor Antagonists," Presented by T. J. Smillie before the 17th MALTO Medicinal Chemistry-Pharmacognosy Meeting (1990), Oklahoma City, OK.
44. A. H. Bond and R. D. Rogers, "Macrocyclic Complexation Chemistry of the Environmentally Toxic Metals," Presented by A. H. Bond before the 13th Mid-West Environmental Chemistry Workshop (1990), Urbana, IL, Abstract 21.
45. R. D. Rogers, "Investigation of Macrocyclic and Polyfunctional Acyclic Chelating Agents in the Development of Improved f-Element Extractants," Presented by R. D. Rogers before the 13th Mid-West Environmental Chemistry Workshop (1990), Urbana, IL, Abstract 20.
46. A. H. Bond and R. D. Rogers, "Synthetic and Crystallographic Studies of Novel Crown Ether and Polyethylene Glycol Complexes of Bi^{3+}," Presented by Andrew H. Bond before the Argonne Undergraduate Symposium (1990), Argonne, IL, Abstract 91.
47. S. E. Huggins, A. H. Bond, A. N. Rollins, and R. D. Rogers, "Crystallographic Investigations of Polymer Crown-Ether Model Compounds," Presented by S. E. Huggins before the 23rd Central/24th Great Lakes Joint Regional ACS Meeting (1991), Indianapolis, IN, Abstract 301.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 97

IPR2020-00770
United Therapeutics EX2007
Page 3647 of 7335

48. A. H. Bond and R. D. Rogers, "Crystallographic Investigations of Crown Ether and Polyethylene Glycol Complexes of Pb^{2+}," Presented by A. H. Bond before the 23rd Central/24th Great Lakes Joint Regional ACS Meeting (1991) Indianapolis, IN, Abstract 302.
49. A. N. Rollins and R. D. Rogers, "Complexation of Mixtures of Hydrated Lanthanum Chloride with Other Hydrated Lanthanide Chloride Salts and 18-Crown-6," Presented by A. N. Rollins before the 23rd Central/24th Great Lakes Joint Regional ACS Meeting (1991), Indianapolis, IN, Abstract 303.
50. R. D. Rogers and A. H. Bond, "Evidence of a Stereochemically Active Lone Pair in the Complexation Chemistry of Bismuth(III) Halides with Crown Ethers and Polyethylene Glycols," Presented by R. D. Rogers before the 23rd Central/24th Great Lakes Joint Regional ACS Meeting (1991), Indianapolis, IN, Abstract 304.
51. A. H. Bond and R. D. Rogers, "Extraction of Bi^{+3} Using Polyethylene Glycol Based Aqueous Biphase Systems," Presented by A. H. Bond before the Amoco/University Poster Session (1991), Naperville, IL.
52. C. B. Bauer, R. D. Rogers, and A. H. Bond, "Aqueous Biphasic Systems for Liquid/Liquid Extraction of Americium, Plutonium, Thorium, and Uranium from Sulfate and Carbonate Media," Presented by C. B. Bauer before the Amoco/University Poster Session (1991), Naperville, IL.
53. Y. Song and R. D. Rogers, "The Investigation of Polyethylene Glycol-Based Aqueous Biphasic Systems for the Extraction of Transition Metal Ions," Presented by Y. Song before the Amoco/University Poster Session (1993), Naperville, IL, Abstract C68.
54. M. W. Brechbiel, O. A. Gansow, C. G. Pippin, R. P. Planalp, and R. D. Rogers, "Synthesis of Polyamino Carboxylate Chelating Agents and X-ray Structural Analysis of Metal Complexes," Presented by R. P. Planalp before the 29th ACS Middle Atlantic Regional Meeting (1995), Washington, DC, Abstract 191.
55. A. H. Bond, C. M. Tomasek, M. J. Gula, F. Chang, E. P. Horwitz, and R. D. Rogers "Concentration, Purification, and Recycle of Dyes from Salt Solutions," Presented by A. H. Bond before the American Association of Textile and Color Chemists/Northern Textile Association 33rd New England Regional Technical Conference (1997), Danvers, MA.
56. B. M. Rapko, B. K. McNamara, and R. D. Rogers, "Coordination Chemistry of Lanthanide Salts with *N,N,N′,N′*-Tetramethylsuccinamide and *N,N,N′,N′*-Tetrahexylsuccinamide," Presented by B. M. Rapko before the 53rd ACS Northwest Regional Meeting (NORM '98) (1998), Pasco, WA, Abstract 065.
57. R. D. Rogers, K. D. Smith, and S. K. Spear, "Aqueous Biphasic Systems: Polyethylene Glycol versus Polyethylene/Polypropylene Glycol Random Copolymer Phase Formation," Presented by K. D. Smith before the 51st Southeast Regional ACS Meeting, SERMACS-99 (1999), Knoxville, TN, Abstract 092.
58. R. D. Rogers, S. T. Griffin, and S. K. Spear, "Partitioning of Mercury using ABEC™ Resins," Presented by S. T. Griffin before the 51st Southeast Regional ACS Meeting, SERMACS-99 (1999), Knoxville, TN, Abstract 214.
59. R. D. Rogers, H. D. Willauer, and J. G. Huddleston, "Polymer-Based Aqueous Biphasic Extraction of Lignin During Alkaline Pulping," Presented by H. D. Willauer before the 51st Southeast Regional ACS Meeting, SERMACS-99 (1999), Knoxville, TN, Abstract 217.
60. R. D. Rogers, A. E. Visser, R. P. Swatloski, and D. H. Hartman, "Liquid/Liquid Extraction of Metal Ions in Room Temperature Ionic Liquids: Cation Effects," Presented by A. E. Visser before the 51st Southeast Regional ACS Meeting, SERMACS-99 (1999), Knoxville, TN, Abstract 595.
61. R. D. Rogers, G. A. Broker, C. V. K. Sharma, and G. J. Szulczewski, "Engineering Tetrapyridylporphyrin Coordination Complexes for Metal Ion Recognition in Crystalline Materials or on Surfaces," Presented by R. D. Rogers before the 51st Southeast Regional ACS Meeting, SERMACS-99 (1999), Knoxville, TN, Abstract 589.
62. R. D. Rogers, "Center for Green Manufacturing," presented by R. D. Rogers before the Green Chemistry Workshop, University of Regina, Energy Research Unit (1999), Regina, Saskatchewan, Canada (Invited Plenary).
63. R. D. Rogers, "Green Chemistry – International Definitions," Presented by R. D. Rogers before the Industries of the Future Alabama Symposium: Sustainable Industry through Green Chemistry and Engineering (2000), Mobile, AL.
64. R. D. Rogers, "R&D in UA's Center for Green Manufacturing," Presented by R. D. Rogers before the Industries of the Future Alabama Symposium: Sustainable Industry through Green Chemistry and Engineering (2000), Mobile, AL.
65. A. E. Visser, R. P. Swatloski, W. M. Reichert, R. D. Rogers, R. Mayton, S. Sheff, A. Wierzbicki, and J. H. Davis, Jr., "Task Specific Ionic Liquids: Urea Thiourea, and Thioether-Derivatized Imidazolium Cations for Hg^{2+} and Cd^{2+} Extraction in Liquid/Liquid Separations, Presented by A. E. Visser before the 52nd Southeast/56th Southwest Combined Regional Meeting of the ACS (2000), New Orleans, LA, Abstract 286.
66. W. M. Reichert, A. E. Visser, R. P. Swatloski, and R. D. Rogers, "Synthesis and Characterization of Novel Environmentally-Benign Solvents: Room Temperature Ionic Liquids," presented by W. M. Reichert before the 52nd Southeast/56th Southwest Combined Regional Meeting of the ACS (2000), New Orleans, LA, Abstract 285.
67. R. D. Rogers, R. P. Swatloski, A. E. Visser, and W. M. Reichert, "Reverse Crystal Engineering: Can We Use the Concepts Learned to Make New Room Temperature Ionic Liquids for Applications as Green Solvent Alternatives?" presented by R. D. Rogers before the 52nd Southeast/56th Southwest Combined Regional Meeting of the ACS (2000), New Orleans, LA, Abstract 203 (Invited Symposium Presentation).
68. R. D. Rogers, "Non-Sugar Products from Sugarcane for the New Millennium: Green Pathways to a Carbohydrate Economy?" Presented by R. D. Rogers to the Louisiana Division of the American Society of Sugar Cane Technologists, Baton Rouge, LA, on 2/6/01.
69. R. D. Rogers, "Innovations in the Sugar Industry," Presented by R. D. Rogers before the 32nd Annual Meeting of the American Society of Sugar Cane Technologists, Florida Division (2001), Belle Glade, FL, no abstract (Invited Keynote Presentation).

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 98

IPR2020-00770
United Therapeutics EX2007
Page 3648 of 7335

70. R. D. Rogers, "From Liquid Clathrates to Ionic Liquids," Presented by R. D. Rogers before the New Directions in Chemistry Symposium (2002), Columbia, MO (Invited Symposium Presentation).
71. R. D. Rogers and J. D. Holbrey, "Challenges and Opportunities in the Use of Ionic Liquids: Separations, Extractions, and the Choice of Ionic Liquid," Presented by R. D. Rogers before the 37th Midwest Regional ACS Meeting (2002), Lawrence, KS, Abstract 070 (Invited Symposium Presentation).
72. R. D. Rogers, G. A. Broker, K. E. Gutowski, and N. J. Bridges, "Crystal Engineering Using Lanthanide Ions as Nodes in Coordination Polymers," Presented by R. D. Rogers before the 54th Southeast Regional ACS Meeting (2002), Charleston, SC, Abstract 118 (Invited Symposium Presentation).
73. S. J. P'Pool, M. A. Klingshirn, J. D. Holbrey, R. D. Rogers, and K. H. Shaughnessy, "Polar, Non-Coordinating Ionic Liquids as Novel Solvents for Coordination Polymerization of Olefins," Presented by S. J. P'Pool before the 54th Southeast Regional ACS Meeting (2002), Charleston, SC, Abstract 275.
74. R. D. Rogers, J. D. Holbrey, and A. E. Visser, "Application of Task Specific Ionic Liquids to the Extraction of Hg^{2+} and Actinides," Presented by R. D. Rogers before the 54th Southeast Regional ACS Meeting (2002), Charleston, SC, Abstract 575 (Invited Symposium Presentation).
75. R. D. Rogers, J. D. Holbrey, and W. M. Reichert, "Polymorphism in 'Ionic Liquids'," Presented by R. D. Rogers before the 38th Midwest Regional ACS Meeting (2003), Columbia, MO, Abstract 364. (Invited Symposium Presentation).
76. S. Spear, J. Holbrey, and R. Rogers, "Ionic liquids as solvents in green chemistry: from fundamental studies to applied implementation," Presented by S. Spear before the 55th Southeast Regional ACS Meeting (2003), Atlanta, GA, Abstract 890.
77. V. A. Cocalia, M. P. Jensen, J. D. Holbrey, S. K. Spear, and R. D. Rogers, "Coordination of Trivalent *f*-elements and Uranyl Ions with Cyanex-272® in the Hydrophobic Ionic Liquid, 1-Decyl-3-methylimidazolium Bis(trifluoro-methanesulfonyl)imide", Presented by V. A. Cocalia at Alabama Actinide Day (2004), Auburn, AL.
78. N. J. Bridges and R. D. Rogers "Actinide Extractions from Nitric Acid using Cyanex 923 in $[C_{10}mim][Tf_2N]$," Presented by N. J. Bridges at Alabama Actinide Day (2004), Auburn, AL.
79. K. E. Gutowski, G. A. Broker, H. D. Willauer, S. K. Spear, and R. D. Rogers "Ionic Liquids in Nuclear Processing and Waste Remediation Applications," Presented by K. E. Gutowski at Alabama Actinide Day (2004), Auburn, AL.
80. S. Memon, K. Caldwell, G. Caldwell, and R. D. Rogers, "Using Caenorhabditis Elegans to Probe the Toxicity of Ionic Liquids," Presented by S. Memon to The University of Alabama College of Arts & Sciences Undergraduate Research and Creative Activity Presentations Competition (2004), Tuscaloosa, AL. (First Place Natural Sciences Division Award)
81. J. H. Poplin, R. P. Swatloski, S. K. Spear, J. D. Holbrey, and R. D. Rogers, "Cellulose-Supported Colorimetric Sensors for Mercury Ion Detection," Presented by J. H. Poplin to The University of Alabama College of Arts & Sciences Undergraduate Research and Creative Activity Presentations Competition (2004), Tuscaloosa, AL. (Third Place Natural Sciences Division Award)
82. J. S. Moulthrop, R. P. Swatloski, R. D. Rogers, and G. Moyna, "High-Resolution ^{13}C NMR Studies of Amylose and Cellulose Oligomers in 1-Butyl-3-methylimidazolium Chloride Solutions," Presented by J. S. Moulthrop to the local Sigma Xi Chapter (2004), Philadelphia, PA.
83. R. D. Rogers, S. K. Spear, and J. D. Holbrey, "Ionic Liquids: Fundamental Studies to Technological Applications in Support of Green Chemistry," Presented by R. D. Rogers before the 60th Southwest Regional ACS Meeting (2004), Ft. Worth, TX, Abstract 265. (Invited Presentation)
84. R. D. Rogers, "Radiochemistry at The University of Alabama," Presented by R. D. Rogers before the Alabama Actinide Day Conference (2005), Tuscaloosa, AL.
85. K. E. Gutowski, D. A. Dixon, and R. D. Rogers "Probing Gas-phase Uranyl-Orthophosphate Structure with Density Functional Theory," Presented by K. E. Gutowski before the Alabama Actinide Day Conference (2005), Tuscaloosa, AL.
86. V. A. Cocalia and R. D. Rogers, "Ionic Liquids and Actinides", Presented by V. A. Cocalia before the Alabama Actinide Day Conference (2005), Tuscaloosa, AL.
87. N. J. Bridges and R. D. Rogers "Aqueous Biphasic Systems (ABS) for the Removal and Recovery of Tc(VI) from High Salt Solutions," Presented by N. J. Bridges before the Alabama Actinide Day Conference (2005), Tuscaloosa, AL.
88. S. B. Memon, G. Caldwell, K. Caldwell, and R. Rogers, "Using *Caenorhabditis elegans* to probe the toxicity of ionic liquids," Presented by S. B. Memon, before the Fourth Annual University of Alabama System Honors Research Day (2005), Birmingham, AL, Abstract A4.
89. W. L. Hough and R. D. Rogers, "Ionic Liquids: The Next Generation of Sweeteners," Presented by W. L. Hough before the Second Annual Undergraduate Research and Creative Activity Oral and Poster Presentations Competition (2005), Tuscaloosa, AL, Abstract.
90. T. B. Wilson and R. D. Rogers, "Thermal Studies of Dual Functional Ionic Liquids," Presented by T. B. Wilson before the Second Annual Undergraduate Research and Creative Activity Oral and Poster Presentations Competition (2005), Tuscaloosa, AL, Abstract.
91. J. H. Poplin and R. D. Rogers, "Utilizing Potentially Green Ionic Liquids: Development of Cellulose Based Magnetic Materials," Presented by J. H. Poplin before the Second Annual Undergraduate Research and Creative Activity Oral and Poster Presentations Competition (2005), Tuscaloosa, AL, Abstract.
92. M. B. Townsend, P. L. Jernigan, M. M. Bailey, S. R. Smith, J. F. Rasco, R. P. Swatloski, R. D. Rogers, and R. D. Hood "Effects of 1-Butyl-3-Methylimidazolium Chloride on Developmental Toxicity in Mice," Presented by M. B. Townsend before the Howard Hughes Poster Session (2005), Tuscaloosa, AL.

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 99

IPR2020-00770
United Therapeutics EX2007
Page 3649 of 7335

93. P. L. Jernigan, M. B. Townsend, M. M. Bailey, S. R. Smith, J. F. Rasco, R. P. Swatloski, R. D. Rogers, and R. D. Hood, "Effects of 1-Decyl-3-Methylimidazolium Chloride on Fetal Development of Mice," Presented by P. L. Jernigan before the Howard Hughes Poster Session (2005), Tuscaloosa, AL.
94. M. L. Moody, J. G. Huddleston, S. T. Griffin, and R. D. Rogers, "Aqueous Influence on the Solvent Properties of Polyethylene Glycol," Presented by M. L. moody before the 57th Southeast/61st Southwest Joint Regional ACS Meeting (2005), Memphis, TN, Abstract Nov 04-098.
95. D. T. Daly and R. D. Rogers, "Multi-Functional Ionic Liquid Compositions Improved Properties for Active Pharmaceutical, Biological, and Nutritional Ingredients," Presented by D. T. Daly before the Biotechnology Association of Alabama Annual Meeting (2006), Birmingham, AL.
96. R. D. Rogers, "Green Chemistry: An Overview," Presented by R. D. Rogers before the Alabama Health and Safety Conference (2006), Tuscaloosa, AL (Keynote Speaker).
97. W. L. Hough and R. D. Rogers, "Dual Function Ionic Liquids," Presented by W. L. Hough before the Third Annual Undergraduate Research and Creative Activity Oral and Poster Presentations Competition (2006), Tuscaloosa, AL, Abstract 16A.
98. M. B. Suggs and R. D. Rogers, "Regeneration of Cellulose Membranes with Ionic Liquids," Presented by M. B. Suggs before the Third Annual Undergraduate Research and Creative Activity Oral and Poster Presentations Competition (2006), Tuscaloosa, AL, Abstract 28A.
99. S. K. Spear, S.T. Griffin, W. M. Reichert, and R. D. Rogers, "Applications of Bio-Solvents to the Nuclear Power Industry," Presented by S. K. Spear before the 5th Southern Bioproducts and Renewable Energy Conference (2006), Choctaw, MS.
100. R. D. Rogers, "Green Chemistry: Can Society and the Chemical Industry Co-Exist?" Presented by R. D. Rogers before the 29th Annual Area Collegiate Chemistry Meeting in conjunction with the Industry-Academe Interaction for Green Chemistry Meeting (2006), Martin, TN. (Invited Panel Participant)
101. R. D. Rogers, R. P. Swatloski, G. Moyna, D. A. Fort, and P. Moyna, "Use of ionic liquids in the study of fruit ripening by high-resolution 13C NMR spectroscopy: 'Green' solvents meet green bananas," by R. D. Rogers before the 37th Great Lakes Regional ACS Meeting (2006), Milwaukee, WI, Abstract 068. (Invited Presentation)
102. R. D. Rogers, "The Evolution of Ionic Liquids - From Solvents and Separations to Advanced Materials and Pharmaceuticals: Examples from the Ionic Liquid Cookbook," Presented to the Queen's University of Belfast QUILL Ionic Liquids Week (2008), Belfast, NI. No Abstract. (Invited Presentation)
103. R. D. Rogers, "Ionic Liquids," The University of Alabama IP Forum (2008), Tuscaloosa, AL.
104. S. Watts, D. Daly, R. Frazier, R. Rogers, and W. Hough-Troutman, "Slow Release of an Active Ingredient from Ionic Liquid Regenerated Cellulose Beads," Presented by S. Watts before The University of Alabama First Annual Undergraduate Research and Creative Activity Conference (2008), Tuscaloosa, AL; Abstract Book. (Second Place Poster)
105. S. Mroczynski, D. Daly, S. Spear, and R. D. Rogers, "Strength from the Sea," Presented by S. Mroczynski before The University of Alabama First Annual Undergraduate Research and Creative Activity Conference (2008), Tuscaloosa, AL.
106. N. Sun, M. Rahman, Y. Qin, M. L. Maxim, and R. D. Rogers, "Dissolution and Separation of Biomass Utilizing Ionic Liquids" Presented by N. Sun before the 60th Southeast Regional Meeting of the American Chemical Society (SERMACS) (2008), Nashville, TN, Abstract 250.
107. N. J. Bridges, T. M. Adams, A. E. Visser, M. J. Williamson, and R. D. Rogers, "Ionic Liquids from Phase Modifier to Solvent for Future Nuclear Fuel Processing," Presented by N. J. Bridges before the 60th Southeast Regional Meeting of the American Chemical Society (SERMACS) (2008), Nashville, TN, Abstract 647.
108. J. Sherrill, J. Beaird, J. F. Rasco, J. M. Sturdivant, M. B. Townsend, P. L. Jernigan, R. D. Hood, R. P. Swatloski, R. D. Rogers, and M. M. Bailey, "Developmental Toxicity of Ionic Liquids," Presented by J. Sherrill before the 86th Annual Meeting of the Alabama Academy of Science (2009), Livingston, AL, Abstract: *J. Alabama Acad. Sci.* **2009**, *80*, 117-118.
109. A. Metlen and R. D. Rogers, "Dithiocarbamate Salts and Ionic Liquids," Poster presented by A. Metlen at the QUILL 10th Anniversary Meeting (March-April 2009), Belfast, Northern Ireland, UK.
110. Y. Zou, J. D. Holbrey, and R. D. Rogers, "Ionic Liquids for Aromatic and Aliphatic Hydrocarbon Separation," Poster presented by Y. Zou at the QUILL 10th Anniversary Meeting (March-April 2009), Belfast, Northern Ireland, UK.
111. R. D. Rogers "Ionic Liquids: At the Intersections," Presented by R. D. Rogers at the QUILL 10th Anniversary Meeting (March-April 2009), Belfast, Northern Ireland, UK.
112. D. M. Drab, J. L. Shamshina, S. Smiglak, C. C. Hines, D. B. Cordes, and R. D. Rogers, "Establishing a flexible synthetic design platform for multi-heterocyclic ionic liquids: Introduction of concept and initial demonstration," Presented by D. M. Drab at the 13th Annual Graduate Student Association Research and Thesis Conference (2010), The University of Alabama, Tuscaloosa, AL, Abstract Book.
113. S. Kyle Lee, W. Hough-Troutman, R. D. Rogers, K. A. Caldwell, and G. A. Caldwell, "Searching for Ionic Liquid Partners That Will Enhance the Neuroprotective Role of Lidocaine," Presented by S. Kyle Lee before the UA Undergraduate Research Competition (2010), Tuscaloosa, AL.
114. R. D. Rogers, "Green Chemistry, Technology, & Innovation," Presented by R. D. Rogers at the Crimson In Green: An Energy Forum (February 17, 2012), Tuscaloosa, AL, No Abstract (Invited Speaker).
115. R. D. Rogers, "Ionic Liquid Solvents for the Grand Challenge Inherent in a Biorefinery: Extraction, Separation, and Processing of Lignin, Cellulose, Hemicellulose, and Chitin" Presented by R. D. Rogers before the Inaugural SEC Symposium: Impact of the Southeast in the World's Renewable Energy Future (Feb. 10-12, 2013), Atlanta, GA, Abstract Book p 34. (Invited Presenter).

IPR2016-00006
SteadyMed - Exhibit 1023 - Page 100

IPR2020-00770
United Therapeutics EX2007
Page 3650 of 7335