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.
10/551,205	11/14/2006	Nicholas S. Bodor	0056192-000024	4092

21839 7590 04/04/2008

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
04/04/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/551,205	BODOR ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35 and 56-98* is/are pending in the application.

4a) Of the above claim(s) *13-35 and 67-81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,56-66 and 82-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

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)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :11 pgs / 14Nov2006, 10Aug2007, 8Nov2007, 4Jan2008.

DETAILED ACTION

This application is the national stage entry of PCT/US04/09387, filed 26 Mar 2004; and claims benefit of provisional application 60/458,922, filed 28 Mar 2003; and claims benefit of provisional application 60/484,756, filed 02 July 2003; and claims benefit of provisional application 60/541,247, filed 04 Feb 2004.

Claims 1-35 and 56-98 are pending in the current application. Claims 13-35 and 67-81, drawn to non-elected inventions, are withdrawn. Claims 1-12, 56-66, and 82-98 are examined on the merits herein.

However, the parent applications provisional application 60/458,922, filed 28 Mar 2003; provisional application 60/484,756, filed 02 July 2003; and provisional application 60/541,247, filed 04 Feb 2004; upon which priority is claimed fail to provide adequate support under 35 U.S.C. 112 for the instant claims 1-12, 56-66, and 82-98 of this application since parent applications 60/458,922, filed 28 Mar 2003; and 60/484,756, filed 02 July 2003 are not seen to disclose the amorphous cladribine-cyclodextrin complex of in the independent claims 1, 56 and 82. Written description for claims 1-11 and 56-65 may be found in provisional application 60/541,247, filed 04 Feb 2004, however no support is found for the percent by weight present in the inclusion complex and the non-inclusion complex of instant claims 12 and 66, the temperature range of about 40 to about 80 °C of claims 82 and 83, the temperature range of about 45 to about 50 °C of claim 85, or the temperature range of about -40 to about -80 °C of claim 89. Thus, the filing date of the instant claims 12, 66, 82, 83, 85, 88 and 89 are deemed to be the filing date of the instant application, 14 Nov 2006. The filing date of instant

claims 1-11, 56-65, 84, 86 and 87 are deemed to be the filing date of provisional application 60/541,247, filed 04 Feb 2004. If applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the earlier priority applications. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

Election/Restrictions

Applicant's election with traverse of the invention of Group I, claims 1-12, 56-66, and 82-98, in the reply filed on 04 Jan 2008 is acknowledged. The traversal is on the ground(s) that the amorphous nature of the complex is part of the special technical feature of the cladribine-cyclodextrin complex in a solid oral dosage form. This is not found persuasive because Schultz et al. (US Patent 6,194,395, of record) explicitly discloses a cladribine-cyclodextrin complex in a solid oral dosage form (column 5, lines 50-52). Further, Schultz et al. references the method of making said solid oral dosage form disclosed in WIPO Publication WO97/18839 (cited in PTO-892), which is drawn to the embodiment wherein the melt-extruded forms consist essentially of amorphous material (page 8, lines 14-15). Therefore WIPO Publication WO97/18839 provides evidence that it was recognized in the prior art that the product disclosed by Schultz et al. inherently includes amorphous cladribine-cyclodextrin complex in a solid oral dosage form. While the International Search Report is factually correct in stating that Schultz et al. is silent about specific ratios of cladribine to cyclodextrin and amorphous forms, a

patent need not teach, and preferably omits, what is well known in the art. By referencing WIPO Publication WO97/18839 Schultz et al. demonstrates that the amorphous cladribine-cyclodextrin complex produced by the melt-extrusion method is well known in the prior art. Finally, to address the scientific issue regarding the equilibrium presence of both the inclusion and non-inclusion complex, while the mathematical equation for the equilibrium of the cladribine-cyclodextrin inclusion complex and the cladribine-cyclodextrin non-inclusion complex would be different for cladribine and cyclodextrin in a solvent versus cladribine and cyclodextrin in a molten state, ie. a liquid mixture absent solvent, the equilibrium and thus equilibrium products would still be present.

The requirement is still deemed proper and is therefore made FINAL.

Claims 13-35 and 67-81 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the reply filed on 04 Jan 2008.

Specification

The disclosure is objected to because of the following informalities:

a) The blanks identifying the provisional patent application numbers on page 23, lines 25 and 27 must be replaced with the application numbers.

b) The minor typographical error “comples” on page 22, line 12.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 11 and 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "saturated" in claims 2, 11 and 57 is a relative term which renders the claim indefinite. The term "saturated" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The following definition for "saturated" is provided in the specification, page 10 lines 1-13:

> The term "saturated" when used in conjunction with a complex of cladribine in amorphous cyclodextrin means that the complex is saturated with cladribine, that is, the complex contains the maximum amount of cladribine which can be complexed (by means of both inclusion and non-inclusion complexes) with a given amount of cyclodextrin under the conditions of complexation used. A phase solubility study can be used to provide this information, as described in more detail hereinafter. (Conditions for the complexation are also described in more detail below.) Alternatively, a saturated complex may be arrived at empirically by simply adding cladribine to an aqueous solution of the selected cyclodextrin until no more cladribine goes into solution; ultimately, excess cladribine, if any, is removed (by filtration or centrifugation) and the solution lyophilized to provide the dry saturated complex.

The saturated complex is defined in relation to a maximum amount of cladribine which can be complexed under the conditions of complexation used. However, this amount is defined only empirically. A saturated aqueous solution is invoked with regard to this empirically defined maximum amount of cladribine which can be complexed, but the

claims are drawn to a saturated complex in a solid oral dosage form, not a saturated solution. Therefore one of ordinary skill in the art would not be reasonably apprised of the scope of the invention because the maximum amount would have to be determined empirically for each composition. For the purpose of furthering prosecution, Examiner has interpreted the “maximum amount of cladribine which can be complexed” to be the weight ratio of 1:10 for the cladribine:cyclodextrin complex, based on guidance given on page 31, lines 18-20.

Claim 2 recites the limitation "the complex" in line 2. There is insufficient antecedent basis for this limitation in the claim. It is unclear which complex is referred to by the term “the complex," the inclusion complex (a), the non-inclusion complex (b), both complexes or the complex cladribin-cyclodextrin complex.

Similarly, claim 11 recites the limitation “saturated complexes" in line 3. There is insufficient antecedent basis for this limitation in the claim. It is unclear which complex is referred to by the term “complexes," the inclusion complex (a), the non-inclusion complex (b), both complexes or the complex cladribin-cyclodextrin complex.

The term "a point located on a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin" in claim 11 is a relative term which renders the claim indefinite. The term "a point located on a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The broadness of the term “a point

located on a phase solubility diagram" does not necessarily render the term indefinite. However, no standard is given for what "phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin" is referred to in the claim, such as what temperature, pressure, or solvent this phase solubility diagram describes. Therefore one of ordinary skill in the art would not be reasonably apprised of the scope of the invention from the term "a point located on a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 11, 56-60, 82-90 and 94-98 are rejected under 35 U.S.C. 102(b) as being anticipated by Schultz et al. (US Patent 6,194,395, published 27 Feb 2001, of record) as evidenced by Baert et al. (WIPO Publication WO97/18839, published 29 May 1997, cited in PTO-892).

Schultz et al. discloses a solid pharmaceutical oral dosage form of cladribine comprising cladribine and cyclodextrin (column 2, lines 31-39), meeting the limitations of instant claims 1 and 56. The disclosed product is substantially identical to a product-by-process meeting the limitations of instant claims 82-90 and 94-96. Schultz et al. discloses the use of β- and γ-cyclodextrins (column 2, lines 56-58) and derivatives

wherein one or more cyclodextrin hydroxy groups are replaced with groups such as methyl, hydroxypropyl, carboxymethyl (column 3, lines 26-27) or sulfobutylcyclodextrins (column 4, lines 22-24), meeting the limitations of instant claims 3-5 and 58-60. The phrase "one or more cyclodextrin hydroxy groups" combined with the absence of specific structural details of which hydroxyl group is substituted with a methyl group meets the limitation of "randomly methylated β-cyclodextrins" of instant claims 3 and 58. Schultz et al. discloses the solid oral dosage form in the form of a tablet (column 5, lines 37-38) including the excipients sorbitol and magnesium stearate (column 6, lines 2-7), disclosing a product that is substantially identical to a product-by-process meeting the limitations of instant claims 97 and 98. Schultz et al. discloses an oral dosage form comprising up to 15 mg cladribine and cyclodextrin from 100 to 500 mg, which would lead one of skill in the art to instantly envision a cladribine to cyclodextrin ratio ranging from 15 mg:100 mg to 15mg:500 mg, or 1:6.67 to 1:33.3 by weight (column 6, lines 23-31). These values molar ratios that correspond to "a point located on a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin," meeting the limitations of instant claim 11. The language of instant claim 11 as disclosed requires only that the point be located on a phase solubility diagram for said complexes, not that the point be located on the curve defining a saturated complex such as the curve disclosed in the Figure, meaning that any composition according to claim 1 necessarily meets the limitations of instant claim 11 as disclosed. The instant specification suggests that maximum amount of cladribine which can be complexed gives a weight ratio of 1:10 for the cladribine:cyclodextrin complex. Therefore a

composition comprising the cladribine:cyclodextrin complex that contains a cladribine to cyclodextrin ratio of 1:6.67 describes a composition that comprises a "saturated" complex and meets the limitations of instant claims 2 and 57. The open language of "comprising" allows for the presence of uncomplexed cladribine in the composition.

Schultz et al. incorporates-by-reference the method of making said solid oral dosage form (Schultz et al.column 5, lines 50-52) disclosed in WIPO Publication WO97/18839, Baert et al., which provides evidence in the embodiment wherein the melt-extruded forms consist essentially of amorphous material (Baert et al. page 8, lines 14-15). Therefore Baert et al. provides evidence that it was recognized in the prior art that the product disclosed by Schultz et al. inherently includes amorphous cladribine-cyclodextrin complex in a solid oral dosage form.

To address the scientific issue regarding the equilibrium presence of both the inclusion and non-inclusion complex, while the equation for the equilibrium of the cladribine-cyclodextrin inclusion complex and the cladribine-cyclodextrin non-inclusion complex would be different for cladribine and cyclodextrin in a solvent versus cladribine and cyclodextrin in a molten state due to the lack of a solvent, the equilibrium and thus equilibrium products, the cladribine-cyclodextrin inclusion complex and the cladribine-cyclodextrin non-inclusion complex, would still be inherent in the product disclosed by Schultz et al.

Claims 82-90 and 94-98 are drawn to a product-by-process. The disclosed product is substantially identical to the instantly claimed product-by-process, an amorphous solid pharmaceutical oral dosage form comprising cladribine and

cyclodextrin. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed. The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.). See MPEP 2113.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented 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. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6-10, 12, 56, 61-66, 82 and 91-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schultz et al. (US Patent 6,194,395, published 27 Feb 2001, of record) in view of Baert et al. (WIPO Publication WO97/18839, published 29 May 1997, cited in PTO-892).

Schultz et al. as evidenced by Baert et al. discloses as above. Schultz et al. implicitly discloses an oral dosage form comprising up to 15 mg cladribine and cyclodextrin from 100 to 500 mg, or a cladribine to cyclodextrin ratio ranging from 1:6.67 to 1:33.3 by weight (column 6, lines 23-31).

Schultz et al. does not specifically disclose the composition comprising a cladribine to cyclodextrin ratio from about 1:10 to about 1:16 (instant claims 6, 7, 10, 61, 62 and 65), or a ratio of about 1:14 (instant claims 8 and 63) or about 1:11 (instant claims 9 and 64). Schultz et al. does not specifically disclose the complex wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b) (instant claims 12 and 66). Schultz et al. does not specifically disclose the product-by-process wherein 12.00 parts by weight of cladribine and 172.50 parts by

weight of hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process (instant claim 91 and 93), to give a cladribine to cyclodextrin ratio of 1:14.38.

Schultz et al. does not specifically disclose the product-by-process wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process (instant claim 92), to give a cladribine to cyclodextrin ratio of 1:10.55.

Baert et al. discloses a solid mixture comprising one or more cyclodextrins and an insoluble active ingredient embedded into the cyclodextrin carrier (abstract), and teaches ratios of active ingredient to cyclodextrin of from about 1:100 to 100:1, from about 1:5 and 5:1 and from about 1:3 to 3:1 (page 11, lines 1-5). These ratios are interpreted as mole ratios because Baert et al. teaches the use of different active ingredients with different molecular weights. A mole ratio of active ingredient to cyclodextrin of about 1:3 for cladribine (MW 285.7 g/mol) and β-cyclodextrin (MW 1135 g/mol) gives a ratio by weight of approximately 1:11.9. The ratio of 1:11.9 meets the limitation of both a ratio of about 1:11 and a ratio of about 1:14 according to the non-limiting definition of "about" as a variance of 20% provided in the instant specification page 9, lines 6-11.

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the solid pharmaceutical oral dosage form of cladribine comprising cladribine and cyclodextrin disclosed by Schultz et al. in the ratios of cladribine and cyclodextrin taught by Baert et al. One of ordinary skill in the art would be motivated to combine the Schultz et al. and Baert et al. because Schultz et al. incorporates-by-

reference Baert et al. and because Baert et al. suggests that improving a similar product according to the teachings of Baert et al. has beneficial properties such as high bioavailability and dissolution rate (Baert et al. page 7, lines 25-27). One of ordinary skill in the art would have an expectation of success because the ratios taught by Baert et al. fall within the range of ratios that is implicitly disclosed by Schultz et al. Schultz et al. in view of Baert et al. does not teach the specific cladribine to cyclodextrin ratios of 1:14.38 or 1:10.55, however these ratios are encompassed by the prior art and Baert et al. suggests optimization of the ratio (Baert et al. page 11, lines 1-5). See also MPEP 2144.05 II.A, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical." Schultz et al. in view of Baert et al. does not specifically disclose the complex wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b). However, it is well known in the art that the formation of an inclusion complex from a non-inclusion complex is an equilibrium process, and the position of this equilibrium is dependent on the concentrations of the cladribine and cyclodextrin. This molecular inclusion equilibrium is a process inherent in the formation of the inclusion complex in both aqueous solutions and hot melt liquid mixtures, and Baert et al. teaches variation of the ratio of cladribine to cyclodextrin and hence their relative concentration.

It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which

there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed, namely the position of the equilibrium process governing formation of an inclusion complex and a non-inclusion complex. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Conclusion

No claim is found to be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jonathan Lau
Patent Examiner
Art Unit 1623

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner, Art Unit 1623

Notice of References Cited	Application/Control No. 10/551,205	Applicant(s)/Patent Under Reexamination BODOR ET AL.	
	Examiner Jonathan S. Lau	Art Unit 1623	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 47/48 — A1

(11) International Publication Number: WO 97/18839

(43) International Publication Date: 29 May 1997 (29.05.97)

(21) International Application Number: PCT/EP96/05118

(22) International Filing Date: 20 November 1996 (20.11.96)

(30) Priority Data:
95203219.1 23 November 1995 (23.11.95) EP
(34) Countries for which the regional or international application was filed: AT et al.

(71) Applicant *(for all designated States except US)*: JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BAERT, Lieven, Elvire, Colette [BE/BE]; Gouden Boomstraat 52/3, B-8000 Brugge (BE). PEETERS, Jozef [BE/BE]; Sint Corneliusstraat 64, B-2430 Beerse (BE). VERRECK, Geert [BE/BE]; Salvialaan 5, B-2980 Zoersel (BE).

(74) Agent: DE CORTE, Filip; Janssen Pharmaceutica N.V., Patent Dept., Turnhoutseweg 30, B-2340 Beerse (BE).

(81) Designated States: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KG, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: SOLID MIXTURES OF CYCLODEXTRINS PREPARED VIA MELT-EXTRUSION

(57) Abstract

Process for preparing a solid mixture comprising one or more cyclodextrins and an insoluble active ingredient characterized in that said process comprises a melt-extrusion step, wherein the active ingredient is embedded into the cyclodextrin carrier.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

SOLID MIXTURES OF CYCLODEXTRINS PREPARED VIA MELT-EXTRUSION

The present invention involves a process for preparing solid mixtures by melt-extrusion comprising one or more active ingredients, preferably one or more practically insoluble active ingredients and one or more cyclodextrins. The invention further concerns pharmaceutical compositions comprising the above mixture.

WO 94/11031, published on May 5, 1994, discloses a method of manufacturing a high-quality enclosure compound using extrusion techniques. In this document the extrusion of cyclodextrins together with an active ingredient is mentioned. However, the document discloses the use of a wet mixture (i.e. including water or another solvent) to feed into the extruder.

French patent application 2,705,677 published on December 2, 1994 describes micro-granules obtained by extrusion-spheronisation containing a cyclodextrin. The extrusion-spheronisation technique is the combination of an agglomeration technique, i.e. extrusion, and a shaping technique, i.e. the spheronisation. Said patent application actually teaches the formation of microgranulates containing β-cyclodextrin (Kleptose®) and microcrystalline cellulose (Avicel®) and as active ingredients ketoprofen and paracetamol. The extrusion technique used in the above-mentioned patent application consists in preforming a humid mass by forcing said human mass through a nozzle thus forming long strands of extruded material. The document does not mention melt-extrusion at all.

EP 0,665,009, published as international application on April 24, 1994, discloses a method of dislocating the crystalline condition of crystalline medicine by extruding said crystalline material as such, i.e. without any excipient such as cyclodextrins.

In J. Pharm. Pharmacolog., vol 44, No 2, pages 73-8, Uekama *et al* show how amorphous nifedipine powders were prepared by spray-drying with hydroxypropyl-β-cyclodextrins. The document does not mention melt-extrusion.

In Pharm. Weekbl. Sci. Ed., 1988, vol 10, No 2, page(s) 80-85, Van Doorne *et al* , the complex formation between β-cyclodextrins and six antimicotic imidazole derivatives was studied. In said study gels and creams comprising antimicotics were prepared

whereby a 1.8 % solution of β-cyclodextrin was added instead of purified water. There is no mentioning of extrusion at all.

In J. Antimicrob. Chemother., 1993, vol 32, No 3, pages 459-463, Hostetler *et al* describe the effect of hydroxypropyl-β-cyclodextrin on the efficacy of oral itraconazole in disseminated murine cryptococcosis. In said document the authors describe how itraconazole is solubilized in hydroxypropyl-β-cyclodextrin resulting in a 100 ml solution. There is no mentioning at all of an extrusion process.

In Jpn. J. Med. Mycol., 1994, vol 35, No 3, page 263-267, Mikami *et al* describe the effect of carrier solvents on the efficacy of oral itraconazole therapy in aspergilossis in mice. Again this document discloses itraconazole being solubilized in hydroxypropyl-β-cyclodextrin. There is no mentioning of extrusion techniques.

In "Effect of 2-Hydroxypropyl-β-cyclodextrin on Crystallization and Polymorphic Transition of Nifedipine in Solid State", Pharmaceutical research, vol 11, No 12, 1994, Uekama et al. describe a glassy mixture of 2-hydroxypropyl-β-cyclodextrin obtained by heating said mixture and immediately cooling said mixture to 0 degrees Celsius. There is no teaching that this mixture can be extruded.

US 5,009,900 describe glassy matrices that are useful for introducing and/or retaining and/or stabilizing the volatile and/or labile components in cooked and uncooked food products. These glassy matrices comprise chemically modified starch having a dextrose equivalent not greater than about 2; maltodextrin, corn syrup solids or a polydextrose, and a mono- or disaccharide. The document does disclose extrusion to form glassy matrices. However, there is no specific mentioning of cyclodextrins and of therapeutically or pharmaceutically active ingredients.

None of the above mentioned documents disclose the present invention.

Although WO 94/11031 and French patent application 2,705,677 disclose extrusion of mixtures of cyclodextrins and actives ingredients, said documents do not mention the use of meltextrusion. The technique described in WO 94/11031 and French patent application 2,705,677 has a main disadvantage, that a humid mass needs to be prepared which requires adding to the cyclodextrin and the active ingredient a certain amount of water and in most cases others solvents such as ethanol or methanol. Removing the water and/or other solvents is often a troublesome production step, which often leads to

irreproducibility because not all of the solvent can be removed. Moreover, with practically insoluble active ingredients the amounts of water and/or adjuvant solvents needed make the above technique unpractical on a production scale. Another disadvantage of the technique described in the prior art is that the drying step can induce unwanted crystallization of the active ingredient.

These problems are solved in the present invention by the use of a melt-extrusion process to form solid mixtures comprising one or more cyclodextrins and insoluble active ingredients.

The present process is advantageously applicable when said active ingredient is sensitive to a solvent such as water or an organic solvent, because it does not require any solvent. The term "sensitive" used herein means that the active ingredient is readily (e.g. within about one hour) influenced by a solvent to such an extent that its physical, chemical and/or biological properties are substantially modified or changed.

The present process is further advantageous because it does not require a drying step, during which insoluble active ingredients often tend to crystallize.

The term "insoluble" hereinabove and hereinunder refers to three categories of compounds, i.e. the "very slightly soluble", "practically insoluble" and "insoluble".

The terms "very slightly soluble", "practically insoluble" or "insoluble" are to be understood as defined in the United States Pharmacopeia 23, NF 18 (1995) page 7, i.e. a "very slightly soluble" compound requires from 1000 to 10,000 parts of solvent for 1 part of solute; a "practically insoluble" or "insoluble" compound requires more than 10,000 parts of solvent for 1 part of solute. The solute referred to in these cases are water or aqueous solutions.

Three examples of this type of insoluble compounds are : itraconazole, loviride and (±)-ethyl (R*,R*)-4-[5-[1-[1-[(4-chlorophenyl)hydroxymethyl]propyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]-2-pyridinyl]-1-piperazinecarboxylate (hereinafter referred to as compound 1).

Itraconazole is an art-known antifungal. Loviride is an art-known anti-retrovirally active compound, particularly useful in treating HIV-infected patients.

(±)-Ethyl (R*,R*)-4-[5-[1-[1-[(4-chlorophenyl)hydroxymethyl]propyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]-2-pyridinyl]-1-piperazinecarboxylate is described as compound No. 3, in WO 95/27704 published on October 19, 1995.

The compounds that are suitable to be used in this technique are compounds that show no appreciable decomposition at the temperatures needed to melt and extrude the mixture of said one or more active ingredients with the cyclodextrin or cyclodextrins.

The term "active ingredient" further refers to compounds or mixtures of compounds which are pharmaceutically or therapeutically or cosmeticallly active for treating humans or animals.

The present invention provides a process for preparing a solid mixture comprising one or more cyclodextrins and an (insoluble) active ingredient, comprising a melt-extrusion step wherein one or more cyclodextrins are combined with the one or more active ingredients.

Melt-extrusion is a polymer extrusion technique which involves embedding an active ingredient in one or more carriers. In this technique the active ingredient and excipients are molten in the extruder and hence embedded in thermoplastic and thermomelting polymers. The resulting molten mass is then forced through one or more nozzles resulting in a thermoplastic strand or strands.

An extruder comprises an inlet structure, a cylindrical structure called "barrel", a die and a screw or screws. A schematic overview is shown in Figure 1.

The inlet structure mostly is funnel shaped.

The barrel may comprise one or more barrel units and the screw or screws extend through them.

Extruders are available in two general types, namely a single-screw extruder comprising one screw and a multi-screw extruder comprising two or more screws. While this invention can be carried out using either type of extruder, the use of a multi-screw extruder, particularly a twin-screw extruder is preferred. A twin-screw extruder (and a multi-screw extruder) is more efficient in that the plural screws interferring with

each other precludes follow-up movement of the active ingredient and, moreover, the intermeshing of the screws provides a high energy output physically.

An interesting mode of operating the screws is to operate them in a corotating mode.

The screw or screws may have different shapes such as, for example, a trapezoidal screw, a trapezoidal cut screw, trapezoidal reverse cut screw, ball screw, kneading paddle and these may be used in the desired combination.

The load fed into the extruder via the inlet structure is forced by the screw or screws to advance, shorn and blended by the screw within the barrel and extruded from the orifice or orifices of the die. The temperature of the barrel or of the barrel units can be controlled via a heating element or even if necessary by a cooling element.

The rotational speed of the screw can be set within the allowable range of the extruder used.

A person skilled in the art is able to select the screw geometry and combination of unit screws. The principal function of the screw is to transport, crush and knead the material that is being extruded.

The orifice configuration may be circular, elliptical, rectangular or hexagonal.

Hence, said melt-extrusion step comprises the following substeps :

a) mixing one or more cyclodextrins with the active ingredient or active ingredients,
b) optionally mixing additives,
c) heating the thus obtained mixture until melting of one of the components,
d) forcing the thus obtained mixture through one or more nozzles;
e) cooling the mixture till it solidifies.

If desired, as mentioned above, the thermomelting mixture comprising one or more cyclodextrins and active ingredient(s) may comprise any suitable additive. When, for instance, the cyclodextrin(s) or the active ingredient(s) or one of the other possible additives is apt to be oxidized, an anti-oxidizing agent may be incorporated, preferably in small amounts, such as, for instance 100 to 5000 ppm when compared to the total weight of the mixture. Furthermore, conventional auxiliary additives such as pigments, flavors, stabilizers, preservatives and buffers may be added.

If necessary conventional pharmacologically acceptable plasticizers, such as long chain alcohols, ethylene glycol, propylene glycol, thriethylene glycol, butanediols, pentanols, hexanols, polyethylene glycols, aromatic carboxylates (e.g. dialkyl phthalates, trimellitates, benzoates or terephthalates), aliphatic dicarboxylates or fatty acid esters can also be added. Preferably however, a plasticizer is not needed.

The term "melting" should be broadly interpreted. "Melting" can also refer to the fact that some transition is made to a glassy state, in which it is possible for one component of the mixture to get embedded into the other. In particular cases, one component will melt and the other component(s) will dissolve in the melt thus forming solid solutions, which show advantageous dissolution properties.

The possible formation of these solid solutions is one of the further advantages of the present invention. It will be appreciated by a person skilled in the art that mixing two or more solids, i.e. one or more cyclodextrins and the active ingredient or ingredients, and subsequently melting these solids together will give rise to different products than when the said solids are first brought into contact with water or another solvent and then extruded.

A characteristic of the melt extruded mixtures of the present invention is the fact that they contain substantially less water or any other solvent than mixtures being extruded in an other way.

Preferably the present melt extruded mixtures contain no water or solvent, apart from the water or solvent that eventually is contained in the crystal structure of the active ingredient.

It will be appreciated that the temperature inside the extruder is an important parameter. When different barrel units are present, different temperatures can be applied. A person skilled in the art is able to establish the required temperatures by taking the desired type of cyclodextrin or cyclodextrins or even the complete mixture that is going to be extruded and observing the behaviour as a function of temperature with the aid of a melting point measuring instrument, such as a Kofler hot bench, a microscope hot stage type or a differential scanning calorimeter, e.g. type DSC 7 Series - Perkin Elmer.

The cooling can be performed without using any auxiliary means, i.e. it most often suffices to let the thermoplastic strand coming out of the extruder cool down to the ambient temperature of the production site. Of course, cooling aids may be used.

Once these thermoplastic strands are cooled down these strands can be milled to obtain a powdered form of the mixture of cyclodextrin or cyclodextrins and the active ingredient.

A person skilled in the art will appreciate that the milling can influence the physical characteristics of the extrudate. During milling the temperature of the material can rise because of the friction and also high shear forces are exerted on the material that is to be milled. Both temperature and mechanical or shear forces can result in a transition of the physical state of the material that is to be milled. A person skilled in the art has sufficient means at his disposal to control temperature and shear forces and thus to control the milling process.

The two processes, i.e. melt extrusion and milling can be combined into one configuration as is shown in Figure 1. The mixture of one or more cyclodextrins and one or more active ingredients in combination with possible other additives is feed via a funnel like inlet. The mixture is then melt-extruded and the mixture is forced through a nozzle onto a conveyor belt. While being transported on the conveyor belt the extrudate cools down. The cooled melt extrudate is fed into a chopper which forms pellets. These pellets may be further milled if required.

This powdered material still has the beneficial properties (high bioavailability, dissolution rate, etc.) and it can be used in the conventional way to prepare pharmaceutical, therapeutical or cosmetical solid dosage forms.

An additional advantage of the present invention is that the active ingredient as well as the cyclodextrins may be transformed in a amorphous form or even that a solid solution is formed. A person skilled in the art will appreciate that this modification of physical state from crystalline to amorphous or to solid solutions is highly advantageous for the dissolution.

The fact whether the melt extruded mixture contains amorphous material or contains a solid solution or consists essentially of amorphous material or a solid solution can be measured or checked using differential scanning calorimetry. When there is crystalline

material present in the melt extruded mixture a differential scanning calorimeter will show an endothermic melting peak. When amorphous material or a solid solution is mainly present in the melt extruded mixture a differential scanning calorimeter will not show an endothermic melting peak. Visual inspection of the melt extrudate allows for a distinction between amorphous material and a solid solution. In case the melt extrudate is opaque then both the cyclodextrin(s) and the active ingredient are in a amorphous form. In case melt extrudate is clear then a solid solution was formed.

Curves of differential scanning calorimetry are shown in Figures 2 to 7.

Interesting embodiments of the present invention are these melt extruded mixtures which consist mainly of amorphous material.

More interesting embodiments of the present invention are these melt extruded mixtures which consist essentially of amorphous material.

Even more interesting embodiments of the present invention are those melt extruded mixtures which consist mainly of a solid solution of the active ingredient or active ingredients in the cyclodextrin or the cyclodextrins.

Preferred embodiments of the present invention are those melt extruded mixtures which consist essentially of a solid solution of the active ingredient or active ingredients in the cyclodextrin or the cyclodextrins.

Another advantage of the present invention is that the granulation step in forming pharmaceutical, therapeutical or cosmetical compositions can be omitted, because the powdered material can simply be mixed with other excipients and compressed into, for instance, tablets or another solid pharmaceutical, therapeutical or cosmetical form.

Depending upon the characteristics of the melt extruded mixture, the size of the pellets of said melt extruded mixture or the mesh of the powder of said melt extruded mixture and, of course, dependent upon the other auxiliaries that are added to the unit dosage forms the unit dosage form may give immediate release or sustained release.

If desired, said solid pharmaceutical form may also be provided with a conventional coating to improve the appearance and/or the flavor (coated tablets) or additionally to target the release of the active ingredient.

Suitable tablets may have the following compositions and may be prepared in a conventional way. The amounts given are of course dependent upon the dose required for the pharmaceutical, therapeutic or cosmetic activity.

Composition A

milled melt extrudate	100 - 500 mg
microcrystalline cellulose	100 - 300 mg
crospovidone	10 - 200 mg
colloidal silicon dioxide	1 - 5 mg
sterotex	2 - 10 mg

Composition B

milled melt extrudate	100 - 500 mg
Microcelac (TM) (1)	200 - 300 mg
crospovidone	70 - 200 mg
talc	20 - 50 mg
sterotex	7 - 10 mg
colloidal silicon dioxide	1 - 5 mg
magnesium stearate	2 - 10 mg

The cyclodextrin to be used in the aforementioned compositions include the pharmaceutically acceptable unsubstituted and substituted cyclodextrins known in the art, more particularly α, β or γ cyclodextrins or the pharmaceutically acceptable derivatives thereof.

Substituted cyclodextrins which can be used in the invention include polyethers described in U.S. Patent 3,459,731. In general, unsubstituted cyclodextrins are reacted with an alkylene oxide, preferably under superatmospheric pressure and at an elevated temperature, in the presence of an alkaline catalyst.
Since a hydroxy moiety of the cyclodextrin can be substituted by an alkylene oxide which itself can react with yet another molecule of alkylene oxide, the average molar substitution (MS) is used as a measure of the average number of moles of the substituting agent per glucose unit. The MS can be greater than 3 and theoretically has no limit.

Further substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-6}alkyl, hydroxyC_{1-6}alkyl, carboxy-C_{1-6}alkyl or C_{1-6}alkyloxycarbonylC_{1-6}alkyl or mixed ethers thereof. In particular such substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-3}alkyl, hydroxyC_{2-4}alkyl or carboxyC_{1-2}alkyl or more in particular by methyl, ethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, carboxy-methyl or carboxyethyl.

In the foregoing definitions the term "C_{1-6}alkyl" is meant to include straight and branched saturated hydrocarbon radicals, having from 1 to 6 carbon atoms, such as, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, 2-methylpropyl, butyl, pentyl, hexyl and the like.

Such ethers can be prepared by reacting the starting cyclodextrin with an appropriate O-alkylating agent or a mixture of such agents in a concentration being selected so that the desired cyclodextrin ether is obtained. The said reaction is preferably conducted in a suitable solvent in the presence of an appropriate base. With such ethers, the degree of substitution (DS) is the average number of substituted hydroxy functions per glucose unit, the DS being thus 3 or less.

In the cyclodextrin derivatives for use in the compositions according to the present invention, the DS preferably is in the range of 0.125 to 3, in particular 0.3 to 2, more in particular 0.3 to 1 and the MS is in the range of 0.125 to 10, in particular of 0.3 to 3 and more in particular 0.3 to 1.5.

Of particular utility in the invention are the β-cyclodextrin ethers, e.g. dimethyl-β-cyclodextrin as described in Drugs of the Future, Vol. 9, No. 8, p. 577-578 by M. Nogradi (1984) and polyethers, e.g. hydroxypropyl β-cyclodextrin and hydroxyethyl β-cyclodextrin, being examples. Such an alkyl ether may be a methyl ether with a degree of substitution of about 0.125 to 3, e.g. about 0.3 to 2. Such a hydroxypropyl cyclodextrin may for example be formed from the reaction between β-cyclodextrin an propylene oxide and may have a MS value of about 0.125 to 10, e.g. about 0.3 to 3.

A more novel type of substituted cyclodextrins is sulfobutylcyclodextrines. These type are also envisaged in the present invention.

The ratio of active ingredient over cyclodextrin may vary widely. For example ratios of 1/100 to 100/1 may be applied. Interesting ratios of active ingredient over cyclodextrin range from about 1/10 to 10/1. More interesting ratios of active ingredient over cyclodextrin range from about 1/5 to 5/1. Most interesting ratios range from about 1/3 to 3/1. Preferred ratio is aabout 1/1.

The use of a mixture of cyclodextrins, either different types (α, β, γ) or different substitution (2-hydropropyl or methyl) or different substitution grades in sometimes recommendable to decrease the melting point.

Description of the drawings

Figure 1 is a schematic representation of a configuration for carrying out the present invention.

Figure 2 is a differential scanning calorimetry curve (DSC curve) of non-milled Batch No 1 material. (see Example 1)

Figure 3 is a differential scanning calorimetry curve of milled Batch No 1 material (see Example 1)

Figure 4 is a differential scanning calorimetry curve of Batch No 2 material (see Example 1)

Figure 5 is a differential scanning calorimetry curve of of Batch No 3 material (see Example 1)

Figure 6 is a differential scanning calorimetry curve of of Batch No 4 material (see Example 1)

Figure 7 is a differential scanning calorimetry curve of of Batch No 5 material (see Example 1)

Example 1

Extruded samples of active ingredient with hydroxypropyl-β-cyclodextrin (HP-β–CD) were obtained using a Twin Screw Extruder type MP19 APV Baker (commercially available from the company APV Baker) with a die having a orifice of 3 mm. The process parameters for each individual experiment are shown in the table 1. This type of extruder has a L/D ratio of 15 and a screw pattern : 4D FS - 4x30 FP - 4x60 FP - 4x90 P - 4x60 RP - 2.5D FS - 2x30 FP - 2x60 FP - 2x90 P - 3x60 RP - 3 DFS. (4D refers to a transportelement having a length of 4 times the screw diameter of the feed screw type; 4x30 FP refers to 4 forward paddles positioned with mutual angle of 30

degrees, 4x60 RP refers to a working zone having reverse paddles positioned with a mutual angle of 60 degrees)

In this type of extruder the mixture is fed by a feeding screw turning a constant feeding speed (v1) (A feeding speed of 10 revolutions per minute amounts to a feeding speed of 1,5 kg per hour) onto the twin transporter screws having a diameter of 18 mm turning at a transporter speed (v2). These speeds are rotational speeds (revolutions per minute).

The mixture is then transported into a first heating zone (t1). Here the rate of transport diminished by a difference of the configuration of the twin transporter screws i.e. the rotational transporter speed v2 remains the same but the material does not progress as quickly.

Subsequently, the molten mass is transported by again normal configuration twin transporter screws to a second heating zone (t2) where the rate of transport is again diminished by a difference of configuration of the twin transporter screws.

After this second heating the thermomelting mixture is transported to the nozzle of the apparatus.

Table 1

mixture	Batch. No	t_1 (°C)	t_2 (°C)	t_p (°C)	v1 (rpm)*	v2 (rpm)*
compound 1 / HP-β-CD : 1/3	1	256	283	280	10	100
itraconazole / HP-β-CD : 1/1	2	263	265	279	10	20
itraconazole / HP-β-CD : 1/3	3	264	265	280	10	20
loviride / HP-β-CD : 1/1	4	274	285	292	10	80
loviride / HP-β-CD : 1/3	5	258	265	274	10	20

* rpm = revolutions per minute

- t_1 : temperature of the first heating zone
- t_2 : temperature of the second heating zone

- t_p : temperature inside the barrel
- v_1 : rate of feeding screw
- v_2 : twin transporter screws speed(rotational).

In every case the mixture of active ingredient and 2-hydroxypropyl-β–CD gave a solid solution.

Example 2

Extruded samples of active ingredient with dimethyl-β-cyclodextrin (DM-β–CD) were obtained using extruder type MP19 - APV Baker with the process parameters as shown in the table 2.

Table 2

mixture	Batch. No.	t_1 (°C)	t_2 (°C)	t_p (°C)	v_1 (1) (rpm)*	v_2 (rpm)*
compound 1 / DM-β-CD : 1/1	6	241	245	254	0	20
itraconazole / DM-β-CD : 1/1	7	239	240	253	0	20
loviride / DM-β-CD : 1/1	8	248	250	263	0	20

* rpm = revolutions per minute
(1) The apparatus was fed manually, without using the feeding screw.
In every case the mixture of active ingredient and DM-β-CD.

- t_1 : temperature of the first heating zone
- t_2 : temperature of the second heating zone
- t_p : temperature inside the barrel
- v_1 : feeding screw speed (rotational)
- v_2 : twin transporter screw speed (rotational).

Example 3

The dissolution of the melt extrudate of Batch No 1 was compared with the dissolution of the "physical mixture" (i.e. the mixture of the two component in the ratio as shown for Batch No. 1, but not melt extruded).

An amount of 100 mg of milled melt extrudate of Batch No 1 was added to a volume of 900 ml of artificial gastric juice at a temperature of 37 degrees Celsius. The stirring method used was the peddle method with a peddle moving at 100 rotations per minute. Using UV spectrometry the relative amount of dissolved extrudate was measured during 1 hour.

The same procedure for the "physical mixture" was followed.

The results of this dissolution process are shown in Table 3

Table 3

time mixture (minutes)	milled extrudate Batch No 1 (% of total amount dissolved)	corresponding physical (% of total amount dissolved)
0	0.00	0.00
5	62.10	1.71
15	70.20	14.67
30	72.63	21.06
45	74.07	26.10
60	74.25	28.35

Example 4

The melting behaviour was measured by using differential scanning calorimetry. The calorimeter used is the Perkin-Elmer 7 Series Thermal Analysis System. In all cases the rate of heating was set at 20 degrees Celsius per minute.

Figure 2 shows the DSC curve of melt extrudate of Batch No 1 before milling. The curve shows no endothermic or exothermic peaks and it was established by visual inspection that the molten material was a clear solution , thus indicating that the non-milled melt extrudate of Batch No 1 is a solid solution.

Figure 3 shows the DSC curve of melt extrudate of Batch No 1 after milling. The curve shows no endothermic or exothermic peaks and it was established by visual inspection that the molten material was a clear solution , thus indicating that the milled melt extrudate of Batch No 1 is a solid solution.

Figure 4 shows the DSC curve of meltextrudate of Batch No 2 before milling. The curve shows no endothermic or exothermic peaks and it was established by visual inspection that the molten material was not a clear solution, thus indicating that the non-milled melt extrudate of Batch No 2 is a mixture of amorphous material.

Figure 5 shows the DSC curve of meltextrudate of Batch No 3 before milling. The curve shows a small endothermic peak. The data on said small peak are as follows : X1 = 117.600 degrees Celsius, X2 = 143.200 degrees Celsius, Peak at 132.695 degrees Celsius, Area is 38.126 mJ, ΔH is 3.768 J/g, Height is 1.520 mW and the onset is at 125.816 degrees Celsius. Said small peak is very probably due to an impurity in the cyclodextrins. It was established that the non-milled melt extrudate of Batch No 3 is a mixture of amorphous material.

Figure 6 shows the DSC curve of meltextrudate of Batch No 4 before milling. The curve shows a few small endothermic peaks. Hence, it was established that the non-milled melt extrudate of Batch No 4 is a mixture of amorphous material containing small amounts of crystalline material

Figure 7 shows the DSC curve of meltextrudate of Batch No 5 before milling. The curve shows no endothermic or exothermic peaks and it was established by visual inspection that the molten material was not a clear solution, thus indicating that the non-milled melt extrudate of Batch No 5 is a mixture of amorphous material.

Example 5

The melt extrudate of Batch No. 1 was milled and sieved. By mixing the appropriate amounts a tablet having the following composition was prepared in an art-known way :

milled extrudate batch No 1	480 mg
microcrystalline cellulose	218 mg
Aerosil	3 mg
magnesium stearate	5 mg
crospovidone	144 mg

Claims

1. Process for preparing a solid mixture comprising one or more cyclodextrins and one or more active ingredients characterized in that said process encompasses a melt-extrusion step, wherein the active ingredient is embedded into the cyclodextrin carrier.

2. A process as claimed in claim 1, wherein the melt-extrusion process comprises the following substeps :
   a) mixing one or more cyclodextrins with one or more active ingredients, and
   b) optionally mixing additives;
   c) heating the thus obtained mixture until melting of one of the components;
   d) forcing the thus obtained mixture through one or more nozzles;
   e) cooling the mixture till it solidifies.

3. A solid mixture obtainable by the process as described in any of claims 1 or 2, with the proviso that nifedipine in combination with 2-hydroxypropyl-β-cyclodextrin is excluded.

4. A solid mixture as claimed in claim 3 characterized in that the active ingredient or active ingredients are insoluble according to the definition of US Pharmacopeia.

5. A solid mixture as claimed in claims 3 or 4, wherein substantially only one type of cyclodextrin is present.

6. A solid mixture as claimed in any of claims 3 to 5 wherein a cyclodextrin is hydroxypropyl-β-cyclodextrin.

7. A solid mixture as claimed in any of claim 3 to 5 wherein a cyclodextrin is dimethyl-β-cyclodextrin.

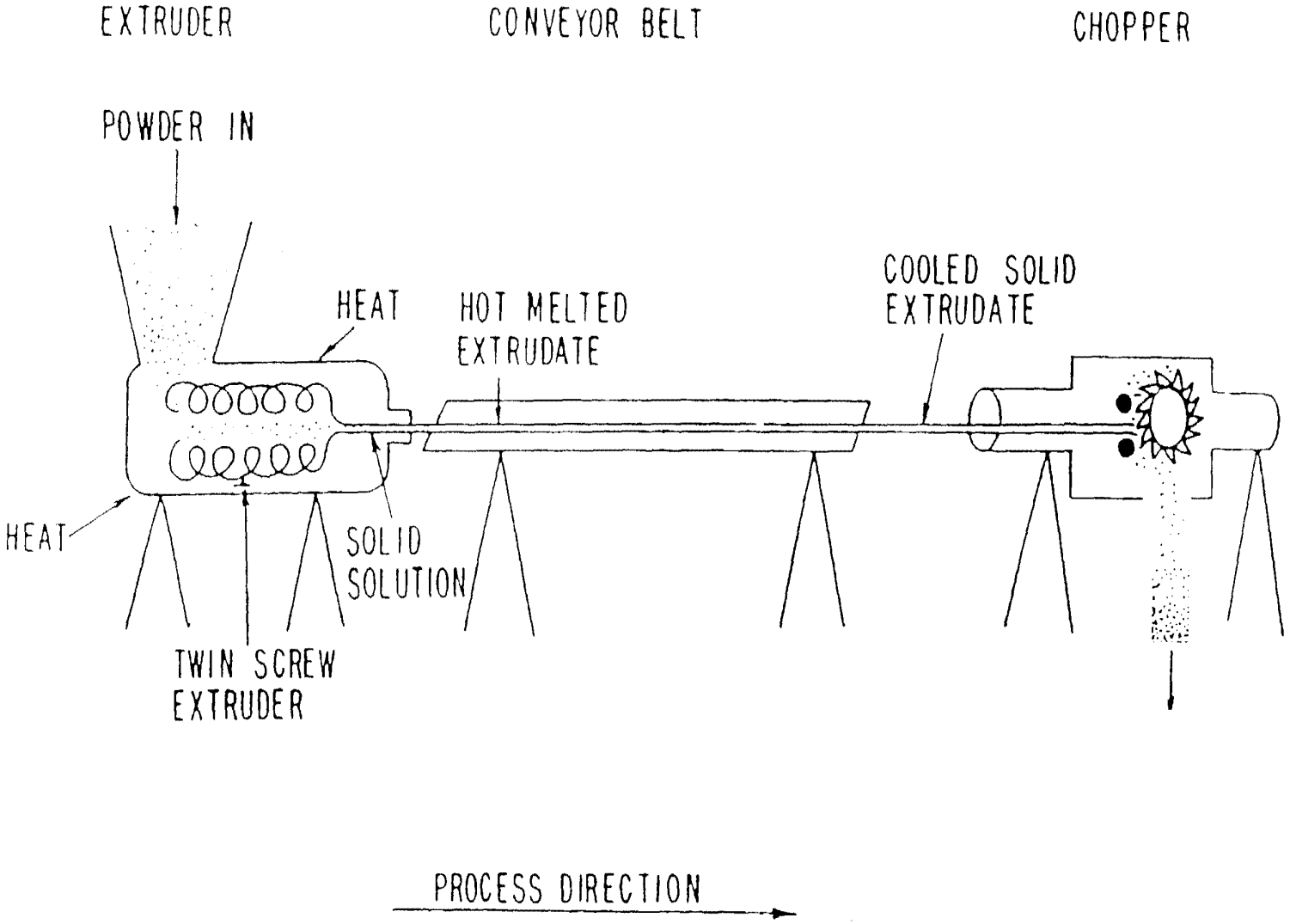
8. A solid mixture as claimed in any of claims 3 to 7, wherein the active ingredient is itraconazole.

9. A solid mixture as claimed in any of claims 3 to 7 wherein the active ingredient is loviride.

10. A solid mixture as claimed in any of claims 3 to 7 wherein the active ingredient is (±)-ethyl (R*,R*)-4-[5-[1-[1-[(4-chlorophenyl)hydroxymethyl]propyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]-2-pyridinyl]-1-piperazinecarboxylate.

11. A pharmaceutical composition comprising milled melt extrudate and other excipients.

12. A process for preparing a pharmaceutical composition as claimed in claim 11 characterized by milling appropriately the solid mixture as claimed in any of claims 4 to 10, intimately mixing the thus obtained powdered material with other pharmaceutically acceptable excipients and further processing into pharmaceutical dosage forms.


EXTRUDER
CONVEYOR BELT
CHOPPER
POWDER IN
HEAT
HOT MELTED EXTRUDATE
COOLED SOLID EXTRUDATE
HEAT
SOLID SOLUTION
TWIN SCREW EXTRUDER
PROCESS DIRECTION

1/7

Fig. 1

Fig. 2

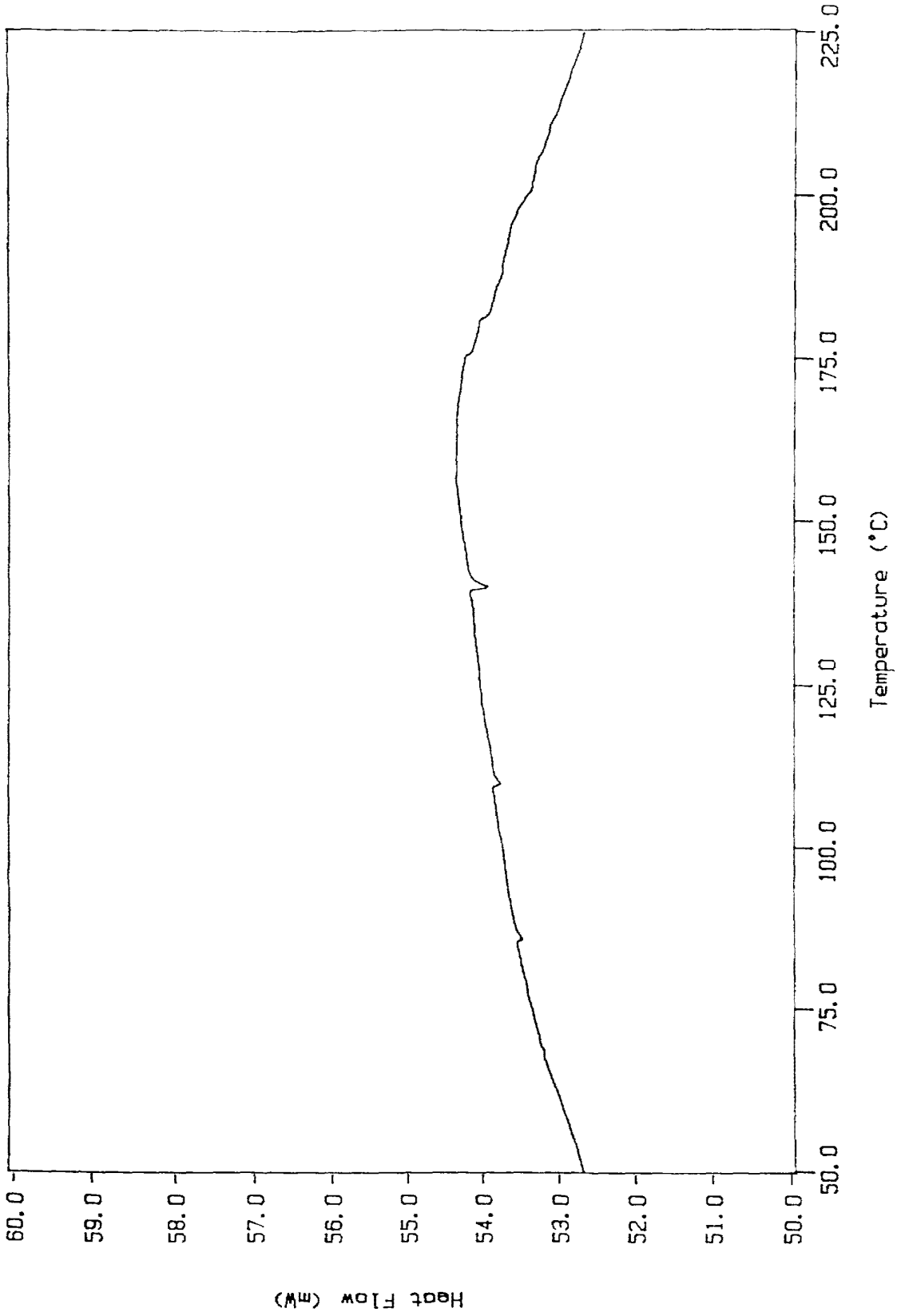

Heat Flow (mW)
60.0
59.0
58.0
57.0
56.0
55.0
54.0
53.0
52.0
51.0
50.0
50.0
75.0
100.0
125.0
150.0
175.0
200.0
225.0
Temperature (°C)

Fig. 3

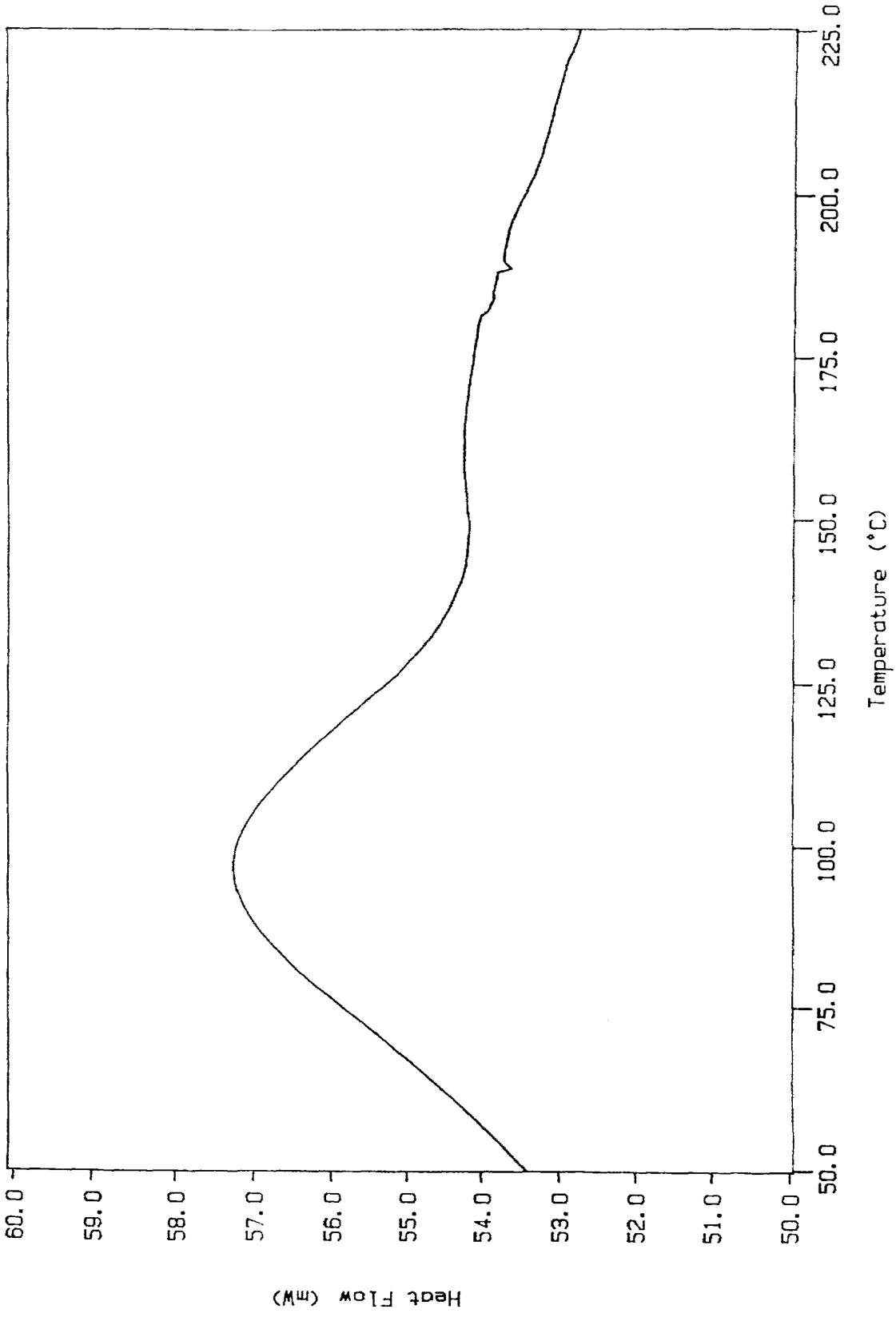

Heat Flow (mW)
60.0
59.0
58.0
57.0
56.0
55.0
54.0
53.0
52.0
51.0
50.0
50.0
75.0
100.0
125.0
150.0
175.0
200.0
225.0
Temperature (°C)

Fig. 4

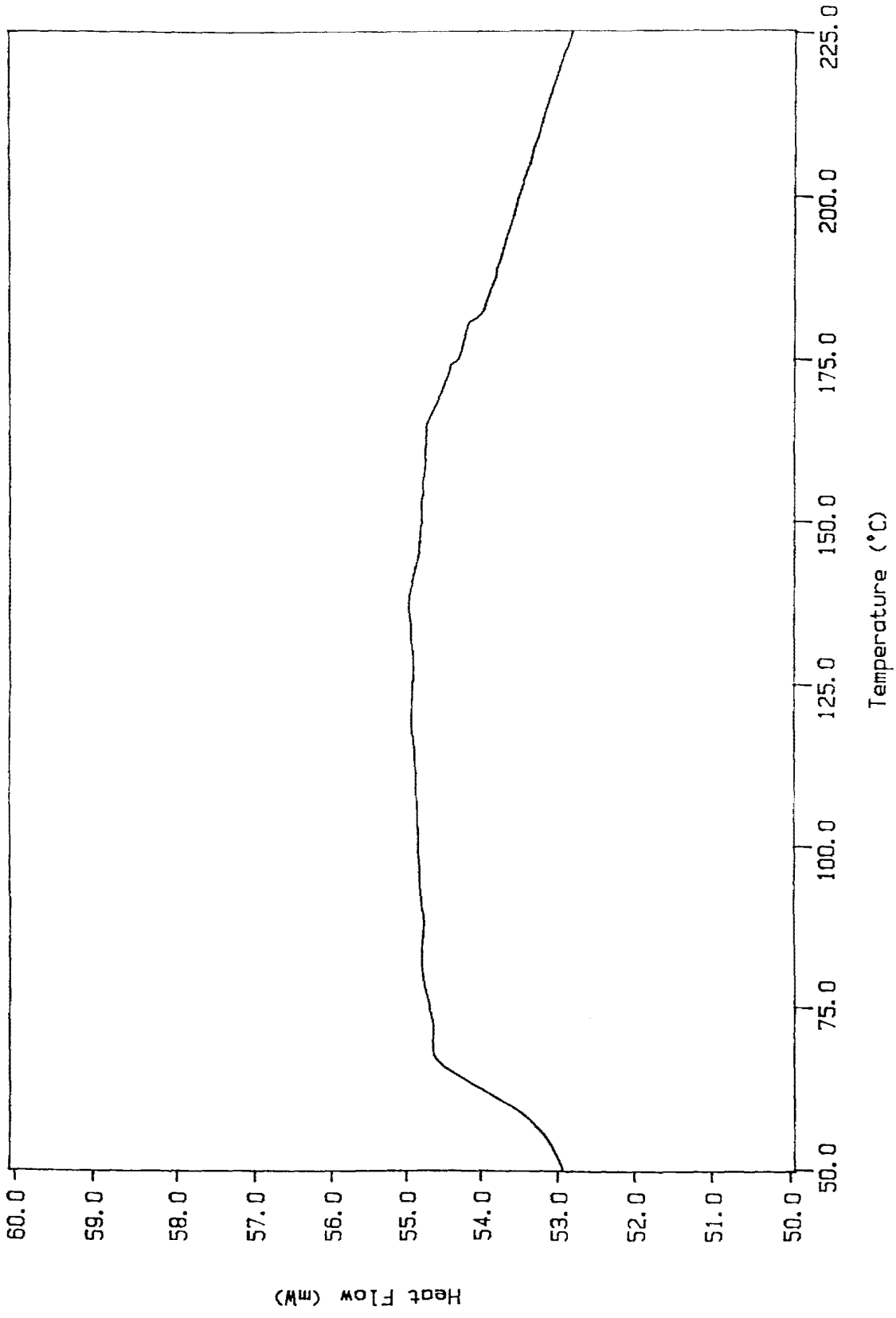

Heat Flow (mW)
60.0
59.0
58.0
57.0
56.0
55.0
54.0
53.0
52.0
51.0
50.0
50.0
75.0
100.0
125.0
150.0
175.0
200.0
225.0
Temperature (°C)

Fig. 5

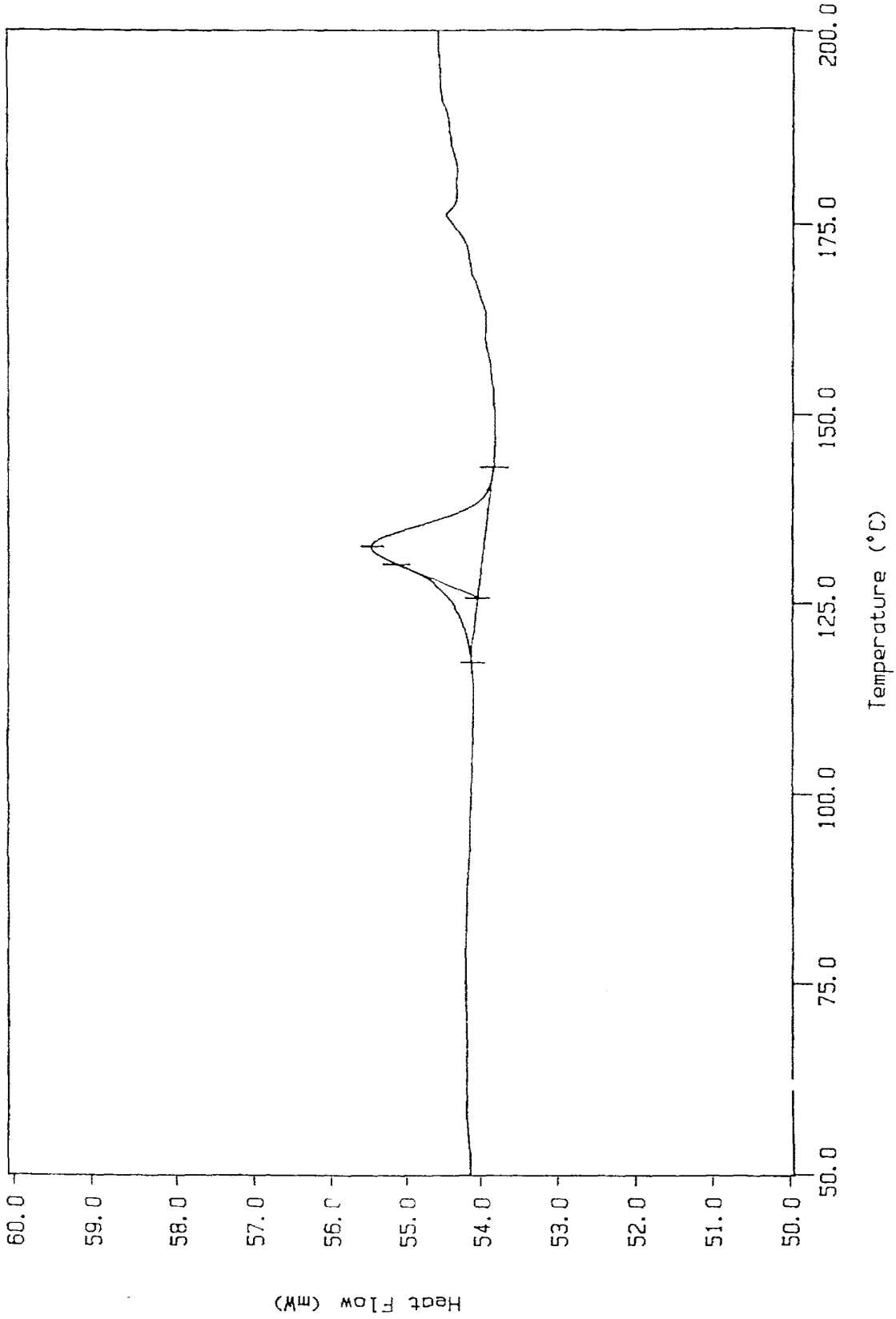

Heat Flow (mW)
60.0
59.0
58.0
57.0
56.0
55.0
54.0
53.0
52.0
51.0
50.0
50.0
75.0
100.0
125.0
150.0
175.0
200.0
Temperature (°C)

Fig. 6

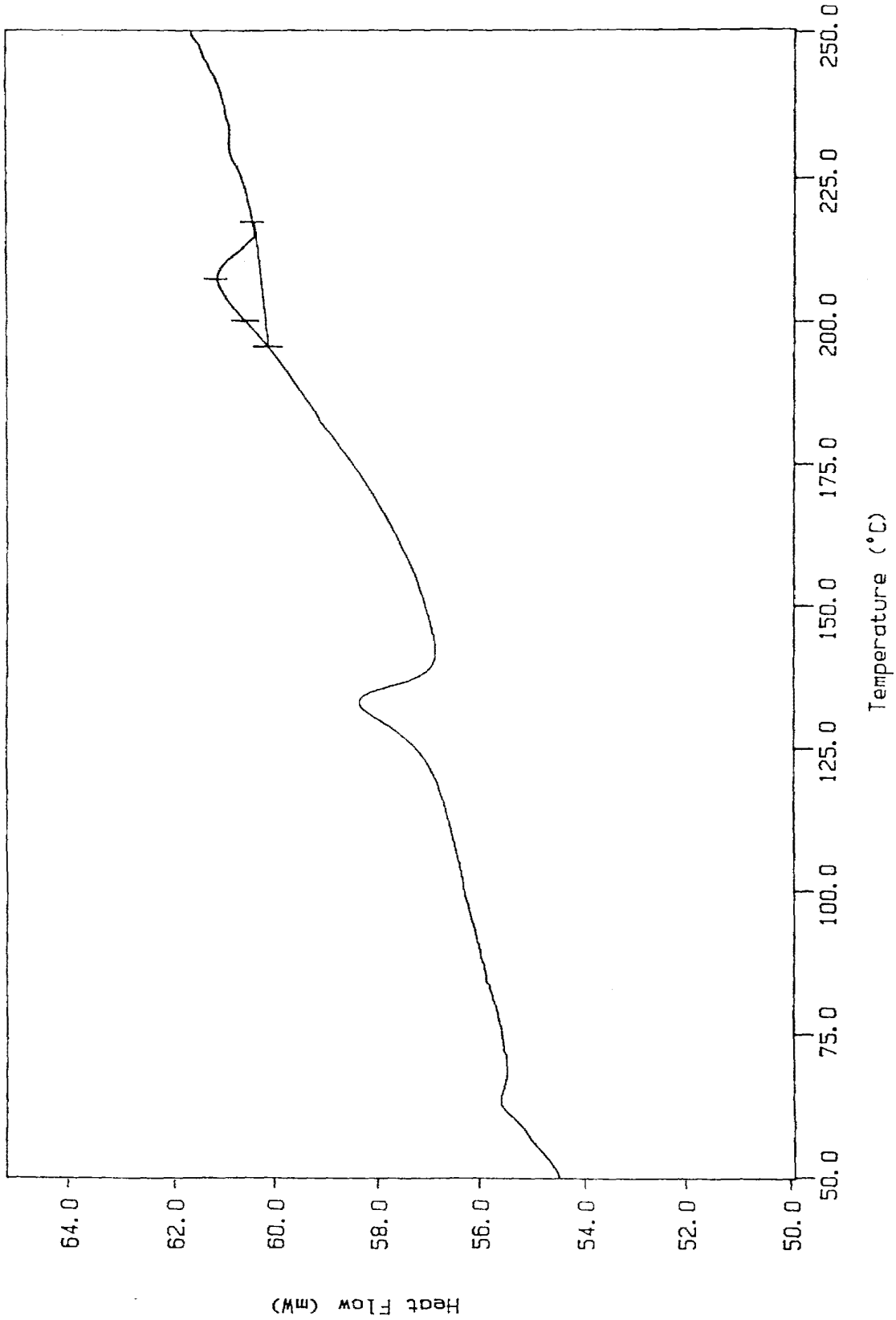
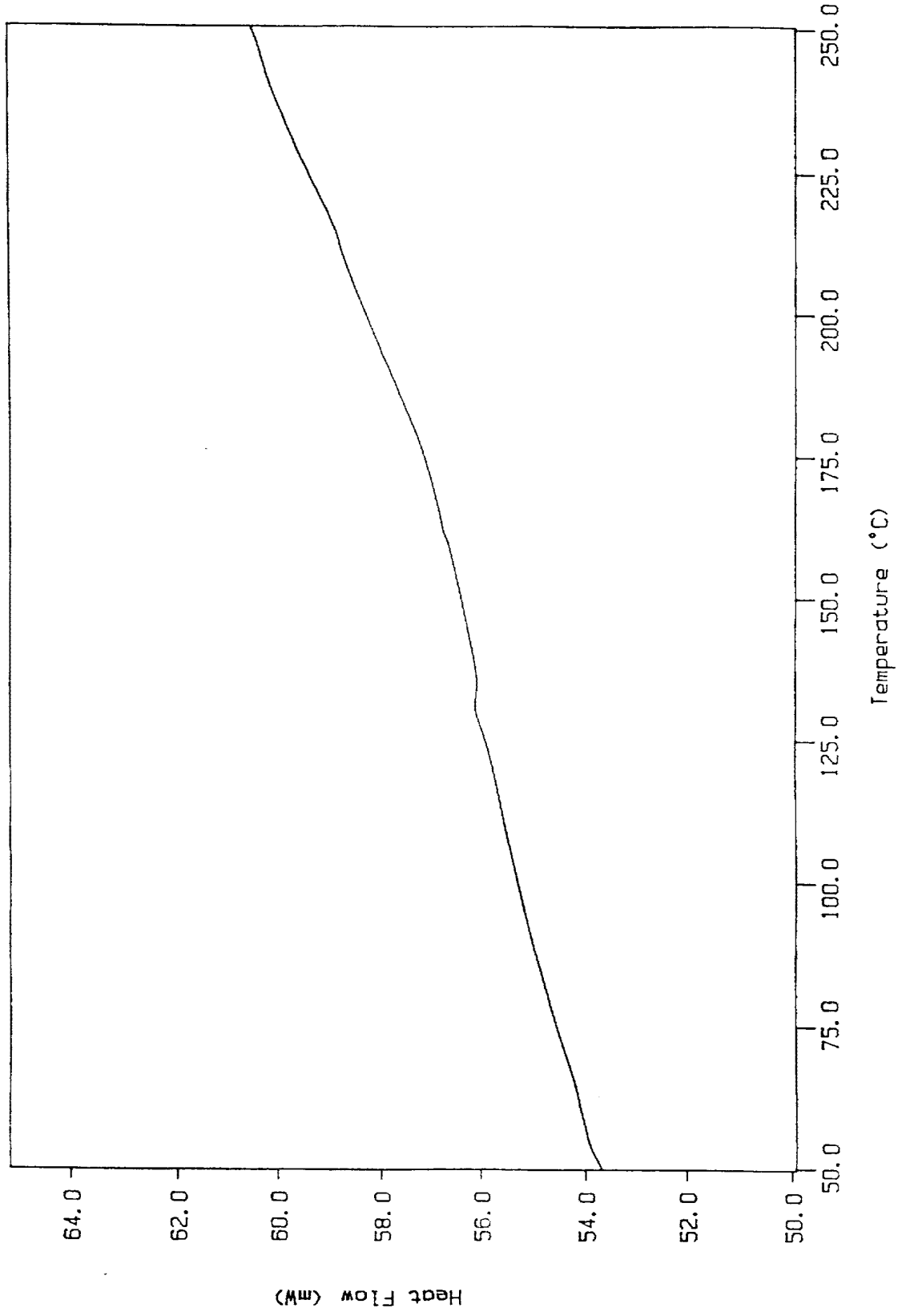

Heat Flow (mW)
64.0
62.0
60.0
58.0
56.0
54.0
52.0
50.0
50.0
75.0
100.0
125.0
150.0
175.0
200.0
225.0
250.0
Temperature (°C)

Fig. 7


Heat Flow (mW)
64.0
62.0
60.0
58.0
56.0
54.0
52.0
50.0
50.0
75.0
100.0
125.0
150.0
175.0
200.0
225.0
250.0
Temperature (°C)

INTERNATIONAL SEARCH REPORT

Int onal Application No
PCT/EP 96/05118

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 11031 A (NIPPON SHINYAKU CO LTD) 26 May 1994 cited in the application see abstract	1-12
Y	FR 2 705 677 A (ROQUETTE FRERES) 2 December 1994 cited in the application see abstract see examples see claims	1-12
X	EP 0 665 009 A (NIPPON SHINYAKU COMPANY, LIMITED.) 2 August 1995 cited in the application see abstract see examples see claims	1-12

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of the international search
24 February 1997

Date of mailing of the international search report
17.03.97

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer
Dullaart, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 96/05118

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. PHARM. PHARMACOL., VOL. 44, NO. 2, PAGE(S) 73-8, 1992, XP002002172 UEKAMA, KANETO ET AL: "Inhibitory effect of 2- hydroxypropyl -.beta.- cyclodextrin on crystal growth of nifedipine during storage: superior dissolution and oral bioavailability compared with poly(vinylpyrrolidone) K-30" cited in the application * paragraph Materials and methods * see figures	1-12
Y	PHARM. WEEKBL. SCI. ED., 1988, VOL. 10, NO. 2, PAGE(S) 80-85, XP002002173 VAN DOORNE H. ET AL: "Formation and antimicrobial activity of complexes of beta- cyclodextrin and some antimycotic imidazole derivatives" cited in the application see abstract * paragraph Results and discussion * see page 85, left-hand column	1-12
Y	J. ANTIMICROB. CHEMOTHER., 1993, VOL. 32, NO. 3, PAGE(S) 459-463, XP002002174 HOSTETLER J.S. ET AL: "Effect of hydroxypropyl-beta-cyclodextrin on efficacy of oral itraconazole in disseminated murine cryptococcosis" cited in the application see abstract * paragraph Results *	1-12
Y	JPN. J. MED. MYCOL., 1994, VOL. 35, NO. 3, PAGE(S) 263-267, XP002002175 MIKAMI Y. ET AL: "Effect of carrier solvents on the efficacy of oral itraconazole therapy in aspergillosis in mice" cited in the application see abstract see figures	1-12
Y	PHARM. RES., VOL. 11, NO. 12, PAGE(S) 1766-70, 1994, XP002002176 HIRAYAMA, FUMITOSHI ET AL: "Effect of 2-hydroxypropyl -.beta.- cyclodextrin on crystallization and polymorphic transition of nifedipine in solid state" cited in the application see abstract * paragraph Results and discussion * -/--	1-12

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/EP 96/05118

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 009 900 A (LEVINE HARRY ET AL) 23 April 1991 cited in the application see examples see claims -----	1-12

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/EP 96/05118

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-7,11-12
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

In view of the large number of compounds, which are defined by the general definition of the active ingredient used in the claims, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

in the claims, and to the general idea underlying the application (see Guidelines, chapter III, paragraph 2.3).

Claims searched incompletely: 1-7,11-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

In tional Application No
PCT/EP 96/05118

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9411031 A	26-05-94	AU 5376994 A	08-06-94
FR 2705677 A	02-12-94	IT 1265964 B	16-12-96
EP 665009 A	02-08-95	AU 5160793 A	09-05-94
		WO 9408561 A	28-04-94
US 5009900 A	23-04-91	CA 2025647 A	03-04-91

Form PCT/ISA/210 (patent family annex) (July 1992)

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10551205	BODOR ET AL.
	Examiner	Art Unit
	Jonathan S Lau	1623

✓	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	11/26/2007	03/26/2008							
	1	÷	✓							
	2	÷	✓							
	3	÷	✓							
	4	÷	✓							
	5	÷	✓							
	6	÷	✓							
	7	÷	✓							
	8	÷	✓							
	9	÷	✓							
	10	÷	✓							
	11	÷	✓							
	12	÷	✓							
	13	÷	N							
	14	÷	N							
	15	÷	N							
	16	÷	N							
	17	÷	N							
	18	÷	N							
	19	÷	N							
	20	÷	N							
	21	÷	N							
	22	÷	N							
	23	÷	N							
	24	÷	N							
	25	÷	N							
	26	÷	N							
	27	÷	N							
	28	÷	N							
	29	÷	N							
	30	÷	N							
	31	÷	N							
	32	÷	N							
	33	÷	N							
	34	÷	N							
	35	÷	N							
	36	-	-							

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10551205	BODOR ET AL.
	Examiner	Art Unit
	Jonathan S Lau	1623

✓	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	11/26/2007	03/26/2008							
	37	-	-							
	38	-	-							
	39	-	-							
	40	-	-							
	41	-	-							
	42	-	-							
	43	-	-							
	44	-	-							
	45	-	-							
	46	-	-							
	47	-	-							
	48	-	-							
	49	-	-							
	50	-	-							
	51	-	-							
	52	-	-							
	53	-	-							
	54	-	-							
	55	-	-							
	56	÷	✓							
	57	÷	✓							
	58	÷	✓							
	59	÷	✓							
	60	÷	✓							
	61	÷	✓							
	62	÷	✓							
	63	÷	✓							
	64	÷	✓							
	65	÷	✓							
	66	÷	✓							
	67	÷	N							
	68	÷	N							
	69	÷	N							
	70	÷	N							
	71	÷	N							
	72	÷	N							

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10551205	BODOR ET AL.
	Examiner	Art Unit
	Jonathan S Lau	1623

✓	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	11/26/2007	03/26/2008							
	73	÷	N							
	74	÷	N							
	75	÷	N							
	76	÷	N							
	77	÷	N							
	78	÷	N							
	79	÷	N							
	80	÷	N							
	81	÷	N							
	82	÷	✓							
	83	÷	✓							
	84	÷	✓							
	85	÷	✓							
	86	÷	✓							
	87	÷	✓							
	88	÷	✓							
	89	÷	✓							
	90	÷	✓							
	91	÷	✓							
	92	÷	✓							
	93	÷	✓							
	94	÷	✓							
	95	÷	✓							
	96	÷	✓							
	97	÷	✓							
	98	÷	✓							

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10551205	BODOR ET AL.
	Examiner	Art Unit
	Jonathan S Lau	1623

SEARCHED

Class	Subclass	Date	Examiner

SEARCH NOTES

Search Notes	Date	Examiner
EAST - inventor name search (Nicholas Bodor; Yogesh Dandiker)	3/26/2008	JSL
EAST - see attached notes	3/26/2008	JSL
Google Scholar - see attached notes	3/26/2008	JSL

INTERFERENCE SEARCH

Class	Subclass	Date	Examiner

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

BIB DATA SHEET

CONFIRMATION NO. 4092

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/551,205	11/14/2006	514	1623	0056192-000024

APPLICANTS

Nicholas S. Bodor, Bal Harbour, FL;
Yogesh Dandiker, Toronto, CANADA;

**** CONTINUING DATA ***************************

This application is a 371 of PCT/US04/09387 03/26/2004
which claims benefit of 60/458,922 03/28/2003
and claims benefit of 60/484,756 07/02/2003
and claims benefit of 60/541,247 02/04/2004

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

04/21/2007

Foreign Priority claimed	☐ Yes ☑ No	☐ Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
35 USC 119(a-d) conditions met	☐ Yes ☑ No					
Verified and Acknowledged	/JONATHAN S LAU/ Examiner's Signature	Initials	FL	1	78	6

ADDRESS

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404
UNITED STATES

TITLE

Oral formulations of cladribine

FILING FEE RECEIVED		
4530	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

BIB (Rev. 05/07).

Google Scholar BETA

Web Images Video News Maps more »

cyclodextrin non-inclusion inclusion 1900 - 2004 Search

Advanced Scholar Search
Scholar Preferences
Scholar Help

Scholar All articles - Recent articles Results 1 - 10 of about 166 for cyclodextrin non-inclusion inclusion with Safesearch on. (0.16 seconds)

All Results
A Berthod
D Armstrong
T Loftsson
W Li
M Másson

Self-association of cyclodextrins and **cyclodextrin** complexes. - all 4 versions »
T Loftsson, M Masson, ME Brewster - J Pharm Sci, 2004 - ncbi.nlm.nih.gov
... formation of noncovalent, dynamic **inclusion** complexes ... which regards drug-**cyclodextrin** interactions as ... the important contribution of **non-inclusion**-based aspects ...
Cited by 29 - Related Articles - Web Search

[CITATION] ... dynamics studies on **inclusion** and **noninclusion** phenomena between b-**cyclodextrin** and new anti- ...
ME Amato, KB Lipkowitz, GM Lombardo, GC Pappalardo - J Chem Soc Perkin Trans, 1996
Cited by 6 - Related Articles - Web Search

Cyclodextrins in Polymer Synthesis: Supramolecular **Cyclodextrin** Complexes of Pyrrole and 3, 4- ...
J Storsberg, H Ritter, H Pielartzik, L Groenendaal - Advanced Materials, 2000 - doi.wiley.com
... a-**Cyclodextrin**/Pyrrole±Complex 1a (**Inclusion** Type) and a-**Cyclodextrin**/ EDT±Complex 2a (**Non-Inclusion** Type): Pyrrole (0.48 g, 7.2 mmol) or EDT (1.02 g, 7.2 ...
Cited by 20 - Related Articles - Web Search

Self-association and **cyclodextrin** solubilization of drugs - all 5 versions »
T Loftsson, A Magnusdottir, M Masson, JF ... - Journal of Pharmaceutical Sciences, 2002 - doi.wiley.com
... that only 1:1 drug/**cyclodextrin** complexes are formed and that the two events, **inclusion** complex formation and solubilization via **non-inclusion** complex for ...
Cited by 23 - Related Articles - Web Search

... enantioselective retention mechanisms on derivatized **cyclodextrin** gas chromatographic chiral ... - all 3 versions »
A Berthod, W Li, DW Armstrong - Analytical Chemistry, 1992 - pubs.acs.org
... **Cyclodextrin inclusion** complex- ation plays a major role in chiral recognition in LC."J2 Early on, Smolkova-Keulemansova and co-workers published GC evidence ...
Cited by 88 - Related Articles - Web Search

The effects of organic salts on the **cyclodextrin** solubilization of drugs - all 6 versions »
T Loftsson, K Matthı´asson, M Másson - International Journal of Pharmaceutics, 2003 - Elsevier
... have shown that α-**cyclodextrin** (αCD) forms both **inclusion** and **non-inclusion** complexes with dicarboxylic acids and that the two types of complexes coexist in ...

Cited by 9 - Related Articles - Web Search

Self Association and **Cyclodextrin** Solubilization of NSAIDs - all 2 versions »

A Magnusdottir, M Másson, T Loftsson - Journal of **Inclusion** Phenomena and Macrocyclic Chemistry, 2002 - Springer
... that the solubility of drugs in a **cyclodextrin** solution is explained not only by **inclusion** complex formation but also by **non-inclusion** association of the **...**
Cited by 9 - Related Articles - Web Search

Thermal dissociation of protonated **cyclodextrin**-amino acid complexes in the gas phase

B Garcia, J Ramirez, S Wong, CB Lebrilla - International Journal of Mass Spectrometry, 2001 - Elsevier
... **cyclodextrin** hosts. The **inclusion** structure is the preferred state for the complexes. Molecular dynamics calculations initiated with **inclusion** and **noninclusion ...**
Cited by 8 - Related Articles - Web Search

Separation Behavior of Common Fullerenes in **Cyclodextrin**-HPLC Based on Computationally-Derived ... - all 2 versions »

CL Copper, KW Whitaker, MJ Sepaniak - Journal of Liquid Chromatography & Related Technologies, 1994 - informaworld.com
... the interaction between the fullerene solutes and the **cyclodextrin ...** (**inclusion** complex) positions. Other evidence of **non-inclusion** interactions is seen by the **...**
Cited by 2 - Related Articles - Web Search

... Molecular Dynamics Investigation on the **Inclusion** of Chiral Agrochemical Molecules in b-**Cyclodextrin** ... - all 3 versions »

B Manunza, S Deiana, M Pintore, G Delogu, C Gessa - Pestic. Sci, 1998 - doi.wiley.com
... GM & Pap- palardo, GC, NMR spectroscopic evidence and molecu- lar dynamics studies on **inclusion** and **non-inclusion** phenomena between beta-**cyclodextrin** and new **...**
Cited by 2 - Related Articles - Web Search

Gooooooooogle ▶

Result Page: 1 2 3 4 5 6 7 8 9 10 **Next**

cyclodextrin non-inclusion inclusion Search

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	97	((NICHOLAS) near2 (BODOR)).INV.	US-PGPUB; USPAT	ADJ	ON	2008/03/26 12:53
L2	1	((YOGESH) near2 (DANDIKER)).INV.	US-PGPUB; USPAT	ADJ	ON	2008/03/26 12:53
L3	2	l1 and cladribine and cyclodextrin	US-PGPUB; USPAT; USOCR	ADJ	ON	2008/03/26 12:54
L4	6	Cladribine and cyclodextrin and (noninclusion or (non inclusion))	US-PGPUB; USPAT; USOCR	ADJ	ON	2008/03/26 13:04
L5	409	cyclodextrin and (noninclusion or (non inclusion))	US-PGPUB; USPAT; USOCR	ADJ	ON	2008/03/26 13:07
L6	137	l5 and melt near9 extru$7	US-PGPUB; USPAT; USOCR	ADJ	ON	2008/03/26 13:07
L7	23	l6 and @ad<="20040326"	US-PGPUB; USPAT; USOCR	ADJ	ON	2008/03/26 13:08
L8	6	l5 and cyclodextrin.ti,ab.	US-PGPUB; USPAT; USOCR	ADJ	ON	2008/03/26 13:08
L9	3	"9718839"	US-PGPUB; USPAT; USOCR; EPO; DERWENT	ADJ	ON	2008/03/26 13:37
S1	3	Cladribine.ti,ab. and cyclodextrin.ti,ab,bsum.	US-PGPUB; USPAT; USOCR	ADJ	ON	2008/03/25 08:51

3/26/2008 1:51:15 PM
C:\Documents and Settings\jlau1\My Documents\EAST\Workspaces\10551205 - cladribine.wsp

Substitute for form 1449/PTO & 1449B/PTO

FOURTH INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	10/551,205
Filing Date	November 14, 2006
First Named Inventor	Nicholas S. Bodor
Examiner Name	
Attorney Docket No.	0056192-000024

U.S. PATENT DOCUMENTS

Examiner Initials	Document Number-Kind Code	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Figures Appear
	US-			
	US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials	Foreign Patent Document: Country Code[1], Number, Kind Code	Publication Date (MM-DD-YYYY)	Name of Patentee or Applicant of Cited Document	STATUS: Translation	Partial Translation	Eng. Lang. Summary	Search Report	IPER	Abstract	Cited in Spec. / Pg. No(s).	

[1]Enter Office that issued the document, by the two-letter code.

OTHER DOCUMENTS

Examiner Initials	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.
/J.L./	PCT International Preliminary Report on Patentability and Written Opinion for International Application No. PCT/US2004/009387, International filing date March 26, 2004.

Examiner Signature	/Jonathan Lau/	Date Considered	03/26/2008

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with M.P.E.P. § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	
Nicholas S. Bodor et al.	Group Art Unit: 1614
Application No.: 10/551,205	Examiner:
Filing Date: November 14, 2006	Confirmation No.: 4092
Title: ORAL FORMULATIONS OF CLADRIBINE	

SECOND
INFORMATION DISCLOSURE STATEMENT
TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Enclosed is a Second Information Disclosure Statement (IDS) and accompanying form PTO-1449 for the above-identified patent application.

☒ No additional fee for submission of an IDS is required.

☐ The fee of $ 180 as set forth in 37 C.F.R. § 1.17(p) is also enclosed.

☐ A statement under 37 C.F.R. § 1.97(e) is also enclosed.

☐ A statement under 37 C.F.R. § 1.97(e), and the fee of $ 180 as set forth in 37 C.F.R. § 1.17(p) are also enclosed.

☐ Charge _____ to Deposit Account No. 02-4800 for the fee due.

☐ A check in the amount of _____ is enclosed for the fee due.

☐ Charge _____ to credit card for the fee due. Form PTO-2038 is attached.

☒ The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800. This paper is submitted in duplicate.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date August 10, 2007

By: Mary Katherine Baumeister
Mary Katherine Baumeister
Registration No. 26254

P.O. Box 1404
Alexandria, VA 22313-1404
703 836 6620

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of Nicholas S. Bodor et al. Application No.: 10/551,205 Filed: November 14, 2006 For: ORAL FORMULATIONS OF CLADRIBINE	Group Art Unit: 1614 Examiner: Confirmation No.: 4092

SECOND INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure as set forth in 37 C.F.R. § 1.56, the accompanying information is being submitted in accordance with 37 C.F.R. §§ 1.97 and 1.98.

Applicants request the Examiner's consideration of the enclosed publication cited during prosecution of the corresponding Chinese application in an Official Action dated May 11, 2007. The publication is listed on the accompanying Form PTO-1449. The reference is in Chinese; therefore, the cited section (page 105, lines 25-29) is accompanied by an English translation thereof. This reference was cited as relevant only to some of the process and product-by-process claims.

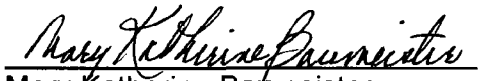
This statement, Form PTO-1449 and enclosed citation and translation are believed to be filed prior to an action on the merits. In addition, the undersigned hereby states under 37 C.F.R. § 1.97(e) that each item of information contained in this information disclosure statement was first cited in any communication from a patent office in a counterpart foreign application not more than three months prior to the filing of this information disclosure statement. Therefore, no fee is required to obtain consideration under 37 C.F.R. §1.97(b) or (c), whichever is applicable.

It is respectfully requested that the Examiner returned an initialed copy of applicants' enclosed Form PTO-1449 with the next official communication or with the first Action on the merits.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: August 10, 2007

By: 
Mary Katherine Baumeister
Registration No. 26254

P.O. Box 1404
Alexandria, VA 22313-1404
703 836 6620

Substitute for form 1449/PTO & 1449B/PTO

SECOND INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known

Application Number	10/551,205
Filing Date	November 14, 2006
First Named Inventor	Nicholas S. Bodor et al.
Examiner Name	
Attorney Docket No.	0056192-000024

U.S. PATENT DOCUMENTS

Examiner Initials	Document Number	Kind Code (if known)	Name of Patentee or Applicant of Cited Document	Issue/Publication Date (MM-DD-YYYY)

FOREIGN PATENT DOCUMENTS

Examiner Initials	Document Number	Kind Code (if known)	Country	Date of Publication (MM-DD-YYYY)	STATUS						
					Translation	Partial Translation	Eng. Lang. Summary	Search Report	IPER	Abstract	Cited in Spec

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials	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.
/J.L./	Gao, Shen, *New Dosage Form and New Technology of Modern Drugs*, first edition, January 2002, Chapter 6, Section 3 (III) Procedures, page 105, lines 25-29 (published by People's Military Medical Publisher), and English translation thereof

Examiner Signature	/Jonathan Lau/	Date Considered	03/26/2008

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with M.P.E.P. § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

Substitute for form 1449/PTO & 1449B/PTO

THIRD INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	10/551,205
Filing Date	November 14, 2006
First Named Inventor	Nicholas S. Bodor
Examiner Name	
Attorney Docket No.	0056192-000024

U.S. PATENT DOCUMENTS

Examiner Initials	Document Number-Kind Code	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Figures Appear
	US-			
	US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials	Foreign Patent Document: Country Code[1], Number, Kind Code	Publication Date (MM-DD-YYYY)	Name of Patentee or Applicant of Cited Document	STATUS: Translation	Partial Translation	Eng. Lang. Summary	Search Report	IPER	Abstract	Cited in Spec. / Pg. No(s).

[1]Enter Office that issued the document, by the two-letter code.

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials	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.
/J.L./	Albertioni et al., "On the bioavailability of 2-chloro-2'-deoxyadenosine (CdA)", Eur J Clin Pharmacol., Vol. 44, pp. 579-582, 1993, Springer-Verlag, Germany
	Ahn et al., "Chiral Recognition in Gas-Phase Cyclodextrin: Amino Acid Complexes-Is the Three Point Interaction Still Valid in the Gas Phase?", J Am Soc Mass Spectrom, Vol. 12, pp. 278-287, 2001, Elsevier Science, Inc., US
	Bakthiar et al., "A study of the complexation between dimethyl-β-cyclodextrin and steroid hormones using electrospray ionization mass spectrometry", Rapid Communications in Mass Spectrometry, Vol. 11, pp. 1478-1481, 1997, John Wiley And Sons Ltd, England
	Beutler et al., "The treatment of chronic progressive multiple sclerosis with cladribine", Proc. Natl. Acad. Sci. USA, Medical Sciences, Vol. 93, pp. 1716-1720, 1996, National Academy of Sciences, US
	Cheng et al., "Measurement of chiral complexes of cyclodextrin and amino acids by electrospray ionization time-of-flight mass spectrometry", J. Mass Spectrom, Vol. 36, pp. 834-836, 2001, John Wiley & Sons, Ltd., England
	Choi et al., "FT-Raman and FT-IR Spectra of the Non-steroidal Anti-inflammatory Drug Ketoprofen Included in Cyclodextrins", Analytical Sciences, Vol. 17 Supplement, pp. i785-i788, 2001, The Japan Society for Analytical Chemistry, Japan
	Giordano et al., "Thermal analysis of cyclodextrins and their inclusion compounds", Thermochimica Acta 380, pp. 123-151, 2001, Elsevier Science B.V., The Netherlands
	Hwang et al., "Water Suppression That Works. Excitation Sculpting Using Arbitrary Waveforms and Pulsed Field Gradients", Journal of Magnetic Resonance, Series A, Vol. 112, pp. 275-279, 1995, Academic Press, Inc., US
	Lamcharfi et al., "Electrospray Ionization Mass Spectrometry in Supramolecular Chemistry: Characterization of Non-covalent Cyclodextrin Complexes", Journal of Mass Spectrometry, Vol. 31, pp. 982-986, 1996, John Wiley & Sons, Ltd., England
	Loftsson et al., "Pharmaceutical Applications of Cyclodextrin. 1. Drug Solubilization and Stabilization", Journal of Pharmaceutical Sciences, Vol. 85, No. 10, pp. 1017-1025, 1996, American Pharmaceutical Association and the American Chemical Society, US
	Meier et al., "The Influence of β- and γ-Cyclodextrin Cavity Size on the Association Constant with Decanoate and Octanoate Anions", Journal of Inclusion Phenomena and Macrocyclic Chemistry, Vol. 40, pp. 291-295, 2001, Kluwer Academic Publishers, The Netherlands
/J.L./	Mura et al., "Interactions of ketoprofen and ibuprofen with β-cyclodextrins in solution and in the solid state", International Journal of Pharmaceutics, Vol. 166, pp. 189-203, 1998, Elsevier Science B.V., The Netherlands

Examiner Signature	/Jonathan Lau/	Date Considered	03/26/2008

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with M.P.E.P. § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next comm[illegible]ication to Applicant.

Substitute for form 1449/PTO & 1449B/PTO

THIRD
INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(use as many sheets as necessary)

Sheet 2 of 2

Complete if Known

Application Number	10/551,205
Filing Date	November 14, 2006
First Named Inventor	Nicholas S. Bodor
Examiner Name	
Attorney Docket No.	0056192-000024

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials	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.
/J.L./	Nolan et al., "Preparation of Vesicles and Nanoparticles of Amphiphilic Cyclodextrins Containing Labile Disulfide Bonds", Langmuir, Vol. 19, pp. 4469-4472, 2003, American Chemical Society, US
/J.L./	Ramanathan et al., "Electrospray Ionization Mass Spectrometric Study of Encapsulation of Amino Acids by Cyclodextrins", J. Am Soc Mass Spectrom, Vol. 6, pp. 866-871, 1995, American Society for Mass Spectrometry, US
/J.L./	Redenti et al., "Raman and Solid State ^{13}C-NMR Investigation of the Structure of the 1 : 1 Amorphous Piroxicam : β-Cyclodextrin Inclusion Compound", Biospectroscopy, Vol. 5, pp. 243-251, 1999, John Wiley & Sons, Inc., US
/J.L./	Sipe et al., "Cladribine in treatment of chronic progressive multiple sclerosis", The Lancet, Vol. 344, pp. 9-13, 1994, Lancet Publishing Group, England
/J.L./	Szejtli, "Introduction and General Overview of Cyclodextrin Chemistry", Chem. Rev., Vol. 98, pp. 1743-1753, 1998, American Chemical Society, US
/J.L./	Uekama et al., "Cyclodextrin Drug Carrier Systems", Chem. Rev., Vol. 98, pp. 2045-2076, 1998, American Chemical Society, US
/J.L./	Uekama et al., "Peracylated β-Cyclodextrins as Novel Sustained-release Carriers for a Water-soluble Drug, Molsidomine", J. Pharm. Pharmacol., Vol. 46, pp. 714-717, 1994, Pharmaceutical Press, England
/J.L./	Taddei et al., "Influence of Environment on Piroxicam Polymorphism: Vibrational Spectroscopic Study", Biopolymers (Biospectroscopy), Vol. 62, pp. 68-78, 2001, John Wiley & Sons, Inc., US

Examiner Signature	/Jonathan Lau/	Date Considered	03/26/2008

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with M.P.E.P. § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

Attorney's Docket No. 0056192-000024

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	**MAIL STOP PCT**
	)	
Nicholas S. Bodor et al.	)	Group Art Unit:
	)	
Application No.: 10/551,205	)	Examiner:
	)	
Filed: PCT/US2004/009387 filed March 26, 2004	)	Confirmation No.: 4092
	)	
For: ORAL FORMULATIONS OF CLADRIBINE	)	
	)	
	)	
	)	

FIRST INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure as set forth in 37 C.F.R. § 1.56, the accompanying information is being submitted in accordance with 37 C.F.R. §§ 1.97 and 1.98. Applicants request the Examiner's consideration of the documents listed on the accompanying Form PTO-1449. All of these documents are cited in the instant specifiation, including the documents cited in the International Search Report (copy enclosed) which was issued in connection with PCT/US2004/009387, filed March 26, 2004, of which this application is the national phase.

Pursuant to 37 C.F.R. § 1.98, a copy of each of the documents cited is enclosed. However, copies of any listed U.S. patents and U.S. patent application publications are not enclosed since it is no longer required according to the July 11, 2003 waiver of the requirement for copies of cited U.S. patents and U.S. patent application publications in national patent applications filed after June 30, 2003 and international applications entering the national stage under 35 U.S.C. § 371 after June 30, 2003.

This Statement, Form PTO-1449 and documents are being submitted within three (3) months of the filing or entry of the national stage of this application or before the first Office Action on the merits, whichever is later. Since these documents are being filed within the time period set forth in 37 C.F.R. § 1.97(b), no fee or statement is required.

The following remarks are offered with respect to the listed documents which are not in English:

DE 31 18 218 is in German. Applicants do not have an English translation. However, an English abstract, together with the citation of the document in the instant specification, are provided to serve as a brief statement of relevance. Applicants consider this a general state of the art reference.

DE 33 17 064 is in German. Applicants do not have an English translation but provides herewith an English abstract. The abstract and citation of the document in the specification serve as a brief statement of relevance. Applicants consider this a general state of the art reference.

EP 0 149 197 B1 is in German, although the claims are also present in English. Applicants enclose a full English translation of this document, which is cited in the instant specification and which applicants consider to be a general state of the art reference.

It is respectfully requested that an Examiner-initialed copy of the accompanying Form PTO-1449 be returned to the undersigned.

Respectfully submitted,

BUCHANAN INGERSOLL AND ROONEY PC

Date: November 14, 2006

By: Mary Katherine Baumeister
Mary Katherine Baumeister
Registration No. 26254

P.O. Box 1404
Alexandria, VA 22313-1404
703 836 6620

Substitute for form 1449/PTO & 1449B/PTO

FIRST INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 2

Complete if Known

Application Number	10/551,205
Filing Date	
First Named Inventor	Nicholas S. Bodor
Examiner Name	
Attorney Docket No.	0056192-000024

U.S. PATENT DOCUMENTS

Examiner Initials	Document Number	Kind Code (if known)	Name of Patentee or Applicant of Cited Document	Issue/Publication Date (MM-DD-YYYY)
/J.L./	4,383,992		Lipari	05-17-1983
	6,239,118	B1	Schatz et al.	05-29-2001
	5,424,296		Saven et al.	06-13-1995
	5,510,336		Saven et al.	04-23-1996
	5,506,214		Beutler	04-09-1996
	4,659,696		Hirai et al.	04-21-1987
	3,459,731		Gramera et al.	08-05-1969
	4,478,995		Shinoda et al.	10-23-1984
	5,310,732		Carson et al.	05-10-1994
	5,401,724		Beutler	03-28-1995
	5,106,837		Carson et al.	04-21-1992
	4,497,803		Harada et al.	02-05-1985
	6,194,395	B1	Schultz et al.	02-27-2001
	6,407,079	B1	Müller et al.	06-18-2002
	4,870,060		Müller	09-26-1989
	4,727,064		Pitha	02-23-1988
	4,596,795		Pitha	06-24-1986
	4,764,604		Müller	08-16-1988
/J.L./	4,535,152		Szejtli et al.	08-13-1985

FOREIGN PATENT DOCUMENTS

Examiner Initials	Document Number	Kind Code (if known)	Country	Date of Publication (MM-DD-YYYY)	STATUS: Translation	Partial Translation	Eng. Lang. Summary	Search Report	IPER	Abstract	Cited in Spec
/J.L./	0 197 571	A2	EP	10-15-1986							X
	90/12035	A1	WO	10-18-1990							X
	31 18 218	A1	DE	04-22-1982						X	X
	33 17 064	A1	DE	11-15-1984						X	X
	2 189 245	A	GB	10-21-1987							X
	0 149 197	B1	EP	07-24-1985	X						X
/J.L./	0 094 157	A1	EP	11-16-1983							X

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials	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.
/J.L./	Tarasiuk et al., "*Stability of 2-Chloro-2'-Deoxyadenosine at Various pH and Temperature*", Archivum Immunologiae et Therapiae Experimentalis, Vol. 42, pp. 13-15, 1994, published by Birkhauser Publishers Ltd., Basel, Switzerland
/J.L./	Romine et al., "*A Double-Blind, Placebo-Controlled, Randomized Trial of Cladribine in Relapsing-Remitting Multiple Sclerosis*", Proceedings of the Association of American Physicians, Vol. 111, No. 1, pp. 35-44, 1999, published by Blackwell Publishing, Malden, MA

Examiner Signature	/Jonathan Lau/	Date Considered	03/26/2008

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with M.P.E.P. § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

Substitute for form 1449/PTO & 1449B/PTO

FIRST INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	10/551,205
Filing Date	
First Named Inventor	Nicholas S. Bodor
Examiner Name	
Attorney Docket No.	0056192-000024

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials	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.
/J.L./	Tortorella et al., Current Opinion on Investigational Drugs, 2(12), pp. 1751-1756, 2001, published by PharmaPress Ltd., London, GB
	Selby et al., "*Safety and Tolerability of Subcutaneous Cladribine Therapy in Progressive Multiple Sclerosis*", Can. J. Neurol Sci., Vol. 25, pp. 295-299, 1998, published by Canadian Journal of Neurological Science, Calgary, Canada
	Rice et al., "*Cladribine and progressive MS Clinical and MRI outcomes of a multicenter controlled trial*", Neurology, Vol. 54, pp. 1145-1155, 2000, published by Lippincott Williams and Wilkins, Hagerstown, MD
	Liliemark et al., "*On the Bioavailability of Oral and Subcutaneous 2-Chloro-2'-Deoxyadenosine in Humans: Alternative Routes of Administration*", Journal of Clinical Oncology, Vol. 10, No. 10, pp. 1514-1518, 1992, published by American Society of Clinicial Oncology, Alexandria, VA
	Karlsson et al., "*Oral cladribine for B-cell chronic lymphocytic leukaemia: report of a phase II trial with a 3-d, 3-weekly schedule in untreated and pretreated patients, and a long-term follow-up of 126 previously untreated patients*", British Journal of Haematology, Vol. 116, pp. 538-548, 2002, published by Blackwell Science Ltd., Oxford, UK
	Liliemark, "*The Clinical Pharmacokinetics of Cladribine*" Clin. Pharmacokinet, Vol. 32 (2), pp. 120-131, 1997, published by Adis International Limited, Wolters Kluwer Health, Yardley, PA
	Nakai et al., "*Effects of Grinding on the Physical and Chemical Properties of Crystalline Medicinals with Microcrystalline Cellulose V: Comparison with Tri-O-methyl-β-cyclodextrin Ground Mixtures*", Chem. Pharm. Bulletin, Vol. 28(5), pp. 1552-1558, 1980, published by Pharmaceutical Society of Japan, Tokyo, Japan
	Saenger, "*Clyclodextrin Inclusion Compounds in Research and Industry*", Angew. Chem. Int. Ed. Engl., Vol. 19, pp. 344-362, 1980, published by Verlag Chemie, GmbH, Weinheim, Germany
/J.L./	Tang et al., "*Design of Freeze-Drying Processes for Pharmaceuticals: Practical Advice*", Pharmaceutical Research, Vol. 21, No. 2, pp. 191-200, 2004, Springer, The Netherlands

Examiner Signature	/Jonathan Lau/	Date Considered	03/26/2008

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with M.P.E.P. § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	**MAIL STOP AMENDMENT**
Nicholas Bodor et al.	)	Group Art Unit: 1623
Application No.: 10/551,205	)	Examiner: JONATHAN S LAU
Filed: November 14, 2006	)	Confirmation No.: 4092
For: ORAL FORMULATIONS OF CLADRIBINE	)	

REPLY AND AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office Action dated April 4, 2008, please first amend the above-identified patent application as follows:

AMENDMENTS TO THE SPECIFICATION:

Please replace the paragraph at page 22, lines 8-16 of the specification with the following amended paragraph:

> The compositions of the invention are particularly suitable as modalities for the treatment of any cladribine-responsive disease. Several disease states responsive to cladribine are well-documented in the literature (see *infra)*. For any target disease state, an effective amount of the complex cladribine-cyclodextrin ~~comples~~ complex, *i.e.* the amorphous mixture of the optimized amorphous saturated cladribine-amorphous cyclodextrin complex with amorphous free cladribine as described above is used (e.g., an amount ~~affective~~ effective for the treatment of multiple sclerosis, rheumatoid arthritis, or leukemia).

Please replace the paragraph at page 23, lines 7-28, of the specification with the following amended paragraph:

> Moreover, the route of administration for which the therapeutically effective dosages are taught in the literature should be taken into consideration. While the instant compositions optimize the bioavailability of cladribine following oral administration, it will be appreciated that even optimal bioavailability from oral dosage forms is not expected to approach bioavailability ~~obtain~~ obtained after intravenous administration, particularly at early time points. Thus, it is often appropriate to increase a dosage suggested for intravenous administration to arrive at a suitable dosage for incorporation into a solid oral dosage form. At the present time, it is envisioned that, for the treatment of multiple sclerosis, 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant solid dosage form would be administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment. Alternatively the patient would

be treated with 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant dosage form once per day for a period of five to seven days per month for a total of six months, followed by eighteen months of no treatment. ~~For further dosing information, see also U.S. Provisional Patent Application No.~~ [[ ]] ~~[IVAX0021-P-USA/Attorney Docket No. 033935-011], and U.S. Provisional Patent Application No.~~ [[ ]] ~~[IVAX0022-P-USA/Attorney Docket No. 033935-012], both entitled "Cladribine Regimen for Treating Multiple Sclerosis", both filed on March 25, 2004 and incorporated by reference herein in their entireties.~~

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. (Currently Amended) A pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture consisting of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein.

2. (Currently Amended) The pharmaceutical composition according to Claim 1, wherein the complex cladribine-cyclodextrin complex is saturated with cladribine.

3. (Previously Presented) The composition according to Claim 1, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

4. (Previously Presented) The composition according to Claim 1, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

5. (Previously Presented) The composition according to Claim 1, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

6. (Previously Presented) The composition according to Claim 1, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

7. (Original) The composition according to Claim 6, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

8. (Original) The composition according to Claim 7, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

9. (Original) The composition according to Claim 7, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

10. (Original) The composition according to Claim 6, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

11. (Currently Amended) The composition according to ~~Claim 1~~ Claim 2, wherein the approximate molar ratio of cladribine to amorphous cyclodextrin corresponds to a point located on the curve of a phase solubility diagram for saturated complex cladribine-cyclodextrin complexes, said curve defining complex saturated complexes of cladribine in varying concentrations of the cyclodextrin.

12. (Previously Presented) The composition according to Claim 1, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

13. (Withdrawn and Currently Amended) A method for enhancing the oral bioavailability of cladribine comprising orally administering to a subject in need thereof a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture consisting of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein.

14. (Withdrawn and Currently Amended) The method according to Claim 13, wherein the complex cladribine-cyclodextrin complex is saturated with cladribine.

15. (Withdrawn) The method according to Claim 13, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

16. (Withdrawn) The method according to Claim 13, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

17. (Withdrawn) The method according to Claim 13, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

18. (Withdrawn) The method according to Claim 13, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

19. (Withdrawn) The method according to Claim 18, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

20. (Withdrawn) The method according to Claim 19, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

21. (Withdrawn) The method according to Claim 19, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

22. (Withdrawn) The method according to Claim 18, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

23. (Withdrawn and Currently Amended) The method according to ~~Claim 13~~ Claim 14, wherein the approximate molar ratio of cladribine to amorphous cyclodextrin corresponds to a point located on the curve of a phase solubility diagram for saturated complex cladribine-cyclodextrin complexes, said curve defining complex saturated complexes of cladribine in varying concentrations of the cyclodextrin.

24. (Withdrawn) The method according to Claim 13, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

25. (Withdrawn and Currently Amended) A method for the treatment of symptoms of a cladribine-responsive condition in a subject suffering from said symptoms comprising orally administering to said subject a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture consisting of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein.

26. (Withdrawn and Currently Amended) The method according to Claim 25, wherein the complex cladribine-cyclodextrin complex is saturated with cladribine.

27. (Withdrawn) The method according to Claim 25, wherein the cladribine-responsive condition is selected from the group consisting of multiple sclerosis, rheumatoid arthritis and leukemia.

28. (Withdrawn) The method according to Claim 27, wherein the cladribine-responsive condition is multiple sclerosis.

29. (Withdrawn) The method according to Claim 25, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

30. (Withdrawn) The method according to Claim 25, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

31. (Withdrawn) The method according to Claim 25, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

32. (Withdrawn) The method according to Claim 31, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

33. (Withdrawn) The method according to Claim 31, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

34. (Withdrawn) The method according to Claim 25, wherein the amorphous cyclodextrin is hydropropyl-γ-cyclodextrin.

35. (Withdrawn) The method according to Claim 25, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

36.-55. (Cancelled)

56. (Currently Amended) A complex cladribine-cyclodextrin complex which is an intimate amorphous admixture consisting of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex.

57. (Currently Amended) The complex cladribine-cyclodextrin complex according to Claim 56, saturated with cladribine.

58. (Currently Amended) The complex cladribine-cyclodextrin complex according to Claim 56, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, randomly methylated β-cyclodextrin, carboxymethyl-β-cyclodextrin or sulfobutyl-β-cyclodextrin.

59. (Currently Amended) The complex cladribine-cyclodextrin complex according to Claim 56, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

60. (Currently Amended) The complex cladribine-cyclodextrin complex according to Claim 56, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

61. (Currently Amended) The complex cladribine-cyclodextrin complex according to Claim 56, wherein the weight ratio of cladribine to amorphous cyclodextrin is from about 1:10 to about 1:16.

62. (Currently Amended) The complex cladribine-cyclodextrin complex according to Claim 61, wherein the amorphous cyclodextrin is hydroxypropyl-β-cyclodextrin.

63. (Currently Amended) The complex cladribine-cyclodextrin complex according to Claim 62, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

64. (Currently Amended) The complex cladribine-cyclodextrin complex according to Claim 62, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

65. (Currently Amended) The complex cladribine-cyclodextrin complex according to Claim 61, wherein the amorphous cyclodextrin is hydroxypropyl-γ-cyclodextrin.

66. (Currently Amended) The complex cladribine-cyclodextrin complex according to Claim 56, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

67. (Withdrawn and Currently Amended) A process for the preparation of a complex cladribine-cyclodextrin complex as claimed in Claim 56, which comprises the steps of:

(i) combining cladribine and an amorphous cyclodextrin in water at a temperature of from about [[40]] 45 to about 80°C and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature; and

(iii) lyophilizing the cooled solution to afford an amorphous product.

68. (Withdrawn) A process according to Claim 67, further comprising a filtration step following step (ii).

69. (Withdrawn) A process according to Claim 67, wherein step (i) is performed at a temperature of from about 45 to about 60°C.

70. (Withdrawn) A process according to Claim 67, wherein step (i) is performed at a temperature of from about 45 to about 50°C.

71. (Withdrawn) A process according to Claim 69, wherein step (i) is performed with stirring.

72. (withdrawn) A process according to Claim 71, wherein step (i) is performed for a period of from about 6 to about 9 hours.

73. (Withdrawn) A process according to Claim 67, wherein step (ii) is performed for a period of from about 6 to about 9 hours.

74. (Withdrawn) A process according to Claim 67, wherein step (iii) comprises an initial freezing stage in which the solution is cooled to from about -40 to about -80° C, and held at said temperature for a period of from about 2 to about 4 hours.

75. (Withdrawn) A process according to Claim 74, wherein, in the initial freezing stage of step (iii), the solution is cooled to about -45°C.

76. (Withdrawn) A process according to Claim 67, wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i).

77. (Withdrawn) A process according to Claim 67, wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i).

78. (Withdrawn) A process according to Claim 76, wherein 825 parts by volume of water are introduced in step (i).

79. (Withdrawn) A process according to Claim 67, wherein the lyophilization step (iii) comprises:

(a) an initial freezing stage in which the complexation solution is brought to from about -40°C to about -80°C for approximately 2 to 4 hours;

(b) a primary drying stage at about -25°C for approximately 80 to 90 hours; and

(c) a secondary drying stage at about 30°C for approximately 15 to 20 hours.

80. (Withdrawn) A process according to Claim 79, wherein stage (a) of the lyophilization is conducted at about -45°C for approximately 3 to 4 hours.

81. (Withdrawn) A process according to Claim 79, wherein stage (b) of the lyophilization is conducted under a pressure of about 100 mTorr.

82. (Currently Amended) A pharmaceutical composition obtainable by a process comprising the steps of:

(i) combining cladribine and an amorphous cyclodextrin in water at a temperature of from about [[40]] 45 to about 80°C and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature;

(iii) lyophilizing the cooled solution to afford an amorphous product; and

(iv) formulating the amorphous product into a solid oral dosage form.

83. (Original) A pharmaceutical composition according to Claim 82, wherein the process further comprises a filtration step following step (i) or (ii).

84. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein step (i) of the process is performed at a temperature of from about 45 to about 60°C.

85. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein step (i) of the process is performed at a temperature of from about 45 to about 50°C.

86. (Previously Presented) A pharmaceutical composition according to Claim 84, wherein step (i) of the process is performed with stirring.

87. (Original) A pharmaceutical composition according to Claim 86, wherein step (i) of the process is performed for a period of from about 6 to about 9 hours.

88. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein step (ii) of the process is performed for a period of from about 6 to about 9 hours.

89. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein step (iii) comprises an initial freezing stage in which the solution is cooled to from about -40 to about -80°C, and held at said temperature for a period of from about 2 to about 4 hours.

90. (Original) A pharmaceutical composition according to Claim 89, wherein, in the initial freezing stage of step (iii), the solution is cooled to about -45°C.

91. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process.

92. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process.

93. (Previously Presented) A pharmaceutical composition according to Claim 91, wherein 825 parts by volume of water are introduced in step (i) of the process.

94. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein the lyophilization step (iii) of the process comprises:

(a) an initial freezing stage in which the complexation solution is brought to from about -40°C to about -80°C for approximately 2 to 4 hours;

(b) a primary drying stage at about -25°C for approximately 80 to 90 hours; and

(c) a secondary drying stage at about 30°C for approximately 15 to 20 hours.

95. (Original) A pharmaceutical composition according to Claim 94, wherein stage (a) of the lyophilization is conducted at about -45°C for approximately 3 to 4 hours.

96. (Previously Presented) A pharmaceutical composition according to Claim 94, wherein stage (b) of the lyophilization is conducted under a pressure of about 100 mTorr.

97. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein the formulation step (iv) of the process comprises blending the complex with magnesium stearate and compressing into tablets.

98. (Original) A pharmaceutical composition according to Claim 97, wherein magnesium stearate is pre-mixed with sorbitol powder before blending with the complex.

REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the following remarks.

THE DRAWINGS

Applicants appreciate the Examiner's acceptance of the drawing as filed.

INFORMATION DISCLOSURE STATEMENTS

Applicants thank the Examiner for considering the four Information Disclosure Statements previously filed herein.

FILING DATES TO WHICH CLAIMS ARE ENTITLED

The Examiner has assessed the filing dates to which he believes the claims which he has examined are entitled. Thus, Claims 1-12, 56-66 and 82-98 have been assessed by the Examiner in regard to the earliest filing date to which he believes they are entitled.

Applicants have amended Claim 82 hereinabove so that step (i) is conducted at a temperature from about 45 to about 80°C rather than from about 40 to about 80°C as previously recited. This revised range is not only supported by the instant application (e.g., page 13, lines 21-25) but also by page 12, lines 20-23, of Provisional Appln. No. 60/541,247, filed February 4, 2004; moreover, step (ii) is disclosed at least on page 14, line 3 and in Example 2 of 60/541,247; step (iii) at least on page 14, line 6 and Example 2 of 60/541,247; and step (iv) at least on page 17, lines 25-27, page 18, lines 7-10 and Example 3 of 60/541,247. Claim 88 is supported at least by page 12, lines 20-22 of 60/541,247. Thus, applicants concur with the Examiner that the filing dates of Claims 1-11, 56-65, 84, 86 and 87 are the filing date of Application No. 60/541,247, filed February 4, 2004, but add that the filing dates of Claims 82 and 88 are also the February 4, 2004 filing date of Application No. 60/541,247.

Applicants concur with the Examiner's assessment that Claims 12, 66, 83, 85 and 89 are entitled to the effective filing date of the present application; however, as

a national phase application, this application and thus Claims 12, 66, 83, 85 and 89 are entitled to the international filing date of PCT/US04/09387, that is, March 26, 2004. The Examiner's reference to November 14, 2006 as the filing date for these claims is incorrect, that date simply being the date on which the requirements of the last of the 371(c)(1), (c)(2) and (c)(4) requirements were received by the USPTO. In the official Notice of Acceptance of Application under 35 U.S.C. 371 and 37 C.F.R. 1.495, it is clearly stated: "The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363)."

Despite the foregoing, it is not understood why the Examiner has found it necessary to assess the priority dates of the examined claims, as no art has been cited which would make it necessary to make such an assessment.

ELECTIONS/RESTRICTIONS

Applicants' election, with traverse, of the invention of Group I, Claims 1-12, 56-66 and 82-98 has been acknowledged and acted upon. Applicants continue to maintain that the amorphous nature of the various entities which make up the complex, that is the intimate amorphous admixture of (a) an amorphous inclusion complex of cladribine with amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex which is formulated into a solid dosage form is not disclosed or suggested by Schultz et al. even when read in conjunction with WO 97/18839, as Schultz et al.'s melt extrusion product would not be inherently the same as applicants' Claim 1 product. Applicants' reasons for so stating are set forth in the discussion of the references herein below. Based on the discussion below, applicants submit that because the elected claims are in fact patentable over the art of record, there is indeed the unifying feature to all of the claims which applicants pointed to earlier. Therefore, the withdrawn claims should be rejoined and examined.

OBJECTIONS TO THE SPECIFICATION

The disclosure has been objected to because of the blanks identifying provisional application numbers on page 23. By the foregoing amendment,

applicants have deleted the entire sentence containing the blanks because the applications in question have been abandoned.

The disclosure has also been objected to because of a typographical error on page 22, line 12. Applicants have corrected the error by the foregoing amendment.

It is believed that these amendments overcome the objections to the specification.

CLAIM REJECTIONS - 35 U.S.C. § 112

Claims 2, 11 and 57 are also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because of use of the term "saturated." Applicants submit that the claims are indeed clear and particularly point out and distinctly claim what applicants regard as their invention.

The Federal Circuit has made it very clear that definiteness of claim language must not be analyzed in a vacuum but rather (1) in light of applicants' specification, (2) in light of the prior art, and (3) in light of the manner in which the claims would be interpreted by one of ordinary skill in the relevant art. When analyzed in accord with Federal Circuit decisions, applicants' claims are definite. Applicants' claims are understandable and define what they regard as their invention; according to the C.C. P.A. decision *In re Kamal et al. (CCPA 1968) 158 USPQ 120*, such claims meet the requirements of the second paragraph of 35 U.S.C. § 112. In an effort to make these claims and others containing similar language even clearer, applicants have modified the language that refers to the saturated complexes to make it clear that it is the complex cladribine-cyclodextrin complexes which are saturated. Applicants have also modified the language of Claim 11; it would of course be apparent to the person of ordinary skill that applicants were referring to a point <u>on the curve</u> of the phase solubility diagram. The claims as amended have the same scope as prior to the amendment; these are not narrowing amendments but merely clarification of the subject matter to which the claims were previously directed.

The Examiner has noted that the term "saturated" is not defined in the claims, but applicants submit that it is the function of the specification, not the claims, to define terms. Applicants have certainly explained what they mean by saturated, not only by the disclosure at page 10, lines 1-13, but also by the disclosure at page 6,

line 20 to page 7, line 2; by the disclosure beginning at page 13, line 14 through page 14, line 16, which details the procedure used to develop the phase solubility curve; and by the disclosure at page 15, lines 5-29. Very specific information is given, not only as to time and temperature and subsequent filtration, on page 13, lines 21-26, but also in the discussion extending from page 16, line 1 to page 17, line 14. The phase solubility diagram and the discussion of the phase solubility diagram in Example 1 (and by reference, the complexation portion of Example 2) describe exactly how this phase solubility diagram/curve was generated. One of ordinary skill need only select a point on the phase solubility curve to identify the proportion of cladribine and cyclodextrin appropriate for the described saturated complexes for the conditions used in applicants' study. Alternatively, one of ordinary skill can repeat applicants' study to obtain the same curve, or can create his/her own phase solubility diagram for other conditions which he/she selects. The point is that applicants' work is reproducible, based on the teachings of their specification; selection of the same conditions as described will afford the same results; thus, the meaning of the claims which use the word "saturated" and which refer to the phase solubility diagram is clear to one of ordinary skill. As to the Examiner's complaint that no standard is given such as temperature, pressure or solvent, this is manifestly untrue for it is perfectly clear that the solvent disclosed in the specification is water and that the temperature and time are discussed with particularity in the specification, including the Examples, as already pointed out. Pressure is not mentioned because the work was carried out at atmospheric pressure, as would be understood by the skilled worker (who would know that pressure need be indicated only if it deviates from atmospheric pressure). Therefore, while there is no need to determine the amounts for each composition, at least when the cyclodextrin is hydroxypropyl-β-cyclodextrin or even hydroxypropyl-γ-cyclodextrin (page 17, lines 9-14) and the phase solubility curve provided by applicants can be used, it would be a very routine matter for one of ordinary skill to create such a curve for other amorphous cyclodextrins or to merely combine cladribine with the chosen cyclodextrin using the conditions specified by applicants and then remove excess cladribine. This is a simple procedure given all of applicants' teachings; it is not rocket science but rather is well within the skill in the art.

For at least the reasons set forth above, applicants submit that the 35 U.S.C. § 112, second paragraph, rejection is untenable and should be withdrawn.

CLAIM REJECTIONS - 35 U.S.C. § 102

Claims 1-15, 11, 56-60, 82-90 and 84-98 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Schultz et al. U.S. Patent No. 6,194,395, as evidenced by Baert et al. WO 97/18839.

Before discussing the cited references, applicants would like to discuss the amendments made to the claims hereinabove which make clearer what applicants regard as their invention. The Examiner is thanked for his very thorough review of the specification and the claim language, which has made it possible for applicants to see that some of their original language might have been open to misinterpretation while other language could be interpreted more broadly than they had intended. The amendments to Claims 2, 11 and 57 (as well as to withdrawn claims containing corresponding language) clarify that it is the entire complex cladribine-cyclodextrin complex which is saturated and that the point is located on the curve defining the saturated complexes as in the Figure. Applicants have also amended Claims 1 and 56 (and thus their dependent claims as well), as well as corresponding withdrawn claims, so that both Claims 1 and 56 now specify that the complex cladribine-cyclodextrin complex is an intimate amorphous admixture consisting of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex. This of course excludes anything else from the complex. Claim 1, drawn to a pharmaceutical composition comprising the complex, has been further amended (as have the withdrawn claims containing corresponding language) to specify that the composition comprises no significant amount of free crystalline cladribine therein. This means that no significant amount of free cladribine can be detected considering the sensitivity of the analytical method; see Example 2, page 31, lines 3-13, where this language finds specific support. Applicants teach throughout this application that free crystalline cladribine which is not in the complex is excluded; see for example, page 13, lines 19-28; page 16, lines 1-12 and 13-28; page 20, line 28 to page 21, line 11; page 21, lines 24-29; Example 1, pages 26-28;

and Example 2, page 28, line 3 to page 29, line 26 and of course page 31, lines 3-13. As described, excess cladribine is typically removed from solutions of the complex by filtering it off after the complex complex has been formed in water; subsequent lyophilization of the filtered solution and minimal further processing affords the claimed solid oral dosage form. Therefore, the claim amendments clearly do not introduce new matter.

The Examiner states that Schultz et al. disclose a solid pharmaceutical oral dosage form comprising cladribine and cyclodextrin and applicants agree. However, the Examiner claims that Schultz et al.'s disclosure meets the limitations of instant Claims 1 and 56, which applicants regard as an unwarranted conclusion. Similarly, applicants find no evidence in Schultz et al. that the Schultz et al. solid product is substantially identical to a product-by-process meeting the limitations of instant Claims 82-90 and 94-96.

Schultz et al. disclose the use of either crystalline or amorphous cyclodextrins for their compositions, since some of those named by the patentees are known to be crystalline while others are known to be amorphous. Applicants' complexes and compositions utilize only amorphous cyclodextrins. Thus, many cyclodextrins disclosed by Schultz et al. would be inoperative in the present invention, as they would afford crystalline rather than amorphous products. In stating that the limitations of Claims 3-5 and 58-60 are met by Schultz et al., the Examiner is focusing only on the cyclodextrins in common; he does not address the basic differences between the Schultz et al. solid dosage form and applicants' products. Applicants will agree, however, that Schultz et al.'s preferred cyclodextrin is hydroxypropyl- β -cyclodextrin, which is a cyclodextrin also specified in many of applicants' claims. Again, applicants do not dispute that the excipients may be (but are not necessarily) the same, but this does not arrive at the products of instant Claims 3 and 58 or 97 or 98. As to the amounts of cladribine and cyclodextrin, Schultz et al. disclose weight ratios of from 1 to about 15 mg. of cladribine to about 100 to 500 mg. of a cyclodextrin; this can give a cladribine:cyclodextrin ratio of anywhere from 1:500 to 15:100, or from 1:500 to 1:6.67. If one took the lower limits of each in ratio to the upper limits of each, one would arrive at ratios from 1:100 to 15:500, or from 1:100 to 1:33.34. Most of the 1:500 to 1:6.67 ratio does not even

encompass applicants' ratio, while the 1:100 to 1:33.34 does not embrace it at all. Certainly no guidance in this respect is given by Schultz et al. Moreover, Claim 11 herein has been reworded to clarify that the point is on the curve, as described in the instant specification, and certainly this feature is not disclosed in any way by Schultz et al. Moreover, the instant claims no longer allow for the presence uncomplexed cladribine in either the composition or the complex.

The Examiner correctly states that the Schultz et al. patent incorporates by reference the method of making their solid oral dosage form by utilizing the melt-extrusion process of Baert et al. The Baert et al. process is carried out by mixing the cyclodextrin and the active ingredient, heating until melting one of the components, forcing the mixture through one or more nozzles, and cooling until the mixture solidifies (page 5, line 24-29). Milling may follow. The term "melting" is used broadly by Baert et al. and includes transition to a glass; in particular cases, one component melts and the other dissolves therein forming solid solutions (page 5, lines 8-12). The extruded material may contain amorphous material or a solid solution (page 7, line 35 to page 8, line 7). While amorphous products are of interest, those which are mainly a solid solution are preferred (page 8, lines 11-23). In Table 1, on page 30, several different mixtures of hydroxypropyl- β -cyclodextrin and selected drugs were subjected to the Baert et al. process. As noted on page 13, lines 5-6, in every case, the mixture using this cyclodextrin gave a solid solution. The Examiner will note from Table 1 that the temperatures used, regardless of the identity of the drug, went as high as 292°C., with the temperatures for the itraconazole/HPβCD mixtures reaching 279°C-280°C. According to *The Merck Index* (copy of excerpt enclosed), itraconazole melts at 166.2°C while HPβCD melts at 278°C according to *LookChem* (copy of excerpt also attached).

In addition to the teachings of Baert et al. noted above, applicants draw the Examiner's attention to three of Baert et al.'s teachings which are of particular importance here:

1. On page 4, lines 5-7, Baert et al state:

   > The compounds that are suitable to be used in this technique are compounds that show no appreciable decomposition at the temperatures needed to melt and extrude the mixture of said

one or more active ingredients with the cyclodextrin or cyclodextrins.

2. On page 6, lines 14-19, Baert et al. state:

> The possible formation of these solid solutions is one of the further advantages of the present invention. It will be appreciated by a person skilled in the art that mixing two or more solids, i.e., one or more cyclodextrins and the active ingredient or ingredients, and subsequently melting these solids together give rise to different products than when the said solids are first brought into contact with water or another solvent and then extruded.

3. While Baert et al. have general teachings regarding ratios of from 1:100 to 100:1, particularly 1:10 to 10:1, especially 1:5 to 5:1, 1:3 to 3:1, preferably 1:1, Table 1 therein uses ratios of active ingredient: HPβCD of 1:3 or 1:1. Table 2 utilizes 1:1 ratios.

The only solid dosage form envisioned by Schultz et al. is a melt-extrusion product of cladribine and cyclodextrin prepared according to Baert et al. There is no evidence that such a product was ever prepared. Indeed, cladribine melts at 220-235°C with decomposition; see the enclosed excerpt from *Linscott's Directory* (copy attached) as well as that from *The Merck Index* (also enclosed). Thus, cladribine decomposes well below the 278°C melting point of HPβCD and well below the temperature used by Baert et al. for their melt extrusion; cladribine is therefore not suitable for the Baert et al. process, according to Baert et al.'s teaching that suitable compounds show no appreciable decomposition at the temperature they use (point 1 above).

Furthermore, Baert et al.'s teaching on page 6 that their melt-extrusion process affords different products than when their solids are first brought into contact with water (point 2 above) militates against the Examiner's finding that a cladribine/cyclodextrin product prepared by Baert et al.'s process is the same as applicants' product, which is, in fact, prepared by first contacting cyclodextrin with water. Indeed, it is the use of water that enables the formation of cyclodextrin-drug complexes; it is by complex formation that the water solubility of many drugs has

been previously improved. There is no teaching by Baert et al. that would lead one of ordinary skill to conclude that Baert et al made solid complexes; indeed, Baert et al. specifically teach on page 6 that their products are different from products obtained by first dissolving cyclodextrin and drug in water. Thus, a melt-extrusion product of cladribine and cyclodextrin cannot anticipate applicants' product which comprises a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture consisting of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein. Applicants' product is prepared by preparing the complex in water; Baert et al. teach they obtain a different product than one that can be obtained from water; moreover, applicants' process uses temperatures up to only about 80°C, far below the decomposition temperature for cladribine and far below the temperatures used by Baert et al. See Claims 82-89 herein.

Further, for an anticipation to be inherent, the reference must always provide applicants' product. There is no reason to assume that Schultz et al's solid product ever is the same as applicants'; indeed, Baert et al. clearly teach that it is different.

For at least the reasons set forth above, the anticipation rejection of Claims 1-5, 11, 56-60, 82-90 and 94-98 based on Schultz et al. as evidenced by Baert et al. is untenable and should be withdrawn.

CLAIM REJECTIONS - 35 U.S.C.§ 103

Claims 1, 6-10, 12, 56, 61-66, 82 and 91-93 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Schultz et al. in view of Baert et al. We respectfully disagree.

Both Schultz et al. and Baert et al. are fully discussed above. In referring to the ratios disclosed by Schultz et al. for their melt extrusion solid dosage form, the Examiner has chosen to ignore the 1 mg. dosage at which the amount of cladribine begins; therefore, the range disclosed by Schultz et al. for cladribine:cyclodextrin varies from about 1:500 to 1:6.67. This is not even in accord with Baert et al.'s ratio of from about 1:1 to about 1:3. And if one uses Schultz et al's ratios proportionately,

low:low and high:high, one arrives at from 1:100 to 15:500 (1:33.34). In the former case, there is absolutely nothing in Schultz et al. that would lead to a specific ratio of from about 1:10 to about 1:16 or about 1:11 or about 1:14; it is applicants' own teachings which lead to these ratios. Likewise, the features of the other claims rejected under 35 U.S.C. § 103 are not disclosed by Schultz et al. Certainly Baert et al doesn't teach these ratios and if one looks at Schultz et al.'s suggested amounts proportionately, applicants' ratios are not even broadly encompassed by the reference. Still further, as noted earlier, Baert et al. clearly teach that the drug-cyclodextrin solid products of their melt extrusion process are distinctly different from products prepared in water; since applicants' products are prepared in water, they cannot possibly be the same as those obtained by the Baert et al. process incorporated by reference by Schultz et al.

Baert et al.'s ratios of active ingredient have been interpreted as mole ratios by the Examiner. There is no good reason for such an interpretation. The Examiner reasons that the fact that the active ingredients have different molecular weights leads to this interpretation, yet there are cyclodextrins of different molecular weights contemplated by Schultz et al. and by the present inventors and the ratios of Schultz et al. are clearly by weight (col. 6, lines 23-31), just as applicants' ratios are clearly weight ratios, e.g., Claim 8. Absent a teaching to the contrary, one of ordinary skill would assume that the ratios of Baert et al. are also weight ratios. At any rate, the Baert et al. melt-extrusion product is not one obtained by complexation in water; Baert et al. teach their melt-extrusion product is different from a product whose preparation begins by dissolving the drug and cyclodextrin in water. Therefore, any product that Schultz et al. might produce from cladribine and cyclodextrin subjected to Baert et al.'s melt extrusion product cannot be the same as applicants' complex cladribine-cyclodextrin complex which must be obtained from an aqueous solution which is treated in a specific manner. Baert et al. never suggests that they obtain a complex by their melt-extrusion process, much less one meeting the requirements of applicants' claims. Indeed, Baert et al. emphasize that their process, which is different, affords a different product than that obtained by first dissolving the drug and cyclodextrin. Likewise, applicants emphasize that applicants' process is strikingly different from Baert et al.'s process and thus logically would not afford the

product which Schultz et al. would be expected to obtain by subjecting cladribine and cyclodextrin to Baert et al.'s process. Moreover, applicants have formed a very special complex which contains a large amount of cladribine as an amorphous inclusion complex and as amorphous free cladribine associated with the cyclodextrin as a non-inclusion complex. Note too that the free cladribine associated with the non-inclusion product is amorphous, in contrast to the cladribine starting material, which is crystalline. Note also that applicants produce their product by first complexing in water at temperatures of from about 45°C to about 80°C, far below the temperatures used by Baert et al. Cladribine actually decomposes at temperatures below that used by Baert et al.

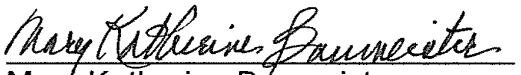
It is clear from the foregoing that a molecular inclusion complexation process, let alone the particular inclusion process utilized by applicants to form their unique complex cladribine-cyclodextrin complex, is not inherent in Baert et al.'s melt extrusion process and that Baert et al.'s process gives a different product. To hold otherwise would be to ignore Baert et al.'s own teachings.

In view of the foregoing, it is submitted that the present application is free of all record rejections and objections. Further, favorable action in the form of a Notice of Allowance is believed to be next in order and is earnestly solicited.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date:October 3, 2008

By: 
Mary Katherine Baumeister
Registration No. 26254

P.O. Box 1404
Alexandria, VA 22313-1404
703 836 6620

Attachments:

"Cladribine", *The Merck Index,* (2001), pp. 407-408, Thirteenth Edition, Merck & Co., Inc., Whitehouse Station, NJ

"Itraconazole", *The Merck Index,* (2001), p. 938, Thirteen Edition, Merck & Co., Inc. Whitehouse Station, NJ

"Hydroxypropyl-beta-cyclodextrin, CAS No. 94035-02-6" *LookChem*, http://www.lookchem.com/cas-940/94035-02-6.html, September 23, 2008

"Non-antibody Products (Kits, Proteins, Microbial Antigens, Tissues, Services, etc.) *Linscott's Directory of Immunological & Biological Reagents*, http://www.linscottsdirectory.com/browse/products/page:36, Records 1,751-1,800 of 130,353, September 11, 2008

THE
MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

THIRTEENTH EDITION

Y

Editorial Staff

Maryadele J. O'Neil, *Senior Editor*
Ann Smith, *Senior Associate Editor*
Patricia E. Heckelman, *Associate Editor*

John R. Obenchain Jr., *Editorial Assistant*
Jo Ann R. Gallipeau, *Technical Assistant*
Mary Ann D'Arecca, *Administrative Associate*

Susan Budavari, *Editor Emeritus*

Published by
Merck Research Laboratories
Division of

MERCK & CO., INC.
Whitehouse Station, NJ

2001

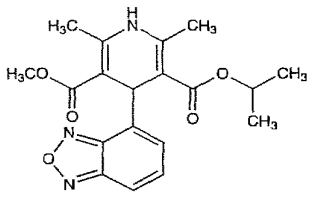
MERCK & CO., INC.
Whitehouse Station, NJ
USA

1st Edition—1889
2nd Edition—1896
3rd Edition—1907
4th Edition—1930
5th Edition—1940
6th Edition—1952
7th Edition—1960
8th Edition—1968
9th Edition—1976
10th Edition—1983
11th Edition—1989
12th Edition—1996

Library of Congress Catalog
Card Number 89-60001
ISBN Number 0911910-13-1

Printed in the USA

angina and coronary artery disease: C. E. Handler, E. Sowton, *ibid.* **27,** 415 (1984); in hypertension: E. B. Nelson *et al., Clin. Pharmacol. Ther.* **40,** 694 (1986). Comparison of hemodynamic effects of enantiomers: R. P. Hof *et al., J. Cardiovasc. Pharmacol.* **8,** 221 (1986). Series of articles on pharmacology and clinical use: *Am. J. Med.* **86,** 1-146 (1989).



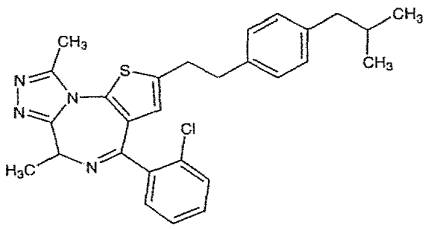
mp 168-170°.

***S*(+)-Form.** PN-205-033. Crystals from ether + hexane, mp 142°. $[\alpha]_D^{20}$ +6.7° (c = 1.5 in ethanol).

***R*(−)-Form.** PN-205-034. Crystals from ether + hexane, mp 140°. $[\alpha]_D^{20}$ −6.7° (c = 1.67 in ethanol).

THERAP CAT: Antihypertensive; antianginal.

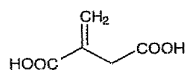
5263. Israpafant. [117279-73-9] 4-(2-Chlorophenyl)-6,-9-dimethyl-2-[2-[4-(2-methylpropyl)phenyl]ethyl]-6*H*-thieno-[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepine; (±)-4-(*o*-chlorophenyl)-2-(*p*-isobutylphenethyl)-6,9-dimethyl-6*H*-thieno[3,2-*f*]-*s*-triazolo[4,3-*a*][1,4]diazepine; Y-24180; Pafnol. $C_{28}H_{29}ClN_4S$; mol wt 489.09. C 68.76%, H 5.98%, Cl 7.25%, N 11.46%, S 6.56%. Platelet activating factor (PAF) antagonist. Prepn: T. Tahara *et al.,* **EP 268242;** *eidem,* **US 4820703** (1988, 1989 both to Yoshitomi). Pharmacology: M. Terasawa *et al., Prostaglandins* **40,** 553 (1990). Receptor binding study: S. Takehara *et al., ibid.* 571. Clinical evaluation in asthma: S. Hozawa *et al., Am. J. Respir. Crit. Care Med.* **152,** 1198 (1995).



Colorless crystals from isopropyl ether, mp 129.5-131.5°. Sol in propylene glycol.

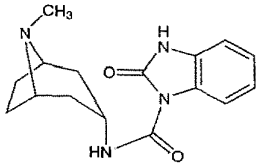
THERAP CAT: Antiasthmatic.

5264. Itaconic Acid. [97-65-4] Methylenesuccinic acid; propylenedicarboxylic acid. $C_5H_6O_4$; mol wt 130.10. C 46.16%, H 4.65%, O 49.19%. Obtained by dry distillation of citric acid and subsequent treatment of the anhydride with water. Produced on a large scale by submerged aerobic fermentation using *Aspergillus terreus* and low cost carbohydrates from beet or cane: Kane *et al.,* **US 2385283** (1945 to Pfizer). Synthesis from propargyl chloride, carbon monoxide, nickel carbonyl and water: Chiusoli, **US 3025320** (1962 to Montecatini).



Hygroscopic crystals; characteristic odor. d 1.63. mp 162-164° with decompn. Also reported as mp 172° [Kinoshita, *Acta Phytochem. (Japan)* **5,** 273 (1931)]. One gram dissolves in 12 ml water, 5 ml alcohol; very slightly sol in benzene, chloroform, ether, carbon disulfide, petr ether. *Keep well closed.*

5265. Itasetron. [123258-84-4] 2,3-Dihydro-*N*-[(3-*endo*)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-2-oxo-1*H*-benzimidazole-1-carboxamide; 2-oxo-*N*-1α*H*,5α*H*-tropan-3α-yl-1-benzimidazoline-1-carboxamide. $C_{16}H_{20}N_4O_2$; mol wt 300.35. C 63.98%, H 6.71%, N 18.65%, O 10.65%. Serotonin ($5\text{-}HT_3$) receptor antagonist. Prepn: M. Turconi *et al.,* **EP 309423** (1989 to Istituto De Angeli); *eidem,* **US 5223511** (1993 to Boehringer, Ing.); M. Turconi *et al., J. Med. Chem.* **33,** 2101 (1990). Pharmacology: *idem et al., Eur. J. Pharmacol.* **203,** 203 (1991). Mode of action: M. B. Passani *et al., Brit. J. Pharmacol.* **112,** 695 (1994). Clinical efficacy and tolerability: H. Goldschmidt *et al., Anti-Cancer Drugs* **8,** 436 (1997). Review of therapeutic potential: M. B. Passani, R. Corradetti, *CNS Drug Reviews* **2,** 195-213 (1996).

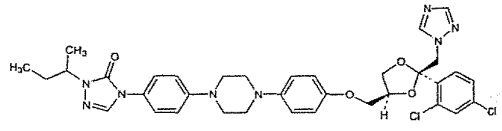


Crystals from acetonitrile, mp 205-207°. LD_{50} in mice, rats (mg/kg): 56, 62 i.v. (Passani).

Hydrochloride. [127618-28-4] DAU 6215. $C_{16}H_{20}N_4O_2$.HCl; mol wt 336.82. Colorless crystals, mp 270°.

THERAP CAT: Antiemetic.

5266. Itraconazole. [84625-61-6] 4-[4-[4-[4-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one; (±)-1-*sec*-butyl-4-[*p*-[4-[*p*-[[(2*R**,4*S**)-2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ²-1,2,4-triazolin-5-one; oriconazole; R-51211; Itrizole; Sporanox; Triasporin. $C_{35}H_{38}Cl_2N_8O_4$; mol wt 705.65. C 59.57%, H 5.43%, Cl 10.05%, N 15.88%, O 9.07%. Orally active antimycotic structurally related to ketoconazole, *q.v.* Prepn: J. Heeres, L. J. J. Backx, **EP 6711;** *eidem,* **US 4267179** (1980, 1981 both to Janssen); J. Heeres *et al., J. Med. Chem.* **27,** 894 (1984). *In vitro* activity: A. Espinel-Ingroff *et al., Antimicrob. Ag. Chemother.* **26,** 5 (1984). HPLC determn in biological samples: R. Woestenborghs *et al., J. Chromatog.* **413,** 332 (1987). Symposium on pharmacology and clinical efficacy: *Rev. Infect. Dis.* **9,** Suppl 1, S1-S152 (1987). Toxicity data: H. Van Cauteren *et al., ibid.* S43. Review of clinical pharmacokinetics: J. Heykants *et al., Mycoses* **32,** Suppl 1, 67-87 (1989); of clinical efficacy in dermatophytosis: P. De Doncker, G. Cauwenbergh, *Brit. J. Clin. Pract.* **Suppl. 71,** 118-122 (1990). *Review:* A. M. Sugar, *Curr. Clin. Topics Inf. Dis.* **13,** 74-98 (1993).



Crystals from toluene, mp 166.2°. pKa 3.7. Lipophilic; partition coefficient (*n*-octanol/aq buffer of pH 8.1): 5.66. Practically insol in water and dil acidic solns. LD_{50} (14 day) in mice, rats, dogs (mg/kg): >320, >320, >200 orally (Van Cauteren).

THERAP CAT: Antifungal.

5267. Itramin Tosylate. [13445-63-1] 2-Aminoethanol nitrate mono(4-methylbenzenesulfonate); 2-aminoethanol nitrate mono-*p*-toluenesulfonate; 2-nitratoethylaminotoluene-*p*-sulfonate; Cardisan; Tostram; Nilatil. $C_9H_{14}N_2O_6S$; mol wt 278.28. C 38.85%, H 5.07%, N 10.07%, O 34.50%, S 11.52%. Prepn: **SE 168308** (1959 to Aktiebolaget Pharmacia), *C.A.* **54,** 24405d (1960).

THE MERCK INDEX

AN ENCYCLOPEDIA OF
CHEMICALS, DRUGS, AND BIOLOGICALS

THIRTEENTH EDITION

Editorial Staff

Maryadele J. O'Neil, *Senior Editor*
Ann Smith, *Senior Associate Editor*
Patricia E. Heckelman, *Associate Editor*

John R. Obenchain Jr., *Editorial Assistant*
Jo Ann R. Gallipeau, *Technical Assistant*
Mary Ann D'Arecca, *Administrative Associate*

Susan Budavari, *Editor Emeritus*

Published by
Merck Research Laboratories
Division of

MERCK & CO., INC.
Whitehouse Station, NJ

2001

MERCK & CO., INC.
Whitehouse Station, NJ
USA

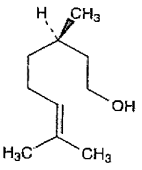
1st Edition—1889
2nd Edition—1896
3rd Edition—1907
4th Edition—1930
5th Edition—1940
6th Edition—1952
7th Edition—1960
8th Edition—1968
9th Edition—1976
10th Edition—1983
11th Edition—1989
12th Edition—1996

Library of Congress Catalog
Card Number 89-60001
ISBN Number 0911910-13-1

Printed in the USA

α-citronellal. [141-26-4] 3,7-Dimethyl-7-octenal; rhodinal. Liquid. bp_{14} 51°. n_D^{20} 1.4410. $[\alpha]_D^{20}$ +9.75°.
USE: In soap perfumes; insect repellent.

2354. β-Citronellol. [106-22-9] 3,7-Dimethyl-6-octen-1-ol; 2,6-dimethyl-2-octen-8-ol; citronellol; cephrol. $C_{10}H_{20}O$; mol wt 156.26. C 76.86%, H 12.90%, O 10.24%. *l*-Form is a constituent of rose and geranium oils. *d*-Form occurs in Ceylon and Java citronella oils. History: J. L. Simonsen, L. N. Owen, *The Terpenes* **vol. I** (University Press, Cambridge, 2nd ed, 1947). Prepn of (±)-form: Adams, Garvey, *J. Am. Chem. Soc.* **48,** 477 (1926); Ofner *et al., Helv. Chim. Acta* **42,** 2577 (1959). Prepn of (+)-form: Rienäcker, Ohloff, *Angew. Chem.* **73,** 240 (1961); Naves, Tullen, *Helv. Chim. Acta* **44,** 1867 (1961); Eschinazi, *J. Org. Chem.* **26,** 3072 (1961); Rienäcker, *Chimia* **27,** 97 (1973); C. G. Overberger, J. L. Weise, *J. Am. Chem. Soc.* **90,** 3525 (1968); T. Sato *et al., Tetrahedron Letters* **1980,** 3377. Prepn of (−)-form: Ohloff, *loc. cit.;* Rienäcker, *loc. cit.;* Shono *et al., Tetrahedron Letters* **1974,** 1295; K. Mori, T. Sugai, *Synthesis* **1982,** 752. Synthesis of (+) or (−)-form from isoprene: Hidai *et al., Chem. Commun.* **1975,** 170. Stereospecific prepn via microbiological *(Saccharomyces cerevisiae)* reduction: P. Gramatica *et al., Experientia* **38,** 775 (1982). Manuf: Woroch *et al.;* Bain; Webb, **US 2990422**; **US 3005845**; **US 3028431** (1961, 1961, 1962, all to Glidden); Eschinasi, **US 3052730** (1962 to Givaudan). Abs config of the (+)-form: Freudenberg, Hohmann, *Ann.* **584,** 54 (1953); Freudenberg, Lwowski, *ibid.* **587,** 213 (1954). NMR, HPLC determn of *R/S* enantiomer ratios: D. Valentine *et al., J. Org. Chem.* **41,** 62 (1976). *See also* Rhodinol.



R-(+)-β-Citronellol

(+)-Form. Oily liquid, bp 224.5°, bp_{10} 108.4°, d_4^{20} 0.8550. n_D^{20} 1.4559. $[\alpha]_D^{20}$ +5.22°. Very slightly sol in water, miscible with with alcohol, ether.

(−)-Form. β-Rhodinol; Levocitrol. bp_{10} 108-109°. d_4^{18} 1.4576. $[\alpha]_D^{20}$ −4.76°.

(±)-Form. Dihydrogeraniol. $d_4^{23.5}$ 0.851. $n_D^{23.5}$ 1.454.
USE: In perfumery.

2355. Citrulline. [372-75-8] N^5-(Aminocarbonyl)-L-ornithine; δ-ureidonorvaline; α-amino-δ-ureidovaleric acid; N^5-carbamylornithine. $C_6H_{13}N_3O_3$; mol wt 175.19. C 41.13%, H 7.48%, N 23.99%, O 27.40%. $H_2NCONH(CH_2)_3CH(NH_2)$-COOH. An amino acid, first isolated from the juice of watermelon, *Citrullus vulgaris* Schrad., *Cucurbitaceae:* Wada, *Biochem. Z.* **224,** 420 (1930); isoln from casein: Wada, *ibid.* **257,** 1 (1933). Synthesis from ornithine through copper complexes: Kurtz, *J. Biol. Chem.* **122,** 477 (1938); by alkaline hydrolysis of arginine: Fox, *ibid.* **123,** 687 (1938); from cyclopentanone oxime: Fox *et al., J. Org. Chem.* **6,** 410 (1941). Crystallization: Matsuda *et al.,* **JP 71 174** (1971 to Ajinomoto), *C.A.* **74,** 126056u (1971). Crystal and molecular structure: Naganathan, Venkatesan, *Acta Crystallogr.* **27B,** 1079 (1971); Ashida *et al., ibid.* **28B,** 1367 (1972). Use in asthenia and hepatic insufficiency: **FR 2198739** (1974 to Hublot & Vallet), *C.A.* **82,** 144952c (1975). Clinical trial in treatment of lysinuric protein intolerance: J. Rajantie *et al., J. Pediatr.* **97,** 927 (1980); T. O. Carpenter *et al., N. Engl. J. Med.* **312,** 290 (1985).
Prisms from methanol + water, mp 222°. $[\alpha]_D^{20}$ +3.7° (c = 2). pK_1 2.43; pK_2 9.41. Sol in water. Insol in methanol, ethanol.

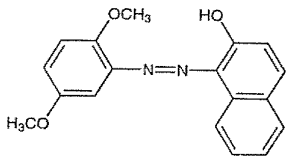
Hydrochloride. [34312-10-2] $C_6H_{13}N_3O_3$ HCl. Crystals, dec 185°. $[\alpha]_D^{22}$ +17.9° (c = 2).

Malate (salt). [54940-97-5] Stimol. $C_6H_{13}N_3O_3.C_4H_6O_5$; mol wt 309.27.
THERAP CAT: Treatment of asthenia.

2356. Citrullol. [1390-93-8] $C_{22}H_{38}O_4$; mol wt 366.53. C 72.09%, H 10.45%, O 17.46%. From fruit pulp of *Citrullus colocynthis* Schrad., *Cucurbitaceae:* Power, Moore, *J. Chem. Soc.* **97,** 99 (1910); Power, Salway, *ibid.* **103,** 399, 1022 (1913); Khadem, Rahman, *Tetrahedron Letters* **1962,** 1137.
Crystals, mp 282-283°. uv max: 242, 272, 282 nm (log ε 2.85, 2.68, 2.68). Sol in pyridine; practically insol in usual organic solvents.

Diacetate. $C_{26}H_{42}O_6$. Crystals, mp 162°.

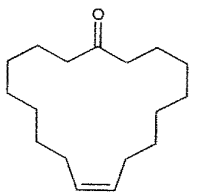
2357. Citrus Red 2. [6358-53-8] 1-[(2,5-Dimethoxyphenyl)azo]-2-naphthalenol; C.I. Solvent Red 80; C.I. 12156. $C_{18}H_{16}N_2O_3$; mol wt 308.33. C 70.12%, H 5.23%, N 9.09%, O 15.57%. Prepn: H. W. Elley, H. W. Daudt, **US 2224904** (1940 to Du Pont). Metabolism: J. L. Radomski, *J. Pharmacol. Exp. Ther.* **134,** 100 (1961); **136,** 378 (1962). Toxicology: M. Sharratt *et al., Food Cosmet. Toxicol.* **4,** 493 (1966). Review of carcinogenicity studies: *IARC Monographs* **8,** 101-106. *See also Colour Index* **vol. 4** (3rd ed., 1971) p 4033.



Crystals, mp 155-157°. Slightly sol in water; partially sol in ethanol and vegetable oils.
USE: To color orange skins.

2358. Civet. Zibeth. Unctuous secretion from receptacles between the anus and genitalia of both male and female civet cat. *Constit.* Civetone and similar compds.
Semi-solid, yellowish to brown unctuous substance; unpleasant, subacrid, bitter taste; fusible and burns without leaving much residue. Insol in water; partly sol in hot alcohol or in ether.
USE: As a fixative in perfumery.

2359. Civetone. [542-46-1] (*Z*)-9-Cycloheptadecen-1-one. $C_{17}H_{30}O$; mol wt 250.42. C 81.54%, H 12.07%, O 6.39%. 17-Membered macrocyclic musk, constituent of civet: Ruzicka, *Helv. Chim. Acta* **9,** 230 (1926); Ruzicka *et al., ibid.* **10,** 695 (1927). Occurs in nature as *cis*-form. Synthesis of *cis*-civetone: Stoll *et al., ibid.* **31,** 543 (1948); J. Tsuji, T. Mondai, *Tetrahedron Letters* **1977,** 3285; E. Seoane *et al., Chem. & Ind. (London)* **1978,** 165. Synthesis of *trans*-form: H. Hunsdiecker, *Ber.* **77,** 185 (1944); H. H. Mathur, S. C. Bhattacharyya, *J. Chem. Soc.* **1968,** 114. Crystal and molecular structure of *cis*-civetone: G. Bernardinelli, R. Gerdil, *Helv. Chim. Acta* **65,** 558 (1982).

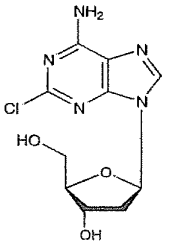


(cis)-form

Crystals, mp 31-32°. Musky odor becoming pleasant in extreme dilns. d_4^{33} 0.917. bp_{742} 342°; bp_2 59°. $n_D^{33.4}$ 1.4830.
USE: In perfumery.

2360. Cladribine. [4291-63-8] 2-Chloro-2′-deoxyadenosine; 2-chloro-6-amino-9-(2-deoxy-β-D-*erythro*-pentofuran-

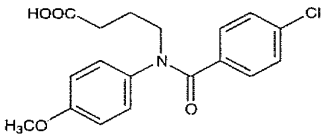
osyl)purine; 2-chlorodeoxyadenosine; 2-CdA; CldAdo; NSC-105014-F; Leustatin. $C_{10}H_{12}ClN_5O_3$; mol wt 285.69. C 42.04%, H 4.23%, Cl 12.41%, N 24.51%, O 16.80%. Substituted purine nucleoside with antileukemic activity. Prepn as intermediate in synthesis of 2-deoxynucleosides: H. Venner, *Ber.* **93,** 140 (1960); M. Ikehara, H. Tada, *J. Am. Chem. Soc.* **85,** 2344 (1963); *eidem, ibid.* **87,** 606 (1965). Synthesis and biological activity: L. F. Christensen *et al., J. Med. Chem.* **15,** 735 (1972). Stereospecific synthesis: Z. Kazimierczuk *et al., J. Am. Chem. Soc.* **106,** 6379 (1984); R. K. Robins, G. R. Revankar, **EP 173059**; *eidem,* **US 4760137** (1986, 1988 both to Brigham Young Univ.). Specific toxicity to lymphocytes: D. A. Carson *et al., Proc. Nat. Acad. Sci. USA* **77,** 6865 (1980); *eidem, Blood* **62,** 737 (1983). Mechanism of action: S. Seto *et al., J. Clin. Invest.* **75,** 377 (1985). Clinical evaluation in chronic lymphocytic leukemia: L. D. Piro *et al., Blood* **72,** 1069 (1988); in hairy cell leukemia: *eidem, N. Engl. J. Med.* **322,** 1117 (1990).



Crystals from water, softens at 210-215°, solidifies and turns brown (Christensen). Also reported as crystals from ethanol, mp 220° (softens), resolidifies, turns brown and does not melt below 300° (Kazimierczuk). $[\alpha]_D^{25}$ −18.8° (c = 1 in DMF). uv max in 0.1*N* NaOH: 265 nm; in 0.1*N* HCl: 265 nm.

THERAP CAT: Antineoplastic.

2361. Clanobutin. [30544-61-7] 4-[(4-Chlorobenzoyl)-(4-methoxyphenyl)amino]butanoic acid; 4-[*p*-chloro-*N*-(*p*-methoxyphenyl)benzamido]butyric acid; *N*-(*p*-chlorobenzoyl)-γ-(*p*-anisidino)butyric acid; Bykahepar. $C_{18}H_{18}ClNO_4$; mol wt 347.80. C 62.16%, H 5.22%, Cl 10.19%, N 4.03%, O 18.40%. Prepn: K. Klemm *et al.,* **DE 1917036** corresp to **US 3780095** (1971, 1973 both to Byk-Gulden). Series of articles on synthesis, physical and pharmacological properties: *Arzneimittel-Forsch.* **29,** 1-15 (1979). *In vitro* biochemical study: H. Wolf *et al., Biochem. Pharmacol.* **29,** 1649 (1980). Effect on bile excretion in rats, dogs: P. Berchtold *et al., Arzneimittel-Forsch.* **30,** 1878 (1980).

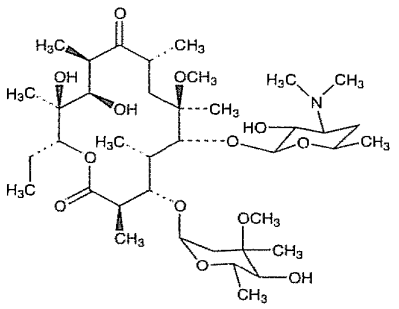


Cryst from ethyl acetate, mp 115-116°. pKa 5.04. Soly in water at 37°: 4.02×10^{-2} mol/l at pH 7. LD_{50} in rats (mg/kg): >2000 orally; 570 i.v. (Klemm).

THERAP CAT: Choleretic.

THERAP CAT (VET): Choleretic; in treatment of piroplasmosis and anaplasmosis.

2362. Clarithromycin. [81103-11-9] 6-*O*-Methylerythromycin; A-56268; TE-031; Biaxin; Clathromycin; Cyllind; Klacid; Klaricid; Macladin; Naxy; Veclam; Zeclar. $C_{38}H_{69}NO_{13}$; mol wt 747.95. C 61.02%, H 9.30%, N 1.87%, O 27.81%. Semisynthetic macrolide antibiotic; derivative of erythromycin, *q.v.* Prepn: Y. Watanabe *et al.,* **EP 41355**; *eidem,* **US 4331803** (1981, 1982 both to Taisho); and *in vitro* antibacterial activity: S. Morimoto *et al., J. Antibiot.* **37,** 187 (1984). *In vitro* and *in vivo* antibacterial activity: P. B. Fernandes *et al., Antimicrob. Ag. Chemother.* **30,** 865 (1986). Comparative antibacterial spectrum *in vitro:* C. Benson *et al., Eur. J. Clin. Microbiol.* **6,** 173 (1987); H. M. Wexler, S. M. Finegold, *ibid.* 492. HPLC determn in biological fluids: D. Croteau *et al., J. Chromatog.* **419,** 205 (1987). Acute toxicity study: S. Abe *et al., Chemotherapy (Tokyo)* **36,** Suppl. 3, 274 (1988). Symposium on pharmacology and comparative clinical studies: *J. Antimicrob. Chemother.* **27,** Suppl. A, 1-124 (1991). Comprehensive description: I. I. Salem, *Anal. Profiles Drug Subs. Excip.,* **24,** 45-85, (1996).



Colorless needles from chloroform + diisopropyl ether (1:2), mp 217-220° (dec). Also reported as crystals from ethanol, mp 222-225° (Morimoto). uv max ($CHCl_3$): 288 nm (ε 27.9). uv max ($CHCl_3$): 240, 288 nm; (methanol): 211, 288 nm. $[\alpha]_D^{24}$ −90.4° (c = 1 in $CHCl_3$). Stable at acidic pH. LD_{50} in male, female mice, male, female rats (mg/kg): 2740, 2700, 3470, 2700 orally, 1030, 850, 669, 753 i.p., >5000 all s.c. (Abe).

THERAP CAT: Antibacterial.

2363. Clathrates. Compounds that are capable of trapping other substances within their own crystal lattices. The cavities of the host molecules are classified as cages, tunnels, or layered types, depending on the way they include guest molecules. The geometry of the cavities limits the guest molecules by size and shape, rather than by chemical similarity with the host molecules. Among common clathrates are ***molecular sieves***, ***cyclotriphosphazenes***, and ***Dianin's compound***, as well as hydroquinone, cyclodextrins, *o*-thymotide, and deoxycholic acid, *q.q.v.* ***Cavitands*** are organic hosts with enforced (rigid) cavities: D. J. Cram, *Science* **219,** 1177 (1983); R. C. Helgeson *et al., Chem. Commun.* **1983,** 101. Comprehensive book: *Clathrate Compounds,* V. M. Bhatnagar, Ed. (Chemical Pub. Co., New York, 1970) 244 pp. *Reviews:* D. D. MacNicol *et al., Chem. Soc. Rev.* **7,** 65-87 (1978); E. C. Makin, "Clathration" in *Kirk-Othmer Encyclopedia of Chemical Technology* Vol. 6 (Wiley-Interscience, New York, 3rd ed., 1979) pp 178-189.

USE: As complexing agent; stabilizing agent. In analytical separations.

2364. Clavulanic Acid. [58001-44-8] [2*R*-(2α,3*Z*,5α)]-3-(2-Hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo-[3.2.0]heptane-2-carboxylic acid; MM 14151. $C_8H_9NO_5$; mol wt 199.16. C 48.25%, H 4.55%, N 7.03%, O 40.17%. β-Lactamase inhibitor. Antibiotic produced by *Streptomyces clavuligerus;* first reported naturally occurring fused β-lactam containing oxygen. Isoln: M. Cole *et al.,* **DE 2517316** (1975 to Beecham), *C.A.* **84,** 72635t (1976); A. G. Brown *et al., J. Antibiot.* **29,** 668 (1976). Structure, x-ray crystallography: T. T. Howarth *et al., Chem. Commun.* **1976,** 266. Total synthesis of (±)-form: P. H. Bentley *et al., ibid.* **1977,** 748, 905; *eidem, Tetrahedron Letters* **1979,** 1889. β-Lactamase inhibition and antibacterial spectrum: C. Reading, M. Cole, *Antimicrob. Ag. Chemother.* **11,** 852 (1977). Mechanism of action: B. G. Spratt *et al., ibid.* **12,** 406 (1977). Antibacterial activity, pharmacology and clinical efficacy of combination with amoxicillin: A. P. Ball *et al., Lancet* **1,** 620 (1980); R. N. Brogden *et al., Drugs* **22,** 337-362 (1981). *In vitro* and *in vivo* synergism with ticarcillin: R. Sutherland *et al., Am. J. Med.* **79,** Suppl. 5B, 13 (1985).

Hydroxypropyl-beta-cyclodextrin
CAS No:94035-02-6

Name: Hydroxypropyl-beta-cyclodextrin

Synonyms: beta-Hydroxypropylcyclodextrin
beta-Cyclodextrin, 2-hydroxypropyl ether
HPB
2-Hydroxypropyl-beta-cyclodextrin
128446-35-5

CAS Number: 94035-02-6

Molecular Formula: $C_{42}(H)_{70-n}O_{35}(C_3H_7)_n$

Melting Point: 278 °C

Safety Description: S24/25 Details

Inquire now List of Suppliers for **Hydroxypropyl-beta-cyclodextrin** Country

Onbio Inc.
Introduction:HYDROXYPROPYL-BETA-CYCLODEXTRIN
United St

Yiming Fine Chemicals Co., Ltd.
Introduction:mp : 267 °C (dec.)
China (Mair

storage temp. : 2-8°C

solubility : H2O: 45 % (w/v)

form : solution (clear, colorless)

[Hangzhou]86-571-85889139 85459303 85459719 ext.8015

Linscott's Directory of Immunological & Biological Reagents

Page 36 of 2,608 **Records 1,751 - 1,800 of 130,353**

Name	Description	Size	Catalog #	Supplier	
CKBB	Recombinant Human Creatine Kinase BB Isoenzyme	10µg, 50µg, 1mg	CKI- 268	PROSPEC-TANY TECHNOGENE LTD.	More In
Ckdk6	The RP-39008 Ckdk6 protein is a partial length (aa 1-327) bacterially expressed recombinant protein.RP-39008 is suitable for use as a control in ELISA and Western blot applications.The RP-39008 protein is GST-tagged.	10 ug	RP-39008	ABR - AFFINITY BIOREAGENTS INC.	More In
CKMM	Human Creatine Kinase MM	200µg, 1mg, 10mg	CKI- 273	PROSPEC-TANY TECHNOGENE LTD.	More In
CKS-17	Sequence: Leu-Gln-Asn-Arg-Arg-Gly-L eu-Asp-Leu-Leu-Phe-Leu-Ly s-Glu-Gly-Gly-LeuStorage and Stability: Lyophilized powder may be stored at 4?C for short-term only. Reconstitute to nominal volume by adding sterile 40-50% glycerol and store at -20?C. R...	1mg	C5818-05	UNITED STATES BIOLOGICAL	More In
CKS-17 (7-12)	Sequence: Leu-Asp-Leu-Leu-Phe-LeuSt orage and Stability: Lyophilized powder may be stored at 4?C for short-term only. Reconstitute to nominal volume by adding sterile 40-50% glycerol and store at -20?C. Reconstituted product is stable for 12 months...	25mg	C5818-05A	UNITED STATES BIOLOGICAL	More In

CKS-17	This Peptide CKS-17 is considered as the major immunosuppressive site of retroviral TM protein. It can suppress T effector cell function in vitro. It has been shown that CKS-17 causes an imbalance of human types 1 and 2 cytokines and inhibition of...	0.5 mg	06-271-83162	GENWAY BIOTECH INC.	**More In**
CKS-17	This Peptide CKS-17 is considered as the major immunosuppressive site of retroviral TM protein. It can suppress T effector cell function in vitro. It has been shown that CKS-17 causes an imbalance of human types 1 and 2 cytokines and inhibition of...	1 mg	06-271-83162	GENWAY BIOTECH INC.	**More In**
CARCINOEMBRYONIC ANTIGEN (CL)	testing/assay service	n/a	n/a	RDL REFERENCE LABORATORY INC.	**More In**
CASPASE-3/7 (CL)	n/a	n/a	n/a	PROMEGA CORPORATION	**More In**
CASPASE-8 (CL)	n/a	n/a	n/a	PROMEGA CORPORATION	**More In**
CASPASE-9 (CL)	n/a	n/a	n/a	PROMEGA CORPORATION	**More In**
CASPASE (CL)	n/a	n/a	n/a	PROMEGA CORPORATION	**More In**
CL 218872	Benzodiazepine agonist displaying selectivity for α1 subunit-containing GABAA receptors (Ki values are 130, 1820, 1530, > 10000, 490 and > 10000 nM for α1, α2, α3, α4, α5 and α6-subunit containing re...	10mg, 50mg	1709	TOCRIS BIOSCIENCE	**More In**
CL-387,785	Irreversibly inhibits EGF-receptor (EGFR) kinase activity in vivo (IC50 = 250-490 pM) as well as EGF-stimulated autophosphorylation of tyrosine residues in the EGFR in vivo (IC50 = 5 nM). Blocks EGF-mediated growth in A431 cells. Inhibits prolifer...	n/a	233100	CALBIOCHEM/EMD BIOSCIENCES	**More In**
	A selective inhibitor of MMP-13 (IC50 = 10 μM).				

CL-82198	Binds to the S1' pocket of MMP-13 with its morpholine ring adjacent to the catalytic zinc atom. Does not inhibit MMP-1, MMP-9, and TACE.	n/a	233105	CALBIOCHEM/EMD BIOSCIENCES	**More In**
Calphostin C, Cladosporium cladosporioides	A cell permeable, highly specific inhibitor of protein kinase C (IC50 = 50 nM) that interacts with the protein's regulatory domain by competing at the binding site of diacylglycerol and phorbol esters. Does not compete with Ca2+ or phospholi...	n/a	208725	CALBIOCHEM/EMD BIOSCIENCES	**More In**
Cladribine	It is a substituted purine nucleoside with antileukemic activity.Melting Point: 220-235?C dec.Solubility: Methanol, Water	50mg	C5819-75	UNITED STATES BIOLOGICAL	**More In**
Clarithromycin	A semi-synthetic macrolide antibiotic. A derivative of erythromycin.Melting Point: 217-220?C dec.Solubility: Chloroform, Ethanol	50mg	C5829	UNITED STATES BIOLOGICAL	**More In**
Clavulanic Acid	A B-Lactamase inhibitor.	10mg	C5836	UNITED STATES BIOLOGICAL	**More In**
CLIC3	The RP-39009 CLIC3 protein is a full length bacterially expressed recombinant protein.RP-39009 is suitable for use as a control in ELISA and Western blot applications.The RP-39009 amino acid sequence corresponds to the NCBI accession number NP_004...	10 ug	RP-39009	ABR - AFFINITY BIOREAGENTS INC.	**More In**
Clidinium Bromide	An anticholinergic. Used as an antispasmodic.Melting Point: 240-241?C	5g	C5840-75	UNITED STATES BIOLOGICAL	**More In**
	A metal ion chelator that crosses the blood brain barrier and acts as a neurotoxic antibiotic. Reported to dissolve				

Clioquinol	senile plaques and reduce amyloid's ability to clump together, apparently by trapping the Cu2+ and Zn2+ that stud these depos...	n/a	233165	CALBIOCHEM/EMD BIOSCIENCES	**More In**
CLK3, active	n/a	10 ug	14-724	MILLIPORE	**More In**
CLK2, active	n/a	10 ug	14-774	MILLIPORE	**More In**
Clofarabine	ISecond generation purine nucleoside analog; antimetabolite that inhibits DNA synthesis and resists deamination by adenosine deaminase. Antineoplastic.Melting Point: 225-227?C	10mg	C5843-55	UNITED STATES BIOLOGICAL	**More In**
Clofarabine	Deoxycytidine kinase (dCK) substrate. Phosphorylated to form clofarabine triphosphate, which competes with dATP for DNA polymerase- α and - ε and potently inhibits ribonucleotide reductase (IC50 = 65 nM). Induces apoptosis by directl...	10mg, 50mg	2600	TOCRIS BIOSCIENCE	**More In**
CLOFIBRATE	n/a	n/a	n/a	CAYMAN CHEMICAL CO.	**More In**
Clofibrate	PPAR agonist (EC50 values are 50, 500 and > 100 μM at PPAR α, PPAR γ and PPAR δ respectively). Antihyperlipoproteinemic.	1g	0824	TOCRIS BIOSCIENCE	**More In**
Clofibric acid	PPAR agonist. Antihyperlipoproteinemic.	1g	0825	TOCRIS BIOSCIENCE	**More In**
Clofibrate	An anti-hyperlipoproteinemic agent believed to act by inhibiting cholesterol biosynthesis. Activates PPARα and induces cytochrome P450 4A1 and 4A3. Imparts protection against acetaminophen toxicity and increases hepatic glutathione levels.	n/a	231405	CALBIOCHEM/EMD BIOSCIENCES	**More In**
Clofulbicyne	n/a	1 mg.	TXL9001-1	ACCURATE CHEMICAL & SCIENTIFIC CO.	**More In**

Clofulbicyne	n/a	5x1 mg.	TXL9001-5	ACCURATE CHEMICAL & SCIENTIFIC CO.	**More In**
Clomifene citrate	International Chemical Reference Substances are established upon the advice of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. They are supplied primarily for use in physical and chemical tests and assays described in t...	100 mg	9930259	W.H.O. COLLABORATING CENTRE	**More In**
Clomiphene, Citrate	An unducer of ovulation. A gonad-stimulating principle.Melting Point: 116.5-118?CSolubility: Methanol	10g	C5843-65	UNITED STATES BIOLOGICAL	**More In**
Cloning	>1500 bp into 3 different expression vectors	n/a	PE05-0003	HYPEROMICS FARMA INC.	**More In**
Cloning	<1500 bp into 3 different expression vectors	n/a	PE05-0002	HYPEROMICS FARMA INC.	**More In**
Clopidogrel Carboxylic Acid	A metabolite of the drug Clopidogrel.Solubility: Methanol, Water	5mg	C5849-01	UNITED STATES BIOLOGICAL	**More In**
CLOSTRIPAIN Clostridium	n/a	n/a	n/a	PROMEGA CORPORATION	**More In**
Clotrimazole	An antifungal agent that acts as a potent and specific inhibitor of the Ca2+-activated K+ channel (Gardos channel; IC50 = 650 nM). Prevents K+ loss and dehydration of sickled erythrocytes.	n/a	233230	CALBIOCHEM/EMD BIOSCIENCES	**More In**
Clozapine	An antipsychotic.Melting Point: 183-184? CSolubility: Acetone, Ether	250mg	C5866	UNITED STATES BIOLOGICAL	**More In**
Clozapine	Atypical antipsychotic drug, with a much lower tendency to cause extrapyramidal side effects than conventional neuroleptics. Displays a broad range of pharmacological actions; the antipsychotic effects are thought to be mediated principally by 5-H...	50mg, 500mg	0444	TOCRIS BIOSCIENCE	**More In**

CLTB	The RP-39010 CLTB protein is a full length bacterially expressed recombinant protein.RP-39010 is suitable for use as a control in ELISA and Western blot applications.The RP-39010 amino acid sequence corresponds to the NCBI accession number NP_0018...	10 ug	RP-39010	ABR - AFFINITY BIOREAGENTS INC.	**More In**
Aldosterone-3 CMO (BSA)	The major mineralcorticoid, which is secreted almost independently of ACTH from the pitutitary, is aldosterone. Aldosterone secretion is controlled mostly by the levels of potassium and sodium in serum and a blood pressure control system called th...	5mg	A1350-04	UNITED STATES BIOLOGICAL	**More In**
Androstenedione-3 (CMO)	Androstenedione was discovered in 1935. It is naturally produced in men and women. It is a direct precursor to the hormone testosterone. The liver converts androstenedione to testosterone.Precursor:4-Androsten-3,17-dione-3Sto rage and Stability:Lyo...	10mg	A2292-02	UNITED STATES BIOLOGICAL	**More In**
CMPD-1	Non-ATP-competitive, selective inhibitor of p38 α-mediated MK2a (mitogen-activated protein kinase-activated protein kinase 2a) phosphorylation (apparent Ki = 330 nM). Does not inhibit p38 α-mediated phosphorylation of the two other kno...	10mg, 50mg	2186	TOCRIS BIOSCIENCE	**More In**
CMV	Glycine Extract	mL	0810003GE	ZEPTOMETRIX CORP.	**More In**
CMV	Cytomegalovirus (AD169) Infected Cell Extract. Used for IgG assays - Control is NHDF AV043	n/a	CV001	EASTCOAST BIO INC.	**More In**
	Cytomegalovirus				

CMV	Gradient Purified. Used for IgM assays.	n/a	CV046	EASTCOAST BIO INC.	More In
CMV	Cytomegalovirus Ag slides for FA. Made to Order	n/a	CG015	EASTCOAST BIO INC.	More In
CMV	Part Pure	n/a	J43010	BIOSPACIFIC INC.	More In

Page 36 of 2,608 **Records 1,751 - 1,800 of 130,353**

[1] « 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 |

Search Non-Antibody Products

Home | Antibody Search | Other Products/Services Search | List Your Products | About Us | Links | Contact Us

Linscott's Directory of Immunological & Biological Reagents

Page 36 of 2,608 **Records 1,751 - 1,800 of 130,353**

Name	Description	Size	Catalog #	Supplier	
CKBB	Recombinant Human Creatine Kinase BB Isoenzyme	10µg, 50µg, 1mg	CKI- 268	PROSPEC-TANY TECHNOGENE LTD.	More In
Ckdk6	The RP-39008 Ckdk6 protein is a partial length (aa 1-327) bacterially expressed recombinant protein.RP-39008 is suitable for use as a control in ELISA and Western blot applications.The RP-39008 protein is GST-tagged.	10 ug	RP-39008	ABR - AFFINITY BIOREAGENTS INC.	More In
CKMM	Human Creatine Kinase MM	200µg, 1mg, 10mg	CKI- 273	PROSPEC-TANY TECHNOGENE LTD.	More In
CKS-17	Sequence: Leu-Gln-Asn-Arg-Arg-Gly-L eu-Asp-Leu-Leu-Phe-Leu-Ly s-Glu-Gly-Gly-LeuStorage and Stability: Lyophilized powder may be stored at 4?C for short-term only. Reconstitute to nominal volume by adding sterile 40-50% glycerol and store at -20?C. R...	1mg	C5818-05	UNITED STATES BIOLOGICAL	More In
CKS-17 (7-12)	Sequence: Leu-Asp-Leu-Leu-Phe-LeuSt orage and Stability: Lyophilized powder may be stored at 4?C for short-term only. Reconstitute to nominal volume by adding sterile 40-50% glycerol and store at -20?C. Reconstituted product is stable for 12 months...	25mg	C5818-05A	UNITED STATES BIOLOGICAL	More In

CKS-17	This Peptide CKS-17 is considered as the major immunosuppressive site of retroviral TM protein. It can suppress T effector cell function in vitro. It has been shown that CKS-17 causes an imbalance of human types 1 and 2 cytokines and inhibition of...	0.5 mg	06-271-83162	GENWAY BIOTECH INC.	**More In**
CKS-17	This Peptide CKS-17 is considered as the major immunosuppressive site of retroviral TM protein. It can suppress T effector cell function in vitro. It has been shown that CKS-17 causes an imbalance of human types 1 and 2 cytokines and inhibition of...	1 mg	06-271-83162	GENWAY BIOTECH INC.	**More In**
CARCINOEMBRYONIC ANTIGEN (CL)	testing/assay service	n/a	n/a	RDL REFERENCE LABORATORY INC.	**More In**
CASPASE-3/7 (CL)	n/a	n/a	n/a	PROMEGA CORPORATION	**More In**
CASPASE-8 (CL)	n/a	n/a	n/a	PROMEGA CORPORATION	**More In**
CASPASE-9 (CL)	n/a	n/a	n/a	PROMEGA CORPORATION	**More In**
CASPASE (CL)	n/a	n/a	n/a	PROMEGA CORPORATION	**More In**
CL 218872	Benzodiazepine agonist displaying selectivity for α1 subunit-containing GABAA receptors (Ki values are 130, 1820, 1530, > 10000, 490 and > 10000 nM for α1, α2, α3, α4, α5 and α6-subunit containing re...	10mg, 50mg	1709	TOCRIS BIOSCIENCE	**More In**
CL-387,785	Irreversibly inhibits EGF-receptor (EGFR) kinase activity in vivo (IC50 = 250-490 pM) as well as EGF-stimulated autophosphorylation of tyrosine residues in the EGFR in vivo (IC50 = 5 nM). Blocks EGF-mediated growth in A431 cells. Inhibits prolifer...	n/a	233100	CALBIOCHEM/EMD BIOSCIENCES	**More In**
	A selective inhibitor of MMP-13 (IC50 = 10 μM).				

CL-82198	Binds to the S1' pocket of MMP-13 with its morpholine ring adjacent to the catalytic zinc atom. Does not inhibit MMP-1, MMP-9, and TACE.	n/a	233105	CALBIOCHEM/EMD BIOSCIENCES	**More In**
Calphostin C, Cladosporium cladosporioides	A cell permeable, highly specific inhibitor of protein kinase C (IC50 = 50 nM) that interacts with the protein's regulatory domain by competing at the binding site of diacylglycerol and phorbol esters. Does not compete with Ca2+ or phospholi...	n/a	208725	CALBIOCHEM/EMD BIOSCIENCES	**More In**
Cladribine	It is a substituted purine nucleoside with antileukemic activity.Melting Point: 220-235?C dec.Solubility: Methanol, Water	50mg	C5819-75	UNITED STATES BIOLOGICAL	**More In**
Clarithromycin	A semi-synthetic macrolide antibiotic. A derivative of erythromycin.Melting Point: 217-220?C dec.Solubility: Chloroform, Ethanol	50mg	C5829	UNITED STATES BIOLOGICAL	**More In**
Clavulanic Acid	A B-Lactamase inhibitor.	10mg	C5836	UNITED STATES BIOLOGICAL	**More In**
CLIC3	The RP-39009 CLIC3 protein is a full length bacterially expressed recombinant protein.RP-39009 is suitable for use as a control in ELISA and Western blot applications.The RP-39009 amino acid sequence corresponds to the NCBI accession number NP_004...	10 ug	RP-39009	ABR - AFFINITY BIOREAGENTS INC.	**More In**
Clidinium Bromide	An anticholinergic. Used as an antispasmodic.Melting Point: 240-241?C	5g	C5840-75	UNITED STATES BIOLOGICAL	**More In**
	A metal ion chelator that crosses the blood brain barrier and acts as a neurotoxic antibiotic. Reported to dissolve				

Clioquinol	senile plaques and reduce amyloid's ability to clump together, apparently by trapping the Cu2+ and Zn2+ that stud these depos...	n/a	233165	CALBIOCHEM/EMD BIOSCIENCES	**More In**
CLK3, active	n/a	10 ug	14-724	MILLIPORE	**More In**
CLK2, active	n/a	10 ug	14-774	MILLIPORE	**More In**
Clofarabine	ISecond generation purine nucleoside analog; antimetabolite that inhibits DNA synthesis and resists deamination by adenosine deaminase. Antineoplastic.Melting Point: 225-227?C	10mg	C5843-55	UNITED STATES BIOLOGICAL	**More In**
Clofarabine	Deoxycytidine kinase (dCK) substrate. Phosphorylated to form clofarabine triphosphate, which competes with dATP for DNA polymerase- α and - ε and potently inhibits ribonucleotide reductase (IC50 = 65 nM). Induces apoptosis by directl...	10mg, 50mg	2600	TOCRIS BIOSCIENCE	**More In**
CLOFIBRATE	n/a	n/a	n/a	CAYMAN CHEMICAL CO.	**More In**
Clofibrate	PPAR agonist (EC50 values are 50, 500 and > 100 μM at PPAR α, PPAR γ and PPAR δ respectively). Antihyperlipoproteinemic.	1g	0824	TOCRIS BIOSCIENCE	**More In**
Clofibric acid	PPAR agonist. Antihyperlipoproteinemic.	1g	0825	TOCRIS BIOSCIENCE	**More In**
Clofibrate	An anti-hyperlipoproteinemic agent believed to act by inhibiting cholesterol biosynthesis. Activates PPARα and induces cytochrome P450 4A1 and 4A3. Imparts protection against acetaminophen toxicity and increases hepatic glutathione levels.	n/a	231405	CALBIOCHEM/EMD BIOSCIENCES	**More In**
Clofulbicyne	n/a	1 mg.	TXL9001-1	ACCURATE CHEMICAL & SCIENTIFIC CO.	**More In**

Clofulbicyne	n/a	5x1 mg.	TXL9001-5	ACCURATE CHEMICAL & SCIENTIFIC CO.	**More In**
Clomifene citrate	International Chemical Reference Substances are established upon the advice of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. They are supplied primarily for use in physical and chemical tests and assays described in t...	100 mg	9930259	W.H.O. COLLABORATING CENTRE	**More In**
Clomiphene, Citrate	An unducer of ovulation. A gonad-stimulating principle.Melting Point: 116.5-118?CSolubility: Methanol	10g	C5843-65	UNITED STATES BIOLOGICAL	**More In**
Cloning	>1500 bp into 3 different expression vectors	n/a	PE05-0003	HYPEROMICS FARMA INC.	**More In**
Cloning	<1500 bp into 3 different expression vectors	n/a	PE05-0002	HYPEROMICS FARMA INC.	**More In**
Clopidogrel Carboxylic Acid	A metabolite of the drug Clopidogrel.Solubility: Methanol, Water	5mg	C5849-01	UNITED STATES BIOLOGICAL	**More In**
CLOSTRIPAIN Clostridium	n/a	n/a	n/a	PROMEGA CORPORATION	**More In**
Clotrimazole	An antifungal agent that acts as a potent and specific inhibitor of the Ca2+-activated K+ channel (Gardos channel; IC50 = 650 nM). Prevents K+ loss and dehydration of sickled erythrocytes.	n/a	233230	CALBIOCHEM/EMD BIOSCIENCES	**More In**
Clozapine	An antipsychotic.Melting Point: 183-184? CSolubility: Acetone, Ether	250mg	C5866	UNITED STATES BIOLOGICAL	**More In**
Clozapine	Atypical antipsychotic drug, with a much lower tendency to cause extrapyramidal side effects than conventional neuroleptics. Displays a broad range of pharmacological actions; the antipsychotic effects are thought to be mediated principally by 5-H...	50mg, 500mg	0444	TOCRIS BIOSCIENCE	**More In**

CLTB	The RP-39010 CLTB protein is a full length bacterially expressed recombinant protein.RP-39010 is suitable for use as a control in ELISA and Western blot applications.The RP-39010 amino acid sequence corresponds to the NCBI accession number NP_0018...	10 ug	RP-39010	ABR - AFFINITY BIOREAGENTS INC.	**More In**
Aldosterone-3 CMO (BSA)	The major mineralcorticoid, which is secreted almost independently of ACTH from the pitutitary, is aldosterone. Aldosterone secretion is controlled mostly by the levels of potassium and sodium in serum and a blood pressure control system called th...	5mg	A1350-04	UNITED STATES BIOLOGICAL	**More In**
Androstenedione-3 (CMO)	Androstenedione was discovered in 1935. It is naturally produced in men and women. It is a direct precursor to the hormone testosterone. The liver converts androstenedione to testosterone.Precursor:4-Androsten-3,17-dione-3Sto rage and Stability:Lyo...	10mg	A2292-02	UNITED STATES BIOLOGICAL	**More In**
CMPD-1	Non-ATP-competitive, selective inhibitor of p38 α-mediated MK2a (mitogen-activated protein kinase-activated protein kinase 2a) phosphorylation (apparent Ki = 330 nM). Does not inhibit p38 α-mediated phosphorylation of the two other kno...	10mg, 50mg	2186	TOCRIS BIOSCIENCE	**More In**
CMV	Glycine Extract	mL	0810003GE	ZEPTOMETRIX CORP.	**More In**
CMV	Cytomegalovirus (AD169) Infected Cell Extract. Used for IgG assays - Control is NHDF AV043	n/a	CV001	EASTCOAST BIO INC.	**More In**
	Cytomegalovirus				

CMV	Gradient Purified. Used for IgM assays.	n/a	CV046	EASTCOAST BIO INC.	**More In**
CMV	Cytomegalovirus Ag slides for FA. Made to Order	n/a	CG015	EASTCOAST BIO INC.	**More In**
CMV	Part Pure	n/a	J43010	BIOSPACIFIC INC.	**More In**

Page 36 of 2,608 **Records 1,751 - 1,800 of 130,353**

[1] « **29** | **30** | **31** | **32** | **33** | **34** | **35** | **36** | **37** | **38** | **39** | **40** |

Search Non-Antibody Products

Home | **Antibody Search** | **Other Products/Services Search** | **List Your Products** | **About Us** | **Links** | **Contact Us**

Electronic Patent Application Fee Transmittal

Application Number:	10551205
Filing Date:	14-Nov-2006
Title of Invention:	Oral formulations of cladribine
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Filer:	Mary Katherine Baumeister/Diana Francis
Attorney Docket Number:	0056192-000024

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

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:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1110	1110

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**1110**

Electronic Acknowledgement Receipt

EFS ID:	4054303
Application Number:	10551205
International Application Number:	
Confirmation Number:	4092
Title of Invention:	Oral formulations of cladribine
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Customer Number:	21839
Filer:	Mary Katherine Baumeister/Diana Francis
Filer Authorized By:	Mary Katherine Baumeister
Attorney Docket Number:	0056192-000024
Receipt Date:	03-OCT-2008
Filing Date:	14-NOV-2006
Time Stamp:	10:37:12
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$1110
RAM confirmation Number	5296
Deposit Account	024800
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. 1.492 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section ' ' (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	005619224TL.pdf	106535 802ec79ff5c0d1ec5dba3514562c642abd4a9181	no	2
Warnings:					
Information:					
2	Extension of Time	005619224EOT.pdf	46723 dc7eb25d6272e05224cf13c539e286ac0a2e3259	no	1
Warnings:					
Information:					
3	Amendment/Req. Reconsideration-After Non-Final Reject	005619224AMEND.pdf	4488479 b527124e797383c9425f8fece79d8cd57c4ee563	no	48
Warnings:					
Information:					
4	Fee Worksheet (PTO-06)	fee-info.pdf	30075 a665357a4ed17d1ebac948c63e3acee571ae5f56	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	4671812		

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	**MAIL STOP AMENDMENT**
Nicholas Bodor et al.	)	Group Art Unit: 1623
Application No.: 10/551,205	)	Examiner: JONATHAN S LAU
Filing Date: November 14, 2006	)	Confirmation No.: 4092
Title: ORAL FORMULATIONS OF CLADRIBINE	)	

AMENDMENT/REPLY TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Enclosed is a reply for the above-identified patent application.

☒ A Petition for Extension of Time is enclosed.

☐ _____ Terminal Disclaimer(s) and the ☐ $ 65 ☐ $ 130 fee per Disclaimer due under 37 C.F.R. § 1.20(d) are enclosed.

☒ Also enclosed is/are: copies of the attachments listed on page 26 of Reply and Amendment.

☐ Small entity status is hereby claimed.

☐ Applicant(s) requests continued examination under 37 C.F.R. § 1.114 and enclose the ☐ $ 405 ☐ $ 810 fee due under 37 C.F.R. § 1.17(e).

☐ Applicant(s) requests that any previously unentered after final amendments not be entered. Continued examination is requested based on the enclosed documents identified above.

☐ Applicant(s) previously submitted _____ on _____ for which continued examination is requested.

☐ Applicant(s) requests suspension of action by the Office until at least _____, which does not exceed three months from the filing of this RCE, in accordance with 37 C.F.R. § 1.103(c). The required fee under 37 C.F.R. § 1.17(i) is enclosed.

☐ A Request for Entry and Consideration of Submission under 37 C.F.R. § 1.129(a) (1809/2809) is also enclosed.

☒ No additional claim fee is required.

☐ An additional claim fee is required, and is calculated as shown below:

AMENDED CLAIMS					
	No. of Claims	**Highest No. of Claims Previously Paid For**	**Extra Claims**	**Rate**	**Additional Fee**
Total Claims	78	78	0	x $ 50 (1202)	$ 0
Independent Claims	5	5	0	x $ 210 (1201)	0
☐ If Amendment adds multiple dependent claims, add $ 370 (1203)					$ 0
Total Claim Amendment Fee					**$ 0**
☐ Small Entity Status claimed - subtract 50% of Total Claim Amendment Fee					0
TOTAL ADDITIONAL CLAIM FEE DUE FOR THIS AMENDMENT					**$ 0**

☐ Charge _____ to Deposit Account No. 02-4800 for the fee due.

☐ A check in the amount of _____ is enclosed for the fee due.

☐ Charge_____ to credit card for the fee due. Form PTO-2038 is attached.

☒ The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.20(d) and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date October 3, 2008

By: Mary Katherine Baumeister
Mary Katherine Baumeister
Registration No. 26254

P.O. Box 1404
Alexandria, VA 22313-1404
703 836 6620

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	**MAIL STOP AMENDMENT**
Nicholas Bodor et al.	Group Art Unit: 1623
Application No.: 10/551,205	Examiner: JONATHAN S LAU
Filing Date: November 14, 2006	Confirmation No.: 4092
Title: ORAL FORMULATIONS OF CLADRIBINE	

PETITION FOR EXTENSION OF TIME

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The following extension of time is requested to: extend the period for response to the Office Action dated April 4, 2008 for

Three Months to October 6, 2008 ☒ $ 1110 ☐ $ 525

☐ The shortened statutory period has been reset by an Advisory Action dated _____.

☐ An Extension fee in the amount of _____ is enclosed.

☒ Charge $ 1110 to Deposit Account No. 02-4800.

☐ Charge _____ to credit card. Form PTO-2038 is attached.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17 and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: October 3, 2008

By: Mary Katherine Baumeister
Mary Katherine Baumeister
Registration No. 26254

P.O. Box 1404
Alexandria, VA 22313-1404
703 836 6620

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/551,205	11/14/2006	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 10/03/2008

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 78	Minus	** 78	= 0	X $ =		OR	X $52=	0
Independent (37 CFR 1.16(h))	* 4	Minus	***6	= 0	X $ =		OR	X $220=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/SHERRY A. DAVIS/

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.
10/551,205	11/14/2006	Nicholas S. Bodor	0056192-000024	4092

21839 7590 01/07/2009

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
01/07/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/551,205	BODOR ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35 and 56-98* is/are pending in the application.

4a) Of the above claim(s) *13-35 and 67-81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12, 56-66, and 82-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

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)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is responsive to Applicant's Amendment and Remarks, filed 03 Oct 2008, in which claims 1, 2, 11, 13, 14, 23, 25, 26, 56-67 and 82 are amended to change the scope and breadth of the claim.

This application is the national stage entry of PCT/US04/09387, filed 26 Mar 2004; and claims benefit of provisional application 60/458,922, filed 28 Mar 2003; and claims benefit of provisional application 60/484,756, filed 02 July 2003; and claims benefit of provisional application 60/541,247, filed 04 Feb 2004.

The filing date of the instant claims 12, 66, 83, 85 and 89 are deemed to be the filing date of the instant application which is the filing date of PCT/US04/09387, 26 Mar 2004. The filing date of instant claims 1-11, 56-65, 82, 84 and 86-88 are deemed to be the filing date of provisional application 60/541,247, filed 04 Feb 2004.

Claims 1-35 and 56-98 are pending in the current application. Claims 13-35 and 67-81, drawn to non-elected inventions, are withdrawn.

Election/Restrictions

Applicant's remarks regarding the requirement for restriction are moot as the requirement was made FINAL in the Office Action mailed 04 Apr 2008.

As recited in the Office Action mailed 06 Dec 2006, where applicant elects claims directed to the product, and the product claims are subsequently found allowable,

withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

Objections Withdrawn

Applicant's Amendment, filed 03 Oct 2008, with respect to objections to the specification has been fully considered and is persuasive, as the identified informalities are corrected.

This rejection has been **withdrawn**.

Rejections Withdrawn

Applicant's Amendment, filed 03 Oct 2008, with respect to claims 2, 11 and 57 rejected under 35 U.S.C. 112, second paragraph, as being indefinite has been fully considered and is persuasive, as amended claims 2 and 11 recite the complex cladribin-cyclodextrin complex and amended claim 11 recites the definite term of a point on a specifically defined curve on a phase solubility diagram for saturated complexes of cladribine in varying concentrations of the cyclodextrin and Applicant's remarks regarding the definition of saturated is persusaive.

This rejection has been **withdrawn**.

Applicant's Amendment, filed 03 Oct 2008, with respect to claims 1-5, 11, 56-60, 82-90 and 94-98 rejected under 35 U.S.C. 102(b) as being anticipated by Schultz et al. (US Patent 6,194,395, published 27 Feb 2001, of record) has been fully considered and is persuasive, as Schultz et al. is not seen to disclose the composition comprising no significant amount of free crystalline cladribine therein (amended claim 1) or the complex consisting of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex (amended claim 56) explicitly, implicitly or inherently.

This rejection has been **withdrawn**.

The following are new or modified grounds of rejection necessitated by Applicant's Amendment, filed 03 Oct 2008, in which claims 1, 2, 11, 13, 14, 23, 25, 26, 56-67 and 82 are amended to change the scope and breadth of the claim. Claims 2-12, 57-66 and 82-83 depend from claims 1 and 56 directly or indirectly, and incorporate all limitations therein, including changes to the scope and breadth of the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented 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. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 1-12, 56-66 and 82-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schultz et al. (US Patent 6,194,395, published 27 Feb 2001, of record) in view of Baert et al. (WIPO Publication WO97/18839, published 29 May 1997, of record).

Schultz et al. discloses a solid pharmaceutical oral dosage form of cladribine comprising cladribine and cyclodextrin (column 2, lines 31-39). The disclosed product is substantially identical to the product-by-process. Schultz et al. discloses the use of β- and γ-cyclodextrins (column 2, lines 56-58) and derivatives wherein one or more cyclodextrin hydroxy groups are replaced with groups such as methyl, hydroxypropyl, carboxymethyl (column 3, lines 26-27) or sulfobutylcyclodextrins (column 4, lines 22-24). The phrase “one or more cyclodextrin hydroxy groups” combined with the absence of specific structural details of which hydroxyl group is substituted with a methyl group meets the limitation of “randomly methylated β-cyclodextrins”. Schultz et al. discloses the solid oral dosage form in the form of a tablet (column 5, lines 37-38) including the

excipients sorbitol and magnesium stearate (column 6, lines 2-7), disclosing a product that is substantially identical to a product-by-process meeting the limitations of the instant claims invention. Schultz et al. discloses an oral dosage form comprising up to 15 mg cladribine and cyclodextrin from 100 to 500 mg, which would lead one of skill in the art to instantly envision a cladribine to cyclodextrin ratio ranging from 15 mg:100 mg to 15mg:500 mg, or 1:6.67 to 1:33.3 by weight (column 6, lines 23-31). The instant specification suggests that maximum amount of cladribine which can be complexed gives a weight ratio of 1:10 for the cladribine:cyclodextrin complex. Therefore a composition comprising the cladribine:cyclodextrin complex that contains a cladribine to cyclodextrin ratio of 1:6.67 describes a composition that comprises a "saturated" complex and meets the limitations of instant claims 2 and 57. Schultz et al. incorporates-by-reference the method of making said solid oral dosage form (Schultz et al.column 5, lines 50-52) disclosed in WIPO Publication WO97/18839, Baert et al., which provides evidence in the embodiment wherein the melt-extruded forms consist essentially of amorphous material (Baert et al. page 8, lines 14-15). Therefore Baert et al. provides evidence that it was recognized in the prior art that the product disclosed by Schultz et al. inherently includes amorphous cladribine-cyclodextrin complex in a solid oral dosage form. Schultz et al. implicitly discloses an oral dosage form comprising up to 15 mg cladribine and cyclodextrin from 100 to 500 mg, or a cladribine to cyclodextrin ratio ranging from 1:6.67 to 1:33.3 by weight (column 6, lines 23-31).

To address the scientific issue regarding the equilibrium presence of both the inclusion and non-inclusion complex, while the equation for the equilibrium of the

cladribine-cyclodextrin inclusion complex and the cladribine-cyclodextrin non-inclusion complex would be different for cladribine and cyclodextrin in a solvent versus cladribine and cyclodextrin in a molten state due to the lack of a solvent, the equilibrium and thus equilibrium products, the cladribine-cyclodextrin inclusion complex and the cladribine-cyclodextrin non-inclusion complex, would still be inherent in the product disclosed by Schultz et al.

Schultz et al. does not specifically disclose the composition comprising no significant amount of free crystalline cladribine therein (instant claims 1). Schultz et al. does not specifically disclose the composition corresponding to a point located on the curve of a phase solubility diagram for saturated complex cladribine-cyclodextrin complexes, said curve defining complex saturated complexes of cladribine in varying concentrations of the cyclodextrin (instant claim 11). Schultz et al. does not specifically disclose the complex consisting of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex (instant claim 56). Schultz et al. does not specifically disclose the composition comprising a cladribine to cyclodextrin ratio from about 1:10 to about 1:16 (instant claims 6, 7, 10, 61, 62 and 65), or a ratio of about 1:14 (instant claims 8 and 63) or about 1:11 (instant claims 9 and 64). Schultz et al. does not specifically disclose the complex wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b) (instant claims 12 and 66). Schultz et al. does not specifically disclose the product-by-process wherein

12.00 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process (instant claim 91 and 93), to give a cladribine to cyclodextrin ratio of 1:14.38. Schultz et al. does not specifically disclose the product-by-process wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process (instant claim 92), to give a cladribine to cyclodextrin ratio of 1:10.55.

Baert et al. discloses a solid mixture comprising one or more cyclodextrins and an insoluble active ingredient embedded into the cyclodextrin carrier (abstract), and teaches ratios of active ingredient to cyclodextrin of from about 1:100 to 100:1, from about 1:5 and 5:1 and from about 1:3 to 3:1 (page 11, lines 1-5). These ratios are interpreted as mole ratios because Baert et al. teaches the use of different active ingredients with different molecular weights. A mole ratio of active ingredient to cyclodextrin of about 1:3 for cladribine (MW 285.7 g/mol) and β-cyclodextrin (MW 1135 g/mol) gives a ratio by weight of approximately 1:11.9. The ratio of 1:11.9 meets the limitation of both a ratio of about 1:11 and a ratio of about 1:14 according to the non-limiting definition of "about" as a variance of 20% provided in the instant specification page 9, lines 6-11. Such a saturated complex would consist of only (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex, and being a saturated complex corresponds to a point located on the curve of a phase solubility diagram for saturated complex cladribine-cyclodextrin complexes, said curve

defining complex saturated complexes of cladribine in varying concentrations of the cyclodextrin.

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the solid pharmaceutical oral dosage form of cladribine comprising cladribine and cyclodextrin disclosed by Schultz et al. in the ratios of cladribine and cyclodextrin taught by Baert et al. One of ordinary skill in the art would be motivated to combine the Schultz et al. and Baert et al. because Schultz et al. incorporates-by-reference Baert et al. and because Baert et al. suggests that improving a similar product according to the teachings of Baert et al. has beneficial properties such as high bioavailability and dissolution rate (Baert et al. page 7, lines 25-27). One of ordinary skill in the art would have an expectation of success because the ratios taught by Baert et al. fall within the range of ratios that is implicitly disclosed by Schultz et al. Schultz et al. in view of Baert et al. does not teach the specific cladribine to cyclodextrin ratios of 1:14.38 or 1:10.55, however these ratios are encompassed by the prior art and Baert et al. suggests optimization of the ratio (Baert et al. page 11, lines 1-5). See also MPEP 2144.05 II.A, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical." One of ordinary skill in the art would be motivated to optimize the cladribine to cyclodextrin ratio to give the composition comprising no significant amount of free crystalline cladribine therein because Schultz et al. teaches undesireable recrystallization of cladribine in tissue may occur and damage the surround tissue and that complexes with cyclodextrin are known

to solubilize the compound (Schultz et al. column 2, lines 1-15). Schultz et al. in view of Baert et al. does not specifically disclose the complex wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b). However, it is well known in the art that the formation of an inclusion complex from a non-inclusion complex is an equilibrium process, and the position of this equilibrium is dependent on the concentrations of the cladribine and cyclodextrin. This molecular inclusion equilibrium is a process inherent in the formation of the inclusion complex in both aqueous solutions and hot melt liquid mixtures, and Baert et al. teaches variation of the ratio of cladribine to cyclodextrin and hence their relative concentration.

It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed, namely the position of the equilibrium process governing formation of an inclusion complex and a non-inclusion complex. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Claims 82-90 and 94-98 are drawn to a product-by-process. The disclosed product is substantially identical to the instantly claimed product-by-process, an amorphous solid pharmaceutical oral dosage form comprising cladribine and cyclodextrin. “[E]ven though product-by-process claims are limited by and defined by

the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed. The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.). See MPEP 2113.

Response to Applicant's Remarks:

Applicant's Remarks, filed 03 Oct 2008 have been fully considered and not found to be persuasive.

Applicant notes that the method of Baert et al. is drawn to compounds that show no appreciable decomposition at the temperatures needed to melt and extrude the mixture. Applicant provides evidence that cladribine melts with decomposition at 220-235 °C, below the temperatures of the working examples of Baert et al. and below the melting point of HPβCD at 278 °C. This evidence regarding the applicability of the method disclosed by Baert et al. incorporated into Schultz et al. applied to the

disclosure of Schultz et al. has been carefully considered in view of the absence of disclosed working examples within Schultz et al. However it is well known in that art that a mixture of compounds exhibits some magnitude of freezing point depression due to the colligative properties of the mixture (entry for liquid, Britannica Online Encyclopedia, cited in PTO-892), and conversely there is a depression in the melting point. Suzuki et al. 1988 (Chem. Pharm. Bull., 1988, 36(2), p720-725, cited in PTO-892) provides evidence that further freezing point depression is observed for mixtures of butanol and sucrose with cyclodextrins (page 720, abstract and paragraph 2-3) due to the formation of the complex. Suzuki et al. 1993 (Chem. Pharm. Bull., 1993, 41(8), p1444-1447, cited in PTO-892) discloses this freezing point depression is observed in complexes such as barbiturate/CD (page 1444, left column, paragraphs 2-3). Therefore as the evidence provided concerns the melting point of the compounds as pure compounds rather than as the mixture, and in view of the presumption of validity afforded to the issued patent Schultz et al., this remark is not persuasive.

Applicant remarks that Baert et al. teaches the method of Baert et al. gives rise to different products than when said solids are first brought into contact with water or another solvent and then extruded. However, the invention of Baert et al. suggests that the different products given rise to are the solid solutions of the immediately prior statement (page 6, lines 14-15), or a mixture consisting of amorphous material and no crystalline material implied at page 8, lines 10-20.

Applicant's remarks that there is no reason for the interpreting the ratios taught by Baert et al. as mole ratios in view of the teachings of Schultz et al. and the instant

application regarding the disclosure of weight ratios. However, Suzuki et al. 1988 discloses cyclodextrin complexes in terms of the mole ratio (page 722, paragraph 3) and Suzuki et al. 1993 discloses the cyclodextrin complexes in terms of the stoichimetic ratios (page 1444, left column, paragraphs 1-3), or mole ratios. Therefore the prior art teaches both the interpretation as a mole ratio and a weight ratio. Absent a teaching within Baert et al. specifying the type of ratio intended and in view of the use of both mole ratios and a weight ratios in the prior art in the area of cyclodextrin complexes, one of skill in the art would find either interpretation equally reasonable.

Applicant notes that the product made obvious by Schultz et al. in view of Baert et al. is produced by a different process than the instant product-by-process. However, absent factual evidence of how this process necessarily makes a different product, it is found that the amorphous solid pharmaceutical oral dosage form comprising cladribine and cyclodextrin made obvious by Schultz et al. in view of Baert et al. is substantially identical to the same product may be the process of the instant invention.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jonathan Lau
Patent Examiner
Art Unit 1623

/Shaojia Anna Jiang/
Supervisory Patent Examiner
Art Unit 1623

Notice of References Cited	Application/Control No. 10/551,205	Applicant(s)/Patent Under Reexamination BODOR ET AL.	
	Examiner Jonathan S. Lau	Art Unit 1623	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	entry for liquid, Britannica Online Encyclopedia, http://www.search.eb.com/, accessed online on 31 Dec 2008.
	V	Suzuki et al. Chem. Pharm. Bull., 1988, 36(2), p720-725.
	W	Suzuki et al. Chem. Pharm. Bull., 1993, 41(8), p1444-1447.
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10551205	BODOR ET AL.
	Examiner	Art Unit
	Jonathan S Lau	1623

✓	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	11/26/2007	03/26/2008	01/02/2009						
	1	÷	✓	✓						
	2	÷	✓	✓						
	3	÷	✓	✓						
	4	÷	✓	✓						
	5	÷	✓	✓						
	6	÷	✓	✓						
	7	÷	✓	✓						
	8	÷	✓	✓						
	9	÷	✓	✓						
	10	÷	✓	✓						
	11	÷	✓	✓						
	12	÷	✓	✓						
	13	÷	N	N						
	14	÷	N	N						
	15	÷	N	N						
	16	÷	N	N						
	17	÷	N	N						
	18	÷	N	N						
	19	÷	N	N						
	20	÷	N	N						
	21	÷	N	N						
	22	÷	N	N						
	23	÷	N	N						
	24	÷	N	N						
	25	÷	N	N						
	26	÷	N	N						
	27	÷	N	N						
	28	÷	N	N						
	29	÷	N	N						
	30	÷	N	N						
	31	÷	N	N						
	32	÷	N	N						
	33	÷	N	N						
	34	÷	N	N						
	35	÷	N	N						
	36	-	-	-						

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10551205	BODOR ET AL.
	Examiner	Art Unit
	Jonathan S Lau	1623

✓	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	11/26/2007	03/26/2008	01/02/2009						
	37	-	-	-						
	38	-	-	-						
	39	-	-	-						
	40	-	-	-						
	41	-	-	-						
	42	-	-	-						
	43	-	-	-						
	44	-	-	-						
	45	-	-	-						
	46	-	-	-						
	47	-	-	-						
	48	-	-	-						
	49	-	-	-						
	50	-	-	-						
	51	-	-	-						
	52	-	-	-						
	53	-	-	-						
	54	-	-	-						
	55	-	-	-						
	56	÷	✓	✓						
	57	÷	✓	✓						
	58	÷	✓	✓						
	59	÷	✓	✓						
	60	÷	✓	✓						
	61	÷	✓	✓						
	62	÷	✓	✓						
	63	÷	✓	✓						
	64	÷	✓	✓						
	65	÷	✓	✓						
	66	÷	✓	✓						
	67	÷	N	N						
	68	÷	N	N						
	69	÷	N	N						
	70	÷	N	N						
	71	÷	N	N						
	72	÷	N	N						

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10551205	BODOR ET AL.
	Examiner	Art Unit
	Jonathan S Lau	1623

✓	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	11/26/2007	03/26/2008	01/02/2009						
	73	÷	N	N						
	74	÷	N	N						
	75	÷	N	N						
	76	÷	N	N						
	77	÷	N	N						
	78	÷	N	N						
	79	÷	N	N						
	80	÷	N	N						
	81	÷	N	N						
	82	÷	✓	✓						
	83	÷	✓	✓						
	84	÷	✓	✓						
	85	÷	✓	✓						
	86	÷	✓	✓						
	87	÷	✓	✓						
	88	÷	✓	✓						
	89	÷	✓	✓						
	90	÷	✓	✓						
	91	÷	✓	✓						
	92	÷	✓	✓						
	93	÷	✓	✓						
	94	÷	✓	✓						
	95	÷	✓	✓						
	96	÷	✓	✓						
	97	÷	✓	✓						
	98	÷	✓	✓						

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10551205	BODOR ET AL.
	Examiner	Art Unit
	Jonathan S Lau	1623

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST - inventor name search (Nicholas Bodor; Yogesh Dandiker)	3/26/2008	JSL
EAST - see attached notes	3/26/2008	JSL
Google Scholar - see attached notes	3/26/2008	JSL

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

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.
10/551,205	11/14/2006	Nicholas S. Bodor	0056192-000024	4092

21839 7590 06/18/2009

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
06/18/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Interview Summary	Application No.	Applicant(s)	
	10/551,205	BODOR ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Jonathan S. Lau*.

(2) *Shaojia Anna Jiang*.

(3)*Mary Katherine Baumeister*.

(4)*Nicholas Bodor*.

Date of Interview: *10 Jun 2009*.

Type: a)☐ Telephonic b)☐ Video Conference
c)☒ Personal [copy given to: 1)☒ applicant 2)☐ applicant's representative]

Exhibit shown or demonstration conducted: d)☐ Yes e)☒ No.
If Yes, brief description: *n/a*.

Claim(s) discussed: *1*.

Identification of prior art discussed: *Van Axel Castelli et al. (J. Pharm. Sci. 2008)*.

Agreement with respect to the claims f)☐ was reached. g)☒ was not reached. h)☐ N/A.

Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: *Applicant will consider filing an RCE. Applicant will consider filing an amendment to clarify claim language. Applicant explained how the physical mixture of cladribine-CD is distinguished from the complex. Applicant discussed how the data of Van Axel Castelli et al. applies to the prior art of record*.

(A fuller description, if necessary, and a copy of the amendments which the examiner agreed would render the claims allowable, if available, must be attached. Also, where no copy of the amendments that would render the claims allowable is available, a summary thereof must be attached.)

THE FORMAL WRITTEN REPLY TO THE LAST OFFICE ACTION MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a reply to the last Office action has already been filed, APPLICANT IS GIVEN A NON-EXTENDABLE PERIOD OF THE LONGER OF ONE MONTH OR THIRTY DAYS FROM THIS INTERVIEW DATE, OR THE MAILING DATE OF THIS INTERVIEW SUMMARY FORM, WHICHEVER IS LATER, TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW. See Summary of Record of Interview requirements on reverse side or on attached sheet.

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623

Patent
Attorney's Docket No. 0056192-000024

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	**MAIL STOP RCE**
Nicholas S. Bodor et al.	Group Art Unit: 1623
Application No.: 10/551,205	Examiner: JONATHAN S LAU
Filing Date: November 14, 2006	Confirmation No.: 4092
Title: ORAL FORMULATIONS OF CLADRIBINE	

REQUEST FOR CONTINUED EXAMINATION (RCE) TRANSMITTAL LETTER

MAIL STOP RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Customer Number **21839**

Sir:

Applicant(s) requests continued examination under 37 C.F.R. § 1.114 of the above-identified application and encloses the ☐ $405 ☒ $810 fee due under 37 C.F.R. § 1.17(e).

1. ☐ A. Applicant(s) requests that any previously unentered after final amendments not be entered. Continued examination is requested based on the enclosed documents identified in item 2 below.

   ☐ B. Applicant(s) previously submitted the following documents for which continued examination is requested:

   ☐ Consider the amendment(s)/reply under 37 C.F.R. § 1.116 previously filed on _____.

   ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____.

   ☐ Other: _____

2. The following documents are enclosed with this submission:

   ☒ Amendment/Reply

   ☐ Affidavit(s)/Declaration(s)

   ☒ Information Disclosure Statement, form PTO-1449, (4) documents

   ☒ Petition for Extension of Time

   ☐ Other: [List Other documents filed with submission here]

3. ☐ Small entity status is hereby claimed.

☐ No additional claim fee is required.

☒ The fee is calculated below on the basis of the highest number of claims already paid for in this application prior to this submission:

					FEES
Examination Fee (1801)					$ 810
	No. of Claims		**Extra Claims**	**Rate**	
Total Claims	56	78	0	x 52 (1202)	$ 0
Independent Claims	4	5	0	x 220 (1201)	$ 0
If multiple dependent claims are presented, add $ 390					$ 0
Total Fee					$ 810
☐ Small Entity Status claimed - subtract 50% of Total Application Fee					$ 0
TOTAL FEE DUE					$ 810

4. ☐ Charge _____ to Deposit Account No. **02-4800** for the fee due.

5. ☐ A check in the amount of _____ is enclosed for the fee due.

6. ☒ Charge $ 810 to credit card for the fee due. Form PTO-2038 is attached.

7. ☐ Applicant(s) requests suspension of action by the Office until at least _____, which does not exceed three months from the filing of this RCE, in accordance with 37 C.F.R. § 1.103(c). The required fee under 37 C.F.R. § 1.17(i) is enclosed.

8. ☒ The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800. This paper is submitted in duplicate.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: July 6, 2009

By: Mary Katherine Baumeister
Mary Katherine Baumeister
Registration No. 26254

P.O. Box 1404
Alexandria, VA 22313-1404
703 836 6620

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	**MAIL STOP RCE**
Nicholas S. Bodor et al.	Group Art Unit: 1623
Application No.: 10/551,205	Examiner: JONATHAN S LAU
Filed: November 14, 2006	Confirmation No.: 4092
For: ORAL FORMULATIONS OF CLADRIBINE	

REPLY AND AMENDMENT ACCOMPANYING FILING OF REQUEST FOR CONTINUED EXAMINATION (RCE) PURSUANT TO 37 C.F.R. § 1.114

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office Action dated January 7, 2009, and in connection with Applicants' Request for Continued Examination, please first amend the above-identified patent application as follows:

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. (Currently Amended) A pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture consisting of (a) an amorphous inclusion complex of cladribine with ~~an~~ the amorphous cyclodextrin hydroxypropyl-β-cyclodextrin and (b) amorphous free cladribine associated with said amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein, said composition having a weight ratio of cladribine to said amorphous cyclodextrin of from about 1:10 to about 1:16.

2. (Previously Presented) The pharmaceutical composition according to Claim 1, wherein the complex cladribine-cyclodextrin complex is saturated with cladribine.

3-7. (Cancelled))

8. (Currently Amended) The composition according to ~~Claim 7~~ Claim 1, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

9. (Currently Amended) The composition according to ~~Claim 7~~ Claim 1, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

10. (Cancelled)

11. (Currently Amended) The composition according to Claim 2, wherein the approximate molar ratio of cladribine to said amorphous cyclodextrin corresponds to a point located on the curve of a phase solubility diagram for saturated complex cladribine-cyclodextrin complexes, said curve defining complex saturated complexes of cladribine in varying concentrations of the cyclodextrin.

12. (Previously Presented) The composition according to Claim 1, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

13. (Withdrawn and Currently Amended) A method for enhancing the oral bioavailability of cladribine comprising orally administering to a subject in need thereof a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture consisting of (a) an amorphous inclusion complex of cladribine with ~~an~~ the amorphous cyclodextrin hydroxypropyl-β-cyclodextrin and (b) amorphous free cladribine associated with said amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein, said composition having a weight ratio of cladribine to said amorphous cyclodextrin of from about 1:10 to about 1:16.

14. (Withdrawn) The method according to Claim 13, wherein the complex cladribine-cyclodextrin complex is saturated with cladribine.

15-19. (Cancelled)

20. (Withdrawn and Currently Amended) The method according to ~~Claim 19~~ Claim 13, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

21. (Withdrawn and Currently Amended) The method according to ~~Claim 19~~ Claim 13, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

22. (Cancelled)

23. (Withdrawn and Currently Amended) The method according to Claim 14, wherein the approximate molar ratio of cladribine to said amorphous cyclodextrin corresponds to a point located on the curve of a phase solubility diagram for saturated complex cladribine-cyclodextrin complexes, said curve defining complex saturated complexes of cladribine in varying concentrations of the cyclodextrin.

24. (Withdrawn) The method according to Claim 13, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

25. (Withdrawn and Currently Amended) A method for the treatment of symptoms of a cladribine-responsive condition in a subject suffering from said symptoms comprising orally administering to said subject a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture consisting of (a) an amorphous inclusion complex of cladribine with ~~an~~ the amorphous cyclodextrin hydroxypropyl-β-cyclodextrin and (b) amorphous free cladribine associated with said amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein, said composition having a weight ratio of cladribine to said amorphous cyclodextrin of from about 1:10 to about 1:16.

26. (Withdrawn) The method according to Claim 25, wherein the complex cladribine-cyclodextrin complex is saturated with cladribine.

27. (Withdrawn) The method according to Claim 25, wherein the cladribine-responsive condition is selected from the group consisting of multiple sclerosis, rheumatoid arthritis and leukemia.

28. (Withdrawn) The method according to Claim 27, wherein the cladribine-responsive condition is multiple sclerosis.

29-31. (Cancelled)

32. (Withdrawn and Currently Amended) The method according to ~~Claim 31~~ Claim 25, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

33. (Withdrawn and Currently Amended) The method according to ~~Claim 31~~ Claim 25, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

34. (Cancelled)

35. (Withdrawn) The method according to Claim 25, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

36.-55. (Cancelled)

56. (Currently Amended) A complex cladribine-cyclodextrin complex which is an intimate amorphous admixture consisting of (a) an amorphous inclusion complex of cladribine with ~~an~~ the amorphous cyclodextrin hydroxypropyl-β-cyclodextrin and (b) amorphous free cladribine associated with said amorphous cyclodextrin as a non-inclusion complex, said complex cladribine-

cyclodextrin complex having a weight ratio of cladribine to said amorphous cyclodextrin of from about 1:10 to about 1:16.

57. (Previously Presented) The complex cladribine-cyclodextrin complex according to Claim 56, saturated with cladribine.

58-62. (Cancelled)

63. (Currently Amended) The complex cladribine-cyclodextrin complex according to ~~Claim 62~~ Claim 56, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:14.

64. (Currently Amended) The complex cladribine-cyclodextrin complex according to ~~Claim 62~~ Claim 56, wherein the weight ratio of cladribine to hydroxypropyl-β-cyclodextrin is about 1:11.

65. (Cancelled)

66. (Previously Presented) The complex cladribine-cyclodextrin complex according to Claim 56, wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b).

67. (Withdrawn and Currently Amended) A process for the preparation of a complex cladribine-cyclodextrin complex as claimed in Claim 56, which comprises the steps of:

(i) combining cladribine and ~~an~~ the amorphous cyclodextrin in water at a temperature of from about 45 to about 80°C and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature; and

(iii) lyophilizing the cooled solution to afford an amorphous product.

68. (Withdrawn) A process according to Claim 67, further comprising a filtration step following step (ii).

69. (Withdrawn) A process according to Claim 67, wherein step (i) is performed at a temperature of from about 45 to about 60°C.

70. (Withdrawn) A process according to Claim 67, wherein step (i) is performed at a temperature of from about 45 to about 50°C.

71. (Withdrawn) A process according to Claim 69, wherein step (i) is performed with stirring.

72. (Withdrawn) A process according to Claim 71, wherein step (i) is performed for a period of from about 6 to about 9 hours.

73. (Withdrawn) A process according to Claim 67, wherein step (ii) is performed for a period of from about 6 to about 9 hours.

74. (Withdrawn) A process according to Claim 67, wherein step (iii) comprises an initial freezing stage in which the solution is cooled to from about -40 to about -80° C, and held at said temperature for a period of from about 2 to about 4 hours.

75. (Withdrawn) A process according to Claim 74, wherein, in the initial freezing stage of step (iii), the solution is cooled to about -45°C.

76. (Withdrawn) A process according to Claim 67, wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i).

77. (Withdrawn) A process according to Claim 67, wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i).

78. (Withdrawn) A process according to Claim 76, wherein 825 parts by volume of water are introduced in step (i).

79. (Withdrawn) A process according to Claim 67, wherein the lyophilization step (iii) comprises:

(a) an initial freezing stage in which the complexation solution is brought to from about -40°C to about -80°C for approximately 2 to 4 hours;

(b) a primary drying stage at about -25°C for approximately 80 to 90 hours; and

(c) a secondary drying stage at about 30°C for approximately 15 to 20 hours.

80. (Withdrawn) A process according to Claim 79, wherein stage (a) of the lyophilization is conducted at about -45°C for approximately 3 to 4 hours.

81. (Withdrawn) A process according to Claim 79, wherein stage (b) of the lyophilization is conducted under a pressure of about 100 mTorr.

82. (Currently Amended) A pharmaceutical composition <u>according to Claim 1</u> obtainable by a process comprising the steps of:

(i) combining cladribine and ~~an~~ <u>the</u> amorphous cyclodextrin <u>hydroxypropyl-β-cyclodextrin</u> in water at a temperature of from about 45 to about 80°C and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature;

(iii) lyophilizing the cooled solution to afford an amorphous product; and

(iv) formulating the amorphous product into a solid oral dosage form.

83. (Original) A pharmaceutical composition according to Claim 82, wherein the process further comprises a filtration step following step (i) or (ii).

84. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein step (i) of the process is performed at a temperature of from about 45 to about 60°C.

85. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein step (i) of the process is performed at a temperature of from about 45 to about 50°C.

86. (Previously Presented) A pharmaceutical composition according to Claim 84, wherein step (i) of the process is performed with stirring.

87. (Original) A pharmaceutical composition according to Claim 86, wherein step (i) of the process is performed for a period of from about 6 to about 9 hours.

88. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein step (ii) of the process is performed for a period of from about 6 to about 9 hours.

89. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein step (iii) comprises an initial freezing stage in which the solution is cooled to from about -40 to about -80°C, and held at said temperature for a period of from about 2 to about 4 hours.

90. (Original) A pharmaceutical composition according to Claim 89, wherein, in the initial freezing stage of step (iii), the solution is cooled to about -45°C.

91. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process.

92. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process.

93. (Previously Presented) A pharmaceutical composition according to Claim 91, wherein 825 parts by volume of water are introduced in step (i) of the process.

94. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein the lyophilization step (iii) of the process comprises:

(a) an initial freezing stage in which the complexation solution is brought to from about -40°C to about -80°C for approximately 2 to 4 hours;

(b) a primary drying stage at about -25°C for approximately 80 to 90 hours; and

(c) a secondary drying stage at about 30°C for approximately 15 to 20 hours.

95. (Original) A pharmaceutical composition according to Claim 94, wherein stage (a) of the lyophilization is conducted at about -45°C for approximately 3 to 4 hours.

96. (Previously Presented) A pharmaceutical composition according to Claim 94, wherein stage (b) of the lyophilization is conducted under a pressure of about 100 mTorr.

97. (Previously Presented) A pharmaceutical composition according to Claim 82, wherein the formulation step (iv) of the process comprises blending the complex with magnesium stearate and compressing into tablets.

98. (Original) A pharmaceutical composition according to Claim 97, wherein magnesium stearate is pre-mixed with sorbitol powder before blending with the complex.

REMARKS

In connection with applicants' Request for Continued Examination (RCE), applicants respectfully request entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.114, and in light of the remarks which follow.

STATUS OF CLAIMS

Claims 1, 2, 8, 9, 11-14, 20, 21, 23-28, 32, 33, 35, 56, 57, 63, 64 and 66-98 remain in this application. Claims 3-7, 10, 15-19, 22, 29-31, 34, 58-62 and 65 have been cancelled by the foregoing amendment, without prejudice or disclaimer, which Claims 36-55 were previously cancelled. Claims 1, 8, 9, 11, 13, 20, 21, 23, 25, 32, 33, 56, 63, 64, 67 and 82 have been amended hereinabove. Claims 1, 2, 8, 9, 11, 12, 56, 57, 63, 64, 66 and 82-98 are under examination. Claims 13, 14, 20, 21, 23-28, 32, 33, 35 and 67-81 have been withdrawn from consideration as drawn to non-elected subject matter. However, the withdrawn claims have been amended to be commensurate in scope with the examined claims as amended so that they may ultimately be rejoined.

STATEMENT OF SUBSTANCE OF INTERVIEW

Applicants acknowledge and thank Examiners Lau and Jiang for the courtesy of the personal interview granted to the inventor, Nicholas S. Bodor, and to applicants' undersigned representative, on June 10, 2009.

At the interview, applicants' representative indicated that an RCE would be filed. The claim language was discussed and it was agreed that support for the word "free" would be investigated and the claim clarified in this respect, if necessary. It was also proposed that in order to expedite prosecution, the independent claims be amended to recite only a particular amorphous cyclodextrin, namely hydropropyl-β-cyclodextrin, for which data was discussed, as well as a weight ratio range of cladribine to the cyclodextrin of from about 1:10 to about 1:16 (as set forth in, for

example, Claim 6); these suggestions were looked upon favorably by the Examiners following a detailed discussion, first of the references relied upon by the Examiner and then of the Van Axel Castelli et al. , *J. Pharm.Sci.* 2008 submitted at the interview. The Van Axel Castelli et al. publication, a further copy of which is submitted herewith and listed on the accompanying Form PTO-1449, was shown to fully support the data in the specification for the claimed subject matter, to distinguish the instant complex from physical mixtures and to show the correctness of applicants' previous arguments with respect to the obviousness rejection based on Schultz et al. in view of Baert et al. Rather than repeating these discussions in detail, in this interview summary, applicants will repeat these discussions in detail in the remarks below. Finally, applicants provided several recent internet news reports concerning clinical trials of the product, further copies of which are appended.

DISCUSSION OF CLAIM AMENDMENTS

Claim 1 has been amended to specify "the amorphous cyclodextrin hydroxypropyl-β-cyclodextrin," rather than "an amorphous cyclodextrin"; this feature was previously recited, for example, in original Claim 4. Claim 1 has been further amended to specify that the weight ratio of cladribine to said amorphous cyclodextrin in said composition is from about 1:10 to about 1:16; this feature was previously recited, for example, in original Claim 6. As for the use of the word 'free" in association with "cladribine," the expression "free cladribine" simply means cladribine not in the inclusion complex; see page 7, lines 24-25, where "free cladribine" is clearly defined. Therefore, it is appropriate to retain this word in the claims; amorphous free cladribine is associated with the amorphous cyclodextrin as the non-inclusion complex (b) while there is no significant amount of free crystalline cladribine in the composition. As for the subject matter cancelled from Claim 1 or from any of the other claims, applicants of course reserve the right to file a continuing application thereon.

Claims 3-7 have been cancelled as either outside the scope of the claims or redundant in light of the amendment of Claim 1.

Claims 8 and 9 have been amended so that they depend from Claim 1, which contains the features of original Claim 7, and Claim 10 has been cancelled as outside the scope of amended Claim 1.

A minor linguistic amendment has been made to Claim 11 to make it more consistent with amended Claim 1.

Claim 13 has been amended to be commensurate in scope with Claim 1.

Claims 15-19 have been cancelled as either outside the scope of Claim 13 as amended or redundant in light of the amendment of Claim 13; Claims 20 and 21 have been amended so that they depend from Claim 13; and Claim 22 has been cancelled as outside the scope of amended Claim 13. All of these amendments are consistent with the amendment of Claim 1.

A minor linguistic amendment has been made to Claim 23 to make it more consistent with amended Claim 13.

Claim 25 has been amended to be commensurate in scope with Claim 1.

Claims 29-31 and 34 have been cancelled as either outside the scope of Claim 25 as amended or redundant in light of the amendment of Claim 25.

Claims 32-33 have been amended to depend from Claim 25, which contains the features of the claim upon which they previously depended.

Claim 56 has been amended to be consistent with Claim 1. Claims 58-62 and 65 have accordingly been cancelled as outside the scope of amended Claim 56 or redundant in light of the amendment of Claim 56. The dependencies of Claims 63 and 64 have been amended accordingly.

A minor linguistic amendment has been made to Claim 67 to make it more consistent with amended Claim 56.

Finally, Claim 82 has been amended so that it depends from Claim 1 and the language has been amended to specify the amorphous cyclodextrin hydroxypropyl-β-cyclodextrin consistent with Claim 1.

It is apparent from the foregoing that no new matter has been introduced by the amendments made.

FILING DATES ACCORDED TO CLAIMS

Applicants thank the Examiner for considering their remarks, particularly with respect to the international filing date. The PCT filing date of March 26, 2004 has been accorded to Claims 12, 66, 83, 85 and 89, while all other claims are deemed to be entitled to the February 4, 2004 filing date of U.S. Provisional Appln. No. 60/541,247.

ELECTIONS/RESTRICTIONS

As noted above, applicants have amended the withdrawn claims to be commensurate in scope with the product claims, so that the withdrawn claims can be ultimately rejoined.

OBJECTIONS WITHDRAWN

The Examiner's withdrawal of the previous objections to the specification is noted, with appreciation.

REJECTIONS WITHDRAWN

The withdrawal of the previous rejections under 35 U.S.C. §§ 112, second paragraph, and 102(b) are likewise noted, with appreciation.

CLAIM REJECTIONS - 35 U.S.C. § 103

Claims 1-12, 56-66 and 82-83 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Schultz et al. US Patent No. 6,194,395 in view of Baert et al. WO 97/18839, both previously made of record. It is submitted that this rejection cannot be maintained against any of the claims now in this application.

As explained at the interview, Schultz et al. describe two kinds of cyclodextrin formulations of cladribine, i.e., "soluble aqueous formulations of cladribine with

cyclodextrin solubilizers which are injectable in humans, as well as oral solid dosage forms containing a mixture of cladribine and cyclodextrins." (Emphasis added). See col., 1, lines 6-10, of the Schultz et al. patent. Applicants do not dispute the fact that Schultz et al. disclose hydroxypropyl-β-cyclodextrin (HPβCD), which is amorphous, but Schultz et al. disclose crystalline cyclodextrins as well. Indeed, Schultz et al. teach aqueous formulations containing a cladribine/HPβCD complex in solution for injectable use. On the other hand, Schultz et al. clearly teach that their solid oral dosage forms are mixtures of cladribine and cyclodextrin as set forth not only in col. 1, lines 8-10 ("oral solid dosage forms containing a mixture of cladribine and cyclodextrin") but also in col. 5, lines 50-64. There it is indicated that the solid oral dosage forms may be prepared as disclosed in Baert et al. WO 97/18837; this is in fact the only method disclosed by Schultz et al. for preparing the solid oral dosage forms. In col. 5, beginning at line 52, it is stated that "solid mixtures of the cyclodextrins with the active ingredient are prepared via melt-extrusion....the cladribine active ingredient and the cyclodextrins are mixed with other optional ingredients and then heated until melting occurs. The mixture is then extruded through an extruder having one or more nozzles." As set forth in col. 6 of the Schultz et al. patent, a typical oral dosage form has a formulation containing, as a milled extrudate, 1 mg to 15 mg of cladribine and 100 to 500 mg of cyclodextrin, and as excipients, 100 to 300 mg of microcrystalline cellulose, 10 to 200 mg of crospovidone, 1 to 5 mg of colloidal silicon dioxide and 2 to 10 mg of sterotex. Schultz et al. do not disclose or suggest to the ordinary skilled pharmaceutical scientist solid oral formulation of cladribine/cyclodextrin complexes as claimed herein. As noted at the interview, and as will be explained in detail below with reference to the Van Axel Castelli et al. article, the characteristics of a complex and a physical mixture are distinctly different; Schultz et al.'s solid mixtures of cladribine and cyclodextrin cannot be assumed to be the same as applicants' product, which is a complex cladribine-cyclodextrin complex. Even if the broad ratios of Schultz et al.'s mixtures encompass the ratios in applicants' complexes, having the same ratio does not give a physical mixture the same properties as a complex, a fact which is clearly shown by the Van Axel Castelli et al. document discussed in detail below.

As further noted at the interview, the Baert et al. WO document, incorporated by reference in Schultz et al., for its melt-extrusion method of making solid oral dosage forms, describes amorphous materials and solid solutions but does not teach or suggest that its solid dosage form products include amorphous cyclodextrin-drug complexes. On the contrary Baert et al. teach that:

(a) Prior art problems are solved by Baert et al. by the use of a melt-extrusion process to form solid mixtures comprising one or more cyclodextrins and insoluble active ingredients (Emphasis added; see page 3, lines 7-9).

(b) The compounds suitable for use in Baert et al.'s process "are compounds that show no appreciable decomposition at the temperatures needed to melt and extrude the mixture of said one or more active ingredients with the cyclodextrin or cyclodextrins" (page 4, lines 5-7).

(c) Baert et al. teach that the characteristics of their products are different from those of a product obtained in water, since it is stated on page 6, lines 15-19:

> It will be appreciated by a person skilled in the art that mixing two or more solids, i.e., one or more cyclodextrins and the active ingredient or ingredients, and subsequently melting these solids together will give rise to different products than when the said solids are first brought into contact with water or another solvent and then extruded.

(d) Baert et al.'s process uses very high temperatures; note Table 1 on page 12, where several different drugs are mixed with HPβCD and melt-extruded, with temperatures of around 280°C being utilized and the products in every case as noted on page 13, lines 5-6, being solid solutions.

(e) Baert et al. do not mention cladribine; indeed, applicants have previously shown that cladribine is known to decompose at the high temperatures used by Baert et al. and thus cladribine falls in the group of compounds Baert et al. teaches are unsuitable for use in their process [point (b) above].

(f) Baert et al. in no way teach or suggest that their products contain complexes.

The unsuitability of Baert et al.'s temperatures and hence for the Baert et al. process as applied to cladribine with cyclodextrin, specifically with HPβCD, is furthermore proved by data in the Van Axel Castelli et al. article, as discussed in more detail below.

Also at the interview, to provide background with respect to drug/cyclodextrin complexation, applicants brought to the Examiners' attention, the Loftsson and Brewster cyclodextrin review article previously made of record in applicants' Third Information Disclosure Statement; see Loftsson et al., "Pharmaceutical Application of Cyclodextrins. 1. Drug Solubilization and Stabilization," *Journal of Pharmaceutical Sciences,* Vol. 85, No. 10, pp. 1017-1025, 1996, American Pharmaceutical Association and the American Chemical Society, US. The Loftsson and Brewster review article shows that it was known in the art that:

(a) Cyclodextrin/drug complexation typically is carried out in aqueous media, not by mixing in the absence of water (page 1020, left column, first full paragraph).

(b) This complexation involves many different forces (van der Waals, hydrogen bonding, etc.) and the use of water is essential to the formation of complexes (page 1018, right column, second full paragraph to page 1020, left column, noting in particular the mention of release of water molecules from the cyclodextrin cavity as a driving force for drug-cyclodextrin complex formation).

(c) The complexes have different properties from mere physical mixtures of drugs and cyclodextrins, for example in terms of drug solubilization and drug stabilization (pages 1020-1024), a fact shown for HPβD and cladribine in the Van Axel Castelli et al. article discussed below.

(d) The amorphous cyclodextrins such as HPβCD have almost countless isomeric and variably substituted forms and upon complexation result in amorphous products which are mixtures of countless complexes (page 1018, left column, line 12 from the bottom, to page 1018, right column line 2).

To address applicants' position that use of cladribine in Baert et al.'s melt extrusion product is inappropriate because of the fact that the decomposition temperature of cladribine is lower than the Baert et al. process's temperature, the Examiner has cited several additional documents (the Britannica Online excerpt and

the two Suzuki et al. articles). Applicants believe that these documents are irrelevant for at least the following reasons:

(a) These references relate to freezing point depression and teach nothing about decomposition of cladribine at the high temperatures used in the Baert et al. process.

(b) These references relate only to crystalline cyclodextrins (α- and β-cyclodextrin), which give crystalline complexes from water and not to amorphous cyclodextrins such as HPβCD, which give amorphous complexes from water, these different kinds of complexes exhibiting different properties; moreover, neither Schultz et al. nor Baert et al. even remotely suggest that their solid oral dosage forms contain cyclodextrin/drug complexes, both characterizing their solid products as mixtures.

(c) The experimental data provided in the Van Axel Castelli et al. article and discussed below prove that cladribine and an amorphous cyclodextrin such as HPβCD do not form an eutectic mixture; rather, Van Axel Castelli et al. as discussed below, shows that cladribine, whether in a complex or in a mixture with HPβCD, decomposes at temperatures far below those used for this cyclodextrin in the Baert et al. process.

Turning to the Van Axel Castelli et al. article, which was discussed in detail by Dr. Bodor at the interview, a further copy of which is provided herewith and which is listed on the accompanying form PTO-1449, the following remarks are offered:

The Van Axel Castelli et al. article shows that an inclusion complex of cladribine and 2-hydroxypropyl-β-cyclodextrin has properties which are different from those of the cyclodextrin, those of cladribine and those of physical mixtures of the cyclodextrin with cladribine. These differences were discussed at length by Dr. Bodor at the interview with respect to various analyses conducted by Van Axel Castelli et al. and can be summarized as follows:

(a) Thermo gravimetric analysis (TGA) was conducted over the temperature range from 25°C to 360°C for (a) cladribine, (b) HPβCD, (c) their inclusion complex and (d) their physical mixture and the results are shown in Fig. 2. Fig. 2a, the TGA curve for cladribine itself, shows decomposition of cladribine starting at about 200°C. Fig. 2b, the TGA curve for HPβCD, shows a mass loss of

6% at 30°C to about 140°C, due to dehydration, and decomposition at about 300°C. Fig. 2c, the TGA curve for the cladribine/HPβCD complex, shows water loss between 20°C and 100°C and a decomposition process starting at about 250°C. Fig. 2d, the TGA curve for the cladribine plus HPβCD physical mixture, shows a multi-stage decomposition pathway; the first decomposition stage between room temperature and 100°C is due to loss of water from the cyclodextrin, whereas the second decomposition stage, observed at temperatures above 200°C, is due to the decomposition of cladribine. Fig. 2d also shows that heating the mixture to high temperatures does not lead to complexation but rather to decomposition of cladribine. Comparing the TGA for the complex with that of the physical mixture shows a slower degradation for the complex than for the mixture. Nevertheless, cladribine, whether in a complex or in a mixture with HPβCD, decomposes at temperatures far below those used for HPβCD-containing products in the Baert et al. process.

(b) Differential scanning calorimetry (DSC) analysis was conducted and the results shown in Fig. 3 for (a) cladribine, (b) HPβCD, (c) cladribine/HPβCD complex, (d) cladribine plus HPβCD physical mixtures, and (e) cladribine plus HPβCD kneading product. The authors note that the DSC trace of cladribine shows two endothermic events (Fig. 3a), the first at 206.3°C being close to the cladribine decomposition onset temperature and corresponding to the melting transition, and the second at 211.9°C, which is during the decomposition process, and probably is due to a decomposition product of cladribine. The DSC profile for the cyclodextrin (Fig. 3b) confirms an endothermic event corresponding to water loss from about 40°C to about 100°C. The authors further note that the DSC curves of the inclusion complex (Fig. 3c), physical mixture (Fig. 3d) and kneading product (Fig. 3e) all show a broad thermal event from about 40 to 140°C, due to water loss in the cyclodextrin. In addition, the physical mixture and the kneading product are observed to feature two endothermic events around 200°C; these can be attributed to free cladribine in the mixture and kneading product. In contrast, Fig. 3c, the DSC trace for the complex, shows only one endothermic event, which occurs in the high temperature region, at 234.5°C; this is considerably higher than the degradation onset of pure cladribine around 200°C (Fig.2a), while the latter also characterizes the mixtures. As

noted by the authors, the absence of thermal events typical of pure cladribine shows a loss of cladribine crystalline character for the complex. This also confirms DSC data for the products of instant Examples 1 and 2 reported on page 31 of the instant specification and correlates well with applicants' x-ray diffraction traces for the products of Examples 1 and 2 reported on page 31 of the specification, where no peaks for crystalline cladribine were found in the complexes;

(c) FT-IR and FT-Raman spectroscopy were also recorded by Van Axel Castelli et al. In Figures 5 and 6, the FT-IR and FT-Raman spectra of cladribine alone (a), cladribine/cyclodextrin physical mixture (b), cladribine/cyclodextrin complex (c) and cyclodextrin alone (d) were compared. The authors indicate that the IR spectrum of the physical mixture (Fig. 5b) can be interpreted as the sum of the spectra for pure crystalline cladribine (Fig. 5a) and pure HPβCD (Fig. 5d), also supported by Fig. 6. The authors continue:

> In contrast, both IR and Raman spectra of the inclusion complex show clear differences with respect to those of the physical mixture. In particular, markers of the crystalline phase of cladribine (arrows on Figs. 4 and 5) cannot be found in the spectra of the inclusion complex.

The authors further find that their data suggest that, when part of an inclusion complex, cladribine is present in a different (non-crystalline) phase relative to that of pure crystalline cladribine and that direct interaction between cladribine molecules is prevented. Further, they note that the amorphous phase has to be attributed to the formation of molecular complexes where the interaction between cladribine and HPβCD shields cladribine molecules, thus preventing crystallization.

(d) Van Axel Castelli et al. also used nuclear magnetic resonance spectroscopy to better understand the molecular interactions in the cladribine/cyclodextrin complex. To obtain direct proof of complex formation, the authors conducted a 2D ROESY experiment, the results of which showed a typical inner portion of HPβCD, confirming that a host-guest inclusion complex had formed between cladribine and HPβCD. Further, the authors conducted ^{13}C CP-MAS NMR experiments and reported the spectra in Fig. 10 for cladribine (a), cladribine +

HPβCD physical mixture (b) and cladribine/ HPβCD complex (c). In the cladribine spectrum (Fig. 10a), the authors observed sharp peaks due to cladribine's high degree of crystallinity. The spectrum for the physical mixture (Fig. 10b) corresponds to the sum of the spectra of the two components, with no resonance peaks or line broadening, showing no intermolecular interaction in the mixture, the solid being composed of distinct ordered domains of each component. In the spectrum for the complex, no shift in the HPβCD signals are detected, whereas the cladribine resonances are broadened and only slightly detectable. The authors note that this indicates that no crystalline domains of cladribine are present.

(e) Van Axel Castelli et al. also conducted DSC and TGA thermal profiles for tablets of the cladribine/ HPβCD complex and found them comparable to those for the cladribine/ HPβCD complex itself. Moreover, even stressed tablets showed no notable differences in the DSC thermal profile, which demonstrated that they were storage stable even under less than ideal conditions.

(f) Van Axel Castelli et al. conclude that thermal analyses, vibrational analyses, and solid-state NMR all indicate that cladribine behaves differently when in the complex compared with the physical mixture or kneading product, while ROESY provides evidence for the existence of an internal complex between cladribine and HPβCD. They further conclude that tablets of the complex are not affected by their manufacturing from the complex itself and are storage stable. These tablets have been used in a successful clinical trial for oral treatment of patients with MS (CLARITY trial).

Information about the clinical trials of this product was presented at the interview and copies of several articles appearing on the internet are appended and listed on the accompanying Form PTO-1449. The product is expected to be the first marketed oral product for the treatment of multiple sclerosis.

In summary, applicants submit that the obviousness rejection based on Schultz et al. in view of Baert et al. is untenable and should be withdrawn. The data provided by Van Axel Castelli et al. conclusively show that cladribine, whether alone, in a physical mixture with HPβCD, or even in a cladribine/HPβCD complex, decomposes at temperatures far lower than those used by Baert et al. for melt extruding drugs with the same cyclodextrin. The data further show that heating a

physical mixture of cladribine with HPβCD to high temperatures does not result in a complex of cladribine and in fact the cladribine in the mixture decomposes long before the melting point for HPβCD is reached. Thus, the Baert et al. process is not suitable for making a melt extrudate of cladribine with hydroxypropyl-β-cyclodextrin and moreover such a product prepared according to Baert et al. would not contain a complex of cladribine with the cyclodextrin as claimed in this application. The Schultz et al. oral dosage form prepared by the Baert et al. process simply cannot contain a cladribine/cyclodextrin complex.

Claims 82-98 are drawn to a product-by-process. These claims have been amended above and now depend directly or indirectly from Claim 1 and thus contain all of the Claim 1 limitations. Applicants have shown that the Claim 1 composition is free of the art, therefore, the product-by-process claims are also patentable over the art.

CONCLUSION

In view of the foregoing, it is believed that all record rejections have been overcome. Further, favorable action in the form of a Notice of Allowance is believed to be in order and is earnestly solicited.

In the event that there are any remaining issues which could be resolved in a telephone discussion, the Examiner is urged to telephone the undersigned at the number given below so that such issues can be promptly resolved.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: July 6, 2009

By: 
Mary Katherine Baumeister
Registration No. 26254

P.O. Box 1404
Alexandria, VA 22313-1404
703 836 6620

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	**MAIL STOP RCE**
Nicholas S. Bodor et al.	)	Group Art Unit: 1623
Application No.: 10/551,205	)	Examiner: JONATHAN S LAU
Filing Date: November 14, 2006	)	Confirmation No.: 4092
Title: ORAL FORMULATIONS OF CLADRIBINE	)	

PETITION FOR EXTENSION OF TIME

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The following extension of time is requested to: extend the period for response to the Office Action dated January 7, 2009 for

Three Months to July 7, 2009 ☒ $ 1110 ☐ $ 555

☐ The shortened statutory period has been reset by an Advisory Action dated _____.

☐ An Extension fee in the amount of _____ is enclosed.

☐ Charge _____ to Deposit Account No. 02-4800.

☒ Charge $ 1110 to credit card.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17 and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: July 6, 2009

By: Mary Katherine Baumeister
Mary Katherine Baumeister
Registration No. 26254

P.O. Box 1404
Alexandria, VA 22313-1404
703 836 6620

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	**MAIL STOP RCE**
Nicholas S. Bodor et al.	Group Art Unit: 1623
Application No.: 10/551,205	Examiner: JONATHAN S LAU
Filed: November 14, 2006	Confirmation No.: 4092
For: ORAL FORMULATIONS OF CLADRIBINE	

FIFTH INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure as set forth in 37 C.F.R. § 1.56, the accompanying information is being submitted in accordance with 37 C.F.R. §§ 1.97 and 1.98. Applicants request the Examiner's consideration of the documents listed on the accompanying Form PTO-1449.

Pursuant to 37 C.F.R. § 1.98, a copy of each of the documents cited is enclosed.

This Statement, Form PTO-1449 and the listed documents are submitted before the mailing of a first Office Action after the filing of a Request for Continued Examination under 37 C.F.R. § 1.114. Continued examination is requested and the fee required under 37 C.F.R. § 1.17(e) accompanies the present submission.

These documents are not prior art. They are submitted to support positions taken and statements made at the interview of June 10, 2009, and in the accompanying Reply and Amendment.

It is respectfully requested that an Examiner-initialed copy of the accompanying Form PTO-1449 be returned to the undersigned with the next official communication.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: July 6, 2009

By: Mary Katherine Baumeister
Mary Katherine Baumeister
Registration No. 26254

P.O. Box 1404
Alexandria, VA 22313-1404
703 836 6620

Substitute for form 1449/PTO & 1449B/PTO

FIFTH
INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known

Application Number	10/551,205
Filing Date	November 14, 2006
First Named Inventor	Nicholas Bodor et al.
Examiner Name	JONATHAN S LAU
Attorney Docket No.	0056192-000024

U.S. PATENT DOCUMENTS

Examiner Initials	Document Number-Kind Code	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Figures Appear
	US-			
	US-			
	US-			
	US-			
	US-			
	US-			
	US-			
	US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials	Foreign Patent Document: Country Code[1], Number, Kind Code	Publication Date (MM-DD-YYYY)	Name of Patentee or Applicant of Cited Document	STATUS: Translation	Partial Translation	Eng. Lang. Summary	Search Report	IPER	Abstract	Cited in Spec. / Pg. No(s).	

[1]Enter Office that issued the document, by the two-letter code.

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials	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.
	VAN AXEL CASTELLI et al. "Characterisation of an Inclusion Complex Between Cladribine and 2-Hydroxypropyl-β-Cyclodextrin," *J. Pharm. Sci.*, Vol. 97, No. 9, September 2008, pp. 3897-3906, Wiley InterScience and the American Pharmacists Association, US
	Drugs.com, "Oral Investigational Treatment Cladribine Tablets for Multiple Sclerosis Significantly Reduced Relapse Rate in Phase III Pivotal Trial," accessed online February 3, 2009, at http://www.drugs.com/clinical_trials/oral-investigational-cladribine-multiple-sclerosis
	"Serono's Oral Cladribine for the Treatment of Multiple Sclerosis Awarded Fast Track Status by FDA", accessed online February 3, 2009 at http://prnewswire.com
	Merck Serono News Release, "Two-year Phase III Data Presented at AAN 61st Annual Meeting Show Positive Outcome of Cladribine Tablets in Patients with Multiple Sclerosis", April 29/30, 2009, available online.

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with M.P.E.P. § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

Electronic Patent Application Fee Transmittal

Application Number:	10551205
Filing Date:	14-Nov-2006
Title of Invention:	Oral formulations of cladribine
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Filer:	Mary Katherine Baumeister/Diana Francis
Attorney Docket Number:	0056192-000024

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

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:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1110	1110

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for continued examination	1801	1	810	810
		Total in USD ($)		**1920**

Electronic Acknowledgement Receipt

EFS ID:	5646212
Application Number:	10551205
International Application Number:	
Confirmation Number:	4092
Title of Invention:	Oral formulations of cladribine
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Customer Number:	21839
Filer:	Mary Katherine Baumeister/Diana Francis
Filer Authorized By:	Mary Katherine Baumeister
Attorney Docket Number:	0056192-000024
Receipt Date:	06-JUL-2009
Filing Date:	14-NOV-2006
Time Stamp:	14:56:32
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1920
RAM confirmation Number	1123
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	le Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Request for Continued Examination (RCE)	005619224RCE.pdf	90784 0a3f977b11066c7fb83255ee7b1eda088f93eb31	no	2
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
2	Amendment Submitted/Entered with Filing of CPA/RCE	005619224AMEND.pdf	1075305 33c26f229b011365e5e3f8da0e88f02f1aef5898	no	23
Warnings:					
Information:					
3	Extension of Time	005619224EOT.pdf	37913 0bf008b044c44e1fce154c47dc27c157b8e10f31	no	1
Warnings:					
Information:					
4	Transmittal Letter	005619224IDS.pdf	55438 5f88cc209e05e028c3f58fbca301aab1d9fd971e	no	2
Warnings:					
Information:					
5	Information Disclosure Statement (IDS) Filed (SB/08)	005619224FM1449.pdf	83648 7e31fed9accd04c2b5c599422b5d8bc937dc239e	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
6	NPL Documents	005619224doc1.pdf	818436 2d1a660202450a9cbfbdab4378aa8b5a753d6bd9	no	10
Warnings:					
Information:					
7	NPL Documents	005619224doc2.pdf	193153 deb023f1e5aa2f00f86a21ae7c810ddae960c627	no	2
Warnings:					
Information:					
8	NPL Documents	005619224doc3.pdf	161326 b970aa5aba2e459980ba714c93c013f77b5f14d8	no	2
Warnings:					
Information:					

9	NPL Documents	005619224doc4.pdf	255777 a7ffcf31509126f75ce46cfaa0d81ffd476489a8	no	5
Warnings:					
Information:					
10	Fee Worksheet (PTO-875)	fee-info.pdf	32200 133981f4df8125f6615ec7c18bdf74b586c6197e	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	2803980	

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.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/551,205	11/14/2006	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 07/06/2009	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 56	Minus	** 78	= 0	X $ =		OR	X $52=	0
Independent (37 CFR 1.16(h))	* 5	Minus	***6	= 0	X $ =		OR	X $220=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/PAUL M. STANBACK/

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.
10/551,205	11/14/2006	Nicholas S. Bodor	0056192-000024	4092

21839 7590 09/17/2009
BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
LAU, JONATHAN S	
ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
09/17/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/551,205	BODOR ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,8,9,11-14,20,21,23-28,32,33,35,56,57,63,64 and 67-98* is/are pending in the application.

4a) Of the above claim(s) *13,14,20,21,23-28,32,33,35 and 67-81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,8,9,11,56,57,63,64 and 82-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

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)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 page / 06 July 2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06 July 2009 has been entered.

This Office Action is responsive to Applicant's Amendment and Remarks, filed 06 July 2009, in which claims 1 and 56 are amended to change the scope and breadth of the claim; claims 8, 9, 11, 63, 64 and 82 are amended to change dependency; claims 3-7, 10, 15-19, 22, 29-31, 34, 58-62 and 65 are canceled; and withdrawn claims 13, 20, 21, 23, 25, 32, 33 and 67 are amended.

This application is the national stage entry of PCT/US04/09387, filed 26 Mar 2004; and claims benefit of provisional application 60/458,922, filed 28 Mar 2003; and claims benefit of provisional application 60/484,756, filed 02 July 2003; and claims benefit of provisional application 60/541,247, filed 04 Feb 2004.

The filing date of the instant claims 12, 83, 85 and 89 are deemed to be the filing date of the instant application which is the filing date of PCT/US04/09387, 26 Mar 2004.

The filing date of instant claims 1, 2, 8, 9, 11, 56, 57, 63, 64, 82, 84 and 86-98 are deemed to be the filing date of provisional application 60/541,247, filed 04 Feb 2004.

Claims 1, 2, 8, 9, 11-14, 20, 21, 23-28, 32, 33, 35, 56, 57, 63, 64 and 67-98 are pending in the current application. Claims 13, 14, 20, 21, 23-28, 32, 33, 35 and 67-81, drawn to non-elected inventions, are withdrawn. Claims 1, 2, 8, 9, 11, 56, 57, 63, 64 and 82-98 are examined on the merits herein.

Rejections Withdrawn

Applicant's Amendment and Remarks, filed 06 July 2009, with respect to claims 1-12, 56-66 and 82-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schultz et al. (US Patent 6,194,395, published 27 Feb 2001, of record) in view of Baert et al. (WIPO Publication WO97/18839, published 29 May 1997, of record) has been fully considered and is persuasive, as claims 3-7, 10, 58-62 and 65 are canceled and Applicant's remarks supported by the evidence of Van Axel Castelli et al. provided by Applicant in IDS mailed 06 July 2009 is persuasive that the product taught by Schultz et al. in view of Baert et al. is structurally different from the instant invention as claimed and therefore the product taught by Schultz et al. in view of Baert et al. does not teach all limitations of the of instant invention as claimed.

This rejection has been **withdrawn**.

The following are new grounds of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented 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. Patentability shall not be negatived by the manner in which the invention was made.

Amended Claims 1, 2, 8, 9, 11, 56, 57, 63, 64 and 82-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schultz et al. (US Patent 6,194,395, published 27 Feb 2001, of record) in view of Wrenn Jr. (US Patent 6,174,873, issued 16 Jan 2001, cited in PTO-892) and in view of Loftsson et al. (US Patent 6,699,849, filed 16 Feb 1999, cited in PTO-892).

Schultz et al. discloses a solid pharmaceutical oral dosage form of cladribine comprising cladribine and cyclodextrin (column 2, lines 31-39). Schultz et al. teaches β-cyclodextrins are known to possess the ability to form inclusion complexes and to have concomitant solubilizing properties (column 2, lines 10-15). Schultz et al. discloses the use of β-cyclodextrins (column 2, lines 56-58) and derivatives wherein one or more cyclodextrin hydroxy groups are replaced with groups such as hydroxypropyl (column 3, lines 26-27). Schultz et al. discloses the solid oral dosage form in the form of a tablet (column 5, lines 37-38) including the excipients sorbitol and magnesium stearate (column 6, lines 2-7). Schultz et al. discloses an oral dosage form comprising up to 15 mg cladribine and cyclodextrin from 100 to 500 mg, which would lead one of skill in the art to instantly envision a cladribine to cyclodextrin ratio ranging from 15 mg:100 mg to 15mg:500 mg, or 1:6.67 to 1:33.3 by weight (column 6, lines 23-31). Schultz et al.

implicitly discloses an oral dosage form comprising up to 15 mg cladribine and cyclodextrin from 100 to 500 mg, or a cladribine to cyclodextrin ratio ranging from 1:6.67 to 1:33.3 by weight (column 6, lines 23-31).

Schultz et al. does not specifically disclose the composition comprising no significant amount of free crystalline cladribine therein (instant claims 1). Schultz et al. does not specifically disclose the composition corresponding to a point located on the curve of a phase solubility diagram for saturated complex cladribine-cyclodextrin complexes, said curve defining complex saturated complexes of cladribine in varying concentrations of the cyclodextrin (instant claim 11). Schultz et al. does not specifically disclose the complex consisting of (a) an amorphous inclusion complex of cladribine with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex (instant claim 56). Schultz et al. does not specifically disclose the composition comprising a cladribine to cyclodextrin ratio from about 1:10 to about 1:16 (instant claims 6, 7, 10, 61, 62 and 65), or a ratio of about 1:14 (instant claims 8 and 63) or about 1:11 (instant claims 9 and 64). Schultz et al. does not specifically disclose the complex wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b) (instant claims 12 and 66). Schultz et al. does not specifically disclose the product-by-process wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process (instant claim 91 and 93), to give a cladribine to cyclodextrin ratio of 1:14.38. Schultz et al. does not specifically disclose

the product-by-process wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process (instant claim 92), to give a cladribine to cyclodextrin ratio of 1:10.55.

Wrenn Jr. teaches solid formulations for oral administration of adenosine analogs (abstract). Wrenn Jr. teaches the adenosine analogs include cladribine (column 6, lines 35-40). Wrenn Jr. teaches it is desirable to improve the solubility and absorption characteristics of poorly water soluble drugs by formulating the adenosine analog in an amorphous form together with solubilizing excipients (column 12, lines 25-30). Wrenn Jr. teaches the stabilization by absorption using a polymer that prevents recrystallization and the combination of the amorphous form and the solubilizing characteristics of the excipients enhances the solubility of the adenosine analog, and the amorphous drug complex may be formulated into a tablet system (column 12, lines 30-40).

Loftsson et al. teaches it is known in the art that substituted cyclodextrins show an increased aqueous solubility and that such chemical modification transforms crystalline cyclodextrins into amorphous mixtures increasing their aqueous solubility (column 1, lines 35-45). Loftsson et al. teaches it is known in the art that in aqueous solution cyclodextrins form complexes with many drugs (column 2, lines 1-10). Loftsson et al. teaches various methods of preparation of drug-cyclodextrin complexes are known in the art, including preparation of a solid complex by evaporation or freeze-drying following formation of the complex by equilibration (column 2, lines 20-40). Loftsson et al. teaches purine derivatives are compatible with said cyclodextrin complexes (column 9, lines 50-55).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine Schultz et al. in view of Wrenn Jr. and in view of Loftsson et al. Schultz et al. teaches solid formulations for oral administration of cladribine and cyclodextrin. Wrenn Jr. is drawn the field of solid formulations for oral administration of adenosine analogs such as cladribine. Loftsson et al. teaches the level of skill in the art with regard to cyclodextrin complexes including complexes with purine derivatives. One of ordinary skill in the art would have been motivated to combine Schultz et al. in view of Wrenn Jr. and in view of Loftsson et al. because Schultz et al. teaches Schultz et al. teaches undesirable recrystallization of cladribine in tissue may occur and damage the surrounding tissue and that complexes with cyclodextrin are known to solubilize the compound, Wrenn Jr. teaches it is desirable to improve the solubility and absorption characteristics of poorly water soluble drugs by formulating the adenosine analog in an amorphous form together with solubilizing excipients, and Loftsson et al. teaches it is known in the art that complexes with substituted cyclodextrin give amorphous mixtures increasing their aqueous solubility. One of ordinary skill in the art would have a reasonable expectation of success in combining Schultz et al. in view of Wrenn Jr. and in view of Loftsson et al. to render obvious a product that meets all limitation of the instant invention because Wrenn Jr. teaches the stabilization of the adenosine analog by absorption using a polymer that prevents recrystallization and Loftsson et al. teaches modified cyclodextrins that form amorphous mixtures and preparation of a solid complex by evaporation or freeze-drying, which is expected to give a non-crystalline product. Schultz et al. in view of Wrenn Jr. and in view of Loftsson et al. does not teach the

specific cladribine to cyclodextrin ratios of 1:14.38 or 1:10.55, however these ratios are encompassed by the prior art and Schultz et al. teaches it is within the level of skill in the art to optimize the ratio of cyclodextrin relative too cladribine (column 4, lines 35-45). See also MPEP 2144.05 II.A, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical." One of ordinary skill in the art would be motivated to optimize the cladribine to cyclodextrin ratio to give the composition comprising no significant amount of free crystalline cladribine therein because Schultz et al. teaches undesirable recrystallization of cladribine in tissue may occur and damage the surrounding tissue and that complexes with cyclodextrin are known to solubilize the compound (Schultz et al. column 2, lines 1-15). Schultz et al. in view of Wrenn Jr. and in view of Loftsson et al. does not specifically disclose the complex wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b). However, Loftsson et al. teaches formation of an inclusion complex from a non-inclusion complex in an aqueous solution is an equilibrium process, and the position of this equilibrium is dependent on the concentrations of the cladribine and cyclodextrin.

Claims 82-90 and 94-98 are drawn to a product-by-process. The disclosed product is substantially identical to the instantly claimed product-by-process, a pharmaceutical solid oral dosage form comprising an amorphous inclusion complex of cladribine and cyclodextrin and a non-inclusion complex of an amorphous cladribine

and an amorphous cyclodextrin. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed. The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.). See MPEP 2113.

Conclusion

No claim is found to be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jonathan Lau
Patent Examiner
Art Unit 1623

/Shaojia Anna Jiang/
Supervisory Patent Examiner
Art Unit 1623

Notice of References Cited	Application/Control No. 10/551,205	Applicant(s)/Patent Under Reexamination BODOR ET AL.	
	Examiner Jonathan S. Lau	Art Unit 1623	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,174,873	01-2001	Wrenn, Jr., Simeon M.	514/45
*	B	US-6,699,849	03-2004	Loftsson et al.	514/58
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10551205	BODOR ET AL.
	Examiner	Art Unit
	Jonathan S Lau	1623

✓	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	11/26/2007	03/26/2008	01/02/2009	09/10/2009					
	1	÷	✓	✓	✓					
	2	÷	✓	✓	✓					
	3	÷	✓	✓	-					
	4	÷	✓	✓	-					
	5	÷	✓	✓	-					
	6	÷	✓	✓	-					
	7	÷	✓	✓	-					
	8	÷	✓	✓	✓					
	9	÷	✓	✓	✓					
	10	÷	✓	✓	-					
	11	÷	✓	✓	✓					
	12	÷	✓	✓	✓					
	13	÷	N	N	N					
	14	÷	N	N	N					
	15	÷	N	N	-					
	16	÷	N	N	-					
	17	÷	N	N	-					
	18	÷	N	N	-					
	19	÷	N	N	-					
	20	÷	N	N	N					
	21	÷	N	N	N					
	22	÷	N	N	-					
	23	÷	N	N	N					
	24	÷	N	N	N					
	25	÷	N	N	N					
	26	÷	N	N	N					
	27	÷	N	N	N					
	28	÷	N	N	N					
	29	÷	N	N	-					
	30	÷	N	N	-					
	31	÷	N	N	-					
	32	÷	N	N	N					
	33	÷	N	N	N					
	34	÷	N	N	-					
	35	÷	N	N	N					
	36	-	-	-	-					

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10551205	BODOR ET AL.
	Examiner	Art Unit
	Jonathan S Lau	1623

✓	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	11/26/2007	03/26/2008	01/02/2009	09/10/2009					
	37	-	-	-	-					
	38	-	-	-	-					
	39	-	-	-	-					
	40	-	-	-	-					
	41	-	-	-	-					
	42	-	-	-	-					
	43	-	-	-	-					
	44	-	-	-	-					
	45	-	-	-	-					
	46	-	-	-	-					
	47	-	-	-	-					
	48	-	-	-	-					
	49	-	-	-	-					
	50	-	-	-	-					
	51	-	-	-	-					
	52	-	-	-	-					
	53	-	-	-	-					
	54	-	-	-	-					
	55	-	-	-	-					
	56	÷	✓	✓	✓					
	57	÷	✓	✓	✓					
	58	÷	✓	✓	-					
	59	÷	✓	✓	-					
	60	÷	✓	✓	-					
	61	÷	✓	✓	-					
	62	÷	✓	✓	-					
	63	÷	✓	✓	✓					
	64	÷	✓	✓	✓					
	65	÷	✓	✓	-					
	66	÷	✓	✓	-					
	67	÷	N	N	N					
	68	÷	N	N	N					
	69	÷	N	N	N					
	70	÷	N	N	N					
	71	÷	N	N	N					
	72	÷	N	N	N					

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10551205	BODOR ET AL.
	Examiner	Art Unit
	Jonathan S Lau	1623

✓	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	11/26/2007	03/26/2008	01/02/2009	09/10/2009					
	73	÷	N	N	N					
	74	÷	N	N	N					
	75	÷	N	N	N					
	76	÷	N	N	N					
	77	÷	N	N	N					
	78	÷	N	N	N					
	79	÷	N	N	N					
	80	÷	N	N	N					
	81	÷	N	N	N					
	82	÷	✓	✓	✓					
	83	÷	✓	✓	✓					
	84	÷	✓	✓	✓					
	85	÷	✓	✓	✓					
	86	÷	✓	✓	✓					
	87	÷	✓	✓	✓					
	88	÷	✓	✓	✓					
	89	÷	✓	✓	✓					
	90	÷	✓	✓	✓					
	91	÷	✓	✓	✓					
	92	÷	✓	✓	✓					
	93	÷	✓	✓	✓					
	94	÷	✓	✓	✓					
	95	÷	✓	✓	✓					
	96	÷	✓	✓	✓					
	97	÷	✓	✓	✓					
	98	÷	✓	✓	✓					

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10551205	BODOR ET AL.
	Examiner	Art Unit
	Jonathan S Lau	1623

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST - inventor name search (Nicholas Bodor; Yogesh Dandiker)	3/26/2008	JSL
EAST - see attached notes	3/26/2008	JSL
Google Scholar - see attached notes	3/26/2008	JSL
EAST - see attached notes	9/10/2009	JSL
Google Scholar - see attached notes	9/10/2009	JSL
STN - CAPlus file - see attached notes	9/10/2009	JSL

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

Absorbable stent comprising coating for controlling degradation and maintaining pH ...
JZ Zhao - US Patent App. 11/297,944, 2005 - Google Patents
... everoli- mus, pimecrolimus, tacrolimus, paclitaxel, **cladribine** as well as **...** zirconia, yittrium tetragonal polycrystalline zirconia, **amorphous** silicon, **amorphous ...**
All 4 versions

USE OF TRI-SUBSTITUTED GLYCEROL COMPOUNDS FOR THE TREATMENT OF ...
A ZANDER, F AYUKETANG, W Richter, L Weber ... - 2008 - freepatentsonline.com
... The term "**amorphous**", as used herein, refers to a solid in which **...** non-Hodgkin lymphomas, AML), clofarabine (ALL), pentostatine (CLL), and **cladribine** (CLL), and **...**
All 3 versions

Polymeric stent having modified molecular structures in both the hoops and selected ...
R Burgermeister, JH Contiliano, V Dave, Y ... - US Patent App. 11/440,807, 2006 - Google Patents
... internal structure modifications may be utilized to create devices having specific gross characteristics such as crys- talline and **Amorphous** morphology and **...**
All 6 versions

Polymeric stent having modified molecular structures in the flexible connections
R Burgermeister, JH Contiliano, V Dave, Y ... - US Patent App. 11/441,370, 2006 - Google Patents
... internal structure modifications may be utilized to create devices having specific gross characteristics such as crys- talline and **amorphous** morphology and **...**
All 5 versions

Drug-eluting articles with improved drug release profiles
R Falotico, JZ Zhao - US Patent App. 11/300,821, 2005 - Google Patents
... prepared from D-, L-PLA and PGA are typically **amorphous** in nature **...** molecular weight drugs, such as mycophenolate acid (MPA), estradiol, **cladribine**, probucol, etc **...**
All 4 versions

Oral administration of adenosine analogs- •pharmcast.com
SM Wrenn Jr - US Patent 6,174,873, 2001 - Google Patents
... deaminase and 2-chloro-2'-deoxyadenosine (also known as **cladribine** or 2CDA **...** the solubility of other- wise insoluble adenosine analogs in an **amorphous** state in **...**
Cited by 3 - Related articles - All 7 versions

Polymeric stent having modified molecular structures in the flexible connectors and in the ...
R Burgermeister, JH Contiliano, V Dave, Y ... - US Patent App. 11/440,774, 2006 - Google Patents
... internal structure modifications may be utilized to create devices having specific gross characteristics such as crys- talline and **amorphous** morphology and **...**
All 6 versions

Polymeric stent having modified molecular structures in the flexible connectors and the radial ...
R Burgermeister, JH Contiliano, V Dave, Y ... - US Patent App. 11/440,764, 2006 - Google Patents
... internal structure modifications may be utilized to create devices having specific gross characteristics such as crys- talline and **amorphous** morphology and **...**
All 6 versions

Hoogsteen vs. Watson-Crick Base Pairing: Incorporation of 2-Substituted Adenine-and 7- ...
N Ramzaeva, E Michalek, Z Kazimierczuk, F ... - Chemistry & Biodiversity, 2007 - interscience.wiley.com
... Synthetic 2-chloro-2'-deoxyadenosine (**cladribine**, Cl 2 A d , Leustatin ; 1a) [18–22] has gained considerable interest due to its toxicity toward T- and B **...**
Related articles - BL Direct - All 2 versions

USE OF ROLL COMPACTED PYROGENICALLY PRODUCED SILICON DIOXIDE IN ...
R Hofmann, A Gray, M Drechsler, P It - 2007 - freepatentsonline.com
... content, specific gravity, refractive index, color or **amorphous** form **...** cholera vaccine; chorionic gonadotropin; cidofovir; cisplatin; **cladribine**; clidinium bromide **...**
All 3 versions

◀ Goooooooooooooogle ▶
Result Page: **Previous** 1 2 3 4 5 6 7 8 9 10 11 12 13 **Next**

Scholar **All articles** Recent articles Results **1** - **10** of about **132**. (**0.09** sec)

Cyclodextrin cladribine formulations
TW Schultz, R Naeff... - US Patent 6,194,395, 2001 - Google Patents
... For example, suitable tablets may be prepared in the 65 conventional way having one or more of the following excipients: **Cladribine Cyclodextrin** 1 mg to 15 mg **...**
All 2 versions

Oral formulations of **cladribine**
NS Bodor, Y Dandiker - US Patent App. 10/551,205, 2004 - Google Patents
... Cl. A61K 31/724 (2006.01) C07H 3/06 (2006.01) (52) US Cl (57) ABSTRACT 514/58; 536/123.1 Provided are compositions of **cladribine** and **cyclodextrin** which are **...**
All 6 versions

[CITATION] ORAL FORMULATIONS OF **CLADRIBINE**
Y DANDIKER, NS BODOR

Pharmaceutical compositions comprising **cyclodextrins**
RPG Vandecruys - US Patent App. 09/445,297, 1999 - Google Patents
... to the total weight of drug compound, acid, **cyclodextrin** and organic **...** antineoplastic agents and antimetabo- lites (adriamycine, **cladribine**, dactinomycin, dauno **...**
Cited by 1 - Related articles - All 7 versions

Cyclodextrin-based materials, compositions and uses related thereto
SH Pun, NC Bellocq, ME Davis... - US Patent App. 10/681,745, 2003 - Google Patents
... 10,2004 (54) **CYCLODEXTRIN**-BASED MATERIALS, COMPOSITIONS AND USES RELATED THERETO (75) Inventors: Suzie Hwang Pun, Torrance, CA (US); Nathalie C. Bellocq **...**
All 2 versions

Pregelatinized starch in a controlled release formulation
RPG Vandecruys, EMJ Jans - US Patent App. 10/674,701, 2003 - Google Patents
... capecitabine, gemcitab- ine, mercaptopurine, thioguanine, **cladribine**, methotrexate; [0042 **...** this purpose, the recommended amount of **cyclodextrin** or derivatives **...**
All 9 versions

Pharmaceutical formulation of decitabine
C Tang, R Joshi-Hangal - US Patent App. 11/009,540, 2004 - Google Patents
... formulations. In particular, decitabine is formulated with a **cyclodextrin** compound to stabilize and/or enhance solubility of the drug. **...**
All 6 versions

Inhibitor of tumor metastasis or recurrence
K Sudo, T Houkan, P It - 1998 - freepatentsonline.com
... an emulsifier, a buffer, a preservative, **cyclodextrin**, sodium hydroxide etc. **...** butosin, calcium folinate, calcium levofolinate, **cladribine**, emitefur, fludarabine **...**
All 2 versions

Pharmaceutical formulation of cytidine analogs and derivatives
C Tang, R Joshi-Hangal - US Patent App. 11/010,189, 2004 - Google Patents
... In particular, the cytidine analog or derivative is formulated with a **cyclodextrin** compound to stabilize and/or enhance solubility of the drug. **...**
All 6 versions

Methods for treating carbonic anhydrase mediated disorders
JL Masferrer, JM O'neal - US Patent App. 10/367,384, 2003 - Google Patents
Page 1. US 20030220376A1 (19) United States (12) Patent Application Publication (io> Pub. NO.: US 2003/0220376 Al Masferrer et al. (43) Pub. Date: Nov. **...**
All 6 versions

Gooooooooooogle ▶
Result Page: 1 2 3 4 5 6 7 8 9 10 **Next**

cladribine cyclodextrin Search

Go to Google Home - About Google - About Google Scholar

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	1036	purine and cyclodextrin and complex and amorphous	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 13:47
S2	348	S1 and @ad<="20040204"	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 13:48
S3	1	"6,699,849".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 13:48
S4	1	purine and cyclodextrin and complex and amorphous	EPO; DERWENT	ADJ	ON	2009/09/10 13:48
S5	1	"20040186075".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 13:49
S8	1	S3 and purine and cyclodextrin and complex and amorphous and solid	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 13:53
S9	1	S5 and purine and cyclodextrin and complex and amorphous and solid	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 13:53
S10	1	"5,024,998".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 13:55
S11	1	S10 and purine and cyclodextrin and complex and amorphous and solid	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 13:56
S12	1	amorphous near3 cladribine	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 13:59
S13	1	"6174873".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 14:03
S15	1	S13 and (purine or cyclodextrin or complex or amorphous or solid)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 14:03
S16	1	(amorphous near9 cladribine) or (amorphous same cladribine)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 14:08
S17	4260	cladribine	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 14:23
S18	299	S17 and cyclodextrin and complex and amorphous and solid	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 14:23
S19	66	S18 and @ad<="20040204"	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 14:23
S20	1	cladribine and cyclodextrin and amorphous	EPO; DERWENT	ADJ	ON	2009/09/10 14:25

S21	420	(adenosine or purine or cladribine).ti,ab,bsum. and cyclodextrin and complex and amorphous and solid	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 14:28
S22	429	(adenosine or purine or cladribine).ti,ab,bsum. and cyclodextrin and (complex or inclusion) and amorphous and solid	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 14:28
S23	236	(adenosine or purine or cladribine).ti,ab,bsum. and cyclodextrin.ti,ab,bsum,clm. and (complex or inclusion) and amorphous and solid	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 14:29
S24	124	S23 and @ad<="20040204"	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 14:29
S25	1	"20040127404".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 14:45
S26	1	"5,773,423".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 14:55
S27	1	S26 and (purine or cyclodextrin or complex or amorphous or solid)	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 14:55
S28	235	(adenosine or purine or cladribine).ti,ab,bsum. and cyclodextrin.ti,ab,bsum. and (complex or inclusion) and amorphous and solid	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 14:57
S29	123	S28 and @ad<="20040204"	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 14:57
S30	6	(adenosine or purine or cladribine).ti,ab. and cyclodextrin.ti,ab,bsum. and (complex or inclusion) and amorphous and solid	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 14:57
S31	1	(adenosine or purine or cladribine).ti,ab. and cyclodextrin.ti,ab. and (complex or inclusion) and amorphous and solid	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 14:57
S32	5	(adenosine or purine or cladribine).ti,ab,bsum. and cyclodextrin.ti,ab. and (complex or inclusion) and amorphous and solid	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 14:58
L1	1	"6,194,395".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2009/09/10 17:12

EAST Search History (Interference)

<This search history is empty>

9/10/2009 5:51:50 PM
C:\Documents and Settings\jlau1\My Documents\EAST\Workspaces\10551205 - RCE.wsp

Substitute for form 1449/PTO & 1449B/PTO

FIFTH
INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known

Application Number	10/551,205
Filing Date	November 14, 2006
First Named Inventor	Nicholas Bodor et al.
Examiner Name	JONATHAN S LAU
Attorney Docket No.	0056192-000024

U.S. PATENT DOCUMENTS

Examiner Initials	Document Number-Kind Code	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Figures Appear
	US-			
	US-			
	US-			
	US-			
	US-			
	US-			
	US-			
	US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials	Foreign Patent Document: Country Code[1], Number, Kind Code	Publication Date (MM-DD-YYYY)	Name of Patentee or Applicant of Cited Document	STATUS: Translation	Partial Translation	Eng. Lang. Summary	Search Report	IPER	Abstract	Cited in Spec. / Pg. No(s).	

[1]Enter Office that issued the document, by the two-letter code.

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials	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.
/J.L./	VAN AXEL CASTELLI et al. "Characterisation of an Inclusion Complex Between Cladribine and 2-Hydroxypropyl-β-Cyclodextrin," *J. Pharm. Sci.*, Vol. 97, No. 9, September 2008, pp. 3897-3906, Wiley InterScience and the American Pharmacists Association, US
/J.L./	*Drugs.com*, "Oral Investigational Treatment Cladribine Tablets for Multiple Sclerosis Significantly Reduced Relapse Rate in Phase III Pivotal Trial," accessed online February 3, 2009, at http://www.drugs.com/clinical_trials/oral-investigational-cladribine-multiple-sclerosis
/J.L./	"Serono's Oral Cladribine for the Treatment of Multiple Sclerosis Awarded Fast Track Status by FDA", accessed online February 3, 2009 at http://prnewswire.com
/J.L./	Merck Serono News Release, "Two-year Phase III Data Presented at AAN 61st Annual Meeting Show Positive Outcome of Cladribine Tablets in Patients with Multiple Sclerosis", April 29/30, 2009, available online.

Examiner Signature	/Jonathan Lau/	Date Considered	09/10/2009

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with M.P.E.P. § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

Did you mean: ***pyrene*** cyclodextrin complex amorphous

Cyclodextrins in the pharmaceutical field
O Bekers, EV Uijtendaal, JH Beijnen, A Bult ... - Drug Development and Industrial Pharmacy, 1991 - informaworld.com
... action of the **cyclodextrin**-trans-glycosidase enzyme on a medium containing starch. **...**
entirely or at least partially into the cavity, an inclusion **complex** may be **...**
Cited by 106 - Related articles - All 3 versions

High-energy **cyclodextrin** complexes
T Loftsson, M Masson, E Stefansson - US Patent App. 10/750,340, 2004 - Google Patents
... administering the **cyclodextrin**-drug **complex** thus obtained **...** trin, hydroxypropyl-y-
cyclodextrin and y-**cyclodextrin**. **...** for use herein are **purine** derivatives, which **...**
Related articles - All 6 versions

Cyclodextrin complexes of benzodiazepines
T Loftsson, M Masson, E Stefansson - US Patent 6,699,849, 2004 - Google Patents
... can transform the crystal- line **cyclodextrins** into **amorphous** mixtures increasing **...**
are formed or 15 broken during the drug-**cyclodextrin complex** formation, the **...**
Related articles - All 2 versions

... and characterisation of sulfated amphiphilic α-, β-and γ-**cyclodextrins**: application to the ...
A Dubes, G Degobert, H Fessi, H Parrot- ... - Carbohydrate research, 2003 - Elsevier
... 1) is an acyclic synthetic analogue of **purine** nucleosides with **...** and coworkers[28.]
who demonstrated that β-**cyclodextrin** forms a 1:1 **complex** with acyclovir **...**
Cited by 6 - Related articles - All 4 versions

Production of podophyllotoxin from Podophyllum hexandrum: a potential natural product for ...
A Giri, M Lakshmi Narasu - Cytotechnology, 2000 - Springer
... **purine** synthesis and inhibition of **purine** incorporation into **...** Podophyllum resin is
an **amorphous** powder, light **...** β-**cyclodextrin complex** resulted in enhanced podo **...**
Cited by 27 - Related articles - BL Direct - All 5 versions

2, 6, 9-Substituted **purine** derivatives and their use in the treatment of proliferative disorders
PM Fischer, M Jarman, T McDonald, B Nutley ... - US Patent App. 10/742,237, 2003 - Google Patents
... seeks to provide new 2,6,9- substituted **purine** derivatives, particularly **...** Formation
of a drug- **cyclodextrin complex** may modify the solubility, dissolution rate **...**
All 6 versions

Pharmaceutical formulations for parenteral use
NS Bodor - US Patent 5,024,998, 1991 - Google Patents
... from sweetener hydrolysis 'Tuttle also describes use of 2,6-di-0-methyl-/3-**cyclodextrin**
and 2,3,6-tri-0-methyl-/3-**cyclodextrin** to form the inclusion **complex**. **...**
Cited by 13 - Related articles - All 6 versions

COMBINATION OF CRYSTALLINE FORM OF A RIBOFURANOSYLURONAMIDE ...
T SILK, J SMITH - 2003 - freepatentsonline.com
... is capable of dissolving both **amorphous** 6- [(2, 2 **...** 4-piperidyl] ureido}
ethyl)-9H-**purine**- 2-carboxamide **...** Formation of a drug-**cyclodextrin complex** may modify **...**

All 4 versions

CRYSTALLINE FORM OF A RIBOFURANOSYLURONAMIDE DERIVATIVE; A HUMAN ...
T SILK, J SMITH - 2003 - freepatentsonline.com
... is capable of dissolving both **amorphous** 6- [(2, 2 **...** 4-piperidyl] ureido} ethyl)-9H-**purine**-2-carboxamide **...** Formation of a drug-**cyclodextrin complex** may modify the **...**
All 4 versions

Redox systems for brain-targeted drug delivery
NS Bodor - US Patent 5,017,566, 1991 - Google Patents
... from sweetener hydrolysis 'Turtle also describes use of 2,6-di-O-methyl-£-**cyclodextrin** and 2,3,6-tri-O-methyl £-**cyclodextrin** to form the inclu- sion **complex**. **...**
Cited by 1 - Related articles - All 5 versions

Did you mean to search for: ***pyrene*** cyclodextrin complex amorphous

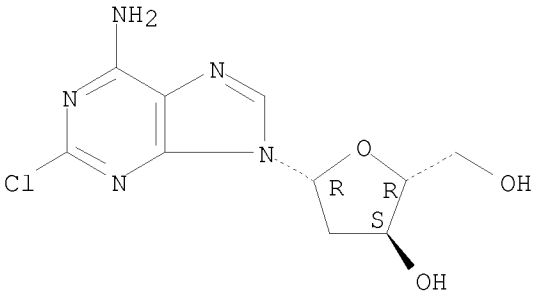
Gooooooooogle ▶
Result Page: 1 2 3 4 5 6 7 8 9 10 **Next**

```
Connecting via Winsock to STN



Welcome to STN International!  Enter x:x

LOGINID:ssptajsl1623

PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2


* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page for STN Seminar Schedule - N. America
 NEWS  2  DEC 01   ChemPort single article sales feature unavailable
 NEWS  3  JUN 01   CAS REGISTRY Source of Registration (SR) searching
                   enhanced on STN
 NEWS  4  JUN 26   NUTRACEUT and PHARMAML no longer updated
 NEWS  5  JUN 29   IMSCOPROFILE now reloaded monthly
 NEWS  6  JUN 29   EPFULL adds Simultaneous Left and Right Truncation
                   (SLART) to AB, MCLM, and TI fields
 NEWS  7  JUL 09   PATDPAFULL adds Simultaneous Left and Right
                   Truncation (SLART) to AB, CLM, MCLM, and TI fields
 NEWS  8  JUL 14   USGENE enhances coverage of patent sequence location
                   (PSL) data
 NEWS  9  JUL 27   CA/CAplus enhanced with new citing references
 NEWS 10  JUL 16   GBFULL adds patent backfile data to 1855
 NEWS 11  JUL 21   USGENE adds bibliographic and sequence information
 NEWS 12  JUL 28   EPFULL adds first-page images and applicant-cited
                   references
 NEWS 13  JUL 28   INPADOCDB and INPAFAMDB add Russian legal status data
 NEWS 14  AUG 10   Time limit for inactive STN sessions doubles to 40
                   minutes
 NEWS 15  AUG 18   COMPENDEX indexing changed for the Corporate Source
                   (CS) field
 NEWS 16  AUG 24   ENCOMPLIT/ENCOMPLIT2 reloaded and enhanced
 NEWS 17  AUG 24   CA/CAplus enhanced with legal status information for
                   U.S. patents
 NEWS 18  SEP 09   50 Millionth Unique Chemical Substance Recorded in
                   CAS REGISTRY

 NEWS EXPRESS MAY 26 09 CURRENT WINDOWS VERSION IS V8.4,
              AND CURRENT DISCOVER FILE IS DATED 06 APRIL 2009.

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
 NEWS LOGIN    Welcome Banner and News Items

Enter NEWS followed by the item number or name to see news on that
specific topic.

  All use of STN is subject to the provisions of the STN customer
  agreement.  This agreement limits use to scientific research.  Use
  for software development or design, implementation of commercial
  gateways, or use of CAS and STN data in the building of commercial
  products is prohibited and may result in loss of user privileges
  and other penalties.
```

```
* * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 13:38:46 ON 10 SEP 2009

=> b reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.22       0.22

FILE 'REGISTRY' ENTERED AT 13:38:55 ON 10 SEP 2009
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2009 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:    8 SEP 2009  HIGHEST RN 1181456-82-5
DICTIONARY FILE UPDATES:   8 SEP 2009  HIGHEST RN 1181456-82-5

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 26, 2009.

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=> e cladribine/cn
E1            1     CLADRASTIN/CN
E2            1     CLADRASTIN 7-O-Β-D-GLUCOSIDE/CN
E3            1 --> CLADRIBINE/CN
E4            1     CLADRIBINE 5'-DIPHOSPHATE/CN
E5            1     CLADRIBINE 5'-MONOPHOSPHATE/CN
E6            1     CLADRIBINE 5'-TRIPHOSPHATE/CN
E7            1     CLADRIN/CN
E8            1     CLAENONE/CN
E9            1     CLAF EX/CN
E10           1     CLAF HS GRADE/CN
E11           1     CLAF HS(T)/CN
E12           1     CLAF MS(T)/CN

=> s e3
L1            1 CLADRIBINE/CN

=> d l1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2009 ACS on STN
RN   4291-63-8  REGISTRY
ED   Entered STN:  16 Nov 1984
CN   Adenosine, 2-chloro-2'-deoxy-  (CA INDEX NAME)
OTHER NAMES:
```

CN 2-CdA
CN 2-Chloro-2'-deoxy-β-adenosine
CN 2-Chloro-2'-deoxyadenosine
CN 2-Chloro-6-amino-9-(2-deoxy-β-D-erythro-pentofuranosyl)purine
CN 2-Chlorodeoxyadenosine
CN Biodribin
CN Cladarabine
CN ***Cladribine***
CN CldAdo
CN Jk 6251
CN Leustat
CN Leustatin
CN NSC 105014
CN NSC 105014-F
CN RWJ 26251
FS STEREOSEARCH
DR 24757-90-2
MF C10 H12 Cl N5 O3
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DRUGU, EMBASE, HSDB*, IMSCOSEARCH, IMSDRUGNEWS, IMSPATENTS, IMSPRODUCT, IMSRESEARCH, IPA, MEDLINE, MRCK*, PHAR, PROMT, PROUSDDR, PS, RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1482 REFERENCES IN FILE CA (1907 TO DATE)
47 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1491 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> e cyclodextrin/cn
E1 1 CYCLODEX G-TA/CN
E2 1 CYCLODEXTRAN GLUCANOTRANSFERASE/CN
E3 1 --> CYCLODEXTRIN/CN
E4 2 CYCLODEXTRIN ABC TRANSPORTER, PERMEASE PROTEIN (STREPTOCOCCUS AGALACTIAE STRAIN A909)/CN
E5 1 CYCLODEXTRIN BETA W 7M1.8/CN
E6 1 CYCLODEXTRIN CH/CN
E7 1 CYCLODEXTRIN GLUCANOTRANSFERASE/CN
E8 1 CYCLODEXTRIN GLUCANOTRANSFERASE (ARCHAEOGLOBUS FULGIDUS STRA

```
                  IN 7324 GENE CGT)/CN
E9          1     CYCLODEXTRIN GLUCANOTRANSFERASE (BACILLUS G1-2004 PRECURSOR)
                  /CN
E10         1     CYCLODEXTRIN GLUCANOTRANSFERASE (BACILLUS STRAIN G1 PRECURSO
                  R)/CN
E11         1     CYCLODEXTRIN GLUCANOTRANSFERASE (PYROCOCCUS KODAKARAENSIS ST
                  RAIN KOD1 GENE CGT PRECURSOR)/CN
E12         1     CYCLODEXTRIN GLUCANOTRANSFERASE (STREPTOCOCCUS PYOGENES STRA
                  IN MGAS10270 GENE AMYA)/CN

=> s e3
L2          1 CYCLODEXTRIN/CN

=> d l2

L2   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2009 ACS on STN
RN   12619-70-4  REGISTRY
ED   Entered STN:  16 Nov 1984
CN   Cyclodextrin  (CA INDEX NAME)
OTHER NAMES:
CN   β-100
CN   Celdex
CN   Celdex CH 20
CN   Celdex CH 30
CN   Celdex SH 20
CN   Celdex SH 40
CN   Celdex SL 20
CN   Celdex TB 50
CN   Cycloamylose
CN   Cyclodextrins
CN   Rhodocap L 20
CN   Ringdex P
CN   Ringdex PK
CN   Schardinger dextrin
DR   856575-11-6, 131076-21-6, 100091-36-9
MF   Unspecified
CI   COM, MAN
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, BIOSIS, BIOTECHNO, CA, CAPLUS,
       CASREACT, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DRUGU,
       EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, NAPRALERT, PIRA, PROMT, TOXCENTER,
       USPAT2, USPATFULL, USPATOLD

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

            7381 REFERENCES IN FILE CA (1907 TO DATE)
            1869 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
            7411 REFERENCES IN FILE CAPLUS (1907 TO DATE)


=> b caplus
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                     ENTRY    SESSION
FULL ESTIMATED COST                                  15.28      15.50

FILE 'CAPLUS' ENTERED AT 13:39:31 ON 10 SEP 2009
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
```

FILE COVERS 1907 - 10 Sep 2009 VOL 151 ISS 11
FILE LAST UPDATED: 9 Sep 2009 (20090909/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2009
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2009

CAplus now includes complete International Patent Classification (IPC)
reclassification data for the third quarter of 2009.

This file contains CAS Registry Numbers for easy and accurate
substance identification.

The ALL, BIB, MAX, and STD display formats in the CA/CAplus family
of databases have been updated to include new citing references
information. This enhancement may impact record import into
database management software. For additional information, refer
to NEWS 9.

```
=> s l1 and l2
          1493 L1
          7414 L2
L3          12 L1 AND L2

=> s l3 and py<=2004
      25141550 PY<=2004
L4            6 L3 AND PY<=2004

=> d l3 ibib abs 1-12
```

L3 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2009:1016541 CAPLUS
TITLE: Implantable biodegradable medical good impregnated with magnetic particles and optionally drugs for treatment following tumor surgery
INVENTOR(S): Jordan, Andreas
PATENT ASSIGNEE(S): Magforce Nanotechnologies AG, Germany
SOURCE: PCT Int. Appl., 45pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009100716	A2	20090820	WO 2009-DE196	20090211
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
DE 102008008522	A1	20090813	DE 2008-102008008522	20080211
PRIORITY APPLN. INFO.:			DE 2008-102008008522A	20080211
			US 2008-71084P P	20080411

AB The present invention relates to implantable and preferably biol. metabolizable medical products comprising nanoparticles, and the use thereof for thermotherapeutic treatment following surgical removal of tumors and cancers. ABSThe medical good is implanted after tumor surgery; magnetic field causes the beads to heat the wound area; in combination with a drug the antitumor and antimicrobial activity can be effected. Thus iron oxide magnetic particles were prepared from iron dichloride and iron trichloride solution by precipitation in sodium hydroxide; the suspension was diluted to 5 weight% iron oxide. A wound pad composed of calcium alginate and sodium CM-cellulose was impregnated with the nanoparticle-containing suspension.

L3 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER:	2009:971041 CAPLUS
TITLE:	Implantable biodegradable medical good impregnated with magnetic particles and optionally drugs for treatment following tumor surgery
INVENTOR(S):	Jordan, Andreas
PATENT ASSIGNEE(S):	Magforce Nanotechnologies AG, Germany
SOURCE:	Ger. Offen., 19pp. CODEN: GWXXBX
DOCUMENT TYPE:	Patent
LANGUAGE:	German
FAMILY ACC. NUM. COUNT:	2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 102008008522	A1	20090813	DE 2008-102008008522	20080211
WO 2009100716	A2	20090820	WO 2009-DE196	20090211
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,				

TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: DE 2008-102008008522A 20080211
US 2008-71084P P 20080411

AB The invention concerns biodegradable medical goods that contain magnetic micro- or nanoparticles and optionally drugs. The medical good is implanted after tumor surgery; magnetic field causes the beads to heat the wound area; in combination with a drug the antitumor and antimicrobial activity can be effected. Thus iron oxide magnetic particles were prepared from iron dichloride and iron trichloride solution by precipitation in sodium hydroxide; the suspension was diluted to 5 weight% iron oxide. A wound pad composed of calcium alginate and sodium CM-cellulose was impregnated with the nanoparticle-containing suspension.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:674934 CAPLUS
DOCUMENT NUMBER: 149:17767
TITLE: Compositions of Chk1 kinase inhibitor for cancer treatment
INVENTOR(S): Colvin, Anita A.; Koppenol, Sandy; Wisdom, Wendy A.
PATENT ASSIGNEE(S): Icos Corporation, USA
SOURCE: PCT Int. Appl., 107 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008067027	A2	20080605	WO 2007-US80150	20071002
WO 2008067027	A3	20090416		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
AU 2007325576	A1	20080605	AU 2007-325576	20071002
CA 2673483	A1	20080605	CA 2007-2673483	20071002
EP 2063879	A2	20090603	EP 2007-871106	20071002
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS				
IN 2009MN00498	A	20090522	IN 2009-MN498	20090309
KR 2009065537	A	20090622	KR 2009-707975	20090417

PRIORITY APPLN. INFO.: US 2006-853056P P 20061020
WO 2007-US80150 W 20071002

OTHER SOURCE(S): MARPAT 149:17767

AB Compns. containing at least one Chk1 kinase inhibitor and at lease one cyclodextrin are disclosed. Also disclosed are methods of treating a

proliferative disorders, especially cancer or potentiating a cancer treatment with a composition comprising at least one Chk1 inhibitor and at least one cyclodextrin. Thus, an injection solution was formulated containing a disubstituted urea Chk1 inhibitor 50 mg, Captisol 16.66 mg, HCl and NaOH to pH 4.5, and water to 1 mL. Captisol improved chemical stability of the Chk1 inhibitor compared to a solution containing a Chk1 inhibitor mesylate salt and dextrose. Degradation of Chk1 inhibitor was found to be accelerated by moisture and heat. After storage at 40°/75% RH, the Captisol-containing formulation contained 3.06 and 4.96% of related impurities after 1 and 2 mo, resp., while the non-Captisol containing formulation contained 4.41 and 7.10% of impurities at the resp. time points.

L3 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:993749 CAPLUS
DOCUMENT NUMBER: 147:330433
TITLE: Composition and method for topical treatment of tar-responsive dermatological disorders
INVENTOR(S): Yu, Ruey J.; Van Scott, Eugene J.; Lee, Yaling
PATENT ASSIGNEE(S): Tristrata, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 15pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20070207222	A1	20070906	US 2007-680227	20070228
AU 2007223560	A1	20070913	AU 2007-223560	20070228
AU 2007223560	A2	20081016		
CA 2644311	A1	20070913	CA 2007-2644311	20070228
WO 2007103687	A2	20070913	WO 2007-US62975	20070228
WO 2007103687	A3	20081211		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
EP 1998788	A2	20081210	EP 2007-757636	20070228
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS				
JP 2009528382	T	20090806	JP 2008-557487	20070228
CN 101460060	A	20090617	CN 2007-80015758	20081031

PRIORITY APPLN. INFO.: US 2006-778128P P 20060301
WO 2007-US62975 W 20070228

AB The present invention relates to a composition including a wax and a therapeutically effective amount of tar for topical treatment of a tar-responsive dermatol. disorder, the composition being in liquid or light gel form when at a temperature selected from room temperature and a temperature of skin of a

mammal upon application of the composition to the skin of the mammal. The invention also relates to a method of treating a tar-responsive dermatol. disorder by topically applying the composition to skin of a mammal, preferably a human, that is affected by the disorder. Thus, a fast-drying liquid tar composition was formulated containing coal tar solution 15 g, ethanol 42 g, propylene glycol 5 g, cyclomethicone (DC 345) 15 g, tri-Et citrate 5 g, Brij 93 10 g, liquid wax DIADD (dioctyldodecyl dodecanedioate) 5 g, and an optional fragrance 3 g. Topical application of the composition for 4 mo to a human subject having plaque psoriasis resulted in 90% improvement of clin. signs of disorder.

L3 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:1202261 CAPLUS
DOCUMENT NUMBER: 145:495768
TITLE: Soft tissue implants, anti-scarring agents, and therapeutic compositions
INVENTOR(S): Hunter, William L.; Toleikis, Philip M.; Gravett, David M.; Maiti, Arpita; Liggins, Richard T.; Takacs-Cox, Aniko; Avelar, Rui; Signore, Pierre E.; Loss, Troy A. E.; Hutchinson, Anne; McDonald-Jones, Gaye; Lakhani, Fara
PATENT ASSIGNEE(S): Angiotech International A.-G., Switz.
SOURCE: PCT Int. Appl., 2979 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006121521	A2	20061116	WO 2006-US11690	20060331
WO 2006121521	A3	20070111		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
WO 2006121522	A2	20061116	WO 2006-US11726	20060331
WO 2006121522	A3	20080502		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AP, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, EA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, EP, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, OA, BF, BJ, CF, CG, CI, CM,				

GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2005-679293P P 20050510
US 2005-679962P P 20050510
US 2005-679291P P 20050510

AB Soft tissue implants (e.g., breast, pectoral, chin, facial, lip, and nasal implants) are used in combination with an anti-scarring agent in order to inhibit scarring that may otherwise occur when the implant is placed within an animal.

L3 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:493530 CAPLUS
DOCUMENT NUMBER: 143:32415
TITLE: Soft tissue implants and anti-scarring agents
INVENTOR(S): Hunter, William L.; Gravett, David M.; Toleikis, Philip M.; Maiti, Arpita
PATENT ASSIGNEE(S): Angiotech International A.-G., Switz.
SOURCE: PCT Int. Appl., 2592 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 19
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005051444	A2	20050609	WO 2004-US39465	20041122
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 20050148512	A1	20050707	US 2004-986230	20041110
US 20050181977	A1	20050818	US 2004-986231	20041110
CN 101094613	A	20071226	CN 2004-80031664	20041110
AU 2004293075	A1	20050609	AU 2004-293075	20041122
CA 2536192	A1	20050609	CA 2004-2536192	20041122
WO 2005051232	A2	20050609	WO 2004-US39346	20041122
WO 2005051232	A3	20051208		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2006055008	A2	20060526	WO 2004-US39353	20041122
WO 2006055008	A3	20090416		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,				

GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE,
IS, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG,
CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE,
LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ,
MD, RU, TJ, TM, AP, EA, EP, OA

EP 1687041	A2	20060809	EP 2004-812062		20041122
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR, IS, YU					
CN 1878514	A	20061213	CN 2004-80033341		20041122
JP 2007514472	T	20070607	JP 2006-541689		20041122
US 20050149158	A1	20050707	US 2004-409		20041129
US 20050175662	A1	20050811	US 2004-451		20041129
US 20050175661	A1	20050811	US 2004-999205		20041129
US 20050186243	A1	20050825	US 2004-97		20041129
US 20050186242	A1	20050825	US 2004-999204		20041129
US 20050191331	A1	20050901	US 2004-1419		20041130
US 20050175663	A1	20050811	US 2004-1791		20041202
US 20050181008	A1	20050818	US 2004-1786		20041202
US 20050181011	A1	20050818	US 2004-1792		20041202
US 20050143817	A1	20050630	US 2004-6899		20041207
US 20050177103	A1	20050811	US 2004-6314		20041207
US 20050177225	A1	20050811	US 2004-6895		20041207
US 20050181004	A1	20050818	US 2004-6289		20041207
US 20060147492	A1	20060706	US 2006-343809		20060131
CN 101420970	A	20090429	CN 2004-80033576		20060515
IN 2006KN01694	A	20070511	IN 2006-KN1694		20060619
IN 2006KN01695	A	20070511	IN 2006-KN1695		20060619
IN 2006KN01698	A	20070511	IN 2006-KN1698		20060619
PRIORITY APPLN. INFO.:			US 2003-523908P	P	20031120
			US 2003-524023P	P	20031120
			US 2003-525226P	P	20031124
			US 2003-526541P	P	20031203
			US 2004-578471P	P	20040609
			US 2004-586861P	P	20040709
			US 2004-986230	A	20041110
			US 2004-986231	A	20041110
			US 2003-518785P	P	20031110
			US 2004-582833P	P	20040624
			US 2004-986450	A1	20041110
			WO 2004-US37930	W	20041110
			WO 2004-US39183	W	20041122
			WO 2004-US39346	W	20041122
			WO 2004-US39353	W	20041122
			WO 2004-US39465	W	20041122

AB The invention relates to soft tissue implants for use in cosmetic or reconstructive surgery and to compns. to make the implants resistant to growth by inflammatory scar tissue. Thus, a silicone gel containing paclitaxel was used as a filling in breast implant.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L3 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:1036851 CAPLUS
DOCUMENT NUMBER: 142:696

TITLE: Synergistic treatment of cancer using immunomers in conjunction with chemotherapeutic agents
INVENTOR(S): Kandimalla, Ekambar R.; Agrawal, Sudhir; Wang, Daqin
PATENT ASSIGNEE(S): Hybridon, Inc., USA
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004103301	A2	20041202	WO 2004-US15313	20040514
WO 2004103301	A3	20051103		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004241093	A1	20041202	AU 2004-241093	20040514
CA 2526212	A1	20041202	CA 2004-2526212	20040514
US 20050009773	A1	20050113	US 2004-846167	20040514
US 7569554	B2	20090804		
EP 1628531	A2	20060301	EP 2004-752345	20040514
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
JP 2006528697	T	20061221	JP 2006-533117	20040514
MX 2005012421	A	20060222	MX 2005-12421	20051116
US 20080206265	A1	20080828	US 2008-20694	20080128

PRIORITY APPLN. INFO.:	US 2003-471247P	P	20030516
	US 2004-846167	A1	20040514
	WO 2004-US15313	W	20040514

OTHER SOURCE(S): MARPAT 142:696
AB The invention discloses the therapeutic use of immunostimulatory oligonucleotides and/or immunomers in combination with chemotherapeutic agents to provide a synergistic therapeutic effect.
OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:857358 CAPLUS
DOCUMENT NUMBER: 141:337747
TITLE: Oral formulations of cladribine
INVENTOR(S): Bodor, Nicholas S.; Dandiker, Yogesh
PATENT ASSIGNEE(S): Ivax Corporation, USA
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004087101	A2	20041014	WO 2004-US9387	20040326
WO 2004087101	A3	20050203		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2004226437	A1	20041014	AU 2004-226437	20040326
CA 2520523	A1	20041014	CA 2004-2520523	20040326
EP 1608344	A2	20051228	EP 2004-758442	20040326
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK				
BR 2004008848	A	20060404	BR 2004-8848	20040326
CN 1787809	A	20060614	CN 2004-80012713	20040326
CN 100408028	C	20080806		
JP 2006521403	T	20060921	JP 2006-509371	20040326
ZA 2005007935	A	20070328	ZA 2005-7935	20040326
ZA 2005007939	A	20070328	ZA 2005-7939	20040326
US 20070197468	A1	20070823	US 2004-551205	20040326
MX 2005010329	A	20060531	MX 2005-10329	20050927
NO 2005004945	A	20051124	NO 2005-4945	20051025
PRIORITY APPLN. INFO.:			US 2003-458922P P	20030328
			US 2003-484756P P	20030702
			US 2004-541247P P	20040204
			WO 2004-US9387 W	20040326

AB Provided are compns. of cladribine and cyclodextrin which are especially suited for the oral administration of cladribine. The formulations may be used to treat patients with multiple sclerosis.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2004:857357 CAPLUS

DOCUMENT NUMBER: 141:337746

TITLE: Cladribine formulations for improved oral and transmucosal delivery

INVENTOR(S): Bodor, Nicholas S.

PATENT ASSIGNEE(S): Ivax Corporation, USA

SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2004087100 A2 20041014 WO 2004-US9384 20040326
WO 2004087100 A3 20050303
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
AU 2004226435 A1 20041014 AU 2004-226435 20040326
CA 2520522 A1 20041014 CA 2004-2520522 20040326
EP 1608343 A2 20051228 EP 2004-758440 20040326
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK
BR 2004008895 A 20060411 BR 2004-8895 20040326
CN 1787810 A 20060614 CN 2004-80012714 20040326
JP 2006526009 T 20061116 JP 2006-509370 20040326
ZA 2005007935 A 20070328 ZA 2005-7935 20040326
ZA 2005007939 A 20070328 ZA 2005-7939 20040326
MX 2005010330 A 20060531 MX 2005-10330 20050927
US 20070065492 A1 20070322 US 2005-551094 20050928
IN 2005DN04555 A 20070817 IN 2005-DN4555 20051006
NO 2005004944 A 20051124 NO 2005-4944 20051025
PRIORITY APPLN. INFO.: US 2003-458922P P 20030328
US 2003-484756P P 20030702
US 2004-541246P P 20040204
WO 2004-US9384 W 20040326

AB Provided are compns. of cladribine and cyclodextrin which are especially suited for the oral and buccal administration of cladribine.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2004:780831 CAPLUS
DOCUMENT NUMBER: 141:282824
TITLE: Controlled release implant formulations for cell-schedule dependent anticancer agents
INVENTOR(S): Warren, Stephen L.; Dadey, Eric J.; Zhou, Mingxing; Dunn, Richard L.
PATENT ASSIGNEE(S): Atrix Laboratories, Inc., USA
SOURCE: PCT Int. Appl., 127 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004081196	A2	20040923	WO 2004-US7650	20040311
WO 2004081196	A3	20041223		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,

NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
TD, TG

AU 2004219595	A1	20040923	AU 2004-219595	20040311
CA 2518791	A1	20040923	CA 2004-2518791	20040311
EP 1622540	A2	20060208	EP 2004-719856	20040311
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
JP 2007525429	T	20070906	JP 2006-507133	20040311
US 20060121085	A1	20060608	US 2005-222668	20050909
PRIORITY APPLN. INFO.:			US 2003-454100P	P 20030311
			US 2003-505124P	P 20030922
			WO 2004-US7650	W 20040311

AB The present invention provides a flowable composition suitable for use as a controlled release implant. The composition includes: (a) a biodegradable, biocompatible thermoplastic polymer that is at least substantially insol. in aqueous medium, water or body fluid; (b) a cell-cycle dependent biol. agent, a schedule-dependent biol. agent, a metabolite thereof, a pharmaceutically acceptable salt thereof, or a prodrug thereof; and (c) a biocompatible organic liquid, at standard temperature and pressure, in which the
thermoplastic polymer is soluble The present invention also provides a method of treating cancer in a mammal. The present invention also provides a method of blocking, impeding, or otherwise interfering with cell cycle progression at the G1-phase, G1/S interphase, S-phase, G2/M interface or M-phase of the cell cycle in a mammal. The methods includes administering to a mammal an effective amount of a flowable composition of the present invention. Examples demonstrate the feasibility and efficacy potential for intratumoral delivery of Floxuridine in the Atrigel (glycolide-lactide copolymer) delivery system to an animal tumor model.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2002:521462 CAPLUS
DOCUMENT NUMBER: 137:88442
TITLE: Incensole and furanogermacrens and compounds in treatment for inhibiting neoplastic lesions and microorganisms
INVENTOR(S): Shanahan-Pendergast, Elisabeth
PATENT ASSIGNEE(S): Ire.
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002053138	A2	20020711	WO 2002-IE1	20020102
WO 2002053138	A3	20020919		
W: AE, AG, AT, AU, BB, BG, CA, CH, CN, CO, CU, CZ, LU, LV, MA, MD,				

UA, UG, US, VN, YU, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, AT, BE, CH, CY, DE, ES, FI, ML, MR, NE, SN, TD, TG

AU 2002219472	A1	20020716	AU 2002-219472	20020102
EP 1351678	A2	20031015	EP 2002-727007	20020102
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 20040092583	A1	20040513	US 2004-250535	20040102
PRIORITY APPLN. INFO.:			IE 2001-2	A 20010102
			WO 2002-IE1	W 20020102

OTHER SOURCE(S): MARPAT 137:88442

AB The invention discloses the use of incensole and/or furanogermacrens, derivs. metabolites and precursors thereof in the treatment of neoplasia, particularly resistant neoplasia and immunodysregulatory disorders. These compds. can be administered alone or in combination with conventional chemotherapeutic, antiviral, antiparasite agents, radiation and/or surgery. Incensole and furanogermacren and their mixture showed antitumor activity against various human carcinomas and melanomas and antimicrobial activity against Staphylococcus aureus and Enterococcus faecalis.

OS.CITING REF COUNT: 19 THERE ARE 19 CAPLUS RECORDS THAT CITE THIS RECORD (19 CITINGS)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2001:300514 CAPLUS
DOCUMENT NUMBER: 134:331617
TITLE: Oil-in-water emulsion compositions for polyfunctional active ingredients
INVENTOR(S): Chen, Feng-jing; Patel, Mahesh V.
PATENT ASSIGNEE(S): Lipocine, Inc., USA
SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001028555	A1	20010426	WO 2000-US28835	20001018
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 20020107265	A1	20020808	US 1999-420159	19991018
US 6720001	B2	20040413		
PRIORITY APPLN. INFO.:			US 1999-420159	A 19991018

AB Pharmaceutical oil-in-water emulsions for delivery of polyfunctional active ingredients with improved loading capacity, enhanced stability, and reduced irritation and local toxicity are described. Emulsions include an aqueous phase, an oil phase comprising a structured triglyceride, and an emulsifier. The structured triglyceride of the oil phase is substantially free of triglycerides having three medium chain (C6-C12) fatty acid

moieties, or a combination of a long chain triglyceride and a polarity-enhancing polarity modifier. The present invention also provides methods of treating an animal with a polyfunctional active ingredient, using dosage forms of the pharmaceutical emulsions. For example, an emulsion was prepared, with cyclosporin A as the polyfunctional active ingredient dissolved in an oil phase including a structured triglyceride (Captex 810D) and a long chain triglyceride (safflower oil). The composition contained (by weight) cyclosporin A 1.0, Captex 810D 5.0, safflower oil 5.0, BHT 0.02, egg phospholipid 2.4, dimyristoylphosphatidyl glycerol 0.2, glycerol 2.25, EDTA 0.01, and water up to 100%, resp.

OS.CITING REF COUNT: 17 THERE ARE 17 CAPLUS RECORDS THAT CITE THIS RECORD (17 CITINGS)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

(FILE 'HOME' ENTERED AT 13:38:46 ON 10 SEP 2009)

FILE 'REGISTRY' ENTERED AT 13:38:55 ON 10 SEP 2009
E CLADRIBINE/CN
L1 1 S E3
E CYCLODEXTRIN/CN
L2 1 S E3

FILE 'CAPLUS' ENTERED AT 13:39:31 ON 10 SEP 2009
L3 12 S L1 AND L2
L4 6 S L3 AND PY<=2004

=> logoff hold

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	40.24	55.74

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-9.84	-9.84

SESSION WILL BE HELD FOR 120 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 13:42:04 ON 10 SEP 2009

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:ssptajsl1623

PASSWORD:
* * * * * * RECONNECTED TO STN INTERNATIONAL * * * * * *
SESSION RESUMED IN FILE 'CAPLUS' AT 14:31:02 ON 10 SEP 2009
FILE 'CAPLUS' ENTERED AT 14:31:02 ON 10 SEP 2009

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION

```
FULL ESTIMATED COST                                    40.24      55.74

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)       SINCE FILE      TOTAL
                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                   -9.84      -9.84

=> d his

     (FILE 'HOME' ENTERED AT 13:38:46 ON 10 SEP 2009)

     FILE 'REGISTRY' ENTERED AT 13:38:55 ON 10 SEP 2009
                E CLADRIBINE/CN
L1              1 S E3
                E CYCLODEXTRIN/CN
L2              1 S E3

     FILE 'CAPLUS' ENTERED AT 13:39:31 ON 10 SEP 2009
L3             12 S L1 AND L2
L4              6 S L3 AND PY<=2004

=> s l2 and (purine or adenosine) and (inclusion or complex) and amorphous
           7414 L2
          42133 PURINE
          12214 PURINES
          46736 PURINE
                  (PURINE OR PURINES)
          98553 ADENOSINE
            819 ADENOSINES
          98749 ADENOSINE
                  (ADENOSINE OR ADENOSINES)
         135543 INCLUSION
          73659 INCLUSIONS
         181483 INCLUSION
                  (INCLUSION OR INCLUSIONS)
        1507827 COMPLEX
         816567 COMPLEXES
        1831504 COMPLEX
                  (COMPLEX OR COMPLEXES)
         301262 AMORPHOUS
              5 AMORPHOUSES
         301266 AMORPHOUS
                  (AMORPHOUS OR AMORPHOUSES)
L5              0 L2 AND (PURINE OR ADENOSINE) AND (INCLUSION OR COMPLEX) AND AMOR
                  PHOUS

=> s l2 and (purine or adenosine) and (inclusion or complex)
           7414 L2
          42133 PURINE
          12214 PURINES
          46736 PURINE
                  (PURINE OR PURINES)
          98553 ADENOSINE
            819 ADENOSINES
          98749 ADENOSINE
                  (ADENOSINE OR ADENOSINES)
         135543 INCLUSION
          73659 INCLUSIONS
         181483 INCLUSION
                  (INCLUSION OR INCLUSIONS)
```

```
       1507827 COMPLEX
        816567 COMPLEXES
       1831504 COMPLEX
                 (COMPLEX OR COMPLEXES)
L6          13 L2 AND (PURINE OR ADENOSINE) AND (INCLUSION OR COMPLEX)

=> s l6 and py<=2004
      25141550 PY<=2004
L7           8 L6 AND PY<=2004

=> d l7 1-8 ibib abs

L7   ANSWER 1 OF 8  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:        2002:521462  CAPLUS
DOCUMENT NUMBER:         137:88442
TITLE:                   Incensole and furanogermacrens and compounds in
                         treatment for inhibiting neoplastic lesions and
                         microorganisms
INVENTOR(S):             Shanahan-Pendergast, Elisabeth
PATENT ASSIGNEE(S):      Ire.
SOURCE:                  PCT Int. Appl., 68 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     ---------------     ----   --------    --------------------   --------
     WO 2002053138        A2    20020711    WO 2002-IE1            20020102 <--
     WO 2002053138        A3    20020919
         W:  AE, AG, AT, AU, BB, BG, CA, CH, CN, CO, CU, CZ, LU, LV, MA, MD,
             UA, UG, US, VN, YU, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, AT, BE, CH, CY, DE, ES, FI,
             ML, MR, NE, SN, TD, TG
     AU 2002219472        A1    20020716    AU 2002-219472         20020102 <--
     EP 1351678           A2    20031015    EP 2002-727007         20020102 <--
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
     US 20040092583       A1    20040513    US 2004-250535         20040102 <--
PRIORITY APPLN. INFO.:                       IE 2001-2           A  20010102
                                             WO 2002-IE1         W  20020102
OTHER SOURCE(S):         MARPAT 137:88442
AB   The invention discloses the use of incensole and/or furanogermacrens,
     derivs. metabolites and precursors thereof in the treatment of neoplasia,
     particularly resistant neoplasia and immunodysregulatory disorders.  These
     compds. can be administered alone or in combination with conventional
     chemotherapeutic, antiviral, antiparasite agents, radiation and/or
     surgery.  Incensole and furanogermacren and their mixture showed antitumor
     activity against various human carcinomas and melanomas and antimicrobial
     activity against Staphylococcus aureus and Enterococcus faecalis.
OS.CITING REF COUNT:     19    THERE ARE 19 CAPLUS RECORDS THAT CITE THIS
                               RECORD (19 CITINGS)
REFERENCE COUNT:         4     THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS
                               RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7   ANSWER 2 OF 8  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:        2000:95053  CAPLUS
DOCUMENT NUMBER:         132:242544
```

TITLE: Advanced statistical evaluation of ***complex*** formation constant from electrophoretic data
AUTHOR(S): Bartak, P.; Bednar, P.; Kubacek, L.; Stransky, Z.
CORPORATE SOURCE: Trida Svobody 8, Centre of Bioanalytical Research, Palacky University, Olomouc, 771 46, Czech Rep.
SOURCE: Analytica Chimica Acta (***2000***), 407(1-2), 327-336
CODEN: ACACAM; ISSN: 0003-2670
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new method for the estimation of ***complex*** formation consts. is presented. The method is based on electrophoretically measured effective mobilities and applied to the estimation of the ***complex*** formation constant in respect to interactions between nitrogen heterocyclic bases and cyclodextrines. The calcn. of consts. is based on the linearization of the dependence between effective mobility and the cyclodextrine concentration and the application of an advanced statistical evaluation procedure. ***Complex*** formation consts. 14.8 and 63.2 l/mol were obtained for the interaction of pyridinium and benzylaminopurinium with dimethyl-β-cyclodextrin (DM-β-CD), resp. Consts. in the order of magnitude 101-102 l/mol were obtained for some other ***purine*** derivs. The proposed procedure, in connection with the math. software for matrix operations, is rather simple and gives much more valuable outputs than commonly used concepts.

OS.CITING REF COUNT: 8 THERE ARE 8 CAPLUS RECORDS THAT CITE THIS RECORD (8 CITINGS)
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2000:65552 CAPLUS
DOCUMENT NUMBER: 132:127462
TITLE: Particles, in particular micro- or nanoparticles, of crosslinked mono- and oligosaccharides, their production, and cosmetic, pharmaceutical, or food compositions containing them
INVENTOR(S): Perrier, Eric; Rey-Goutenoire, Sylvie; Buffevant, Chantal; Levy, Marie-Christine; Pariot, Nadine; Edwards, Florence; Andry, Marie-Christine
PATENT ASSIGNEE(S): Coletica, Fr.
SOURCE: Ger. Offen., 34 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19932216	A1	20000127	DE 1999-19932216	19990709 <--
DE 19932216	B4	20051208		
FR 2780901	A1	20000114	FR 1998-8809	19980709 <--
FR 2780901	B1	20000929		
NL 1012517	C2	20000111	NL 1999-1012517	19990705 <--
KR 2000011579	A	20000225	KR 1999-27476	19990708 <--
KR 799407	B1	20080130		
JP 2000038402	A	20000208	JP 1999-196705	19990709 <--

JP 3437797	B2	20030818			
US 6197757	B1	20010306	US 1999-350131		19990709 <--
ES 2155793	A1	20010516	ES 1999-1547		19990709 <--
ES 2155793	B1	20011201			
IT 1311514	B1	20020313	IT 1999-TO599		19990709 <--

PRIORITY APPLN. INFO.: FR 1998-8809 A 19980709

AB Particles consisting of ≥1 mono- or oligosaccharide, which are surface-crosslinked in emulsion by esterification of primary OH groups on the saccharides with a polyfunctional acylating agent, are useful as carriers or encapsulating agents for various hydrophilic or lipophilic active substances in preparation of cosmetic, pharmaceutical, or food compns. The particles are biocompatible, biodegradable, and suitable for stabilization and protection of sensitive active substances or for their sustained release. The crosslinking reaction preferably occurs in a water-in-oil emulsion at room temperature and results in formation of a membrane of crosslinked saccharide surrounding an aqueous phase. The saccharide may be a cyclodextrin; by forming an ***inclusion*** compound with an active substance, it can be used to remove or harvest the latter from a liquid medium, or alternatively can slowly release an active substance from an ***inclusion*** compound Thus, 6 mL of a 10% solution of dihydroxyacetone (a ketose) in 1M carbonate buffer (pH 11) was emulsified in 30 mL cyclohexane containing 5% Span 85, and with continued stirring, 40 mL of a 5% solution of terephthaloyl chloride in CHCl3-cyclohexane (1:4 by volume); after 30 min, the microcapsules were collected and washed. These microcapsules dissolved slowly in 1% Na2CO3 solution or in PEG owing to alcoholysis of the ester bonds; the released dihydroxyacetone reacted with glycine to form a brown color. The microcapsules can therefore be used in cosmetic tanning prepns.

OS.CITING REF COUNT: 9 THERE ARE 9 CAPLUS RECORDS THAT CITE THIS RECORD (10 CITINGS)

L7 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1999:549161 CAPLUS
DOCUMENT NUMBER: 131:175082
TITLE: High-energy cyclodextrin-drug ***complexes*** with increased bioavailability
INVENTOR(S): Loftsson, Thorsteinn; Masson, Mar; Stefansson, Einar
PATENT ASSIGNEE(S): Cyclops, Iceland
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9942111	A1	19990826	WO 1999-IS3	19990216 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2320772	A1	19990826	CA 1999-2320772	19990216 <--
AU 9926385	A	19990906	AU 1999-26385	19990216 <--

AU 759280	B2	20030410			
EP 1067942	A1	20010117	EP 1999-906440		19990216 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
NZ 505951	A	20030228	NZ 1999-505951		19990216 <--
JP 2003522207	T	20030722	JP 2000-532126		19990216 <--
US 6699849	B1	20040302	US 1999-250185		19990216 <--
US 20040186075	A1	20040923	US 2004-750940		20040105 <--
PRIORITY APPLN. INFO.:			US 1998-75544P	P	19980223
			US 1999-250185	A1	19990216
			WO 1999-IS3	W	19990216

AB Methods for enhancing the complexation efficiency of a drug with cyclodextrin and for enhancing the availability of a drug following administration of a cyclodextrin-drug ***complex.*** Phenytoin-2-hydroxypropyl β-cyclodextrin ***complexes*** were prepared, lyophilized to a powder which can be formulated into tablets. The bioavailability of phenytoin was enhanced.

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1997:727151 CAPLUS

DOCUMENT NUMBER: 128:23072

ORIGINAL REFERENCE NO.: 128:4531a,4534a

TITLE: Oligosaccharide analogs of polysaccharides. Part 14. Carbocyclic cyclodextrin analogs. Synthesis of all trimeric and tetrameric isomers by homo- and heterocoupling of 1,4-cis-diethynylated 1,5-anhydroglucitols

AUTHOR(S): Burli, Roland; Vasella, Andrea

CORPORATE SOURCE: Lab. Organische Chemie, ETH-Zentrum, Zurich, CH-8092, Switz.

SOURCE: Helvetica Chimica Acta (***1997***), 80(7), 2215-2237
CODEN: HCACAV; ISSN: 0018-019X

PUBLISHER: Verlag Helvetica Chimica Acta

DOCUMENT TYPE: Journal

LANGUAGE: English

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Hetero- or homocoupling of protected 1,4-cis-diethynylated 1,5-anhydroglucitols leads to 2 isomeric cyclotrimers and to 4 isomeric cyclotetramers. The C1-sym. cyclotrimer I and the C1- and the C2-sym. cyclotetramers II and III, resp., were prepared The cyclotrimer I was prepared by intramol., oxidative homocoupling and, alternatively, by a 1-pot trimerization/cyclization of the monomer. Oxidative homocoupling was used for the cyclization of appropriate tetramers to II and III. The acyclic tetramers were made by sequential Cadiot-Chodkiewicz coupling or by a combination of a Cadiot-Chodkiewicz reaction and an intermol., oxidative homocoupling. The solid-state conformation of a C4-sym. cyclotetramer corresponds well to the one predicted by force-field calcns. The water-solubilities of cyclotrimers and -tetramers, their calculated

conformations, and the D-***adenosine*** binding properties of the cyclotetramers were compared.
OS.CITING REF COUNT: 20 THERE ARE 20 CAPLUS RECORDS THAT CITE THIS RECORD (20 CITINGS)

L7 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1994:711646 CAPLUS
DOCUMENT NUMBER: 121:311646
ORIGINAL REFERENCE NO.: 121:56853a,56856a
TITLE: Proton Transfer and n → π* Transition in the Photophysics of 1,N6-Ethenoadenosine
AUTHOR(S): Agbaria, Rezik A.; Parola, Abraham H.; Gill, David
CORPORATE SOURCE: Department of Physics, Ben-Gurion University, Beer-Sheva, 84105, Israel
SOURCE: Journal of Physical Chemistry (***1994***), 98(50), 13280-5
CODEN: JPCHAX; ISSN: 0022-3654
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The photophys. characteristics of 1,N6-enthenoadenosine (εAdo) show irregularities in terms of the expected photophysics from a pH equilibrium between two forms that absorb light at different wavelengths. Furthermore, a comparison between the absorption spectra of ***purine***, adenine, and εAdo leads to the conclusion that εAdo does not follow the adenine, but rather has more in common with the ***purine.*** The adenine itself does not follow its parent compound, ***purine.*** We, therefore, reinterpret the absorption of εAdo, such as the unprotonated form has two absorption bands, the second of which is an n → π* transition, whereas the protonated form has only one π → π* absorption band, which overlaps with the first absorption band of the unprotonated form. The n → π* absorption "disappeared" upon protonation, apparently due to stabilization of the lone-pair electrons. Under these presumptions, the photophysics of εAdo is no longer peculiar. Transitions to and from both excited singlet states, Sππ* and Snπ*, along with the relative order of their resp. triplets, are shown to play an active role in the photophysics of εAdo. Therefore, the reported multiple emissions from εAdo, at low temperature, are to be expected. The reported observations in the literature provide evidence for the multiple excited states of εAdo. In the present work, cyclodextrins provide a powerful tool in the photophys. study of εAdo. In particular, cyclodextrin host isolation matrix (CHIM) provides a unique environment that can be applied to mimic the photophysics of the isolated mol. in the gas phase or at low temps.
OS.CITING REF COUNT: 4 THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD (4 CITINGS)

L7 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1994:69602 CAPLUS
DOCUMENT NUMBER: 120:69602
ORIGINAL REFERENCE NO.: 120:12359a,12362a
TITLE: Preparation and use of polyanionic polymer-based conjugates targeted to vascular endothelial cells
INVENTOR(S): Thorpe, Philip E.
PATENT ASSIGNEE(S): University of Texas System, USA; Imperial Cancer Research Technology Ltd.
SOURCE: PCT Int. Appl., 117 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9318793	A1	19930930	WO 1993-US2619	19930322 <--
W: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, KP, KR, LU, MG, MN, MW, NL, NO, PL, PT, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR				
US 5474765	A	19951212	US 1992-856018	19920323 <--
AU 9338166	A	19931021	AU 1993-38166	19930322 <--
EP 632728	A1	19950111	EP 1993-907633	19930322 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT				
US 5762918	A	19980609	US 1994-307745	19941205 <--
PRIORITY APPLN. INFO.:			US 1992-856018 A2	19920323
			WO 1993-US2619 A	19930322

AB An anionic polymer (e.g. a heparin derivative) is linked to an active agent (especially a steroid), preferably by a selectively hydrolyzable bond, for delivery of the active agent to vascular endothelial cells. The conjugates are useful as angiogenesis inhibitors for treatment of e.g. cancer, arthritis, and diabetic blindness. Thus, heparin was condensed with adipic dihydrazide and then with cortisol; the cortisol:heparin mol ratio in the product was 8-9. This conjugate was markedly acid labile, suppressed DNA synthesis and cell migration in human umbilical vein endothelial cells, retarded or abolished the vascularization of sponges in vivo, and retarded lung tumor growth in mice by 65%. No adverse effects of the conjugate were detected, and equivalent treatments with a mixture of heparin and cortisol were significantly less effective in all cases.

OS.CITING REF COUNT: 11 THERE ARE 11 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 1993:637813 CAPLUS
DOCUMENT NUMBER: 119:237813
ORIGINAL REFERENCE NO.: 119:42169a,42172a
TITLE: Dye transfer thermal printing process. VI. Prevention of image decoloration in dye transfer recording
AUTHOR(S): Kusakawa, Hideaki; Enmanji, Koe
CORPORATE SOURCE: Kanazawa Inst. Technol., Nonoichi, 721, Japan
SOURCE: Denshi Shashin Gakkaishi (***1993***), 32(1), 3-6
CODEN: DSHGDD; ISSN: 0387-916X
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB The thermal dye transfer color ink, which is developed to have same sensitivity as the com. used thermal printing paper for G-II type facsimile, is composed of dyes such as SOT-Blue 2, -Red 2G, and -Yellow 5 with suitable binder polymers. The light fastness of these dyes is low. Thus, it is necessary to improve it, especially, for -Blue 2. Decoloration of the dye is prevented either by charge-transfer ***complex*** formation or the ***inclusion*** of the dyes. For binder polymers such as PMMA, in which the dye is dissolved rather than dispersed, it is not possible to form charge-transfer ***complexes*** and improvement of light fastness is not observed For polar binder polymers such as poly(vinyl alc.), in which the dye and electron-acceptor particles are dispersed rather than dissolved, it was necessary to add electron-acceptor to form

complexes. The dye mol. is too large for cyclodextrin to enclose it, and, accordingly, the improvement in light fastness was not so remarkable.

```
=> logoff hold
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      87.64     103.14

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                         ENTRY    SESSION
CA SUBSCRIBER PRICE                                     -16.40     -16.40

 SESSION WILL BE HELD FOR 120 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 14:32:22 ON 10 SEP 2009
```

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	**MAIL STOP AMENDMENT**
Nicholas Bodor et al.	Group Art Unit: 1623
Application No.: 10/551,205	Examiner: JONATHAN S LAU
Filed: November 14, 2006	Confirmation No.: 4092
For: ORAL FORMULATIONS OF CLADRIBINE	

REPLY TO OFFICIAL ACTION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office Action dated September 17, 2009, the following remarks are offered:

REMARKS

Applicants request reexamination and reconsideration of the subject application pursuant to and consistent with 37 C.F.R. § 1.112 in light of the following:

STATUS OF CLAIMS

Claims 1, 2, 8, 9, 11-14, 20, 21, 23-28, 32, 33, 35, 56, 57, 63, 64 and 66-98 remain in this application. Claims 13, 14, 20, 21, 23-28, 32, 33, 35 and 67-81 have been withdrawn from consideration. Claims 1, 2, 8, 9, 11, 12, 56, 57, 63, 64, 66 and 82-98 are under examination.

It is respectfully pointed out that, while the other claims under examination have been rejected, Claims 12 and 66 are not indicated to be rejected in the Office Action Summary or in the rejection set forth in page 4 of the Office Action. Clarification is requested.

INFORMATION DISCLOSURE STATEMENTS

Applicants thank the Examiner for considering the documents cited in their Fifth Information Disclosure Statement filed July 6, 2009. A Sixth Information Disclosure Statement is filed herewith. The document listed on the accompanying form PTO-1449 is discussed in the remarks which follow.

REJECTION WITHDRAWN

The Examiner's previous rejection under 35 U.S.C. § 103(a) based on Schultz et al. in view of Baert et al. has been withdrawn.

CLAIM REJECTIONS - 35 U.S.C. § 103

Amended Claims 1, 2, 8, 9, 11, 56, 57, 63, 64 and 82-98 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Schultz et al. US Patent No. 6,194,395, in view of Wrenn Jr. US Patent No. 6,174,873 and in view of Loftsson et al. US Patent 6,699,849. Applicants believe that this rejection is untenable against any of the claims in this application.

APPLICANTS' INVENTION

While the Examiner has withdrawn his previous obviousness rejection based on Schultz et al. in view of Baert et al., the Examiner nevertheless clings to his interpretation of particular features of Schultz et al. to the exclusion of what the Schultz et al. patent as a whole teaches to one of ordinary skill in the art.

First, applicants would like to once again draw the Examiner's attention to the essential features of applicants' invention as set forth in independent Claims 56 and 1, as well as in Claim 82.

Claim 56 is drawn to a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture consisting of: (a) an amorphous inclusion complex of cladribine with the amorphous cyclodextrin hydroxypropyl-β-cyclodextrin (HPβCD) and (b) amorphous free cladribine associated with said amorphous cyclodextrin as a non-inclusion complex, said complex cladribine-cyclodextrin complex having a weight ratio of cladribine to said amorphous cyclodextrin of from about 1:10 to about 1:16. This is a complex complex of cladribine and hydroxypropyl-β-cyclodextrin (HPβCD) in which there is an intimate mixture consisting of two different complexes, first an amorphous inclusion complex of cladribine and HPβCD (itself an amorphous cyclodextrin) and secondly a non-inclusion complex in which amorphous free cladribine is associated with the amorphous cyclodextrin HPβCD, and moreover this complex complex has a very particular weight ratio of cladribine to HPβCD of from about 1:10 to about 1:16.

The cladribine/ HPβCD complex of the invention has many properties that distinguish it from a mere mixture of hydroxypropyl-β-cyclodextrin and cladribine as was fully and convincingly shown by the data provided in the Van Axel Castelli et al. document provided with applicants' previous response and discussed in great detail therein.

The unique cladribine/hydroxypropyl-β-cyclodextrin complex defined in Claim 56 is an essential feature of applicants' unique pharmaceutical composition as claimed in Claim 1. Claim 1 is drawn to a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture consisting of (a) an amorphous inclusion complex of cladribine with the amorphous

cyclodextrin hydroxypropyl-β-cyclodextrin and (b) amorphous free cladribine associated with said amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein, said composition having a weight ratio of cladribine to said amorphous cyclodextrin of from about 1:10 to about 1:16. Thus, in addition to the special features of the complex complex itself as already discussed, it is essential that the pharmaceutical composition comprise no significant amount of free crystalline cladribine therein and that the complex complex be formulated into a solid oral dosage form. Neither the complex complex nor the pharmaceutical composition comprises any significant amount of free crystalline cladribine; this is excluded from the complex complex by use of the closed "consisting of" language in defining the components of the admixture therein.

Claim 82 is a product-by-process claim which specifies the steps applicants have found to provide the unique pharmaceutical composition of Claim 1, which in turn contains as an essential feature the precisely defined unique complex complex of Claim 56. Thus, Claim 82 is drawn to a pharmaceutical composition according to Claim 1 obtainable by a process comprising the steps of:

(i) combining cladribine and the amorphous cyclodextrin hydroxypropyl-β-cyclodextrin in water at a temperature of from about 45 to about 80°C and maintaining said temperature for a period of from about 6 to about 24 hours;

(ii) cooling the resultant aqueous solution to room temperature;

(iii) lyophilizing the cooled solution to afford an amorphous product; and

(iv) formulating the amorphous product into a solid oral dosage form.

The time and temperature conditions set forth in part (i) are especially critical to formation of the Claim 56 complex complex and ultimately to formation of the Claim 1 pharmaceutical composition.

The Examiner relies upon Schultz et al. for disclosing a solid pharmaceutical dosage form comprising cladribine and cyclodextrin at column 2, lines 31-39. These lines do not indicate the nature of the relationship between the cladribine and the cyclodextrin. However, as applicants pointed out to the Examiner previously, Schultz et al. elsewhere disclose that their oral solid dosage forms contain a mixture of cladribine and cyclodextrin; see column 1, lines 8-10. Reference to solid mixtures is

also made by Schultz et al. in column 5, lines 50-64. Schultz et al. teach inclusion complex formation in solution but only to form injectable solutions. As to ratios, Schultz et al.'s weight ratios for their solid oral dosage form are 1 mg to 15 mg of cladribine and 100 mg to 500 mg of cyclodextrin (col. 6, lines 23-31). This does not lead one of ordinary skill to "instantly envision" a cladribine:cyclodextrin ratio ranging from 15 mg:100mg to 15 mg:500 mg, but rather from 1 mg:500 mg to 15 mg:100 mg. This is not 1:6.67 to 1:33.3, it is 1:500::1:6.67, a much broader ratio range than that stated by the Examiner. Further, as applicants previously pointed out, Schultz et al.'s ratio is for a mixture, not for a complex. Virtually any ratio could be present in a mixture. Such does not suggest what ratios would be not only possible but also advantageous in a complex.

While applicants agree that Schultz et al. do not disclose any of the many features noted by the Examiner in the paragraph spanning pages 5-6 of the Official Action, it is pointed out that Schultz et al. also do not suggest applicants' complex complex (as defined in Claim 56) or a pharmaceutical composition comprising applicants' complex complex formulated into a solid oral dosage form comprising no significant amount of free crystalline cladribine (as defined in Claim 1) or a process for preparing such a pharmaceutical formulation (as defined in Claim 82). However, what is missing from Schultz et al. is not supplied by the secondary references, Wrenn, Jr. and Loftsson et al.

It is agreed that the Wrenn, Jr. patent is directed to solid formulations for oral administration and that the adenosine analogs therein include cladribine. Wrenn, Jr.'s teaching in column 12, lines 25-30 is part of his discussion of an INDAS system. As noted at line 25, INDAS takes the form of a high energy matrix tablet. Production of that matrix tablet involves including adenosine analogs in an amorphous form together with a combination of energy, excipients and unique processing procedures. Wrenn, Jr. goes on to state (col. 12, lines 30-40) that once included in the desirable physical form, the resultant high energy complex may be stabilized by an absorption process that utilizes a novel polymer cross-linked technology to prevent recrystallization. The combination of the change in the physical state of the adenosine analogs coupled with the solubilizing characteristics of the excipients employed enhances the solubility of the adenosine analogs. The resulting absorbed

amorphous drug complex granulate may then, according to Wrenn, Jr., be formulated with a gel-forming erodable tablet system to promote substantially smooth or continuous absorption. As set forth in Wrenn, Jr.'s Claim 1, his oral dosage form comprises an acid-labile 2'-deoxyadenosine analog which chemically decomposes in the acid environment and one or more components which inhibit that decomposition selected from the group consisting of erodible matrix, enteric coating, solid dispersion and ion exchange resin. In Claim 8, Wrenn, Jr. specifies that the composition is in a controlled-release mechanism. In Claim 10, the controlled-release mechanism may be an INDAS system, among others. Thus, while Wrenn, Jr. suggests amorphous forms of the drug, this is in the context of its being only one part of the INDAS system he is describing. Wrenn, et al. in no way suggests cyclodextrin complexation, much less how to make or how to use the specific complex complex of applicants' claims, which has nothing to do with novel polymer cross-linking technology. Indeed, cyclodextrins are not polymers and do not provide cross-linking! Wrenn, Jr. neither discloses nor suggests what applicants have done, which is to provide an intimate admixture consisting of (a) an amorphous inclusion complex of cladribine with HPβCD, and (b) amorphous free cladribine associated with said HPβCD as a non-inclusion complex, which is formulated into a solid oral dosage form comprising no significant amount of free crystalline cladribine therein, the cladribine:HPβCD ratio being from about 1:10 to about 1:16. There is no cladribine/cyclodextrin inclusion complex in Wrenn, Jr. and there is no non-inclusion complex there either, much less the remotest suggestion of applicants' invention as claimed herein. Indeed, Wrenn, Jr. is not remotely relevant to the present invention.

We turn now to Loftsson et al., which does indeed relate to cyclodextrins. Indeed, the very Loftsson and Brewster cyclodextrin review article referenced on page 18 of applicants' July 6, 2009 response and previously made of record in applicants' Third Information Disclosure Statement is referenced in column 2, lines 20-24 of the Loftsson et al. patent relied upon by the Examiner. Applicants already acknowledged many basic teachings in the cyclodextrin art, including the amorphous nature of HPβCD. Applicants agree that the statements made by the Examiner on page 6 of the Official Action about cyclodextrins are correct, with one notable exception. Loftsson et al do not teach that purine derivatives are, without

qualification, compatible with cyclodextrin for forming complexes. The Examiner has taken page 9, lines 50-55 completely out of context, as explained below.

The Loftsson et al. patent is aimed at enhancing the cyclodextrin complexation efficiency of certain structural classes of drugs by relying on reversible ring opening. In the OBJECTS AND SUMMARY OF THE INVENTION in columns 4-6, the Examiner's attention is drawn in particular to column 5, line 43 to column 6, line 49, where various aspects of the Loftsson et al. invention are summarized. In each of these aspects, the drug is defined as "having a structure comprising at least one heterocyclic ring having a total of from 4 to 7 ring atoms, of which from 1 to 3 are hetero ring atoms, each of said hetero ring atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imide, hemiacetal or hemiketal..." (Emphasis added). See also the wording of the claims of Loftsson et al.'s PCT counterpart, WO 99/42111, submitted with the accompanying IDS, which repeat this language. (The US claims recite only benzodiazepines, all of which have a cycle imine structure.) Thus, when Loftsson et al. disclose in columns 8-9 groups of preferred drugs, the patentees are speaking in the context of the quoted language; in other words, their purines are not any purines but are only ones which are susceptible to reversible ring opening. In the case of purines, Loftsson et al. disclose that the drugs are preferably caffeine, theophylline, etophylline, proxyphylline or theobromine. It is immediately apparent that cladribine, whose structure is depicted on page 1 of the instant application and in column 1 of Schultz et al., does not have the requisite imine, enamine, lactone, lactam, thiolactam, anhydride, imide, hemiacetal or hemiketal structure and thus is not susceptible to reversible ring opening and it not appropriate for use in Loftsson et al.'s invention. Moreover, as would be readily apparent to one of ordinary skill, cladribine is a nucleoside analog; it is a purine base in glycosidic linkage with a sugar, which is a ribofuranose. Loftsson et al. do not remotely suggest nucleosides or nucleoside analogs.

Secondly, the process described by Loftsson et al. for complexing their drugs with cyclodextrin is conducted at a pH level below about 5, preferably between about 3 and about 5, in the case of basic drugs such as benzodiazepine. See column 10 and the Examples, especially beginning with Example 3. The work described is

carried out in solution. Generally, the suspension of drug in aqueous cyclodextrin solution is heated in a sealed container in an autoclave, presumably to encourage ring openings at acidic pH. There is no specific disclosure of a solid oral dosage form that applicants can locate Furthermore, it is well-known that cladribine is acid-labile; as noted by Schultz et al., use of the compound orally has been limited by this fact. See col. 1, lines 36-51 of Schultz et al. Thus, one of ordinary skill would not be motivated to subject cladribine to the methods of Loftsson et al.'s patent, first because it does not even meet the structural requirements for use therein and secondly because it would decompose at the low pH levels favored by Loftsson et al. There is indeed no suggestion of cladribine in the Loftsson et al. patent.

While various methods of preparing drug-cyclodextrin complexes have been known in the art, applicants have found that a very carefully controlled series of steps are required to produce the instantly claimed complex complex and pharmaceutical composition containing it. The time and temperature specified in Claim 82 in step (i) are essential, for example, for production of applicants' unique products. The sum total of the conditions used by applicants together with the fact that cladribine is a nucleoside analog and thus has not only a particular purine ring but also a ribofuranose sugar ring surprisingly gives a very complex product when combined with HPβCD, because the hydroxyl groups on the ribofuranose ring in cladribine are able to hydrogen-bond to the hydroxyls on the exterior of the cyclodextrin ring, while the purine ring of cladribine is able to be at least partially included in the cavity of the cyclodextrin ring. This provides a very unique result which could not have been predicted. The present invention takes advantage of both parts (purine base + sugar) of the structure of cladribine so as to provide an intimate amorphous admixture consisting of (a) an amorphous inclusion complex of cladribine with HPβCD and (b) amorphous free cladribine associated with HPβCD as a non-inclusion complex (which is multiple hydrogen bond mediated as explained above), which then is further formulated into a solid oral dosage form, the composition comprising no significant amount of free crystalline cladribine therein, the composition having a weight ratio of cladribine to said amorphous cyclodextrin of from about 1:10 to about 1:16. There is no suggestion in the art of this complex complex or of how to obtain it; the cited references in combination fail to lead one of

ordinary skill to this result. Thus, the subject matter of Claims 1, 5 and 82 is free of the outstanding rejection. The same is true of independent Claims 13 and 25 which contain all of the limitations of Claim 1. The more specific claims herein are even more remote from the prior art.

With respect to the product-by-process claims, applicants agree that the product of Claim 82 is the same as the product of Claim 1. Claims 82-90 and 94-98 are, however, patentable for all of the reasons set forth above with respect to Claim 1.

CONCLUSION

In view of the foregoing, it is submitted that all claims in this application are free of the record rejections. Further, favorable action in the form of a Notice of Allowance is believed to be next in order and is earnestly solicited.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: December 16, 2009

By: Mary Katherine Baumeister
Mary Katherine Baumeister
Registration No. 26254

Customer No. 21839
703 836 6620

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	**MAIL STOP AMENDMENT**
Nicholas Bodor et al.	Group Art Unit: 1623
Application No.: 10/551,205	Examiner: JONATHAN S LAU
Filing Date: November 14, 2006	Confirmation No.: 4092
Title: ORAL FORMULATIONS OF CLADRIBINE	

SIXTH
INFORMATION DISCLOSURE STATEMENT
TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Enclosed is a Sixth Information Disclosure Statement (IDS) and accompanying form PTO-1449 for the above-identified patent application.

☐ No additional fee for submission of an IDS is required.

☒ The fee of $ 180 as set forth in 37 C.F.R. § 1.17(p) is also enclosed.

☐ A statement under 37 C.F.R. § 1.17(p) is also enclosed.

☐ A statement under 37 C.F.R. § 1.97(e), and the fee of $ 180 as set forth in 37 C.F.R. § 1.17(p) are also enclosed.

☐ Charge _____ to Deposit Account No. 02-4800 for the fee due.

☒ Charge $ 180 to credit card for the fee due. Form PTO-2038 is attached.

☒ The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL AND ROONEY PC

Date December 16, 2009

By: Mary Katherine Baumeister
Mary Katherine Baumeister
Registration No. 26254

Customer No. 21839
703 836 6620

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	**MAIL STOP AMENDMENT**
Nicholas Bodor et al.	Group Art Unit: 1623
Application No.: 10/551,205	Examiner: JONATHAN S LAU
Filed: November 14, 2006	Confirmation No.: 4092
For: ORAL FORMULATIONS OF CLADRIBINE	

SIXTH INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure as set forth in 37 C.F.R. § 1.56, the accompanying information is being submitted in accordance with 37 C.F.R. §§ 1.97 and 1.98. Applicants request the Examiner's consideration of the document listed on the accompanying Form PTO-1449.

Pursuant to 37 C.F.R. § 1.98, a copy of the document cited is enclosed.

This Statement, Form PTO-1449 and document are being submitted after the issuance of an Official Action on the merits but prior to the final action, therefore under 37 C.F.R. § 1.97(c), the fee set forth in 37 C.F.R. § 1.17(p) is enclosed.

A fee of $ 180 as set forth in 37 C.F.R. § 1.17(p) is enclosed.

It is respectfully requested that an Examiner-initialed copy of Form PTO-1449 be returned to the undersigned.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: December 16, 2009

By: Mary Katherine Baumeister
Mary Katherine Baumeister
Registration No. 26254

Customer No. 21839
703 836 6620

Substitute for form 1449/PTO & 1449B/PTO

SIXTH
INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known

Application Number	10/551,205
Filing Date	November 14, 2006
First Named Inventor	Nicholas Bodor et al.
Examiner Name	JONATHAN S LAU
Attorney Docket No.	0056192-000024

U.S. PATENT DOCUMENTS

Examiner Initials	Document Number-Kind Code	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Figures Appear
	US-			
	US-			
	US-			
	US-			
	US-			
	US-			
	US-			
	US-			
	US-			
	US-			
	US-			
	US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials	Foreign Patent Document: Country Code[1], Number, Kind Code	Publication Date (MM-DD-YYYY)	Name of Patentee or Applicant of Cited Document	STATUS: Translation	Partial Translation	Eng. Lang. Summary	Search Report	IPER	Abstract	Cited in Spec. / Pg. No(s).	
	WO 99/42111	08-26-1999	CYCLOPS, EHF								

[1]Enter Office that issued the document, by the two-letter code.

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials	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.

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with M.P.E.P. § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/715, C08B 37/16

A1

(11) International Publication Number: **WO 99/42111**

(43) International Publication Date: 26 August 1999 (26.08.99)

(21) International Application Number: PCT/IS99/00003

(22) International Filing Date: 16 February 1999 (16.02.99)

(30) Priority Data:
60/075,544 23 February 1998 (23.02.98) US

(71) Applicant: CYCLOPS, EHF. [IS/IS]; Borgartun 7, IS–105 Reykjavik (IS).

(72) Inventors: LOFTSSON, Thorsteinn; Sorlaskjol 44, IS–107 Reykjavik (IS). MASSON, Mar; Fjolnisvegur 1, IS–101 Reykjavik (IS). STEFANSSON, Einar; Fjardaras 13, IS–110 Reykjavik (IS).

(74) Agent: LOFTSSON, Thorsteinn; University of Iceland, Dept. of Pharmacy, Hagi at Hofsvallagata, P.O. Box 7210, IS–127 Reykjavik (IS).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: HIGH–ENERGY CYCLODEXTRIN COMPLEXES

(57) Abstract

Methods for enhancing the complexation efficiency of a drug with cyclodextrin and for enhancing the availability of a drug following administration of a cyclodextrin–drug complex.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

HIGH-ENERGY CYCLODEXTRIN COMPLEXES

BACKGROUND OF THE INVENTION

Field of the Invention:

The invention relates to methods for enhancing the complexation of a heterocyclic drug with cyclodextrin and to methods for enhancing the availability of a heterocyclic drug following administration of a cyclodextrin-drug complex.

Background Art:

Cyclodextrins are a group of structurally related saccharides which are formed by enzymatic cyclization of starch by a group of amylases termed glycosyltransferases. Cyclodextrins are cyclic oligosaccharides, consisting of (α-1,4)-linked α-D-glucopyranose units, with a somewhat lipophilic central cavity and a hydrophilic outer surface. The most common naturally occurring cyclodextrins are α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin consisting of 6, 7 and 8 glucopyranose units, respectively. Of these three derivatives, β-cyclodextrin appears to be the most useful pharmaceutical complexing agent due to its cavity size, availability, low cost and other properties.

The natural cyclodextrins, in particular β-cyclodextrin, have limited aqueous solubility and their complex formation with lipophilic drugs often results in precipitation of solid drug-cyclodextrin complexes. Thus, the solubility of β-cyclodextrin in water is only about 18.5 mg/ml at room temperature. This low aqueous solubility is, at least partly, associated with strong intramolecular hydrogen bonding in the cyclodextrin crystal lattice. Substitution of any of the hydrogen bond-forming hydroxyl groups, even by hydrophobic moieties such as methoxy groups, will increase the aqueous solubility of β-cyclodextrin. In addition, since these manipulations frequently produce large numbers of isomeric

products, chemical modification can transform the crystalline cyclodextrins into amorphous mixtures increasing their aqueous solubility.

Cyclodextrin derivatives of current pharmaceutical interest include the hydroxypropyl derivatives of α-, β- and γ-cyclodextrin, sulfoalkylether cyclodextrins such as sulfobutylether β-cyclodextrin, alkylated cyclodextrins such as the randomly methylated β-cyclodextrin, and various branched cyclodextrins such as glucosyl- and maltosyl-β-cyclodextrin (T. Loftsson and M.E. Brewster, "Cyclodextrins as pharmaceutical excipients", *Pharm. Technol. Eur.*, 9(5), 26-34 (1997); T. Loftsson and M.E. Brewster, "Pharmaceutical applications of cyclodextrins. I. Drug solubilization and stabilization", *J. Pharm. Sci.* 85(10), 1017-1025 (1996); R.A. Rajewski and V.J. Stella, "Pharmaceutical applications of cyclodextrins. 2. In vivo drug delivery", *J. Pharm. Sci.* 85(11), 1142-1169 (1996); T. Irie and K. Uekama, "Pharmaceutical applications of cyclodextrins. 3. Toxicological issues and safety evaluation", *J. Pharm. Sci.*, 86(2), 147-162 (1997); V.J. Stella and R.A. Rajewski, "Cyclodextrins: their future in drug formulation and delivery", *Pharm. Res.*, 14(5), 556-567 (1997); T. Loftsson, "Increasing the cyclodextrin complexation of drugs and drug bioavailability through addition of water-soluble polymers", *Pharmazie*, 53, 733-740 (1998)).

Preparation of cyclodextrin inclusion complexes

In aqueous solutions, cyclodextrins form complexes with many drugs through a process in which the water molecules located in the central cavity are replaced by either the whole drug molecule, or more frequently, by some lipophilic portion of the drug structure. Once included in the cyclodextrin cavity, the drug molecules may be dissociated through complex dilution, by replacement of the included drug by some other suitable molecule (such as dietary lipids or bile salts in the GI tract) or, if the complex is located in close approximation to a lipophilic biological membrane (such as the mucosal membrane of the GI tract),

the drug may be transferred to the matrix for which it has the highest affinity. Importantly, since no covalent bonds are formed or broken during the drug-cyclodextrin complex formation, the complexes are in dynamic equilibrium with free drug and cyclodextrin molecules (R.A. Rajewski and V.J. Stella, "Pharmaceutical applications of cyclodextrins. 2. In vivo drug delivery", *J. Pharm. Sci.* 85(11), 1142-1169 (1996)).

Various methods have been applied to the preparation of drug-cyclodextrin complexes (T. Loftsson and M.E. Brewster, "Pharmaceutical applications of cyclodextrins. I. Drug solubilization and stabilization", *J. Pharm. Sci.* 85(10), 1017-1025 (1996); T. Loftsson and M.E. Brewster, "Cyclodextrins as pharmaceutical excipients", *Pharm. Technol. Eur.*, 9(5), 26-34 (1997)). In solution, the complexes are usually prepared by addition of an excess amount of the drug to an aqueous cyclodextrin solution. The suspension formed is equilibrated (for periods of up to one week at the desired temperature) and then filtered or centrifuged to form a clear drug-cyclodextrin complex solution. Since the rate determining step in complex formation is often the phase to phase transition of the drug molecule, it is sometimes possible to shorten this process by formation of supersaturated solutions through sonication followed by precipitation. For preparation of the solid complexes, the water is removed from the aqueous drug-cyclodextrin solutions by evaporation or sublimation, e.g. spray-drying or freeze-drying. Other methods can also be applied to prepare solid drug-cyclodextrin complexes including kneading methods, co-precipitation, neutralization and grinding techniques. In the kneading method, the drug is added to an aqueous slurry of a poorly water-soluble cyclodextrin such as β-cyclodextrin. The mixture is thoroughly mixed, often at elevated temperatures, to yield a paste which is then dried. This technique can frequently be modified so that it can be accomplished in a single step with the aid of commercially available mixers which can be operated at temperatures over 100 °C and under vacuum. The kneading

method is a cost-effective means for preparing solid cyclodextrin complexes of poorly water-soluble drugs. Co-precipitation of a cyclodextrin complex through addition of organic solvent is also possible. Unfortunately, the organic solvents used as precipitants can interfere with complexation which makes this approach less attractive than the kneading method. However, we have discovered that some organic solvents under some specific conditions, e.g. 10% (v/v) aqueous acetic acid solution, can enhance the complexation. Solid complexes of ionizable drugs can sometimes be prepared by the neutralization method wherein the drug is dissolved in an acidic (for basic drugs) or basic (for acidic drugs) aqueous cyclodextrin solution. The solubility of the drug is then lowered through appropriate pH adjustments (i.e. formation of the unionized drug) to force the complex out of solution. Finally, solid drug-cyclodextrin complexes can be formed by the grinding of a physical mixture of the drug and cyclodextrin and then heating the mixture in a sealed container to 60 to 90 °C.

Methods for enhancing cyclodextrin complexation

For a variety of reasons including cost, production capabilities and toxicology, the amounts of cyclodextrin which can be used in most drug formulations is limited (T. Loftsson and M.E. Brewster, "Cyclodextrins as pharmaceutical excipients", *Pharm. Technol. Eur.*, 9(5), 26-34 (1997); T. Loftsson, "Increasing the cyclodextrin complexation of drugs and drug bioavailability through addition of water-soluble polymers", *Pharmazie*, 53, 733-740 (1998)).

If one drug molecule (D) forms a complex with one cyclodextrin molecule (CD), then the complexation efficiency ([D-CD]/[CD]) will be equal to the intrinsic solubility of the drug (S_0) times the stability constant of the drug-cyclodextrin complex (K_C). In aqueous cyclodextrin solutions saturated with drug, the concentration of free drug ([D]) is approximately equal to S_0. Thus,

increased complexation efficiency can be obtained by either increasing S_0 or by increasing K_C or by increasing both simultaneously. Addition of organic solvents, such as ethanol, to the aqueous complexation media can result in enhanced complexation efficiency through increase in S_0. Drug ionization can increase the complexation efficiency through increase in S_0. Addition of certain low molecular weight acids, such as acetic, citric, malic, or tartaric acid, to aqueous complexation media can enhance cyclodextrin solubilization of basic drugs through increase in S_0 (i.e. salt formation, pH changes and lowering melting point) and/or increase in the apparent K_C. Water-soluble polymers can increase the complexation efficiency through increase in the apparent K_C. Furthermore, it is often possible to enhance cyclodextrin complexation even further by using several different methods simultaneously to enhance the cyclodextrin complexation. Pharmaceutical applications of these and other methods have been reviewed (See T. Loftsson, "Increasing the cyclodextrin complexation of drugs and drug bioavailability through addition of water-soluble polymers", *Pharmazie*, 53, 733-740 (1988); T. Loftsson and M.E. Brewster, "Cyclodextrins as pharmaceutical excipients", *Pharm. Technol. Eur.*, 9(5), 26-34 (1997); T. Loftsson and M.E. Brewster, "Pharmaceutical applications of cyclodextrins. I. Drug solubilization and stabilization", *J. Pharm. Sci.* 85(10), 1017-1025 (1996)).

Permeability of drugs through biological membranes

The cyclodextrin molecules are relatively large (molecular weight ranging from almost 1000 to over 1500), with a hydrated outer surface, and under normal conditions, cyclodextrin molecules will only permeate biological membranes with considerable difficulty (R.A. Rajewski and V.J. Stella, "Pharmaceutical applications of cyclodextrins. 2. In vivo drug delivery", *J. Pharm. Sci.* 85(11), 1142-1168 (1996); T. Irie and K. Uekama, "Pharmaceutical applications of cyclodextrins. 3. Toxicological issues and safety evaluation", *J. Pharm. Sci.*

86(2), 147-162 (1997); K.-H. Frömming and J. Szejtli, *Cyclodextrins in pharmacy*, Kluwer Academic Publishers, Dordrecht, The Netherlands, 1994; T. Loftsson and J.H. Ólafsson, "Cyclodextrins: new drug delivery systems in dermatology", *Int. J. Dermatol.*, 37, 241-246 (1998); T. Loftsson and E. Stefánsson, "Effect of cyclodextrins on topical drug delivery to the eye", *Drug Dev. Ind. Pharm.* 23(5), 473-481 (1997)). It is generally recognized that cyclodextrins act as true carriers by keeping the hydrophobic drug molecules in solution and deliver them to the surface of the biological membrane, e.g. skin, mucosa or the eye cornea, where they partition into the membrane. The relatively lipophilic membrane has low affinity for the hydrophilic cyclodextrin molecules and therefore they remain in the aqueous membrane exterior, e.g. the aqueous vehicle system, salvia or the tear fluid. Conventional penetration enhancers, such as alcohols and fatty acids, disrupt the lipid layers of the biological barrier. Cyclodextrins, on the other hand, act as penetration enhancers by increasing drug availability at the surface of the biological barrier. Furthermore, addition of water-soluble polymer, such as polyvinylpyrrolidone, apparently increase even further the availability of the drug molecules at the surface of the biological membrane resulting in enhanced drug bioavailability (T. Loftsson, "Increasing the cyclodextrin complexation of drugs and drug bioavailability through addition of water-soluble polymers", *Pharmazie*, 53, 733-740 (1998); T. Loftsson, M. Másson and E. Stefánsson, "Cyclodextrins as Permeation enhancers", *Proceedings of the 17th Pharmaceutical Technology Conference and Exhibition*, Volume 2, Dublin, 24-26 March, 1998, pp. 313-324).

OBJECTS AND SUMMARY OF THE INVENTION

Enhancing complexation efficiency

It is possible to enhance the cyclodextrin (CD) complexation efficacy, or efficiency, of drugs (D), and other "guest" molecules, by either increasing the

apparent stability constant (K_C) of the drug-cyclodextrin complex (D-CD) or increasing the apparent intrinsic solubility (S_0) of the drug. For example, K_C can be increased by addition of water-soluble polymers to the aqueous complexation media and S_0 can be increased by ionization of the drug molecule, as described previously. However, increased complexation efficiency by itself does not necessarily result in increased drug availability in the aqueous complexation media or increased drug availability from solid drug-cyclodextrin complexes. On the other hand, if the drug-cyclodextrin complexes are prepared under conditions which ensure enhanced complexation and if the complexation efficiency decreases upon administration, then enhanced drug availability will be observed. Thus, the present invention involves: i) enhancement of the complexation efficiency and ii) reduction of the complexation efficiency after administration. For example, it is possible to enhance the complexation efficiency of many ionizable drugs by preparing the complexes at a pH where the drug is ionized but obtain decreased efficiency upon administration due to pH changes and consequent decreased ionization. One example of such a drug is phenytoin (pKa 8.1). Its solubility in water at room temperature (25 °C) is only 18 μg/ml at pH 5 and 32 μg/ml at pH 8 (P.A. Schwartz, C.T. Rhodes and J.W. Cooper, "Solubility and ionisation characters of phenytoin", *J. Pharm. Sci.*, 66, 994-997 (1977)). Addition of 25% (w/v) 2-hydroxypropyl-β-cyclodextrin to the aqueous solutions increases the solubility of phenytoin to 5.0 mg/ml at pH 5 and 6.4 mg/ml at pH 8, which is 280- and 200-fold solubility enhancement, respectively. Although the apparent stability constant (K_C) of the phenytoin-cyclodextrin complex is much larger for the drug in the unionized form than for the anionic form, it is possible to obtain much higher total solubility by increasing the apparent intrinsic solubility (S_0) of the drug (T. Loftsson and N. Bodor, "Effects of 2-hydroxypropyl-β-cyclodextrin on the aqueous solubility of drugs and transdermal delivery of 17β-estradiol", *Acta Pharm. Nord.*, 1, 185-194 (1989)). However, if the pH 8.0 solution was placed in

an environment which would decrease the pH from 8 to 5 (e.g. topical application to the skin), then a supersaturated solution would be formed which would result in enhanced drug availability (e.g. it would result in enhanced transdermal drug delivery). Other means to enhance S_0 include reversible derivation (e.g. prodrug formation) of the guest molecule and addition of certain low molecular weight acids. The value of K_C can, for example, be increased by addition of certain low molecular weight acids, by addition of water-soluble polymers to the aqueous complexation media or by using mixed solvent systems such as aqueous 10% (v/v) acetic acid. For example, addition of the polymers and heating in an autoclave (to 120-140°C for 20-40 minutes) does not only increase the complexation but it has also been shown to enhance transdermal and transcorneal drug delivery (T. Loftsson and A.M. Sigurdardottir, "Cyclodextrins as skin penetration enhancers", in J. Szejtli and L. Szente (Eds.) *Proceedings of the Eighth International Symposium on Cyclodextrins*, Kluwer Academic Publishers, 1996, pp. 403-406; T. Loftsson and E. Stefansson, "Effect of cyclodextrins on topical drug delivery to the eye", *Drug Devel. Ind. Pharm.*, 23(5), 473-481 (1997)). As shown in **Table 1** below, it is not enough to add the polymers to the complexation medium. Addition of polymers to the unheated vehicles did not enhance the transdermal delivery of enalaprilat. However, heating the vehicles after addition of the polymers resulted in significant enhancement. The effect of the polymers on the transdermal delivery of enalaprilat can, at least partly, be explained by decreased complexation efficiency (i.e. decrease in K_C) at the skin surface.

Table 1. The effect of heating on transdermal delivery of enalaprilat from 10% (w/v) HPβCD solutions at pH 5.0 containing 2.5% enalaprilat in a suspension. The concentration of dissolved enalaprilat was between 2.0 and 2.3% (w/v).

Donor phase (w/v per cent)	Flux (mg h^{-1} cm^{-2}) Un-heated	Heated	Ratio
HPβCD	18±2	-	-
HPβCD, 0.25% PVP	16±6	23±7	1.4
HPβCD, 0.10% HPMC	14±3	37±12	2.6

In one aspect of the present invention there is provided a method for enhancing the complexation efficacy, i.e. efficiency, of a drug with cyclodextrin, said drug having a structure comprising at least one heterocyclic ring having a total of from 4 to 7 ring atoms, of which from 1 to 3 are hetero ring atoms, each of said hetero ring atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imide, hemiacetal or hemiketal, said method comprising subjecting said drug to chemically reversible ring-opening so that at least a portion (at least 0.1% by weight) thereof is in ring-opened form, and complexing said drug with cyclodextrin.

In a related aspect of the invention, there is provided a method for enhancing the complexation efficiency of a drug with cyclodextrin, said drug having a structure comprising at least one heterocyclic ring having a total of from 4 to 7 ring atoms, of which from 1 to 3 are hetero ring atoms, each of said hetero ring atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imide, hemiacetal

or hemiketal, said method comprising complexing said drug with cyclodextrin in an aqueous medium under conditions which effect chemically reversible ring-opening of at least a portion (at least 0.1% by weight) of said drug.

In another aspect of the invention, there is provided a method for enhancing the availability of a drug following administration of a cyclodextrin-drug complex to a warm-blooded animal in need of same, said drug having a structure comprising at least one heterocyclic ring having a total of from 4 to 7 ring atoms of which from 1 to 3 are hetero ring atoms, each of said hetero ring atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imine, hemiacetal or hemiketal, said method comprising complexing said drug with cyclodextrin in an aqueous medium under conditions which effect chemically reversible ring-opening of at least a portion (at least 0.1% by weight) of said drug to enhance the complexation efficiency, followed by administering the cyclodextrin-drug complex thus obtained to said animal under conditions which reduce the complexation efficiency.

In still another aspect, the present invention provides a method for enhancing the availability of a basic drug (i.e. a proton acceptor) following administration of a cyclodextrin-drug complex to a warm-blooded animal in need of same, said basic drug having a structure comprising at least one heterocyclic ring having a total of from 4 to 7 ring atoms, of which from 1 to 3 are hetero ring atoms, each of said hetero ring atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imide, hemiacetal or hemiketal, said method comprising subjecting said basic drug to complexation in an aqueous medium at a pH level below the pKa+2 value of said basic drug to enhance the complexation efficiency, followed by administering the cyclodextrin-drug complex thus obtained to said animal under conditions which reduce the complexation efficiency.

In yet another aspect, the present invention provides a method for enhancing the availability of an acidic drug following administration of a cyclodextrin-drug complex to a warm-blooded animal in need of same, said acidic drug having a structure comprising at least one heterocyclic ring having a total of 4 to 7 ring atoms, of which from 1 to 3 are hetero ring atoms, each of said hetero ring atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imide, hemiacetal or hemiketal, said method comprising subjecting said acidic drug to complexation in an aqueous medium at a pH level above the pKa-2 value of said acidic drug to enhance the complexation efficiency, followed by administering the cyclodextrin-drug complex thus obtained to said animal under conditions which reduce the complexation efficiency.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph illustrating the effect of pH on the phase-solubility of phenytoin (pKa 8.1) in aqueous hydroxypropyl-β-cyclodextrin (HPβCD) solutions at 25°C at pH 10.19 (◆); pH 7.55 (■) and pH 2.74 (●);

Fig. 2 is a graph illustrating the effect of pH on the solubility of alprazolam (pKa 2.4) in aqueous 10% (w/v) HPβCD solutions at room temperature;

Fig. 3 is a graph illustrating the effect of pH (i.e. the diazepine ring-opening) on the solubility of midazolam (pKa 6.2) in pure aqueous buffer solutions (●), aqueous buffer solutions containing 10% (w/v) HPβCD (■) and aqueous buffer solutions containing both 10% (w/v) HPβCD and 0.10% (w/v) hydroxypropyl methylcellulose (HPMC) (◆) at room temperature;

Fig. 4 is a graph illustrating the effects of cyclodextrins, pH and 10% (v/v) acetic acid on the solubility of midazolam in aqueous solutions: pure aqueous buffer solution (▲); aqueous 10% (v/v) acetic acid solution (●); 10% w/v HPβCD solution containing 0.10% (w/v) HPMC in aqueous 10% (v/v) acetic acid solution

(■); 10% (w/v) aqueous sulfobutyl ether-β-cyclodextrin (SBEβCD) solution in aqueous 10% (v/v) acetic acid solution (◆); and

Fig. 5 is a graph plotting the concentration in ng/ml of midazolam in serum after intravenous administration of 2 mg of a commercial intravenous formulation of midazolam (○) and nasal administration of 4.8 mg of a nasal formulation of midazolam prepared in accord with the present invention (Δ), against time in minutes, where each point represents the mean value and error bars represent standard deviation.

DETAILED DESCRIPTION OF THE INVENTION

The following table (**Table 2**) lists some of the currently available cyclodextrins contemplated for use in the present invention.

Table 2. Some of the currently available cyclodextrins obtained by substitution of the OH-groups located on the edge of the cyclodextrin ring. Since both the number of substituents and their location will affect the physicochemical properties of the cyclodextrin molecules, such as their aqueous solubility and complexing abilities, each derivative listed should be regarded as a group of closely related cyclodextrin derivatives.

Type	α-Cyclodextrin derivatives	β-Cyclodextrin derivatives	γ-Cyclodextrin derivatives
Alkylated:			
	Methyl	Methyl	Methyl
		Ethyl	
	Butyl	Butyl	Butyl
			Pentyl
Hydroxylalkylated:			
		Hydroxyethyl	Hydroxyethyl
	2-Hydroxypropyl	2-Hydroxypropyl	2-Hydroxypropyl
		2-Hydroxybutyl	
Esterified:			
	Acetyl	Acetyl	Acetyl
		Propionyl	
		Butyryl	
	Succinyl	Succinyl	Succinyl
		Benzoyl	
		Palmityl	
		Toluenesulfonyl	
Esterified and alkylated:			
		Acetyl methyl	
		Acetyl butyl	
Branched:			
	Glucosyl	Glucosyl	Glucosyl
	Maltosyl	Maltosyl	Maltosyl
Ionic:			
	Carboxymethyl ether	Carboxymethyl ether	Carboxymethyl ether
		Carboxymethyl ethyl	
	Phosphate ester	Phosphate ester	Phosphate ester
		3-Trimethylammonium-2-hydroxypropyl ether	
		Sulfobutyl ether	
Polymerized:			
	Simple polymers	Simple polymers	Simple polymers
	Carboxymethyl	Carboxymethyl	Carboxymethyl

Particularly preferred cyclodextrins for use herein are hydroxypropyl-β-cyclodextrin, β-cyclodextrin sulfobutyl ether, the branched β-cyclodextrins (especially glucosyl-β-cyclodextrin and maltosyl-β-cyclodextrin), β-cyclodextrin, hydroxypropyl-γ-cyclodextrin and γ-cyclodextrin.

In preferred aspects of the present invention, the drug for use herein is one having a structure comprising at least one heterocyclic ring. The heterocyclic ring generally has a total of 4 to 7 ring atoms, of which from 1 to 3 are hetero ring atoms. While each hetero ring atom can be nitrogen, oxygen or sulfur, heterocycles having at least one nitrogen or oxygen ring atom are preferred. Preferably, the drug has at least one heterocyclic ring which is a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imide, hemiacetal or hemiketal.

Especially desirable drugs for use in accord with the present invention are benzodiazepines. Benzodiazepines contain a benzene ring fused with a diazepine ring which is a 7-membered ring with nitrogen atoms in positions 1 and 4. By way of example, the chemical name of alprazolam is 8-chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine, the chemical name of midazolam is 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine and that of triazolam is 8-chloro-6-(o-chlorophenyl)-1-methyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine. Thus, all of these compounds have the 1,4-benzodiazepine structure with a double bond between nitrogen atom number 4 and carbon atom number 5 (which gives the molecule a cyclic imine structure). The benzodiazepines are cyclic imines. They are all basic, i.e. they are proton acceptors. Preferred benzodiazepines for use herein are alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, diazepam, nitrazepam, oxazepam, midazepam, lorazepam, prazepam, quazepam, triazolam, temazepam and lorazolam. Especially preferred are midazolam, alprazolam, clonazepam, lorazepam and triazolam.

Another group of preferred drugs for use herein consists of the barbituric acid derivatives. The barbituric acids contain a 2,4,6-trihydroxypyrimidine (also called 2,4,6-trioxohexahydropyrimidine) ring in their structure, a 6-member ring with nitrogen in positions 1 and 3. Thus, the chemical name of barbital is 5,5-diethyl-2,4,6(1H,3H,5H)-pyrimidinetrione and that of phenobarbital is 5-ethyl-5-phenyl-2,4,6(1H,3H,5H)-pyrimidinetrione. The barbituric acids can be characterized as cyclic amides or lactams (cyclic amides are called lactams) or imides (which are nitrogen analogues of cyclic anhydrides). Barbituric acids are weak acids. Preferred barbituric acid derivatives are barbital, butobarbital, amobarbital, phenobarbital, aprobarbital, secobarbital, crotylbarbital, cyclobarbital, phenobarbital, hexobarbital, methylphenobarbital, thiopental, isopropylbromallylbarbituric acid, cyclohexenylallylthiobarbituric acid and their salts. Thiopental is 5-ethyldihydro-5-(1-methylbutyl)-2-thioxo-4,6(1H,5H)-pyrimidinedione, i.e. one = O moiety in the barbituric acid structure has been replaced by = S.

Yet another group of preferred drugs for use in the present invention consists of the hydantoins. Hydantoins are, like barbituric acids, cyclic urea derivatives. The ring-opened acyl derivatives of hydantoins and barbituric acids are sometimes called ureides. Both hydantoins and barbituric acids can form urea upon hydrolysis. Hydantoins contain a 2,4-imidazolidinedione ring in their structure, a 5-membered ring with nitrogen in positions 1 and 3. The chemical name of, for example, phenytoin, is 5,5-diphenyl-2,4-imidazolidinedione. Hydantoins are closely related to barbituric acids and are acids like them.

Still another group of preferred drugs for use in the present invention consists of pyrazole derivatives. The expression "pyrazole derivatives" as used herein includes drugs containing a pyrazole ring, 3-pyrazoline ring or pyrazolidine ring in their structure, all of which are 5-membered rings with nitrogens in positions 1 and 2. These compounds are either basic or acidic. Preferred pyrazole

derivatives for use herein include phenazone, phenylphenazone, metamidazole, phenylbutazone, oxyphenbutazone and sulfinpyrazone.

Yet another group of drugs preferred for use herein consists of imidazole derivatives. The expression "imidazole derivatives" as used herein includes drugs containing an imidazole, imidazoline or imidazolidine ring in their structure. These are 5-membered rings with nitrogen atoms in positions 1 and 3. These compounds are either basic or acidic. Preferred compounds of this type include histamine, miconazole, pilocarpine, naphazoline and clonidine.

Another group of preferred drugs for use in this invention are pyrimidine derivatives. These drugs contain a 6-membered ring with nitrogen atoms in positions 1 and 3. These derivatives are usually basic. Preferred pyrimidine derivatives include thiamine, trimethoprim, orotic acid, methylthiouracyl and prothiouracyl.

Still another group of preferred drugs for use herein are purine derivatives, which contain purine, that is, imidazo(4,5-d)pyrimidine, in their structures. These drugs are frequently basic but some of them are acidic. Preferred purine derivatives include caffeine, theophylline, etophylline, proxyphylline and theobromine.

Cyclic drugs having heterocyclic rings characterized as enamines, lactones, lactams, thiolactams, anhydrides, imides, imines, hemiacetals and hemiketals are thus appropriate for use in preferred embodiments of the invention, in which ring opening of the heterocyclic ring takes place.

In various aspects of the present invention, the drug is subjected to chemically reversible ring-opening so that at least a portion thereof is in ring-opened form. The portion in ring-opened form is at least 0.1% by weight, preferably at least 1 or 2% by weight, more preferably at least 5% by weight of said drug. In aqueous formulations, the amount of drug in ring-opened form is frequently from about 5 to about 10% by weight and usually no more than about

50%. In solid formulations, the portion of drug in ring-opened form can generally be much higher, frequently about 50% or more, and sometimes even about 90 to 95%.

When the method of the invention comprises complexing the drug with cyclodextrin in an aqueous medium under conditions which effect chemically reversible ring-opening of at least a portion (at least 0.1% by weight) of the drug, the complexation is advantageously conducted at a pH level which affords ring-opening of at least 5% by weight of said drug. Preferably the complexation is conducted at a pH level of below about 5.

In one preferred embodiment, the drug is a basic drug, especially a benzodiazepine, and the complexation is conducted at a pH level of below about 5. It is also preferred that the cyclodextrin is hydroxypropyl-β-cyclodextrin, β-cyclodextrin sulfobutyl ether, a branched β-cyclodextrin (especially glucosyl β-cyclodextrin or maltosyl-β-cyclodextrin), β-cyclodextrin, hydroxypropyl-γ-cyclodextrin or γ-cyclodextrin. It is also preferred that the benzodiazepine is alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, diazepam, nitrazepam, oxazepam, midazepam, lorazepam, prazepam, quazepam, triazolam, temazepam or loprazolam; and that the cyclodextrin-drug complex thus obtained be formulated as a nasal spray, sublingual tablet or parenteral solution, especially when formulated suitable for use in producing a sedative, anti-anxiety, anticonvulsant or muscle relaxant effect, most especially as a pre-anaesthetic medication, or to supplement anaesthesia, to induce and/or maintain anaesthesia or to induce a hypnotic effect. In especially preferred embodiments, the benzodiazepine is midazolam, alprazolam, clonazepam, lorazepam or triazolam; the cyclodextrin is hydroxypropyl-β-cyclodextrin, β-cyclodextrin sulfobutyl ether, a branched β-cyclodextrin (especially glucosyl β-cyclodextrin or maltosyl β-cyclodextrin), β-cyclodextrin, hydroxypropyl-γ-

cyclodextrin or γ-cyclodextrin; and the complexation is conducted at a pH level below about 5, preferably between about 3 and about 5.

In another embodiment of the present method utilizing chemically reversible ring-opening described above, the drug is an acidic drug.

In yet another embodiment of the present method utilizing chemically reversible ring-opening described above, the drug is a barbituric acid derivative, a hydantoin, a pyrazole derivative, an imidazole derivative, a pyrimidine derivative or a purine derivative. When the drug is a barbituric acid derivative, it is preferably barbital, butobarbital, amobarbital, phenobarbital, aprobarbital, secobarbital, crotylbarbital, cyclobarbital, phenobarbital, hexobarbital, methylphenobarbital, thiopental, isopropylbromallylbarbituric acid, or cyclohexenylallylthiobarituric acid, or a salt thereof. When the drug is a hydantoin, it is preferably phenytoin. When the drug is a pyrazole derivative, it is preferably phenazone, propylphenazone, metamidazole, phenylbutazone, oxyphenbutazone or sulfinpyrazone. When the drug is an imidazole derivative, it is preferably histamine, miconazole, pilocarpine, naphazoline or clonidine. When the drug is a pyrimidine derivative, it is preferably thiamine, trimethoprim, orotic acid, methylthiouracyl or prothiouracyl. When the drug is a purine derivative, it is preferably caffeine, theophylline, etophylline, proxyphylline or theobromine.

When the present invention comprises complexing the drug with cyclodextrin in an aqueous medium under conditions which effect chemically reversible ring-opening of at least a portion (at least 0.1% by weight) of the drug to enhance the complexation efficacy, followed by administering the cyclodextrin-drug complex thus obtained to said animal under conditions which reduce the complexation efficacy, the complexation is generally conducted at a pH level which affords ring-opening of at least 5% by weight of the drug. Preferably, the complexation is conducted at a pH level of below about 5, especially between about 3 and about 5. The cyclodextrin is preferably hydroxypropyl-β-

cyclodextrin, β-cyclodextrin sulfobutyl ether, a branched β-cyclodextrin (especially glucosyl-β-cyclodextrin or maltosyl-β-cyclodextrin), β-cyclodextrin, hydroxypropyl-γ-cyclodextrin or γ-cyclodextrin. The drug is preferably a benzodiazepine, especially midazolam, alprazolam, clonazepam, lorazepam or triazolam. The cyclodextrin-drug complex is preferably administered in the form of an aqueous solution or a hydrogel, particularly as a nasal spray or nasal drops, or as a parenteral solution. As a nasal spray of a benzodiazepine, the aqueous solution is advantageously brought to a pH level of below about 6, preferably below about 4.7, most especially to a pH between about 3 and about 4.7. When administered as a solid, the cyclodextrin-drug complex is preferably formulated as a tablet for oral, buccal or sublingual administration. The water may be removed from the aqueous complexation medium after formation of the cyclodextrin-drug complex.

When the present invention comprises subjecting a basic drug to complexation in an aqueous medium at a pH level below the pKa+2 value of said basic drug to enhance the complexation efficiency, followed by administering the cyclodextrin-drug complex thus obtained to an animal under conditions which reduce the complexation efficiency, the basic drug is preferably a benzodiazepine. Benzodiazepines of particular interest are alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, diazepam, nitrazepam, oxazepam, midazepam, lorazepam, prazepam, quazepam, triazolam, temazepam and loprazolam. Particularly preferred benzodiazepines are alprazolam, midazolam, clonazepam, lorazepam and triazolam. The cyclodextrin-benzodiazepine complex obtained in the complexation step is preferably formulated as a nasal spray, sublingual tablet or parenteral solution, which is preferably administered in an effective sedative, anti-anxiety, anticonvulsant or muscle relaxant amount, particularly as a pre-anaesthetic

medication, or to supplement anaesthesia, to induce and/or maintain anaesthesia or to induce a hypnotic effect. In this general aspect of the invention, the pH level of the aqueous complexation medium is advantageously selected so that it also affords ring-opening of at least 5% by weight of the drug. For the benzodiazepines, the complexation is preferably conducted at a pH level of below about 5, most preferably between about 3 and about 5. Also in this general aspect of the invention, in one preferred embodiment, the complexation is carried out in the presence of from about 0.001 to about 5% (weight/volume) of a pharmacologically inactive, pharmaceutically acceptable water-soluble polymer at a temperature of from about 30°C to about 150°C. Preferably, the polymer is a cellulose derivative or a polyvinyl polymer; more preferably, the polymer is methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl methylcellulose, hydroxypropyl ethylcellulose, hydroxyethyl ethylcellulose, sodium carboxymethylcellulose or polyvinylpyrrolidone. An especially preferred cellulose derivative is hydroxypropyl methylcellulose. A method for enhancing drug-cyclodextrin complexation utilizing a pharmacologically inactive water-soluble polymer is described in Loftsson United States Patents No. 5,324,718 and No. 5,472,954. In another preferred embodiment of this general aspect of the invention, the complexation is also carried out in the presence of acetic acid and/or one or more pharmaceutically acceptable salts of acetic acid, the acetate-water ratio of the aqueous complexation medium being from about 1:1000 to about 2:1, preferably from about 1:100 to about 1:1, more preferably from about 1:20 to about 1:4. Preferably, the drug is midazolam and the cyclodextrin is hydroxypropyl-β-cyclodextrin, β-cyclodextrin sulfobutyl ether, a branched β-cyclodextrin (especially glucosyl-β-cyclodextrin or maltosyl-β-cyclodextrin), β-cyclodextrin, hydroxypropyl-γ-cyclodextrin or γ-cyclodextrin.

When the present invention comprises subjecting an acidic drug to complexation in an aqueous medium at a pH level above the pKa-2 value of said acidic drug to enhance the complexation efficiency, followed by administering the cyclodextrin-drug complex thus obtained to an animal under conditions which reduce the complexation efficiency, preferably the pH level of the aqueous complexation medium is selected such that it also affords ring-opening of at least 5% by weight of said drug.

In order to further illustrate the present invention and the advantages thereof, the following specific examples are given, it being understood that same are intended only as illustrative and in no way limitative of the invention.

Example 1

Phenytoin (5,5-diphenylhydantoin) is a water-insoluble weak acid (pKa 8.1) which forms a somewhat water-soluble anion in alkaline solution. Solubility (S) of phenytoin at three different pH levels was determined in aqueous solutions containing various amounts of 2-hydroxypropyl-β-cyclodextrin (HPβCD) of molar substitution (MS) = 0.9, i.e. (a) pH 2.74±0.18 (SD), (b) pH 7.55±0.12, and (c) pH 10.19±0.14. Excess amount of the drug was added to the aqueous HPβCD solution and the suspension formed sonicated for one hour at room temperature (23°C). After equilibration at 25°C in a water-bath for three days, the suspension was filtered through a 0.45 μm membrane filter, diluted with aqueous methanolic solution and the amount of dissolved phenytoin determined by a high pressure liquid chromatographic method (HPLC). **FIG. 1** illustrates the effect of pH on the phase-solubility of phenytoin (pKa 8.1) in aqueous HPβCD solutions at 25°C. The results set forth in **FIG. 1** show significant enhancement in the HPβCD solubilization (i.e. the efficiency of the complexation) of the drug at pH 10.19 (◆) where the drug is mainly in the ionized form. Formation of phenytoin-HPβCD complexes at pH 10.19 can result in enhanced bioavailability of phenytoin. For

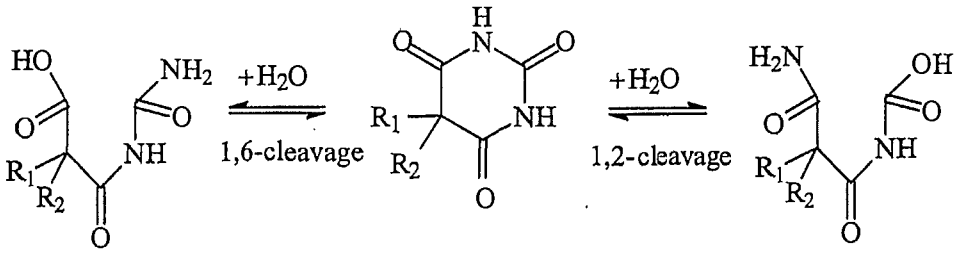
example, topical application of such a solution to the skin will result in lowering of pH, which will decrease the efficiency of the complexation, which again will result in enhanced permeability of phenytoin into and through the skin. Also, formation of phenytoin-HPβCD complexes at pH of about 10 (e.g. in aqueous ammonia solutions) and lyophilization of the complex will result in phenytoin-HPβCD complex powder which can, for example, be formulated into tablets. The bioavailability of phenytoin from such tablets will be enhanced compared to the phenytoin availability from tablets containing phenytoin-HPβCD complex prepared at lower pH, e.g. at pH 2.7 (●) or 7.6 (■).

Example 2

Alprazolam is a water-insoluble weak base (pKa 2.41) which forms a somewhat water-soluble cation in acidic solution. Solubility (S) of alprazolam at several different pH levels was determined in aqueous solutions containing 10% (w/v) 2-hydroxypropyl-β-cyclodextrin (HPβCD) of molar substitution (MS) = 0.3. Excess amount of the drug was added to the aqueous HPβCD solution and the suspension formed heated in a sealed container in an autoclave (120-140°C for 20-40 minutes). After equilibration at room temperature (22-23°C) for seven days, the suspension was filtered through a 0.45 μm membrane filter, diluted with aqueous methanolic solution and the amount of dissolved alprazolam determined by a high pressure liquid chromatographic method (HPLC). **FIG. 2** illustrates the effect of pH on the solubility of alprazolam (pKa 2.4) in aqueous 10% (w/v) HPβCD solutions at room temperature. The results set forth in **FIG. 2** show significant enhancement in the HPβCD solubilization (i.e. the efficiency of the complexation) of the drug at a pH at which the drug is mainly in the ionized form. The sharp increase in the solubility can, however, only partly be explained by the ionization of the alprazolam molecule.

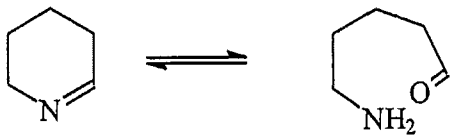
Example 3

Several drugs which have a nitrogen-containing heterocycle in their structure are known to undergo reversible ring-opening which frequently is pH dependent. For example, barbituric acids undergo reversible ring cleavage (H.J. Roth, K. Eger and R. Troschütz, *Pharmaceutical Chemistry. Volume 2. Drug Analysis*. Ellis Horwood, 1991, pp. 308-309):



Another example of such reversible ring-opening is the opening of cyclic imines through formation of an aldehyde or ketone and a primary amine:

Another example of such reversible ring-opening is the opening of cyclic imines through formation of an aldehyde or ketone and a primary amine:



An example of such structure is the 1*H*-1,4-diazepine ring which, for example, is an essential structure of the benzodiazepine derivatives. These structural changes are pH-dependent and reversible, and it is known that the open form frequently co-exists with the closed one in several commercial products. One example is the *iv* solution of midazolam (Dormicum™ from F. Hoffmann-LaRoche & Ltd,

Switzerland) where the drug is partly in the open form (M. Gerecke, "Chemical structure and properties of midazolam compared with other benzodiazepines", *Br. J. Clin. Pharmac.*, 11S-16S (1983)). However, the open form of midazolam is rapidly converted to the closed one upon *iv* administration.

We have determined the effect of pH and cyclodextrins, i.e. HPβCD MS 0.3, sulfobutylether β-cyclodextrin (SBEβCD) with degree of substitution (DS) = 6.4, α-cyclodextrin (αCD) and γ-cyclodextrin (γCD) on the ring-opening of several benzodiazepines. The cyclodextrin concentration was 10% (w/v) and the benzodiazepine concentration was $1x10^{-4}$ M. The concentration of the closed form was determined immediately after dissolving the benzodiazepine in the aqueous cyclodextrin solution and again 24 hours later (i.e. after equilibration at 23°C). Preliminary experiments had shown that equilibrium between the closed and the open form was attained within 3 hours at 23°C.

It is clear from the results displayed in **Table 3** below that a large fraction of the benzodiazepines (over 50% at pH below 2) are in the open form at low pH and that the fraction of open form frequently increases upon addition of cyclodextrin to the aqueous solution. For example, at pH 3 about 60% of alprazolam in aqueous HPβCD solution is in the open form. This will increase the apparent intrinsic solubility (S_0). This increase in S_0 will result in enhanced complexation efficiency. The observed increase in the complexation efficiency will result in enhanced cyclodextrin solubilization of the benzodiazepines in aqueous solutions.

Table 3. The effect of pH and cyclodextrins on the fraction of the open form of several benzodiazepines at room temperature (approx. 23 °C).

Benzodiazepine	Cyclodextrin	pH	Fraction open
Alprazolam (pKa 2.4)	None	2	0.82
		3	0.56
		4	0.33
	HPβCD	2	0.89
		3	0.60
		4	0.23
	SBEβCD	2	0.96
		3	0.84
		4	0.33
	αCD	2	0.94
		3	0.79
		4	0.25
	γCD	2	0.81
		3	0.41
		4	0.42
Diazepam (pKa 3.3)	None	2	0.30
		3	0.23
		4	0.15
	HPβCD	2	0.65
		3	0.29
		4	0.15
	SBEβCD	2	0.63
		3	0.56
		4	0.22
	αCD	2	0.67
		3	0.51
		4	0.13
	γCD	2	0.41
		3	0.17
		4	0.13

Table cont. on next page.

Benzodiazepine	Cyclodextrin	pH	Fraction open
Midazolam (pKa 6.2)	None	2	0.74
		3	0.28
		4	0.18
	HPβCD	2	0.56
		3	0.18
		4	0.23
	SBEβCD	2	0.81
		3	0.39
		4	0.11
	αCD	2	0.79
		3	0.32
		4	0.10
	γCD	2	0.61
		3	0.21
		4	0.17
Triazolam	None	2	0.53
(pKa between 2 and 3)		3	0.08
		4	0.00
	HPβCD	2	0.51
		3	0.09
		4	0.00
	SBEβCD	2	0.71
		3	0.25
		4	0.00
	αCD	2	0.75
		3	0.23
		4	0.00
	γCD	2	0.33
		3	0.01
		4	0.00

Example 4

Midazolam is a water-insoluble weak base (pKa 6.2) which forms a somewhat water-soluble cation in acidic solution. Solubility (S) of midazolam at several different pH levels was determined in: a) pure aqueous buffer solutions (i.e. without HPβCD and HPMC); b) aqueous buffer solutions containing 10% (w/v) 2-hydroxypropyl-β-cyclodextrin (HPβCD) of molar substitution (MS) = 0.3; and c) aqueous solutions containing 10% (w/v) 2-hydroxypropyl-β-cyclodextrin (HPβCD) of molar substitution (MS) = 0.3 and 0.10% (w/v) hydroxypropyl methylcellulose (HPMC) 4000. Excess amount of the drug was added to the aqueous solution and the suspension formed was heated in a sealed container in an autoclave (120-140°C for 20-40 minutes). After equilibration at room temperature (22-23°C) for seven days, the suspension was filtered through a 0.45 μm membrane filter, diluted with aqueous methanolic solution and the amount of dissolved midazolam determined by a high pressure liquid chromatographic method (HPLC). **FIG. 3** illustrates the effect of pH (i.e. the ring-opening) on the solubility of midazolam (pKa 6.2) in pure aqueous buffer solutions (●), aqueous buffer solutions containing 10% (w/v) HPβCD (■), and aqueous buffer solutions containing both 10% (w/v) HPβCD and 0.10% (w/v) HPMC (◆) at room temperature. The results set forth in **FIG. 3** show significant enhancement in the HPβCD solubilization (i.e. the efficiency of the complexation) of the drug at pH levels where the drug exists partly in the open form. Addition of HPMC significantly improves the efficiency.

Example 5

Solubility (S) of midazolam at several different pH levels was determined in: a) pure aqueous buffer solutions (i.e. without cyclodextrin, polymer or acetic acid); b) aqueous buffer solutions containing 10% (v/v) acetic acid as a co-solvent; c) aqueous buffer solutions containing 10% (w/v) sulfobutylether β-cyclodextrin

(SBEβCD) and 10% (v/v) acetic acid as a co-solvent; and d) aqueous buffer solutions containing 10% (w/v) 2-hydroxypropyl-β-cyclodextrin (HPβCD), 0.10% (w/v) hydroxypropyl methylcellulose (HPMC) and 10% (v/v) acetic acid as a co-solvent. Excess amount of the drug was added to the aqueous HPβCD solution and the suspension formed was heated in a sealed container in an autoclave (120-140°C for 20-40 minutes). After equilibration at room temperature (22-23°C) for seven days, the suspension was filtered through a 0.45 μm membrane filter, diluted with aqueous methanolic solution and the amount of dissolved midazolam determined by a high pressure liquid chromatographic method (HPLC). **FIG. 4** illustrates the effects of cyclodextrins, pH and 10% (v/v) acetic acid on the solubility of midazolam in aqueous solutions: pure aqueous buffer solution (▲); aqueous 10% (v/v) acetate solution (●); 10% (w/v) HPβCD solution containing 0.10% (w/v) HPMC in aqueous 10% (v/v) acetic acid solution (■); 10% (w/v) aqueous SBEβCD solution in aqueous 10% (v/v) acetate (◆). The results set forth in **FIG. 4** show that addition of 10% (v/v) acetic acid significantly improves the complexation. Addition of the acetic acid increases the value of S_0 without having any significant effect on the value of $K_{C,}$ which significantly improves the complexation efficiency and, consequently, enhances the cyclodextrin solubilization of the drug. Midazolam carries a positive charge at acidic pH and, thus, the negatively charged SBEβCD forms a more stable complex than the uncharged HPβCD with midazolam at these conditions. Addition of 10% (v/v) acetic acid as a co-solvent resulted in a small decrease in the fraction of the open ring form of the drug.

Example 6

Female hairless mice were sacrificed by cervical dislocation and their full-thickness skins removed. The outer surface of the skin was rinsed with 35% (v/v) methanol in water and subsequently with distilled water to remove any

contamination. The skin was placed in Franz diffusion cells. The receptor phase consisted of phosphate buffer saline pH 7.4. The skin diffusion cells were stirred with a magnetic bar and kept at 37°C by circulating water through an external jacket. The donor phase (2.0 ml) consisted of a solution of the drug in aqueous 7% (w/v) SBEβCD solution pH 3.3, or aqueous cyclodextrin solution where the pH had been raised from 3.3 to 4.1 (by addition of NaOH) before it was applied to the skin. The alprazolam concentration in the donor phase was 1.85 mg/ml at pH 3.3. Samples (200 μl) of receptor phase were removed from the cells at various time intervals up to 48 hours and replaced with a fresh buffer solution. The samples were kept frozen until analyzed by HPLC. The flux was calculated from the linear part of each permeability profile and the permeability coefficient obtained by dividing the flux with the concentration of dissolved drug in the donor phase. The results set forth in **Table 4** show clearly that raising the pH from 3.3 to 4.1 increases the flux though biological membranes such as hairless mouse skin.

Table 4. The flux of alprazolam through hairless mouse skin. The donor phase consisted of aqueous pH 3.3 buffer solution containing 7% (w/v) SBEβCD saturated with the drug. In one case the pH of the donor phase was kept constant at pH 3.3, but in the other case the pH was raised to 4.1 (by addition of NaOH) before it was applied to the skin. The alprazolam concentration in the donor phase was 1.85 mg/ml at pH 3.3.

Donor phase	Flux ($mg/cm^2/h$)	Ratio
Without increasing the pH	3.91×10^{-4}	1.0
Increasing the pH from 3.3 to 4.1	4.56×10^{-4}	1.2

Example 7

The effect of cyclodextrins and organic solvents on the rate of diazepine ring-closure of several selected benzodiazepines was investigated. Stock solutions containing $1.0x10^{-3}$ M of the benzodiazepine in 0.10 M aqueous hydrochloric acid solution (pH approx. 1.1) were prepared and stored at 37.0°C. The benzodiazepines were in the ring-open form in these stock solutions. Aqueous 0.50 M tris buffer (pH 7.50) solution was prepared. The observed first-order rate constant for the closing (i.e. formation) of the benzodiazepine ring was determined in the following reaction media: a) pure aqueous tris buffer solution; b) aqueous tris buffer solution containing 10% (w/v) cyclodextrin; c) tris buffer solution containing 10% (w/v) cyclodextrin and 10% (v/v) ethanol (EtOH); d) tris buffer solution containing 10% (w/v) cyclodextrin and 50% (v/v) EtOH; e) tris buffer solution containing 10% (w/v) cyclodextrin and 10% (v/v) dimethylsulfoxide (DMSO); and f) tris buffer solution containing 10% (w/v) cyclodextrin and 50% (w/v) DMSO. The stock solution (30 μl) was added to 1.50 ml of the reaction media which had previously been equilibrated to 37.0°C and the first-order rate constant for the appearance of the closed form determined from the appearance of the closed form as observed on HPLC. **Tables 5, 6 and 7** show the effects of cyclodextrins, EtOH and DMSO on the observed first-order rate constant for the regeneration of alprazolam, triazolam and midazolam, respectively. In pure aqueous buffer solutions, addition of EtOH and DMSO decreases somewhat the rate of ring closure, at least in the case of alprazolam and midazolam. Addition of cyclodextrin or the organic solvents have insignificant effect on the pH under these conditions. The dielectric constant of the reaction medium will, however, decrease upon addition of the organic solvents. It is possible that this decrease in the dielectric constant will reduce the ability of the reaction media to stabilize the transition state which could explain the decrease in the observed rate constant. Addition of cyclodextrin decreased significantly, in all cases, the rate of ring

closure. The cyclodextrins formed stable complexes with the ring-open form of the drug and, thus, the rate decreased upon addition of cyclodextrin. Addition of EtOH or DMSO to the cyclodextrin-containing reaction media resulted in increase in the rate, compared to reaction media containing only cyclodextrin, which could be due to decreased complexation of the diazepine ring-open form. EtOH and DMSO will compete with the diazepine ring-open form for a space in the cyclodextrin cavity resulting in decreased complexation.

Table 5. The effect of cyclodextrins, ethanol (EtOH) and dimethylsulfoxide (DMSO) on the first-order rate constant for the formation of the diazepine ring, i.e. regeneration of alprazolam, at pH 7.5 and 37°C.

	The observed first-order rate constant $x10^{-2}$ (min^{-1})				
Cyclodextrin	Pure water	10% EtOH	50% EtOH	10% DMSO	50% DMSO
No CD	14.2	11.5	7.24	9.68	10.7
10% RMβCD	2.97	4.90	6.70	3.97	7.92
10% HPβCD	3.30	5.23	7.07	4.44	8.57
10% SBEβCD	3.11	5.18	5.82	4.77	9.36

Table 6. The effect of cyclodextrins, ethanol (EtOH) and dimethylsulfoxide (DMSO) on the first-order rate constant for the formation of the diazepine ring, i.e. regeneration of triazolam, at pH 7.5 and 37°C.

	The observed first-order rate constant $x10^{-2}$ (min^{-1})				
Cyclodextrin	Pure water	10% EtOH	50% EtOH	10% DMSO	50% DMSO
No CD	1.32	1.31	1.84	1.28	1.37
10% RMβCD	0.64	0.92	1.00	0.78	1.12
10% HPβCD	0.66	0.92	1.02	0.79	1.14
10% SBEβCD	0.58	0.82	0.97	0.73	1.13

Table 7. The effect of cyclodextrins, ethanol (EtOH) and dimethylsulfoxide (DMSO) on the first-order rate constant for the formation of the diazepine ring, i.e. regeneration of midazolam, at pH 7.5 and 37°C.

	The observed first-order rate constant $x10^{-2}$ (min^{-1})				
Cyclodextrin	Pure water	10% EtOH	50% EtOH	10% DMSO	50% DMSO
No CD	17.9	12.6	8.41	13.8	10.9
10% RMβCD	3.05	4.24	6.99	4.94	8.48
10% HPβCD	2.77	3.86	6.53	3.36	8.40
10% SBEβCD	1.30	3.30	6.50	2.24	8.55

Example 8

The bioavailability of midazolam in a nasal spray according to the invention was evaluated. The composition of the midazolam nasal spray was as follows: midazolam 1.70% (w/v), sulfobutylether β-cyclodextrin sodium salt (Captisol®) 14.00% (w/v), benzalkonium chloride 0.02% (w/v), sodium edetate (EDTA tetrasodium) 0.10% (w/v), hydroxypropyl methylcellulose 0.10% (w/v), phosphoric acid 0.50% (v/v), sodium hydroxide *quantum satis ad* pH 4.35 in purified water. The intravenous (iv) dose was fixed at 2 mg (Dormicum™ 5 mg/ml iv solution from F. Hoffmann-La Roche & Ltd., Switzerland) but the intranasal (in) dose was 0.06 mg/kg or 4.84 mg (285 μl nasal spray) on the average. This was a cross-over study where each individual received both the iv and in formulation (via nasal spray) with a one week resting period between administrations. Serum samples were collected at various time points after administration of the drug and the midazolam concentration determined with an HPLC method. **Fig. 5** illustrates the concentration profile of midazolam in serum after administration of 2 mg of midazolam *intravenously* (○) or 4.8 mg of midazolam *intranasally* (Δ). Each point represents the mean value; error bars represent standard deviation. The bioavailability of midazolam after intranasal

administration was determined to be 61% and the mean C_p^{max} was determined to be 52 ng/ml at 12 min after intranasal administration of the drug. Sedation was not observed after the iv administration but sedation was observed in all three individuals within 10 min after intranasal administration of the drug. This sedation lasted for about one and one-half hours. Insignificant irritation was observed in the three individuals tested after intranasal administration of the drug.

While the invention has been described in terms of various preferred embodiments, the person skilled in the art will appreciate that various modifications, substitutions, omissions and changes can be made without departing from the spirit thereof. Accordingly, it is intended that the scope of the present invention be limited solely by the scope of the following claims, including equivalents thereof.

WHAT IS CLAIMED IS:

1. A method for enhancing the complexation efficiency of a drug with cyclodextrin, said drug having a structure comprising at least one heterocyclic ring having a total of from 4 to 7 ring atoms, of which from 1 to 3 are hetero ring atoms, each of said hetero ring atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imide, hemiacetal or hemiketal, said method comprising subjecting said drug to chemically reversible ring-opening so that at least 0.1% by weight thereof is in ring-opened form, and complexing said drug with cyclodextrin.

2. A method according to Claim 1, comprising complexing said drug with cyclodextrin in an aqueous medium under conditions which effect chemically reversible ring-opening of at least 0.1% by weight of said drug.

3. A method for enhancing the availability of a drug following administration of a cyclodextrin-drug complex to a warm-blooded animal in need of same, said drug having a structure comprising at least one heterocyclic ring having a total of from 4 to 7 ring atoms of which from 1 to 3 are hetero ring atoms, each of said hetero ring atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imine, hemiacetal or hemiketal, said method comprising complexing said drug with cyclodextrin in an aqueous medium under conditions which effect chemically reversible ring-opening of at least 0.1% by weight of said drug to enhance the complexation efficiency, followed by administering the cyclodextrin-drug complex thus obtained to said animal under conditions which reduce the complexation efficiency.

4. A method for enhancing the availability of a basic drug (i.e., a proton acceptor) following administration of a cyclodextrin-drug complex to a warm-blooded animal in need of same, said basic drug having a structure comprising at least one heterocyclic ring having a total of from 4 to 7 ring atoms, of which from 1 to 3 are hetero ring atoms, each of said hetero ring atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imide, hemiacetal or hemiketal, said method comprising subjecting said basic drug to complexation in an aqueous medium at a pH level below the pKa+2 value of said basic drug to enhance the complexation efficiency, followed by administering the cyclodextrin-drug complex thus obtained to said animal under conditions which reduce the complexation efficiency.

5. A method for enhancing the availability of an acidic drug following administration of a cyclodextrin-drug complex to a warm-blooded animal in need of same, said acidic drug having a structure comprising at least one heterocyclic ring having a total of 4 to 7 ring atoms, of which from 1 to 3 are hetero ring atoms, each of said hetero ring atoms being selected from nitrogen, oxygen and sulfur, said ring being a cyclic imine, enamine, lactone, lactam, thiolactam, anhydride, imide, hemiacetal or hemiketal, said method comprising subjecting said acidic drug to complexation in an aqueous medium at a pH level above the pKa-2 value of said acidic drug to enhance the complexation efficiency, followed by administering the cyclodextrin-drug complex thus obtained to said animal under conditions which reduce the complexation efficiency.

6. A method according to any one of Claims 2 to 4, wherein the complexation is conducted under conditions which effect chemically reversible ring-opening of at least 1% by weight of said drug, preferably wherein the

complexation is conducted at a pH level which affords ring-opening of at least 5% by weight of said drug.

7. A method according to Claim 5, wherein the complexation is conducted under conditions which effect chemically reversible ring-opening of at least 1% by weight of said drug, preferably wherein the complexation is conducted at a pH level which affords ring-opening of at least 5% by weight of said drug.

8. A method according to any one of Claims 1-4 and 6, wherein the complexation is conducted at a pH level of below about 5.

9. A method according to any one of Claims 1-3, 6 and 8, wherein the drug is a basic drug.

10. A method according to any one of Claims 1-4, 6, 8, and 9, wherein the drug is a benzodiazepine.

11. A method according to Claim 10, wherein the benzodiazepine is alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepam, demoxazepam, flumazenil, flurazepam, halazepam, midazolam, nordazepam, medazepam, diazepam, nitrazepam, oxazepam, midazepam, lorazepam, prazepam, quazepam, triazolam, temazepam or loprazolam.

12. A method according to any one of Claims 1-4, 6 and 8-11, wherein the cyclodextrin is hydroxypropyl-β-cyclodextrin, β-cyclodextrin sulfobutyl ether, β-cyclodextrin, γ-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

13. A method according to Claim 5 or 7, wherein the cyclodextrin is hydroxypropyl-β-cyclodextrin, β-cyclodextrin sulfobutyl ether, β-cyclodextrin, γ-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

14. A method according to any one of Claims 10-12, followed by formulating the cyclodextrin-drug complex thus obtained as a nasal spray, sublingual tablet or parenteral solution.

15. A method according to Claim 14, wherein the nasal spray, sublingual tablet or parenteral solution is formulated to be suitable for use in producing a sedative, anti-anxiety, anticonvulsant or muscle relaxant effect, preferably for use as a pre-anaesthetic medication, or to supplement anaesthesia, to induce and maintain anaesthesia or to induce a hypnotic effect.

16. A method according to Claim 15, wherein the benzodiazepine is alprazolam, clonazepam, lorazepam, midazolam or triazolam.

17. A method according to any one of Claims 1-4, 6 and 8-12, wherein the complexation is conducted at a pH level between about 3 and about 5.

18. A method according to Claim 1 or 2, wherein the drug is an acidic drug and the complexation is conducted under conditions which effect chemically reversible ring-opening of at least 1% by weight of said drug, preferably wherein the complexation is conducted at a pH level which affords ring-opening of at least 5% by weight of said drug.

19. A method according to Claim 1 or 2, wherein the drug is a barbituric acid derivative, a hydantoin, a pyrazole derivative, an imidazole

derivative, a pyrimidine derivative or a purine derivative, and the complexation is conducted under conditions which effect chemically reversible ring-opening of at least 1% by weight of said drug, preferably wherein the complexation is conducted at a pH level which affords ring-opening of at least 5% by weight of said drug.

20. A method according to Claim 19, wherein the barbituric acid derivative is barbital, butobarbital, amobarbital, phenobarbital, aprobarbital, secobarbital, crotylbarbital, cyclobarbital, phenobarbital, hexobarbital, methylphenobarbital, thiopental, isopropylbromallylbarbituric acid, or cyclohexenylallylthiobarituric acid, or a salt thereof; or wherein the hydantoin is phenytoin; or wherein the pyrazole derivative is phenazone, propylphenazone, metamidazole, phenylbutazone, oxyphenbutazone or sulfinpyrazone; or wherein the imidazole derivative is histamine, miconazole, pilocarpine, naphazoline or clonidine; or wherein the pyrimidine derivative is thiamine, trimethoprim, orotic acid, methylthiouracyl or prothiouracyl; or wherein the purine derivative is caffeine, theophylline, etophylline, proxyphylline or theobromine.

21. A method according to Claim 3, wherein the cyclodextrin-drug complex is administered in the form of an aqueous solution or a hydrogel.

22. A method according to Claim 21, wherein the cyclodextrin-drug complex is administered as a nasal spray or nasal drops.

23. A method according to Claim 21, wherein the cyclodextrin-drug complex is administered as a parenteral solution.

24. A method according to Claim 21, wherein the aqueous solution is at a pH level of below about 6 and is administered as a nasal spray.

25. A method according to Claim 24, wherein the pH level of the nasal spray is below about 4.7, preferably wherein the pH level of the nasal spray is between about 3 and about 4.7.

26. A method according to Claim 3, wherein the drug is a benzodiazepine, the complexation is conducted at a pH level which affords ring-opening of at least 5% by weight of said drug, said pH level being below about 5, and the cyclodextrin-drug complex is administered as a solid.

27. A method according to Claim 26, wherein the solid cyclodextrin-drug complex is administered as a tablet formulated for oral, buccal or sublingual administration.

28. A method according to Claim 3, wherein the water is removed from the aqueous complexation medium after formation of the cyclodextrin-drug complex.

29. A method according to Claim 4, wherein the drug is a benzodiazepine and the complexation is carried out at a pH level which affords ring-opening of at least 5% by weight of said drug and in the presence of from about 0.001 to about 5% (weight/volume) of a pharmacologically inactive, pharmaceutically acceptable water-soluble polymer at a temperature of from about 30°C to about 150°C.

30. A method according to Claim 29, wherein the polymer is a cellulose derivative or a polyvinyl polymer.

31. A method according to Claim 30, wherein the polymer is methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl methylcellulose, hydroxypropyl ethylcellulose, hydroxyethyl ethylcellulose, sodium carboxymethylcellulose or polyvinylpyrrolidone.

32. A method according to Claims 4 or 29, wherein the drug is a benzodiazepine and the complexation is carried out at a pH level which affords ring-opening of at least 5% by weight of said drug and in the presence of at least one member of the group consisting of acetic acid and its pharmaceutically acceptable salts, the acetate-water ratio of the aqueous complexation medium being from about 1:1000 to about 2:1.

33. A method according to Claim 32, wherein the drug is midazolam and the cyclodextrin is hydroxypropyl-β-cyclodextrin, β-cyclodextrin sulfobutyl ether, β-cyclodextrin, γ-cyclodextrin or hydroxypropyl-γ-cyclodextrin.

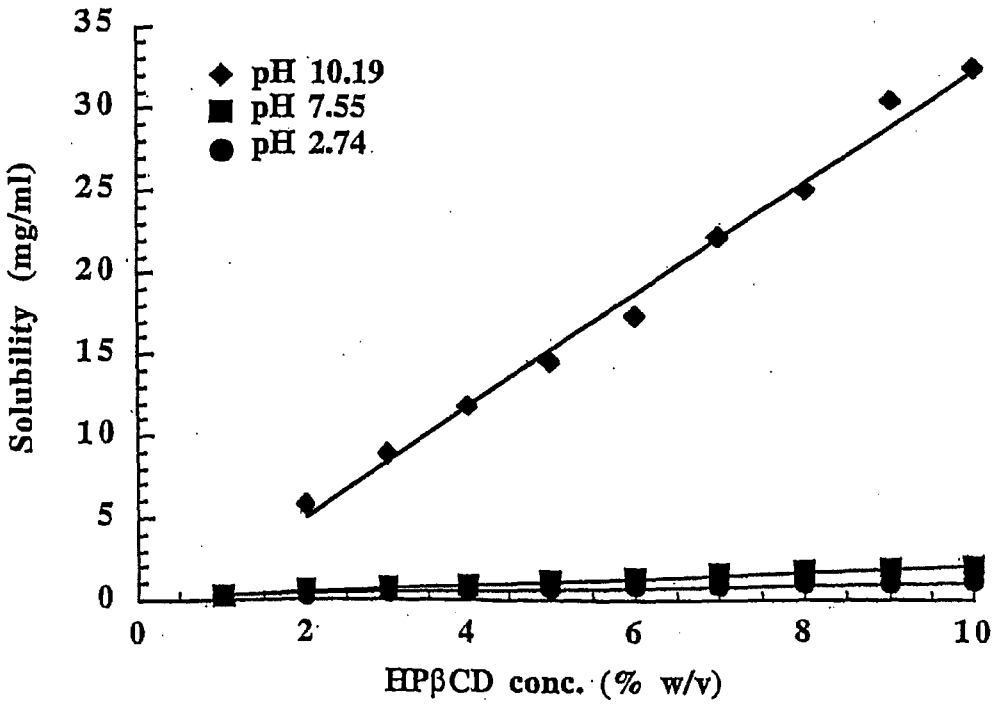

35
30
25
20
15
10
5
0
Solubility (mg/ml)
pH 10.19
pH 7.55
pH 2.74
0
2
4
6
8
10
HPβCD conc. (% w/v)

Figure 1

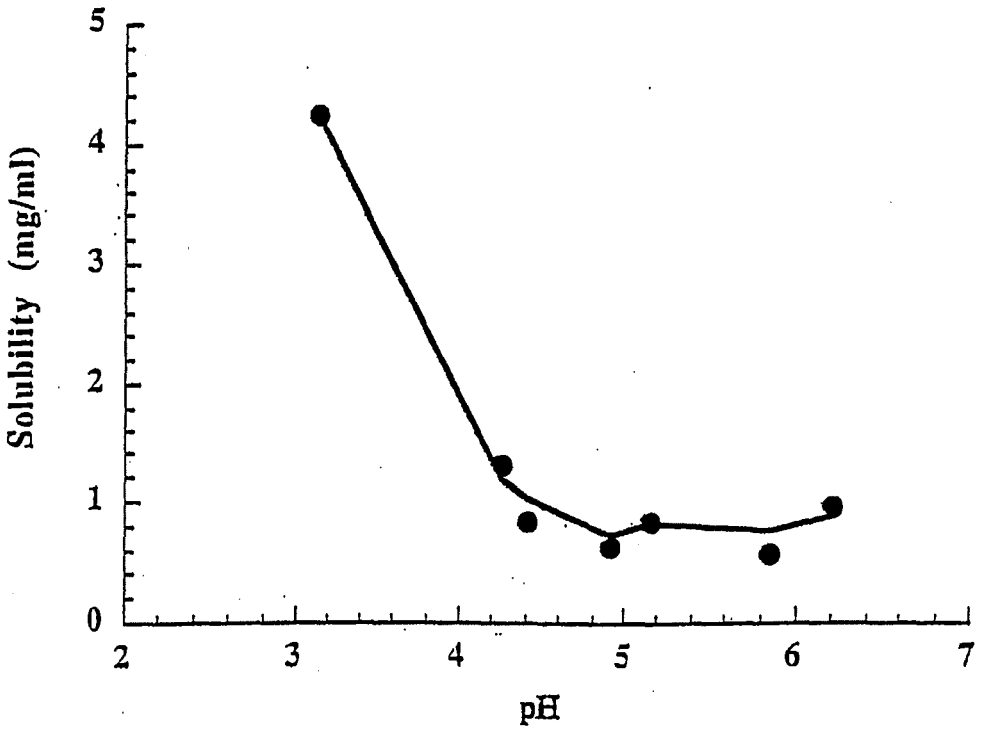


Figure 2

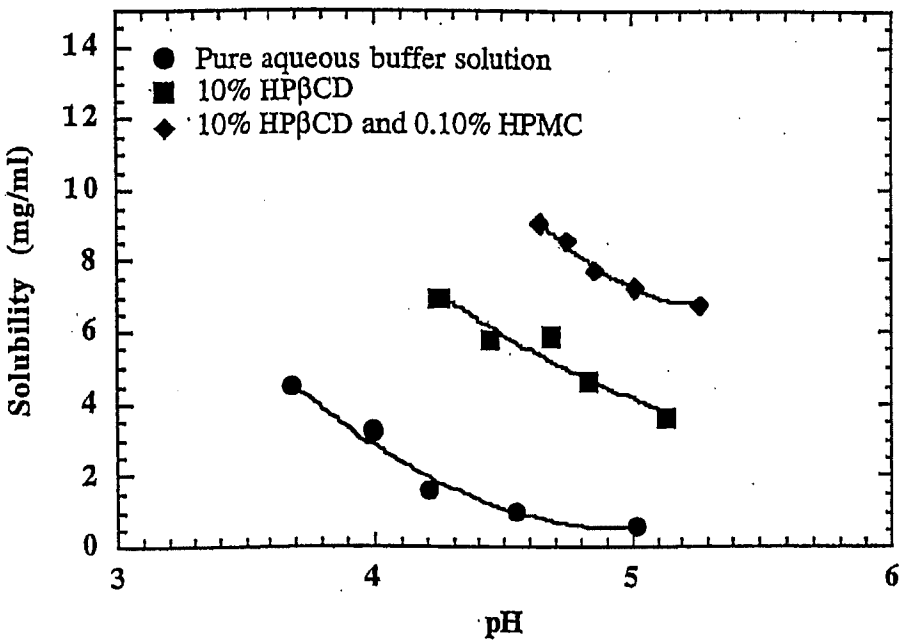

Pure aqueous buffer solution
10% HPβCD
10% HPβCD and 0.10% HPMC
Solubility (mg/ml)
pH
0
2
4
6
8
10
12
14
3
4
5
6

Figure 3

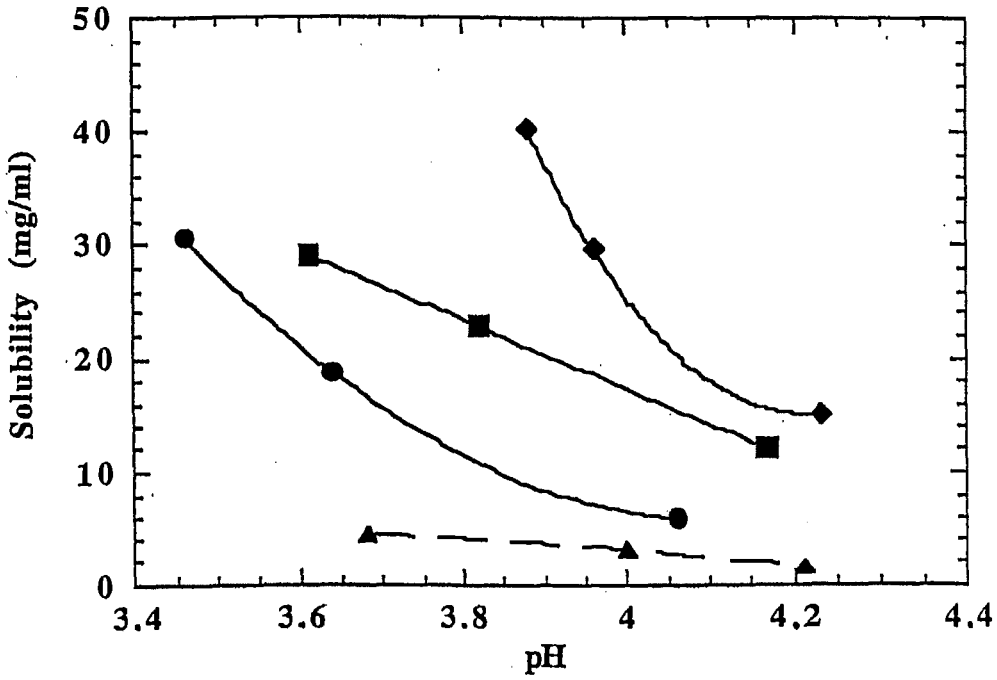


Figure 4

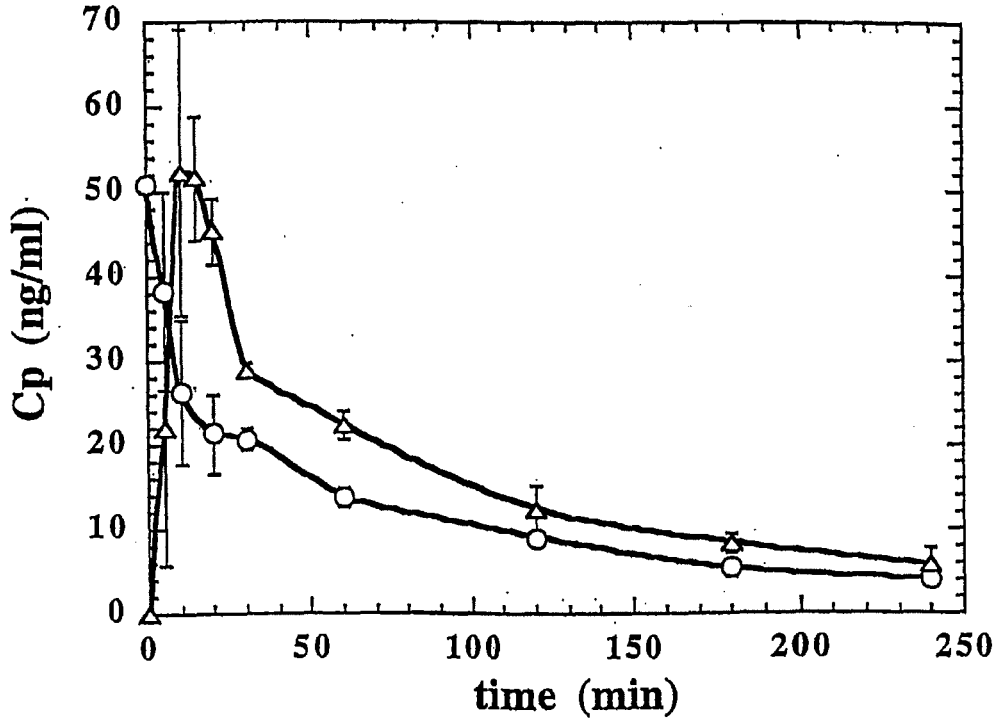


Figure 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IS 99/00003

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/715, C08B 37/16
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K, C08B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	International Journal of Pharmaceutics, Volume 73, 1991, Injoon Oh et al, "Stability and solubilization of oxathiin carboxanilide, a novel anti-HIV agent" page 23 - page 31	1-9,12-13, 17-18,21,23, 28,30,31,33
A	--	10,11,14-16, 19,20,22, 24-27,32
A	US 5324718 A (THORSTEINN LOFTSSON), 28 June 1994 (28.06.94)	1-33
	--	
A	US 5472954 A (THORSTEINN LOFTSSON), 5 December 1995 (05.12.95)	1-33
	--	

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 June 1999	19 -06- 1999
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson/Els Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IS 99/00003

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9402518 A1 (THE UNIVERSITY OF KANSAS), 3 February 1994 (03.02.94) -- --------	1-33

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IS99/00003

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 3-5,7,13,21-33
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant s protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

03/05/99

International application No.
PCT/IS 99/00003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5324718 A	28/06/94	AT 177647 T	15/04/99
		DE 69323937 D	00/00/00
		EP 0579435 A,B	19/01/94
		SG 49182 A	18/05/98
		US 5472954 A	05/12/95
US 5472954 A	05/12/95	AT 177647 T	15/04/99
		DE 69323937 D	00/00/00
		EP 0579435 A,B	19/01/94
		SG 49182 A	18/05/98
		US 5324718 A	28/06/94
WO 9402518 A1	03/02/94	AU 672814 B	17/10/96
		AU 4779993 A	14/02/94
		CA 2119154 A,C	03/02/94
		EP 0620828 A	26/10/94
		JP 6511513 T	22/12/94
		US 5376645 A	27/12/94

Form PCT/ISA/210 (patent family annex) (July 1992)

Electronic Patent Application Fee Transmittal

Application Number:	10551205
Filing Date:	14-Nov-2006
Title of Invention:	Oral formulations of cladribine
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Filer:	Mary Katherine Baumeister/Diana Francis
Attorney Docket Number:	0056192-000024

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

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:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	6649992
Application Number:	10551205
International Application Number:	
Confirmation Number:	4092
Title of Invention:	Oral formulations of cladribine
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Customer Number:	21839
Filer:	Mary Katherine Baumeister/Diana Francis
Filer Authorized By:	Mary Katherine Baumeister
Attorney Docket Number:	0056192-000024
Receipt Date:	16-DEC-2009
Filing Date:	14-NOV-2006
Time Stamp:	15:40:55
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$180
RAM confirmation Number	2125
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	le Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Transmittal Letter	005619224TL.pdf	50718 9d3feab457f9e99bf8c54ceec2a11d1ebd0afc20	no	1
Warnings:					
Information:					
2	Amendment/Req. Reconsideration-After Non-Final Reject	005619224AMEND.pdf	481410 1ce21e4cbf70b501cc1e5fb52f53eba7dd3a6b6a	no	9
Warnings:					
Information:					
3	Transmittal Letter	005619224TLIDS.pdf	40409 9862f50235f5110dba0a51c095a0b8118ec1b46d	no	1
Warnings:					
Information:					
4	Transmittal Letter	005619224IDS.pdf	47767 18cfeaad625f8dc7255a9a3c667da58f8593914b	no	2
Warnings:					
Information:					
5	Information Disclosure Statement (IDS) Filed (SB/08)	0056192241449.pdf	64666 a23e947132649ee0e0a119b6c07b06da495987c8	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
6	Foreign Reference	005619224ref.pdf	1864081 3848a30c436978462410f72650d3b601e398a9a7	no	51
Warnings:					
Information:					
7	Fee Worksheet (PTO-875)	fee-info.pdf	29880 b86076ccc915b1c052c62bdb2d1c0fc663371100	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2578931		

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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	**MAIL STOP AMENDMENT**
Nicholas Bodor et al.	Group Art Unit: 1623
Application No.: 10/551,205	Examiner: JONATHAN S LAU
Filing Date: November 14, 2006	Confirmation No.: 4092
Title: ORAL FORMULATIONS OF CLADRIBINE	

AMENDMENT/REPLY TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Enclosed is a reply for the above-identified patent application.

☐ A Petition for Extension of Time is enclosed.

☐ _____ Terminal Disclaimer(s) and the ☐ $ 70 ☐ $ 140 fee per Disclaimer due under 37 C.F.R. § 1.20(d) are enclosed.

☒ Also enclosed is/are: Sixth Information Disclosure Statement Transmittal, Sixth Information Disclosure Statement, PTO Form-1449, and (1) document.

☐ Small entity status is hereby claimed.

☒ No additional claim fee is required.

☐ An additional claim fee is required, and is calculated as shown below:

AMENDED CLAIMS					
	No. of Claims	**Highest No. of Claims Previously Paid For**	**Extra Claims**	**Rate**	**Additional Fee**
Total Claims	56	78	0	x $ 52 (1202)	$ 0
Independent Claims	4	5	0	x $ 220 (1201)	0
☐ If Amendment adds multiple dependent claims, add $ 390 (1203)					$ 0
Total Claim Amendment Fee					**$ 0**
☐ Small Entity Status claimed - subtract 50% of Total Claim Amendment Fee					0
TOTAL ADDITIONAL CLAIM FEE DUE FOR THIS AMENDMENT					**$ 0**

☐ Charge _____ to Deposit Account No. 02-4800 for the fee due.

☐ Charge_____ to credit card for the fee due. Form PTO-2038 is attached.

☒ The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.20(d) and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date December 16, 2009

By: Mary Katherine Baumeister
Mary Katherine Baumeister
Registration No. 26254

Customer No. 21839
703 836 6620

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
10/551,205	11/14/2006	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☐ RATE ($)	SMALL ENTITY ☐ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 12/16/2009	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 56	Minus	** 78	= 0	X $ =		OR	X $52=	0
Independent (37 CFR 1.16(h))	* 5	Minus	***6	= 0	X $ =		OR	X $220=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/WILLIAM N. PHILLIPS/

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.
10/551,205	11/14/2006	Nicholas S. Bodor	0056192-000024	4092

21839 7590 03/30/2010

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
03/30/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com
offserv@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/551,205	BODOR ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,8,9,11-14,20,21,23-28,32,33,35,56,57,63,64 and 67-98* is/are pending in the application.

4a) Of the above claim(s) *13,14,20,21,23-28,32,33,35 and 67-81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 8, 9, 11, 56, 57, 63, 64 and 82-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

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)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 pg / 16 Dec 2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is responsive to Applicant's Amendment and Remarks, filed 16 Dec 2009.

This application is the national stage entry of PCT/US04/09387, filed 26 Mar 2004; and claims benefit of provisional application 60/458,922, filed 28 Mar 2003; and claims benefit of provisional application 60/484,756, filed 02 July 2003; and claims benefit of provisional application 60/541,247, filed 04 Feb 2004.

The filing date of the instant claims 12, 83, 85 and 89 are deemed to be the filing date of the instant application which is the filing date of PCT/US04/09387, 26 Mar 2004. The filing date of instant claims 1, 2, 8, 9, 11, 56, 57, 63, 64, 82, 84 and 86-98 are deemed to be the filing date of provisional application 60/541,247, filed 04 Feb 2004.

Claims 1, 2, 8, 9, 11-14, 20, 21, 23-28, 32, 33, 35, 56, 57, 63, 64 and 67-98 are pending in the current application. Claims 13, 14, 20, 21, 23-28, 32, 33, 35 and 67-81, drawn to non-elected inventions, are withdrawn. Claims 1, 2, 8, 9, 11, 56, 57, 63, 64 and 82-98 are examined on the merits herein.

Rejections Withdrawn

Applicant's Remarks, filed 16 Dec 2009, with respect to claims 1, 2, 8, 9, 11, 56, 57, 63, 64 and 82-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schultz et al. (US Patent 6,194,395, published 27 Feb 2001, of record) in view of Wrenn

Jr. (US Patent 6,174,873, issued 16 Jan 2001, cited in PTO-892) and in view of Loftsson et al. (US Patent 6,699,849, filed 16 Feb 1999, cited in PTO-892) has been fully considered and is persuasive, as Applicant is persuasive that one of ordinary skill in the art would not have a reasonable expectation of success in combining the teaching of Wrenn Jr. drawn to a an amorphous formulation using a polymer cross-linked technology with the teaching of Schultz et al. drawn to a solid pharmaceutical oral dosage form of cladribine comprising cladribine and cyclodextrin.

This rejection has been **withdrawn**.

The following are new grounds of rejection not necessitated by Applicant's Amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented 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. Patentability shall not be negatived by the manner in which the invention was made.

Amended Claims 1, 2, 8, 9, 11, 56, 57, 63, 64 and 82-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schultz et al. (US Patent 6,194,395, published 27 Feb 2001, of record) in view of Pitha (US Patent 4,727,064, issued 23 Feb 1988, provided by Applicant in IDS mailed 4 Apr 2008) and in view of Loftsson J Pharm Sci 2002 (Journal of Pharmaceutical Sciences, 2002, 91(11), p2307-2316, cited in PTO-892).

Schultz et al. discloses a solid pharmaceutical oral dosage form of cladribine comprising cladribine and cyclodextrin (column 2, lines 31-39). Schultz et al. teaches β-cyclodextrins are known to possess the ability to form inclusion complexes and to have concomitant solubilizing properties (column 2, lines 10-15). Schultz et al. discloses the use of β-cyclodextrins (column 2, lines 56-58) and derivatives wherein one or more cyclodextrin hydroxy groups are replaced with groups such as hydroxypropyl (column 3, lines 26-27). Schultz et al. discloses the solid oral dosage form in the form of a tablet (column 5, lines 37-38) including the excipients sorbitol and magnesium stearate (column 6, lines 2-7). Schultz et al. discloses an oral dosage form comprising up to 15 mg cladribine and cyclodextrin from 100 to 500 mg, which renders obvious to one of skill in the art the sub-range of a cladribine to cyclodextrin ratio ranging from 15 mg:100 mg to 15mg:500 mg, or 1:6.67 to 1:33.3 by weight (column 6, lines 23-31). Schultz et al. implicitly discloses an oral dosage form comprising up to 15 mg cladribine and cyclodextrin from 100 to 500 mg, or a cladribine to cyclodextrin ratio ranging from 1:6.67 to 1:33.3 by weight (column 6, lines 23-31).

Schultz et al. does not specifically disclose the composition comprising no significant amount of free crystalline cladribine therein (instant claims 1). Schultz et al. does not specifically disclose the composition corresponding to a point located on the curve of a phase solubility diagram for saturated complex cladribine-cyclodextrin complexes, said curve defining complex saturated complexes of cladribine in varying concentrations of the cyclodextrin (instant claim 11). Schultz et al. does not specifically disclose the complex consisting of (a) an amorphous inclusion complex of cladribine

with an amorphous cyclodextrin and (b) amorphous free cladribine associated with amorphous cyclodextrin as a non-inclusion complex (instant claim 56). Schultz et al. does not specifically disclose the composition comprising a cladribine to cyclodextrin ratio from about 1:10 to about 1:16 (instant claims 6, 7, 10, 61, 62 and 65), or a ratio of about 1:14 (instant claims 8 and 63) or about 1:11 (instant claims 9 and 64). Schultz et al. does not specifically disclose the complex wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b) (instant claims 12 and 66). Schultz et al. does not specifically disclose the product-by-process wherein 12.00 parts by weight of cladribine and 172.50 parts by weight of hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process (instant claim 91 and 93), to give a cladribine to cyclodextrin ratio of 1:14.38. Schultz et al. does not specifically disclose the product-by-process wherein 16.35 parts by weight of cladribine and 172.50 parts by weight of the hydroxypropyl-β-cyclodextrin are introduced in step (i) of the process (instant claim 92), to give a cladribine to cyclodextrin ratio of 1:10.55.

Pitha teaches a pharmaceutical combination of drug and amorphous cyclodextrin to give a stable amorphous state that improves dissolution properties of the drug and absorption by the body (column 1, lines 10-15) and that prevents crystallization processes within the pharmaceutical preparation (column 1, lines 20-25). Pitha teaches the embodiment wherein the amorphous cyclodextrin is hydroxypropyl-beta-cyclodextrin (table 1 spanning columns 3 and 4). Pitha teaches the product made

by freeze-drying, or lyophilizing, a solution of cyclodextrin and drug (column 7, lines 5-40).

Loftsson J Pharm Sci 2002 teaches drug/cyclodextrin complexes self-associate to form water-soluble aggregates as non-inclusion complexes in addition to formation of the inclusion complex (abstract). Loftsson J Pharm Sci 2002 teaches the formation of only the drug/cyclodextrin inclusion complex is a general assumption (page 2307, section Introduction), and that drug/cyclodextrin complexes self-associate to form water-soluble aggregates as non-inclusion complexes (page 2315, section Conclusions).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine Schultz et al. in view of Pitha and in view of Loftsson J Pharm Sci 2002. Schultz et al. teaches solid formulations for oral administration of cladribine and cyclodextrin. One of ordinary skill in the art would have been motivated to combine Schultz et al. in view of Pitha because Schultz et al. teaches undesirable recrystallization of cladribine in tissue may occur and damage the surrounding tissue and that complexes with cyclodextrin are known to solubilize the compound and Pitha teaches the pharmaceutical combination of drug and amorphous cyclodextrin to give a stable amorphous state that improves dissolution properties of the drug and absorption by the body. One of ordinary skill in the art would have a reasonable expectation of success in combining Schultz et al. in view of Pitha because Pitha teaches a application of a wide variety of drugs in the complex taught by Pitha and Schultz et al. teaches the formation of the cladribine and cyclodextrin complex in solution. Schultz et al. in view of Pitha and in view of Loftsson J Pharm Sci 2002 does not teach the specific cladribine to

cyclodextrin ratios of 1:14.38 or 1:10.55, however these ratios are encompassed by the prior art and Schultz et al. teaches it is within the level of skill in the art to optimize the ratio of cyclodextrin relative to cladribine (column 4, lines 35-45). See also MPEP 2144.05 II.A, "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical." One of ordinary skill in the art would be motivated to optimize the cladribine to cyclodextrin ratio to give the composition comprising no significant amount of free crystalline cladribine therein because Schultz et al. teaches undesirable recrystallization of cladribine in tissue may occur and damage the surrounding tissue (Schultz et al. column 2, lines 1-15).

Loftsson J Pharm Sci 2002 provides evidence that the property of self-association of the drug/cyclodextrin complex is necessarily present in the drug/cyclodextrin composition taught by Schultz et al. in view of Pitha. Therefore there is reasonable evidence to conclude that the process of self-association of the drug/cyclodextrin complex at the ratio taught by Schultz et al. in view of Pitha would necessarily result in both inclusion complexes and non-inclusion complexes and wherein from about 30 to about 40 percent by weight of the cladribine is in the inclusion complex (a) and from about 70 to about 60 percent by weight of the cladribine is in the non-inclusion complex (b). See also MPEP 2112.

Claims 82-90 and 94-98 are drawn to a product-by-process. The disclosed product is substantially identical to the instantly claimed product-by-process, a pharmaceutical solid oral dosage form comprising an amorphous inclusion complex of

cladribine and cyclodextrin and a non-inclusion complex of an amorphous cladribine and an amorphous cyclodextrin as detailed above. "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed. The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.). See MPEP 2113.

Response to Applicant's Remarks:

Applicant's Remarks, filed 16 Dec 2009, have been fully considered and not found to be persuasive in view of the new grounds of rejection.

Applicant's note that the invention disclosed by Schultz et al. via a melt-extrusion process results in the formation of the mixture and not a complex of cladribine and cyclodextrin in solid form, as provided by evidence in Van Axel Castelli et al. However, MPEP 2121.01 II. provides a non-enabling reference may qualify as prior art for the

purpose of determining obviousness under 35 U.S.C. 103. Schultz et al. discloses the melt-extrusion as one method of preparing solid oral dosage forms (col 5, line 50), thus the teaching of Schultz et al. does not teach away from the combination of Schultz et al. in view of Pitha, teaching a product made by freeze-drying, and in view of Loftsson J Pharm Sci 2002 to support a conclusion of obviousness.

Conclusion

No claim is found to be allowable.

This Office Action details new grounds of rejection not necessitated by Applicant's Amendment. Therefore this Office Action is Non-Final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jonathan Lau
Patent Examiner
Art Unit 1623

/Shaojia Anna Jiang/
Supervisory Patent Examiner
Art Unit 1623

Notice of References Cited	Application/Control No. 10/551,205	Applicant(s)/Patent Under Reexamination BODOR ET AL.	
	Examiner Jonathan S. Lau	Art Unit 1623	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Loftsson et al. Journal of Pharmaceutical Sciences, 2002, 91(11), p2307-2316.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10551205	BODOR ET AL.
	Examiner	Art Unit
	Jonathan S Lau	1623

✓	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	11/26/2007	03/26/2008	01/02/2009	09/10/2009	03/25/2010				
	1	÷	✓	✓	✓	✓				
	2	÷	✓	✓	✓	✓				
	3	÷	✓	✓	-	-				
	4	÷	✓	✓	-	-				
	5	÷	✓	✓	-	-				
	6	÷	✓	✓	-	-				
	7	÷	✓	✓	-	-				
	8	÷	✓	✓	✓	✓				
	9	÷	✓	✓	✓	✓				
	10	÷	✓	✓	-	-				
	11	÷	✓	✓	✓	✓				
	12	÷	✓	✓	✓	✓				
	13	÷	N	N	N	N				
	14	÷	N	N	N	N				
	15	÷	N	N	-	-				
	16	÷	N	N	-	-				
	17	÷	N	N	-	-				
	18	÷	N	N	-	-				
	19	÷	N	N	-	-				
	20	÷	N	N	N	N				
	21	÷	N	N	N	N				
	22	÷	N	N	-	-				
	23	÷	N	N	N	N				
	24	÷	N	N	N	N				
	25	÷	N	N	N	N				
	26	÷	N	N	N	N				
	27	÷	N	N	N	N				
	28	÷	N	N	N	N				
	29	÷	N	N	-	-				
	30	÷	N	N	-	-				
	31	÷	N	N	-	-				
	32	÷	N	N	N	N				
	33	÷	N	N	N	N				
	34	÷	N	N	-	-				
	35	÷	N	N	N	N				
	36	-	-	-	-	-				

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10551205	BODOR ET AL.
	Examiner	Art Unit
	Jonathan S Lau	1623

✓	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	11/26/2007	03/26/2008	01/02/2009	09/10/2009	03/25/2010				
	37	-	-	-	-	-				
	38	-	-	-	-	-				
	39	-	-	-	-	-				
	40	-	-	-	-	-				
	41	-	-	-	-	-				
	42	-	-	-	-	-				
	43	-	-	-	-	-				
	44	-	-	-	-	-				
	45	-	-	-	-	-				
	46	-	-	-	-	-				
	47	-	-	-	-	-				
	48	-	-	-	-	-				
	49	-	-	-	-	-				
	50	-	-	-	-	-				
	51	-	-	-	-	-				
	52	-	-	-	-	-				
	53	-	-	-	-	-				
	54	-	-	-	-	-				
	55	-	-	-	-	-				
	56	÷	✓	✓	✓	✓				
	57	÷	✓	✓	✓	✓				
	58	÷	✓	✓	-	-				
	59	÷	✓	✓	-	-				
	60	÷	✓	✓	-	-				
	61	÷	✓	✓	-	-				
	62	÷	✓	✓	-	-				
	63	÷	✓	✓	✓	✓				
	64	÷	✓	✓	✓	✓				
	65	÷	✓	✓	-	-				
	66	÷	✓	✓	-	-				
	67	÷	N	N	N	N				
	68	÷	N	N	N	N				
	69	÷	N	N	N	N				
	70	÷	N	N	N	N				
	71	÷	N	N	N	N				
	72	÷	N	N	N	N				

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10551205	BODOR ET AL.
	Examiner	Art Unit
	Jonathan S Lau	1623

✓	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	11/26/2007	03/26/2008	01/02/2009	09/10/2009	03/25/2010				
	73	÷	N	N	N	N				
	74	÷	N	N	N	N				
	75	÷	N	N	N	N				
	76	÷	N	N	N	N				
	77	÷	N	N	N	N				
	78	÷	N	N	N	N				
	79	÷	N	N	N	N				
	80	÷	N	N	N	N				
	81	÷	N	N	N	N				
	82	÷	✓	✓	✓	✓				
	83	÷	✓	✓	✓	✓				
	84	÷	✓	✓	✓	✓				
	85	÷	✓	✓	✓	✓				
	86	÷	✓	✓	✓	✓				
	87	÷	✓	✓	✓	✓				
	88	÷	✓	✓	✓	✓				
	89	÷	✓	✓	✓	✓				
	90	÷	✓	✓	✓	✓				
	91	÷	✓	✓	✓	✓				
	92	÷	✓	✓	✓	✓				
	93	÷	✓	✓	✓	✓				
	94	÷	✓	✓	✓	✓				
	95	÷	✓	✓	✓	✓				
	96	÷	✓	✓	✓	✓				
	97	÷	✓	✓	✓	✓				
	98	÷	✓	✓	✓	✓				

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10551205	BODOR ET AL.
	Examiner	Art Unit
	Jonathan S Lau	1623

SEARCHED

Class	Subclass	Date	Examiner

SEARCH NOTES

Search Notes	Date	Examiner
EAST - inventor name search (Nicholas Bodor; Yogesh Dandiker)	3/26/2008	JSL
EAST - see attached notes	3/26/2008	JSL
Google Scholar - see attached notes	3/26/2008	JSL
EAST - see attached notes	9/10/2009	JSL
Google Scholar - see attached notes	9/10/2009	JSL
STN - CAPlus file - see attached notes	9/10/2009	JSL
EAST - see attached notes	3/25/2010	JSL
Google Scholar - see attached notes	3/25/2010	JSL

INTERFERENCE SEARCH

Class	Subclass	Date	Examiner

Google scholar cyclodextrin non-inclusion Search Advanced Scholar Search Scholar Preferences

Scholar Articles and patents anytime include citations Results 1 - 10 of about 456. (0.23 sec)

Self-association of **cyclodextrins** and **cyclodextrin** complexes

T Loftsson, M Másson, ME ... - Journal of ..., 2004 - interscience.wiley.com

... 107 Reykjavik, Iceland. Telephone: 354-525-4464; Fax: 354-525-4071. Keywords. **cyclodextrin** • self-association • complexation • **non-inclusion** • aggregates • phase-solubility • solubilization. Abstract. **Cyclodextrins** are useful ...

Cited by 76 - Related articles - BL Direct - All 4 versions

... on inclusion and **non-inclusion** phenomena between β-**cyclodextrin** and new anti- ...

ME Amato, KB Lipkowitz, GM Lombardo, GC ... - Journal of the Chemical ..., 1996 - rsc.org

The formation of supramolecular complexes of -CD with new generation anti-Alzheimer's agents of the 1,2,3,4-tetrahydro-9-aminoacridine family (tacrine hydrochloride, 1, velnacrine maleate, 2 and suronacrine maleate, 3), has been studied using molecular dynamics ...

Cited by 13 - Related articles - BL Direct

Cyclodextrins and their pharmaceutical applications unironaLit [PDF]

T Loftsson, D Duchêne - International journal of pharmaceutics, 2007 - Elsevier

... period, 1970 to present 2.3.1. Production of **cyclodextrins** 2.3.2. **Cyclodextrin** derivatives 2.3.3. Industrial applications of **cyclodextrins** 2.3.4. Inclusion and **non-inclusion** complexes 2.3.5. Methods to enhance the complexation efficiency 2.3.6. **Cyclodextrin** aggregates 2.3.7. Drug ...

Cited by 113 - Related articles - All 5 versions

Evaluation of **cyclodextrin** solubilization of drugs

T Loftsson, D Hreinsdóttir, M Másson - International journal of ..., 2005 - Elsevier

... However, **cyclodextrins** (the hosts) are also known to form **non-inclusion** complexes (Loftsson et al., 2002 and Loftsson et al., 2004b). Most lipophilic compounds (the guests) form apparent 1:1 guest/host complex although apparent higher order complexes are not uncommon. ...

Cited by 79 - Related articles - All 4 versions

[PDF] Non-chromatographic analytical uses of **cyclodextrins** rsc.org [PDF]

L Szente, J Szejtli - The Analyst, 1998 - rsc.org

... From a mechanistic standpoint, the selectivity of the interaction seems to involve partially a **non-**

inclusion process, because of the high ... detectors and indicators Numerous papers and patents have been dedicated to the use of **cyclodextrins** and **cyclodextrin** inclusion complexes ...
Cited by 28 - Related articles - View as HTML - BL Direct - All 4 versions

The effects of organic salts on the **cyclodextrin** solubilization of drugs
T Loftsson, K Matthiasson, M Másson - International journal of ..., 2003 - Elsevier
... For example, Gabelica et al. have shown that α-**cyclodextrin** (αCD) forms both inclusion and **non-inclusion** complexes with dicarboxylic acids and that the two types of complexes coexist in aqueous solutions ([Gabelica et al]). ...
Cited by 21 - Related articles - All 4 versions

Influence of response factors on determining equilibrium association constants of ...
V Gabelica, N Galic, F Rosu, C ... - Journal of Mass ..., 2003 - interscience.wiley.com
... **cyclodextrin**. This may be due to the fact that **cyclodextrin** is neutral in solution, whereas the complex is charged, but it can also stem from the fact that a significant proportion of the complex is in a **non-inclusion** geometry. The ...
Cited by 48 - Related articles - BL Direct - All 7 versions

Cyclodextrins as pharmaceutical solubilizers [unroma1.it [PDF]]
ME Brewster, T Loftsson - Advanced drug delivery reviews, 2007 - Elsevier
... Other solubilizing attribute may include the ability to form **non-inclusion** based complexes, the formation of aggregates and related domains and the ability of **cyclodextrins** to form and stabilize supersaturated drug solutions. ...
Cited by 99 - Related articles - All 7 versions

Cyclodextrin solubilization of the antibacterial agents triclosan and triclocarban: ...
MS Duan, N Zhao, ÍB Össurardóttir, T ... - International journal of ..., 2005 - Elsevier
... the **cyclodextrin** solubilization of drugs. It is thought that these additives enhance the **cyclodextrin** complexation of drugs by forming **non-inclusion** complexes with **cyclodextrins** and their complexes. For example, it has been shown ...
Cited by 22 - Related articles - All 4 versions

Self-association and **cyclodextrin** solubilization of drugs
T Loftsson, A Magnúsdóttir, M Másson, ... - Journal of ..., 2002 - interscience.wiley.com
... studies. Furthermore, the results indicate that drug/**cyclodextrin** complexes can self-associate to form water-soluble aggregates, which then can further solubilize the drug through **non-inclusion** complexation. © 2002 Wiley-Liss, Inc. ...
Cited by 50 - Related articles - BL Direct - All 3 versions

Gooooooooogle

Result Page: 1 2 3 4 5 6 7 8 9 10 Next

cyclodextrin non-inclusion Search

Go to Google Home - About Google - About Google Scholar

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	1	"6194395".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/25 14:14
S2	1	"6699849".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/25 14:15
S3	1	"6174873".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/25 14:21
S4	1148	cladribine and cyclodextrin	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/25 14:23
S5	271	S4 and @ad<="20040326"	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/25 14:23
S6	75	S5 and (amorphous or noncrystal$5 or non-crystal $5)	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/25 14:24
S7	3	S6 and ((cladribine same cyclodextrin) or (cladribine near9 cyclodextrin))	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/25 14:25
S8	20	((adenosine same cyclodextrin) or (adenosine near9 cyclodextrin)) and (amorphous or noncrystal$5 or non-crystal$5) and @ad<="20040326"	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/25 14:38
S9	1	S2 and (amorphous or noncrystal$5 or non-crystal $5)	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/25 14:43
S10	1	S3 and (amorphous or noncrystal$5 or non-crystal $5)	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/25 14:48
S11	32	cladribine.ti,ab,bsum. and cyclodextrin and (amorphous or noncrystal$5 or non-crystal$5) and @ad<="20040326"	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/25 15:11

S12	0	cladribine.ti,ab,bsum. and "cyclodextrin.ti,ab,bsum" and (amorphous or noncrystal$5 or non-crystal $5) and @ad<="20040326"	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/25 15:12
S13	17	cladribine.ti,ab,bsum. and cyclodextrin.ti,ab,bsum. and (amorphous or noncrystal$5 or non-crystal$5) and @ad<="20040326"	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/25 15:12
S14	1	"4727064".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/25 15:46
S15	1	"7115586".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/25 16:20
S16	1	"20030109492".pn.	US-PGPUB; USPAT; USOCR	ADJ	ON	2010/03/25 16:22

EAST Search History (Interference)

<This search history is empty>

3/25/2010 5:57:25 PM
C:\Documents and Settings\jlau1\My Documents\EAST\Workspaces\10551205 - amorphous cladribine CD.wsp

Substitute for form 1449/PTO & 1449B/PTO

SIXTH INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known

Application Number	10/551,205
Filing Date	November 14, 2006
First Named Inventor	Nicholas Bodor et al.
Examiner Name	JONATHAN S LAU
Attorney Docket No.	0056192-000024

U.S. PATENT DOCUMENTS

Examiner Initials	Document Number-Kind Code	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines Where Relevant Passages or Figures Appear
	US-			
	US-			
	US-			
	US-			
	US-			
	US-			
	US-			
	US-			
	US-			
	US-			
	US-			
	US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials	Foreign Patent Document: Country Code[1], Number, Kind Code	Publication Date (MM-DD-YYYY)	Name of Patentee or Applicant of Cited Document	STATUS: Translation	Partial Translation	Eng. Lang. Summary	Search Report	IPER	Abstract	Cited in Spec. / Pg. No(s).	
/J.L./	WO 99/42111	08-26-1999	CYCLOPS, EHF								

[1]Enter Office that issued the document, by the two-letter code.

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials	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.

Examiner Signature	/Jonathan Lau/	Date Considered	03/25/2010

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with M.P.E.P. § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	**MAIL STOP AMENDMENT**
Nicholas Bodor et al.	Group Art Unit: 1623
Application No.: 10/551,205	Examiner: JONATHAN S LAU
Filed: November 14, 2006	Confirmation No.: 4092
For: ORAL FORMULATIONS OF CLADRIBINE	

REPLY TO OFFICIAL ACTION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Office Action dated March 30, 2010, the following remarks are offered:

REMARKS

Applicants request reexamination and reconsideration of the subject application pursuant to and consistent with 37 C.F.R. § 1.112 in light of the following:

STATUS OF CLAIMS

The status of the claims under examination has been misstated. Claims 1, 2, 8, 9, 11-14, 20, 21, 23-28, 32, 33, 35, 56, 57, 63, 64 and 66-98 remain in this application. Claims 13, 14, 20, 21, 23-28, 32, 33, 35 and 67-81 have been withdrawn from consideration as drawn to non-elected subject matter. Claims 1, 2, 8, 9, 11, 12, 56, 57, 63, 64, 66 and 82-98 are under examination. It is again pointed out that Claims 12 and 66 were not included in the previous rejection and are not included in the current rejection. Clarification is requested.

INFORMATION DISCLOSURE STATEMENT

Applicants appreciate the Examiner's consideration of the December 16, 2009 Information Disclosure Statement and the return of the initialed Form PTO-1449.

REJECTIONS WITHDRAWN

Applicants appreciate the Examiner's withdrawal of the previous 35 U.S.C. § 103(a) rejection.

CLAIM REJECTIONS - 35 U.S.C. § 103(a)

Claims 1, 2, 8, 9, 11, 56, 57, 63, 64 and 82-98 have been rejected as being unpatentable over Schultz et al. US 6194395 in view of Pitha US 4727064 and in view of Loftsson et al., J. Pharm. Sci., 2002, 91(11), pp. 2307-2316. Applicants believe that all of the claims under examination, that is, all of Claims 1, 2, 8, 9, 11, 12, 56, 57, 63, 64, 66 and 82-98 are patentable over this combination of references.

Applicants have previously established that, while Schultz et al. describe inclusion complex formation in solution to form injectable solutions, Schultz et al. describe solid formulations which are mixtures, not complexes, of cladribine and cylodextrin. Applicants have already shown, particularly with reference to the experiments described in the Van Axel Castelli et al. paper previously submitted, that

contrary to Schultz et al., the instantly claimed cladribine/cyclodextrin complex is not a simple mixture of the ingredients and has different properties from a mixture of cladribine and cyclodextrin. Therefore, the ratios of cladribine and cyclodextrin in Schultz et al.'s solid are irrelevant to the ratios of cladribine and cylodextrin in the presently claimed complexes. The fact remains that Schultz et al. only discloses complexes in solutions for injection, not for solid oral dosage forms.

Moreover, in making his rejection, the Examiner has taken a teaching of Schultz et al. completely out of context and from this he has constructed a rejection which is improper. Specifically, the Examiner states that Schultz et al. teach undesirable recrystallization of cladribine in tissue may occur and damage surrounding tissue (col. 2, lines 1-2), and on this teaching he builds his position about solid oral formulations of cladribine/cyclodextrin complexes. However, the passage in Schultz et al. relied upon by the Examiner needs to be read together with the preceding passages in col. 1., which clearly refers only to injectable formulations of high osmolality when injected by the subcutaneous route (sentence bridging columns 1 and 2 of Schultz et al.). The passage quoted has therefore no relation to solid oral dosage forms. After oral absorption, no crystallization in any tissue could or would occur. Thus, it cannot provide any motivation to one of ordinary skill to combine Schultz et al with the other cited references.

Nevertheless, Pitha US 4727064 has been cited in combination with Schultz et al. Indeed, Pitha was prior art cited during the examination of the Schultz et al. patent, as is evident from the fact that it is listed on the face of the Schultz et al. patent. The Pitha patent issued eleven years before the Schultz et al. application was filed and was clearly available to Schultz et al. at the time of the Schultz et al. invention. Nevertheless, Schultz et al. turned to inclusion complex formulation only as a way of providing suitable injectable formulations of cladribine. In contrast, for solid dosage forms they suggested simple mixtures. Moreover, Pitha did not even address cladribine as such, much less the fact that it is acid-labile and unstable in the acidic environment of the gastrointestinal system (Schultz et al., col. 1, lines 47-51). It is not seen how one of ordinary skill would be motivated to try to combine Pitha with Schultz et al. to provide an alternate solution for solid oral use.

Still further, since there is no mention of cladribine as such in Pitha, preparation of inclusion complexes disclosed therein of, for example, sex hormones (Example 4 in column 7) clearly uses conditions different from those used herein for cladribine.

With respect to the Loftsson et al. J. Pharm. Sci. literature article, applicants believe that the conclusions of the article have been taken out of context. Loftsson et al. do indeed describe particular situations in which self-association of cyclodextrin complexes may explain some observed solubilization phenomena. However, Loftsson et al. first studied the solubility of ibuprofen sodium salt, diflumisal sodium salt, alprazolam, 17β-estradiol and diethylstilbestrol in HPβCD. Then, aqueous HPβCD solutions, previously saturated with the sodium salts of either ibuprofen or diflunisal were saturated with a second drug (17β-estradiol, diethylstilbestrol or alprazolam). On page 2313, left column, first full paragraph, Loftsson et al. summarize their conclusions from these experiments:

> If the solubilization of a given drug (the first drug) is solely attributable to inclusion complex formation and if the slope of the obtained phase-solubility diagram is greater than unity, then it can be assumed that almost all cyclodextrin molecules in the aqueous complexation medium will be forming inclusion complexes with the drug. In this case, the concentration of free cyclodextrin in a saturated drug solution will be very low and under such conditions there will be very little capacity to solubilize a second water-insoluble drug in the same medium. Introduction of a second drug will then always result in some precipitation of the drug that previously was used to saturate the solution. However, if the first drug is partially solubilized through non-inclusion association, then there could be some capacity in the solution to solubilize the second drug in a similar manner as drugs are solubilized in micelles. In other words, with inclusion complexation, we will expect to see a consistent competitive effect between the first drug and the second drug, but if solubilization through non-inclusion association exists in the solution, we can expect to observe a cooperative effect, especially if the complexation efficacy of the second drug is low.

It is clear from the foregoing that Loftsson et al. were dealing with combinations of two drugs, one of which was negatively charged. Loftsson et al. do not mention cladribine or suggest both inclusion and non-inclusion association for it by itself in solid form. The presently claimed subject matter, a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex consisting of (a) an amorphous inclusion complex of cladribine with hydroxypropyl-β-cyclodextrin and (b) amorphous free cladribine associated with said amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein, said composition having a weight ratio of cladribine to said amorphous cyclodextrin of from about 1:10 to about 1:16, is in no way suggested by the combination of references. See especially Claim 1 and Claim 56, drawn to the complex. Again, we emphasize that the ratios disclosed by Schultz et al. are for simple mixtures, not complexes. There is no reasonable evidence that any of the features of applicants' invention not taught by Schultz et al. are taught by the cited combination of references. Withdrawal of the record rejection is earnestly solicited.

In the event that any issues remain, the Examiner is urged to telephone the undersigned so that such issues can be handled promptly. Further, favorable action in the form of a Notice of Allowance is believed to be next in order and is earnestly solicited. If the Examiner has no intention to allow the application, a personal interview with him and his supervisory Examiner is respectfully requested.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

July 30, 2010

By: Mary Katherine Baumeister
Mary Katherine Baumeister
Registration No. 26254

Customer No. 21839
703 836 6620

Electronic Patent Application Fee Transmittal

Application Number:	10551205
Filing Date:	14-Nov-2006
Title of Invention:	Oral formulations of cladribine
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Filer:	Mary Katherine Baumeister/Diana Francis
Attorney Docket Number:	0056192-000024

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

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:				
Extension-of-Time:				
Extension - 1 month with $0 paid	1251	1	130	130

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**130**

Electronic Acknowledgement Receipt

EFS ID:	8126835
Application Number:	10551205
International Application Number:	
Confirmation Number:	4092
Title of Invention:	Oral formulations of cladribine
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Customer Number:	21839
Filer:	Mary Katherine Baumeister/Diana Francis
Filer Authorized By:	Mary Katherine Baumeister
Attorney Docket Number:	0056192-000024
Receipt Date:	30-JUL-2010
Filing Date:	14-NOV-2006
Time Stamp:	15:13:56
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$130
RAM confirmation Number	1539
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	le Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Transmittal Letter	005619224TL.pdf	46108 514b837dda3d7bc17a03b375ee86b93cc491cc7b	no	1
Warnings:					
Information:					
2	Extension of Time	005619224EOT.pdf	32539 9849dce9867f1291950e618b9ae8a89f067b5f7e	no	1
Warnings:					
Information:					
3	Amendment/Req. Reconsideration-After Non-Final Reject	0056192AMEND.pdf	240956 7dab22c2229c397eb2e738bbba73f765ff25f4eb	no	5
Warnings:					
Information:					
4	Fee Worksheet (PTO-875)	fee-info.pdf	30076 e1a67950cf7faf860bf4703ef1b1857335a35367	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	349679		

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.

<u>New Applications Under 35 U.S.C. 111</u>
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.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
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.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	**MAIL STOP AMENDMENT**
Nicholas Bodor et al.	Group Art Unit: 1623
Application No.: 10/551,205	Examiner: JONATHAN S LAU
Filing Date: November 14, 2006	Confirmation No.: 4092
Title: ORAL FORMULATIONS OF CLADRIBINE	

AMENDMENT/REPLY TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Enclosed is a reply for the above-identified patent application.

☒ A Petition for Extension of Time is enclosed.

☐ _____ Terminal Disclaimer(s) and the ☐ $ 70 ☐ $ 140 fee per Disclaimer due under 37 C.F.R. § 1.20(d) are enclosed.

☐ Also enclosed is/are: _____

☐ Small entity status is hereby claimed.

☒ No additional claim fee is required.

☐ An additional claim fee is required, and is calculated as shown below:

AMENDED CLAIMS					
	No. of Claims	**Highest No. of Claims Previously Paid For**	**Extra Claims**	**Rate**	**Additional Fee**
Total Claims	56	78	0	x $ 52 (1202)	$ 0
Independent Claims	4	5	0	x $ 220 (1201)	0
☐ If Amendment adds multiple dependent claims, add $ 390 (1203)					$ 0
Total Claim Amendment Fee					**$ 0**
☐ Small Entity Status claimed - subtract 50% of Total Claim Amendment Fee					0
TOTAL ADDITIONAL CLAIM FEE DUE FOR THIS AMENDMENT					**$ 0**

☐ Charge _____ to Deposit Account No. 02-4800 for the fee due.

☒ Charge $ 0 to credit card for the fee due.

☒ The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.20(d) and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

By: Mary Katherine Baumeister
Mary Katherine Baumeister
Registration No. 26254

Date July 30, 2010

Customer No. 21839
703 836 6620

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	**MAIL STOP AMENDMENT**
Nicholas Bodor et al.	)	Group Art Unit: 1623
Application No.: 10/551,205	)	Examiner: JONATHAN S LAU
Filing Date: November 14, 2006	)	Confirmation No.: 4092
Title: ORAL FORMULATIONS OF CLADRIBINE	)	

PETITION FOR EXTENSION OF TIME

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The following extension of time is requested to: extend the period for response to the Office Action dated March 30, 2010 for

One Month to July 30, 2010 ☒ $ 130 ☐ $ 65

☐ Charge _____ to Deposit Account No. 02-4800.

☒ Charge $ 130 to credit card.

The Director is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17 and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: July 30, 2010

By: Mary Katherine Baumeister
Mary Katherine Baumeister
Registration No. 26254

Customer No. 21839
703 836 6620

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
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.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 10/551,205	Filing Date 11/14/2006	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☐		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	07/30/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 56	Minus	** 78	= 0	X $ =		OR	X $52=	0
	Independent (37 CFR 1.16(h))	* 5	Minus	***6	= 0	X $ =		OR	X $220=	0
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/LAMONT MCLAUCHLIN/

This collection of information is required by 37 CFR 1.16. 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, 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.

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

21839 7590 10/04/2010

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
LAU, JONATHAN S	
ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 10/04/2010

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,205	11/14/2006	Nicholas S. Bodor	0056192-000024	4092

TITLE OF INVENTION: ORAL FORMULATIONS OF CLADRIBINE

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	01/04/2011

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 SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

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.

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)

21839 7590 10/04/2010

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

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.
10/551,205	11/14/2006	Nicholas S. Bodor	0056192-000024	4092

TITLE OF INVENTION: ORAL FORMULATIONS OF CLADRIBINE

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	01/04/2011

EXAMINER	ART UNIT	CLASS-SUBCLASS
LAU, JONATHAN S	1623	514-045000

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 credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information 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.

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.
10/551,205	11/14/2006	Nicholas S. Bodor	0056192-000024	4092

21839 7590 10/04/2010

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
LAU, JONATHAN S	
ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 10/04/2010

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

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 Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Notice of Allowability	Application No.	Applicant(s)	
	10/551,205	BODOR ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- 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 *Applicant's Amendment and Remarks, filed 30 Jul 2010*.

2. ☒ The allowed claim(s) is/are *1,2,8,9,11-14,20,21,23-26,28,32,33,35,56,57,63,64 and 66-98*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   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.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ 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. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

Jonathan Lau Patent Examiner Art Unit 1623	/Shaojia Anna Jiang/ Supervisory Patent Examiner, Art Unit 1623

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Kathy Baumeister on 27 Sep 2010.

The application has been amended as follows:

Amendment to the Claims

- Claims 25, 27 and 28 are amended as follows:

Claim 25. (Currently Amended) A method for the treatment of ~~symptoms of a cladribine-responsive condition~~ a condition selected from the group consisting of multiple sclerosis, rheumatoid arthtritis and leukemia in a subject suffering from said ~~symptoms~~ condition comprising orally administering to said subject a pharmaceutical composition comprising a complex cladribine-cyclodextrin complex which is an intimate amorphous admixture consisting of (a) an amorphous inclusion complex of cladribine with the amorphous cyclodextrin hydroxypropyl-β-cyclodextrin and (b) amorphous free cladribine associated with said amorphous cyclodextrin as a non-inclusion complex, formulated into a solid oral dosage form, said composition comprising no significant amount of free crystalline cladribine therein, said composition havinq a weiqht ratio of cladribine to said amorphous cyclodextrin of from about 1:10 to about 1:16.

Claim 27. (Canceled)

Claim 28. (Currently Amended) The method according to Claim ~~27~~ 25, wherein the ~~cladribine-responsive~~ condition is multiple sclerosis.

DETAILED ACTION

This Office Action is responsive to Applicant's Amendment and Remarks, filed 30 Jul 2010.

This application is the national stage entry of PCT/US04/09387, filed 26 Mar 2004; and claims benefit of provisional application 60/458,922, filed 28 Mar 2003; and claims benefit of provisional application 60/484,756, filed 02 July 2003; and claims benefit of provisional application 60/541,247, filed 04 Feb 2004.

The filing date of the instant claims 12, 83, 85 and 89 are deemed to be the filing date of the instant application which is the filing date of PCT/US04/09387, 26 Mar 2004. The filing date of instant claims 1, 2, 8, 9, 11, 56, 57, 63, 64, 82, 84 and 86-98 are deemed to be the filing date of provisional application 60/541,247, filed 04 Feb 2004.

Claims 1, 2, 8, 9, 11-14, 20, 21, 23-28, 32, 33, 35, 56, 57, 63, 64 and 66-98 are pending in the current application. Claims 13, 14, 20, 21, 23-28, 32, 33, 35 and 67-81, drawn to non-elected inventions, are rejoined herein. Claim 27 is canceled by Examiner's Amendment herein. Claims 1, 2, 8, 9, 11-14, 20, 21, 23-26, 28, 32, 33, 35, 56, 57, 63, 64 and 66-98 are allowed herein.

Reasons for Allowance

Rejections Withdrawn

Applicant's Remarks, filed 30 Jul 2010, with respect to claims 1, 2, 8, 9, 11, 56, 57, 63, 64 and 82-98 rejected under 35 U.S.C. 103(a) as being unpatentable over Schultz et al. (US Patent 6,194,395, published 27 Feb 2001, of record) in view of Pitha (US Patent 4,727,064, issued 23 Feb 1988, provided by Applicant in IDS mailed 4 Apr 2008) and in view of Loftsson J Pharm Sci 2002 (Journal of Pharmaceutical Sciences, 2002, 91(11), p2307-2316, cited in PTO-892) has been fully considered and is persuasive, as Applicant's remarks are persuasive that Schultz et al. in view of Pitha and in view of Loftsson J Pharm Sci 2002 does not teach a composition comprising amorphous free cladribine associated with said amorphous cyclodextrin as a non-inclusion complex. Applicant notes that dependent claims 12 and 66 were omitted from the statement of rejection, however this is moot in view of the withdrawal of this rejection in view of Applicant's Remarks.

This rejection has been **withdrawn**.

The following is an examiner's statement of reasons for allowance:

The closest prior art is Schultz et al. in view of Pitha and in view of Loftsson J Pharm Sci 2002.

Applicant's Remarks, filed 30 Jul 2010, have been fully considered and found to be persuasive that Schultz et al. in view of Pitha and in view of Loftsson J Pharm Sci 2002 does not teach all features of the instant invention as claimed. None of Schultz et al., Pitha or Loftsson J Pharm Sci 2002 teach or fairly suggest the instant composition comprising amorphous free cladribine associated with said amorphous cyclodextrin as a

non-inclusion complex, and no evidence teaches or fairly suggests that this is an inherent property in the composition that is necessarily present. For example, Pitha teaches crystalline drugs and cyclodextrins that have the ability to form inclusion complexes which are intrinsically amorphous (column 1, lines 25-35), however Pitha does not teach or fairly suggest amorphous free cladribine associated with said amorphous cyclodextrin as a non-inclusion complex and neither Schultz et al. nor Loftsson J Pharm Sci 2002 remedy this. For example, Schultz et al. does not teach or fairly suggest that formation of free cladribine associated with said amorphous cyclodextrin as a non-inclusion complex is necessarily amorphous but rather suggests cladribine will crystallize out of solution (column 1, lines 60-65 and column 2, lines 1-15).

Therefore the prior art does not teach or fairly suggest the instant invention as claimed.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled “Comments on Statement of Reasons for Allowance.”

Conclusion

Claims 1, 2, 8, 9, 11-14, 20, 21, 23-26, 28, 32, 33, 35, 56, 57, 63, 64 and 66-98 are allowed herein.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jonathan Lau
Patent Examiner
Art Unit 1623

/Shaojia Anna Jiang/
Supervisory Patent Examiner
Art Unit 1623

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10551205	BODOR ET AL.
	Examiner	**Art Unit**
	Jonathan S Lau	1623

ORIGINAL		INTERNATIONAL CLASSIFICATION															
CLASS	SUBCLASS	CLAIMED										NON-CLAIMED					
514	46	A	6	1	K	31 / 7076 (2006.01.01)											
CROSS REFERENCE(S)		A	6	1	K	31 / 724 (2006.01.01)											
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)																
514	58																

☐ 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
6	1		17	39	33		49		65	55	81	27	97		
7	2		18		34		50	5	66	12	82	28	98		
	3		19	40	35		51	41	67	13	83				
	4	31	20		36		52	42	68	14	84				
	5	32	21		37		53	43	69	15	85				
	6		22		38		54	44	70	16	86				
	7	33	23		39		55	45	71	17	87				
8	8	34	24		40	1	56	46	72	18	88				
9	9	35	25		41	2	57	47	73	19	89				
	10	36	26		42		58	48	74	20	90				
10	11		27		43		59	49	75	21	91				
11	12	37	28		44		60	50	76	22	92				
29	13		29		45		61	51	77	23	93				
30	14		30		46		62	52	78	24	94				
	15		31		47	3	63	53	79	25	95				
	16	38	32		48	4	64	54	80	26	96				

/Jonathan S Lau/ Examiner.Art Unit 1623 (Assistant Examiner)	9/27/10 (Date)	**Total Claims Allowed:** 55
/Shaojia Anna Jiang/ Supervisory Patent Examiner.Art Unit 1623 (Primary Examiner)	09/27/2010 (Date)	O.G. Print Claim(s) 1 O.G. Print Figure none

U.S. Patent and Trademark Office

Part of Paper No. 20100927

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	10551205	BODOR ET AL.
	Examiner	Art Unit
	Jonathan S Lau	1623

SEARCHED

Class	Subclass	Date	Examiner
514	46, 58	9/27/2010	JSL

SEARCH NOTES

Search Notes	Date	Examiner
EAST - inventor name search (Nicholas Bodor; Yogesh Dandiker)	3/26/2008	JSL
EAST - see attached notes	3/26/2008	JSL
Google Scholar - see attached notes	3/26/2008	JSL
EAST - see attached notes	9/10/2009	JSL
Google Scholar - see attached notes	9/10/2009	JSL
STN - CAPlus file - see attached notes	9/10/2009	JSL
EAST - see attached notes	3/25/2010	JSL
Google Scholar - see attached notes	3/25/2010	JSL
EAST - inventor name search (Nicholas Bodor; Yogesh Dandiker) updated	9/27/2010	JSL

INTERFERENCE SEARCH

Class	Subclass	Date	Examiner
514	46, 58	9/27/2010	JSL

AMENDMENTS TO THE SPECIFICATION:

Please replace the paragraph at page 22, lines 8-16 of the specification with the following amended paragraph:

The compositions of the invention are particularly suitable as modalities for the treatment of any cladribine-responsive disease. Several disease states responsive to cladribine are well-documented in the literature (see *infra).* For any target disease state, an effective amount of the complex cladribine-cyclodextrin ~~comples~~ complex, *i.e.* the amorphous mixture of the optimized amorphous saturated cladribine-amorphous cyclodextrin complex with amorphous free cladribine as described above is used (e.g., an amount ~~affective~~ effective for the treatment of multiple sclerosis, rheumatoid arthritis, or leukemia).

Please replace the paragraph at page 23, lines 7-~~28~~ 29, of the specification with the following amended paragraph:

CMO 11-10-12

Moreover, the route of administration for which the therapeutically effective dosages are taught in the literature should be taken into consideration. While the instant compositions optimize the bioavailability of cladribine following oral administration, it will be appreciated that even optimal bioavailability from oral dosage forms is not expected to approach bioavailability ~~obtain~~ obtained after intravenous administration, particularly at early time points. Thus, it is often appropriate to increase a dosage suggested for intravenous administration to arrive at a suitable dosage for incorporation into a solid oral dosage form. At the present time, it is envisioned that, for the treatment of multiple sclerosis, 10 mg of cladribine in the instant complex cladribine-cyclodextrin complex in the instant solid dosage form would be administered once per day for a period of five to seven days in the first month, repeated for another period of five to seven days in the second month, followed by ten months of no treatment. Alternatively the patient would

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)

21839 7590 10/04/2010

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

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.
10/551,205	11/14/2006	Nicholas S. Bodor	0056192-000024	4092

TITLE OF INVENTION: ORAL FORMULATIONS OF CLADRIBINE

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	01/04/2011

EXAMINER	ART UNIT	CLASS-SUBCLASS
LAU, JONATHAN S	1623	514-045000

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 Buchanan Ingersoll
2 & Rooney PC
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: Ares Trading S.A.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Aubonne, Switzerland

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 6

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 credit any overpayment, to Deposit Account Number 02-4800 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature Mary Katherine Baumeister Date January 4, 2011

Typed or printed name Mary Katherine Baumeister Registration No. 26254

This collection of information 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.

Electronic Patent Application Fee Transmittal

Application Number:	10551205
Filing Date:	14-Nov-2006
Title of Invention:	ORAL FORMULATIONS OF CLADRIBINE
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Filer:	Mary Katherine Baumeister/Diana Francis
Attorney Docket Number:	0056192-000024

Filed as Large Entity

U.S. National Stage under 35 USC 371 Filing Fees

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	1510	1510
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
Printed copy of patent - no color	8001	6	3	18
		Total in USD ($)		**1828**

Electronic Acknowledgement Receipt

EFS ID:	9157246
Application Number:	10551205
International Application Number:	
Confirmation Number:	4092
Title of Invention:	ORAL FORMULATIONS OF CLADRIBINE
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Customer Number:	21839
Filer:	Mary Katherine Baumeister/Diana Francis
Filer Authorized By:	Mary Katherine Baumeister
Attorney Docket Number:	0056192-000024
Receipt Date:	04-JAN-2011
Filing Date:	14-NOV-2006
Time Stamp:	11:06:26
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1828
RAM confirmation Number	9174
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	le Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Issue Fee Payment (PTO-85B)	IssueFee.pdf	118520 1b54aae6db7cf01858924fed8ebc312ed72ce8dd	no	1
Warnings:					
Information:					
2	Fee Worksheet (PTO-875)	fee-info.pdf	33596 ce0d1bfcc1aba05d6eab1c57381ae34f5b94ab1c	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	152116		

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

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,205	02/15/2011	7888328	0056192-000024	4092

21839 7590 01/26/2011

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

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 16 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):

Nicholas S. Bodor, Bal Harbour, FL;
Yogesh Dandiker, Toronto, CANADA;

PTO/SB/80 (11-08)
Approved for use through 11/30/2011. OMB 0651-0035
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.

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(b).

I hereby appoint:

☑ Practitioners associated with the Customer Number: 13974

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(b) to:

☑ The address associated with Customer Number: 13974

OR

☐ Firm or Individual Name			
Address			
City		State	Zip
Country			
Telephone		Email	

Assignee Name and Address:

ARES TRADING S.A.
ZONE INDUSTRIELLE D L'OURIETTAZ
CH-1170 AUBONNE, SWITZERLAND

A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record
The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature		Date 10.04.2012
Name	Bjoern Colin KAHRS ~~Authorized Representative~~	Telephone
Title	Prisca VON BALLMOOS ~~Authorized Representative~~	

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: ARES TRADING S.A.

Application No./Patent No.: 10/551,205/788328 Filed/Issue Date: 11-14-2006/02-15-2011

Titled: ORAL FORMULATIONS OF CLADRIBINE

ARES TRADING S.A. , a Corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy therefore is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Nicholas S. Bodor et al To: IVAX CORPORATION

The document was recorded in the United States Patent and Trademark Office at
Reel 018337, Frame 0636, or for which a copy thereof is attached.

2. From: IVAX CORPORATION To: ARES TRADING S.A.

The document was recorded in the United States Patent and Trademark Office at
Reel 018337, Frame 0696, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Martin A. Bruehs/	MAY 24, 2013
Signature	Date
MARTIN A. BRUEHS	Attorney for Applicant(s)
Printed or Typed Name	Title

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.

Electronic Acknowledgement Receipt

EFS ID:	15868660
Application Number:	10551205
International Application Number:	
Confirmation Number:	4092
Title of Invention:	ORAL FORMULATIONS OF CLADRIBINE
First Named Inventor/Applicant Name:	Nicholas S. Bodor
Customer Number:	21839
Filer:	Martin A. Bruehs/Louie Malloy
Filer Authorized By:	Martin A. Bruehs
Attorney Docket Number:	0056192-000024
Receipt Date:	24-MAY-2013
Filing Date:	14-NOV-2006
Time Stamp:	15:44:33
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		DOC.PDF	91689 0ca5964082b7640fd59aa3cfd62ad8a26053eb0a	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Power of Attorney	1	1
	Assignee showing of ownership per 37 CFR 3.73.	2	3
Warnings:			
Information:			
	Total Files Size (in bytes):	91689	

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

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/551,205	11/14/2006	Nicholas S. Bodor	0056192-000024

CONFIRMATION NO. 4092

POWER OF ATTORNEY NOTICE

21839
BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

OC000000062151006

Date Mailed: 06/24/2013

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 06/21/2013.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/dolipscomb/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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 NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/551,205	11/14/2006	Nicholas S. Bodor	0056192-000024

CONFIRMATION NO. 4092

13974
DENTONS US LLP
P.O. BOX 061080
Chicago, IL 60606-1080

POA ACCEPTANCE LETTER

OC000000062151026

Date Mailed: 06/24/2013

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 06/21/2013.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/dolipscomb/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101