Atty. Dkt. No. 080618-1256

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name: Hitesh BATRA

Title: AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

Prior Appl. No.: 13/548,446

Prior Appl. Filing Date: 7/13/2012

Examiner: Unassigned

Art Unit: Unassigned

CONTINUING PATENT APPLICATION TRANSMITTAL LETTER

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

Commissioner:

Transmitted herewith for filing under 37 C.F.R. § 1.53(b) is a:

[**X**] Continuation [ ] Division [ ] Continuation-In-Part (CIP)

of the above-identified copending prior application in which no patenting, abandonment, or termination of proceedings has occurred. Priority to the above-identified prior application is hereby claimed under 35 U.S.C. § 120 for this continuing application. The entire disclosure of the above-identified prior application is considered as being part of the disclosure of the accompanying continuing application and is hereby incorporated by reference therein.

[ ] Applicant claims small entity status under 37 CFR 1.27.

Enclosed are:

[**X**] Description, Claims, and Abstract (23 pages).

[**X**] Executed Declaration (4 pages).

[**X**] Power of Attorney (1 page).

[**X**] Information Disclosure Statement, Form PTO-SB08.

[**X**] Application Data Sheet (37 CFR 1.76).

The adjustment to the number of sheets for EFS-Web filing follows:

Number of Sheets		**EFS-Web Adjustment**	**Number of Sheets for EFS-Web**
23	x	75%	18

The filing fee is calculated below at the large entity rate:

	Number Filed		**Included in Basic Fee**		**Extra**		Rate		Fee Totals
Basic Filing Fee							$280.00	=	$280.00
Search Fee							$600.00		$600.00
Examination Fee							$720.00		$720.00
Size Fee	18	-	100	= 0		x	$400.00		$0.00
Total Claims:	9	-	20	= 0		x	$80.00	=	$0.00
Independent:	1	-	3	= 0		x	$420.00	=	$0.00
If any Multiple Dependent Claim(s) present:						+	$780.00	=	$0.00
Surcharge under 37 CFR 1.16(e) for late filing of Executed Declaration or late payment of filing fee						+	$140.00	=	$0.00
Prioritized Examination fee (Track I) under 37 C.F.R. § 1.17 (c)									$0.00
Processing Fee (Track I) under 37 C.F.R. § 1.17 (i)									$0.00
TOTAL FILING FEE:								=	$1600.00
Assignment Recordation Fee:						+	$40.00	=	$0.00
Processing Fee under 37 CFR 1.17(i) for Late Filing of English Translation of Application:						+	$140.00	=	$0.00
Publication Fee									$0.00
TOTAL FEE								=	$1600.00

The above-identified fees of $1600.00 are being paid by credit card via EFS-Web.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the

credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,

Date July 2, 2013

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
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Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name: Hitesh BATRA

Title: AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

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AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a Continuation of U.S. Application No. 13/548,446, filed July 13, 2012, which is a Continuation of U.S. Application No. 12/334,731, filed December 15, 2008, which claims priority from U.S. Provisional Patent Application 61/014,232, filed December 17, 2007, the entire contents of which are incorporated herein by reference.

BACKGROUND

[0002] The present invention relates to a process for producing prostacyclin derivatives and novel intermediate compounds useful in the process.

[0003] Prostacyclin derivatives are useful pharmaceutical compounds possessing activities such as platelet aggregation inhibition, gastric secretion reduction, lesion inhibition, and bronchodilation.

[0004] Treprostinil, the active ingredient in Remodulin®, was first described in US patent 4,306,075. Treprostinil, and other prostacyclin derivatives have been prepared as described in Moriarty, et al in *J. Org. Chem.* 2004, 69, 1890-1902, *Drug of the Future*, 2001, 26(4), 364-374, U.S. Pat. Nos. 6,441,245, 6,528,688, 6,765,117 and 6,809,223. Their teachings are incorporated by reference to show how to practice the embodiments of the present invention.

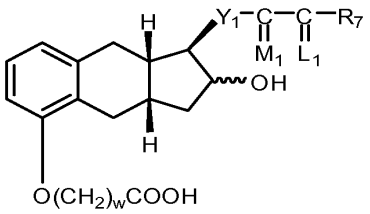
[0005] U.S. Patent No. 5,153,222 describes use of treprostinil for treatment of pulmonary hypertension. Treprostinil is approved for the intravenous as well as subcutaneous route, the latter avoiding septic events associated with continuous intravenous catheters. U.S. patents Nos. 6,521,212 and 6,756,033 describe administration of treprostinil by inhalation for treatment of pulmonary hypertension, peripheral vascular disease and other diseases and conditions. U.S. patent No. 6,803,386 discloses administration of treprostinil for treating cancer such as lung, liver, brain, pancreatic, kidney, prostate, breast, colon and head-neck cancer. U.S. patent application publication No. 2005/0165111 discloses treprostinil treatment of ischemic lesions. U.S. patent No. 7,199,157 discloses that treprostinil treatment improves kidney functions. U.S. patent application publication No. 2005/0282903 discloses treprostinil treatment of neuropathic foot ulcers. U.S. application No. 12/028,471 filed February 8, 2008,

discloses treprostinil treatment of pulmonary fibrosis. U.S. 6,054,486 discloses treatment of peripheral vascular disease with treprostinil. U.S. patent application 11/873,645 filed October 17, 2007 discloses combination therapies comprising treprostinil. U.S. publication No. 2008/0200449 discloses delivery of treprostinil using a metered dose inhaler. U.S. publication No. 2008/0280986 discloses treatment of interstitial lung disease with treprostinil. U.S. application No. 12/028,471 filed February 8, 2008 discloses treatment of asthma with treprostinil. U.S. 7,417,070, 7,384,978 and U.S. publication Nos. 2007/0078095, 2005/0282901, and 2008/0249167 describe oral formulations of treprostinil and other prostacyclin analogs.

[0006] Because Treprostinil, and other prostacyclin derivatives are of great importance from a medicinal point of view, a need exists for an efficient process to synthesize these compounds on a large scale suitable for commercial production.

SUMMARY

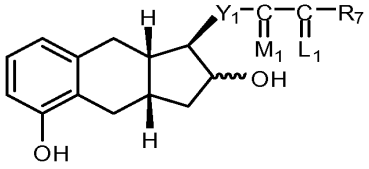
[0007] The present invention provides in one embodiment a process for the preparation of a compound of formula I, hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.



(I)

[0008] The process comprises the following steps:

(a) alkylating a compound of structure II with an alkylating agent to produce a compound of formula III,



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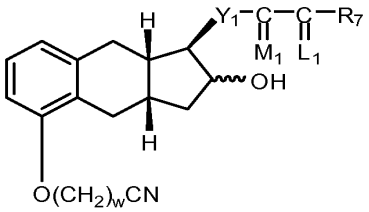


(III)

wherein

w= 1, 2, or 3;

Y_1 is trans-CH=CH-, cis-CH=CH-, $-CH_2(CH_2)_m-$, or -C≡C-; m is 1, 2, or 3;

R_7 is

(1) $-C_pH_{2p}-CH_3$, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH=CH-CH_2-CH_3,

(5) $-(CH_2)_2$-CH(OH)-CH_3, or

(6) $-(CH_2)_3$-CH=$C(CH_3)_2$;

wherein -$C(L_1)$-R_7 taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

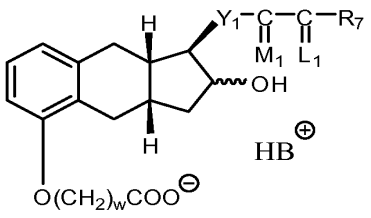
(4) 3-thienyloxymethyl;

M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and

L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

(b) hydrolyzing the product of step (a) with a base,

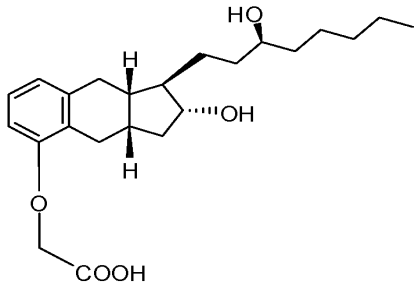
(c) contacting the product of step (b) with a base B to for a salt of formula I_s



(I_s)

(d) reacting the salt from step (c) with an acid to form the compound of formula I.

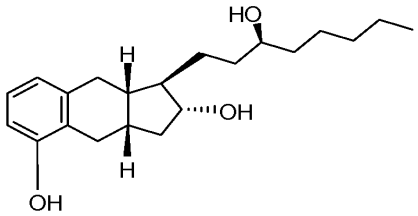
[0009] The present invention provides in another embodiment a process for the preparation of a compound of formula IV.



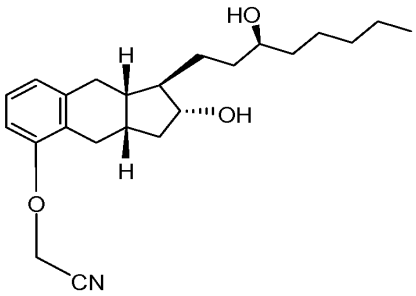
(IV)

[0010] The process comprises the following steps:

(a) alkylating a compound of structure V with an alkylating agent to produce a compound of formula VI,



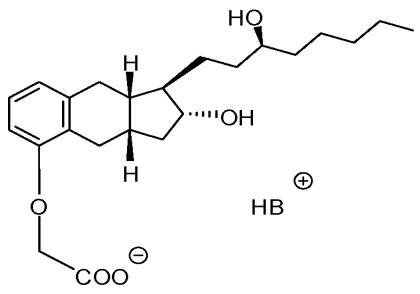
(V)



(VI)

(b) hydrolyzing the product of step (a) with a base,

(c) contacting the product of step (b) with a base B to for a salt of formula IV_s, and



(IV_s)

(d) reacting the salt from step (b) with an acid to form the compound of formula IV.

DETAILED DESCRIPTION

[0011] The various terms used, separately and in combinations, in the processes herein described are defined below.

[0012] The expression "comprising" means "including but not limited to." Thus, other non-mentioned substances, additives, carriers, or steps may be present. Unless otherwise specified, "a" or "an" means one or more.

[0013] C_{1-3}-alkyl is a straight or branched alkyl group containing 1-3 carbon atoms. Exemplary alkyl groups include methyl, ethyl, n-propyl, and isopropyl.

[0014] C_{1-3}-alkoxy is a straight or branched alkoxy group containing 1-3 carbon atoms. Exemplary alkoxy groups include methoxy, ethoxy, propoxy, and isopropoxy.

[0015] C_{4-7}-cycloalkyl is an optionally substituted monocyclic, bicyclic or tricyclic alkyl group containing between 4-7 carbon atoms. Exemplary cycloalkyl groups include but not limited to cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[0016] Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein.

[0017] As used herein, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (*in vitro* or *in vivo*) to provide an active compound. Examples of prodrugs include, but are not limited to,

derivatives of a compound that include biohydrolyzable groups such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues (*e.g.*, monophosphate, diphosphate or triphosphate).

[0018] As used herein, "hydrate" is a form of a compound wherein water molecules are combined in a certain ratio as an integral part of the structure complex of the compound.

[0019] As used herein, "solvate" is a form of a compound where solvent molecules are combined in a certain ratio as an integral part of the structure complex of the compound.

[0020] "Pharmaceutically acceptable" means in the present description being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

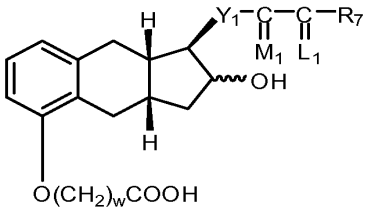
[0021] "Pharmaceutically acceptable salts" mean salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with organic and inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, glycolic acid, maleic acid, malonic acid, oxalic acid, methanesulfonic acid, trifluoroacetic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, ascorbic acid and the like. Base addition salts may be formed with organic and inorganic bases, such as sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, choline and the like. Included in the invention are pharmaceutically acceptable salts or compounds of any of the formulae herein.

[0022] Depending on its structure, the phrase "pharmaceutically acceptable salt," as used herein, refers to a pharmaceutically acceptable organic or inorganic acid or base salt of a compound. Representative pharmaceutically acceptable salts include, *e.g.*, alkali metal salts, alkali earth salts, ammonium salts, water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2, 2 -disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulariate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride,

hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

[0023] The present invention provides for a process for producing treprostinil and other prostacyclin derivatives and novel intermediate compounds useful in the process. The process according to the present invention provides advantages on large-scale synthesis over the existing method. For example, the purification by column chromatography is eliminated, thus the required amount of flammable solvents and waste generated are greatly reduced. Furthermore, the salt formation is a much easier operation than column chromatography. Moreover, it was found that the product of the process according to the present invention has higher purity. Therefore the present invention provides for a process that is more economical, safer, faster, greener, easier to operate, and provides higher purity.

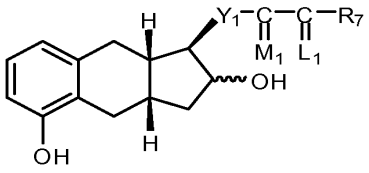
[0024] One embodiment of the present invention is a process for the preparation of a compound of formula I, or a hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.



(I)

[0025] The process comprises the following steps:

(a) alkylating a compound of formula II with an alkylating agent to produce a compound of formula III,



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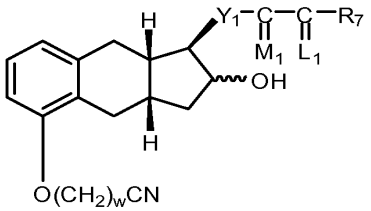


(III)

wherein

w= 1, 2, or 3;

Y_1 is trans-CH=CH-, cis-CH=CH-, $-CH_2(CH_2)_m-$, or -C≡C-; m is 1, 2, or 3;

R_7 is

(1) $-C_pH_{2p}-CH_3$, wherein p is an integer from 1 to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3) alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH=CH-CH_2-CH_3,

(5) $-(CH_2)_2$-CH(OH)-CH_3, or

(6) $-(CH_2)_3$-CH=$C(CH_3)_2$;

wherein $-C(L_1)-R_7$ taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by 1 to 3 (C_1-C_5)alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

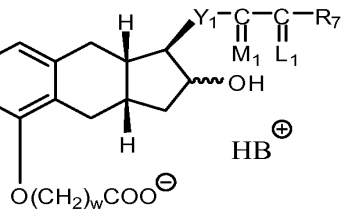
(4) 3-thienyloxymethyl;

M_1 is α-OH:β-R_5 or α-R_5:β-OH or α-OR_1:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and

L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

(b) hydrolyzing the product of step (a) with a base,

(c) contacting the product of step (b) with a base B to for a salt of formula I_s

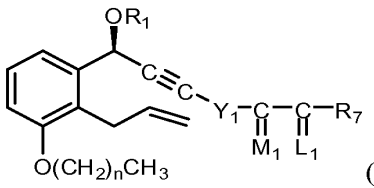


(I_s)

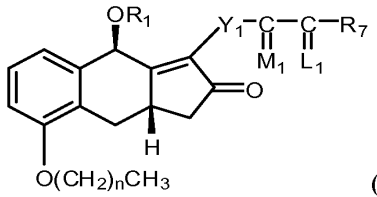
(d) reacting the salt from step (c) with an acid to form the compound of formula I.

[0026] In one embodiment, the compound of formula I is at least 90.0%, 95.0%, 99.0%.

[0027] The compound of formula II can be prepared from a compound of formula XI, which is a cyclization product of a compound of formula X as described in U.S. Pat. No. 6,441,245.



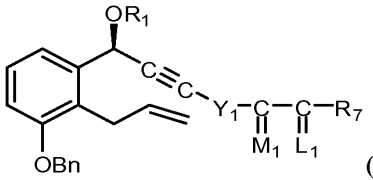
(X)



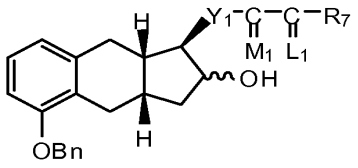
(XI)

Wherein n is 0, 1, 2, or 3.

[0028] The compound of formula II can be prepared alternatively from a compound of formula XIII, which is a cyclization product of a compound of formula XII as described in U.S. Pat. No. 6,700,025.

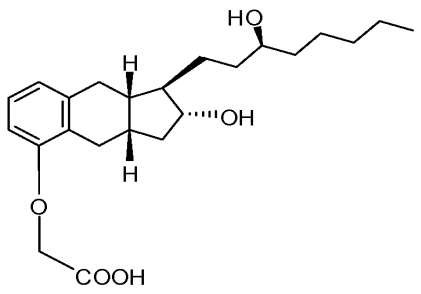


(XII)



(XIII)

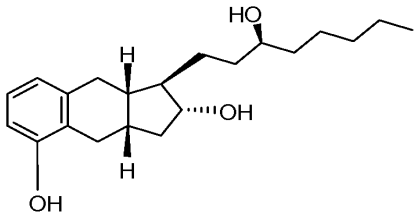
[0029] One embodiment of the present invention is a process for the preparation of a compound having formula IV, or a hydrate, solvate, or pharmaceutically acceptable salt thereof.



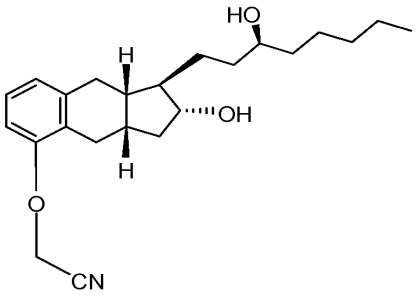
(IV)

[0030] The process comprises

(a) alkylating a compound of structure V with an alkylating agent such as $ClCH_2CN$ to produce a compound of formula VI,



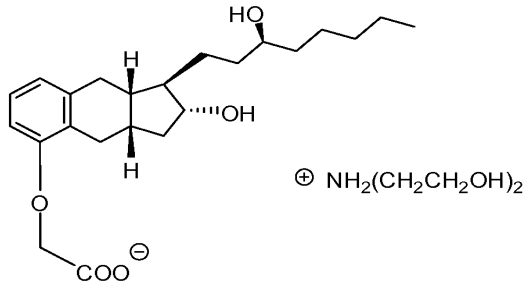
(V)



(VI)

(b) hydrolyzing the product of step (a) with a base such as KOH,

(c) contacting the product of step (b) with a base B such as diethanolamine to for a salt of the following structure, and



(d) reacting the salt from step (b) with an acid such as HCl to form the compound of formula IV.

[0031] In one embodiment, the purity of compound of formula IV is at least 90.0%, 95.0%, 99.0%, 99.5%.

[0032] In one embodiment, the process further comprises a step of isolating the salt of formula IV_s.

[0033] In one embodiment, the base B in step (c) may be ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, or triethanolamine.

[0034] The following abbreviations are used in the description and/or appended claims, and they have the following meanings:

"MW" means molecular weight.

"Eq." means equivalent.

"TLC" means thin layer chromatography.

"HPLC" means high performance liquid chromatography.

"PMA" means phosphomolybdic acid.

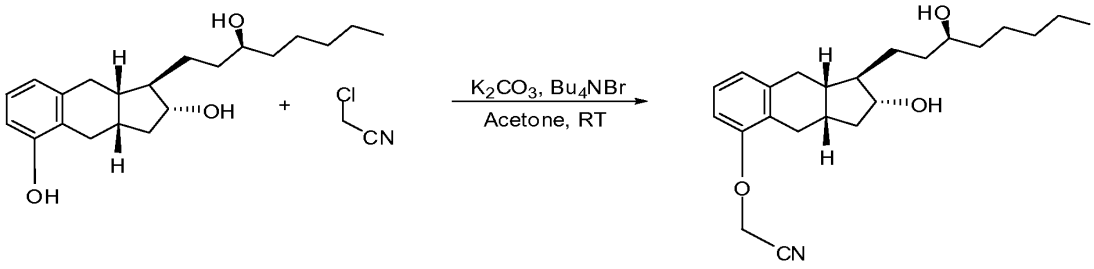
"AUC" means area under curve.

[0035] In view of the foregoing considerations, and specific examples below, those who are skilled in the art will appreciate that how to select necessary reagents and solvents in practicing the present invention.

[0036] The invention will now be described in reference to the following Examples. These examples are not to be regarded as limiting the scope of the present invention, but shall only serve in an illustrative manner.

EXAMPLES

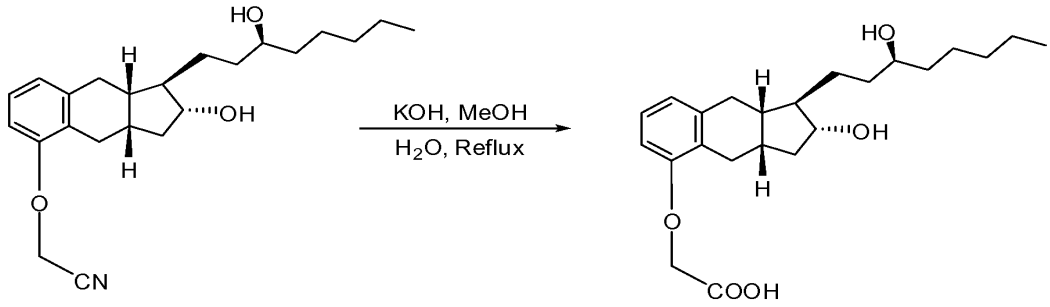
Example 1. Alkylation of Benzindene Triol



Name	MW	Amount	Mol.	Eq.
Benzindene Triol	332.48	1250 g	3.76	1.00
K_2CO_3 (powder)	138.20	1296 g	9.38	2.50
$ClCH_2CN$	75.50	567 g	7.51	2.0
Bu_4NBr	322.37	36 g	0.11	0.03
Acetone	--	29 L	--	--
Celite®545	--	115 g	--	--

[0037] A 50-L, three-neck, round-bottom flask equipped with a mechanical stirrer and a thermocouple was charged with benzindene triol (1250 g), acetone (19 L) and K_2CO_3 (powdered) (1296 g), chloroacetonitrile (567 g), tetrabutylammonium bromide (36 g). The reaction mixture was stirred vigorously at room temperature (23±2°C) for 16-72 h. The progress of the reaction was monitored by TLC. (methanol/CH_2Cl_2; 1:9 and developed by 10% ethanolic solution of PMA). After completion of reaction, the reaction mixture was filtered with/without Celite pad. The filter cake was washed with acetone (10L). The filtrate was concentrated *in vacuo* at 50-55°C to give a light-brown, viscous liquid benzindene nitrile. The crude benzindene nitrile was used as such in the next step without further purification.

Example 2. Hydrolysis of Benzindene Nitrile



Name	MW	Amount	Mol.	Eq.
Benzindene Nitrile	371.52	1397 g*	3.76	1.0
KOH	56.11	844 g	15.04	4.0
Methanol	--	12 L	--	--
Water	--	4.25 L	--	--

*Note: This weight is based on 100% yield from the previous step. This is not isolated yield.

[0038] A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with a solution of benzindene nitrile in methanol (12 L) and a solution of KOH (844 g of KOH dissolved in 4.25 L of water). The reaction mixture was stirred and heated to reflux (temperature 72.2°C). The progress of the reaction was monitored by TLC (for TLC purpose, 1-2 mL of reaction mixture was acidified with 3M HCl to pH 1-2 and extracted with ethyl acetate. The ethyl acetate extract was used for TLC; Eluent: methanol/CH_2Cl_2; 1:9, and developed by 10% ethanolic solution of PMA). After completion of the reaction (~5 h), the reaction mixture was cooled to -5 to 10°C and quenched with a solution of hydrochloric acid (3M, 3.1 L) while stirring. The reaction mixture was concentrated *in vacuo* at 50-55°C to obtain approximately 12-14 L of condensate. The condensate was discarded.

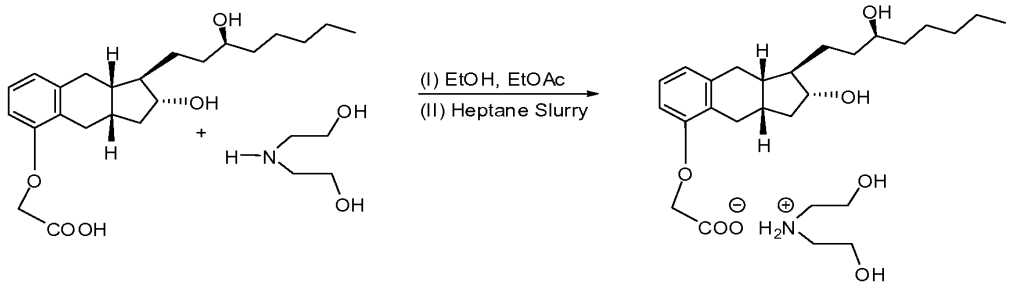
[0039] The aqueous layer was diluted with water (7-8 L) and extracted with ethyl acetate (2 × 6 L) to remove impurities soluble in ethyl acetate. To aqueous layer, ethyl acetate (22 L) was added and the pH of reaction mixture was adjusted to 1-2 by adding 3M HC1 (1.7 L) with stirring. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 11 L). The combined organic layers were washed with water (3 × 10 L) and followed by washing with a solution of $NaHCO_3$ (30 g of $NaHCO_3$ dissolved in 12 L of water). The organic layer was further washed with saturated solution of NaCl (3372 g of NaCl dissolved in water (12 L)) and dried over anhydrous Na_2SO_4 (950-1000 g), once filtered.

[0040] The filtrate was transferred into a 72-L reactor equipped with mechanical stirrer, a condenser, and a thermocouple. To the solution of treprostinil in reactor was added activated carbon (110-130 g). The suspension was heated to reflux (temperature 68-70°C) for at least one hour. For filtration, a pad of Celite®545 (300-600 g) was prepared in sintered glass

funnel using ethyl acetate. The hot suspension was filtered through the pad of Celite®545. The Celite®545 was washed with ethyl acetate until no compound was seen on TLC of the washings.

[0041] The filtrate (pale-yellow) was reduced to volume of 35-40 L by evaporation *in vacuo* at 50-55°C for direct use in next step.

Example 3. Conversion of Treprostinil to Treprostinil Diethanolamine Salt (1:1)



Name	MW	Amount	Mol	Eq
Treprostinil	390.52	1464 g*	3.75	1.0
Diethanolamine	105.14	435 g	4.14	1.1
Ethanol	--	5.1 L	--	--
Ethyl acetate	--	35L**	--	--
Treprostinil Diethanolamine Salt (seed)	--	12 g	--	--

*Note: This weight is based on 100% yield from benzindene triol. It is not isolated yield. The treprostinil was carried from previous step in ethyl acetate solution and used as such for this step.

**Note: The total volume of ethyl acetate should be in range of 35-36 L (it should be 7 times the volume of ethanol used). Approximately 35 L of ethyl acetate was carried over from previous step and additional 1.0 L of ethyl acetate was used for rinsing the flask.

[0042] A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with a solution of treprostinil in ethyl acetate (35-40 L from the previous step), anhydrous ethanol (5.1 L) and diethanolamine (435 g). While stirring, the reaction mixture was heated to 60-75°C, for 0.5-1.0 h to obtain a clear solution. The clear solution was cooled to 55±5°C. At this temperature, the seed of

polymorph B of treprostinil diethanolamine salt (~12 g) was added to the clear solution. The suspension of polymorph B was stirred at this temperature for 1 h. The suspension was cooled to 20±2°C overnight (over a period of 16-24 h). The treprostinil diethanolamine salt was collected by filtration using Aurora filter equipped with filter cloth, and the solid was washed with ethyl acetate (2 × 8 L). The treprostinil diethanolamine salt was transferred to a HDPE/glass container for air-drying in hood, followed by drying in a vacuum oven at 50±5°C under high vacuum.

[0043] At this stage, if melting point of the treprostinil diethanolamine salt is more than 104°C, it was considered polymorph B. There is no need of recrystallization. If it is less than 104°C, it is recrystallized in EtOH-EtOAc to increase the melting point.

Data on Treprostinil Diethanolamine Salt (1:1)

Batch No.	Wt. of Benzindene Triol (g)	Wt. of Treprostinil Diethanolamine Salt (1:1) (g)	Yield (%)	Melting point (°C)
1	1250	1640	88.00	104.3-106.3
2	1250	1528	82.00*	105.5-107.2
3	1250	1499	80.42**	104.7-106.6
4	1236	1572	85.34	105-108

**Note*: In this batch, approximately 1200 mL of ethyl acetate solution of treprostinil before carbon treatment was removed for R&D carbon treatment experiments.

***Note*: This batch was recrystallized, for this reason yield was lower.

Example 4. Heptane Slurry of Treprostinil Diethanolamine Salt (1:1)

Name	Batch No.	Amount	Ratio
Treprostinil Diethanolamine Salt	1	3168 g	1
Heptane	--	37.5 L	12

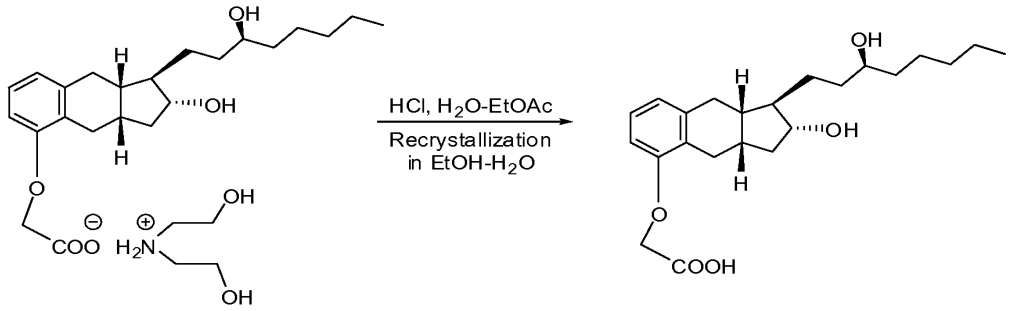
Name	Batch No.	Amount	Ratio
Treprostinil Diethanolamine Salt	2	3071 g	1
Heptane	--	36.0 L	12

[0044] A 50-L, cylindrical reactor equipped with a heating/cooling system, a mechanical stirrer, a condenser, and a thermocouple was charged with slurry of treprostinil diethanolamine salt in heptane (35-40 L). The suspension was heated to 70-80°C for 16-24 h. The suspension was cooled to 22±2°C over a period of 1-2 h. The salt was collected by filtration using Aurora filter. The cake was washed with heptane (15-30 L) and the material was dried in Aurora filter for 1 h. The salt was transferred to trays for air-drying overnight in hood until a constant weight of treprostinil diethanolamine salt was obtained. The material was dried in oven under high vacuum for 2-4 h at 50-55°C.

Analytical data on and Treprostinil Diethanolamine Salt (1:1)

Test	Batch 1	Batch 2
IR	Conforms	Conforms
Residue on Ignition (ROI)	<0.1% w/w	<0.1% w/w
Water content	0.1% w/w	0.0% w/w
Melting point	105.0-106.5°C	104.5-105.5°C
Specific rotation $[\alpha]^{25}_{589}$	+34.6°	+35°
Organic volatile impurities		
• Ethanol	• Not detected	• Not detected
• Ethyl acetate	• Not detected	• <0.05% w/w
• Heptane	• <0.05% w/w	• <0.05% w/w
HPLC (Assay)	100.4%	99.8%
Diethanolamine	Positive	Positive

Example 5. Conversion of Treprostinil Diethanolamine Salt (1:1) to Treprostinil



[0045] A 250-mL, round-bottom flask equipped with magnetic stirrer was charged with treprostinil diethanolamine salt (4 g) and water (40 mL). The mixture was stirred to obtain a clear solution. To the clear solution, ethyl acetate (100 mL) was added. While stirring, 3M HC1 (3.2 mL) was added slowly until pH ~1 was attained. The mixture was stirred for 10 minutes and organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers was washed with water (2 × 100 mL), brine (1 × 50 mL) and dried over anhydrous Na_2SO_4. The ethyl acetate solution of treprostinil was filtered and the filtrate was concentrated under vacuum at 50°C to give off-white solid. The crude treprostinil was recrystallized from 50% ethanol in water (70 mL). The pure treprostinil was collected in a Buchner funnel by filtration and cake was washed with cold 20% ethanolic solution in water. The cake of treprostinil was air-dried overnight and further dried in a vacuum oven at 50°C under high vacuum to afford 2.9 g of treprostinil (Yield 91.4%, purity (HPLC, AUC, 99.8%).

Analytical data on Treprostinil from Treprostinil Diethanolamine Salt (1:1) to Treprostinil

Batch No.	Yield	Purity (HPLC)
1	91.0%	99.8% (AUC)
2	92.0%	99.9% (AUC)
3	93.1%	99.7% (AUC)
4	93.3%	99.7% (AUC)
5	99.0 %	99.8% (AUC)
6	94.6%	99.8% (AUC)

Example 6. Comparison of the former process and a working example of the process according to the present invention

Step No.	Steps	Former Process (Batch size: 500g)	Working example of the Process according to the present invention (Batch size: 5 kg)
Nitrile			
1	Triol weight	500 g	5,000 g
2	Acetone	20 L (1:40 wt/wt)	75 L (1:15 wt/wt)
3	Potassium carbonate	1,300 g (6.4 eq)	5,200 g (2.5 eq)
4	Chloroacetonitrile	470 g (4.2 eq)	2,270 g (2 eq)
5	Tetrabutylammoniu m bromide	42 g (0.08 eq)	145 g (0.03 eq)
6	Reactor size	72-Liter	50- gallon
7	Reflux time	8 hours	No heating, Room temperature (r.t.) 45 h
8	Hexanes addition before filtration	Yes (10 L)	No
9	Filter	Celite	Celite
10	Washing	Ethyl acetate (10 L)	Acetone (50 L)
11	Evaporation	Yes	Yes
12	Purification	Silica gel column Dichloromethane:0.5 L Ethyl acetate: 45 L Hexane: 60 L	No column
13	Evaporation after column	Yes	No
14	Yield of nitrite	109-112 %	Not checked
Treprostinil (intermediate)			
15	Methanol	7.6 L (50-L reactor)	50 L (50-gal reactor)
16	Potassium hydroxide	650 g (8 eq)	3,375g (4 eq)
17	Water	2.2 L	17 L

18	% of KOH	30%	20%
19	Reflux time	3-3.5 h	4-5 h
20	Acid used	2.6 L (3 M)	12 L (3 M)
21	Removal of impurities	3 × 3 L Ethyl acetate	2 × 20 L Ethyl acetate
22	Acidification	0.7 L	6.5 L
23	Ethyl acetate extraction	5 × 17 L = 35 L	90+45+45 = 180 L
24	Water washing	2 × 8 L	3 × 40 L
25	Sodium bicarbonate washing	Not done	120 g in 30L water + 15 L brine
26	Brine washing	Not done	1 × 40 L
27	Sodium sulfate	1 kg	Not done
28	Sodium sulfate filtration	Before charcoal, 6 L ethyl acetate	N/A
29	Charcoal	170 g, reflux for 1.5 h, filter over Celite, 11 L ethyl acetate	Pass hot solution (75°C) through charcoal cartridge and clean filter, 70 L ethyl acetate
30	Evaporation	Yes, to get solid intermediate treprostinil	Yes, adjust to 150 L solution
Treprostinil Diethanolamine Salt			
31	Salt formation	Not done	1,744 g diethanolamine, 20 L ethanol at 60-75°C.
32	Cooling	N/A	To 20°C over weekend; add 40 L ethyl acetate; cooled to 10°C
33	Filtration	N/A	Wash with 70 L ethyl acetate
34	Drying	N/A	Air-dried to constant wt., 2 days
Treprostinil (from 1.5 kg Treprostinil diethanolamine salt)			
35	Hydrolysis	N/A	15 L water + 25 L ethyl acetate + HCl
36	Extraction	N/A	2 × 10 L ethyl acetate
37	Water wash	N/A	3 × 10 L

38	Brine wash	N/A	1 × 10 L
39	Sodium sulfate	N/A	1 kg, stir
40	Filter	N/A	Wash with 6 L ethyl acetate
41	Evaporation	N/A	To get solid, intermediate Treprostinil
42	Crude drying on tray	1 or 3 days	Same
43	Ethanol & water for cryst.	5.1 L + 5.1 L	10.2 L + 10.2 L (same %)
44	Crystallization in	20-L rotavap flask	50-L jacketed reactor
45	Temperature of crystallization	2 h r.t., fridge -0°C 24 h	50°C to 0°C ramp, 0°C overnight
46	Filtration	Buchner funnel	Aurora filter
47	Washing	20% (10 L) cooled ethanol-water	20% (20 L) cooled ethanol-water
48	Drying before oven	Buchner funnel (20 h) Tray (no)	Aurora filter (2.5 h) Tray (4 days)
49	Oven drying	15 hours, 55°C	6-15 hours, 55°C
50	Vacuum	<-0.095 mPA	< 5 Torr
51	UT-15 yield weight	~ 535 g	~ 1,100 g
52	% yield from triol)	~ 91%	~ 89%
53	Purity	~ 99.0%	99.9%

[0046] The quality of treprostinil produced according to this invention is excellent. The purification of benzindene nitrile by column chromatography is eliminated. The impurities carried over from intermediate steps (i.e. alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and the salt formation step. Additional advantages of this process are: (a) crude treprostinil salts can be stored as raw material at ambient temperature and can be converted to treprostinil by simple acidification with diluted hydrochloric acid, and (b) the treprostinil salts can be synthesized from the solution of treprostinil without isolation. This process provides better quality of final product as well as saves significant amount of solvents and manpower in purification of intermediates.

[0047] Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill

in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

[0048] All of the publications, patent applications and patents cited in this specification are incorporated herein by reference in their entirety.

WHAT IS CLAIMED IS:

1. A process for preparing a treprostinil salt, comprising:

combining treprostinil and a base in solution to form a base addition salt;

allowing crystallization of the base addition salt of treprostinil; and

collecting the base addition salt of treprostinil.

2. The process of claim 1, wherein the collected base addition salt of treprostinil is dried and stored.

3. The process of claim 1, wherein the base addition salt is selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.

4. The process of claim 1, further comprising heating the solution of treprostinil and base addition salt.

5. The process of claim 4, further comprising cooling the solution of treprostinil and base addition salt prior to collecting the base addition salt of treprostinil.

6. The process of claim 1, wherein the base comprises an alkali metal cation.

7. The process of claim 6, wherein the alkali metal cation is selected from the group consisting of sodium and potassium.

8. The process of claim 1, wherein the solution comprises a water-miscible organic solvent.

9. The process of claim 1, wherein a mole ratio of the base in solution to treprostinil is about 1.1:1.

ABSTRACT

This present invention relates to an improved process to prepare prostacyclin derivatives. One embodiment provides for an improved process to convert benzindene triol to treprostinil via salts of treprostinil and to purify treprostinil.

PTO/AIA/01 (modified)

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)	080618-1256

Title of Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

As the below named inventor, I hereby declare that:

This declaration is directed to:

☒ The attached application, or

☐ United States application or PCT international application number _____ filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than (5) years, or both.

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LEGAL NAME OF INVENTOR

Inventor: Hitesh BATRA Date (Optional): June 4 2013

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (modified)

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LEGAL NAME OF INVENTOR

Inventor: Sudersan M. TULADHAR Date (Optional): Jun 4, 2013

Signature: _____

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I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Raju PENMASTA Date (Optional): Jun 04 2013

Signature: Raju Penmasta

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (modified)

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)	080618-1256

Title of Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

As the below named inventor, I hereby declare that:

This declaration is directed to:

☒ The attached application, or

☐ United States application or PCT international application number _____ filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: David A. WALSH Date (Optional): June 4, 2013

Signature: David A. Walsh

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

4834-6734-6452.1

PTO/SB/08 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO				*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	Unassigned
				Filing Date	Herewith
Date Submitted: July 2, 2013				**First Named Inventor**	Hitesh BATRA
				Art Unit	Unassigned
(use as many sheets as necessary)				Examiner Name	Unassigned
Sheet	1	of	4	Attorney Docket Number	080618-1256

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	2002/0173672 A1	11/21/2002	Moriarty et al.	
	A2	2004/0176645 A1	09/09/2004	Moriarty et al.	
	A3	2005/0085540 A1	04/21/2005	Phares et al.	
	A4	2005/0101608 A1	05/12/2005	Santel, Donald J.	
	A5	2005/0165111 A1	07/28/2005	Wade et al.	
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	A8	2007/0078182 A1	04/05/2007	Phares et al.	
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FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant	T[6]

Examiner Signature		Date Considered	

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PTO/SB/08 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: July 2, 2013

(use as many sheets as necessary)

Sheet 2 of 4

Complete if Known	
Application Number	Unassigned
Filing Date	Herewith
First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	080618-1256

		Country Code[3]-Number[4]-Kind Code[5] (*if known*)				
	A35	CA 2 710 726 A1	01/22/2012	Alphora Research Inc., CA		
	A36	CN 101891596 A	11/24/2010	Shanghai Techwell Biopharmaceutical Co. Ltd.		A ✓
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	A50	WO 2012/009816 A1	01/26/2012	Alphora Research Inc.		

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
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	A55	BATRA et al., "Crystallization Process Development for a Stable Polymorph of Treprostinil Diethanolamine (UT-15C) by Seeding," Organic Process Research & Development, 2009, 13:242-249.	

Examiner Signature		Date Considered	

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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO				*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	Unassigned
				Filing Date	Herewith
Date Submitted: July 2, 2013				**First Named Inventor**	Hitesh BATRA
				Art Unit	Unassigned
(use as many sheets as necessary)				Examiner Name	Unassigned
Sheet	3	of	4	Attorney Docket Number	080618-1256

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
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Examiner Signature		Date Considered	

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PTO/SB/08 (09-06)
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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO				*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	Unassigned
				Filing Date	Herewith
Date Submitted: July 2, 2013				**First Named Inventor**	Hitesh BATRA
				Art Unit	Unassigned
(use as many sheets as necessary)				Examiner Name	Unassigned
Sheet	4	of	4	Attorney Docket Number	080618-1256

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
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Examiner Signature		Date Considered	

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Electronic Patent Application Fee Transmittal	
Application Number:	
Filing Date:	
Title of Invention:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Stephen Bradford Maebius/Karen Walker
Attorney Docket Number:	080618-1256
Filed as Large Entity	

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	280	280
Utility Search Fee	1111	1	600	600
Utility Examination Fee	1311	1	720	720
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1600**

Electronic Acknowledgement Receipt

EFS ID:	16218977
Application Number:	13933623
International Application Number:	
Confirmation Number:	6887
Title of Invention:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Stephen Bradford Maebius/Karen Walker
Filer Authorized By:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1256
Receipt Date:	02-JUL-2013
Filing Date:	
Time Stamp:	15:42:58
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1600
RAM confirmation Number	2532
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Transmittal of New Application	Transmittal.pdf	96446 a476316d7a590cfb13a156a6843c3edd08d96158	no	3
Warnings:					
Information:					
2		Specification.pdf	221062 bcd26dc1a626af99917c43301d3f945663954df7	yes	23
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Specification		1	21	
	Claims		22	22	
	Abstract		23	23	
Warnings:					
Information:					
3	Oath or Declaration filed	Declaration.pdf	256572 674b08c500ebf0a8829bea1e9875aab84ae857ac	no	4
Warnings:					
Information:					
4	Power of Attorney	POA.pdf	116513 77ebc675ac09a2143d9def4fd3e22d309202a0d0	no	1
Warnings:					
Information:					
5	Miscellaneous Incoming Letter	PrelRemarks.pdf	40225 6f315765b63e4d2c3528bd4f880489eee1cf9e40	no	1
Warnings:					
Information:					
6	Application Data Sheet	ADS.pdf	598265 a9dd26f59f026d8a26aafd0505eb8e988e9b7409	no	6
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Information:					
This is not an USPTO supplied ADS fillable form					
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	Multipart Description/PDF files in .zip description		
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	Transmittal Letter	1	2
	Information Disclosure Statement (IDS) Form (SB08)	3	6

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Information:					
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Warnings:					
Information:					
		Total Files Size (in bytes):	1901721		

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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/AIA/80 (07-12)
Approved for use through 11/30/2014. OMB 0651-0035
U.S. Patent and Trademark Office; U.S DEPARTMENT OF COMMERCE

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(c).

I hereby appoint:

☑ Practitioners associated with Customer Number: 22428

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 a ssigned only to the undersigned according to the USPTO assignment records or assignments docu ments attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

☑ The address associated with Customer Number: 22428

OR

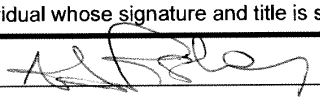
☐	Firm or Individual Name		
	Address		
	City		
	Country		
	Telephone		Email

Assignee Name and Address: United Therapeutics Corporation
1040 Spring Street
Silver Spring, Maryland 20910

A copy of this form, together with a statement under 37 CFR 3.73(c) (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(c) may be completed by one of The practitioners appointed in this form, 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	12/11/12
Name	Andrew J. Fisher	Telephone	202-742-1208
Title	Chief Strategic Officer & Deputy General Counsel		

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Hitesh BATRA et al.

Title: AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

Appl. No.: Unassigned (CON of 13/548,446)

Filing Date: July 2, 2013

Examiner: Unassigned

Art Unit: Unassigned

PRELIMINARY REMARKS

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

Commissioner:

Claims 1-9 are based upon Example 3 (salt formation) and paragraphs 46, 47 and 111.

NOTICE OF THIRD PARTY RELATED PATENT APPLICATION

The above claims are based upon the published claims of WO2012/088607 (which has a pending US national stage of Serial No. 13/520,872) and are presented in compliance with 35 U.S.C. 135 (within 1 year of the publication date of WO2012/088607).

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

By _____

Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

Date July 2, 2013
FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

PTO/AIA/14 (08-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	080618-1256
	Application Number	
Title of Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Hitesh		BATRA	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Herndon	State/Province	VA	Country of Residence	US

Mailing Address of Inventor:

Address 1	2461 Leyland Ridge Road		
Address 2			
City	Herndon	State/Province	VA
Postal Code	20171	Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Sudersan	M.	TULADHAR	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Silver Spring	State/Province	MD	Country of Residence	US

Mailing Address of Inventor:

Address 1	1501 Haddon Manor Court		
Address 2			
City	Silver Spring	State/Province	MD
Postal Code	20904	Country	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Raju		PENMASTA	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	080618-1256
	Application Number	
Title of Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®	

City	Herndon	State/Province	VA	Country of Residence	US

Mailing Address of Inventor:

Address 1	12953 Centre Park Circle #115
Address 2	

City	Herndon	State/Province	VA
Postal Code	20171	Country i	US

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	David	A.	WALSH	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Palmyra	State/Province	VA	Country of Residence	US

Mailing Address of Inventor:

Address 1	56 Wildwood Drive
Address 2	

City	Palmyra	State/Province	VA
Postal Code	22963	Country i	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	22428		
Email Address	IPDocketing@foley.com	Add Email	Remove Email

Application Information:

Title of the Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®		
Attorney Docket Number	080618-1256	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	080618-1256
	Application Number	
Title of Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®	

Publication Information:

☐	Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐	**Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	22428		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
This Application	Continuation of	13/548446	2012-07-13
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/548446	Continuation of	12/334731	2008-12-15
Prior Application Status			Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12/334731	An application claiming the benefit	61/014232	2007-12-17

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	080618-1256
	Application Number	
Title of Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®	

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date o f filing this Authorization.

PTO/AIA/14 (08-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	080618-1256
	Application Number	
Title of Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

(●) Assignee	( ) Legal Representative under 35 U.S.C. 117	( ) Joint Inventor
( ) Person to whom the inventor is obligated to assign.	( ) Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☒

Organization Name	United Therapeutics Corporation

Mailing Address Information For Applicant:

Address 1	1040 Spring Street		
Address 2			
City	Silver Spring	**State/Province**	MD
Country	US	Postal Code	20910
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Non-Applicant Assignee Information:

Providing assignment information in this section does not subsitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

PTO/AIA/14 (03-13)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	080618-1256
	Application Number	
Title of Invention	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®	

Assignee 1

Complete this section only if non-applicant assignee information is desired to be included on the patent application publication in accordance with 37 CFR 1.215(b). Do not include in this section an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest), as the patent application publication will include the name of the applicant(s).

If the Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country [i]		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Signature				Date (YYYY-MM-DD)	2013-07-02
First Name	Stephen B.	Last Name	Maebius	Registration Number	35264

Additional Signature may be generated within this form by selecting the Add button.

This collection of information is required by 37 CFR 1.76. 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 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet 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.**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Hitesh BATRA et al.

Title: AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

Appl. No.: Unassigned (CON of 13/548,446)

Filing Date: Herewith

Examiner: Unassigned

Art Unit: Unassigned

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

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

Commissioner:

Applicant submits herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicants respectfully request that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

Applicant requests that, in accordance with 37 CFR §1.98(d), the Examiner review all applications relied on for an earlier effective filing date under 35 U.S.C. 120, including application no. 12/334,731, filed 12/15/2008; application no. 13/548446, filed 7/13/2012, for copies of references of record therein that are not being provided here; although Applicant would be pleased to provide copies of any such documents at the Examiner's request.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive

any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(b), within three (3) months of the filing date of the application.

Although Applicant believes that no fee is required, the Commissioner is hereby authorized to charge any additional fees which may be due to Deposit Account No. 19-0741.

Respectfully submitted,

Date July 2, 2013

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

PTO/SB/06 (09-11)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/933,623	Filing Date 07/02/2013	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	**280**
☒ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	**600**
☒ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	**720**
TOTAL CLAIMS (37 CFR 1.16(i))	9 minus 20 =	* 0	x $80 =	**0**
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	* 0	x $420 =	**0**
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 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	**1600**

APPLICATION AS AMENDED – PART II

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

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

LDRC
/EVA GILLIS/

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/933,623

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	280
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	600
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	720
TOTAL CLAIMS (37 CFR 1.16(i))	9 minus 20 =	*			OR	x 80 =	0.00
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*				x 420 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 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).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1600

APPLICATION AS AMENDED - PART II

		(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($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	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	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)		RATE($)	ADDITIONAL FEE($)
AMENDMENT B	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 found in the appropriate box in column 1.

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
13/933,623	07/02/2013	Hitesh Batra	080618-1256

CONFIRMATION NO. 6887

POA ACCEPTANCE LETTER

22428
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

OC000000062775736

Date Mailed: 07/25/2013

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/02/2013.

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.

/ttu/

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	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/933,623	07/02/2013	1629	1600	080618-1256	9	1

CONFIRMATION NO. 6887

22428
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

FILING RECEIPT

OC000000062775449

Date Mailed: 07/25/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Hitesh Batra, Herndon, VA;
Sudersan M. Tuladhar, Silver Spring, MD;
Raju Penmasta, Herndon, VA;
David A. Walsh, Palmyra, VA;

Applicant(s)

United Therapeutics Corporation, Silver Spring, MD

Power of Attorney: The patent practitioners associated with Customer Number 22428

Domestic Priority data as claimed by applicant

This application is a CON of 13/548,446 07/13/2012 PAT 8497393
which is a CON of 12/334,731 12/15/2008 PAT 8242305
which claims benefit of 61/014,232 12/17/2007

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 07/23/2013
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/933,623**

Projected Publication Date: 10/31/2013

Non-Publication Request: No

Early Publication Request: No

Title

PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/933,623	07/02/2013	Hitesh Batra	080618-1256

CONFIRMATION NO. 6887

22428
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

PUBLICATION NOTICE

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Title:PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN?

Publication No.US-2013-0289304-A1
Publication Date:10/31/2013

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Date Submitted: NOV 08 2013

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	13/933,623
Filing Date	7/2/2013
First Named Inventor	Hitesh BATRA
Art Unit	1621
Examiner Name	Unassigned
Attorney Docket Number	080618-1256

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] *(if known)*	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	B1	JP 56-122328 A	09/25/1981	Sumitomo Chem. Co.		✓
	B2	JP 59-044340 A	03/12/1984	Sankyo Co. Ltd.		✓

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]

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Citation 3

PATENT ABSTRACTS OF JAPAN

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(43)Date of publication of application : 25 September 1981

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C07C 51/43
C07C 59/62
// A61K 31/557
C07C 177/00

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(22) Date of filing: 29 February 1980

(71)Applicant: SUMITOMO CHEM CO LTD
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KATSUBE SUMIMOTO

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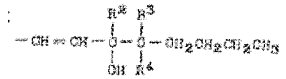
(54) CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN, ITS PREPARATION AND REFINING METHOD

1. TITLE: CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN, ITS PREPARATION AND REFINING METHOD

2. CLAIMS

1. A dicyclohexyl amine salt of a methanoprostacyclin derivative represented by a general formula:

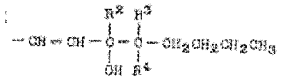
[wherein, R^1 is trithyloxymethyl group, 3-trithyloxy-trans-1-propenyl group and general formula:



(wherein, R^2, R^3, R^4 are each a hydrogen atom or a methyl group)].

2. A method for producing dicyclohexylamine salt of methanoprostacyclin derivative represented by a general formula:

[wherein, R^1 is trithyloxymethyl group, 3-trithyloxy-trans-1-propenyl group and general formula:



(wherein, R^2, R^3, R^4 are each a hydrogen atom or a methyl group)] comprising:
forming a crystalline salt of a mixture of methanoprostacyclin derivative represented by a general formula:

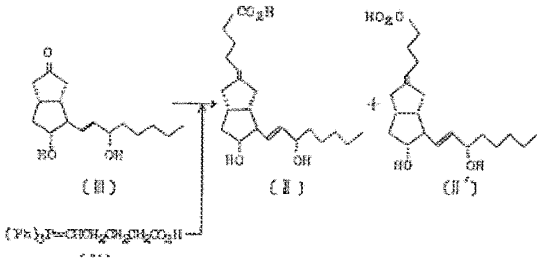
(wherein, R^1 is as described above) and a 7-Z isomer thereof using dicyclohexylamine; and further recrystallizing as necessary.

3. Detailed Description of the Invention

The present invention relates to a crystalline dicyclohexylamine salt of methanoprostacylcin derivative, its preparation and purifying method.

Methanoprostacylcin (II) was discovered as a stable derivative of prostacyclin (PGI_2), which is a natural bioactive substance having a strong thrombocyte aggregation suppression effect (Tetrahedron Letters 2607 (1979)), and it is much more chemically stable compared to prostacyclin, with the same level of strong thrombocyte aggregation suppression effect as PGI_2, and it is an extremely useful compound in the treatment of

arteriosclerosis, cardiac failure or thrombosis. Meanwhile, the total synthesis of methanoprostacylcin and a derivative thereof is reported by several groups aside from the present inventors, but all those methods use the Wittig reaction of ketone derivative (III) and ylide derivative (IV) as shown below.



The reaction has an excellent yield, but holds a severe fault of always generating an unnecessary side product, 7Z-isomer [II'] (the generation ratio is at [II]:[II']=7:2, Tetrahedron Letters 433 (1979)), and the physical property of the two forms are quite similar (the Rf value of 7E-isomer =0.14 and 7Z-isomer =0.17, Tetrahedron Letters 433 (1979)), so it is quite difficult to separate or refine the reaction product. Further, the melting point of the present compound is quite low (68-69°C Tetrahedron Letters 3743 (1978)), so crystallization can be largely inhibited by a minute amount of impurity that enters into the reaction product.

The physiological activity of 7Z isomer [II'] compared to methanoprostacyclin [II] is quite low. For example, a thrombocyte aggregation suppression effect of II' is about 1/100 that of II (Tetrahedron Letters 433 (1979)).

As such, it will be a definite requirement to establish an efficient and industrial separation method in the development of methanoprostacyclin derivative as a pharmacological product.

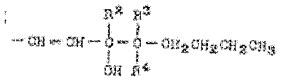
Hence, the present inventors have studied various separation and refining methods ever since their success in synthesizing methanoprostacyclin, and have now successfully developed an easy and industrial refining method. The present invention relates to the new refining method and a new dicyclohexylamine salt of methanoprostacyclin derivative [I] obtained by the method.

A methanoprostacyclin derivative represented by general formula [I], in which one of R^2, R^3, R^4 is a methyl group, has an excellent thrombocyte aggregation suppression effect similar to methanoprostacyclin (JP 54-119444 A), and a methanoprostacyclin derivative, in which R^1 is a trithyloxymethyl group or 3-trithyloxy-trans-1-propenyl group, is essential as an intermediate of a methanoprostacyclin synthesis.

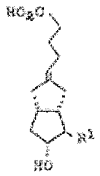
(JP 54-29233 A, JP 54-29236 A)

In the present invention, the dicyclohexylamine salt of methanoprostacyclin derivative represented by a general formula:

[wherein, R^1 is trithyloxymethyl group, 3-trithyloxy-trans-1-propenyl group and general formula:



(wherein, R^2, R^3, R^4 are each a hydrogen atom or a methyl group)] is obtained as described below. That is, the methanoprostacyclin derivative [I] or a methanoprostacyclin derivative [I] comprising a corresponding 7Z-isomer [I']:



(I')

(wherein, R^1 is as shown above)
is mixed with an appropriate amount of dicyclohexylamine (0.7 folds to 1.2 folds by mole) in an appropriate solvent, cooled as necessary, and the precipitated crystal is obtained by filtration.

The dicyclohexylamine salt of methanoprostacyclin derivative [I] obtained above generally has quite a high purity, and its purity can be increased by recrystallization using an appropriate solvent as necessary.

A suitable solvent to be used in the present invention includes alkanol (e.g. ethanol, n-propanol, 180-propanol) and alkanone (e.g. acetone, methylethyl ketone, diethyl ketone, methyl-180 buthyl ketone), and of these, acetone, methylethyl ketone and the like are particularly advantageous.

The dicyclohexylamine salt obtained in the present invention can be easily returned to a free methanoprostacyclin derivative [I] by a common method, and moreover, the obtained methanoprostacyclin derivative shows a good crystal quality compared to those that has not been subjected to refining by the present invention.

Dicyclohexylamine salt of the following exemplary compounds can be easily obtained by the present invention.

2-β-Trithyloxymethyl-3α-hydoxy-7E-(4'-carboxybutylidene)-bicyclo[3,3,0]octane

2-β-(3'-Trithyloxy-trans-1-propenyl)-3α-hydoxy-7E-(4'-carboxybutylidene)-bicyclo[3,3,0]octane

2-β-(3'α-Hydroxy-trans-1'-octenyl)-3α-hydoxy-7E-(4'-carboxybutylidene)-bicyclo[3,3,0]octane

2-β-(3'α-Hydroxy-4',4'-dimethyl-trans-1'-octenyl)-3α-hydoxy-7E-(4'-carboxybutylidene)-bicyclo[3,3,0]octane

2-β-(3'α-Hydroxy-3'β-methyl-trans-1'-octenyl)-3α-hydoxy-7E-(4'-carboxybutylidene)-bicyclo[3,3,0]octane

Next, Examples are given to explain the present invention in detail.

Example 1

The 7-E,Z mixture (0.8 g) of crude 2-β-trithyloxymethyl-3α-hydoxy-7-(4'-carboxybutylidene)-bicyclo[3,3,0]octane obtained by the Wittig reaction of 4-carboxybutylene triphenylphosphorane and 2-β-trithyloxymethyl-3α-hydoxy-bicyclo[3,3,0]octane-7-on was dissolved in acetone, and dicyclohexyl amine of an equivalent mole was introduced under agitation. The mixture was further agitated under room temperature, and the precipitated crystal was obtained by filtering and washed with little acetone to obtain a dicyclohexylamine salt of 2-β-trithyloxymethyl-3α-hydoxy-7E-(4'-carboxybutylidene)-bicyclo[3,3,0]octane.

Melting Point: 69-71°C

Example 2

A brown oil-like matter (0.39 g) of 2-β-(3'α-hydroxy-trans-1'-octenyl)-3α-hydoxy-7E-(4'-carboxybutylidene)-bicyclo[3,3,0]octane containing a 7-Z isomer was dissolved in acetone, and dicyclohexylamine of an equivalent mole was introduced under agitation. The mixture was agitated for 2 hours and left under room temperature, and the precipitated crystal was obtained by filtering to obtain a dicyclohexylamine salt of 2-β-(3'α-hydroxy-trans-1'-octenyl)-3α-hydoxy-7E-(4'-carboxybutylidene)-bicyclo[3,3,0]octane.

Melting Point: 105.5-106.5°C

The above dicyclohexylamine salt was neutralized by a $KHSO_4$ aqueous solution of 0.5 N, then extracted with ether, after which the ether layer was washed with water and dried, and the solvent was removed by distillation under reduced pressure to

obtain a crystal of 2-β-(3'α-hydroxy-trans-1'-octenyl)-3α-hydoxy-7E-(4'-carboxybutylidene)-bicyclo[3,3,0]octane.

Melting Point: 66.5-68°C

⑲ 日本国特許庁（JP）　　⑪ 特許出願公開

⑫ 公開特許公報（A）　　昭56—122328

⑤Int. Cl.³	識別記号	庁内整理番号
C 07 C 59/46		7188—4C
51/43		
59/62		7188—4C
// A 61 K 31/557	AEL	6617—4C
C 07 C 177/00		7430—4H

⑬公開　昭和56年(1981)9月25日

発明の数　2
審査請求　未請求

（全 4 頁）

⑭メタノプロスタサイクリン誘導体の結晶性アミン塩及びその製法及び精製法

⑳特　　願　昭55—25726
㉒出　　願　昭55(1980)2月29日
㉓発　明　者　川上肇
宝塚市売布2丁目14番7号
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㉓発　明　者　勝部純基
豊中市待兼山町10—20
㉑出　願　人　住友化学工業株式会社
大阪市東区北浜5丁目15番地
㉔代　理　人　弁理士　木村勝哉

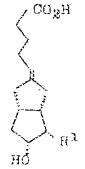
明　　細　　書

1．発明の名称

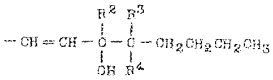
メタノプロスタサイクリン誘導体の結晶性アミン塩及びその製法及び精製法

2．特許請求の範囲

1）一般式



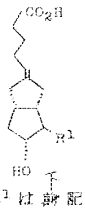
〔式中、R^1はトリチルオキシメチル基、3—トリチルオキシ—トランス—1—プロペニル基及び一般式



（式中、R^2、R^3、R^4は各々水素原子又はメチル基をあらわす。）をあらわす。〕

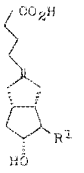
であらわされるメタノプロスタサイクリン誘導体のジシクロヘキシルアミン塩。

2）一般式

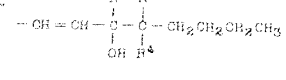


〔式中、R^1は前記のとおりである。〕

であらわされるメタノプロスタサイクリン誘導体及びその7—2異性体の混合物をジシクロヘキシルアミンにより結晶性塩とし、更に必要に応じて再結晶を行なうことを特徴とする一般式



〔R^1はトリチルオキシ基、3—トリチルオキシ—トランス—1—プロペニル基及び一般式



（式中、R^2、

（1）　　（2）

R^3、R^4は各々水素原子又はメチル基をあらわす。）をあらわす。〕

であらわされるメタノプロスタサイクリン誘導体のジシクロヘキシルアミン塩の製法。

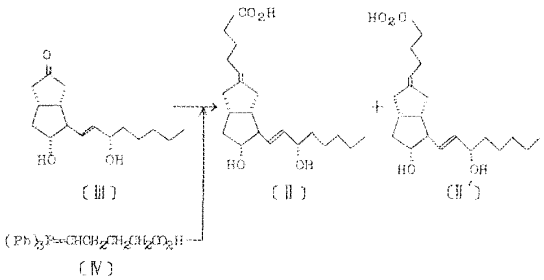
3．発明の詳細な説明

本発明はメタノプロスタサイクリン誘導体の結晶性ジシクロヘキシルアミン塩及びその製法及びその精製法に関するものである。

メタノプロスタサイクリン〔Ⅱ〕は強力な血小板凝集抑制作用を有する天然生理活性物質であるプロスタサイクリン（PGI_2）の安定誘導体として見出されたものであり（テトラヘドロン・レターズ 2607（1979））、プロスタサイクリンに比べてはるかに化学的に安定であり、しかもPGI_2と同等の強い血小板凝集抑制作用を有しており、動脈硬化、心不全又は血栓症等の治療に極めて有用な化合物である。一方、このメタノプロスタサイクリン及びその誘導体の全合成は本発明者等の他にもいくつかのグループにより報告がなされているが、それらの方法はいず

（3）

れも下記の如くケトン誘導体〔Ⅲ〕とイリド誘導体〔Ⅳ〕とのヴィッティッヒ反応を用いるものである。



〔Ⅲ〕　〔Ⅱ〕　〔Ⅱ′〕　〔Ⅳ〕

本反応は収率的には優れているが、常に不要の7Z体〔Ⅱ′〕が副生するという重大な欠点を有しており（生成比は〔Ⅱ〕：〔Ⅱ′〕＝7：2、テトラヘドロン・レターズ 433（1977））、しかも両者の物性が極めて類似しているため（Rf値 7Z体＝0.14、7Z体＝0.17、テトラヘドロン・レターズ 433（1979））分離、精製が極めて困難である。又、本化合物の融点はかなり低く（68～69℃ テトラヘドロン・レターズ 3743

（4）

（1978））、そのため微量の不純物の混入により著しく結晶化が妨げられる。

一方、この7Z異性体〔Ⅱ′〕はメタノプロスタサイクリン〔Ⅱ〕に比べてその薬理活性が極めて低く、たとえばⅡ′の血小板凝集抑制作用はⅡのおよそ1/100である（テトラヘドロン・レターズ 433（1979））。

これらのことから、メタノプロスタサイクリン誘導体を医薬品として開発する場合、この異性体の効率的かつ工業的な分離法の確立が絶対的な要件となる訳である。

そこで本発明者等はメタノプロスタサイクリンの合成に成功して以来種々の分離、精製法について検討を行ない、この度極めて簡便でかつ工業的な精製法を開発することに成功した。本発明はこの新規な精製法及びそれによって得られるメタノプロスタサイクリン誘導体〔Ⅰ〕の新規なジシクロヘキシルアミン塩に関するものである。

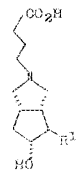
一般式〔Ⅰ〕に於てR^2、R^3、R^4のいずれかがメ

（5）

チル基であらわされるメタノプロスタサイクリン誘導体と同様に優れた血小板凝集抑制作用を有するものであり（特開昭54－119721号公報）、又R^1がトリチルオキシメチル基あるいは3－トリチルオキシ－トランス－1－プロペニル基であらわされるメタノプロスタサイクリン誘導体はメタノプロスタサイクリン合成の中間体として重要なものである。

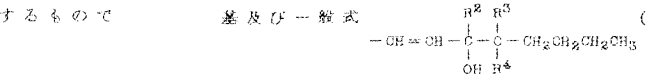
（特願昭54－29233、特願昭54－29236）

本発明によればメタノプロスタサイクリン誘導体〔Ⅰ〕



〔Ⅰ〕

〔式中、R^1はトリチルオキシメチル基、3－トリチルオキシ－トランス－1－プロペニル基及び一般式

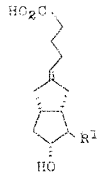


（式中R^2、R^3、R^4は各々水素原子又はメチル基をあ

（6）

らわす。）をあらわす。〕

であらわされるメタノプロスタサイクリン誘導体のジシクロヘキシルアミン塩は以下のようにして得られる。すなわち、メタノプロスタサイクリン誘導体〔Ⅰ〕あるいは対応するラセン異性体〔Ⅰ′〕



〔Ⅰ′〕

〔R^1は前記のとおりである。〕

を含有するメタノプロスタサイクリン誘導体〔Ⅰ〕を適当な溶媒中適当量（0.7倍～1.2倍モル）のジシクロヘキシルアミンと混合し、必要に応じて冷却し、析出した結晶を戸取することにより得られる。

このようにして得られたメタノプロスタサイクリン誘導体〔Ⅰ〕のジシクロヘキシルアミン塩は一般にかなり高純度であるが、必要に応じて

2-β-（3′-トリチルオキシ-トランス-1′-プロペニル）-3α-ヒドロキシ-7E-（ω′-カルボキシプチリデン）-ビシクロ〔3，3，0〕オクタン

2-β-（3′α-ヒドロキシ-トランス-1′-オクテニル）-3α-ヒドロキシ-7E-（ω′-カルボキシプチリデン）ビシクロ〔3，3，0〕オクタン

2-β-（3′α-ヒドロキシ-ω′，ω′-ジメチル-トランス-1′-オクテニル）-3α-ヒドロキシ-7E-（ω′-カルボキシプチリデン）ビシクロ〔3，3，0〕オクタン

2-β-（3′α-ヒドロキシ-3′β-メチル-トランス-1′-オクテニル）-3α-ヒドロキシ-7E-（ω′-カルボキシプチリデン）ビシクロ〔3，3，0〕オクタン

次に実施例をあげて本発明を詳細に説明する。

実施例1

ω-カルボキシプチレントリフェニルホスホラン及び2-β-トリチルオキシメチル-3α-ヒドロキシ-ビシクロ〔3，3，0〕オクタン-7-オンのヴィッティヒ反応によって得た粗2β-トリチルオキシメチル-3α-ヒドロキシ-7-（ω′-カルボキシプチ

リデン）-ビシクロ〔3，3，0〕オクタンの7-E，Z混合物0.8gをアセトン5mlに溶解し、撹拌下等モルのジシクロヘキシルアミンを加注し、更に室温にて撹拌して後、析出した結晶を戸取し、少量のアセトンにて洗浄し2β-トリチルオキシメチル-3α-ヒドロキシ-7E-（ω′-カルボキシプチリデン）-ビシクロ〔3，3，0〕オクタンのジシクロヘキシルアミン塩を得た。

融点　69～72℃

実施例2

7-Z異性体を含有する2β-（3′α-ヒドロキシ-トランス-1′-オクテニル）-3α-ヒドロキシ-7E-（ω′-カルボキシプチリデン）-ビシクロ〔3，3，0〕-オクタンのカッ色油状物0.3gをアセトン3mlに溶解し、撹拌下等モルのジシクロヘキシルアミンを加注し、2時間撹拌後室温にて放置し、析出結晶を戸取することにより2β-（3′α-ヒドロキシ-トランス-1′-オクテニル）-

3α－ヒドロキシ－7β－(4'－カルボキシブチリデン)ビシクロ〔3，3，0〕オクタンのジシクロヘキシルアミン塩を得た。

融点　105.5～106.5℃

上記ジシクロヘキシルアミン塩を0.5NのKHSO₄水溶液で中和し、エーテルにて抽出して後、エーテル層を水洗、乾燥し、減圧下溶媒を留去することにより2β－(3'α－ヒドロキシ－トランス－1'－オクテニル)－3α－ヒドロキシ－7β－(4'－カルボキシブチリデン)ビシクロ〔3，3，0〕オクタンの結晶を得た。

融点　66.5～68℃

（ノ）

Citation 2

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C07C 59/72
C07C 101/30
C07C 149/26
C07C 149/40
// C07C 91/18

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(21)Application number : 57-155205 (71)Applicant : SANKYO CO LTD
(22)Date of filing : 08 September 1982 (72)Inventor : AMAMIYA SHIGEO
KOJIMA KOICHI

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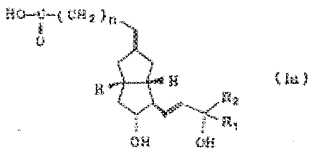
(54) OPTICAL ACTIVE CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN DERIVATIVE AND ITS PREPARATION

TITLE: OPTICAL ACTIVE CRYSTALLINE AMINE SALT OF METHANOPROSTACYCLIN DERIVATIVE AND ITS PREPARATION

CLAIMS

1. A salt of methanoprostacyclin derivative having a general formula:



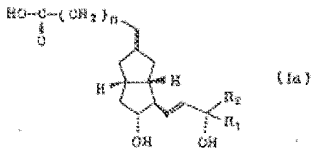
(Ia)

[wherein, R_1 is a hydrogen atom or a methyl group, R_2 is an alkyl group of 1 to 12 carbons, an alkenyl group of 2 to 12 carbons, a formula –A group (wherein, A is a cycloalkyl group of 3 to 8 carbons that can be substituted by a lower alkyl group), a

formula –X-A group (wherein, A is the same as shown above, and X is a methylene group, an ethylene group, a –NH- group, an oxygen atom or a sulfur atom) or a formula  group (wherein, X is the same as shown above, Y is a halogen atom or a trifluoromethyl group), and n is an integer of 1 to 5] and l-threo-2-amino-3-paranitrophenyl-1,3-propanediol (IIa).

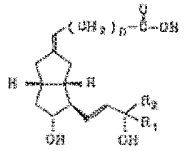
2. A method for preparing a salt of a compound (Ia) and a compound (IIa) comprising:

treating 4 types of mixtures, consisting of a mixture of methanoprostacyclin derivative having a general formula:



(Ia)

[wherein, R_1 is a hydrogen atom or a methyl group, R_2 is an alkyl group of 1 to 12 carbons, an alkenyl group of 2 to 12 carbons, a formula –A group (wherein, A is a cycloalkyl group of 3 to 8 carbons that can be substituted by a lower alkyl group), a formula –X-A group (wherein, A is the same as shown above, and X is a methylene group, an ethylene group, a –NH- group, an oxygen atom or a sulfur atom) or a formula  group (wherein, X is the same as shown above, Y is a halogen atom or a trifluoromethyl group), and n is an integer of 1 to 5] and an X-isotope of a compound (Ia) having a general formula:



(Ib)

(wherein, R_1, R_2 and n are the same as shown above),

a mixture of a compound (Ia) and an antipode compound (Ic) thereof, or

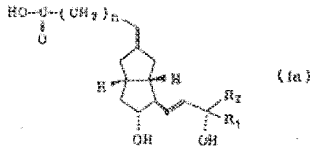
a mixture of a compound (Ia), a compound (Ib), a compound (Ic) and an antipode compound (Id) of compound (Ib),

with l-threo-2-amino-3-paranitrophenyl-1,3-propanediol (IIa) to produce a crystalline salt; then

recrystallizing as necessary.

3. Detailed Description of the Invention

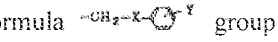
The present invention relates to a salt of a new methanoprostacyclin derivative having a general formula:



(Ia)

and

l-threo-2-amino-3-paranitrophenyl-1,3-propanediol (IIa), which is useful in the separation or refinement of an optical isomer and a stereoisomer, and a preparation method of the same.

In the above formula, R_1 is a hydrogen atom or a methyl group, R_2 is an alkyl group of 1 to 12 carbons, an alkenyl group of 2 to 12 carbons, a formula –A group (wherein, A is a cycloalkyl group of 3 to 8 carbons that can be substituted by a lower alkyl group), a formula –X-A group (wherein, A is the same as shown above, and X is a methylene group, an ethylene group, a –NH- group, an oxygen atom or a sulfur atom) or a formula  group (wherein, X is the same as shown above, Y is a halogen atom or a trifluoromethyl group), and n is an integer of 1 to 5.

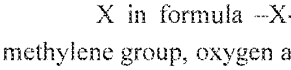
Examples of alkyl groups having 1 to 12 carbons of R_2 include methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, n-pentyl group, isopentyl group, 1-methylpentyl group, 2-methylpentyl group, n-hexyl group, n-heptyl group, 1,1-dimethylpentyl group, 2-ethylpentyl group, n-octyl group, 2-methyloctyl group, n-nonyl group 2-methylnonyl group, 2-ethyloctyl group, n-decyl group, 2-methyldecyl group or 2-ethyldecyl group; and preferably, alkyl groups having 4 to 10 carbons, such as, n-butyl group, isobutyl group, n-pentyl group, isopentyl group, 1-methylpentyl group, 2-methylpentyl group, n-hexyl group, n-heptyl group, 1,1-dimethylpentyl group, 2-ethylpentyl group, n-octyl group, 2-methyloctyl group, or 2-ethyloctyl group; and more preferably, n-pentyl group, 1-methylpentyl group, n-hexyl group or 2-methylhexyl group.

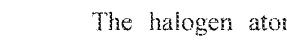
Examples of alkenyl groups having 2 to 12 carbons of R_2 include vinyl group, allyl group, 2-butenyl group, 2-pentenyl group, 3-pentenyl group, 2-methyl-3-pentenyl group, 4-methyl-3-pentenyl group, 1-methyl-4-pentenyl group, 4-hexenyl group, 5-hexenyl group, 1,4-dimethyl-3-pentenyl group, 5-heptenyl group, 6-methyl-5-heptenyl group, 2,6-dimethyl-5-heptenyl group, 1,1,6-trimethyl-5-heptenyl group, 6-methyl-5-octenyl group, 2,6-dimethyl-5-ocetenyl group, 6-ethyl-5-octenyl group, 2-methyl-6-ethyl-5-octenyl group or 2,6-diethyl-5-octenyl group; and preferably

alkenyl groups having 4 to 12 carbons, such as 2-butenyl group, 2-pentenyl group, 3-pentenyl group, 2-methyl-3-pentenyl group, 4-methyl-3-pentenyl group, 1-methyl-4-pentenyl group, 4-hexenyl group, 5-hexenyl group, 1,4-dimethyl-3-pentenyl group, 5-heptenyl group, 6-methyl-5-heptenyl group, 2,6-dimethyl-5-heptenyl group, 1,1,6-trimethyl-5-heptenyl group, 6-methyl-5-octenyl group, 2,6-dimethyl-5-octenyl group, 6-ethyl-5-octenyl group, 2-methyl-6-ethyl-5-octenyl group or 2,6-diethyl-5-octenyl group; and more preferably, 2-pentenyl group, 4-hexenyl group, 5-hexenyl group, 6-methyl-5-heptenyl group or 2,6-dimethyl-5-heptenyl group.

Examples of lower alkyls constituting substituents of formula –A group and formula –X-A group of R_2 include methyl group, ethyl group, n-propyl group, n-butyl group or isobutyl group, and preferably a methyl group or an ethyl group.

Examples of cycloalkyl groups having 3 to 8 carbons in formula –A group and formula –X-A group of R_2 include cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group or cyclooctyl group; and preferably, cyclopentyl group or cyclohexyl group.

X in formula –X-A group or formula  group of R_2 is preferably methylene group, oxygen atom or sulfur atom.

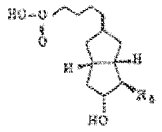
The halogen atom constituting Y in formula  group of R_2 is fluorine atom, chlorine atom, bromine atom, or iodine atom; and preferably, fluorine atom or chlorine atom. The letter n is preferably an integer of 3 to 5, and more preferably, the integer 3.

Or else, compound (Ia) can preferably be a compound constituted of R_1 being a hydrogen atom or a methyl group; R_2 being the above alkyl group having 4 to 10 carbons; the above alkenyl group having 4 to 12 carbons; a cyclopentyl group or cyclohexyl group that can be substituted with a methyl group or an ethyl group; a cyclopentyl methyl group, cyclohexyl methyl group, cyclopentyl amino group, cyclohexyl amino group, cyclopentyl oxy group, cyclohexyl oxy group, cyclopentyl thio group or cyclohexyl thio group that can be substituted with a methyl group or an ethyl group; a 2-phenylethyl group, anilinomethyl group, phenoxymethyl group or phenylthiomethyl group having a phenyl ring that can be substituted with a fluorine atom, chlorine atom or a trifluoromethyl group; and n being an integer of 3 to 5.

Compound (Ia) can more preferably be a compound constituted of R_1 being a hydrogen atom or a methyl group, R_2 being a n-pentyl group, 1-methylpentyl group, n-hexyl group, 2-methylhexyl group, 2-pentenyl group, 4-hexenyl group, 5-hexenyl group, 6-methyl-5-heptenyl group, 2,6-dimethyl-5-heptenyl group, cyclopentyl group, 3-ethylcyclopentyl group, cyclohexyl group, 3-methylcyclohexyl group,

cyclopentylmethyl group, 3-methylcyclopentylmethyl group, cyclohexylmethyl group, 3-ethylcyclohexylmethyl group, cyclopentyloxy group, 3-methylcyclopentyloxy group, cyclohexyloxy group, cyclopentyl thio group, cyclohexyl thio group, 3-methylcyclohexyl thio group, 2-phenylethyl group, 2-(m-fluorophenyl)ethyl group, 2-(p-fluorophenyl)ethyl group, 2-(o-chlorophenyl)ethyl group, 2-(p-chlorophenyl)ethyl group, 2-(m-trifluoromethylphenyl)ethyl group, 2-(p-trifluoromethylphenyl)ethyl, phenoxymethyl, m-fluorophenoxymethyl, p-chlorophenoxymethyl, p-trifluorophenoxymethyl, phenylthiomethyl, o-fluorophenylthiomethyl, m-chlorophenylthiomethyl or p-trifluoromethylphenylthio methyl group, and n being an integer 3.

Methanoprostacyclin derivative is a chemically stable prostacyclin derivative, and its development as an advantageous therapeutic agent of thrombosis, etc. is in progress. The compound includes many asymmetric carbons and double bonds, so it has various optical isomers and stereoisomers, and a target compound cannot be obtained by synthesis without the above isomer entering the product. For separation of isomers of methanoprostacyclin derivatives, the separation of compound (IIIa) using dicyclohexylamine from a mixture of a compound having a general formula:



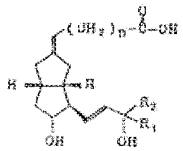
(IIIa)

(wherein, R_3 is trithyloxymethyl group, 3-trithyloxy-trans-1-propenyl group) and a 5Z-isomer (IIIb) of the same (JP 56-122328 A).

The present inventors conducted extensive studies for many years concerning the separation of isomers of the methanoprostacyclin derivatives, and found a new carbonic acid-amine salt that is useful for separating the E, Z-isomers based on double bonds more efficiently than known technology and also separate an optical isomer based on asymmetric carbon, and thus completed the invention.

The salt of a compound (Ia) and a compound (IIa) relating to the present invention is produced by the following method.

The salt can be obtained by treating 4 types of mixtures, consisting of a mixture of compound (Ia) and a Z-isotope of a compound (Ia) having a general formula:



(Ib)

(wherein, R_1, R_2 and n are the same as shown above),
a mixture of a compound (Ia) and an antipode compound (Ic) thereof, or
a mixture of a compound (Ia), a compound (Ib), a compound (Ic) and an antipode compound (Id) of compound (Ib), in an inert solvent to produce a crystalline salt, then recrystallizing as necessary.

Examples of the inert solvent to be used include water; aliphatic hydrocarbons, such as n-pentane, n-hexane, n-octane; and aromatic hydrocarbons, such as benzene, toluene, xylene; halogenated hydrocarbons, such as dichloromethane, chloroform, carbon tetrachloride; ethers, such as ether, tetrahydrofuran, dioxane; esters, such as methyl acetate, ethyl acetate; nitriles, such as acetonitrile, benzonitrile; ketones, such as acetone, methylethyl ketone; alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, sec-butanol, t-butanol, n-amyl alcohol, sec-amyl alcohol, t-amyl alcohol, isoamyl alcohol, sec-isoamino alcohol, active amyl alcohol, or mixtures of such solvents; and preferably, esters or mixtures of esters with the above various solvents; and more preferably, esters or mixtures of alcohols and esters.

The amount of compound (IIIa) to be used is an equivalent of 0.7 to 1.5 against carbonic acid, and preferably an equivalent of 0.9 to 1.1 against carbonic acid.

The temperature to produce a salt of compounds (Ia), (Ib), (Ic) and (Id) with compound (IIa) is normally around room temperature and the recrystallization of the above salt is performed by preferably heating to 50°C to 100°C to produce a supersaturated solution, then precipitating crystals at -10°C to 50°C.

Further, a salt of compound (Ic) and d-threo-2-amino-3-paranitrophenyl-1,3-propanediol (IIb) can be produced by a similar method as the one mentioned above.

The salt of compound (Ia) and compound (IIa) or the salt of compound (Ic) and compound (IIb), produced by the above method, can be formed into compound (Ia) or compound (Ic), which have excellent pharmacological effects. An exemplary method of obtaining such compound (Ia) or compound (Ic) is to dissolve an appropriate salt in a little water, add a dilute alkali solution to the water to induce precipitation of an amine compound (IIa) or (IIb), filter out the amine compound, add a dilute acid to acidify the solution, and then extract the above compound with a water-immiscible solvent, removing the solvent from the liquid extract by distillation.

Compounds (Ia), (Ib), (Ic) and (Id), which are used as the starting material of the present method, can be readily produced according to a known method (JP 54-95552 A, JP 54-130543 A or JP 55-28945 A).

Next, the invention is described in more detail by the Examples.

Example 1

L-threo-2-amino-3-paranitrophenyl-1,3-propanediol salt of (8S,9R,11R,12R,15S,17R)-6,9-methylene-11,15-dihydroxy-17-methyl-20-isopropylideneprost-5(E),13(E)-dienoic acid

A mixture of (8S,9R,11R,12R,15S,17R)-6,9-methylene-11,15-dihydroxy-17-methyl-20-isopropylideneprost-5(E),13(E)-dienoic acid and its 5(Z)-isomer (at about 6.5:3.5) in an amount of 0.38 g and an equivalent amount of l-threo-2-amino-3-paranitrophenyl-1,3-propanediol was thermally dissolved in ethyl acetate containing isopropanol at 10%, and recrystallized at room temperature to obtain the desired salt of 5(E)-isomer in an amount of 0.26 g.

Melting point: 68-70°C

IR spectrum (Nujol) cm^{-1}:

1350, 1375, 1460, 1520, 3350

NMR spectrum (CD_3OD) δ ppm:

5.50 (2H, m, )

7.93 (4H, q, )

Example 2

L-threo-amino-3-paranitrophenyl-1,3-propanediol salt of (8S,9R,11R,12R,15S)-6,9-methylene-11,15-dihydroxyprost-5(E),13(E)-dienoic acid

a) Method using an E,Z-mixture

A mixture of (8S,9R,11R,12R,15S)-6,9-methylene-11,15-dihydroxyprost-5(E),13(E)-dienoic acid and its 5(Z)-isomer (at about 6.5:3.5) in an amount of 0.10 g and an equivalent amount of l-threo-2-amino-3-paranitrophenyl-1,3-propanediol was thermally dissolved in ethyl acetate containing ethanol, and recrystallized at room temperature to obtain the desired salt of 5(E)-isomer in an amount of 0.07 g.

Melting point: 55-65°C

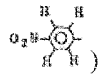
IR spectrum (liquid film) cm^{-1}:

1040, 1350, 1405, 1530, 3250

NMR spectrum (CD_3OD) δ ppm:

0.88 (3H, t, )

5.50 (2H, m, )

7.93 (4H, q, )

b) Method using an antipode mixture

A mixture of (8S,9R,11R,12R,15S)-6,9α-methylene-11α,15α-dihydroxyprost-5(E),13(E)-dienoic acid and its antipode (at 1:1) in an amount of 63 mg and 38 mg of l-threo-2-amino-3-paranitrophenyl-1,3-propanediol was processed as in a) to obtain the desired salt in an amount of 40 mg.

Example 3

L-threo-2-amino-3-paranitrophenyl-1,3-propanediol salt of (8R,9R,11R,12R,15S)-6,9-methylene-11,15-dihydroxy-15-cyclopentyl-16,17,18,19,20-pentanolprost-5(E),13(E)-dienoic acid

A mixture of (8S,9R,11R,12R,15S)-6,9-methylene-11,15-dihydroxy-15-cyclopentyl-16,17,18,19,20-pentanolprost-5(E),13(E)-dienoic acid and its 5(Z)-isomer (at about 8:2) in an amount of 63 mg and an equivalent amount of l-threo-2-amino-3-paranitrophenol-1,3-propanediol was thermally dissolved in ethyl acetate containing isopropanol at 10%, and recrystallized at room temperature to obtain the desired salt of 5(E)-isomer.

Melting point: 90-92°C

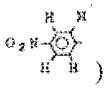
IR spectrum (Nujol) cm^{-1}:

1350, 1460, 1520, 2600, 2850, 3350

NMR spectrum (CD_3OD) δ ppm:

5.26 (1H, t, )

5.52 (2H, m, )

7.95 (4H, q, )

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発明の数　2
審査請求　未請求

（全 6 頁）

⑤④メタノプロスタサイクリン誘導体の光学活性結晶性アミン塩およびその製法

⑳特　　願　昭57—155205
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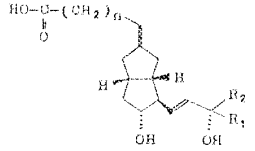
明　細　書

1. 発明の名称

メタノプロスタサイクリン誘導体の光学活性結晶性アミン塩およびその製法

2. 特許請求の範囲

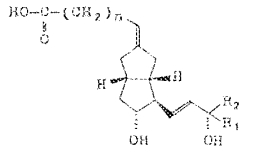
1) 一般式



(Ia)

〔式中、R_1は水素原子またはメチル基を示し、R_2は炭素数1乃至12個を有するアルキル基、炭素数2乃至12個を有するアルケニル基、式 -A 基（式中、Aは低級アルキル基によつて置換されてもよい炭素数3乃至8個のシクロアルキル基を示す。）、式 -X-A 基（式中、Aは前述したものと同意義を示し、Xはメチレン基、エチレン基、-NH- 基、酸素原子または硫黄原子を示す。）または式 $-CH_2-X-$  基（式中、Xは前述したものと同意義を示し、Yはハロゲン原子またはトリフルオロメチル基を示す。）を示し、nは1乃至5の整数を示す。〕を有するメタノプロスタサイクリン誘導体とL-スレオ-2-アミノ-3-パラニトロフエニル-1,3-プロパンジオール（Ba）との塩。

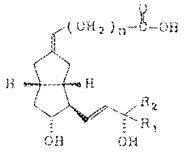
2) 一般式



(Ia)

〔式中、R_1は水素原子またはメチル基を示し、R_2は炭素数1乃至12個を有するアルキル基、炭素数2乃至12個を有するアルケニル基、式 -A 基（式中、Aは低級アルキル基によつて置換されてもよい炭素数3乃至8個のシクロアルキル基を示す。）、式 -X-A 基（式中、Aは前述したものと同意義を示し、Xはメチレン基、エチレン基、-NH- 基、酸素原子または硫黄原

子を示す。）または式 $-CH_2-X-$  基（式中、Xは前述したものと同意義を示し、Yはハロゲン原子またはトリフルオロメチル基を示す。）を示し、nは1乃至5の整数を示す。］を有するメタノプロスタサイクリン誘導体と一般式



(Ib)

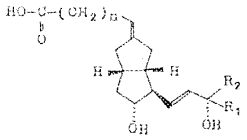
（式中、R_1、R_2およびnは前述したものと同意義を示す。）を有する化合物(Ia)のZ-異性体との混合物、

化合物(Ia)とその対掌体化合物(Ic)との混合物または

化合物(Ia)、化合物(Ib)、化合物(Ic)および化合物(Id)の対掌体化合物(Id)からなる4種類の混合物とL-スレオ-2-アミノ-3-パラニトロフェニル-1,3-プロパンジオール(IIa)を作用させて結晶性塩を製造し、次いで必要に応じて、再結晶をすることを特徴とする化合物(Ia)と化合物(IIa)との塩の製法。

3. 発明の詳細な説明

本発明は光学および立体異性体の分離、精製に有用でありかつ新規な一般式



(Ia)

を有するメタノプロスタサイクリン誘導体とL-スレオ-2-アミノ-3-パラニトロフェニル-1,3-プロパンジオール(IIa)との塩およびその製法に関する。

上記式中、R_1は水素原子またはメチル基を示し、R_2は炭素数1乃至12個を有するアルキル基、炭素数2乃至12個を有するアルケニル基、式$-A$ 基（式中、Aは低級アルキル基によつて置換されてもよい炭素数3乃至8個のシクロアルキル基を示す。）、式$-X-A$ 基（式中、Aは前述したものと同意義を示し、Xはメチレン基、エチレン基、$-SH-$ 基、酸素原子または硫黄原子を示す。）または式 $-CH_2-X-$  基（式中、Xは前述したものと同意義を示し、Yはハロゲン原子またはトリフルオロメチル基を示す。）を示し、nは1乃至5の整数を示す。

R_2の炭素数1乃至12個を有するアルキル基としては例えばメチル、エチル、n-プロピル、イソプロピル、n-ブチル、イソブチル、n-ペンチル、イソペンチル、1-メチルペンチル、2-メチルペンチル、n-ヘキシル、n-ヘプチル、1,1-ジメチルペンチル、2-エチルペンチル、n-オクチル、2-メチルオクチル、n-ノニル、2-メチルノニル、2-エチルオクチル、n-デシル、2-メチルデシルまたは2-エチルデシル基をあげることができ、好適には炭素数4乃至10個を有するアルキル基、例えばn-ブチル、イソブチル、n-ペンチル、イソペンチル、1-メチルペンチル、2-メチルペンチル、n-ヘキシル、n-ヘプチル、1-ジメチルペンチル、2-エチルペンチル、n-オクチル、2-メチルオクチルまたは2-エチルオクチル基をあげることができ、さらに好適にはn-ペンチル、1-メチルペンチル、n-ヘキシルまたは2-メチルヘキシル基をあげることができる。

R_2の炭素数2乃至12個を有するアルケニル基としては例えばビニル、アリル、2-ブテニル、2-ペンテニル、3-ペンテニル、2-メチル-3-ペンテニル、4-メチル-3-ペンテニル、1-メチル-4-ペンテニル、4-ヘキセニル、5-ヘキセニル、1,4-ジメチル-3-ペンテニル、5-ヘプテニル、6-メチル-5-ヘプテニル、2,6-ジメチル-5-ヘプテニル、1,1,6-トリメチル-5-ヘプテニル、6-メチル-5-オクテニル、2,6-ジメチル-5-オクテニル、6-エチル-5-オクテニル、2-メチル-6-エチル-5-オクテニルまたは2,6-ジエチル-5-オクテニル基をあげることができ、好適には炭素数4乃至12個

を有するアルケニル基、例えば2-ブテニル、2-ペンテニル、3-ペンテニル、2-メチル-3-ペンテニル、4-メチル-3-ペンテニル、1-メチル-4-ペンテニル、4-ヘキセニル、5-ヘキセニル、1,4-ジメチル-3-ペンテニル、5-ヘプテニル、6-メチル-5-ヘプテニル、2,6-ジメチル-5-ヘプテニル、1,1,6-トリメチル-5-ヘプテニル、6-メチル-5-オクテニル、2,6-ジメチル-5-オクテニル、8-エチル-5-オクテニル、2-メチル-6-エチル-5-オクテニルまたは2,6-ジエチル-5-オクテニル基をあげることができ、さらに好適には2-ペンテニル、4-ヘキセニル、5-ヘキセニル、6-メチル-5-ヘプテニルまたは2,6-ジメチル-5-ヘプテニル基をあげることができる。

R_2における式-A基および式-X-A基の置換分である低級アルキル基としては例えばメチル、エチル、n-プロピル、n-ブチルまたはイソブチル基をあげることができ、好適にはメチル

またはエチル基である。

R_2における式-A基および式-X-A基の炭素数3乃至8個を有するシクロアルキル基としては例えばシクロプロピル、シクロブチル、シクロペンチル、シクロヘキシル、シクロヘプチルまたはシクロオクチル基をあげることができ、好適にはシクロペンチルまたはシクロヘキシル基をあげることができる。

R_2における式-X-A基または式-CH_2-X-基のXは好適にはメチレン基、酸素原子または硫黄原子である。

R_2における式-CH_2-X-  基に含まれるYのハロゲン原子は弗素、塩素、臭素または沃素原子であり、好適には弗素または塩素原子である。nは好適には3乃至5の整数であり、さらに好適には3の整数である。

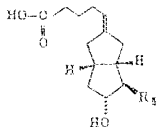
または化合物(Ia)において、好適にはR_1が水素原子またはメチル基であり、R_2が前記の炭素数4乃至10個を有するアルキル基；前記の炭素数4乃至12個を有するアルケニル基；

メチル若しくはエチル基で置換されてもよいシクロペンチル若しくはシクロヘキシル基；メチル若しくはエチル基で置換されてもよいシクロペンチルメチル、シクロヘキシルメチル、シクロペンチルアミノ、シクロヘキシルアミノ、シクロペンチルオキシ、シクロヘキシルオキシ、シクロペンチルチオ若しくはシクロヘキシルチオ基；フェニル環が弗素原子、塩素原子若しくはトリフルオロメチル基で置換されてもよい2-フェニルエチル、アニリノメチル、フェノキシメチル若しくはフェニルチオメチル基であり、nが3乃至5の整数である化合物をあげることができる。

化合物(Ia)において、さらに好適にはR_1が水素原子またはメチル基であり、R_2がn-ペンチル、1-メチルペンチル、n-ヘキシル、2-メチルヘキシル、2-ペンテニル、4-ヘキセニル、5-ヘキセニル、6-メチル-5-ヘプテニル、2,6-ジメチル-5-ヘプテニル、シクロペンチル、3-エチルシクロペンチル、シクロヘキシル、3-メチルシクロヘキシル、シクロペンチルメチル、3-メチルシクロペンチルメチル、シクロヘキシルメチル、3-エチルシクロヘキシルメチル、シクロペンチルオキシ、3-メチルシクロペンチルオキシ、シクロヘキシルオキシ、シクロペンチルチオ、シクロヘキシルチオ、3-メチルシクロヘキシルチオ、2-フェニルエチル、2-(m-フルオロフェニル)エチル、2-(p-フルオロフェニル)エチル、2-(o-クロロフェニル)エチル、2-(p-クロロフェニル)エチル、2-(m-トリフルオロメチルフェニル)エチル、2-(p-トリフルオロメチルフェニル)エチル、フェノキシメチル、m-フルオロフェノキシメチル、p-クロロフェノキシメチル、p-トリフルオロフェノキシメチル、フェニルチオメチル、o-フルオロフェニルチオメチル、m-クロロフェニルチオメチルまたはp-トリフルオロメチルフェニルチオメチル基であり、nが3の整数である化合物をあげることができ

る。

メタノプロスタサイクリン誘導体は化学的に安定なプロスタサイクリン誘導体で血栓症等の優れた治療剤として開発が進められている。この化合物は数多くの不斉炭素および二重結合を有しているため、種々の光学異性体および立体異性体が存在し、合成によって目的化合物を得るには上記異性体の混入は避けられない。メタノプロスタサイクリン誘導体の異性体の分離に関しては、一般式



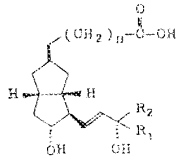
(IIa)

(式中、R_5はトリチルオキシメチル基、3-トリチルオキシ-トランス-1-プロペニル基等を示す。)を有する化合物とその5Z-異性体(IIb)との混合物からジシクロヘキシルアミンを用いて、化合物(IIa)を分離できることが知られている(特開昭56-122328号公報)。

本発明者らはメタノプロスタサイクリン誘導体の異性体の分離について、長年に亘り鋭意検討を行った結果、二重結合に基づくE,Z-異性体を公知技術よりも効率よく分離し、しかも不斉炭素に基づく光学異性体をも分離するために有用な新規カルボン酸-アミン塩を見出して本発明を完成した。

本発明に係る化合物(Ia)と化合物(Ba)との塩は以下の方法に従って製造される。

化合物(Ia)と一般式



(Ib)

(式中、R_1, R_2およびnは前述したものと同意義を示す。)を有する化合物(Ia)のZ-異性体との混合物、

化合物(Ia)とその対掌体化合物(Ic)との混合物または

化合物(Ia)、化合物(Ib)、化合物(Ic)および化合物(Id)の対掌体化合物(Id)からなる4種類の混合物に不活性溶剤中、化合物(Ba)を作用させ結晶性塩を製造し、次いで必要に応じて、再結晶することによって得ることができる。

使用される不活性溶剤としては、水、例えばn-ペンタン、n-ヘキサン、n-オクタンのような脂肪族炭化水素類、ベンゼン、トルエン、キシレンのような芳香族炭化水素類、ジクロロメタン、クロロホルム、四塩化炭素のようなハロゲン化炭化水素類、エーテル、テトラヒドロフラン、ジオキサンのようなエーテル類、酢酸メチル、酢酸エチルのようなエステル類、アセトニトリル、ベンゾニトリルのようなニトリル類、アセトン、メチルエチルケトンのようなケトン類、メタノール、エタノール、n-プロパノール、イソプロパノール、n-ブタノール、イソブタノール、sec-ブタノール、t-ブタノール、n-アミルアルコール、sec-アミルアルコール、t-アミルアルコール、イソアミルアルコール、sec-イソアミノアルコール、活性アミルアルコールのようなアルコール類またはこれら溶剤の混合物をあげることができるが、好適にはエステル類またはエステル類と上記以外の溶剤との混合物であり、特に好適にはエステル類またはアルコール類とエステル類の混合物である。

使用される化合物(Ba)の量はカルボン酸に対して0.7乃至1.5当量であり、好適には0.9乃至1.1当量である。

化合物(Ia)、(Ib)、(Ic)および(Id)と化合物(Ba)との塩を製造する温度は通常室温付近であり、上記塩の再結晶は好適には50℃乃至100℃に加熱して、過飽和溶液とし、次いで-10℃乃至50℃で結晶を析出させることによって行われる。

また、上述と同様な方法に従って、化合物(Ic)とd-スレオ-2-アミノ-3-パラニトロフェニル-1,3-プロパンジオール(Bb)との塩も製造することができる。

以上のように製造された化合物(Ia)と化合物(IIa)との塩または化合物(Ic)と化合物(IIb)との塩は常法に従つて、薬理作用のすぐれた化合物(Ia)または化合物(Ic)に導くことができる。例えば相当する塩を少量の水に溶解させ、希アルカリ水溶液を加え、析出したアミン化合物(IIa)または(IIb)を沪去した後、希酸を加えて溶液を酸性となし、水不混和性溶剤で抽出し、抽出液から溶剤を留去することによつて得ることができる。

本方法に原料として用いられる化合物(Ia)，(Ib)，(Ic)および(Id)は公知の方法に従つて容易に製造することができる(特開昭54-95552号，特開昭54-130543号または特開昭55-28945号公報)。

次に実施例をあげて、さらに発明を具体的に説明する。

実施例1

(8S，9R，11R，12R，15S，17R)-6,9-メチレン-11，15-ジヒドロキシ-17-メチル-20-イソプロピリデンプロスト-5(E)，13(E)-ジエン酸のL-スレオ-2-アミノ-3-パラニトロフエニル-1,3-プロパンジオール塩

(8S，9R，11R，12R，15S，17R)-6,9-メチレン-11，15-ジヒドロキシ-17-メチル-20-イソプロピリデンプロスト-5(E)，13(E)-ジエン酸とその5(Z)-異性体との混合物(約65対35) 0.36 gと当量のL-スレオ-2-アミノ-3-パラニトロフエニル-1,3-プロパンジオールを10 %のイソプロパノールを含む酢酸エチルに加熱溶解して室温にて再結晶することにより目的の5(E)-異性体の塩0.26 gを得た。

融点 68 - 70 ℃

IRスペクトル(Nujol) cm^{-1} :

1350，1375，1480，1520，3350

NMRスペクトル(CD_3OD) δ ppm :

5.50 (2H，m， )

7.93 (4H，q，)

実施例2

(8S，9R，11R，12R，15S)-6,9-メチレン-11，15-ジヒドロキシプロスト-5(E)，13(E)-ジエン酸のL-スレオ-アミノ-3-パラニトロフエニル-1,3-プロパンジオール塩

ⓐ E，Z-混合物を用いる方法

(8S，9R，11R，12R，15S)-6,9-メチレン-11，15-ジヒドロキシプロスト-5(E)，13(E)-ジエン酸とその5(Z)-異性体との混合物(約6.5対3.5) 0.10 gと当量のL-スレオ-2-アミノ-3-パラニトロフエニル-1,3-プロパンジオールをエタノールを含む酢酸エチルに加熱溶解して室温にて再結晶することにより目的の5(E)-異性体の塩を0.07 g得た。

融点 55 - 65 ℃

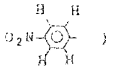
IRスペクトル(液状フイルム) cm^{-1} :

1040，1350，1405，1530，3250

NMRスペクトル(CD_3OD) δ ppm :

0.88 (3H，t， )

5.50 (2H，m，)

7.93 (4H，q， )

ⓑ 対掌体混合物を用いる方法

(8S，9R，11R，12R，15S)-6,9α-メチレン-11α，15α-ジヒドロキシプロスト-5(E)，13(E)-ジエン酸とその対掌体との混合物(1対1) 63 mgと38 mgのL-スレオ-2-アミノ-3-パラニトロフエニル-1,3-プロパンジオールをⓐと同様に処理して目的の塩48 mgを得た。

実施例3

(8R，9R，11R，12R，15S)-6,9-メチレン-11，15-ジヒドロキシ-15-シクロペンチル-16，17，18，19，20-ペンタノルプロスト-5(E)，13(E)-ジエン酸のL-スレオ-2-アミノ-3-パラニトロフエニル

－1,3－プロパンジオール塩

(8S,9R,11R,12R,15S)－6,9－メチレン－11,15－ジヒドロキシ－15－シクロペンチル－16,17,18,19,20－ペンタノルプロスト－5(E),13(E)－ジエン酸とその5(Z)－異性体との混合物(約8対2)63mgと当量のビース(2－アミノ－3－パラニトロフェノール)－1,3－プロパンジオールを10%イソプロパノールを含む酢酸エチルに加熱溶解して室温にて再結晶することにより目的とする5(E)－異性体の塩を得た。

融点 90 ～ 92℃

IRスペクトル(Nujol) cm^{-1} :

1350, 1460, 1520, 2500, 2850, 3330

NMRスペクトル(CD_3OD) δ ppm :

5.26 (1H, t, )

5.52 (2H, m, )

7.95 (4H, q, O_2N－ )

特許出願人　三共株式会社

代理人　弁理士 穐田正治

Electronic Acknowledgement Receipt	
EFS ID:	17350100
Application Number:	13933623
International Application Number:	
Confirmation Number:	6887
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Alexey V. Saprigin/Karen Walker
Filer Authorized By:	Alexey V. Saprigin
Attorney Docket Number:	080618-1256
Receipt Date:	08-NOV-2013
Filing Date:	02-JUL-2013
Time Stamp:	12:01:47
Application Type:	Utility under 35 USC 111(a)

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		IDS.pdf	3035020 e4e460e9f257d3c34bf0c35162bd934dc8ead353	yes	3

	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Transmittal Letter		1	2	
	Information Disclosure Statement (IDS) Form (SB08)		3	3	
Warnings:					
Information:					
2	Non Patent Literature	JPOA.pdf	142089 1dee47e022f23e2278906438e74fd0f45f6eba31	no	3
Warnings:					
Information:					
3	Foreign Reference	JP56122328.pdf	6584699 835582526c6ff06fbb9d1aef3919a0557edd4b92	no	10
Warnings:					
Information:					
4	Foreign Reference	JP59044340.pdf	11483009 0ceb2c76ce5863b398ee97a8b16382c7ef2a5375	no	14
Warnings:					
Information:					
		Total Files Size (in bytes):	21244817		

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

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/933,623
Filing Date:	7/2/2013
Examiner:	Unassigned
Art Unit:	1621
Confirmation Number:	6887

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

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

Commissioner:

Applicants submit herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicants respectfully request that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith.

CONCISE EXPLANATION OF RELEVANCE

An English translation is provided for foreign language Documents B1 and B2.

Foreign language Documents B1 and B2 were cited during the prosecution of the corresponding Japanese application in an Office Action dated August 13, 2013. An English translation of the Japanese Office Action is submitted herewith and sets forth the portion of the document considered relevant by the examiner.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(b), before the mailing date of the first Office Action on the merits.

Although Applicants believe that no fee is required, the Commissioner is hereby authorized to charge any additional fees which may be due to Deposit Account No. 19-0741.

Respectfully submitted,

Date NOV 08 2013

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (415) 984-9810
Facsimile: (415) 434-4507

Alexey V. Saprigin
Agent for Applicants
Registration No. 56,439

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/933623
Filing Date:	7/2/2013
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation Number:	6887

PRELIMINARY AMENDMENT UNDER 37 CFR § 1.115

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

Commissioner:

Prior to examination of the present Continuing Application, Applicants respectfully request that the application be amended as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this document. **Remarks** begin on page 4 of this document.

Amendments to the Claims:

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

Listing of Claims:

1. (Original) A process for preparing a treprostinil salt, comprising:

combining treprostinil and a base in solution to form a base addition salt;

allowing crystallization of the base addition salt of treprostinil; and

collecting the base addition salt of treprostinil.

2. (Original) The process of claim 1, wherein the collected base addition salt of treprostinil is dried and stored.

3. (Original) The process of claim 1, wherein the base addition salt is selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.

4. (Original) The process of claim 1, further comprising heating the solution of treprostinil and base addition salt.

5. (Original) The process of claim 4, further comprising cooling the solution of treprostinil and base addition salt prior to collecting the base addition salt of treprostinil.

6. (Original) The process of claim 1, wherein the base comprises an alkali metal cation.

7. (Original) The process of claim 6, wherein the alkali metal cation is selected from the group consisting of sodium and potassium.

8. (Original) The process of claim 1, wherein the solution comprises a water-miscible organic solvent.

9. (Original) The process of claim 1, wherein a mole ratio of the base in solution to treprostinil is about 1.1:1.

10. (New) A pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof, said composition prepared by a process comprising providing a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps, forming a salt of treprostinil by combining the starting batch and a base, isolating the treprostinil salt, and preparing a pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof from the isolated treprostinil salt, whereby a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition, and wherein said alkylation is alkylation of benzindene triol.

11. (New) The pharmaceutical composition of claim 10, wherein the salt is isolated in crystalline form.

12. (New) The pharmaceutical composition of claim 11, wherein the isolated salt is at least 99.8% pure.

13. (New) The pharmaceutical composition of claim 10, wherein the base is selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.

14. (New) The pharmaceutical composition of claim 13, wherein the base is diethanolamine.

15. (New) The pharmaceutical composition of claim 10, wherein the base is combined with treprostinil that has not been previously isolated.

16. (New) The pharmaceutical composition of claim 10, wherein the isolated salt is stored at ambient temperature.

17. (New) The pharmaceutical composition of claim 10, which is a pharmaceutical solution.

REMARKS

Applicants respectfully request that the foregoing amendments be made prior to examination of the present application.

CLAIMS STATUS

Applicants have added claims 10-17. Support for new claims may be found throughout the specification as filed and, in particular, on pages 11-20. No new matter has been added.

After the amendment, pending claims include original claims 1-9 and new claims 10-17.

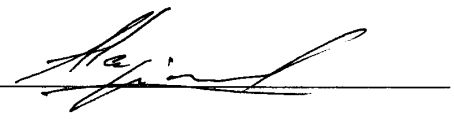
Applicant believes that the present application is in condition for allowance. Favorable consideration of the application is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

CONCLUSION

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date April 3, 2014

By 

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (415) 984-9810
Facsimile: (415) 434-4507

Alexey V. Saprigin
Agent for Applicants
Registration No. 56,439

Electronic Acknowledgement Receipt	
EFS ID:	18663584
Application Number:	13933623
International Application Number:	
Confirmation Number:	6887
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Alexey V. Saprigin/Karen Walker
Filer Authorized By:	Alexey V. Saprigin
Attorney Docket Number:	080618-1256
Receipt Date:	03-APR-2014
Filing Date:	02-JUL-2013
Time Stamp:	14:10:38
Application Type:	Utility under 35 USC 111(a)

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		PrelAmend.pdf	188041 4b9570e08ee4c4374a63eed8532cd89c62706eb3	yes	5

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Claims	2	3
	Applicant Arguments/Remarks Made in an Amendment	4	5
Warnings:			
Information:			
	Total Files Size (in bytes):	188041	

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 (09-11)
Approved for use through 1/31/2014. 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 13/933,623	Filing Date 07/02/2013	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	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 $310 ($155 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	

APPLICATION AS AMENDED – PART II

AMENDMENT	04/03/2014	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 17	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

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

LIE
/TONI HAKIM/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/933623
Filing Date:	7/2/2013
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation Number:	6887

PRELIMINARY AMENDMENT UNDER 37 CFR § 1.115

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

Commissioner:

Prior to examination of the present Continuing Application, Applicants respectfully request that the application be amended as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this document. **Remarks** begin on page 5 of this document.

Amendments to the Claims:

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

Listing of Claims:

1. (Original) A process for preparing a treprostinil salt, comprising:

combining treprostinil and a base in solution to form a base addition salt;

allowing crystallization of the base addition salt of treprostinil; and

collecting the base addition salt of treprostinil.

2. (Original) The process of claim 1, wherein the collected base addition salt of treprostinil is dried and stored.

3. (Original) The process of claim 1, wherein the base addition salt is selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.

4. (Original) The process of claim 1, further comprising heating the solution of treprostinil and base addition salt.

5. (Original) The process of claim 4, further comprising cooling the solution of treprostinil and base addition salt prior to collecting the base addition salt of treprostinil.

6. (Original) The process of claim 1, wherein the base comprises an alkali metal cation.

7. (Original) The process of claim 6, wherein the alkali metal cation is selected from the group consisting of sodium and potassium.

8. (Original) The process of claim 1, wherein the solution comprises a water-miscible organic solvent.

9. (Original) The process of claim 1, wherein a mole ratio of the base in solution to treprostinil is about 1.1:1.

10. (Previously Presented) A pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof, said composition prepared by a process comprising providing a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps, forming a salt of treprostinil by combining the starting batch and a base, isolating the treprostinil salt, and preparing a pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof from the isolated treprostinil salt, whereby a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition, and wherein said alkylation is alkylation of benzindene triol.

11. (Previously Presented) The pharmaceutical composition of claim 10, wherein the salt is isolated in crystalline form.

12. (Previously Presented) The pharmaceutical composition of claim 11, wherein the isolated salt is at least 99.8% pure.

13. (Previously Presented) The pharmaceutical composition of claim 10, wherein the base is selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.

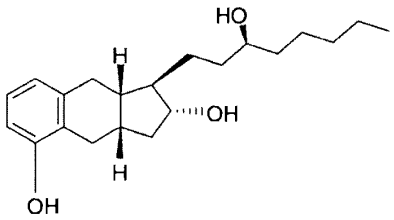
14. (Previously Presented) The pharmaceutical composition of claim 13, wherein the base is diethanolamine.

15. (Previously Presented) The pharmaceutical composition of claim 10, wherein the base is combined with treprostinil that has not been previously isolated.

16. (Previously Presented) The pharmaceutical composition of claim 10, wherein the isolated salt is stored at ambient temperature.

17. (Previously Presented) The pharmaceutical composition of claim 10, which is a pharmaceutical solution.

18. (New) A process of preparing a pharmaceutical product comprising treprostinil or a pharmaceutically acceptable salt thereof, comprising alkylating a triol intermediate of the formula:



hydrolyzing the resulting compound to form treprostinil, forming a salt of treprostinil stable at ambient temperature, storing the treprostinil salt at ambient temperature, and preparing a pharmaceutical product from the treprostinil salt after storage, wherein the pharmaceutical product comprises treprostinil or a pharmaceutically acceptable salt thereof.

19. (New) A pharmaceutical product prepared by the process of claim 18.

REMARKS

Applicants respectfully request that the foregoing amendments be made prior to examination of the present application.

CLAIMS STATUS

Applicants have added claims 18 and 19. Support for new claims may be found throughout the specification as filed and, in particular, on pages 11-20. No new matter has been added.

After the amendment, claims 1-19 are pending.

Applicants believe that the present application is in condition for allowance. Favorable consideration of the application is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

CONCLUSION

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date APR 25 2014

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (415) 984-9810
Facsimile: (415) 434-4507

Alexey V. Saprigin
Agent for Applicants
Registration No. 56,439

Electronic Acknowledgement Receipt	
EFS ID:	18858852
Application Number:	13933623
International Application Number:	
Confirmation Number:	6887
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Stephen Bradford Maebius/Karen Walker
Filer Authorized By:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1256
Receipt Date:	25-APR-2014
Filing Date:	02-JUL-2013
Time Stamp:	11:29:23
Application Type:	Utility under 35 USC 111(a)

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		PrelAmend.pdf	158940 48ee6a8704917022ea83deb75b0522403b6e8ae8	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Preliminary Amendment	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	6
Warnings:			
Information:			
	Total Files Size (in bytes):	158940	

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 (09-11)
Approved for use through 1/31/2014. 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 13/933,623	Filing Date 07/02/2013	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)		
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	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 $310 ($155 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	

APPLICATION AS AMENDED – PART II

AMENDMENT	04/25/2014	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 19	Minus	** 20	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

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

LIE
/KIMBERLY PANNELL/

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: AUG 26 2014

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	13/933,623
Filing Date	7/2/2013
First Named Inventor	Hitesh BATRA
Art Unit	1672
Examiner Name	Yevgeny Valenrod
Attorney Docket Number	080618-1256

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	C1	4,306,076	12/15/1981	Nelson	
	C2	4,668,814	05/26/1987	Aristoff	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	C3	Patterson et al., "Acute Hemodynamic Effects of the Prostacyclin Analog 15AU81 in Severe Congestive Heart Failure," Am. J. Cardio., 1995, 75:26A-33A.	
	C4	Whittle et al., "Antithrombotic Assessment and Clinical Potential of Prostacyclin Analogues," Progress in Medicinal Chemistry, Ellis et al. Eds., 1984, Chapter 6, Vol. 21, 238-279.	

Examiner Signature		Date Considered	

4852-8371-3565.1

Electronic Acknowledgement Receipt	
EFS ID:	19969185
Application Number:	13933623
International Application Number:	
Confirmation Number:	6887
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Alexey V. Saprigin/Karen Walker
Filer Authorized By:	Alexey V. Saprigin
Attorney Docket Number:	080618-1256
Receipt Date:	26-AUG-2014
Filing Date:	02-JUL-2013
Time Stamp:	15:30:37
Application Type:	Utility under 35 USC 111(a)

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		IDS.pdf	270724 b978b0a4ab36b69b0122849c05c828b6b5261137	yes	3

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	2
	Information Disclosure Statement (IDS) Form (SB08)	3	3

Warnings:					
Information:					
2	Non Patent Literature	Whittle.pdf	4935289 b9e5989007764f5ff6701a600028680cce419534	no	24
Warnings:					
Information:					
3	Non Patent Literature	Patterson.pdf	4073207 df0ebecea373810dffd0ef570193ee13218fcc20	no	10
Warnings:					
Information:					
		Total Files Size (in bytes):	9279220		

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.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/933,623
Filing Date:	7/2/2013
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation Number:	6887

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

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

Commissioner:

Applicants submit herewith documents for the Examiner's consideration in accordance with 37 CFR §§1.56, 1.97 and 1.98.

Applicants respectfully request that each listed document be considered by the Examiner and be made of record in the present application and that an initialed copy of Form PTO/SB/08 be returned in accordance with MPEP §609.

The submission of any document herewith is not an admission that such document constitutes prior art against the claims of the present application or that such document is considered material to patentability as defined in 37 CFR §1.56(b). Applicants do not waive any rights to take any action which would be appropriate to antedate or otherwise remove as a competent reference any document submitted herewith.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(b), before the mailing date of the first Office Action on the merits.

Although Applicants believe that no fee is required, the Commissioner is hereby authorized to charge any additional fees which may be due to Deposit Account No. 19-0741.

Respectfully submitted,

Date AUG 26 2014

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (415) 984-9810
Facsimile: (415) 434-4507

Alexey V. Saprigin
Agent for Applicants
Registration No. 56,439

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.
13/933,623	07/02/2013	Hitesh Batra	080618-1256	6887

22428 7590 12/10/2014

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

EXAMINER	
VALENROD, YEVGENY	

ART UNIT	PAPER NUMBER
1672	

NOTIFICATION DATE	DELIVERY MODE
12/10/2014	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):

ipdocketing@foley.com

Office Action Summary	Application No. 13/933,623	Applicant(s) BATRA ET AL.	
	Examiner YEVGENY VALENROD	Art Unit 1672	AIA (First Inventor to File) Status No

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS 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 7/2/13.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

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

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ 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*

5)☒ Claim(s) 1-19 is/are pending in the application.

5a) Of the above claim(s) 10-19 is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) 1-9 is/are rejected.

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

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

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

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

11)☐ 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).

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).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** 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) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 7/2/13; 11/8/13; 8/26/14.

3) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-9, drawn to a process for preparing a treprostinil salt, classified in 562/466.

II. Claims 10-17, drawn to a pharmaceutical composition, classified in 514/530.

III. Claims 18-19, drawn to a process for preparing a pharmaceutical composition and, classified in 514/530.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the pharmaceutical composition can be created a solution of treprostinil sodium as obtained by Phares et al. (US 2005/0085540) paragraph [0051].

Inventions I and III II and III are directed to related processes. The related inventions are distinct if: (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect;

(2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the inventions as claimed are directed to distinct processes and neither process requires the other for functionality. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and/or examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of an invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103 or pre-AIA 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Alexey V. Saprigin on 12/3/14 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-9. Affirmation of this election must be made by applicant in replying to this Office action.

Claims 10-19 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be corrected in compliance with 37 CFR 1.48(a) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. A request to correct inventorship under 37 CFR 1.48(a) must be accompanied by an application data sheet in accordance with 37 CFR 1.76 that identifies each inventor by his or her legal name and by the processing fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 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 and 8 are rejected under pre-AIA 35 U.S.C. 102b as being anticipated by Phares et al. (US 2005/0085540).

Phares discloses preparation of diethanolamine salt of treprostinil. To prepare said salt Phares discloses dissolving treprostinil acid in 1:1 molar ratio mixture of ethanol:water, adding diethanolamine and, heating the solution, adding antisolvent and subsequently cooling the solution (paragraph [0105]). This product is labeled crystalline

form A and is characterized (paragraph [0331]). Form A is described as a crystalline anhydrous material. While Phares et al fail to disclose the base to treprostinil ratio, since a 1:1 salt is formed, it is inherent that about 1.1:1 ratio is used.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 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.

Claims 6 and 7 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Phares et al. (US 2005/0085540) in view of Aristoff (US 4,486.598).

Phares discloses preparation of diethanolamine salt of treprostinil. To prepare said salt Phares discloses dissolving treprostinil acid in 1:1 molar ratio mixture of ethanol:water, adding diethanolamine and, heating the solution, adding antisolvent and subsequently cooling the solution (paragraph [0105]). Phares also discloses the sodium salt of treprostinil in paragraph [0051] but fails to teach a method of preparing such salt.

Secondary reference

Aristoff teaches that compounds of the same general formula as treprostinil can be made into solid salt forms by reacting with a stoichiometric amount of the base such

as sodium hydroxide in water and adding a water miscible solvent to produce a solid product (column 20, lines 24-34).

Obviousness

One skilled in the art would have found it obvious to prepare the sodium salt of treprostinil by addition of stoichiometric amount of sodium hydroxide to an aqueous solution of treprostinil acid and obtaining solid crystals of treprostinil sodium. Aristoff describes this procedure and Phares provides an example of this proceedure with diethanolamine as the base. One skilled in the art would therefore find both motivation, provided by Phares, and expectation of success provided by Phare and Aristoff.

Conclusion

Claims 1-19 are pending

Claims 1-9 are rejected

Claims 10-19 are withdrawn

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yevgeny Valenrod whose telephone number is 571-272-9049. The examiner can normally be reached on 8:30am-5:00pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. 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.

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1672

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	13/933,623	BATRA ET AL.	
	Examiner	Art Unit	
	YEVGENY VALENROD	1672	

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

(1) *YEVGENY VALENROD*. (3)_____.

(2) *Alexey V. Saprigin*. (4)_____.

Date of Interview: *04 December 2014*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1-19*.

Identification of prior art discussed: *none*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

A restriction requirement for claims 1-9 was discussed. A provisional election of Group I, claims 1-9 was made telephonically. .

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/YEVGENY VALENROD/ Primary Examiner, Art Unit 1672	

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13933623	BATRA ET AL.
	Examiner	Art Unit
	YEVEGENY VALENROD	1672

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST	12/5/2014	YV
STN	12/5/2014	YV
Inventor	12/5/2014	YV

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

	/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13933623	BATRA ET AL.
	Examiner	Art Unit
	YEVEGENY VALENROD	1672

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	12/05/2014								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	✓								
	6	✓								
	7	✓								
	8	✓								
	9	✓								
	10	N								
	11	N								
	12	N								
	13	N								
	14	N								
	15	N								
	16	N								
	17	N								
	18	N								
	19	N								

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BIB DATA SHEET

CONFIRMATION NO. 6887

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/933,623	07/02/2013	~~562~~ 562/466	1672	080618-1256

APPLICANTS

United Therapeutics Corporation, Silver Spring, MD, Assignee (with 37 CFR 1.172 Interest);

INVENTORS

Hitesh Batra, Herndon, VA;
Sudersan M. Tuladhar, Silver Spring, MD;
Raju Penmasta, Herndon, VA;
David A. Walsh, Palmyra, VA;

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

This application is a CON of 13/548,446 07/13/2012 PAT 8497393
which is a CON of 12/334,731 12/15/2008 PAT 8242305
which claims benefit of 61/014,232 12/17/2007

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

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

07/23/2013

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☑ Yes ☐ No Verified and Acknowledged /YEVEGENY VALENROD/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		VA	0	9	1

ADDRESS

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109
UNITED STATES

TITLE

PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®

FILING FEE RECEIVED		
1600	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).

PTO/SB/08 (modified)

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: AUG 26 2014

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	13/933,623
Filing Date	7/2/2013
First Named Inventor	Hitesh BATRA
Art Unit	1672
Examiner Name	Yevgeny Valenrod
Attorney Docket Number	080618-1256

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	C1	4,306,076	12/15/1981	Nelson	
	C2	4,668,814	05/26/1987	Aristoff	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	C3	Patterson et al., "Acute Hemodynamic Effects of the Prostacyclin Analog 15AU81 in Severe Congestive Heart Failure," Am. J. Cardio., 1995, 75:26A-33A.	
	C4	Whittle et al., "Antithrombotic Assessment and Clinical Potential of Prostacyclin Analogues," Progress in Medicinal Chemistry, Ellis et al. Eds., 1984, Chapter 6, Vol. 21, 238-279.	

Examiner Signature	/Yevgeny Valenrod/	Date Considered	12/05/2014

4852-8371-3565.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /YV/

PTO/SB/08 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: NOV 08 2013

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	13/933,623
Filing Date	7/2/2013
First Named Inventor	Hitesh BATRA
Art Unit	1621
Examiner Name	Unassigned
Attorney Docket Number	080618-1256

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	B1	JP 56-122328 A	09/25/1981	Sumitomo Chem. Co.		✓
	B2	JP 59-044340 A	03/12/1984	Sankyo Co. Ltd.		✓

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]

Examiner Signature	/Yevgeny Valenrod/	Date Considered	12/05/2014

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP . if possible. and . 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 . This collection is estimated to take 2 hours 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, 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.**

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4816-8827-3174.1

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* * * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 16:30:14 ON 04 DEC 2014

=> file reg
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                             ENTRY    SESSION
FULL ESTIMATED COST                                           0.24       0.24

FILE 'REGISTRY' ENTERED AT 16:30:25 ON 04 DEC 2014
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=>
Uploading C:\Users\yvalenrod\Documents\STN Express 8.4\Queries\13933623.str

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L1 HAS NO ANSWERS
L1              STR
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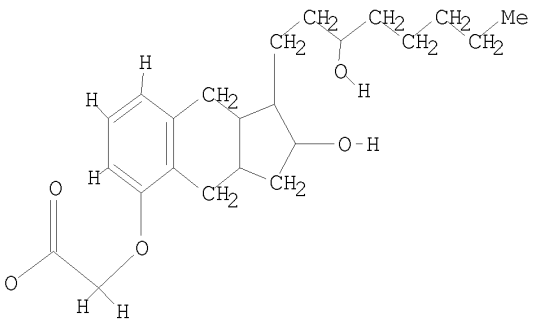


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Structure attributes must be viewed using the Structure Drawing program.
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SAMPLE SCREEN SEARCH COMPLETED -      351 TO ITERATE

100.0% PROCESSED      351 ITERATIONS                              2 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:         5896 TO     8144
PROJECTED ANSWERS:               2 TO      124

L2            2 SEA SSS SAM L1

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100.0% PROCESSED     6824 ITERATIONS                             48 ANSWERS
SEARCH TIME: 00.00.01

L3           48 SEA SSS FUL L1

=> file caplus
COST IN U.S. DOLLARS                              SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   218.84     219.08

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FILE COVERS 1907 - 4 Dec 2014 VOL 161 ISS 24
FILE LAST UPDATED: 3 Dec 2014 (20141203/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Nov 2014
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Sep 2014

CAplus includes complete International Patent Classification (IPC)
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CAplus now includes the comprehensive Cooperative Patent Classification
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```

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This file contains CAS Registry Numbers for easy and accurate
substance identification.

=> s l3
L4          342 L3

=> s l4 and sodium
        1887634 SODIUM
L5           82 L4 AND SODIUM

=> file reg
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                     ENTRY    SESSION
FULL ESTIMATED COST                                   3.26     222.34

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DICTIONARY FILE UPDATES:   3 DEC 2014  HIGHEST RN 1637711-86-4

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=>
Uploading C:\Users\yvalenrod\Documents\STN Express 8.4\Queries\13933623-2.str

L6      STRUCTURE UPLOADED

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L6 HAS NO ANSWERS
L6              STR
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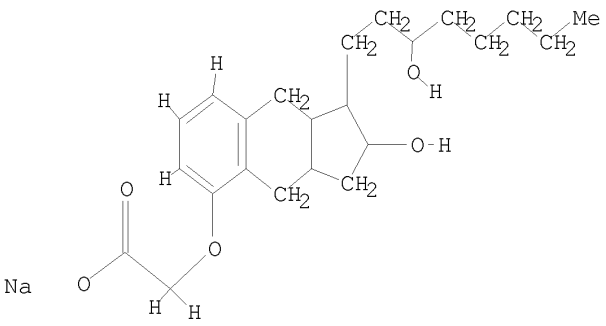

Structure attributes must be viewed using the Structure Drawing program.

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SAMPLE SCREEN SEARCH COMPLETED -       11 TO ITERATE

100.0% PROCESSED       11 ITERATIONS                              0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
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PROJECTED ANSWERS:               0 TO        0

L7            0 SEA SSS SAM L6

=> s l6 full
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SEARCH TIME: 00.00.01

L8            0 SEA SSS FUL L6

=> file caplus
COST IN U.S. DOLLARS                              SINCE FILE      TOTAL
                                                     ENTRY    SESSION
FULL ESTIMATED COST                                 218.84     441.18

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FILE COVERS 1907 - 4 Dec 2014 VOL 161 ISS 24
FILE LAST UPDATED: 3 Dec 2014 (20141203/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Nov 2014
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Sep 2014

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This file contains CAS Registry Numbers for easy and accurate
substance identification.

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=> s l5 and sodium hydroxide
       1887634 SODIUM
        552796 HYDROXIDE
        217847 SODIUM HYDROXIDE
                  (SODIUM(W)HYDROXIDE)
L9            9 L5 AND SODIUM HYDROXIDE

=> d l9 ibib abs hitstr 1-
YOU HAVE REQUESTED DATA FROM 9 ANSWERS - CONTINUE? Y/(N):y

L9   ANSWER 1 OF 9  CAPLUS  COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER:         2013:1118676  CAPLUS
DOCUMENT NUMBER:          159:236398
TITLE:                    Crystal form of prostaglandin analogue, and
                          preparation method and use thereof
INVENTOR(S):              Tang, Zhijun; Liu, Yubin; He, Bingming; Yang, Jun; Ji,
                          Xiaoming
PATENT ASSIGNEE(S):       Shanghai Techwell Biopharmaceutical Co., Ltd., Peop.
                          Rep. China
SOURCE:                   PCT Int. Appl., 28pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 Chinese
FAMILY ACC. NUM. COUNT:   2
PATENT INFORMATION:

     PATENT NO.           KIND  DATE        APPLICATION NO.          DATE
     ---------------      ----  --------    ---------------------    --------
     WO 2013104317         A1   20130718    WO 2013-CN70295          20130110
         W:  AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
             BZ, CA, CH, CL, 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,
             PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK,
             SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
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         RW: AL, 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, RS,
             SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
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MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM

CN 103193626 A 20130710 CN 2012-10005635 20120110

EP 2808318 A1 20141203 EP 2013-736455 20130110

R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR

PRIORITY APPLN. INFO.: CN 2012-10005635 A 20120110

WO 2013-CN70295 W 20130110

AB Provided are a crystal form B of a compound, and preparation method and use thereof. The X-ray powder diffraction (XRPD) chart of the crystal form B has characteristic peaks at the following diffraction angles: 2.9±0.2°, 6.5±0.2°, 12.6±0.2°, 13.1±0.2° and 20.6±0.2°.

IT 81846-19-7, Treprostinil

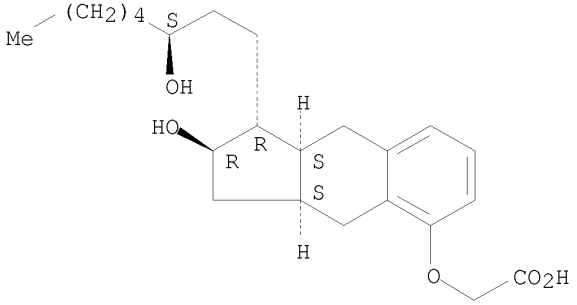
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(crystal form of prostaglandin analog, and preparation method and use thereof)

RN 81846-19-7 CAPLUS

CN Acetic acid, 2-[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2013:1115692 CAPLUS

DOCUMENT NUMBER: 159:236391

TITLE: Crystal form of prostaglandin analogue, and preparation method and use thereof

INVENTOR(S): Tang, Zhijun; Liu, Yubin; He, Bingming; Yang, Jun; Ji, Xiaoming

PATENT ASSIGNEE(S): Shanghai Techwell Biopharmaceutical Co., Ltd., Peop. Rep. China

SOURCE: PCT Int. Appl., 32pp.; Chemical Indexing Equivalent to 159:250026 (CN)

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Chinese

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2013104318 A1 20130718 WO 2013-CN70296 20130110
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, 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, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AL, 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, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM
CN 103193627 A 20130710 CN 2012-10006216 20120110
EP 2803657 A1 20141119 EP 2013-736169 20130110
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR
PRIORITY APPLN. INFO.: CN 2012-10006216 A 20120110
WO 2013-CN70296 W 20130110

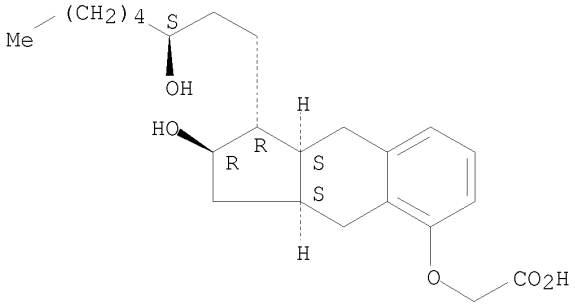
AB Disclosed are a crystal form A of a compound and preparation method and use thereof. The X-ray powder diffraction (XRPD) chart of the crystal form A has characteristic peaks at the following 2θ angles: 2.9±0.2°, 13.6±0.2°, 17.3±0.2° and 18.6±0.2°.

IT 81846-19-7, Treprostinil
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(crystal form of prostaglandin analog, and preparation method and use thereof)

RN 81846-19-7 CAPLUS

CN Acetic acid, 2-[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2013:1083374 CAPLUS
DOCUMENT NUMBER: 159:250026
TITLE: Preparation and application of crystal form of prostaglandin analog
INVENTOR(S): Tang, Zhijun; Liu, Yubin; He, Bingming; Yang, Jun; Ji, Xiaoming

PATENT ASSIGNEE(S): Shanghai Techwell Biopharmaceutical Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing, 16pp.; Chemical Indexing Equivalent to 159:236391 (WO)
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 103193627	A	20130710	CN 2012-10006216	20120110
WO 2013104318	A1	20130718	WO 2013-CN70296	20130110
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RW: AL, 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, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, RU, TJ, TM				
EP 2803657	A1	20141119	EP 2013-736169	20130110
R: AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR				

PRIORITY APPLN. INFO.:		
CN 2012-10006216	A	20120110
WO 2013-CN70296	W	20130110

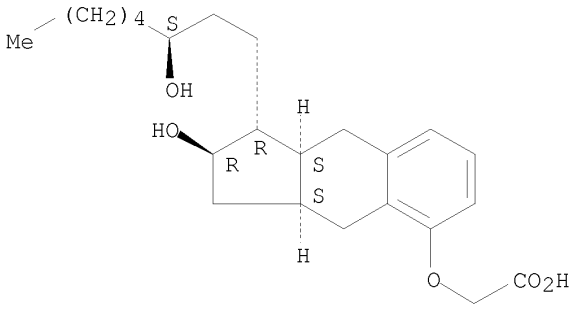
AB The invention relates to crystal form A of a compound The X-ray powder diffraction pattern of crystal form A has characteristics at the following 2θ angles: 2.9±>0.2°, 13.6±>0.2°, 17.3±>0.2°, and 18.6±>0.2°.

IT 81846-19-7, Treprostinil
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(crystal form of prostaglandin analog, and preparation method and use thereof)

RN 81846-19-7 CAPLUS

CN Acetic acid, 2-[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]- (CA INDEX NAME)

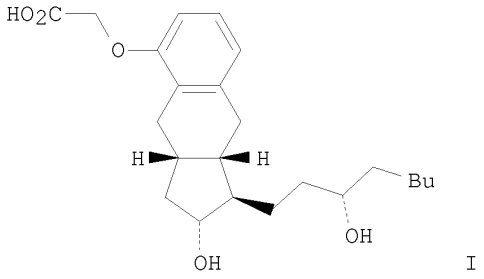
Absolute stereochemistry. Rotation (-).



L9 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:960685 CAPLUS
DOCUMENT NUMBER: 157:165338
TITLE: Process for preparation of salts of treprostinil
INVENTOR(S): Giust, Walter; Souza, Fabio; Oudenes, Jan; Gorin, Boris; Bejan, Elena
PATENT ASSIGNEE(S): Alphora Research Inc., Can.
SOURCE: PCT Int. Appl., 19pp.; Chemical Indexing Equivalent to 157:165337 (CA)
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2012088607	A1	20120705	WO 2011-CA50804	20111222
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, 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, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, 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, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2726599	A1	20120630	CA 2010-2726599	20101230
US 20140024856	A1	20140123	US 2013-13520872	20131008

PRIORITY APPLN. INFO.: CA 2010-2726599 A 20101230
WO 2011-CA50804 W 20111222
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 157:165338
GI



I

AB This invention provides a process for the preparation of salts of treprostinil (I). For example, 5 M sodium hydroxide (0.61 mL, 3.05 mmol) was added dropwise to a solution of treprostinil (1.021 g, 2.61 mmol) in acetone (25 mL) while maintaining an internal temperature below 30 °C and pH at 8-9.

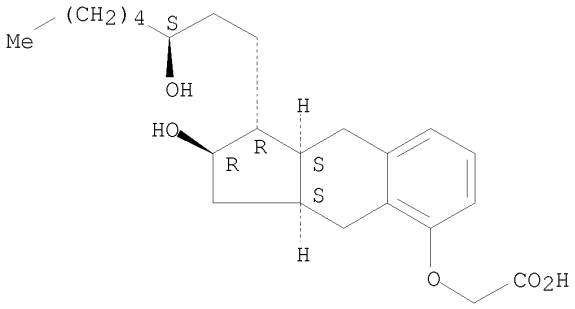
After 15 min under agitation, a fiber like solid began to crystallize from the reaction mixture The mixture was stirred 1 h at room temperature then cooled to
0-5 °C and stirred at this temperature for another hour. The solid was filtered, rinsed with acetone, and dried under vacuum to yield 0.95 g (99.67% purity, 88% yield) of a white solid.

IT 81846-19-7P
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of salts of treprostinil)

RN 81846-19-7 CAPLUS

CN Acetic acid, 2-[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

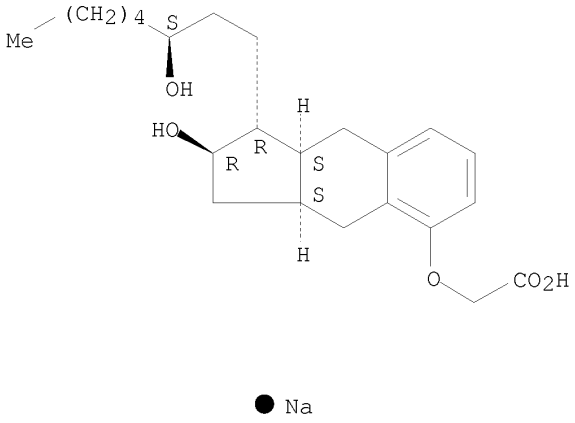


IT 289480-64-4P 1384244-82-9P 1384244-83-0P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of salts of treprostinil)

RN 289480-64-4 CAPLUS

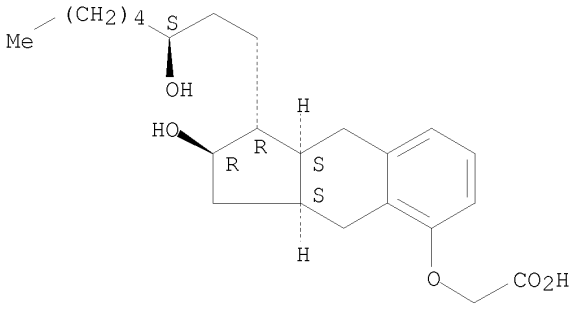
CN Acetic acid, 2-[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]-, sodium salt (1:1) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 1384244-82-9 CAPLUS
CN Acetic acid, 2-[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]-, lithium salt (1:1) (CA INDEX NAME)

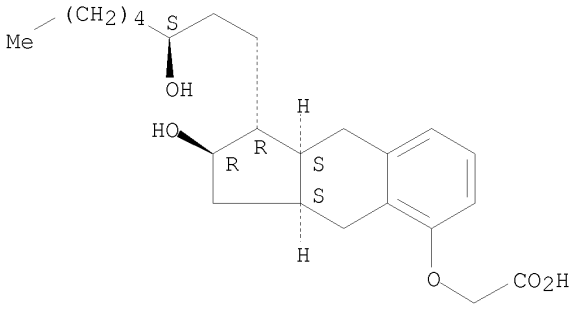
Absolute stereochemistry. Rotation (-).



● Li

RN 1384244-83-0 CAPLUS
CN Acetic acid, 2-[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]-, potassium salt (1:1) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● K

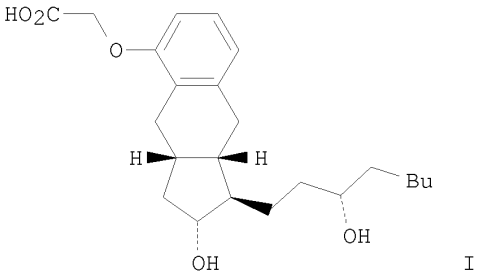
OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2012:953727 CAPLUS
DOCUMENT NUMBER: 157:165337
TITLE: Process for preparation of salts of treprostinil

INVENTOR(S): Giust, Walter; Souza, Fabio; Oudenes, Jan; Gorin, Boris; Bejan, Elena
PATENT ASSIGNEE(S): Alphora Research Inc., Can.
SOURCE: Can. Pat. Appl., 17pp.; Chemical Indexing Equivalent to 157:165338 (WO)
CODEN: CPXXEB
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2726599	A1	20120630	CA 2010-2726599	20101230
WO 2012088607	A1	20120705	WO 2011-CA50804	20111222
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, 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, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AL, 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, RS, SE, SI, SK, SM, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 20140024856	A1	20140123	US 2013-13520872	20131008

PRIORITY APPLN. INFO.: CA 2010-2726599 A 20101230
WO 2011-CA50804 W 20111222
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 157:165337
GI



I

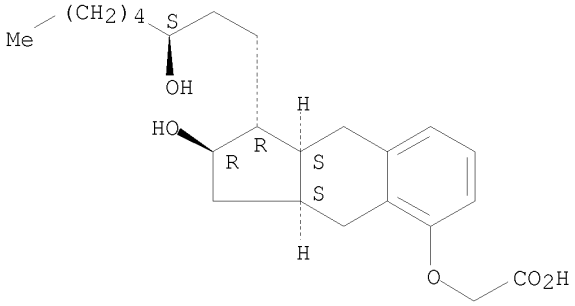
AB This invention provides a process for the preparation of salts of treprostinil (I). For example, 5 M sodium hydroxide (0.61 mL, 3.05 mmol) was added dropwise to a solution of treprostinil (1.021 g, 2.61 mmol) in acetone (25 mL) while maintaining an internal temperature below 30 °C and pH at 8-9. After 15 min under agitation, a fiber like solid began to crystallize from the reaction mixture The mixture was stirred 1 h at room temperature then cooled to 0-5 °C and stirred at this temperature for another hour. The solid was filtered, rinsed with acetone, and dried under vacuum to yield 0.95 g (99.67% purity, 88% yield) of a white solid.
IT 81846-19-7P, Treprostinil

RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of salts of treprostinil)

RN 81846-19-7 CAPLUS

CN Acetic acid, 2-[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



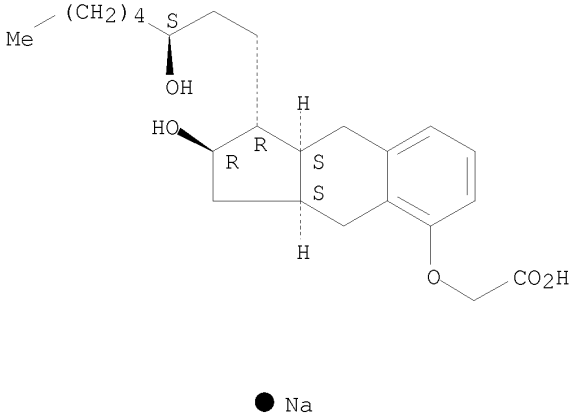
IT 289480-64-4P 1384244-82-9P 1384244-83-0P

RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of salts of treprostinil)

RN 289480-64-4 CAPLUS

CN Acetic acid, 2-[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]-, sodium salt (1:1) (CA INDEX NAME)

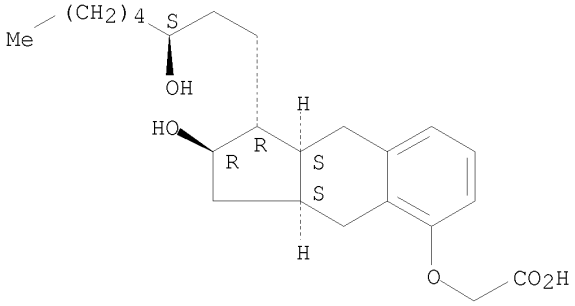
Absolute stereochemistry. Rotation (-).



RN 1384244-82-9 CAPLUS

CN Acetic acid, 2-[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]-, lithium salt (1:1) (CA INDEX NAME)

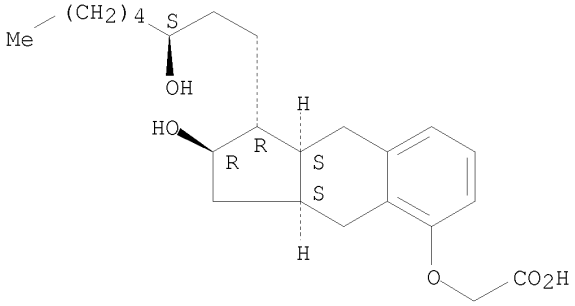
Absolute stereochemistry. Rotation (-).



● Li

RN 1384244-83-0 CAPLUS
CN Acetic acid, 2-[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]-, potassium salt (1:1) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



● K

L9 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2009:767183 CAPLUS
DOCUMENT NUMBER: 151:86694
TITLE: An improved process to prepare treprostinil
INVENTOR(S): Batra, Hitesh; Tuladhar, Sudersan M.; Penmasta, Raju; Walsh, David A.
PATENT ASSIGNEE(S): United Therapeutics Corporation, USA
SOURCE: PCT Int. Appl., 30pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2009078965		A1	20090625	WO 2008-US13686	20081212
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, 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				
CA 2710205		A1	20090625	CA 2008-2710205	20081212
KR 2010105852		A	20100930	KR 2010-7015955	20081212
EP 2252570		A1	20101124	EP 2008-861602	20081212
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CN 101903324		A	20101201	CN 2008-80121181	20081212
CN 101903324		B	20130703		
JP 2011506599		T	20110303	JP 2010-539440	20081212
CN 103274926		A	20130904	CN 2013-10217718	20081212
US 20090163738		A1	20090625	US 2008-334731	20081215
US 8242305		B2	20120814		
IN 2010CN03640		A	20101015	IN 2010-CN3640	20100615
US 20120283470		A1	20121108	US 2012-13548446	20120713
US 8497393		B2	20130730		
US 20130267734		A1	20131010	US 2013-13910583	20130605
US 8748657		B2	20140610		
US 20130289304		A1	20131031	US 2013-13933623	20130702
JP 2014114317		A	20140626	JP 2014-25577	20140213

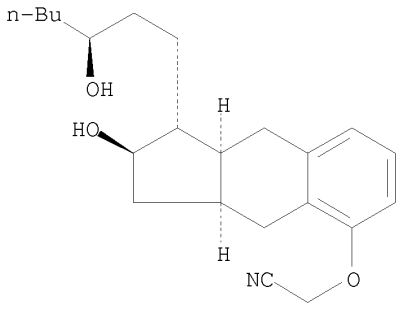
PRIORITY APPLN. INFO.:

US 2007-61014232	P	20071217
CN 2008-80121181	A3	20081212
JP 2010-539440	A3	20081212
WO 2008-US13686	W	20081212
US 2008-334731	A1	20081215
US 2012-13548446	A1	20120713

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

OTHER SOURCE(S): MARPAT 151:86694

GI



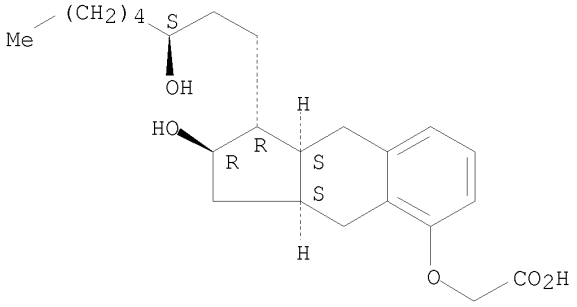
AB This present invention relates to an improved process to prepare prostacyclin derivs. One embodiment provides for an improved process to convert a benzindene triol to treprostinil via salts of treprostinil and to purify treprostinil.

IT 81846-19-7P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(improved process to prepare treprostinil)

RN 81846-19-7 CAPLUS

CN Acetic acid, 2-[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



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

L9 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2014 ACS on STN

ACCESSION NUMBER: 2009:295869 CAPLUS

DOCUMENT NUMBER: 150:313958

TITLE: Buffer solutions having selective bactericidal activity against gram-negative bacteria

INVENTOR(S): Jeffs, Roger; Zaccardelli, David

PATENT ASSIGNEE(S): United Therapeutics Corporation, USA

SOURCE: PCT Int. Appl., 31pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009033039	A2	20090312	WO 2008-US75425	20080905
WO 2009033039	A3	20090430		
WO 2009033039	A9	20090625		

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, 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, AP, EA, EP, OA

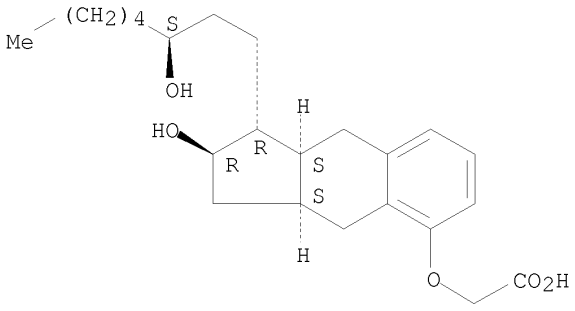
CA 2698721	A1	20090312	CA 2008-2698721		20080905
EP 2200650	A2	20100630	EP 2008-829225		20080905
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, MK, RS					
KR 2010074169	A	20100701	KR 2010-7007338		20080905
CN 101827612	A	20100908	CN 2008-80106046		20080905
JP 2010538092	T	20101209	JP 2010-524190		20080905
CN 103181893	A	20130703	CN 2013-10078895		20080905
EP 2711024	A1	20140326	EP 2013-188882		20080905
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR					
IN 2010CN01357	A	20100903	IN 2010-CN1357		20100310
JP 2013241468	A	20131205	JP 2013-177161		20130828
PRIORITY APPLN. INFO.:			US 2007-60970716	P	20070907
			CN 2008-80106046	A3	20080905
			EP 2008-829225	A3	20080905
			JP 2010-524190	A3	20080905
			WO 2008-US75425	W	20080905

AB Buffer solns. for pharmaceutical prepns. that have bactericidal activity preferentially against gram neg. bacteria are provided. The buffers have a pH of >10 or <4.5 with low buffer capacity. Methods of their use in reducing the occurrence of blood stream infections in a mammal are also provided. The results show no compatibility problems for the dilute treprostinil solns. in any of diluent solns. The appearance of all solns. was clear, colorless and free from visible particulate matter.

IT 81846-19-7 289480-64-4, Treprostinil sodium
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(buffer solns. having selective bactericidal activity against gram-neg. bacteria)

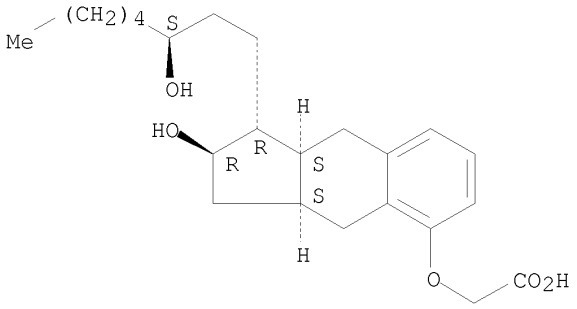
RN 81846-19-7 CAPLUS
CN Acetic acid, 2-[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 289480-64-4 CAPLUS
CN Acetic acid, 2-[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]-, sodium salt (1:1) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L9 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2005:1863 CAPLUS
DOCUMENT NUMBER: 142:79968
TITLE: Inhalable formulations for treating pulmonary hypertension and methods of using same
INVENTOR(S): Chaudry, Imtiaz
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 14 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20040265238	A1	20041230	US 2003-609233	20030627
AU 2004251014	A1	20050106	AU 2004-251014	20040618
AU 2004251014	B2	20101125		
CA 2530632	A1	20050106	CA 2004-2530632	20040618
CA 2530632	C	20120306		
WO 2005000270	A2	20050106	WO 2004-EP6629	20040618
WO 2005000270	A3	20050512		
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				
EP 1638525	A2	20060329	EP 2004-740073	20040618
EP 1638525	B1	20120307		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				

BR 2004011904	A	20060808	BR 2004-11904	20040618
CN 1822817	A	20060823	CN 2004-80020228	20040618
CN 1822817	B	20121010		
JP 2007519604	T	20070719	JP 2006-516000	20040618
JP 5571867	B2	20140813		
AT 548025	T	20120315	AT 2004-740073	20040618
KR 2012068052	A	20120626	KR 2012-7015386	20040618
ES 2384384	T3	20120704	ES 2004-740073	20040618
RU 2491072	C2	20130827	RU 2010-152753	20040618
IN 2005KN02508	A	20061013	IN 2005-KN2508	20051206
MX 2005013539	A	20060309	MX 2005-13539	20051213
US 20060104913	A1	20060518	US 2005-316458	20051222
ZA 2006000773	A	20070530	ZA 2006-773	20060126
HK 1093017	A1	20130719	HK 2006-113768	20061214
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US 20110265786	A1	20111103	US 2011-13020429	20110203
AU 2011200464	A1	20110224	AU 2011-200464	20110204
AU 2011200464	B2	20120809		
JP 2012001549	A	20120105	JP 2011-172929	20110808

PRIORITY APPLN. INFO.:

US 2003-609233	A	20030627
AU 2004-251014	A3	20040618
JP 2006-516000	A3	20040618
KR 2005-7025128	A3	20040618
RU 2006-102206	A3	20040618
WO 2004-EP6629	W	20040618
IN 2005-KN2508	A3	20051206

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

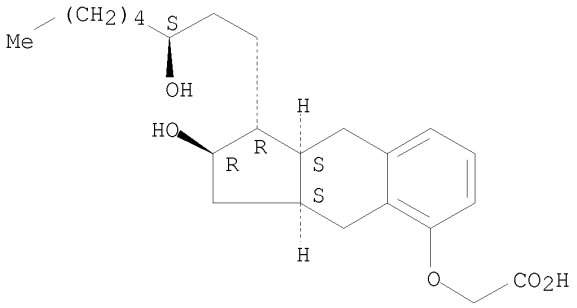
AB The present invention is directed to an inhalable formulation for the treatment of pulmonary hypertension in a mammal (e.g., humans), wherein the formulation comprises at least one hypertension reducing agent, including but not limited to an angiotensin converting enzyme inhibitor, angiotensin receptor blocker, β-blocker, calcium-channel blocker or vasodilator, or any combination thereof. The formulations of the present invention may be a solution or suspension, and preferably are suitable for administration via nebulization. The present invention is also directed to a method and kit for treating a mammal suffering from pulmonary hypertension. An inhalant solution composition containing enalapril 0.2-10, sodium chloride 2-10 mg/mL, sodium hydroxide q.s, and water q.s. was formulated.

IT 289480-64-4, Treprostinil sodium
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhalable formulations for treating pulmonary hypertension and methods of using same)

RN 289480-64-4 CAPLUS

CN Acetic acid, 2-[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]-, sodium salt (1:1) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L9 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2014 ACS on STN
ACCESSION NUMBER: 2002:655127 CAPLUS
DOCUMENT NUMBER: 137:185355
TITLE: Process for stereoselective synthesis of prostacyclin derivatives
INVENTOR(S): Moriarty, Robert M.; Penmasta, Raju; Guo, Liang; Rao, Munagala S.; Staszewski, James P.
PATENT ASSIGNEE(S): United Therapeutics Corporation, USA
SOURCE: U.S., 15 pp., Cont.-in-part of U. S. Ser. No. 481,390. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6441245	B1	20020827	US 2000-541521	20000403
CA 2847985	A1	19990506	CA 1998-2847985	19981026
US 20020087025	A1	20020704	US 2002-75439	20020215
US 6528688	B2	20030304		
US 20020173672	A1	20021121	US 2002-184907	20020701
US 6765117	B2	20040720		

PRIORITY APPLN. INFO.: US 1997-957736 B1 19971024
US 2000-481390 A2 20000112
CA 1998-2307163 A3 19981026
US 2000-541521 A3 20000403
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): CASREACT 137:185355; MARPAT 137:185355
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB An improved method is described for making 9-deoxy-PGF1-type compds.; in contrast to the prior art, the method is stereoselective and requires fewer steps than the known methods for making these compds.; the method

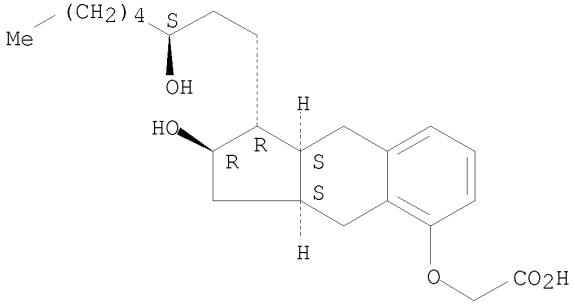
comprises cyclization of alkyne I [Z = O, S, CH2, NR8; R8 = H, alkyl; X = H, CN, OR9, CO2R9; R9 = alkyl, THP, TBDMS; n = 0 - 3; Y1 = cis- or trans-CH:CH, CH2(CH2)m, C.tplbond.C; m = 1 - 3; R1 = PG; R7 = CpH2p, (un)substituted OPh, Ph, CH2Ph, CH2CH2Ph, CH2CH2CH2Ph, cis-CH:CHEt, (CH2)2CH(OH)Me, (CH2)3CH:CMe2; PG = alc. protective group; CL1R7 = C4-7-cycloalkyl, 2-(2-furyl)ethyl, 2-(3-thienyl)ethoxy, {(3-thienyl)oxy}methyl; M1 = α-OH:β-R5, α-R5:β-OH, α-OR1:β-R5, α-R5:β-OR1; R5 =H, Me; R1 = PG; L1 = α-R3:β-R4, α-R3:β-R4; R3, R4 = H, Me, F] into tricycle II by cobalt-mediated cyclization with Co2(CO)8. Thus, III, was prepared from 3-MeOC6H4CH2OH via C-allylation, condensation of 2-allyl-3-methoxybenzaldehyde with (S)-5-(tetrahydropyranyloxy)decyne and cobalt-mediated cyclization of alkenynol IV.

IT 81846-19-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(stereoselective synthesis of prostacyclin derivs. from 3-methoxybenzyl alc.)

RN 81846-19-7 CAPLUS

CN Acetic acid, 2-[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> s remodulin/prep
             0 REMODULIN/CT
       6135071 PREP/RL
L10          0 REMODULIN/PREP
                 (REMODULIN/CT (L) PREP/RL)

=> s remodulin
L11         31 REMODULIN

=> s l11 and sodium hydroxide
       1887634 SODIUM
        552796 HYDROXIDE
        217847 SODIUM HYDROXIDE
                 (SODIUM(W)HYDROXIDE)
L12          0 L11 AND SODIUM HYDROXIDE

=> s l11 and sodium carbonate
       1887634 SODIUM
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        525668 CARBONATE
         92929 SODIUM CARBONATE
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L13          0 L11 AND SODIUM CARBONATE

=> s l11 and sodium bicarbonate
       1887634 SODIUM
         99212 BICARBONATE
         42780 SODIUM BICARBONATE
                 (SODIUM(W)BICARBONATE)
L14          0 L11 AND SODIUM BICARBONATE
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PTO/SB/08 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: July 2, 2013

(use as many sheets as necessary)

Sheet 1 of 4

Complete if Known	
Application Number	Unassigned
Filing Date	Herewith
First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	080618-1256

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	2002/0173672 A1	11/21/2002	Moriarty et al.	
	A2	2004/0176645 A1	09/09/2004	Moriarty et al.	
	A3	2005/0085540 A1	04/21/2005	Phares et al.	
	A4	2005/0101608 A1	05/12/2005	Santel, Donald J.	
	A5	2005/0165111 A1	07/28/2005	Wade et al.	
	A6	2005/0282903 A1	12/22/2005	Wade et al.	
	A7	2005/0282901 A1	12/22/2005	Phares et al.	
	A8	2007/0078182 A1	04/05/2007	Phares et al.	
	A9	2007/0078095 A1	04/05/2007	Phares et al.	
	A10	2008/0200449 A1	08/21/2008	Olschewski et al.	
	A11	2008/0249167 A1	10/09/2008	Phares et al.	
	A12	2008/0280986 A1	11/13/2008	Wade et al.	
	A13	2009/0036465 A1	02/05/2009	Roscigno et al.	
	A14	2009/0163738 A1	06/25/2009	Batra et al.	
	A15	4,306,075 A	12/15/1981	Aristoff, Paul A.	
	A16	4,424,376 A	01/03/1984	Moniot et al.	
	A17	4,463,183 A	07/31/1984	Haslanger, Martin F.	
	A18	4,486,598 A	12/04/1984	Aristoff, Paul A.	
	A19	4,544,764 A	10/01/1985	Aristoff, Paul A.	
	A20	4,668,814 A	05/26/1987	Aristoff, Paul A.	
	A21	4,683,330 A	07/28/1987	Aristoff, Paul A.	
	A22	5,153,222 A	10/06/1992	Tadepalli et al.	
	A23	6,054,486 A	04/25/2000	Crow et al.	
	A24	6,441,245 B1	08/27/2002	Moriarty et al.	
	A25	6,521,212 B1	02/18/2003	Cloutier et al.	
	A26	6,528,688 B2	03/04/2003	Moriarty et al.	
	A27	6,700,025 B2	03/02/2004	Moriarty et al.	
	A28	6,756,033 B2	06/29/2004	Cloutier et al.	
	A29	6,765,117 B2	07/20/2004	Moriarty et al.	
	A30	6,803,386 B2	10/12/2004	Shorr et al.	
	A31	6,809,223 B2	10/26/2004	Moriarty et al.	
	A32	7,199,157 B2	04/03/2007	Wade et al.	
	A33	7,384,978 B2	06/10/2008	Phares et al.	
	A34	7,417,070 B2	08/26/2008	Phares et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant	T[6]

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /YV/

PTO/SB/08 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: July 2, 2013

(use as many sheets as necessary)

Sheet 2 of 4

Complete if Known	
Application Number	Unassigned
Filing Date	Herewith
First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	080618-1256

		Country Code[3]-Number[4]-Kind Code[5] *(if known)*				
	A35	CA 2 710 726 A1	01/22/2012	Alphora Research Inc., CA		
	A36	CN 101891596 A	11/24/2010	Shanghai Techwell Biopharmaceutical Co. Ltd.		A ✓
	A37	CN 101891715 A	11/24/2010	Shanghai Techwell Biopharmaceutical Co. Ltd.		A ✓
	A38	EP 0 004 335 A2	10/03/1979	Hoechst AG		A
	A39	EP 0 087 237 B1	05/14/1986	The Upjohn Company		
	A40	EP 0 159 784 B1	06/07/1989	The Upjohn Company		
	A41	EP 0 175 450 B1	03/22/1989	The Upjohn Company		
	A42	EP 0 496 548 A1	07/29/1992	Purdue Research Foundation		
	A43	WO 98/39337 A1	09/11/1998	Hoechst AG		A
	A44	WO 99/21830 A1	05/06/1999	United Therapeutics Corporation		
	A45	WO 03/070163 A2	08/28/2003	United Therapeutics Corporation		
	A46	WO 2005/007081 A2	01/27/2005	United Therapeutics Corporation		
	A47	WO 2007/134292 A2	11/22/2007	United Therapeutics Corporation		
	A48	WO 2008/100977 A2	08/21/2008	N.V. Organon		
	A49	WO 2009/117095 A1	09/24/2009	Arena Pharmaceuticals, Inc.		
	A50	WO 2012/009816 A1	01/26/2012	Alphora Research Inc.		

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A51	ALEXANDER et al., "The Synthesis of Benzindene Prostacyclin Analogs as Potential Antiulcer Agents," Prostaglandins, 1986, 32(5):647-653.	
	A52	ARISTOFF et al., "Synthesis and Structure-Activity Relationship of Novel Stable Prostacyclin Analogs," Advances in Prostaglandin, Thromboxane, and Leukotriene Research, Samuelsson et al., .Eds., 1983, 11:267-274	
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	A54	ARISTOFF et al., "Total Synthesis of a Novel Antiulcer Agent via a Modification of the Intramolecular Wadsworth-Emons-Wittig Reaction," J. Am. Chem. Soc., 1985, 107:7967-7974.	
	A55	BATRA et al., "Crystallization Process Development for a Stable Polymorph of Treprostinil Diethanolamine (UT-15C) by Seeding," Organic Process Research & Development, 2009, 13:242-249.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /YV/

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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: July 2, 2013

(use as many sheets as necessary)

Sheet 3 of 4

Complete if Known	
Application Number	Unassigned
Filing Date	Herewith
First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	080618-1256

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A56	BELCH et al., "Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of AS-013, a Prostaglandin E1 Prodrug, in Patients with Intermittent Claudication," Circulation, May 6, 1997, 95(9):2298-2302.	
	A57	CHEMBURKAR et al., "Dealing with the Impact of Ritonavir Polymorphs on the Late Stages of Bulk Drug Process Development," Organic Process Research & Development, 2000, 4:413-417.	
	A58	CHUNG et al., "Promoters for the (Alkyne)hexacarbonyldicobalt-Based Cyclopentenone Synthesis," Organometallics, 1993, 12:220-223.	
	A59	CLARK et al., "High-Performance Liquid Chromatographic Method for Determining the Enantiomeric Purity of a Benzindene Prostaglandin by a Diastereomeric Separation," Journal of Chromatography, 1987, 408:275-283.	
	A60	HARDINGER et al., "Triply-Convergent Syntheses of Two Homochiral Arene-Fused Prostacyclin Analogs Related to U68,215," Bioorganic & Medicinal Chemistry Letters, 1991, 1(1):79-82.	
	A61	HICKS et al., "A Practical Titanium-Catalyzed Synthesis of Bicyclic Cyclopentenones and Allylic Amines," J. Org. Chem., 1996, 61:2713-2718.	
	A62	JEONG et al., "Catalytic Version of the Intramolecular Pauson-Khand Reaction," J. Am. Chem. Soc., 1994, 116:3159-3160.	
	A63	KHAND et al., "Organocobalt Complexes. Part II. Reaction of Acetylenehexacarbonyl-dicobalt Complexes, $(R^1C_2R^2)Co_2(CO)_6$, with Norbornene and its Derivatives," J. Chem. Soc., J.C.S. Perkin I., 1973, 977-981.	
	A64	MATHRE et al., "A Practical Enantioselective Synthesis of α,α-Diaryl-2-pyrrolidinemethanol. Preparation and Chemistry of the Corresponding Oxazaborolidines," J. Org. Chem., 1991, 56:751-762.	
	A65	Moriarty et al., "The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil)," *J. Org. Chem.* 2004, 69, 1890-1902.	
	A66	MULZER et al., "Asymmetric Synthesis of Carbacyclin Precursors by Pauson-Khand Cyclization," Liebigs Ann. Chem., 1988, 891-897.	
	A67	NELSON, Norman A., "Prostaglandin Nomenclature," J. Med. Chem., September 1974, 17(9):911-918.	
	A68	PAGENKOPF et al., "Photochemical Promotion of the Intramolecular Pauson-Khand Reaction. A New Experimental Protocol for Cobalt-Catalyzed [2 + 2 + 1] Cycloadditions," J. Am. Chem. Soc., 1996, 118:2285-2286.	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /YV/

PTO/SB/08 (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: July 2, 2013

(use as many sheets as necessary)

Sheet 4 of 4

Complete if Known	
Application Number	Unassigned
Filing Date	Herewith
First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	080618-1256

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A69	PAGENKOPF, Brian L., "Substrate and Reagent Control of Diastereoselectivity in Transition Metal-Mediated Process: Development of a Catalytic Photo Promoted Pauson-Khand Reaction," Diss. Abstr. Int., 57(12):7535, 1977, Abstract.	
	A70	PAULSON, Peter L., "The Khand Reaction," Tetrahedron, 1985, 41(24):5855-5860.	
	A71	SCHORE, Neil E., "Transition-Metal-Mediated Cycloaddition Reactions of Alkynes in Organic Synthesis," Chem. Rev., 1988, 88:1081-1119.	
	A72	SHAMBAYATI et al., "N-Oxide Promjoted Pauson-Khand Cyclizations at Room Temperature," Tetrahedron Letters, 1990, 31(37):5289-5292.	
	A73	SNELL et al., "Investigating the Effect of Impurities on Macromolecule Crystal Growth in Microgravity," Crystal Growth & Design, 2001, 1(2):151-158.	
	A74	Sorbera et al. "UT-15. Treatment of Pulmonary Hypertension Treatment of Peripheral Vascular Disease," *Drug of the Future*, 2001, 26(4), 364-374.	
	A75	TAKANO et al., "Enantiodivergent Synthesis of Both Enantiomers of Sulcatol and Matsutake Alcohol from (R)-Epichlorohydrin," Chemistry Letters, 1987, 2017-2020.	
	A76	VIEDMA, Cristobal, "Selective Chiral Symmetry Breaking during Crystallization: Parity Violation of Cryptochiral Environment in Control?" Crystal Growth & Design, 2007, 7(3):553-556.	
	A77	ZHANG et al., "A Nickel(0)-Catalyzed Process for the Transformation of Enynes to Bicyclic Cyclopentenones," J. Org. Chem., 1996, 61:4498-4499.	

Examiner Signature	/Yevgeny Valenrod/	Date Considered	12/05/2014

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. 1 Applicant's unique citation designation number (optional). 2 See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. 3 Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). 4 For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. 5 Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. 6 Applicant is to place a check mark here if English language Translation is attached.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /YV/

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1	("6765117").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/12/05 14:11
L2	1	("8497393").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/12/05 14:11
L3	1	("7999007").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/12/05 14:11
L4	1	("8653137").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/12/05 14:11
L5	1	("8658694").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/12/05 14:11
L6	18	((Hitesh) near2 (Batra)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2014/12/05 14:11
L7	14	((Sudersan) near2 (Tuladhar)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2014/12/05 14:11
L8	24	((Raju) near2 (Penmasta)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2014/12/05 14:11
L9	227	((David) near2 (Walsh)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2014/12/05 14:11
L10	247	L6 or L7 or L8 or L9	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L11	15	L10 and treprostinil	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L12	8	L11 and (base adj addition)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11

EAST Search History (Prior Art)

L13	1	("20020173672").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/12/05 14:11
L14	1	("20050085540").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/12/05 14:11
L15	160	treprostinil same (sodium or potassium) same salt	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L16	2	L15 same crystal	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L17	8	L15 same crystallization	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L18	1	("4486598").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/12/05 14:11
L19	1	("4306075").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/12/05 14:11
L20	37	treprostinil same (sodium adj hydroxide)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L21	5	L20 same (ethanol or methaol)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L22	32	L20 not L21	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11

EAST Search History (Prior Art)

L23	17	L22 same (crystal or crystallized or solid or crystallization)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L24	148	treprostinil adj sodium	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L25	15	L24 same (sodium adj hydroxide)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L26	14	L25 not L23	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L27	5	treprostinil same (sodium adj hydroxide) same salt	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L28	37	treprostinil same (sodium adj hydroxide)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L29	10	treprostinil same (potassium adj hydroxide)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L30	44	L28 or L29	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11

EAST Search History (Prior Art)

L31	22	L30 same solid	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L32	0	L31 same crystal	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L33	21	L31 not L25	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L34	0	L32 not L12	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L35	19	L33 not L12	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L36	840	(562/466).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/12/05 14:11
L37	24	L36 and treprostinil	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L38	483	L36 and (sodium same salt)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11
L39	20	L37 and (sodium same salt)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11

EAST Search History (Prior Art)

L40	1	("20040265238").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2014/12/05 14:11
L41	0	remodulin same crystallization	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2014/12/05 14:11

EAST Search History (Interference)

		< This search history is empty>				

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/933,623
Filing Date:	7/2/2013
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation Number:	6887

REPLY UNDER 37 CFR § 1.111

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

Commissioner:

This paper responds to the outstanding non-final Office Action dated December 10, 2014.

Amendments to the Specification begin on page 2 of this document.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this document.

Remarks begin on page 6 of this document.

Amendments to the Specification:

Please amend the specification as follows:

Amend the paragraph on page 3, lines 21-22, as follows:

M_1 is α-OH:β-R_5 or α-R_5:β-OH or ~~α-OR_4:β-R_5~~ α-OR_2:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and

Amend the paragraph on page 8, lines 22-23, as follows:

M_1 is α-OH:β-R_5 or α-R_5:β-OH or ~~α-OR_4:β-R_5~~ α-OR_2:β-R_5 or α-R_5:β-OR_2, wherein R_5 is hydrogen or methyl, R_2 is an alcohol protecting group, and

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 process for preparing a pharmaceutical product comprising treprostinil or a treprostinil salt, comprising:
combining treprostinil and a base in solution to form a base addition salt;
allowing crystallization of the base addition salt of treprostinil; [[and]]
collecting the base addition salt of treprostinil, storing the collected base addition salt, and preparing a pharmaceutical product comprising treprostinil or a treprostinil salt from the base addition salt after storage.

2. (Canceled)

3. (Original) The process of claim 1, wherein the base addition salt is selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.

4. (Original) The process of claim 1, further comprising heating the solution of treprostinil and base addition salt.

5. (Original) The process of claim 4, further comprising cooling the solution of treprostinil and base addition salt prior to collecting the base addition salt of treprostinil.

6. (Original) The process of claim 1, wherein the base comprises an alkali metal cation.

7. (Original) The process of claim 6, wherein the alkali metal cation is selected from the group consisting of sodium and potassium.

8. (Original) The process of claim 1, wherein the solution comprises a water-miscible organic solvent.

9. (Original) The process of claim 1, wherein a mole ratio of the base in solution to treprostinil is about 1.1:1.

10. (Withdrawn) A pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof, said composition prepared by a process comprising providing a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps, forming a salt of treprostinil by combining the starting batch and a base, isolating the treprostinil salt, and preparing a pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof from the isolated treprostinil salt, whereby a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition, and wherein said alkylation is alkylation of benzindene triol.

11. (Withdrawn) The pharmaceutical composition of claim 10, wherein the salt is isolated in crystalline form.

12. (Withdrawn) The pharmaceutical composition of claim 11, wherein the isolated salt is at least 99.8% pure.

13. (Withdrawn) The pharmaceutical composition of claim 10, wherein the base is selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.

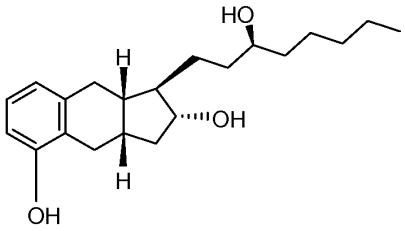
14. (Withdrawn) The pharmaceutical composition of claim 13, wherein the base is diethanolamine.

15. (Withdrawn) The pharmaceutical composition of claim 10, wherein the base is combined with treprostinil that has not been previously isolated.

16. (Withdrawn) The pharmaceutical composition of claim 10, wherein the isolated salt is stored at ambient temperature.

17. (Withdrawn) The pharmaceutical composition of claim 10, which is a pharmaceutical solution.

18. (Withdrawn) A process of preparing a pharmaceutical product comprising treprostinil or a pharmaceutically acceptable salt thereof, comprising alkylating a triol intermediate of the formula:



hydrolyzing the resulting compound to form treprostinil, forming a salt of treprostinil stable at ambient temperature, storing the treprostinil salt at ambient temperature, and preparing a pharmaceutical product from the treprostinil salt after storage, wherein the pharmaceutical product comprises treprostinil or a pharmaceutically acceptable salt thereof.

19. (Withdrawn) A pharmaceutical product prepared by the process of claim 18.

20. (New) The method of claim 1, wherein said preparing comprises converting the base addition salt after storage into treprostinil by acidification.

21. (New) The method of claim 1, wherein the quantity of the base addition salt corresponds to a large scale synthesis.

22. (New) A pharmaceutical product prepared by the method of claim 21.

REMARKS

Applicants respectfully request reconsideration and allowance of the present application.

The specification has been amended on pages 3 and 8 to correct inadvertent typographical errors.

Status of Claims

Applicants have canceled claim 2, without prejudice or disclaimer. Applicants reserve the right to file one or more continuing applications directed to the canceled subject matter.

Applicants have amended claim 1, without prejudice or disclaimer. Applicants reserve the right to file one or more continuing applications directed to the subject matter omitted by the present amendment. Support for the amended claim may be found throughout the specification as filed and, in particular, in canceled claim 2. No new matter has been added.

Applicants have added new claims 20-22. Support for the new claims may be found throughout the specification as filed and in particular, in paragraph 0006, 0046, and 0048. No new matter has been added.

After the amendment, the pending claims include claims a) examined 1 and 3-9; b) withdrawn claims 10-19 and c) new claims 20-22.

Election/Restrictions

Applicants confirm the election of Group I, claims 1-9, without traverse. Applicants request examination of new claims 20 and 22 as a part of elected Group I.

The rejections under 35 USC § 102

Claims 1-5 and 8 stand rejected as anticipated by Phares et al. (US2005/0085540). Applicants respectfully traverse.

Phares does not teach at least one element of the claimed invention. For example, Phares does not teach "storing the collected base addition salt" as amended claim 1 recites. Although examined claim 2 contained a "drying and storing" element, the PTO failed to indicate a particular place where Phares teaches this element. The portion of Phares relied upon by the PTO relates to producing a salt that is itself an end product, rather than an intermediate for storage. Moreover, it was not known prior to the present invention that collecting and storing a base addition salt of treprostinil would facilitate large scale synthesis of pharmaceutical products comprising treprostinil or treprostinil salts, as recited in claim 21. Prior to the present invention, treprostinil had to be refrigerated during storage, which significantly increased the cost of production on a large scale as it was not known that the salt form was more stable. Accordingly, Applicants request withdrawal of the rejection.

The rejections under 35 USC § 103(a)

Claims 6 and 7 stand rejected as obvious over Phares et al. (US2005/0085540) in view of Aristoff (US 4,486,598). Applicants respectfully traverse.

Applicants disagree with the PTO's interpretation of Aristoff and reserve the right to provide additional comments on Aristoff in the future. At the same time, Aristoff cannot remedy the above-mentioned deficiencies of Phares at least because Aristoff does not teach or suggest the "storing" step of claim 1, which is necessarily included in claims 6 and 7. Furthermore, the combination of references does not disclose or suggest the advantages of the present process explained above. In sum, because Phares and Aristoff do not teach or suggest all the elements of amended claim 1, the PTO failed to establish a *prima facie* case of obviousness. Accordingly, Applicants request withdrawal of the rejection.

Concluding Remarks

Applicants believe that the application is in condition for allowance. Favorable reconsideration is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance prosecution.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date January 26, 2015

By /Stephen B. Maebius/

FOLEY & LARDNER LLP
Customer Number: 22428
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Facsimile: (415) 434-4507

Stephen B. Maebius
Agent for Applicants
Registration No. 35,264

Electronic Acknowledgement Receipt	
EFS ID:	21309559
Application Number:	13933623
International Application Number:	
Confirmation Number:	6887
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Stephen Bradford Maebius/Diana Meinecke
Filer Authorized By:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1256
Receipt Date:	26-JAN-2015
Filing Date:	02-JUL-2013
Time Stamp:	15:39:56
Application Type:	Utility under 35 USC 111(a)

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		111Response.pdf	137893 dcccafb25fb480161e18c7dc9da1bc7c64aa200d	yes	8

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment Copy Claims/Response to Suggested Claims	1	1
	Specification	2	2
	Claims	3	5
	Applicant Arguments/Remarks Made in an Amendment	6	8
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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.

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/933,623	Filing Date 07/02/2013	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	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 $310 ($155 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	

APPLICATION AS AMENDED – PART II

AMENDMENT	01/26/2015	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 21	Minus	** 20	= 1	X $80 =	80
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**80**

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

LIE
/SULONDA D. STEVENSON/

Document code: WFEE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/933,623	07/02/2013	Hitesh Batra	080618-1256	6887

22428 7590 03/19/2015

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EXAMINER	
VALENROD, YEVGENY	

ART UNIT	PAPER NUMBER
1672	

NOTIFICATION DATE	DELIVERY MODE
03/19/2015	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):

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Office Action Summary	Application No. 13/933,623	Applicant(s) BATRA ET AL.	
	Examiner YEVGENY VALENROD	Art Unit 1672	AIA (First Inventor to File) Status No

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS 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 *1/26/15*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

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

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ 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*

5)☒ Claim(s) *1 and 3-22* is/are pending in the application.

5a) Of the above claim(s) *10-19 and 22* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1, 3-9 and 20-21* is/are rejected.

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

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

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

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

11)☐ 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).

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).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** 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) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Election/Restrictions

Newly added claims 20 and 21 are directed to a process for preparing a pharmaceutical product and further limit the independent claim 1 from which they depend. Claims 20 and 21 have been added to the elected Group I.

Newly added claim 22 is directed to a pharmaceutical product and has been added to the non-elected Group II.

Claims 1, 3-9 and 20-21 are examined.

Applicants remarks filed 1/26/15 have been considered.

Rejection of claims 1-5 and 8 under 35 USC 102(b) is withdrawn in view of applicants amendments.

Rejection of claims 6 and 7 under 35 USC 103(a) is withdrawn in view of applicants amendments and in favor of a new rejection under 35 USC 103(a).

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 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.

Claims 1, 3-9 and 20-21 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Phares et al. (US 2005/0085540) in view of Aristoff (US 4,486.598).

Scope of prior art

Phares discloses preparation of diethanolamine salt of treprostinil. To prepare said salt Phares discloses dissolving treprostinil acid in 1:1 molar ratio mixture of ethanol:water, adding diethanolamine and, heating the solution, adding antisolvent and subsequently cooling the solution (paragraph [0105]). Phares also discloses the sodium salt of treprostinil in paragraph [0051] but fails to teach a method of preparing such salt.

Ascertaining the difference

While Phares teaches the sodium salt of treprostinil, he fails to disclose a method of obtaining said sodium salt. (claims 6 and 7)

While Phares teaches preparation of treprostinil diethanolamine salt and provides an X-ray powder diffraction spectrum of the product, he fails to specifically recite the step of storing the base addition salt and a step of preparing a pharmaceutical product from said salt.

Secondary reference

Aristoff teaches that compounds of the same general formula as treprostinil can be made into solid salt forms by reacting with a stoichiometric amount of the base such

as sodium hydroxide in water and adding a water miscible solvent to produce a solid product (column 20, lines 24-34).

Obviousness

Regarding the sodium salt of treprostinil:

One skilled in the art would have found it obvious to prepare the sodium salt of treprostinil by addition of stoichiometric amount of sodium hydroxide to an aqueous solution of treprostinil acid and obtaining solid crystals of treprostinil sodium. Aristoff describes this procedure and Phares provides an example of this proceedure with diethanolamine as the base. One skilled in the art would therefore find both motivation, provided by Phares, and expectation of success provided by Phares and Aristoff.

Regarding the limitation directed to storing the treprostinil salt and preparing a pharmaceutical product:

The step of storing the treprostinil diethanolamine salt is inherently met by Phares. Examiner is interpreting the term “storing” to mean a time period between preparation of treprostinil salt and its use in preparation of a pharmaceutical product. Said limitation is inherently met by Phares. Phares teaches preparation of pharmaceutical products and administration of said compounds to a subject (paragraphs [0049], [0071], [0072], [0074]). It is inherent that some time elapses between preparation of a compound and its use in preparation of a pharmaceutical formulation. Phares describes obtaining an X-ray diffraction spectrum of treprostinil

diethanolamine. It is inherent that while obtaining the X-ray diffraction spectrum the compound is being stored.

While Phares et al do not disclose large scale production of the treprostinil salt, one skilled in the art would have found it reasonable to produce said compound on a large scale. The compound of Phares is a prodrug for a well-known pharmaceutical and one would have found it obvious to produce treprostinil diethanolamine on a large scale.

Regarding converting the treprostinil salt back to treprostinil:

Phares discloses that the prodrug itself does not have pharmacological activity. One skilled in the art would have found it obvious to convert the salt back into the active form.

Reply to Applicants' remarks.

Applicants have argued that prior to applicants' invention treprostinil had to be refrigerated during storage while the claimed salts are suitable for storage without refrigeration.

This argument is not found persuasive for the following reasons:

1) Phares discloses preparation of the salt not of the treprostinil itself.

2) Applicants state that is was known to store treprostinil while refrigerated. The instant claims are not limited to storing at room temperature and therefore storing while refrigerated would be obvious since according to applicants it's already known in the art. The argument is therefore not commensurate in scope with what is being claimed.

3) Applicants are arguing unexpected results (storage stability) without providing any evidence of support.

Conclusion

Claims 1, 3-22 are pending

Claims 10-19 and 22 are withdrawn

Claims 1, 3-9 and 20-21 are rejected

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 Yevgeny Valenrod whose telephone number is 571-272-9049. The examiner can normally be reached on 8:30am-5:00pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. 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.

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1672

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13933623	BATRA ET AL.
	Examiner	Art Unit
	YEVEGENY VALENROD	1672

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST	3/12/2015	YV
Inventor	3/12/2015	YV

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

	/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13933623	BATRA ET AL.
	Examiner	Art Unit
	YEVEGENY VALENROD	1672

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	12/05/2014	03/11/2015							
	1	✓	✓							
	2	✓	-							
	3	✓	✓							
	4	✓	✓							
	5	✓	✓							
	6	✓	✓							
	7	✓	✓							
	8	✓	✓							
	9	✓	✓							
	10	N	N							
	11	N	N							
	12	N	N							
	13	N	N							
	14	N	N							
	15	N	N							
	16	N	N							
	17	N	N							
	18	N	N							
	19	N	N							
	20		✓							
	21		✓							
	22		N							

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1	("6765117").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/03/12 11:44
L2	1	("8497393").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/03/12 11:44
L3	1	("7999007").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/03/12 11:44
L4	1	("8653137").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/03/12 11:44
L5	1	("8658694").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/03/12 11:44
L6	19	((Hitesh) near2 (Batra)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2015/03/12 11:44
L7	15	((Sudersan) near2 (Tuladhar)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2015/03/12 11:44
L8	25	((Raju) near2 (Penmasta)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2015/03/12 11:44
L9	229	((David) near2 (Walsh)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2015/03/12 11:44
L10	249	L6 or L7 or L8 or L9	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L11	16	L10 and treprostinil	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L12	8	L11 and (base adj addition)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44

EAST Search History (Prior Art)

L13	1	("20020173672").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/03/12 11:44
L14	1	("20050085540").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/03/12 11:44
L15	167	treprostinil same (sodium or potassium) same salt	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L16	2	L15 same crystal	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L17	8	L15 same crystallization	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L18	1	("4486598").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/03/12 11:44
L19	1	("4306075").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/03/12 11:44
L20	39	treprostinil same (sodium adj hydroxide)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L21	6	L20 same (ethanol or methaol)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L22	33	L20 not L21	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44

EAST Search History (Prior Art)

L23	18	L22 same (crystal or crystallized or solid or crystallization)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L24	159	treprostinil adj sodium	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L25	16	L24 same (sodium adj hydroxide)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L26	15	L25 not L23	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L27	6	treprostinil same (sodium adj hydroxide) same salt	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L28	39	treprostinil same (sodium adj hydroxide)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L29	10	treprostinil same (potassium adj hydroxide)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L30	46	L28 or L29	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44

EAST Search History (Prior Art)

L31	24	L30 same solid	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L32	0	L31 same crystal	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L33	22	L31 not L25	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L34	0	L32 not L12	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L35	20	L33 not L12	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L36	845	(562/466).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/03/12 11:44
L37	27	L36 and treprostinil	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L38	485	L36 and (sodium same salt)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44
L39	21	L37 and (sodium same salt)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44

EAST Search History (Prior Art)

L40	1	("20040265238").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/03/12 11:44
L41	0	remodulin same crystallization	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/03/12 11:44

EAST Search History (Interference)

		<This search history is empty>				

Electronic Patent Application Fee Transmittal	
Application Number:	13933623
Filing Date:	02-Jul-2013
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Kristel Schorr/Karen Walker
Attorney Docket Number:	080618-1256
Filed as Large Entity	
Filing Fees for Utility under 35 USC 111(a)	

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 1 month with $0 paid	1251	1	200	200
Miscellaneous:				
		Total in USD ($)		**200**

Electronic Acknowledgement Receipt	
EFS ID:	22783400
Application Number:	13933623
International Application Number:	
Confirmation Number:	6887
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Kristel Schorr/Karen Walker
Filer Authorized By:	Kristel Schorr
Attorney Docket Number:	080618-1256
Receipt Date:	30-JUN-2015
Filing Date:	02-JUL-2013
Time Stamp:	12:05:49
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$200
RAM confirmation Number	11418
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Fee Worksheet (SB06)	fee-info.pdf	31283 116a07f808bbb7ad25d6f8edacfd8853d83dd370	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	31283

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

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/933,623
Filing Date:	7/2/2013
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation Number:	6887

REPLY UNDER 37 C.F.R. § 1.116

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

Commissioner:

This paper responds to the outstanding Final Office Action dated March 19, 2015.

Amendments to the Claims are reflected in the listing of claims, which begins on page 2 of this document.

Remarks begin on page 5 of this document.

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 process for preparing a pharmaceutical product comprising treprostinil or a treprostinil salt, comprising:
combining treprostinil and a base in solution to form a base addition salt;
allowing crystallization of the base addition salt of treprostinil;
collecting the base addition salt of treprostinil, storing the collected base addition salt at ambient temperature, and preparing a pharmaceutical product comprising treprostinil or a treprostinil salt from the base addition salt after the storage.

2. (Canceled)

3. (Original) The process of claim 1, wherein the base addition salt is selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.

4. (Original) The process of claim 1, further comprising heating the solution of treprostinil and base addition salt.

5. (Original) The process of claim 4, further comprising cooling the solution of treprostinil and base addition salt prior to collecting the base addition salt of treprostinil.

6. (Original) The process of claim 1, wherein the base comprises an alkali metal cation.

7. (Original) The process of claim 6, wherein the alkali metal cation is selected from the group consisting of sodium and potassium.

8. (Original) The process of claim 1, wherein the solution comprises a water-miscible organic solvent.

9. (Original) The process of claim 1, wherein a mole ratio of the base in solution to treprostinil is about 1.1:1.

10. (Withdrawn) A pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof, said composition prepared by a process comprising providing a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps, forming a salt of treprostinil by combining the starting batch and a base, isolating the treprostinil salt, and preparing a pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof from the isolated treprostinil salt, whereby a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition, and wherein said alkylation is alkylation of benzindene triol.

11. (Withdrawn) The pharmaceutical composition of claim 10, wherein the salt is isolated in crystalline form.

12. (Withdrawn) The pharmaceutical composition of claim 11, wherein the isolated salt is at least 99.8% pure.

13. (Withdrawn) The pharmaceutical composition of claim 10, wherein the base is selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.

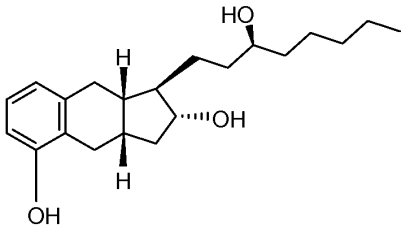
14. (Withdrawn) The pharmaceutical composition of claim 13, wherein the base is diethanolamine.

15. (Withdrawn) The pharmaceutical composition of claim 10, wherein the base is combined with treprostinil that has not been previously isolated.

16. (Withdrawn) The pharmaceutical composition of claim 10, wherein the isolated salt is stored at ambient temperature.

17. (Withdrawn) The pharmaceutical composition of claim 10, which is a pharmaceutical solution.

18. (Withdrawn) A process of preparing a pharmaceutical product comprising treprostinil or a pharmaceutically acceptable salt thereof, comprising alkylating a triol intermediate of the formula:



hydrolyzing the resulting compound to form treprostinil, forming a salt of treprostinil stable at ambient temperature, storing the treprostinil salt at ambient temperature, and preparing a pharmaceutical product from the treprostinil salt after storage, wherein the pharmaceutical product comprises treprostinil or a pharmaceutically acceptable salt thereof.

19. (Withdrawn) A pharmaceutical product prepared by the process of claim 18.

20. (Previously Presented) The method of claim 1, wherein said preparing comprises converting the base addition salt after storage into treprostinil by acidification.

21. (Previously Presented) The method of claim 1, wherein the quantity of the base addition salt corresponds to a large scale synthesis.

22. (Withdrawn) A pharmaceutical product prepared by the method of claim 21.

23. (New) The method of claim 20, wherein said converting produces a batch of treprostinil, which has a purity level of treprostinil of at least 99.7% as determined by HPLC.

24. (New) The method claim 23, wherein the batch contains at least 2.9 g of treprostinil.

25. (New) The method of claim 20, wherein said converting produces a batch of treprostinil, which has a purity level of treprostinil of at least 99.8% as determined by HPLC.

26. (New) The method claim 25, wherein the batch contains at least 2.9 g of treprostinil.

27. (New) The method claim 20, wherein the batch contains at least 2.9 g of treprostinil.

REMARKS

Applicants respectfully request reconsideration and allowance of the present application.

Status of Claims

Applicants have amended claim 1, without prejudice or disclaimer. Applicants reserve the right to file one or more continuing applications directed to any subject matter notwithstanding the present amendment. Support for the amended claim may be found throughout the specification as filed and, in particular, in paragraph 0046. No new matter has been added.

Applicants have added new claims 23-27. Support for the new claims may be found throughout the specification as filed, including paragraphs 0045-0046. No new matter has been added.

After the amendment, the pending claims include a) examined claims 1, 3-9 and 20-21; b) withdrawn claims 10-19 and 22; and c) new claims 23-27, which should be examined in the present application.

The Rejections Under 35 U.S.C. § 103(a)

Claims 1, 3-9 and 20-21 stand rejected as obvious over Phares et al. (U.S. Patent Application Publication No. 2005/0085540) in view of Aristoff (U.S. Patent No. 4,486,598). Applicants respectfully request reconsideration in light of the remarks below and the accompanying Rule 132 Declaration of Dr. Liang Guo ("Guo Declaration") providing comparative evidence.

The PTO has failed to establish a *prima facie* case of obviousness because the references relied upon by the examiner do not teach each and every limitation of the pending claims.

Phares does not teach "storing the collected base addition salt at ambient temperature, and preparing a pharmaceutical product comprising treprostinil or a treprostinil salt from the base addition salt after the storage," as recited in claim 1. The PTO acknowledges that Phares "fails to specifically recite the step of storing the base addition salt and a step of preparing a pharmaceutical product from said salt." Office Action at p. 3.

To remedy these deficiencies, the PTO interprets "the term 'storing' to mean a time period between preparation of treprostinil salt and its use in preparation of a pharmaceutical product." Thus, the PTO argues that the storing limitation is inherently met by Phares because "[i]t is inherent that some time elapses between preparation of a compound and its use in preparation of a pharmaceutical formulation." Office Action at p. 4.

Yet the PTO's interpretation of the term "storing" is too broad even under the broadest reasonable interpretation standard. Even under the broadest reasonable interpretation standard, the PTO may not erase the meaning of a step in a method claim that is tied to the preamble. The claim is directed to "preparing a pharmaceutical product." In the accompanying Guo Declaration, Dr. Liang Guo explains that a person of ordinary skill in the art would recognize that the term "stored" in the expression "crude treprostinil salts can be stored as raw material at ambient temperature" in paragraph 0046 of the specification as filed means stored for a period of at least three months. Guo Declaration at ¶ 6. Thus, "storing" in the context of "preparing a pharmaceutical product" would be understood by one of ordinary skill in the art to mean a period of at least three months. Based on this understanding of "storing," Phares clearly does not meet the storing element of claim 1. Moreover, Aristoff cannot remedy the deficiencies of Phares, and the PTO has not argued otherwise.

Storing treprostinil in the salt form provides unexpected advantages over storing treprostinil in the free acid form because treprostinil in the salt form is more stable at ambient temperature than free acid. Treprostinil in the free acid form is not stable at ambient temperature, such as 25°C:

> The anhydrous form is not stable at room temperature. Stability tests show that the anhydrous TREPROSTINIL is not stable at 25°C. and dimers formed upon standing. A larger amount of dimers can form at higher temperatures. However, dimer formation is negligible at 5°C. Therefore, anhydrous treprostinil must be refrigerated for storage and transport. In the past, treprostinil had to be refrigerated and shipped with ice packs to maintain low (2°C-8°C) temperatures.

See, e.g., U.S. patent no. 8,350,079 ("the '079 patent"), column 2, lines 58-65. The '079 patent provides experimental evidence of instability of treprostinil in the free acid form at the ambient temperature in the table presented in column 6, lines 50-63. Dr. Liang Guo reproduces this table in the Guo Declaration and explains that the table's data demonstrate that free acid treprostinil is not stable at ambient temperature because of significant formation of dimer defects, such as 750W93 and 751W93. Guo Declaration at ¶ 8. Due to such instability, free acid treprostinil is usually stored and transported at low temperatures, such as 2°C-8°C, in order to reduce for the formation of the dimer defects. Guo Declaration at ¶ 8.

Dr. Guo presents stability data at 25°C for several batches of treprostinil diethanolamine (Guo Declaration at ¶ 9), and upon comparing these data with the stability data for treprostinil in the free acid form, Dr. Guo concludes that "treprostinil diethanolamine is more stable than free acid treprostinil when stored at the ambient temperature because concentrations of dimer defects (750W93 and 751W93) grow in free acid treprostinil with the storage time, while in the treprostinil diethanolamine batches, concentrations of the dimer defects remain essentially below the detection level even after 6 months of storage." Guo Declaration at ¶ 10. Thus, Applicants request withdrawal of the rejection in view of superior stability at ambient temperature for treprostinil in a salt form compared to free acid treprostinil.

The rejection of claim 20 should be withdrawn for an additional reason. The cited references do not teach or suggest "converting the base addition salt after storage into treprostinil by acidification." On p. 5 of the Office Action, the PTO states that "Phares discloses that the prodrug itself does not have pharmacological activity. One skilled in the art would have found it

obvious that the salt back into the active." The PTO's use of "prodrug" apparently refers to the salt. Yet Phares discloses that the salt itself is the active ingredient, as shown by the examples employing it for use in an oral composition. One of ordinary skill in the art would therefore not be motivated to convert the salt back to free acid based upon Phares.

In sum, at least because of the reasons discussed above, Applicants request withdrawal of the rejection as directed to claim 20.

New claims 23-27

New claims 23-27 should be allowable at least because they depend on claim 1, which is allowable over the cited references for the reasons discussed above.

Concluding Remarks

Applicants believe that the application is in condition for allowance. Favorable reconsideration is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance prosecution.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date Aug. 11, 2015

By /Stephen B. Maebius/

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (415) 984-9810
Facsimile: (415) 434-4507

Stephen B. Maebius
Attorney for Applicants
Registration No. 35,264

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/933,623
Filing Date:	7/2/2013
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation Number:	6887

DECLARATION UNDER 37 C.F.R. § 1.132 OF DR. LIANG GUO

I, Liang Guo, do hereby declare:

1. I am Executive Vice President of Chemical R&D and Production, United Therapeutics Corporation. I understand that United Therapeutics Corporation owns U.S. patent application no. 13/933,623.

2. I am a U.S. citizen.

3. I have not received compensation for providing this declaration beyond my standard compensation as an employee of United Therapeutics Corporation. That compensation is in no way dependent on the content of the opinions expressed in this declaration.

4. I have a Ph.D. degree in chemistry from University of Illinois at Chicago and have worked continuously in the pharmaceutical and/or organic chemistry industry since

obtaining my Ph.D. My curriculum vitae, which is attached as Appendix A, provides additional details on my qualifications and experience related to chemistry and the pharmaceutical industry.

5. I have reviewed the Final Office Action dated March 19, 2015 ("Final Office Action") in the above-identified application and the cited references.

6. Paragraph 0046 of the above-identified application states that "crude treprostinil salts can be stored as raw material at ambient temperature." Based on my training and experience in the industry, a person working in the field of pharmaceutical chemistry would recognize that the term "stored" in this statement means stored for a period of at least three months. Appendix B provides U.S. Food and Drug Administration's (FDA's) Guidance for Industry on "Q1A(R2) Stability Testing of New Drug Substances and Products." According to this document, the minimal interval between two test points while establishing a stability profile of a stored drug substance is three months, see e.g. Appendix B, ¶ 2.1.6. In view of this information, a person working in the field of pharmaceutical chemistry would know that the term "stored" in the context of storing a drug substance to be used for preparing a pharmaceutical product means storing for at least three months.

7. Treprostinil diethanolamine salt is more stable than free acid treprostinil when stored at ambient temperature (25°C) based on a comparison of stability date for these two compounds.

8. Exemplary stability data for free acid treprostinil at 25°C is presented in the following Table from column 6 of U.S. patent no. 8,350,079:

Stability Data for Treprostinil (TREPROSTINIL) at 25° C.
Lot No. 01 A07002 (Anhydrous)

Test	Initial	3 months	6 months
Physical examination	White powder	White powder	White powder
Water (Karl Fischer)	0.4%	0.7%	0.8%
HPLC Assay			
Treprostinil	99.6%	98.1%	95.4%
750W93	0.2	1.2	1.5
751W93	0.3	0.9	1.1

750W93 is an ester dimer of treprostinil, 751W93 is a 3-hydroxy dimer of treprostinil. The data demonstrate that free acid treprostinil is not stable at ambient temperature over certain periods of time because of significant formation of dimer defects, such as 750W93 and 751W93. Due to such instability, free acid treprostinil is usually stored and transported at lower temperatures, such as 2°C-8°C, in order to reduce for the formation of the dimer impurities.

9. Exemplary stability data at 25°C for several batches of treprostinil diethanolamine is presented below:

A) Lot no. 02C08008.

Batch size 2,758 g.

Test	Initial	3 months	6 months
Visual Appearance	A white solid	A white solid	A white solid
Water	0.2%	0.2%	0.3%
Treprostinil Assay by HPLC	99.0%	99.4%	98.2%
750W93 by HPLC	< 0.05%	< 0.05%	< 0.05%
751W93 by HPLC	< 0.05%	< 0.05%	< 0.05%

B) Lot no. 02B12002.

Batch size 5,672 g.

Test	Initial	3 months	6 months
Visual Appearance	A white solid	A white solid	A white solid
Water	0.1%	0.1%	0.1%
Treprostinil Assay by HPLC	99.5%	98.9%	99.6%
750W93 by HPLC	ND	ND	ND
751W93 by HPLC	ND	ND	ND

C) Lot no. 02B11007

Batch size 5,580.24g.

Test	Initial	3 months	6 months
Visual Appearance	A white solid	A white solid	A white solid
Water	0.4%	0.2%	0.2%
Treprostinil Assay by HPLC	100.2%	99.6%	99.8%
750W93 by HPLC	ND	ND	ND
751W93 by HPLC	ND	ND	ND

D) Lot no. 02K10056

Batch size 4628g.

Test	Initial	3 months	6 months
Visual Appearance	A white solid	A white solid	A white solid
Water	0.1%	0.2%	0.1%
Treprostinil Assay by HPLC	100.5%	100.3%	100.2%
750W93 by HPLC	ND	ND	ND
751W93 by HPLC	ND	ND	ND

E) Lot no. 02D10016

Batch size 4628g.

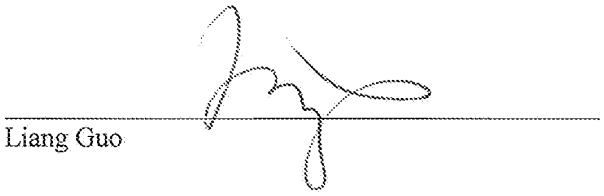
Test	Initial	3 months	6 months
Visual Appearance	A white solid	A white solid	A white solid
Water	0.2%	0.2%	0.1%
Treprostinil Assay by HPLC	99.7%	100.1%	99.6%
750W93 by HPLC	ND	ND	ND
751W93 by HPLC	ND	ND	ND

The data shown in this table was generated by United Therapeutics Corporation in the course of its business. The data were not generated for the purposes of this patent application or any other patent application. I was involved in both requesting these tests and reviewing their results, and I am familiar with how the data was generated.

10. The data above show that treprostinil diethanolamine is more stable than free acid treprostinil when stored at ambient temperature over certain periods of time because concentrations of dimer impurities (750W93 and 751W93) grow in free acid treprostinil with longer storage time, while in the treprostinil diethanolamine batches, concentrations of the dimer defects remain essentially below the detection level even after 6 months of storage.

11. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this ___4th_____ day of _____August_____, 2015.



Liang Guo

APPENDIX A

LIANG GUO, Ph. D.

2015-Present, EVP of Chemical R&D and Production, United Therapeutics, Silver Spring, MD

Responsible for the chemical R&D activities and the chemical API manufacturing.

2006-2014, Senior Vice President, Production, United Therapeutics, Silver Spring, MD

Responsible for the API (UT-15 and UT15C) manufacturing.

2000 -- 2006, Vice President, Production, United Therapeutics, Chicago, Illinois

Responsible for the API manufacturing.

1995 – 2000, Vice President, SynQuest, Inc., Chicago, Illinois

Responsible for all the activities in UT-15 bulk drug manufacturing.

Responsible for production regarding custom manufacturing.

Responsible for business development.

1991 – 1995, Production Manager, SynQuest, Inc., Chicago, Illinois

Directed the design and the synthesis of sphingolipid.

Directed the design and synthesis of squalamine and its analogs, the potential antibacterial drugs.

Designed and synthesized of Vitamin D metabolites as potential cancer prevention and therapeutic agents.

Developed a new method for the synthesis of Vitamin D metabolites and analogs.

Synthesized Vitamin D metabolites under GMP conditions for clinical trials as potential drugs for treatment of psoriasis and cancer.

Designed and synthesized radiolabeled Vitamin D metabolites for use in imaging Vitamin D receptors.

1987 – 1991 **Research Assistant, Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois**

Developed a novel method of intramolecular cyclopropanation by decomposition of iodonium ylides.

Application of the hypervalent iodine chemistry in the synthesis of Vitamin D A-ring synthon.

Application of the hypervalent iodine chemistry in the synthesis of prostaglandin E1.

A new method for the functionalization of bicyclic carbonyl compounds via hypervalent iodine chemistry.

Synthesis and functionalization of estrones and indoles ruthenium complexes.

Synthesis of high energy compounds.

EDUCATION:

MPM (Master of Project Management), 2005, Keller Graduate School, Chicago, Illinois.

MBA (Master of Business Administration), 2004, Keller Graduate School of Management, Chicago, Illinois.

Ph.D., Organic Chemistry, 1991, University of Illinois at Chicago, Chicago, Illinois.

M.S., Organic Chemistry, 1988, University of Illinois at Chicago, Chicago, Illinois.

APPENDIX B

Guidance for Industry

Q1A(R2) Stability Testing of New Drug Substances and Products

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2003
ICH

Revision 2

Guidance for Industry

Q1A(R2) Stability Testing of New Drug Substances and Products

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Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
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http://www.fda.gov/cder/guidance/index.htm

or

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Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm.
(Tel) Voice Information System at 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2003
ICH

Revision 2

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Contains Nonbinding Recommendations

Guidance for Industry[1]

Q1A(R2) Stability Testing of New Drug Substances and Products

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION (1) [2]

This guidance is the second revision of *Q1A Stability Testing of New Drug Substances and Products,* which was first published in September 1994 and revised in August 2001. The purpose of this revision is to harmonize the intermediate storage condition for zones I and II with the long-term condition for zones III and IV recommended in the ICH guidance *Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV.* The changes made in this second revision are listed in the attachment to this guidance.

A. Objectives of the Guidance (1.1)

This guidance is intended to define what stability data package for a new drug substance or drug product is sufficient for a registration application within the three regions of the European Union (EU), Japan, and the United States. It does not seek to address the testing for registration in or export to other areas of the world. The guidance exemplifies the core stability data package for new drug substances and products, but leaves sufficient flexibility to encompass the variety of different practical situations that may be encountered due to specific scientific considerations and characteristics of the materials being evaluated. Alternative approaches can be used when there are scientifically justifiable reasons.

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[1] This guidance was developed within the Expert Working Group (Quality) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document was endorsed by the ICH Steering Committee at *Step 4* of the ICH process, February 2003. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

[2] Arabic numbers reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process.

B. Scope of the Guidance (1.2)

The guidance addresses the information to be submitted in registration applications for new molecular entities and associated drug products. This guidance does not currently seek to cover the information to be submitted for abbreviated or abridged applications, variations, or clinical trial applications.

Specific details of the sampling and testing for particular dosage forms in their proposed container closures are not covered in this guidance.

Further guidance on new dosage forms and on biotechnological/biological products can be found in ICH guidances *Q1C Stability Testing for New Dosage Forms* and *Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*, respectively.

C. General Principles (1.3)

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity, and light, and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions.

The choice of test conditions defined in this guidance is based on an analysis of the effects of climatic conditions in the three regions of the EU, Japan, and the United States. The mean kinetic temperature in any part of the world can be derived from climatic data, and the world can be divided into four climatic zones, I-IV. This guidance addresses climatic zones I and II. The principle has been established that stability information generated in any one of the three regions of the EU, Japan, and the United States would be mutually acceptable to the other two regions, provided the information is consistent with this guidance and the labeling is in accord with national/regional requirements.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. GUIDANCE (2)

A. Drug Substance (2.1)

1. General (2.1.1)

Information on the stability of the drug substance is an integral part of the systematic approach to stability evaluation.

2. Stress Testing (2.1.2)

Stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of drug product involved.

Stress testing is likely to be carried out on a single batch of the drug substance. The testing should include the effect of temperatures (in 10°C increments (e.g., 50°C, 60°C) above that for accelerated testing), humidity (e.g., 75 percent relative humidity or greater) where appropriate, oxidation, and photolysis on the drug substance. The testing should also evaluate the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension. Photostability testing should be an integral part of stress testing. The standard conditions for photostability testing are described in ICH *Q1B Photostability Testing of New Drug Substances and Products*.

Examining degradation products under stress conditions is useful in establishing degradation pathways and developing and validating suitable analytical procedures. However, such examination may not be necessary for certain degradation products if it has been demonstrated that they are not formed under accelerated or long-term storage conditions.

Results from these studies will form an integral part of the information provided to regulatory authorities.

3. Selection of Batches (2.1.3)

Data from formal stability studies should be provided on at least three primary batches of the drug substance. The batches should be manufactured to a minimum of pilot scale by the same synthetic route as production batches and using a method of manufacture and procedure that simulates the final process to be used for production batches. The overall quality of the batches of drug substance placed on formal stability studies should be representative of the quality of the material to be made on a production scale.

Other supporting data can be provided.

4. Container Closure System (2.1.4)

The stability studies should be conducted on the drug substance packaged in a container closure system that is the same as or simulates the packaging proposed for storage and distribution.

5. Specification (2.1.5)

Specification, which is a list of tests, references to analytical procedures, and proposed acceptance criteria, is addressed in ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* and *Q6B*

Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Biotechnological/Biological Products. In addition, specification for degradation products in a drug substance is discussed in ICH *Q3A Impurities in New Drug Substances*.

Stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes. Validated stability-indicating analytical procedures should be applied. Whether and to what extent replication should be performed should depend on the results from validation studies.

6. Testing Frequency (2.1.6)

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the drug substance. For drug substances with a proposed retest period of at least 12 months, the frequency of testing at the long-term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed retest period.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that the results from accelerated studies are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is recommended.

7. Storage Conditions (2.1.7)

In general, a drug substance should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

The long-term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed retest period. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated, and, where appropriate, intermediate storage conditions for drug substances are detailed in the sections below. The general case should apply if the drug substance

is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

a. General case (2.1.7.1)

Study	Storage condition	Minimum time period covered by data at submission
Long-term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

* It is up to the applicant to decide whether long-term stability sturdies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.
** If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and *significant change* occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. Testing at the intermediate storage condition should include all tests, unless otherwise justified. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

Significant change for a drug substance is defined as failure to meet its specification.

b. Drug substances intended for storage in a refrigerator (2.1.7.2)

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

Data from refrigerated storage should be assessed according to the evaluation section of this guidance, except where explicitly noted below.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed retest period should be based on the real time data available at the long-term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition (e.g., during shipping or handling). This discussion can be supported, if appropriate, by further testing on a single batch of the drug substance for a period shorter than

3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a drug substance through 6 months when a significant change has occurred within the first 3 months.

c. Drug substances intended for storage in a freezer (2.1.7.3)

Study	Storage condition	Minimum time period covered by data at submission
Long-term	-20°C ± 5°C	12 months

For drug substances intended for storage in a freezer, the retest period should be based on the real time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for drug substances intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition (e.g., during shipping or handling).

d. Drug substances intended for storage below -20°C (2.1.7.4)

Drug substances intended for storage below -20°C should be treated on a case-by-case basis.

8. Stability Commitment (2.1.8)

When available long-term stability data on primary batches do not cover the proposed retest period granted at the time of approval, a commitment should be made to continue the stability studies postapproval to firmly establish the retest period.

Where the submission includes long-term stability data on three production batches covering the proposed retest period, a postapproval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

- If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue these studies through the proposed retest period.

- If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue these studies through the proposed retest period and to place additional production batches, to a total of at least three, on long-term stability studies through the proposed retest period.

- If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long-term stability studies through the proposed retest period.

The stability protocol used for long-term studies for the stability commitment should be the same as that for the primary batches, unless otherwise scientifically justified.

9. Evaluation (2.1.9)

The purpose of the stability study is to establish, based on testing a minimum of three batches of the drug substance and evaluating the stability information (including, as appropriate, results of the physical, chemical, biological, and microbiological tests), a retest period applicable to all future batches of the drug substance manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned retest period.

The data may show so little degradation and so little variability that it is apparent from looking at the data that the requested retest period will be granted. Under these circumstances, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

An approach for analyzing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95 percent, one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall retest period should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the real time data from the long-term storage condition beyond the observed range to extend the retest period can be undertaken at approval time if justified. This justification should be based, for example, on what is known about the mechanism of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size, and/or existence of supporting stability data. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

Any evaluation should cover not only the assay, but also the levels of degradation products and other appropriate attributes.

10. Statements/Labeling (2.1.10)

A storage statement should be established for the labeling in accordance with relevant national/regional requirements. The statement should be based on the stability evaluation of the drug substance. Where applicable, specific instructions should be provided, particularly for drug substances that cannot tolerate freezing. Terms such as *ambient conditions* or *room temperature* should be avoided.

A retest period should be derived from the stability information, and a retest date should be displayed on the container label if appropriate.

B. Drug Product (2.2)

1. General (2.2.1)

The design of the formal stability studies for the drug product should be based on knowledge of the behavior and properties of the drug substance, results from stability studies on the drug substance, and experience gained from clinical formulation studies. The likely changes on storage and the rationale for the selection of attributes to be tested in the formal stability studies should be stated.

2. Photostability Testing (2.2.2)

Photostability testing should be conducted on at least one primary batch of the drug product if appropriate. The standard conditions for photostability testing are described in ICH Q1B.

3. Selection of Batches (2.2.3)

Data from stability studies should be provided on at least three primary batches of the drug product. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. Two of the three batches should be at least pilot scale batches, and the third one can be smaller if justified. Where possible, batches of the drug product should be manufactured by using different batches of the drug substance.

Stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing is applied.

Other supporting data can be provided.

4. Container Closure System (2.2.4)

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and

container label). Any available studies carried out on the drug product outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

5. Specification (2.2.5)

Specification, which is a list of tests, references to analytical procedures, and proposed acceptance criteria, including the concept of different acceptance criteria for release and shelf life specifications, is addressed in ICH Q6A and Q6B. In addition, specification for degradation products in a drug product is addressed in ICH *Q3B Impurities in New Drug Products*.

Stability studies should include testing of those attributes of the drug product that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content (e.g., antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system). Analytical procedures should be fully validated and stability indicating. Whether and to what extent replication should be performed will depend on the results of validation studies.

Shelf life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences between the shelf life and release acceptance criteria based on the stability evaluation and the changes observed on storage. Any differences between the release and shelf life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated during drug development on the product in its final formulation (except for preservative concentration) intended for marketing. A single primary stability batch of the drug product should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf life acceptance criteria for preservative content.

6. Testing Frequency (2.2.6)

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the drug product. For products with a proposed shelf life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is recommended.

Reduced designs (i.e., matrixing or bracketing), where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied if justified.

7. Storage Conditions (2.2.7)

In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

Stability testing of the drug product after constitution or dilution, if applicable, should be conducted to provide information for the labeling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in-use period on primary batches as part of the formal stability studies at initial and final time points, and if full shelf life, long-term data will not be available before submission, at 12 months or the last time point for which data will be available. In general, this testing need not be repeated on commitment batches.

The long-term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated, and, where appropriate, intermediate storage conditions for drug products are detailed in the sections below. The general case should apply if the drug product is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

a. General case (2.2.7.1)

Study	Storage condition	Minimum time period covered by data at submission
Long-term*	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

* It is up to the applicant to decide whether long-term stability sturdies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.
** If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are condcuted at 25°C ± 2°C/60% RH ± 5% RH and *significant change* occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

In general, *significant change* for a drug product is defined as one or more of the following (as appropriate for the dosage form):

- A 5 percent change in assay from its initial value, or failure to meet the acceptance criteria for potency when using biological or immunological procedures
- Any degradation product's exceeding its acceptance criterion
- Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., color, phase separation, resuspendibility, caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions.
- Failure to meet the acceptance criterion for pH
- Failure to meet the acceptance criteria for dissolution for 12 dosage units

b. Drug products packaged in impermeable containers (2.2.7.2)

Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.

c. Drug products packaged in semipermeable containers (2.2.7.3)

Aqueous-based products packaged in semipermeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below. Ultimately, it should be demonstrated that aqueous-based drug products stored in semipermeable containers can withstand low relative humidity environments. Other comparable approaches can be developed and reported for nonaqueous, solvent-based products.

Study	Storage condition	Minimum time period covered by data at submission
Long-term *	25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH	12 months
Intermediate**	30°C ± 2°C/65% RH ± 5% RH	6 months
Accelerated	40°C ± 2°C/not more than (NMT) 25% RH	6 months

* It is up to the applicant to decide whether long-term stability sturdies are performed at 25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH.
** If 30°C ± 2°C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition.

When long-term studies are conducted at 25°C ± 2°C/40% RH ± 5% RH and significant change other than water loss occurs during the 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be performed, as described under the general case, to evaluate the temperature effect at 30°C. A significant change in water loss alone at the accelerated storage condition does not necessitate testing at the intermediate storage condition. However, data should be provided to demonstrate that the drug product will not have significant water loss throughout the proposed shelf life if stored at 25°C and the reference relative humidity of 40 percent RH.

A 5 percent loss in water from its initial value is considered a significant change for a product packaged in a semipermeable container after an equivalent of 3 months' storage at 40°C/NMT 25 percent RH. However, for small containers (1 mL or less) or unit-dose products, a water loss of 5 percent or more after an equivalent of 3 months' storage at 40°C/NMT 25 percent RH may be appropriate if justified.

An alternative approach to studying at the reference relative humidity as recommended in the table above (for either long-term or accelerated testing) is performing the stability studies under higher relative humidity and deriving the water loss at the reference relative humidity through calculation. This can be achieved by experimentally determining the permeation coefficient for the container closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation

coefficient for a container closure system can be experimentally determined by using the worst case scenario (e.g., the most diluted of a series of concentrations) for the proposed drug product.

Example of an approach for determining water loss:

For a product in a given container closure system, container size, and fill, an appropriate approach for deriving the water loss rate at the reference relative humidity is to multiply the water loss rate measured at an alternative relative humidity at the same temperature by a water loss rate ratio shown in the table below. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated.

For example, at a given temperature (e.g., 40°C), the calculated water loss rate during storage at NMT 25 percent RH is the water loss rate measured at 75 percent RH multiplied by 3.0, the corresponding water loss rate ratio.

Alternative relative humidity	**Reference relative humidity**	**Ratio of water loss rates at a given temperature**
60% RH	25% RH	1.9
60% RH	40% RH	1.5
65% RH	35% RH	1.9
75% RH	25% RH	3.0

Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can also be used.

d. Drug products intended for storage in a refrigerator (2.2.7.4)

Study	**Storage condition**	**Minimum time period covered by data at submission**
Long-term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

If the drug product is packaged in a semipermeable container, appropriate information should be provided to assess the extent of water loss.

Data from refrigerated storage should be assessed according to the evaluation section of this guidance, except where explicitly noted below.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available from the long-term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition (e.g., during shipment and handling). This discussion can be supported, if appropriate, by further testing on a single batch of the drug product for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a product through 6 months when a significant change has occurred within the first 3 months.

e. Drug products intended for storage in a freezer (2.2.7.5)

Study	Storage condition	Minimum time period covered by data at submission
Long-term	-20°C ± 5°C	12 months

For drug products intended for storage in a freezer, the shelf life should be based on the real time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for drug products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition.

f. Drug products intended for storage below -20°C (2.2.7.6)

Drug products intended for storage below -20°C should be treated on a case-by-case basis.

8. Stability Commitment (2.2.8)

When available long-term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies postapproval to firmly establish the shelf life.

Where the submission includes long-term stability data from three production batches covering the proposed shelf life, a postapproval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

- If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue the long-term studies through the proposed shelf life and the accelerated studies for 6 months.

- If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue the long-term studies through the proposed shelf life and the accelerated studies for 6 months, and to place additional production batches, to a total of at least three, on long-term stability studies through the proposed shelf life and on accelerated studies for 6 months.

- If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long-term stability studies through the proposed shelf life and on accelerated studies for 6 months.

The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

Where intermediate testing is called for by a significant change at the accelerated storage condition for the primary batches, testing on the commitment batches can be conducted at either the intermediate or the accelerated storage condition. However, if significant change occurs at the accelerated storage condition on the commitment batches, testing at the intermediate storage condition should also be conducted.

9. Evaluation (2.2.9)

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including particular attributes of the dosage form (e.g., dissolution rate for solid oral dosage forms).

The purpose of the stability study is to establish, based on testing a minimum of three batches of the drug product, a shelf life and label storage instructions applicable to all future batches of the drug product manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf life.

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

An approach for analyzing data of a quantitative attribute that is expected to change with time is to determine the time at which the 95 percent one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of the degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the real time data from the long-term storage condition beyond the observed range to extend the shelf life can be undertaken at approval time if justified. This justification should be based, for example, on what is known about the mechanisms of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size, and/or existence of supporting stability data. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

Any evaluation should consider not only the assay but also the degradation products and other appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of the mass balance and different stability and degradation performance.

10. Statements/Labeling (2.2.10)

A storage statement should be established for the labeling in accordance with relevant national/regional requirements. The statement should be based on the stability evaluation of the drug product. Where applicable, specific instruction should be provided, particularly for drug products that cannot tolerate freezing. Terms such as *ambient conditions* or *room temperature* should be avoided.

There should be a direct link between the label storage statement and the demonstrated stability of the drug product. An expiration date should be displayed on the container label.

GLOSSARY (3)

The following definitions are provided to facilitate interpretation of the guidance.

Accelerated testing: Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long-term stability studies, can be used to assess longer term chemical effects at nonaccelerated conditions and to evaluate the effect of short-term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

Bracketing: The design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, package size) are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container closure system.

Climatic zones: The four zones in the world that are distinguished by their characteristic, prevalent annual climatic conditions. This is based on the concept described by W. Grimm (*Drugs Made in Germany*, 28:196-202, 1985 and 29:39-47, 1986).

Commitment batches: Production batches of a drug substance or drug product for which the stability studies are initiated or completed postapproval through a commitment made in the registration application.

Container closure system: The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system.

Dosage form: A pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.

Drug product: The dosage form in the final immediate packaging intended for marketing.

Drug substance: The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.

Excipient: Anything other than the drug substance in the dosage form.

Expiration date: The date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf life specification, if stored under defined conditions, and after which it must not be used.

Formal stability studies: Long-term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the retest period of a drug substance or the shelf life of a drug product.

Impermeable containers: Containers that provide a permanent barrier to the passage of gases or solvents (e.g., sealed aluminum tubes for semi-solids, sealed glass ampoules for solutions).

Intermediate testing: Studies conducted at 30°C/65% RH and designed to moderately increase the rate of chemical degradation or physical changes for a drug substance or drug product intended to be stored long-term at 25°C.

Long-term testing: Stability studies under the recommended storage condition for the retest period or shelf life proposed (or approved) for labeling.

Mass balance: The process of adding together the assay value and levels of degradation products to see how closely these add up to 100 percent of the initial value, with due consideration of the margin of analytical error.

Matrixing: The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems.

Mean kinetic temperature: A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation.

When establishing the mean kinetic temperature for a defined period, the formula of J. D. Haynes *(J. Pharm. Sci.,* 60:927-929, 1971) can be used.

New molecular entity: An active pharmaceutical substance not previously contained in any drug product registered with the national or regional authority concerned. A new salt, ester, or noncovalent bond derivative of an approved drug substance is considered a new molecular entity for the purpose of stability testing under this guidance.

Pilot scale batch: A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For

solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is larger.

Primary batch: A batch of a drug substance or drug product used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf life, respectively. A primary batch of a drug substance should be at least a pilot scale batch. For a drug product, two of the three batches should be at least pilot scale batch, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch.

Production batch: A batch of a drug substance or drug product manufactured at production scale by using production equipment in a production facility as specified in the application.

Retest date: The date after which samples of the drug substance should be examined to ensure that the material is still in compliance with the specification and thus suitable for use in the manufacture of a given drug product.

Retest period: The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be retested for compliance with the specification and then used immediately. A batch of drug substance can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For most biotechnological/biological substances known to be labile, it is more appropriate to establish a shelf life than a retest period. The same may be true for certain antibiotics.

Semipermeable containers: Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by absorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial pressure gradient. Examples of semipermeable containers include plastic bags and semirigid, low-density polyethylene (LDPE) pouches for large volume parenterals (LVPs), and LDPE ampoules, bottles, and vials.

Shelf life (also referred to as expiration dating period): The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

Specification: See ICH Q6A and Q6B.

Specification, Release: The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug product at the time of its release.

Specification, Shelf life: The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug substance throughout its retest period, or that a drug product should meet throughout its shelf life.

Storage condition tolerances: The acceptable variations in temperature and relative humidity of storage facilities for formal stability studies. The equipment should be capable of controlling the storage condition within the ranges defined in this guidance. The actual temperature and humidity (when controlled) should be monitored during stability storage. Short-term spikes due to opening of doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be addressed and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effect assessed.

Stress testing (drug substance): Studies undertaken to elucidate the intrinsic stability of the drug substance. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

Stress testing (drug product): Studies undertaken to assess the effect of severe conditions on the drug product. Such studies include photostability testing (see ICH Q1B) and specific testing of certain products (e.g., metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

Supporting data: Data, other than those from formal stability studies, that support the analytical procedures, the proposed retest period or shelf life, and the label storage statements. Such data include (1) stability data on early synthetic route batches of drug substance, small-scale batches of materials, investigational formulations not proposed for marketing, related formulations, and product presented in containers and closures other than those proposed for marketing; (2) information regarding test results on containers; and (3) other scientific rationales.

REFERENCES (4)[3]

ICH Q1B Photostability Testing of New Drug Substances and Products

ICH Q1C Stability Testing for New Dosage Forms

ICH Q3A Impurities in New Drug Substances

ICH Q3B Impurities in New Drug Products

ICH Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products

ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

ICH Q6B Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Biotechnological/Biological Products

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at http://www.fda.gov/cder/guidance/index.htm

ATTACHMENT
List of Revision 2 Changes

The revisions to this *Q1A* guidance result from adoption of the ICH guidance *Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV*. The following changes were made.

1. The intermediate storage condition has been changed from 30°C ± 2°C/60% RH ± 5% RH to 30°C ± 2°C/65% RH ± 5% RH in the following sections:

   - II.A.7.a (2.1.7.1) Drug Substance - Storage Conditions - General case
   - II.B.7.a (2.2.7.1) Drug Product - Storage Conditions - General case
   - II.B.7.c (2.2.7.3) Drug products packaged in semipermeable containers
   - Glossary (3) *Intermediate testing*

2. 30°C ± 2°C/65% RH ± 5% RH has been added as a suitable alternative long-term storage condition to 25°C ± 2°C/60% RH ± 5% in the following sections:

   - II.A.7.a (2.1.7.1) Drug Substance - Storage Conditions - General case
   - II.B.7.a (2.2.7.1) Drug Product - Storage Conditions - General case

3. 30°C ± 2°C/35% RH ± 5% RH has been added as a suitable alternative long-term storage condition to 25°C ± 2°C/40% RH ± 5% and the corresponding example for the ratio of water-loss rates has been included in the following section:

   - II.B.7.c (2.2.7.3) Drug products packaged in semipermeable containers

Midstream switch of the intermediate storage condition from 30°C ± 2°C/60% RH ± 5% RH to 30°C ± 2°C/65% RH ± 5% RH can be appropriate provided that the respective storage conditions and the date of the switch are clearly documented and stated in the registration application.

It is recommended that registration applications contain data from complete studies at the intermediate storage condition 30°C ± 2°C/65% RH ± 5% RH, if applicable, by three years after the date of publication of this revised guideline in the respective ICH tripartite region.

Electronic Patent Application Fee Transmittal	
Application Number:	13933623
Filing Date:	02-Jul-2013
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Stephen Bradford Maebius/Jasmine Bibbs
Attorney Docket Number:	080618-1256
Filed as Large Entity	
Filing Fees for Utility under 35 USC 111(a)	

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in Excess of 20	1202	5	80	400
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Extension - 2 months with $200 paid	1252	1	400	400
Miscellaneous:				
		Total in USD ($)		**800**

Electronic Acknowledgement Receipt	
EFS ID:	23178994
Application Number:	13933623
International Application Number:	
Confirmation Number:	6887
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Stephen Bradford Maebius/Jasmine Bibbs
Filer Authorized By:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1256
Receipt Date:	11-AUG-2015
Filing Date:	02-JUL-2013
Time Stamp:	16:19:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$800
RAM confirmation Number	2823
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		080618-1256ResptoFinal.pdf	134980 dd068b80731bf9743f2c4cdc34483460bae4f7c4	yes	9
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Response After Final Action		1	1	
	Claims		2	4	
	Applicant Arguments/Remarks Made in an Amendment		5	9	
Warnings:					
Information:					
2	Affidavit-traversing rejectns or objectns rule 132	080618-1256ExecutedLiangGuoDeclaration.pdf	6117198 aca24a23916a8f4c53cc7b84422e787079430296	no	10
Warnings:					
Information:					
3	Affidavit-traversing rejectns or objectns rule 132	080618-1256AppendixB.pdf	187379 ae7217b7234a3e5b10a0a14f21225f6ea5296521	no	25
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	32932 20a9c4a0eeaf60a1080ddb31c6f795ae3e3c5cd4	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	6472489		

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 (09-11)
Approved for use through 1/31/2014. 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 13/933,623	Filing Date 07/02/2013	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	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 $310 ($155 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	

APPLICATION AS AMENDED – PART II

AMENDMENT	08/11/2015	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 26	Minus	** 21	= 5	X $80 =	400
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**400**

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

LIE
/KIM DOWNING/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

22428 7590 08/27/2015

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

EXAMINER	
VALENROD, YEVGENY	
ART UNIT	PAPER NUMBER
1672	

DATE MAILED: 08/27/2015

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/933,623	07/02/2013	Hitesh Batra	080618-1256	6887

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	11/27/2015

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 02/11)

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

22428 7590 08/27/2015
Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/933,623	07/02/2013	Hitesh Batra	080618-1256	6887

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	11/27/2015

EXAMINER	ART UNIT	CLASS-SUBCLASS
VALENROD, YEVGENY	1672	562-466000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29 — NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27 — NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status. — NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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.
13/933,623	07/02/2013	Hitesh Batra	080618-1256	6887

22428 7590 08/27/2015

Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

EXAMINER	
VALENROD, YEVGENY	

ART UNIT	PAPER NUMBER
1672	

DATE MAILED: 08/27/2015

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	13/933,623	BATRA ET AL.	
	Examiner	Art Unit	
	YEVGENY VALENROD	1672	

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

(1) *YEVGENY VALENROD*. (3)_____.

(2) *Alexei Saprigin*. (4)_____.

Date of Interview: *20 August 2015*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *10-19 and 22*.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

It was agreed that the withdrawn clames will be canceled by the Examiners amendment. Election was made without traverse in the reply filed on 1/26/15 .

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/YEVGENY VALENROD/ Primary Examiner, Art Unit 1672	

Notice of Allowability	Application No. 13/933,623	Applicant(s) BATRA ET AL.	
	Examiner YEVGENY VALENROD	Art Unit 1672	AIA (First Inventor to File) Status No

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

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *reply filed on 8/11/15*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1,3-9,20,21 and 23-27*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *8/20/15* .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1672

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

This application is in condition for allowance except for the presence of claims 10-19 and 22 directed to a pharmaceutical composition non-elected without traverse. Accordingly, claims 10-19 and 22 have been cancelled.

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.

The application has been amended as follows:

IN THE CLAIMS:

Claims 10-19 and 22 have been canceled.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to YEVGENY VALENROD whose telephone number is (571)272-9049. The examiner can normally be reached on mon-fri 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on 5712722919. 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.

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1672

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	13/933,623	BATRA ET AL.	
	Examiner	Art Unit	
	YEVGENY VALENROD	1672	

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

(1) *YEVGENY VALENROD*. (3)_____.

(2) *Alexei Saprigin*. (4)_____.

Date of Interview: *20 August 2015*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *10-19 and 22*.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

It was agreed that the withdrawn clames will be canceled by the Examiners amendment. Election was made without traverse in the reply filed on 1/26/15 .

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/YEVGENY VALENROD/ Primary Examiner, Art Unit 1672	

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13933623	BATRA ET AL.
	Examiner	Art Unit
	YEVEGENY VALENROD	1672

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	12/05/2014	03/11/2015	08/21/2015						
1	1	✓	✓	=						
	2	✓	-	-						
2	3	✓	✓	=						
3	4	✓	✓	=						
4	5	✓	✓	=						
5	6	✓	✓	=						
6	7	✓	✓	=						
7	8	✓	✓	=						
8	9	✓	✓	=						
	10	N	N	-						
	11	N	N	-						
	12	N	N	-						
	13	N	N	-						
	14	N	N	-						
	15	N	N	-						
	16	N	N	-						
	17	N	N	-						
	18	N	N	-						
	19	N	N	-						
9	20		✓	=						
10	21		✓	=						
	22		N	-						
11	23			=						
12	24			=						
13	25			=						
14	26			=						
15	27			=						

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1	("6765117").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/08/21 09:26
L2	1	("8497393").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/08/21 09:26
L3	1	("7999007").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/08/21 09:26
L4	1	("8653137").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/08/21 09:26
L5	1	("8658694").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/08/21 09:26
L6	23	((Hitesh) near2 (Batra)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2015/08/21 09:26
L7	17	((Sudersan) near2 (Tuladhar)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2015/08/21 09:26
L8	26	((Raju) near2 (Penmasta)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2015/08/21 09:26
L9	230	((David) near2 (Walsh)).INV.	US-PGPUB; USPAT; USOCR	OR	ON	2015/08/21 09:26
L10	253	L6 or L7 or L8 or L9	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26
L11	19	L10 and treprostinil	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26
L12	9	L11 and (base adj addition)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26

EAST Search History (Prior Art)

L13	1	("20020173672").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/08/21 09:26
L14	1	("20050085540").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/08/21 09:26
L15	187	treprostinil same (sodium or potassium) same salt	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26
L16	4	L15 same crystal	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26
L17	8	L15 same crystallization	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26
L18	1	("4486598").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/08/21 09:26
L19	1	("4306075").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/08/21 09:26
L20	40	treprostinil same (sodium adj hydroxide)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26
L21	6	L20 same (ethanol or methaol)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26
L22	34	L20 not L21	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26

EAST Search History (Prior Art)

L23	19	L22 same (crystal or crystallized or solid or crystallization)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26
L24	167	treprostinil adj sodium	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26
L25	16	L24 same (sodium adj hydroxide)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26
L26	15	L25 not L23	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26
L27	6	treprostinil same (sodium adj hydroxide) same salt	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26
L28	40	treprostinil same (sodium adj hydroxide)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26
L29	11	treprostinil same (potassium adj hydroxide)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26
L30	48	L28 or L29	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26

EAST Search History (Prior Art)

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L33	23	L31 not L25	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26
L34	0	L32 not L12	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26
L35	21	L33 not L12	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26
L36	858	(562/466).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/08/21 09:26
L37	28	L36 and treprostinil	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26
L38	495	L36 and (sodium same salt)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26
L39	22	L37 and (sodium same salt)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26

EAST Search History (Prior Art)

L40	1	("20040265238").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2015/08/21 09:26
L41	0	remodulin same crystallization	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:26
L42	22	c07c405/0075.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:27
L43	562	c07c51/08.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:27
L44	1948	c07c51/412.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:27
L45	854	c07c213/08.cpc.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:27
L46	3323	l45 or l44 or l43 or l42	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:28
L47	9	l46 and l10	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2015/08/21 09:28

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp

EAST Search History (Interference)

L48	0	c07c405/0075.cpc.	UPAD	OR	ON	2015/08/21 09:28
L49	0	c07c51/08.cpc.	UPAD	OR	ON	2015/08/21 09:29
L50	0	c07c51/412.cpc.	UPAD	OR	ON	2015/08/21 09:29
L51	0	c07c213/08.cpc.	UPAD	OR	ON	2015/08/21 09:29
L52	0	(562/466).CCLS.	UPAD	OR	OFF	2015/08/21 09:29

OK TO ENTER: /YV/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	13/933,623
Filing Date:	7/2/2013
Examiner:	Yevgeny Valenrod
Art Unit:	1672
Confirmation Number:	6887

REPLY UNDER 37 C.F.R. § 1.116

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

Commissioner:

This paper responds to the outstanding Final Office Action dated March 19, 2015.

Amendments to the Claims are reflected in the listing of claims, which begins on page 2 of this document.

Remarks begin on page 5 of this document.

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13933623	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1672

CPC						
Symbol					**Type**	**Version**
C07C		405	/	0075	F	2013-01-01
C07C		51	/	08	I	2013-01-01
C07C		51	/	412	I	2013-01-01
C07C		213	/	08	I	2013-01-01
C07C		51	/	41	I	2013-01-01
A01N		37	/	10	A	2013-01-01
C07C		39	/	12	A	2013-01-01
C07C		39	/	17	A	2013-01-01
C07C		59	/	60	A	2013-01-01
C07C		59	/	72	A	2013-01-01
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			/			
			/			
			/			
			/			

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
C07C		51	/	08	I	1	1	2013-01-01
C07C		59	/	72	I	1	2	2013-01-01
C07C		51	/	412	I	2	1	2013-01-01
C07C		59	/	72	I	2	2	2013-01-01

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	15	
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672	08/21/2015	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13933623	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1672

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION	
CLASS	SUBCLASS	CLAIMED	NON-CLAIMED
562	466	C 0 7 C 51 / 08 (2006.01.01)	

CROSS REFERENCE(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	15	
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672	08/21/2015	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13933623	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1672

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1														
2	3														
3	4														
4	5														
5	6														
6	7														
7	8														
8	9														
9	20														
10	21														
11	23														
12	24														
13	25														
14	26														
15	27														

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 15	
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672 (Primary Examiner)	08/21/2015 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13933623	BATRA ET AL.
	Examiner	Art Unit
	YEVEGENY VALENROD	1672

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST	8/21/2015	YV
Inventor	8/21/2015	YV

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
562	466	8/21/2015	YV
C07C	405/0075; 51/08; 51/412; 213/08	8/21/2015	YV

	/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1672

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

22428 7590 08/27/2015
Foley & Lardner LLP
3000 K STREET N.W.
SUITE 600
WASHINGTON, DC 20007-5109

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/933,623	07/02/2013	Hitesh Batra	080618-1256	6887

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	11/27/2015

EXAMINER	ART UNIT	CLASS-SUBCLASS
VALENROD, YEVGENY	1672	562-466000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 Foley & Lardner LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: United Therapeutics Corporation
(B) RESIDENCE: (CITY and STATE OR COUNTRY): Silver Spring, MD

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☒ Payment by credit card. Form PTO-2038 is attached.
☒ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 19-0741 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ Applicant certifying micro entity status. See 37 CFR 1.29
NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
☐ Applicant asserting small entity status. See 37 CFR 1.27
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
☐ Applicant changing to regular undiscounted fee status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date 8/27/2015
Typed or printed name Stephen B. Maebius Registration No. 35,264

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Electronic Patent Application Fee Transmittal	
Application Number:	13933623
Filing Date:	02-Jul-2013
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1256
Filed as Large Entity	
Filing Fees for Utility under 35 USC 111(a)	

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	1501	1	960	960

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**960**

Electronic Acknowledgement Receipt	
EFS ID:	23330991
Application Number:	13933623
International Application Number:	
Confirmation Number:	6887
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Stephen Bradford Maebius/Karen Walker
Filer Authorized By:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1256
Receipt Date:	27-AUG-2015
Filing Date:	02-JUL-2013
Time Stamp:	16:18:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$960
RAM confirmation Number	2868
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	IFTM.pdf	125393 f32469217077bc8b78a7f9ce3167efc36a8668ab	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30656 14748bab89272e169bab234aabf1de6d2b9acb28	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	156049		

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.

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Alexandria, Virginia 22313-1450
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/933,623	10/13/2015	9156786	080618-1256	6887

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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 46 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.

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APPLICATION NUMBER	PATENT NUMBER	GROUP ART UNIT	REQUEST ID
13/933,623	9156786	1672	102655

PAIR Correspondence Address/Fee Address Change

The following fields have been changed to Customer Number 166905 on 01/03/2020 via Private PAIR in view of the certification copied below that authorized the change.

- Correspondence Address

The address for Customer Number 166905 is:
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I certify, in accordance with 37 CFR 1.4(d)(4) that I am:

An attorney or Agent of Record registered to practice before the Patent and Trademark Office who has been given power of attorney in this application

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