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

Filing Date: 12/12/2008

Examiner: Unassigned

Art Unit: Unassigned

UTILITY PATENT APPLICATION TRANSMITTAL

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

Sir:

Transmitted herewith for filing under 37 C.F.R. § 1.53(b) is the nonprovisional utility patent application of:

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

Enclosed are:

[X] Description, Claims, and Abstract (27 pages).

[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**
27	x	75%	21

The filing fee is calculated below:

	Number Filed		**Included in Basic Fee**		**Extra**		Rate		Fee Totals
Basic Filing Fee							$330.00	=	$330.00
Search Fee							$540.00		$540.00
Examination Fee							$220.00		$220.00
Size Fee	21	-	100	= 0		x	$270.00		$0.00
Total Claims:	19	-	20	= 0		x	$52.00	=	$0.00
Independent:	2	-	3	= 0		x	$220.00	=	$0.00
If any Multiple Dependent Claim(s) present:						+	$390.00	=	$0.00
Surcharge under 37 CFR 1.16(f) for late filing of Executed Declaration and late payment of Basic Filing Fee						+	$130.00	=	$130.00
							SUBTOTAL:	=	$1220.00
[X]							Small Entity Fees Apply (subtract ½ of above):	=	$610.00
							Basic Filing Fee Reduction for Filing via EFS-Web		$83.00
							TOTAL FILING FEE:	=	$527.00
Assignment Recordation Fee:						+		=	$0.00
Processing Fee under 37 CFR 1.17(i) for Late Filing of English Translation of Application:						+	$130.00	=	
TOTAL FEE								=	$527.00

The required filing fees are not enclosed but will be submitted in response to the Notice to File Missing Parts of Application.

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

Respectfully submitted,

Date December 15, 2008

By _____

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

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application 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, 6,809,223 and 6,756,117 Their teachings are incorporated by reference to show how to practice the embodiments of the present invention.

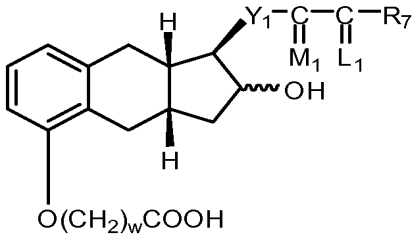
[0005] U.S. Patent No. 5,153,222 describes use of treprostinil for treatment of pulmonary hypertension. Treprostinil is approved for the intravenous as well as subcutaneous route, the latter avoiding septic events associated with continuous intravenous catheters. U.S. patents Nos. 6,521,212 and 6,756,033 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

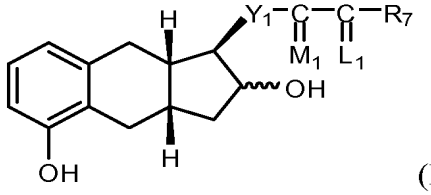
[0007] The present invention provides in one embodiment a process for the preparation of a compound of formula I, hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.



(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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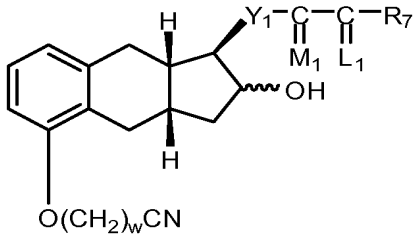


(III)

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

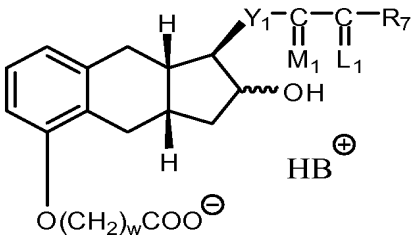
(4) 3-thienyloxymethyl;

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,

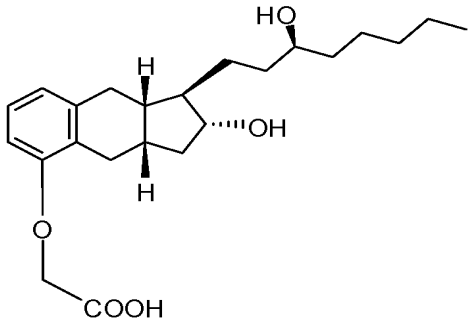
(c) contacting the product of step (b) with a base B to for a salt of formula I_s



(I_s)

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

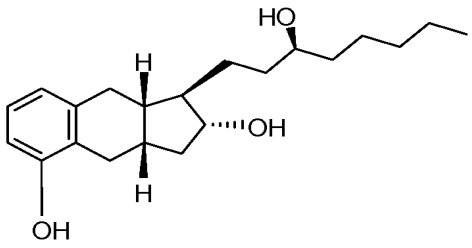
[0009] The present invention provides in another embodiment a process for the preparation of a compound of formula IV.



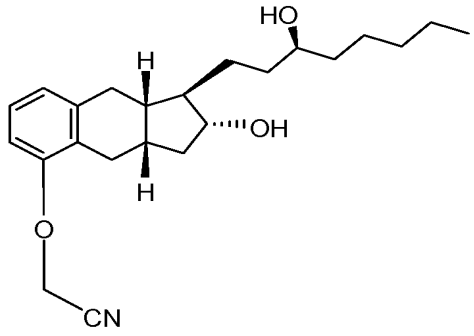
(IV)

[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,



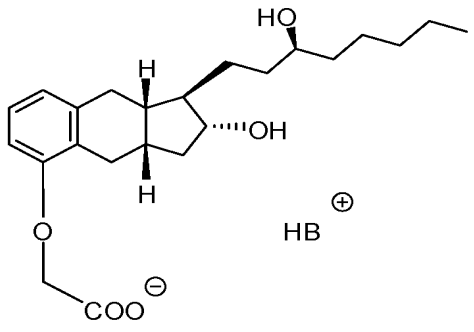
(V)



(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.

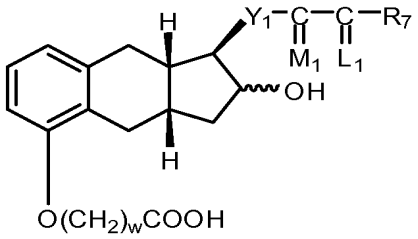
[0021] "Pharmaceutically acceptable salts" mean salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with organic and inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen 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.

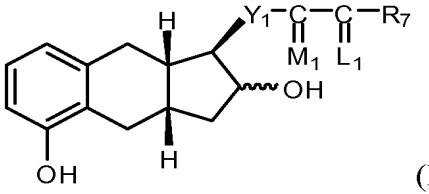
[0024] One embodiment of the present invention is a process for the preparation of a compound of formula I, or a hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.



(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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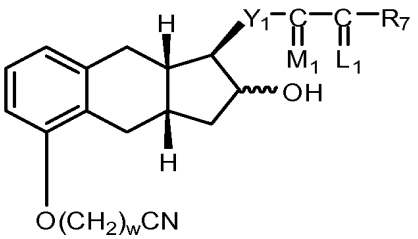


(III)

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

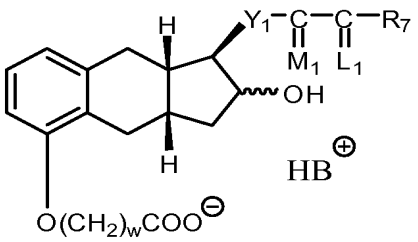
(4) 3-thienyloxymethyl;

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

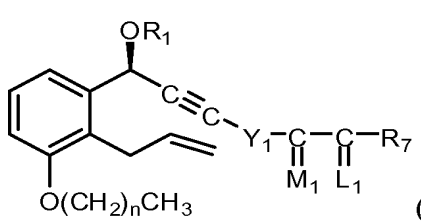


(I_s)

(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.



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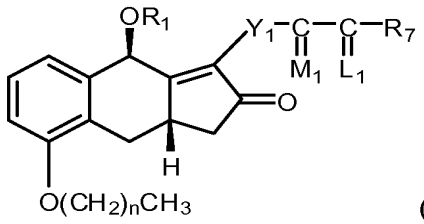
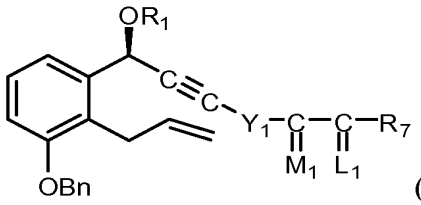


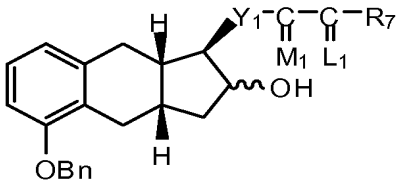
(XI)

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.

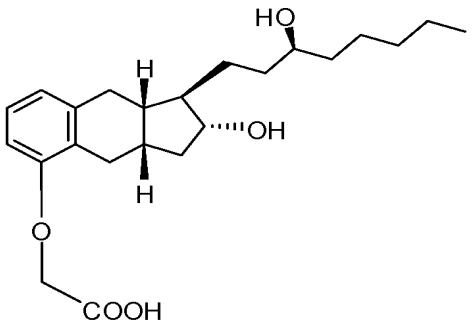


(XII)



(XIII)

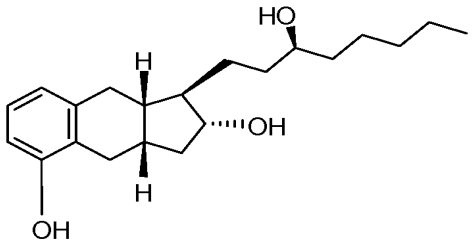
[0029] One embodiment of the present invention is a process for the preparation of a compound having formula IV, or a hydrate, solvate, or pharmaceutically acceptable salt thereof.



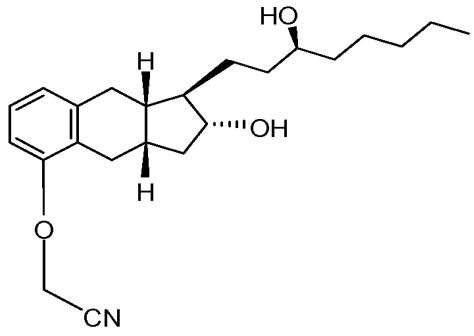
(IV)

[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,



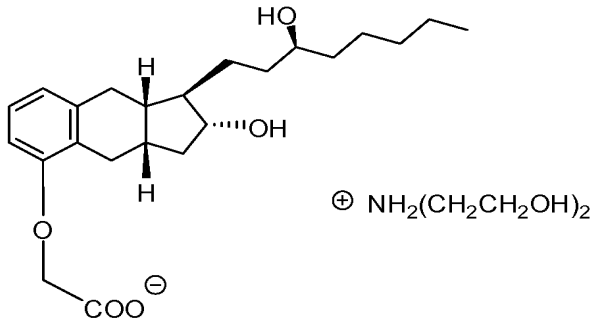
(V)



(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.

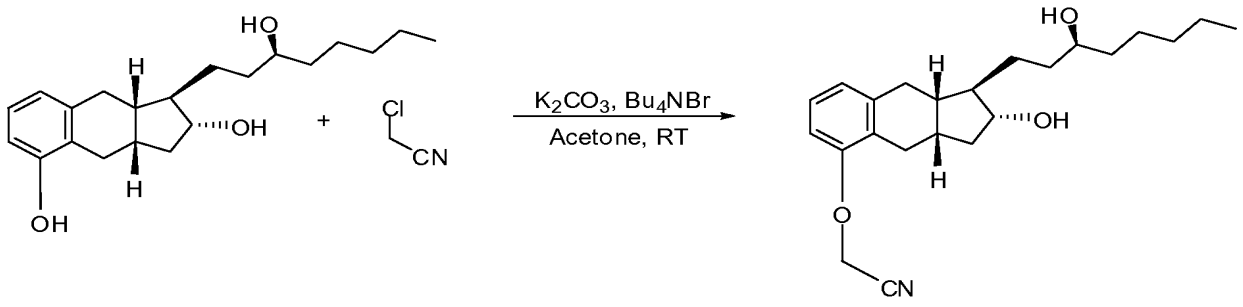
"AUC" means area under curve.

[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

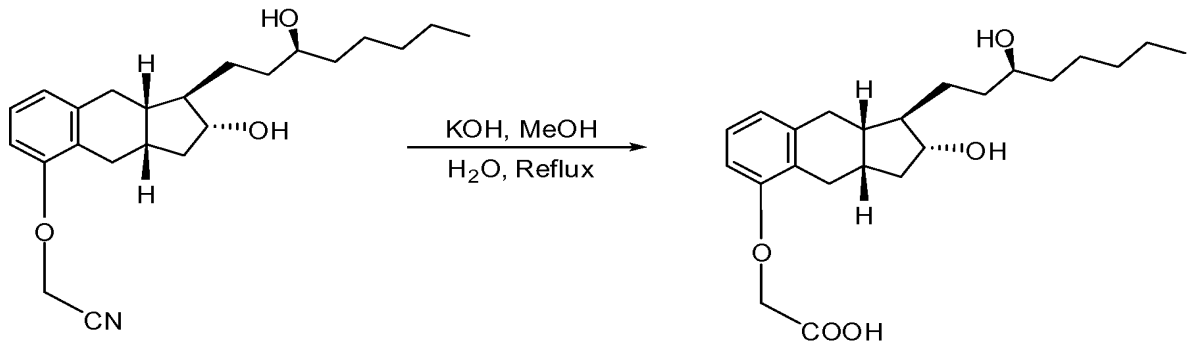
Example 1. Alkylation of Benzindene Triol



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.

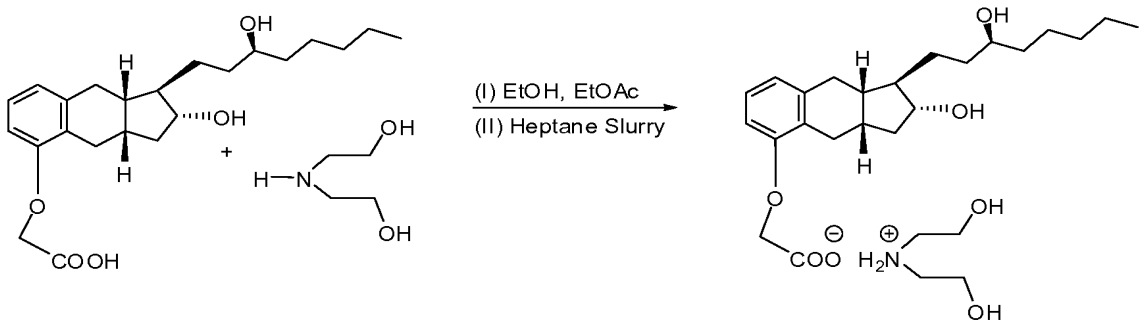
[0039] The aqueous layer was diluted with water (7-8 L) and extracted with ethyl acetate (2 × 6 L) to remove impurities soluble in ethyl acetate. To aqueous layer, ethyl acetate (22 L) was added and the pH of reaction mixture was adjusted to 1-2 by adding 3M HC1 (1.7 L) with stirring. The organic layer 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

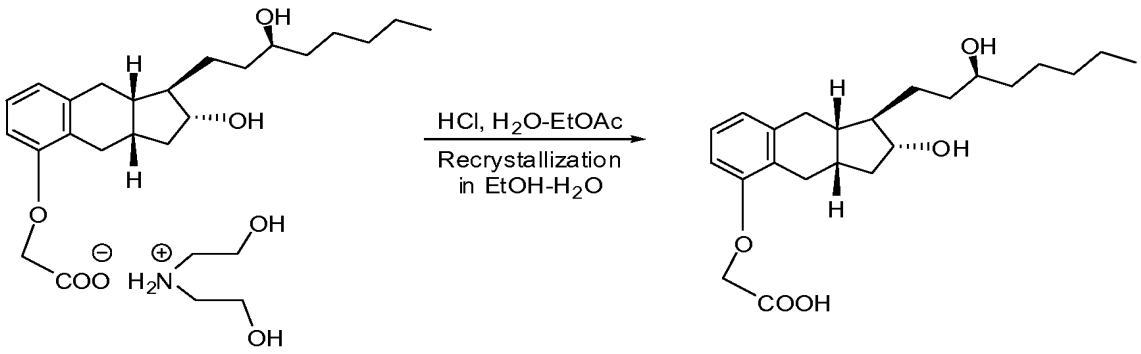
Name	Batch No.	Amount	Ratio
Treprostinil Diethanolamine Salt	2	3071 g	1
Heptane	--	36.0 L	12

[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	Tetrabutylammonium 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%

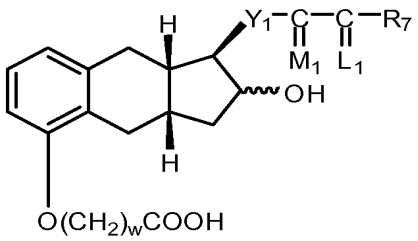
[0046] The quality of treprostinil produced according to this invention is excellent. The purification of benzindene nitrile by column chromatography is eliminated. The impurities carried over from intermediate steps (i.e. alkylation of triol and hydrolysis of benzindene nitrile) are removed during the 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:

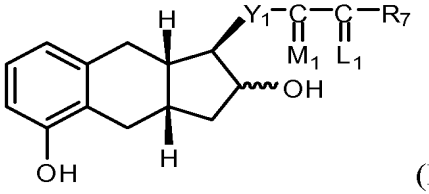
1. A process for the preparation of a compound of formula I, a hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof



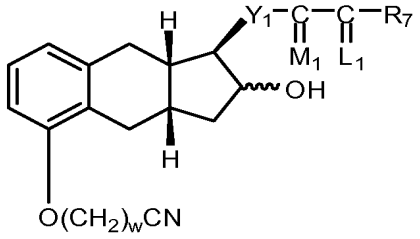
(I)

comprising

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



(II)



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

$-C(L_1)-R_7$ 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

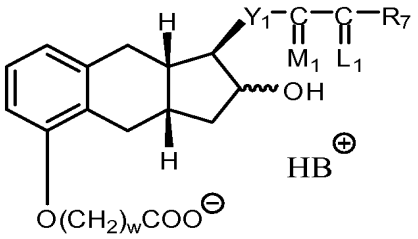
(4) 3-thienyloxymethyl;

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 formula III 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.

2. The process according to claim 1, wherein the purity of compound of formula I is at least 90.0%, 95%, or 99.0%.

3. The process according to claim 1, further comprising a step of isolating the salt of formula I_s.

4. The process according to claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.

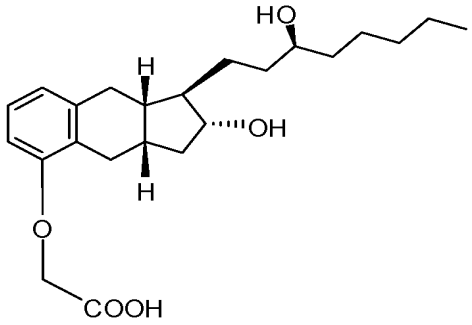
5. The process according to claim 1, wherein the base in step (b) is KOH or NaOH.

6. The process according to claim 1, wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

7. The process according to claim 1, wherein the acid in step (d) is HCl or H_2SO_4.

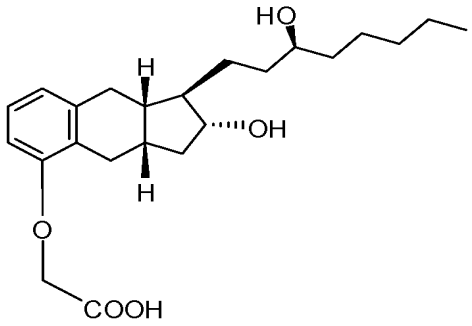
8. The process according to claim 1, wherein Y_1 is $–CH_2CH_2-$; M_1 is α-OH:β-H or α-H:β-OH; $-C(L_1)-R_7$ taken together is $–(CH_2)_4CH_3$; and w is 1.

9. The process according to claim 1, wherein the compound of formula I is a compound of formula IV.



(IV)

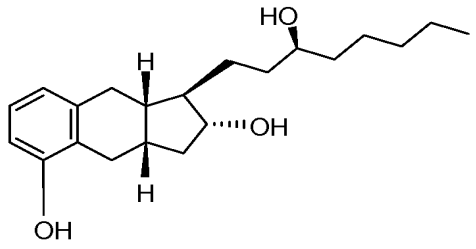
10. A process for the preparation of a compound having formula IV, a hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof



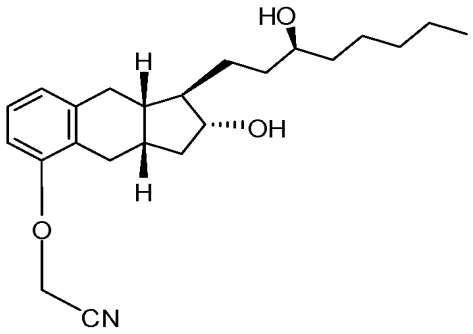
(IV)

comprising

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



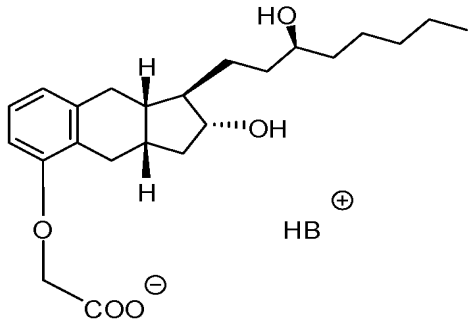
(V)



(VI)

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

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



(IV_s)

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

11. The process according to claim 10, wherein the purity of compound of formula IV is at least 90.0%, 95.0%, 99.0%, or 99.5%.

12. The process according to claim 10, further comprising a step of isolating the salt of formula IV_s.

13. The process according to claim 10, wherein the alkylating agent is $ClCH_2CN$.

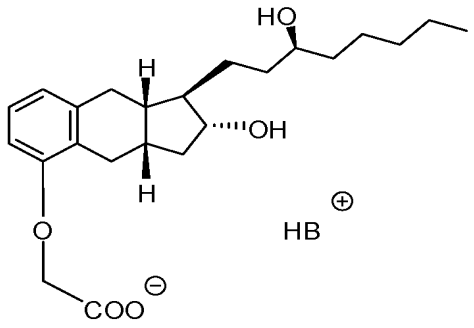
14. The process according to claim 10, wherein the base in step (b) is KOH.

15. The process according to claim 10, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

16. The process according to claim 15, wherein the base B is diethanolamine.

17. The process according to claim 10, wherein the acid in step (d) is HCl.

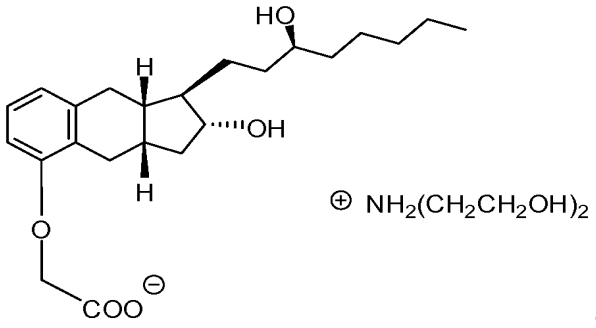
18. A process as claimed in claim 1, wherein the compound produced is a compound of the formula IV_s,



IV_s

wherein the base B is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

19. A process as claimed in claim 1, wherein the compound produced is a compound of the following formula:



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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.

Application Data Sheet

Application Information

Application number::	Unassigned
Filing Date::	12/15/2008
Application Type::	Regular
Subject Matter::	Utility
Suggested classification::	
Suggested Group Art Unit::	
CD-ROM or CD-R?::	None
Computer Readable Form (CRF)?::	No
Title::	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Attorney Docket Number::	080618-0629
Request for Early Publication?::	No
Request for Non-Publication?::	No
Suggested Drawing Figure::	
Total Drawing Sheets::	
Small Entity?::	Yes
Petition included?::	No
Secrecy Order in Parent Appl.?::	No

Applicant Information

Applicant Authority Type::	Inventor
Primary Citizenship Country::	India
Status::	Full Capacity
Given Name::	Hitesh
Family Name::	BATRA
City of Residence::	Herndon
State or Province of Residence::	VA
Country of Residence::	US

Street of mailing address::	2461 Leyland Ridge Road
City of mailing address::	Herndon
State or Province of mailing address::	VA
Postal or Zip Code of mailing address::	20171

Applicant Authority Type::	Inventor
Primary Citizenship Country::	Nepal
Status::	Full Capacity
Given Name::	Sudersan M.
Family Name::	TULADHAR
City of Residence::	Silver Spring
State or Province of Residence::	MD
Country of Residence::	US
Street of mailing address::	1501 Haddon Manor Court
City of mailing address::	Silver Spring
State or Province of mailing address::	MD
Postal or Zip Code of mailing address::	20904

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Raju
Family Name::	PENMASTA
City of Residence::	Herndon
State or Province of Residence::	VA
Country of Residence::	US
Street of mailing address::	12953 Centre Park Circle #115
City of mailing address::	Herndon

State or Province of mailing address::	VA
Postal or Zip Code of mailing address::	20171

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	David A.
Family Name::	WALSH
City of Residence::	Palmyra
State or Province of Residence::	VA
Country of Residence::	US
Street of mailing address::	56 Wildwood Drive
City of mailing address::	Palmyra
State or Province of mailing address::	VA
Postal or Zip Code of mailing address::	22963

Correspondence Information

Correspondence Customer Number::	22428
E-Mail address::	PTOMailWashington@foley.com

Representative Information

Representative Customer Number::	22428	

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This Application	An application claiming the benefit under 35 USC 119(e)	61/014,232	12/17/2007

Foreign Priority Information

Country::	Application number::	Filing Date::	Priority Claimed::

Assignee Information

Assignee Name:: United Therapeutics Corporation

Electronic Acknowledgement Receipt

EFS ID:	4452082
Application Number:	12334731
International Application Number:	
Confirmation Number:	8804
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:	080618-0629
Receipt Date:	15-DEC-2008
Filing Date:	
Time Stamp:	13:07:39
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	Transmittal of New Application	Transmittal.pdf	65197 fd49da2dff67301086377fa3f817af563ecfa93e	no	3

Warnings:

Information:

2		Specification.pdf	235680 d6c5d77400cce89a4f4ba8639e1294a53e312577	yes	27

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Specification	1	21
Claims	22	26
Abstract	27	27

Warnings:

Information:

3	Application Data Sheet	ADS.pdf	64079 52e1f9c98a7a0698a18859da6235faeba27a39c6	no	4

Warnings:

Information:

This is not an USPTO supplied ADS fillable form

Total Files Size (in bytes):	364956

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 (12-04)

Filing Date: **12/15/08**

Approved for use through 7/31/2006. 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 12/334,731

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	82		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	270		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	110		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	19 minus 20 =		x$26		OR	x$52	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*	x$110			x$220	
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			195			390	
			TOTAL	462		TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

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))					N/A		OR	N/A	
						TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

		(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 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))					N/A		OR	N/A	
						TOTAL ADD'T FEE		OR	TOTAL ADD'T 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.

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/334,731	12/15/2008	Hitesh BATRA	080618-0629

CONFIRMATION NO. 8804

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

FORMALITIES LETTER

Date Mailed: 12/31/2008

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  *Applicant must submit $**82** to complete the basic filing fee for a small entity.*
- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $**65** for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this notice.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is $**527** for a small entity
- $**82** Statutory basic filing fee.
- $**65** Surcharge.
- The application search fee has not been paid. Applicant must submit $**270** to complete the search fee.
- The application examination fee has not been paid. Applicant must submit $**110** to complete the examination fee for a small entity in compliance with 37 CFR 1.27.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/rfthomas/

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
12/334,731	12/15/2008	1614	0.00	080618-0629	19	2

CONFIRMATION NO. 8804

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

FILING RECEIPT

OC000000033786953

Date Mailed: 12/31/2008

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**

Applicant(s)

Hitesh BATRA, Herndon, VA;
Sudersan M. TULADHAR, Silver Spring, MD;
Raju PENMASTA, Herndon, VA;
David A. WALSH, Palmyra, VA;

Assignment For Published Patent Application

UNITED THERAPEUTICS CORPORATION

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/014,232 12/17/2007

Foreign Applications

If Required, Foreign Filing License Granted: 12/24/2008

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/334,731**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****

Title

PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN

Preliminary Class

514

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.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

Atty. Dkt. No. 080618-0629

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.: 12/334,731

Filing Date: 12/15/2008

Examiner: Unassigned

Art Unit: 1614

Conf. No.: 8804

TRANSMITTAL OF MISSING PARTS OF PATENT APPLICATION

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

Sir:

In response to the Notice to File Missing Parts of Application mailed December 31, 2008, in the above-identified patent application, transmitted herewith are the missing parts to complete the filing of the subject patent application.

Enclosed are:

[X] Declaration and Power of Attorney (4 pages)

[X] Return Copy of Notice to File Missing Parts

[X] Preliminary Amendment

[X] Information Disclosure Statement

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

Number of Sheets		EFS-Web Adjustment	Number of Sheets for EFS-Web
27	x	75%	21

The filing fee is calculated below:

	Claims as Filed		Included in Basic Fee		Extra Claims		Rate		Fee Totals
Basic Filing Fee, Search Fee & Examination Fee							$1,090.00		$1,090.00
Size Fee	21	-	100	=	0	x	$270.00	=	$0.00
Total Claims:	19	-	20	=	0	x	$52.00	=	$0.00
Indep.:	2	-	3	=	0	x	$220.00	=	$0.00
If any Multiple Dependent Claim(s) present:						+	$390.00	=	$0.00
Surcharge under 37 CFR 1.16(f) for late filing of Executed Declaration and late payment of filing fee						+	$130.00	=	$130.00
Extension fee for response filed within the MONTH month:						+		=	$0.00
							SUBTOTAL:	=	$1,220.00
[X]							Small Entity Fees Apply (subtract ½ of above):	=	$610.00
							Basic Filing Fee Reduction for Filing via EFS-Web		$83.00
							TOTAL FILING FEE:	=	$527.00
Processing Fee under 37 CFR 1.17(i) for Late Filing of English Translation of Application:						+	$130.00	=	$0.00
							TOTAL FEE	=	$527.00
Difference to pay:						-	$0.00	-	$527.00

A credit card payment form in the amount of $527.00 is enclosed in payment of surcharge fee (37 C.F.R. § 1.16(f)).

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 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, applicant hereby petitions 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 2/27/2009 By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4632
Facsimile: (202) 672-5399

Alexey V. Saprigin
Attorney for Applicant
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 NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/334,731	12/15/2008	Hitesh BATRA	080618-0629

CONFIRMATION NO. 8804

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

FORMALITIES LETTER

Date Mailed: 12/31/2008

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee is missing.
  *Applicant must submit $**82** to complete the basic filing fee for a small entity.*
- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $**65** for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this notice.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is $**527** for a small entity
- $**82** Statutory basic filing fee.
- $**65** Surcharge.
- The application search fee has not been paid. Applicant must submit $**270** to complete the search fee.
- The application examination fee has not been paid. Applicant must submit $**110** to complete the examination fee for a small entity in compliance with 37 CFR 1.27.

03/03/2009 AWONDAF1 00000075 12334731

01 FC:4011	82.00 OP
02 FC:2051	65.00 OP
03 FC:2111	270.00 OP
04 FC:2311	110.00 OP

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/rfthomas/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I HEREBY DECLARE:

THAT my residence, post office address, and citizenship are as stated below next to my name;

THAT I believe I am the original, first, and sole inventor (if only one inventor is named below) or an original, first, and joint inventor (if plural inventors are named below or in an attached Declaration) of the subject matter which is claimed and for which a patent is sought on the invention entitled

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

(Attorney Docket No. 080618-0629)

the specification of which (check one)

___ is attached hereto.

_X_ was filed on _December 15, 2008_ as United States Application Number or PCT International Application Number _12/334,731_ and was amended on _____ (if applicable).

THAT I do not know and do not believe that the same invention was ever known or used by others in the United States of America, or was patented or described in any printed publication in any country, before I (we) invented it;

THAT I do not know and do not believe that the same invention was patented or described in any printed publication in any country, or in public use or on sale in the United States of America, for more than one year prior to the filing date of this United States application;

THAT I do not know and do not believe that the same invention was first patented or made the subject of an inventor's certificate that issued in any country foreign to the United States of America before the filing date of this United States application if the foreign application was filed by me (us), or by my (our) legal representatives or assigns, more than twelve months (six months for design patents) prior to the filing date of this United States application;

THAT I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment specifically referred to above;

THAT I believe that the above-identified specification contains a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention, and sets forth the best mode contemplated by me of carrying out the invention; and

THAT I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I HEREBY CLAIM foreign priority benefits under Title 35, United States Code §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number	Country	Foreign Filing Date	Priority Claimed?	Certified Copy Attached?

I HEREBY CLAIM the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

U.S. Provisional Application Number	Filing Date
61/014,232	12/17/2007

I HEREBY CLAIM the benefit under Title 35, United States Code, §120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of

Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Application Number	Parent Filing Date	Parent Patent Number

I HEREBY APPOINT the registered attorneys and agents at Customer Number

22428

to have full power to prosecute this application and any continuations, divisions, reissues, and reexaminations thereof, to receive the patent, and to transact all business in the United States Patent and Trademark Office connected therewith.

I request that all correspondence be directed to:

Stephen B. Maebius
FOLEY & LARDNER LLP
Customer Number: 22428

Telephone: (202) 672-5569
Facsimile: (202) 672-5399

I UNDERSTAND AND AGREE THAT the foregoing attorneys and agents appointed by me to prosecute this application do not personally represent me or my legal interests, but instead represent the interests of the legal owner(s) of the invention described in this application.

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.

Name of first inventor	Hitesh BATRA
Residence	Herndon, Virginia
Citizenship Country	India
Post Office Address	2461 Leyland Ridge Road Herndon, Virginia 20171
Inventor's signature	
Date	1/13/09

Name of second inventor	Sudersan M. TULADHAR
Residence	Silver Spring, Maryland
Citizenship Country	Nepal
Post Office Address	1501 Haddon Manor Court Silver Spring, Maryland 20904
Inventor's signature	
Date	1/13/09

Name of third inventor	Raju PENMASTA
Residence	Herndon, Virginia
Citizenship Country	US
Post Office Address	12953 Centre Park Circle #115 Herndon, Virginia 20171
Inventor's signature	
Date	1/13/09

Name of fourth inventor	David A. WALSH
Residence	Palmyra, Virginia
Citizenship Country	US
Post Office Address	56 Wildwood Drive Palmyra, Virginia 22963
Inventor's signature	
Date	Jan. 13, 2009

Atty. Dkt. No. 080618-0629

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.: 12/334,731

Filing Date: 12/15/2008

Examiner: Unassigned

Art Unit: 1614

Conf. No.: 8804

PRELIMINARY AMENDMENT UNDER 37 CFR 1.115

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

Sir:

Prior to examination of the present Application, Applicant respectfully requests that the application be amended as follows:

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

Remarks begin on page 3 of this document.

Please amend the application as follows:

Amendments to the Specification:

Please amend the specification as follows:

Page 1, amend paragraph [0004] as follows:

[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 ~~and 6,756,117~~. Their teachings are incorporated by reference to show how to practice the embodiments of the present invention.

Page 18, please amend Step 16 of Example 6, as follows:

~~16~~	~~Potassium hydroxide~~	~~650 g (8 eq)~~	~~3,375g (4 eq)~~

16	Potassium hydroxide	650 g (8 eq)	3,375g (4 eq)

REMARKS

Applicant respectfully requests that the foregoing amendments be made prior to examination of the present application.

In the specification, typographical errors are corrected in Paragraph [0004] on page 1, and in Step 16 of Example 6 on page 18.

Favorable consideration of the application as amended 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.

Respectfully submitted,

Date 2/27/2009

By _____
Alexey Saprigin
Reg # 56,439
FOR Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

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

Atty. Dkt. No. 080618-0629

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.: 12/334,731

Filing Date: 12/15/2008

Examiner: Unassigned

Art Unit: 1614

Conf. No.: 8804

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

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

Sir:

Submitted herewith on Form PTO/SB/08 is a listing of documents known to Applicants in order to comply with Applicants' duty of disclosure pursuant to 37 CFR §1.56.

A copy of each non-patent document is being submitted to comply with the provisions of 37 CFR §1.97 and §1.98.

The submission of any document herewith, which is not a statutory bar, is not intended as 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 which is determined to be a *prima facie* art reference against the claims of the present application.

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.

RELEVANCE OF EACH DOCUMENT

All of the documents are in English.

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.

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

Respectfully submitted,

Date 2/27/2009

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4632
Facsimile: (202) 672-5399

Alexey V. Saprigin
Attorney for Applicant
Registration No. 56,439

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
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	12/334,731
Date Submitted: February 27, 2009				**Filing Date**	12/15/2008
				First Named Inventor	Hitesh BATRA
(use as many sheets as necessary)				Art Unit	1614
				Examiner Name	Unassigned
Sheet	1	of	1	Attorney Docket Number	080618-0629

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	2005/0282903 A1	12/22/2005	Wade et al.	
	A2	2005/0282901 A1	12/22/2005	Phares et al.	
	A3	2008/0280986 A1	11/13/2008	Wade et al.	
	A4	2008/0249167 A1	10/09/2008	Phares et al.	
	A5	2008/0200449 A1	08/21/2008	Olschewski et al.	
	A6	2005/0165111 A1	07/28/2005	Wade et al.	
	A7	2007/0078095 A1	04/05/2007	Phares et al.	
	A8	2009/0036465 A1	02/05/2009	Roscigno et al.	
	A9	4,306,075 A	12/15/1981	Aristoff, Paul A.	
	A10	5,153,222 A	10/06/1992	Tadepalli et al.	
	A11	6,054,486 A	04/25/2000	Crow et al.	
	A12	6,441,245 B1	08/27/2002	Moriarty et al.	
	A13	6,521,212 B1	02/18/2003	Cloutier et al.	
	A14	6,528,688 B2	03/04/2003	Moriarty et al.	
	A15	6,700,025 B2	03/02/2004	Moriarty et al.	
	A16	6,756,033 B2	06/29/2004	Cloutier et al.	
	A17	6,765,117 B2	07/20/2004	Moriarty et al.	
	A18	6,803,386 B2	10/12/2004	Shorr et al.	
	A19	6,809,223 B2	10/26/2004	Moriarty et al.	
	A20	7,199,157 B2	04/03/2007	Wade et al.	
	A21	7,384,978 B2	06/10/2008	Phares et al.	
	A22	7,417,070 B2	08/26/2008	Phares et al.	

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]
	A23	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.	
	A24	Sorbera et al. "UT-15. Treatment of Pulmonary Hypertension Treatment of Peripheral Vascular Disease," *Drug of the Future*, 2001, 26(4), 364-374.	

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.

This collection of information is required by 37 CFR 1.97 and 1.98. 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 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

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

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/334,731	12/15/2008	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	19 minus 20 =	* 0	X $26 =	0	OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	* 0	X $110 =	0		X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	0		TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 02/27/2009

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 19	Minus	** 20	= 0	X $26 =	0	OR	X $ =	
Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $110 =	0	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	0	OR	TOTAL ADD'L FEE	

AMENDMENT

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

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

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

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

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

Legal Instrument Examiner:
/GLENN BURNS JR/

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
12/334,731	12/15/2008	1614	527	080618-0629	19	2

CONFIRMATION NO. 8804

UPDATED FILING RECEIPT

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

Date Mailed: 03/16/2009

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**

Applicant(s)

Hitesh BATRA, Herndon, VA;
Sudersan M. TULADHAR, Silver Spring, MD;
Raju PENMASTA, Herndon, VA;
David A. WALSH, Palmyra, VA;

Assignment For Published Patent Application

UNITED THERAPEUTICS CORPORATION

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

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/014,232 12/17/2007

Foreign Applications

If Required, Foreign Filing License Granted: 12/24/2008

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/334,731**

Projected Publication Date: 06/25/2009

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****

Title

PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN

Preliminary Class

514

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.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as

set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: June 22, 2009

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	12/334,731
Filing Date	12/15/2008
First Named Inventor	Hitesh BATRA
Art Unit	1621
Examiner Name	Unassigned
Attorney Docket Number	080618-0629

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
	B1	2002/0173672 A1	11/21/2002	Moriarty et al.	
	B2	4,486,598 A	12/04/1984	Aristoff, Paul A.	

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]
	B3	WO 2007/134292 A2	11/22/2007	United Therapeutics Corporation		

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]
	B4	International Search Report and Written Opinion mailed 6/2/2009 in corresponding PCT/US2008/013686, 14 pages.	

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.

This collection of information is required by 37 CFR 1.97 and 1.98. 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 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
MAEBIUS, Stephen, B.
Attn. Maebius, Stephen B.
Foley & Lardner LLP
Washington Harbour
3000 K Street, N.W., suite 500
Washington, DC 20007-5143
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 080618-0630	Date of mailing *(day/month/year)* 02/06/2009
International application No. PCT/US2008/013686	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant UNITED THERAPEUTICS CORPORATION	International filing date *(day/month/year)* 12/12/2008

1. [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 338.82.70

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

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

Form PCT/ISA/220 (October 2005) *(See notes on accompanying sheet)*

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1–10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43*bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
080618-0630		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2008/013686	12/12/2008	17/12/2007
Applicant		
UNITED THERAPEUTICS CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/013686

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C51/08 C07C51/41 C07C59/62 C07C405/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/173672 A1 (MORIARTY ROBERT M [US] ET AL) 21 November 2002 (2002-11-21) page 4, compound 14 to compound 16; column 12, compound 14 to compound 15, [0078] and [0079]; claims, e.g. claim 8	1-19

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 May 2009	02/06/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sen, Alina

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/013686

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MORIARTY ROBERT M. ET AL: "The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil)" THE JOURNAL OF ORGANIC CHEMISTRY, vol. 69, no. 6, 2004, pages 1890-1902, XP002523983 page 1892, compound 7; page 1895, Scheme 4, compounds 34 to compound 7; page 1902, Excperimental section for compound 34 to compound 7	1-19
X	US 4 486 598 A (ARISTOFF PAUL A [US]) 4 December 1984 (1984-12-04) column 14, line 1-39, e.g. lines 30-31; claim 1	1-19
X	WO 2007/134292 A (UNITED THERAPEUTICS CORP [US]; OLSCHEWSKI HORST [DE]; ROSCIGNO ROBERT) 22 November 2007 (2007-11-22) [0033], [0036] and [0037, e.g. diethanolamine]	1-19

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/013686

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002173672 A1	21-11-2002	US 2002087025 A1	04-07-2002
US 4486598 A	04-12-1984	DE 3363460 D1	19-06-1986
		EP 0087237 A1	31-08-1983
		JP 58154525 A	14-09-1983
		ZA 8300019 A	26-10-1983
WO 2007134292 A	22-11-2007	CA 2654492 A1	22-11-2007
		EP 2026816 A2	25-02-2009
		KR 20090007797 A	20-01-2009
		US 2008200449 A1	21-08-2008

Form PCT/ISA/210 (patent family annex) (April 2005)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2008/013686	12.12.2008	17.12.2007

International Patent Classification (IPC) or both national classification and IPC
INV. C07C51/08 C07C51/41 C07C59/62 C07C405/00

Applicant
UNITED THERAPEUTICS CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Sen, Alina Telephone No. +49 89 2399-8328

Form PCT/ISA/237 (Cover Sheet) (April 2005)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-19
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V.

D1 : US 2002/173672 A1 (MORIARTY ROBERT M [US] ET AL) 21 November 2002 (2002-11-21)
D2 : MORIARTY ROBERT M. ET AL: "The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil)" THE JOURNAL OF ORGANIC CHEMISTRY, vol. 69, no. 6, 2004, pages 1890-1902, XP002523983
D3 : US 4 486 598 A (ARISTOFF PAUL A [US]) 4 December 1984 (1984-12-04)
D4 : WO 2007/134292 A (UNITED THERAPEUTICS CORP [US]; OLSCHEWSKI HORST [DE]; ROSCIGNO ROBERT) 22 November 2007 (2007-11-22)

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of the claims on file is not new in the sense of Article 33(2) PCT in view of the documents D1-D4 indicated in the Search Report (see D1: page 4, compound 14 to compound 16; column 12, compound 14 to compound 15, [0078] and [0079]; claims, e.g. claim 8; see D2: page 1892, compound 7; page 1895, Scheme 4, compounds 34 to compound 7; page 1902, experimental section for compound 34 to compound 7; see D3: column 14, line 1-39, e.g. lines 30-31; claim 1; see D4: [0033], [0036] and [0037, e.g. diethanolamine]).

According to the application, a process for the preparation of prostacyclin derivatives is described comprising alkylating a compound of general structure II with an alkylating agent to produce the corresponding benzindene nitrile which is then hydrolysed with a base. According to the application "a solution of benzindene nitrile and a solution of KOH were stirred and heated to reflux. After completion of the reaction, the reaction mixture was cooled to -5 °C to 10 °C and quenched with a solution of hydrochloric acid while stirring. After conventional work-up, treprostinil was recovered "for direct use in the next step". At the light of Example 3 this next step implies the conversion of treprostinil to the corresponding salt by contacting treprostinil with a base.

This sequence of reaction step is described in the cited art where it is also indicated to alkylate the benzindene triol compound under the exact same experimental conditions also detailed in the application to afford the corresponding benzindene nitrile. As in the present application the compound is hydrolysed in the presence of a base and the reaction mixture quenched with an acid. Starting from the acid compound the various salt forms may be prepared and in this context both documents D3 and D4 describe the preparation of the treprostinil diethanolamine salt by contacting the treprostinil (acid) with the base of choice. This procedure is described in the art and this same procedure is followed in the application at least with regard to its experimental part.

Accordingly it follows that the process claimed is not novel.

An unexpected and surprising effect associated with the process indicated in the claims

or in the description is also not evident.

Re Item VII.
Claim 10 comprises all the features of claim 1 and is therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT).

Re Item VIII.
In claim 1 and in claim 10, on the other hand, it is indicated that after the step of hydrolysing the benzindene nitrile compound with a base, this first salt is contacted with a second base "B" to afford a further salt which is then quenched with an acid to afford the treprostinil compound. A part that, as indicated above, an inconsistency is evident between the subject-matter of the claims and the description of the application, at least with regard to the examples provided, the question raises as to the actual significance of this reaction sequence as ultimately the two bases formed are in any case quenched to afford the acid compound.

The term "prodrug" used in claims 1 and 10 is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claim/s unclear, Article 6 PCT.
The same objection is raised for the term "incorporated herein by reference" and the paragraphs [0035], [0036], [0047] and [0048] which should be deleted.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/ WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003

XS CPRTENFRDE

BNSDOCID: <XS____2006100103CF_I_>

IFW

Atty. Dkt. No. 080618-0629

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.: 12/334,731

Filing Date: 12/15/2008

Examiner: Unassigned

Art Unit: 1621

Conf. No.: 8804

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

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

Sir:

Submitted herewith on Form PTO/SB/08 is a listing of documents known to Applicants in order to comply with Applicants' duty of disclosure pursuant to 37 CFR §1.56.

A copy of each non-U.S. patent document and each non-patent document is being submitted to comply with the provisions of 37 CFR §1.97 and §1.98.

The submission of any document herewith, which is not a statutory bar, is not intended as 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 which is determined to be a *prima facie* art reference against the claims of the present application.

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, and within three (3) months of the mailing date of the foreign search report.

RELEVANCE OF EACH DOCUMENT

All of the documents are in English, and were cited in the International Search Report mailed on June 2, 2009, in corresponding PCT/US2008/013686, a copy of which is also submitted herewith.

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.

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 June 19, 2009

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
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Alexey V. Saprigin
Attorney for Applicant
Registration No. 56,439

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/334,731	12/15/2008	Hitesh BATRA	080618-0629

CONFIRMATION NO. 8804

PUBLICATION NOTICE

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

OC00000036637082

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

Publication No.US-2009-0163738-A1
Publication Date:06/25/2009

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/334,731	12/15/2008	Hitesh BATRA	080618-0629	8804

22428 7590 04/04/2011

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
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EXAMINER	
PUTTLITZ, KARL J	

ART UNIT	PAPER NUMBER
1621	

MAIL DATE	DELIVERY MODE
04/04/2011	PAPER

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.

Office Action Summary	Application No.	Applicant(s)	
	12/334,731	BATRA ET AL.	
	Examiner	Art Unit	
	KARL J. PUTTLITZ	1621	

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *15 December 2008*.

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

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

Disposition of Claims

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

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

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

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

Application Papers

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

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

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

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

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

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6 and 14*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

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

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for sal6s of the recited compounds does not reasonably provide enablement for solvates and hydrates of the recited compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

"The standard for determining whether the specification meets the enablement requirement [in accordance with the statute] was cast in the Supreme Court decision of *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). See also *United States v. Telectronics, Inc.,* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the

art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). Determining enablement is a question of law based on underlying factual findings. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984)." See M.P.E.P. § 2164.

In the instant case the rejected claims cover all solvates and hydrates of the recited compounds. . Based on the above standards, the disclosure must contained sufficient information to enable one skilled in the pertinent art to use this invention without undue experimentation. See M.P.E.P. 2164.01. Given the scope of the claims, it does not.

The state of the art does not support the proposition that any and all solvates or hydrates of the claimed compound can be prepared since the preparation of solvated solids and crystals is largely empirical, see "Crystallization and Precipitation" in Ullmann's Encyclopedia of Industrial Chemistry, Copyright © 2002 by Wiley-VCH Verlag GmbH & Co. KGaA , pp. 1-51 ("Laboratory procedures that can be adopted in the preliminary search for possible polymorphs or solvates include: crystallizing from a wide range of solvents (polar, non-polar, hydrophilic, and hydrophobic) at different

temperatures; chilling saturated solutions rapidly; precipitation by rapid quenching with a liquid non-solvent; heating excess solid with a high boiling solvent; crystallization from the melt or by sublimation, and so on, see Id. at p. 12. However, the instant case goes beyond what is known in the art, because the state of the art for polymorph recovery is very unpredictable, and, as established above, the specification does not offer any guidance on how one of ordinary skill would go about practicing the invention for recovery of every claimed polymorph.

The disclosure fails to remedy 5the state of the art in teaching those of ordinary skill how to prepare solvates and hydrates of the recited compounds without undue experimentation. Specifically, the specification and the examples do not provide sufficient disclosure that would provide one of ordinary skill guidance to practice the invention, given the level of unpredictability in the art. In this regard, the disclosure fails to prepare any hydrate or solvates, mush less teach those of ordinary skill how to select conditions appropriate to prepare the recited hydrates and solvates, M.P.E.P. § 2164.06(b) citing "In *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991), [where the court pointed to a] "limited disclosure by appellants of …particular cyanobacterial genera operative in the claimed invention...." The claims at issue were not limited to any particular genus or species of cyanobacteria and the specification mentioned nine genera and the working examples employed one species of cyano-bacteria."

The examiner understands that there is no requirement that the specification disclose every possible embodiment if there is sufficient guidance given by knowledge

in the art (See M.P.E.P. § 2164.05(a) "[t]he specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).").

However, the instant case goes beyond what is known in the art, because the specification does not offer any guidance on how one of ordinary skill would go about practicing the invention for recovery of every claimed hydrate and solvate.

Applicant is reminded of the heightened enablement for chemical inventions. Specifically, the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. [I]n the field of chemistry generally, there may be times when the well-known unpredictability of

chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. [Footnote omitted.]

Here, the requirement for enablement is not met since the claims go far beyond the enabling disclosure.

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

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

Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear what prodrugs applicant intends to cover.

The structure of the compounds is indefinite since the structure of M1 and L1 is unclear. Specifically the structure of alpha and beta in the definition of the M1 and L1 is unclear. In addition, C=M1 and C=L1 contain double bonds, but this is not present in the structures of claims 9, 10, 18 and 19.

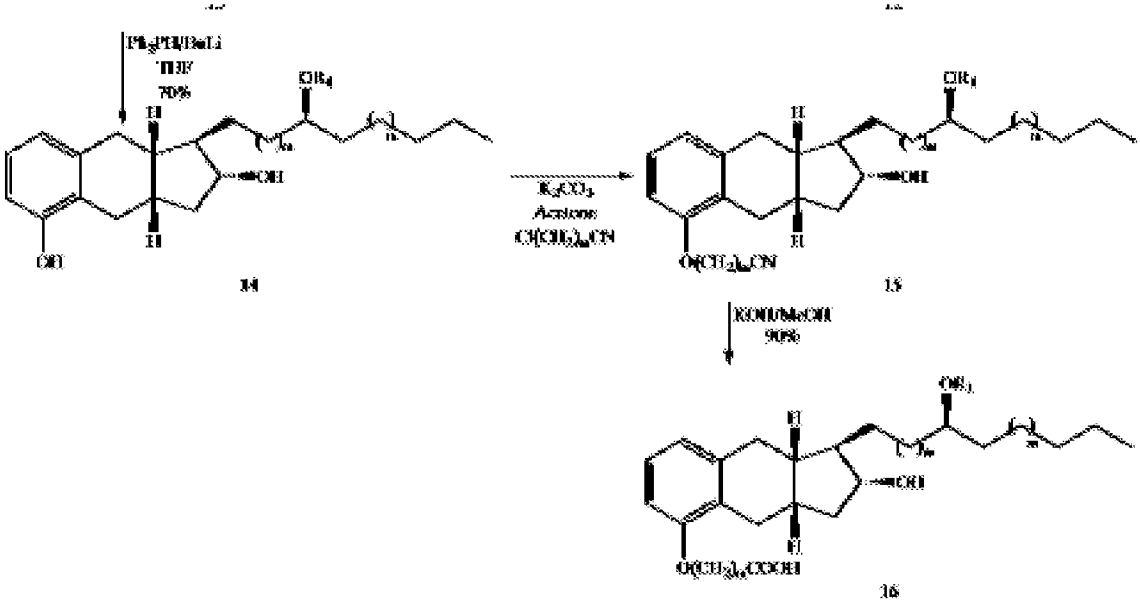
Claim Rejections - 35 USC § 103

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

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-19 rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Publication No. 20020173672, based on an application by Moriarty et al. (Moriarty).

Moriarty teaches the following reaction at page 6, for example:



The difference between the process covered by the rejected claims and the process disclosed by Moriarty is that Moriarty fails to explicitly teach reacting the

product of the hydrolysis step with an acid. However, the product formed asbove is the free acid, and thus, reaction of the product of the hydrolysis step with an acid to form the free acid product is invariable aspect of the process of Moriarty, and thus, prima facie obvious.

Claims 18 and 19 refer to different salts than that disclosed by Moriarty, but these would be dependant on the base used during the hydrolysis step, which is well within the purview of those of ordinary skill, optimizing the process, and thus, prima facie obvious.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karl J. Puttlitz whose telephone number is (571) 272-0645. The examiner can normally be reached on Monday to Friday from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Sullivan, can be reached at telephone number (571) 272-0779. 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).

/Karl J. Puttlitz/

Primary Examiner, Art Unit 1621

Notice of References Cited	Application/Control No. 12/334,731	Applicant(s)/Patent Under Reexamination BATRA ET AL.	
	Examiner KARL J. PUTTLITZ	Art Unit 1621	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2002/0173672	11-2002	Moriarty et al.	558/357
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

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

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	"Crystallization and Precipitation" in Ullmann's Encyclopedia of Industrial Chemistry, Copyright © 2002 by Wiley-VCH Verlag GmbH & Co. KGaA , pp. 1-51
	V	
	W	
	X	

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

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12334731	BATRA ET AL.
	Examiner	Art Unit
	KARL J PUTTLITZ	1621

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
reaction search in file CAPLUSW in STN;search in file	3/30/2011	KP
inventor search in EDAN PALM and EAST (USPGPUB USPAT UPAD); EAST; EASTbsearch in file	3/30/2011	KP
inventor npl search in file CAPLUS in STN; search in file	3/30/2011	KP
reviewed search report in counterpart PCT application	3/30/2011	KP

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

EAST Search History

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	5386	batra.in. or tuladhar.in. or penmasta.in. or walsh.in.	US-PGPUB; USPAT; UPAD	OR	OFF	2011/03/30 16:14
L2	2	l1 and treprostinil	US-PGPUB; USPAT; UPAD	OR	OFF	2011/03/30 16:14

3/30/11 4:15:24 PM

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
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Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	12/334,731
Date Submitted: February 27, 2009				**Filing Date**	12/15/2008
				First Named Inventor	Hitesh BATRA
(use as many sheets as necessary)				Art Unit	1614
				Examiner Name	Unassigned
Sheet	1	of	1	Attorney Docket Number	080618-0629

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	2005/0282903 A1	12/22/2005	Wade et al.	
	A2	2005/0282901 A1	12/22/2005	Phares et al.	
	A3	2008/0280986 A1	11/13/2008	Wade et al.	
	A4	2008/0249167 A1	10/09/2008	Phares et al.	
	A5	2008/0200449 A1	08/21/2008	Olschewski et al.	
	A6	2005/0165111 A1	07/28/2005	Wade et al.	
	A7	2007/0078095 A1	04/05/2007	Phares et al.	
	A8	2009/0036465 A1	02/05/2009	Roscigno et al.	
	A9	4,306,075 A	12/15/1981	Aristoff, Paul A.	
	A10	5,153,222 A	10/06/1992	Tadepalli et al.	
	A11	6,054,486 A	04/25/2000	Crow et al.	
	A12	6,441,245 B1	08/27/2002	Moriarty et al.	
	A13	6,521,212 B1	02/18/2003	Cloutier et al.	
	A14	6,528,688 B2	03/04/2003	Moriarty et al.	
	A15	6,700,025 B2	03/02/2004	Moriarty et al.	
	A16	6,756,033 B2	06/29/2004	Cloutier et al.	
	A17	6,765,117 B2	07/20/2004	Moriarty et al.	
	A18	6,803,386 B2	10/12/2004	Shorr et al.	
	A19	6,809,223 B2	10/26/2004	Moriarty et al.	
	A20	7,199,157 B2	04/03/2007	Wade et al.	
	A21	7,384,978 B2	06/10/2008	Phares et al.	
	A22	7,417,070 B2	08/26/2008	Phares et al.	

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]
	A23	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.	
	A24	Sorbera et al. "UT-15. Treatment of Pulmonary Hypertension Treatment of Peripheral Vascular Disease," *Drug of the Future*, 2001, 26(4), 364-374.	

Examiner Signature	/Karl Puttlitz/	Date Considered	03/30/2011

*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.

This collection of information is required by 37 CFR 1.97 and 1.98. 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 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /KP/

PTO/SB/08 (09-06)
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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: June 22, 2009

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	12/334,731
Filing Date	12/15/2008
First Named Inventor	Hitesh BATRA
Art Unit	1621
Examiner Name	Unassigned
Attorney Docket Number	080618-0629

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
	B1	2002/0173672 A1	11/21/2002	Moriarty et al.	
	B2	4,486,598 A	12/04/1984	Aristoff, Paul A.	

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]
	B3	WO 2007/134292 A2	11/22/2007	United Therapeutics Corporation		

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]
	B4	International Search Report and Written Opinion mailed 6/2/2009 in corresponding PCT/US2008/013686, 14 pages.	

Examiner Signature	/Karl Puttlitz/	Date Considered	03/30/2011

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This collection of information is required by 37 CFR 1.97 and 1.98. 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 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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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /KP/

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FILE COVERS 1907 - 30 Mar 2011  VOL 154 ISS 14
FILE LAST UPDATED: 29 Mar 2011  (20110329/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Feb 2011
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Feb 2011

CAplus now includes complete International Patent Classification (IPC)
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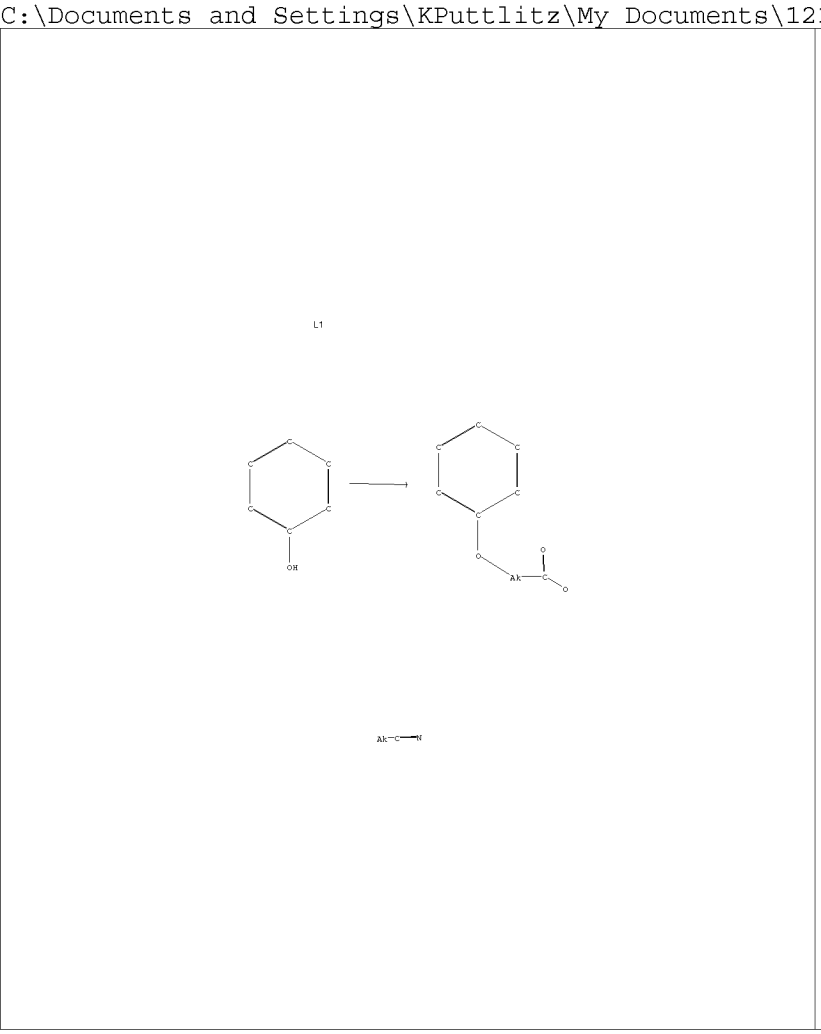

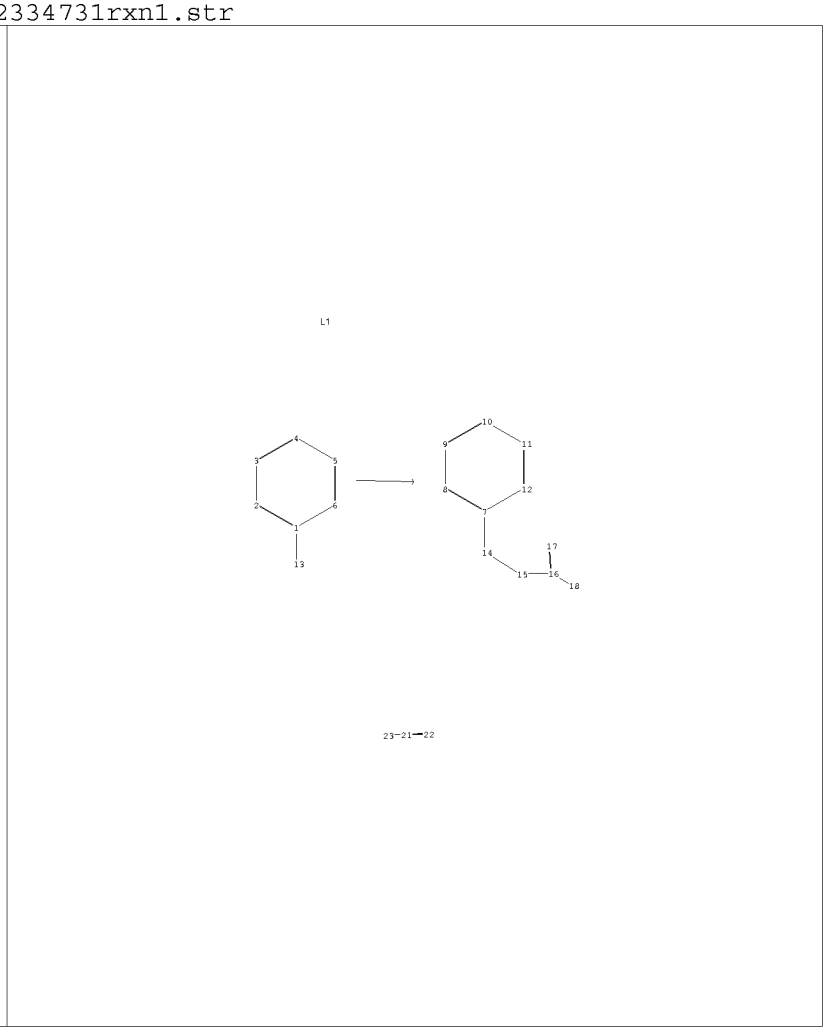


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chain nodes :
    13  14  15  16  17  18  21  22  23
ring nodes :
    1  2  3  4  5  6  7  8  9  10  11  12
chain bonds :
    1-13  7-14  14-15  15-16  16-17  16-18  21-22  21-23
ring bonds :
    1-2  1-6  2-3  3-4  4-5  5-6  7-8  7-12  8-9  9-10  10-11  11-12
exact/norm bonds :
    1-13  7-14  14-15  15-16  16-17  16-18  21-22  21-23
normalized bonds :
    1-2  1-6  2-3  3-4  4-5  5-6  7-8  7-12  8-9  9-10  10-11  11-12


Match level :
    1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom  11:Atom
    12:Atom  13:CLASS  14:CLASS  15:CLASS  16:CLASS  17:CLASS  18:CLASS  21:CLASS  22:CLASS
    23:CLASS
fragments assigned product role:
    containing 7
fragments assigned reactant/reagent role:
    containing 1
    containing 21
node mappings:
    1:7  16:21
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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.:	12/334,731
Filing Date:	12/15/2008
Examiner:	Karl J. Puttlitz
Art Unit:	1621
Confirmation Number:	8804

REPLY UNDER 37 CFR § 1.111

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

Sir:

This paper responds to the Non-Final Office Action dated April 4, 2011. Applicants petition for extension of time to make this response timely.

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

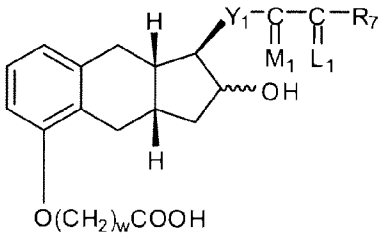
Remarks begin on page 10 of this document.

Amendments to the Claims:

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

Listing of Claims:

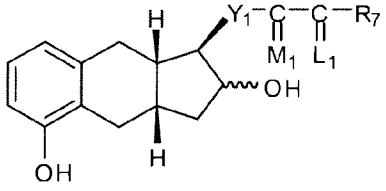
1. (Currently Amended) A process for the preparation of a compound of formula I~~, a hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof~~



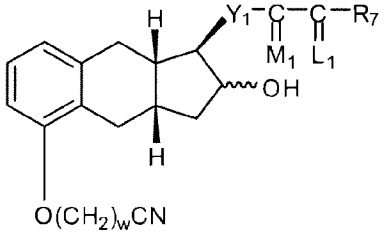
(I)

comprising

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



(II)



(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=$C(CH_3)_2$;

-$C(L_1)$-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

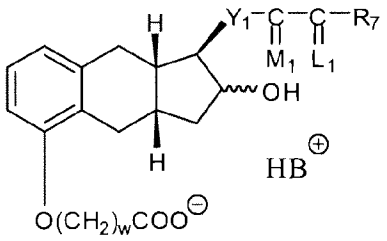
(4) 3-thienyloxymethyl;

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 formula III of step (a) with a base,

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



(I_s) and

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

2. (Currently Amended) The process according to claim [[1]] 20, wherein the product of step (d) has the purity of compound of formula I [[is]] of at least 90.0%~~, 95%, or 99.0%~~.

3. (Original) The process according to claim 1, further comprising a step of isolating the salt of formula I_s.

4. (Original) The process according to claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.

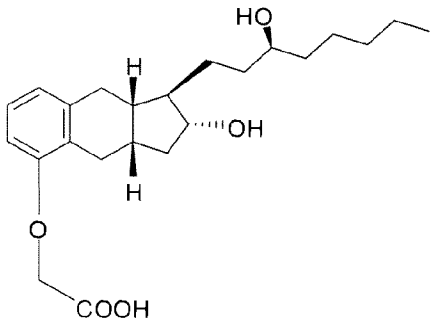
5. (Original) The process according to claim 1, wherein the base in step (b) is KOH or NaOH.

6. (Original) The process according to claim 1, wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

7. (Original) The process according to claim 1, wherein the acid in step (d) is HCl or H_2SO_4.

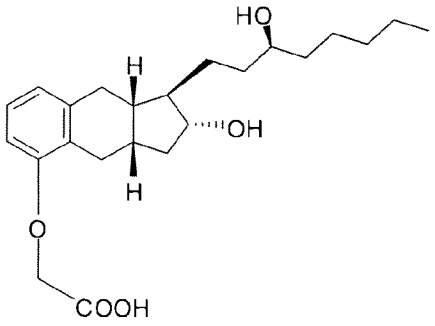
8. (Original) The process according to claim 1, wherein Y_1 is $-CH_2CH_2-$; M_1 is α-OH:β-H or α-H:β-OH; $-C(L_1)-R_7$ taken together is $-(CH_2)_4CH_3$; and w is 1.

9. (Original) The process according to claim 1, wherein the compound of formula I is a compound of formula IV.



(IV)

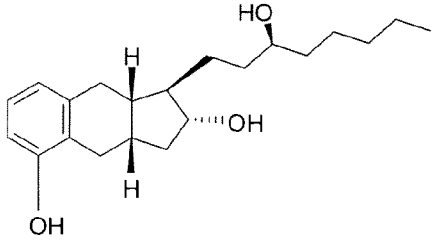
10. (Currently Amended) A process for the preparation of a compound having formula IV, ~~a hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof~~



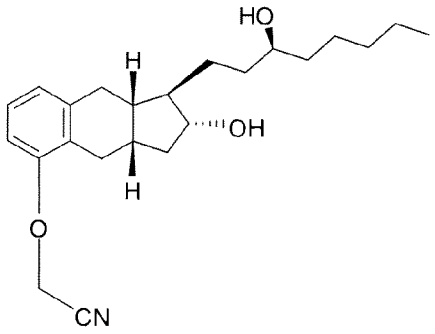
(IV)

comprising

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



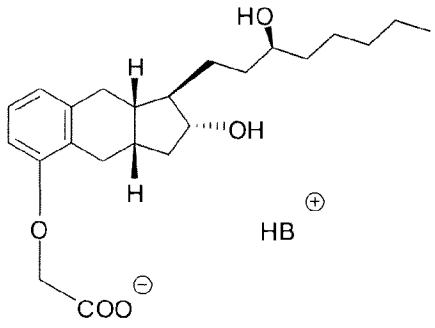
(V)



(VI)

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

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



(IV_s)

(d) reacting the salt <u>formed in step (c)</u> ~~from step of formula IV_s~~ with an acid to form the compound of formula IV.

11. (Currently Amended) The process according to claim [[10]] 22, wherein the product of step (d) has the purity of the compound of formula IV [[is]] of at least 90.0%~~, 95.0%, 99.0%, or 99.5%~~.

12. (Original) The process according to claim 10, further comprising a step of isolating the salt of formula IV_s.

13. (Original) The process according to claim 10, wherein the alkylating agent is $ClCH_2CN$.

14. (Original) The process according to claim 10, wherein the base in step (b) is KOH.

15. (Original) The process according to claim 10, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

16. (Original) The process according to claim 15, wherein the base B is diethanolamine.

17. (Original) The process according to claim 10, wherein the acid in step (d) is HCl.

18. (Canceled)

19. (Canceled)

20. (New) The process of claim 1, which does not include purifying the compound of formula (III) produced in step (a).

21. (New) The process of claim 20, wherein the product of step (d) has the purity of compound of formula I of at least 95%.

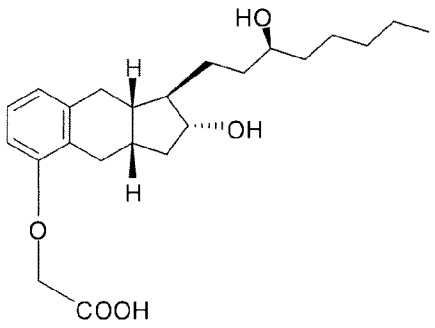
22. (New) The process of claim 10, which does not include purifying the compound of formula (VI) produced in step (a).

23. (New) The process of claim 22, wherein the product of step (d) has the purity of compound of formula I of at least 95%.

24. (New) The process of claim 22, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

25. (New) The process of claim 24, wherein the base B is diethanolamine.

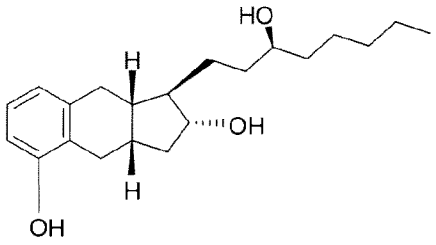
26. (New) A process for the preparation of a compound having formula IV, or pharmaceutically acccptable salt thereof



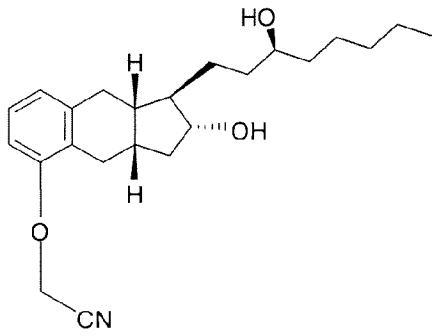
(IV)

comprising

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



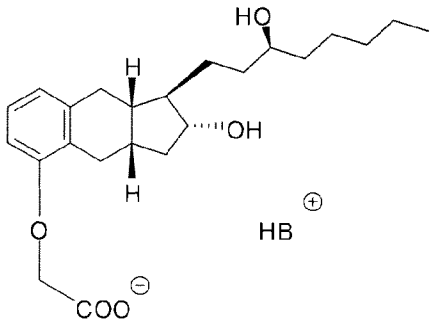
(V)



(VI)

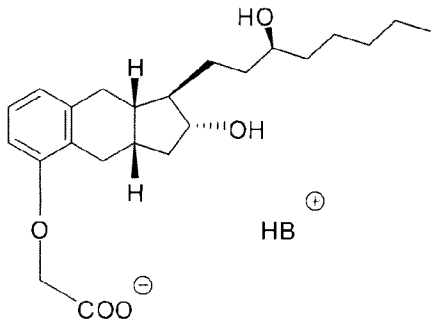
(b) hydrolyzing the product of formula VI of step (a) with a base, and

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



(IV_s), wherein the process does not comprise purifying the compound of formula (VI) produced in step (a).

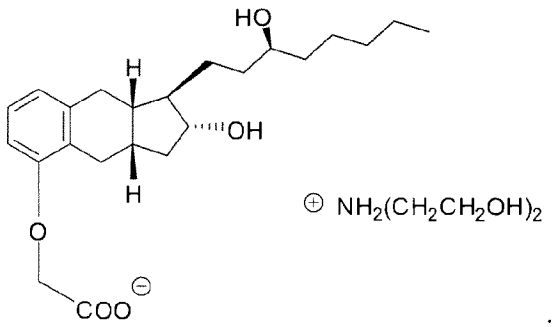
27. (New) The process according to claim 26, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, tricthanolamine, and diethanolamine and wherein the compound produced is a compound of the formula IV_s,



IV_s

wherein the base B is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, tricthanolamine, and diethanolamine.

28. (New) The process according to claim 27, wherein the base B is diethanolamine and wherein the compound produced is a compound of the following formula:



REMARKS

Applicants respectfully request reconsideration and allowance of the present application.

CLAIMS STATUS

Applicants have amended claims 1, 2, 10, 11, without prejudice or disclaimer, to present the claimed invention in a clearer manner and to correct inadvertent typographical errors. Applicants reserve the right to file one or more continuing applications directed to the subject matter omitted by the present amendment. No new matter has been added.

Applicants have canceled claims 18 and 19, without prejudice or disclaimer. Applicants reserve the right to file one or more continuing applications directed to the canceled claims.

Applicants have introduced new claims 20-28. Support for the new claims may be found throughout the specification as filed and, in particular, for claim 20 and 22 in paragraph 0046; for claim 21 in original claim 2; for claim 23 in original claim 11; for claim 24 in original claim 15; for claim 25 in original claim 16; for claim 26 in original claims 10 and paragraph 0046; for claim 27 in original claims 15 and 18; for claim 28 in original claims 16 and 19. No new matter has been added.

After the amendment, pending claims include a) examined claims 1-17 and b) new claims 20-28.

CLAIM REJECTIONS UNDER 35 U.S.C. § 112, ¶ 1

Claims 1-19 stand rejected because, in the PTO's opinion, the specification is not enabling for solvates and hydrates of the recited compounds. Applicants believe that the revised claims set obviates the rejection.

CLAIM REJECTIONS UNDER 35 U.S.C. § 112, ¶ 2

Claims 1-19 stand rejected as indefinite. In particular, the PTO asserted the following deficiencies:

1) "It is unclear what prodrugs applicant intends to cover."

2) "The structure of the compounds is indefinite since the structure of M1 and L1 is unclear. Specifically the structure of alpha and beta in the definition of the M1 and L1 is unclear. In addition, C=M1 and C=L1 contain double bonds, but this is not present in the structures of claims 9, 10, 18 and 19."

Applicants believe that the revised claim set obviates deficiency 1.

Applicants respectfully traverse deficiency 2 because one of ordinary skill in the art would understand that in claim 1's definitions of M1 and L1, α refers to an alpha bond, i.e. a bond which lies above the plane of the molecule, while β refers a beta bond, i.e. a bond, which lies below the plane of the molecule. Thus, for example, M1 being α-OH:β-R_5 means that OH is linked to M1's carbon atom through an alpha bond, thus, lying above the plane of the molecule, while R_5 is linked to M1's carbon through a beta bond, thus, lying below the plane of the molecule. US patent no. 6,765,117 (granted from US application no. 10/184,907 which was published as US 2002/0173,672) provides evidence that one of ordinary skill in the art would understand the definitions of M1 and L1 because the issued claims of this patent contain definitions for M1 and L1 using the same α:β notation as the pending claims.

Applicants respectfully submit that there is no contradiction between the structures of formula IV or IVs in claims 9, 10, 18 and 19, on one hand, and corresponding claim 1's structures containing C=M1 and C=L1, on the other, because one of ordinary skill in the art would understand in view of the definitions of M1 and L1 that C=M1 and C=L1 do not refer to a double bond but instead to two single bonds, namely alpha and beta single bonds. Applicants respectfully submit that the structures of formula IV or IVs in claims 9, 10, 18 and 19 correspond to structures of formula I and Is with M1 being α-OH:β-R_5, wherein R_5 is H, and L1 being α-R_3:β-R_4, wherein R_3 and R_4 are both H.

In sum, for the reasons discussed in this section, Applicants request withdrawal of the rejection.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 1-19 stand rejected as obvious over Moriarty (US 2002/0173672). Applicants respectfully traverse.

On page 7 of the Office Action, the PTO refers to the reaction on Moriarty's page 6. After that the PTO asserts as follows:

> "The difference between the process covered by the rejected claims and the process disclosed by Moriarty is that Moriarty fails to explicitly teach reacting the product of the hydrolysis step with an acid. However, the product formed [above] is the free acid, and thus, reaction of the product of the hydrolysis step with an acid to form the free acid product is invariable aspect of the process of Moriarty, and thus, prima facie obvious."

The PTO failed to establish a *prima facie* case obviousness at least because the PTO relies on factually inaccurate and conclusory statements in its obviousness analysis. Furthermore, the PTO failed to establish a *prima facie* case of obviousness because Moriarty does not teach or suggest steps c) and d) of the pending claims.

The reaction on Moriarty's page 6 (compound 14-compound 15-compound 16) may read only on steps a) and b) of claims 1 and 10, however, Moriarty does not teach or suggest steps c) and d) recited in claims 1 and 10. Applicants respectfully submit that the hydrolyzing step (b) of the pending claims will result in formation a product containing compound of formula I (claim 1) or formula IV (claim 10) in a free acid form. However, the claimed methods do not stop at the product of the hydrolyzing step. Instead, they involve step (c), which results in formation of a salt and step (d), which results in formation of compound of formula I (claim 1) or formula IV (claim 10) from the salt formed in step (c). Applicants respectfully submit that Moriarty does not teach or suggest these steps (steps c) and d)).

For a better understanding of the claimed invention, Applicants respectfully refer the PTO to pages 11-17 of the application as filed, which illustrates the claimed process for

production of treprostinil, which is the compound of formula IV recited in claim 10 or the compound of formula I (claim 1) with M1 being α-OH:β-R_5, wherein R_5 is H, and L1 being α-R_3:β-R_4, wherein R_3 and R_4 are both H. The process on pages 11-17 includes the following steps: a) Alkylation of Benzindene Triol, which results in formation of benzindene nitrile (Example 1, pages 11-12); b) Hydrolysis of Benzindene Nitrile, which results in formation of treprostinil (Example 2, pages 12-14); c) Conversion of Treprostinil to Treprostinil Diethanolamine Salt (Example 3, pages 14-15) and d) Conversion of Treprostinil Diethanolamine to Tresprostinil (Example 5, page 17), which can read on respective steps a-d of claims 1 and 10. The fact that treprostinil in a free acid form was formed in the hydrolyzing step b) demonstrates that the PTO's assertion that "reaction of the product of the hydrolysis step with an acid to form the free acid product is invariable aspect of the process of Moriarty" is factually incorrect.

Applicants respectfully submit that steps c) and d), which Moriarty does not teach or suggest, can provide a number of advantages. For example, due to the salt forming step c, the impurities form alkylating step a) and hydrolyzing step b) can removed, see e.g. paragraph 0046 of the specification as filed. As the result, the purification of benzindene nitrile compound, such as compound (III) or (VI), which purification was required by the prior art, such as Moriarty (see Moriarty's paragraph 0078), can be eliminated (see e.g. paragraph 0046 of the specification as filed) without an adverse effect on the quality of the resulting compound of formula (I) formed in step d. Applicants respectfully submit that new claims 20-23 emphasize the discussed above advantages of the claimed method.

In sum, because the PTO failed to establish a *prima facie* case of obviousness, Applicants request withdrawal of the rejection.

NEW CLAIMS 20-28

New claims 20-25 are new and non-obvious over Moriarty at least because each one of them depends either on claim 1 or claim 10, which are patentable for the reasons discussed above.

New claims 26-28 are new and non-obvious over Moriarty at least because this reference does not teach or suggest contacting step c) of claim 26.

CONCLUSION

Applicants believe that the present application is in condition for allowance. Favorable reconsideration 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.

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, Applicant hereby petitions 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 July 7, 2011

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4632
Facsimile: (202) 672-5399

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

Electronic Patent Application Fee Transmittal

Application Number:	12334731
Filing Date:	15-Dec-2008
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN
First Named Inventor/Applicant Name:	Hitesh BATRA
Filer:	Alexey V. Saprigin
Attorney Docket Number:	080618-0629

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	2202	6	26	156
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 $0 paid	2251	1	65	65
Miscellaneous:				
			Total in USD ($)	**221**

Electronic Acknowledgement Receipt

EFS ID:	10468552
Application Number:	12334731
International Application Number:	
Confirmation Number:	8804
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
Filer Authorized By:	
Attorney Docket Number:	080618-0629
Receipt Date:	07-JUL-2011
Filing Date:	15-DEC-2008
Time Stamp:	15:15:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$221
RAM confirmation Number	1555
Deposit Account	
Authorized User	

File Listing:

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

1	Miscellaneous Incoming Letter	AmendmentTrans070711.pdf	71734 4522ceeb58a4f46e716994d6bf6368ba0c2b2c22	no	2
Warnings:					
Information:					
2	Amendment/Req. Reconsideration-After Non-Final Reject	Amendment070711.pdf	431972 2767fef59c4ed7006e0ef35c0fb6a5ce71996d59	no	14
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32213 97582a17a0d85ac3e49e9bbfc991316b948a06cc	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	535919	

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

Applicant:	Hitesh BATRA et al.
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	12/334,731
Filing Date:	12/15/2008
Examiner:	Karl J. PUTTLITZ
Art Unit:	1621
Confirmation Number:	8804

AMENDMENT TRANSMITTAL

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

Sir:

Transmitted herewith is an amendment in the above-identified application.

[**X**] Small Entity status under 37 C.F.R. § 1.9 and § 1.27 has been established by a previous assertion of Small Entity status.

[**X**] The fee required for additional claims is calculated below:

	Claims As Amended		Previously Paid For		Extra Claims Present		Rate		Additional Claims Fee
Total Claims:	26	-	20	=	6	x	$52.00	=	$312.00
Independent Claims:	3	-	3	=	0	x	$220.00	=	$0.00
					CLAIMS FEE TOTAL			=	$312.00

[**X**] Applicant hereby petitions for an extension of time under 37 C.F.R. §1.136(a) for the total number of months checked below:

[X]	Extension for response filed within the first month:	$130.00	$130.00
		EXTENSION FEE TOTAL:	$130.00
		CLAIMS, EXTENSION AND DISCLAIMER FEE TOTAL:	$442.00
[X]		Small Entity Fees Apply (subtract ½ of above):	$221.00
		TOTAL FEE:	$221.00

The above-identified fees of $221.00 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.

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 extensions fees 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 7, 2011

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4632
Facsimile: (202) 672-5399

Alexey V. Saprigin
Attorney for Applicant
Registration No. 56,439

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

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
12/334,731	12/15/2008	

APPLICATION AS FILED – PART I

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

APPLICATION AS AMENDED – PART II

AMENDMENT 07/07/2011	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 26	Minus	** 20	= 6	X $26 =	156	OR	X $ =	
Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $110 =	0	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	156	OR	TOTAL ADD'L FEE	

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

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

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

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

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

Legal Instrument Examiner:
/KELLY HARRIS/

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.
12/334,731	12/15/2008	Hitesh BATRA	080618-0629	8804

22428 7590 09/19/2011

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

EXAMINER	
VALENROD, YEVGENY	
ART UNIT	PAPER NUMBER
1621	
MAIL DATE	DELIVERY MODE
09/19/2011	PAPER

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.

Office Action Summary	Application No.	Applicant(s)	
	12/334,731	BATRA ET AL.	
	Examiner	Art Unit	
	YEVGENY VALENROD	1621	

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

Period for Reply

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

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

Status

1)☒ Responsive to communication(s) filed on *07 July 2011*.

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) *1-17 and 20-28* is/are pending in the application.

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

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-17 and 20-28* is/are rejected.

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

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

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).

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

Priority under 35 U.S.C. § 119

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

a)☐ All b)☐ Some * c)☐ None of:

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

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

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

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

Attachment(s)

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

DETAILED ACTION

Instant application has been transferred to Examiner Valenrod whose contact information is provided at the end of the instant office action.

Rejection of claims 1-19 under 35 USC 112 1st paragraph has been withdrawn in view of applicants' amendments.

Rejection of claims 1-19 under 35 USC 112 2nd paragraph has been withdrawn in view of applicants' remarks.

Rejection of claims 1-19 under 35 USC 103(a) over Moriarty et al. has been withdrawn in favor of a new rejection.

Claim Rejections - 35 USC § 103

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

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-17 and 20-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moriarty et al. (US 2002/0173672) in view of Phares et al. (US 2005/0085540).

Scope of prior art

Moriarty et al teach steps a), b) and d) of the instant claims. Particularly Moriarty teaches alkylation of compound 14 with $ClCH_2CN$ in the presence of K_2CO_3 in acetone to produce compound 15 (paragraph [0078]). Compound 15 is then hydrolyzed with a base which produces a carboxylate salt and subsequently treated with an acid (HCl) to produce compound 16, which is the product of the instantly claimed process (paragraph [0079]).

Ascertaining the difference between instant claims and prior art

The process of Moriarty differs from the instant claim in that step after the treatment with a base in what corresponds to instant step b), the resulting carboxylate salt is not contacted with additional base B to produce salt of formula IV_s which corresponds to instant step c).

Secondary reference

Phares teaches that treprostinil diethanolamine can be crystalized (figure 20, paragraph [0051]).

Obviousness

One skilled in the art practicing the invention of Moriarty would have found it obvious to add a purification step in order to obtain a more pure product. Since Phares indicated that treprostinil diethanolamine can be crystalized, one skilled in the art would have found it obvious to use this property of the diethanolamine salt in order to purify treprostinil via crystallization. As such in would have been obvious to convert the potassium salt of treprostinil obtained after step b), which is taught by Moriarty, into diethanolamine salt, purify said salt via crystallization followed by acidification as taught my Moriarty to recover treprostinil as a free acid. The instant invention amounts to addition of a purification step via crystallization. Since such a step has been taught in the art, at the time the instantly claimed invention was made one would have found it obvious to make the required modification. Motivation is provided by desire to obtain a more pure product. Expectation of success is provided by Phares when a crystal form of the diethanolamine salt is disclosed.

Limitation directed to purity of the product are inherently met by the combination of Moriarty and Phares. Since the motivation to preform crystallization of the diethanolamine salt is to obtain a pure compound, it stands to reason that the purity of the product would be improved. The exact purity would inherently be same as instantly claimed because the same sequence of steps would be carried out.

Conclusion

Claims 1-17 and 20-28 are pending

Claims 1-17 and 20-28 are rejected

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, Daniel Sullivan can be reached on 571-272-0779. 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/

Yevgeny Valenrod
Patent Examiner

Notice of References Cited	Application/Control No. 12/334,731	Applicant(s)/Patent Under Reexamination BATRA ET AL.	
	Examiner YEVGENY VALENROD	Art Unit 1621	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2005/0085540	04-2005	Phares et al.	514/530
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

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

NON-PATENT DOCUMENTS

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

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

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	3	((HITESH) near2 (BATRA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2011/09/14 12:30
L2	1	((SUDERSAN) near2 (TULADHAR)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2011/09/14 12:30
L3	14	((RAJU) near2 (PENMASTA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2011/09/14 12:30
L4	183	((DAVID) near2 (WALSH)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2011/09/14 12:30
L5	1	"6765117"	USPAT	OR	OFF	2011/09/14 12:31
L6	0	"20020173672"	USPAT	OR	OFF	2011/09/14 12:31
L7	1	("20020173672").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2011/09/14 12:31
L8	0	("2002/0173672").URPN.	USPAT	OR	OFF	2011/09/14 12:31
L9	1	("4306075").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2011/09/14 12:31
L10	1	("6441245").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2011/09/14 12:31
L11	1	("5387713").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2011/09/14 12:31
L12	1	("20050085540").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2011/09/14 12:31
L13	1	("20070078182").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2011/09/14 12:31
L14	1	("20070254032").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2011/09/14 12:31
L15	25	treprostinil diethanolamine	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2011/09/14 12:31
L16	1	("4845598").PN.	USPAT; USOCR	OR	OFF	2011/09/14 12:31

EAST Search History (Prior Art)

L17	1	("4485598").PN.	USPAT; USOCR	OR	OFF	2011/09/14 12:31
L18	1	("4486598").PN.	USPAT; USOCR	OR	OFF	2011/09/14 12:31
L19	1	("4486598").URPN.	USPAT	OR	OFF	2011/09/14 12:31
L20	29	treprostinil same diethanolamine	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2011/09/14 12:31
L21	4	L20 not L15	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2011/09/14 12:31
L22	181	l1 or l2 or l3 or l4	US-PGPUB; USPAT	OR	OFF	2011/09/14 12:31
L23	2	l22 and treprostinil	US-PGPUB; USPAT	OR	OFF	2011/09/14 12:31

EAST Search History (Interference)

		<This search history is empty>				

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* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1           Web Page for STN Seminar Schedule - N. America
 NEWS  2  DEC 21   CAS Learning Solutions -- a new online training experience
 NEWS  3  JAN 24   The new and enhanced DPCI file on STN has been released
 NEWS  4  JAN 26   Improved Timeliness of CAS Indexing Adds Value to
                   USPATFULL and USPAT2 Chemistry Patents
 NEWS  5  JAN 26   Updated MeSH vocabulary, new structured abstracts, and
                   other enhancements improve searching in STN reload of
                   MEDLINE
 NEWS  6  JAN 28   CABA will be updated weekly
 NEWS  7  FEB 23   PCTFULL file on STN completely reloaded
 NEWS  8  FEB 23   STN AnaVist Test Projects Now Available for
                   Qualified Customers
 NEWS  9  FEB 25   LPCI will be replaced by LDPCI
 NEWS 10  MAR 07   Pricing for SELECTing Patent, Application, and Priority
                   Numbers in the USPAT and IFI Database Families is Now
                   Consistent with Similar Patent Databases on STN
 NEWS 11  APR 26   Expanded Swedish Patent Application Coverage in CA/CAplus
                   Provides More Current and Complete Information
 NEWS 12  APR 28   The DWPI (files WPINDEX, WPIDS and WPIX) on STN have been
                   enhanced with thesauri for the European Patent Classifications
 NEWS 13  MAY 02   MEDLINE Improvements Provide Fast and Simple Access to DOI and
                   Chemical Name Information
 NEWS 14  MAY 12   European Patent Classification thesauri added to the INPADOC
                   files, PCTFULL, GBFULL and FRFULL
 NEWS 15  MAY 23   Enhanced performance of STN biosequence searches
 NEWS 16  MAY 23   Free Trial of the Numeric Property Search Feature
                   in PCTFULL on STN
 NEWS 17  JUN 20   STN on the Web Enhanced with New Patent Family Assistant and
                   Updated Structure Plug-In
 NEWS 18  JUN 20   INPADOC databases enhanced with first page images
 NEWS 19  JUN 20   PATDPA database updates to end in June 2011
 NEWS 20  JUN 26   MARPAT Enhancements Save Time and Increase Usability
 NEWS 21  JUL 25   STN adds Australian patent full-text database,
                   AUPATFULL, including the new numeric search feature.
 NEWS 22  AUG 01   CA Sections Added to ACS Publications Web Editions
                   Platform
 NEWS 23  AUG 16   INPADOC: Coverage of German Patent Data resumed,
                   enhanced legal status
 NEWS 24  AUG 18   Upgrade now to STN Express, Version 8.5
 NEWS 25  SEP 01   CAS Journal Coverage Now Includes Ahead-of-Print
                   Articles for More Than 100 Journal Titles
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                   Beginning in March 2012
 NEWS 27  SEP 09   USAN Database Updates Offer Superior Currency on STN(R)

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              AND CURRENT DISCOVER FILE IS DATED 24 JANUARY 2011.

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FILE 'HOME' ENTERED AT 15:44:02 ON 13 SEP 2011

=> file reg
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.23       0.23

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DICTIONARY FILE UPDATES:  12 SEP 2011  HIGHEST RN 1331823-92-7

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=>
Uploading C:\Users\yvalenrod\Documents\STN Express 8.4\Queries\12334731-salt.str

L1      STRUCTURE UPLOADED

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L1 HAS NO ANSWERS
L1              STR
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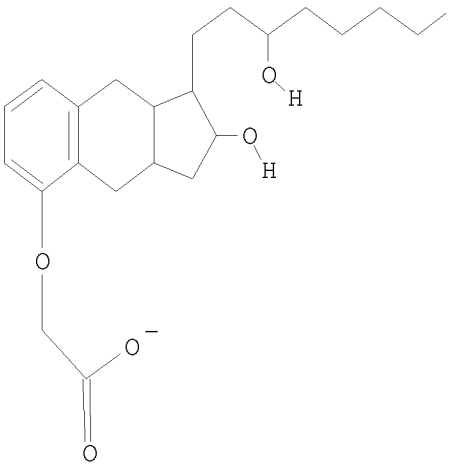

Structure attributes must be viewed using STN Express query preparation.

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SAMPLE SCREEN SEARCH COMPLETED -      127 TO ITERATE

100.0% PROCESSED      127 ITERATIONS                                0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:         1864 TO     3216
PROJECTED ANSWERS:               0 TO        0

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SEARCH TIME: 00.00.01

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L4      STRUCTURE UPLOADED

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100.0% PROCESSED      329 ITERATIONS                                2 ANSWERS
SEARCH TIME: 00.00.01

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                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:         5492 TO     7668
PROJECTED ANSWERS:               2 TO      124
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SEARCH TIME: 00.00.01

L6           35 SEA SSS FUL L4

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                     394.23     394.46

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FILE COVERS 1907 - 13 Sep 2011  VOL 155 ISS 12
FILE LAST UPDATED: 12 Sep 2011  (20110912/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED:  Jun 2011
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE:  Jun 2011

CAplus now includes complete International Patent Classification (IPC)
reclassification data for the second quarter of 2011.

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

=> s l6
L7          199 L6

=> s l7 and ethanolamine
         29810 ETHANOLAMINE
L8           1 L7 AND ETHANOLAMINE

=> s l7 and diethanolamine
         20017 DIETHANOLAMINE
L9           7 L7 AND DIETHANOLAMINE

=> d l9 ibib abs hitstr 1-
YOU HAVE REQUESTED DATA FROM 7 ANSWERS - CONTINUE? Y/(N):n
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=> s l8 or l9
L10          8 L8 OR L9

=> d l10 ibib abs hitstr 1-
YOU HAVE REQUESTED DATA FROM 8 ANSWERS - CONTINUE? Y/(N):y

L10  ANSWER 1 OF 8  CAPLUS  COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER:         2010:1404690  CAPLUS
DOCUMENT NUMBER:          153:627096
TITLE:                    Solid formulations of prostacyclin analogs
INVENTOR(S):              Phares, Kenneth Robert
PATENT ASSIGNEE(S):       United Therapeutics Corporation, USA
SOURCE:                   PCT Int. Appl., 29pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
     WO 2010129757         A1    20101111    WO 2010-US33852         20100506
         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, RO, RS, RU, 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, 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, SD, SL, SZ,
             TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
     US 20100282622        A1    20101111    US 2010-775102          20100506
PRIORITY APPLN. INFO.:                     US 2009-176268P     P    20090507
ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S):          MARPAT 153:627096
AB   Moderate moisture levels, such as greater than 3% but no greater than 7%,
     may be beneficial for solid formulations of certain prostacyclin analogs.
     Accordingly, a solid formulation containing a prostacyclin analog may be
     packaged inside a pharmaceutical packaging with such amount of a desiccant
     or a drying agent that after the storage the solid formulation may have a
     moderate level of moisture in it.  Stability of treprostinil
     diethanolamine tablets at 40° temperature and 75% relative humidity was
     studied.
IT   81846-19-7D, Treprostinil, enantiomers   830354-48-8,
     Treprostinil diethanolamine
     RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
        (solid formulations of prostacyclin analogs)
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 (-).
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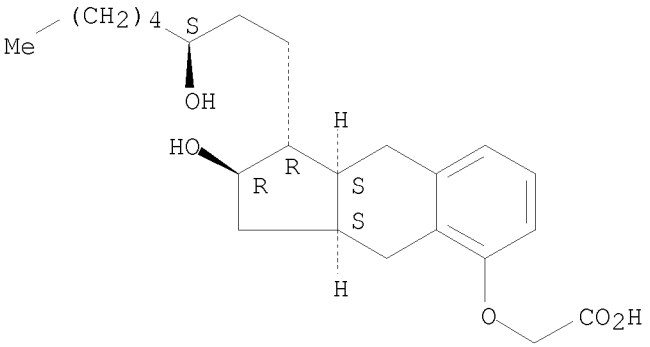
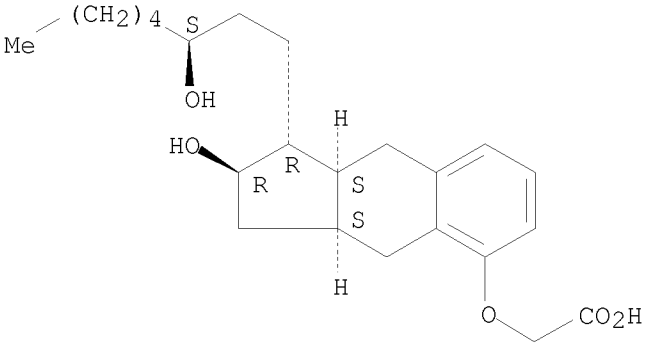


RN 830354-48-8 CAPLUS
CN Acetic acid, 2-[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]-, compd. with 2,2'-iminobis[ethanol] (1:1) (CA INDEX NAME)

CM 1

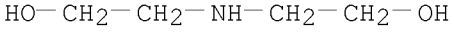
CRN 81846-19-7
CMF C23 H34 O5

Absolute stereochemistry. Rotation (-).



CM 2

CRN 111-42-2
CMF C4 H11 N O2



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2010:923071 CAPLUS
DOCUMENT NUMBER: 154:173338
TITLE: Lack of a pharmacokinetic interaction between oral treprostinil and bosentan in healthy adult volunteers
AUTHOR(S): Gotzkowsky, S. Karl; Dingemanse, Jasper; Lai, Allen; Mottola, David; Laliberte, Kevin
CORPORATE SOURCE: United Therapeutics Corporation, Research Triangle

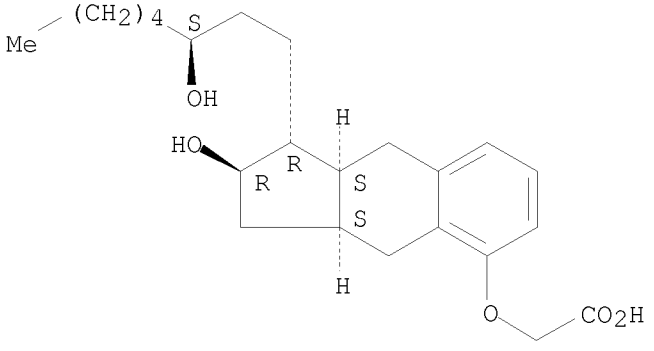
Park, NC, USA
SOURCE: Journal of Clinical Pharmacology (2010), 50(7), 829-834
CODEN: JCPCBR; ISSN: 0091-2700
PUBLISHER: Sage Publications
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Treprostinil diethanolamine is an oral prostacyclin analog currently being evaluated for the treatment of pulmonary arterial hypertension (PAH). Treprostinil is metabolized primarily by cytochrome P 450 (CYP) 2C8 with minor contribution from CYP2C9. It is expected that oral treprostinil will be administered with bosentan, approved for the treatment of PAH and known to induce CYP2C9 and 3A4. This study evaluated whether a drug interaction exists between oral treprostinil, bosentan, and its active metabolite Ro 48-5033 during co-administration. Twenty-four participants were randomized in a 3-way crossover study to oral treprostinil 1 mg twice daily, bosentan 125 mg twice daily, and oral treprostinil 1 mg twice daily and bosentan 125 mg twice daily. Treprostinil geometric mean ratios (GMRs) (90% confidence interval [CIs]) for steady-state AUC0-12 and Cmax (combination/treprostinil) were 0.92 (0.83, 1.03) and 0.96 (0.83, 1.11), resp., whereas bosentan GMRs (combination/bosentan) were 1.02 (0.95, 1.10) and 1.04 (0.94, 1.15), resp., and Ro 48-5033 GMRs were 0.99 (0.93, 1.06) and 1.03 (0.94, 1.13). In conclusion, because the GMR and 90% CI are within the equivalence interval of 0.8 to 1.25, co-administration of oral treprostinil and bosentan did not result in a pharmacokinetic interaction for either agent.

IT 289480-64-4, Remodulin
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(coadministration of oral Remodulin and Tracleer did not show pharmacokinetic interaction and was safe in healthy adult human)

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 (-).



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2009:1402641 CAPLUS

DOCUMENT NUMBER: 151:515307
TITLE: Preparation of treprostinil monohydrate for pharmaceutical formulations
INVENTOR(S): Walsh, David A.
PATENT ASSIGNEE(S): United Therapeutics Corporation, USA
SOURCE: PCT Int. Appl., 22pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2009137066	A1	20091112	WO 2009-US2818		20090507
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
CA 2723540	A1	20091112	CA 2009-2723540		20090507
US 20090281189	A1	20091112	US 2009-437054		20090507
KR 2011010753	A	20110207	KR 2010-7027068		20090507
EP 2300408	A1	20110330	EP 2009-743053		20090507
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, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, AL, BA, RS					
CN 102015613	A	20110413	CN 2009-80116126		20090507
JP 2011519927	T	20110714	JP 2011-508505		20090507
PRIORITY APPLN. INFO.:			US 2008-51509P	P	20080508
			WO 2009-US2818	W	20090507

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT

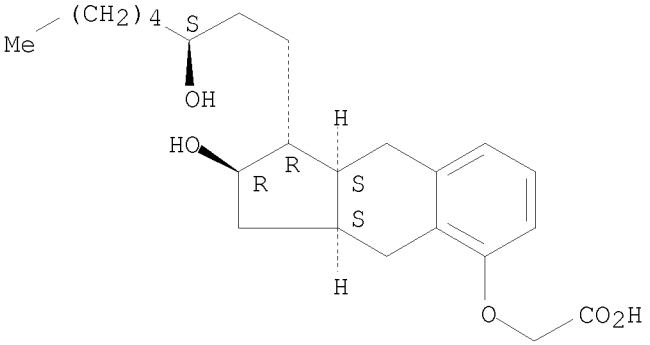
AB There is provided a stable monohydrate form of treprostinil and pharmaceutical formulation comprising the same, method of making and using the same. Treprostinil diethanolamine was dissolved in water and converted to the title compound The monohydrate was more stable than the anhydrous form at ambient temps.

IT 81846-19-7P 1173918-57-4P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of treprostinil monohydrate for pharmaceutical formulations)

RN 81846-19-7 CAPLUS

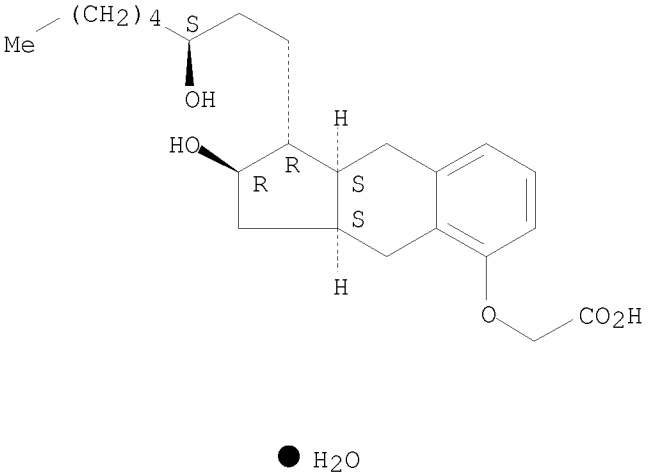
CN Acetic acid, 2-[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]- (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 1173918-57-4 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]-, hydrate (1:1) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

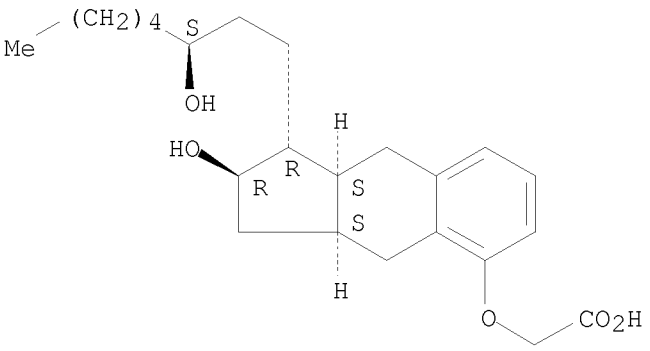


IT 830354-48-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of treprostinil monohydrate for pharmaceutical formulations)
RN 830354-48-8 CAPLUS
CN Acetic acid, 2-[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]-, compd. with 2,2'-iminobis[ethanol] (1:1) (CA INDEX NAME)

CM 1

CRN 81846-19-7
CMF C23 H34 O5

Absolute stereochemistry. Rotation (-).



CM 2

CRN 111-42-2
CMF C4 H11 N O2

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2009:1263383 CAPLUS
DOCUMENT NUMBER: 151:440606
TITLE: Pharmaceutically active compounds with novel medical uses and method of identifying such compounds
INVENTOR(S): Kuhn, Michael; Campillos, Monica; Bork, Peer; Jensen, Lars Juhl; Gavin, Anne-Claude; Petsalaki, Evangelia; Garcia Urdales, Eduardo; Russel, Rob
PATENT ASSIGNEE(S): European Molecular Biology Laboratory (EMBL), Germany
SOURCE: PCT Int. Appl., 161pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2009124755	A1	20091015	WO 2009-EP2620	20090408

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RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2008-43292P P 20080408
OTHER SOURCE(S): MARPAT 151:440606
AB The invention provides a method for identifying a novel medical indication

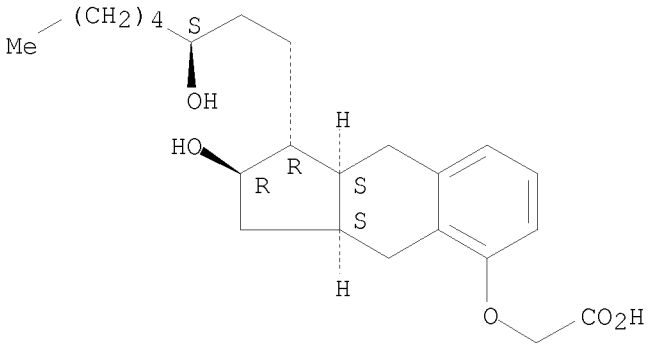
of a pharmaceutically active compound The invention further provides novel medical indications for several pharmaceutically active compds. Specifically, compds. are provided for the prevention and treatment of a disease or disorder treatable with a serotonin-norepinephrine reuptake inhibitor (SNRI), a serotonin receptor antagonist, an estazolam, a dopamine receptor antagonist, a dopamine receptor agonist, an L-type calcium channel blocker, a selective estrogen receptor modulator (SERM), and an antihistamine. Also provided is a pharmaceutically active compound for the prevention or treatment of tachycardia.

IT 81846-19-7, Treprostinil
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutically active compds. with novel medical uses and method of identifying such compds.)

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: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2011 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

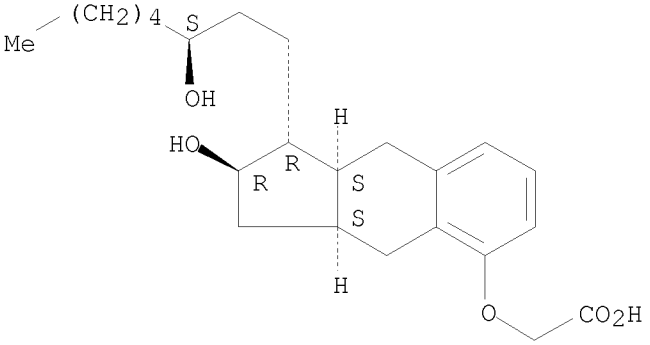
W: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, 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
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					
JP 2011506599	T	20110303	JP 2010-539440		20081212
US 20090163738	A1	20090625	US 2008-334731		20081215
IN 2010CN03640	A	20101015	IN 2010-CN3640		20100615
CN 101903324	A	20101201	CN 2008-80121181		20100617
PRIORITY APPLN. INFO.:			US 2007-14232P	P	20071217
			WO 2008-US13686	W	20081212

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 151:86694
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 (-).



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

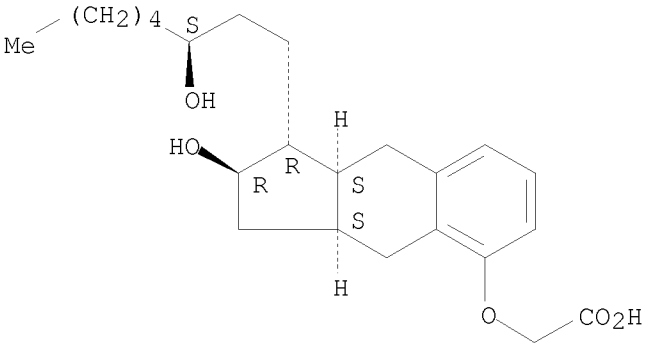
L10 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2009:244077 CAPLUS
DOCUMENT NUMBER: 150:382562
TITLE: Crystallization Process Development for a Stable Polymorph of Treprostinil Diethanolamine (UT-15C) by Seeding
AUTHOR(S): Batra, Hitesh; Penmasta, Raju; Phares, Kenneth; Staszewski, James; Tuladhar, Sudersan M.; Walsh, David A.
CORPORATE SOURCE: Research and Development Department, United Therapeutics Corporation, Silver Spring, MD, 20910,

USA
SOURCE: Organic Process Research & Development (2009), 13(2), 242-249
CODEN: OPRDFK; ISSN: 1083-6160
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Process development of treprostinil diethanolamine salt (UT-15C) involved the development of crystallization and slurry protocols to address the polymorph and morphol. control issues. Two forms of UT-15C were evaluated by differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD) and thermogravimetric anal. (TGA). Two crystallization solvent systems were developed to produce the thermodynamically stable form in high quality and yield. One solvent system gave dense particles while the other gave lighter and fly-away particles. Slurrying the lighter particles in heptane converted them to denser particles. The protocol was executed successfully on large-scale cGMP batches.
IT 830354-48-8
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(crystallization process development for a stable polymorph of treprostinil diethanolamine (UT-15C) by seeding)
RN 830354-48-8 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]-, compd. with 2,2'-iminobis[ethanol] (1:1) (CA INDEX NAME)

CM 1

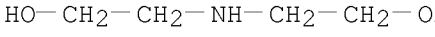
CRN 81846-19-7
CMF C23 H34 O5

Absolute stereochemistry. Rotation (-).



CM 2

CRN 111-42-2
CMF C4 H11 N O2



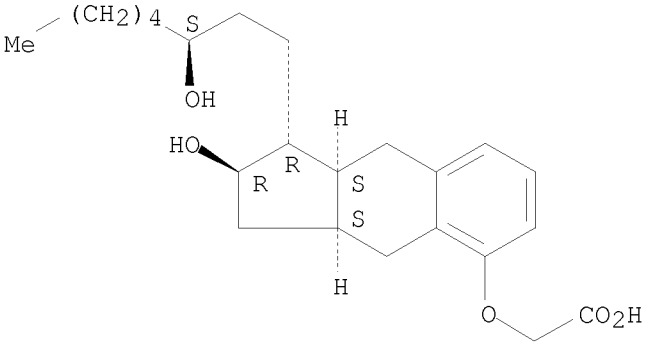
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2007:1242874 CAPLUS
DOCUMENT NUMBER: 147:491667
TITLE: Osmotic drug delivery system comprising prostacylin
INVENTOR(S): Kidane, Argaw; Bhatt, Padmanabh P.
PATENT ASSIGNEE(S): Spernus Pharmaceuticals, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 16 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20070254032	A1	20071101	US 2006-412100	20060427
CA 2649243	A1	20071108	CA 2007-2649243	20070426
WO 2007127216	A2	20071108	WO 2007-US9969	20070426
WO 2007127216	A3	20071227		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, 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, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
EP 2010189	A2	20090107	EP 2007-755989	20070426
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS				
JP 2009535337	T	20091001	JP 2009-507767	20070426
IN 2008DN09177	A	20090327	IN 2008-DN9177	20081103
KR 2009038392	A	20090420	KR 2008-7028877	20081126
CN 101466384	A	20090624	CN 2007-80019545	20081127
PRIORITY APPLN. INFO.:			US 2006-412100 A	20060427
			WO 2007-US9969 W	20070426

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
AB This invention relates to an oral osmotic pharmaceutical delivery system comprises a highly water-soluble drug exhibiting an erratic or an incomplete release profile when formulated in a elementary osmotic pump delivery system and at least one release enhancing agent. Thus, osmotic tablet was prepared comprising treprostinil diethanolamine 0.65%, xylitol 41.0%, Maltrin M150 (wet) 1.4%, Maltrin M150 (dry) 48.20%, sodium lauryl sulfate 5.0%, and meglumine 3.0%.
IT 81846-19-7D, Treprostinil, derivative 830354-48-8
RL: PKT (Pharmacokinetics); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(osmotic drug delivery system comprising prostacylin)
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 (-).

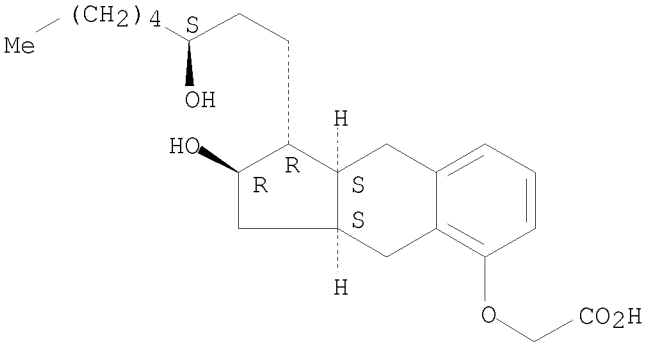


RN 830354-48-8 CAPLUS
CN Acetic acid, 2-[[(1R,2R,3aS,9aS)-2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]-, compd. with 2,2'-iminobis[ethanol] (1:1) (CA INDEX NAME)

CM 1

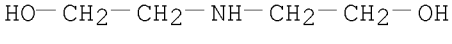
CRN 81846-19-7
CMF C23 H34 O5

Absolute stereochemistry. Rotation (-).



CM 2

CRN 111-42-2
CMF C4 H11 N O2



L10 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2011 ACS on STN
ACCESSION NUMBER: 2005:76235 CAPLUS
DOCUMENT NUMBER: 142:170431
TITLE: Compounds and methods for delivery of prostacyclin analogs
INVENTOR(S): Phares, Ken; Mottola, David
PATENT ASSIGNEE(S): United Therapeutics Corporation, USA
SOURCE: PCT Int. Appl., 122 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005007081	A2	20050127	WO 2004-US16401	20040524
WO 2005007081	A3	20050414		
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				
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CA 2526534	C	20110712		
CA 2736406	A1	20050127	CA 2004-2736406	20040524
US 20050085540	A1	20050421	US 2004-851481	20040524
US 7417070	B2	20080826		
EP 1628654	A2	20060301	EP 2004-776104	20040524
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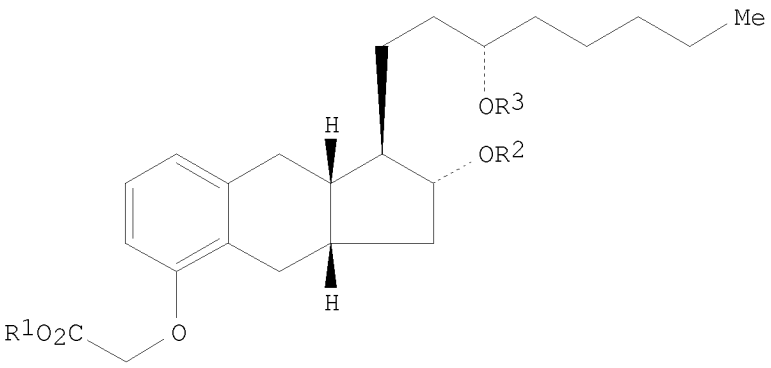
CN 1822826	A	20060823	CN 2004-80020569	20040524
CN 100558351	C	20091111		
JP 2007501281	T	20070125	JP 2006-533395	20040524
CN 101265226	A	20080917	CN 2008-10086199	20040524
CN 101780092	A	20100721	CN 2009-10178738	20040524
US 20050282901	A1	20051222	US 2005-189072	20050726
KR 2006021862	A	20060308	KR 2005-7022319	20051122
IN 2005KN02621	A	20070727	IN 2005-KN2621	20051219
IN 247151	A1	20110401		
US 20070078182	A1	20070405	US 2006-603124	20061122
US 7384978	B2	20080610		
US 20070078095	A1	20070405	US 2006-603219	20061122
US 20070082948	A1	20070412	US 2006-603116	20061122
US 7544713	B2	20090609		
US 20080249167	A1	20081009	US 2008-78955	20080408
US 20110118213	A1	20110519	US 2011-13155	20110125

PRIORITY APPLN. INFO.:	US 2003-472407P	P	20030522
	CA 2004-2526534	A3	20040524
	CN 2004-80020569	A3	20040524
	US 2004-851481	A1	20040524
	WO 2004-US16401	W	20040524
	US 2005-189072	A1	20050726
	US 2006-603124	A3	20061122

ASSIGNMENT HISTORY FOR US PATENT AVAILABLE IN LSUS DISPLAY FORMAT
OTHER SOURCE(S): MARPAT 142:170431
GI



I

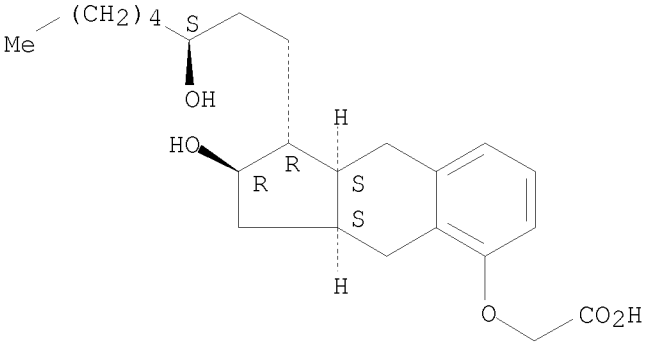
AB This invention pertains generally to prostacyclin analogs and methods for their use in promoting vasodilation, inhibiting platelet aggregation and thrombus formation, stimulating thrombolysis, inhibiting cell proliferation (including vascular remodeling), providing cytoprotection, preventing atherogenesis and inducing angiogenesis. The present compds. can be used to treat pulmonary hypertension. Generally, the compds. and methods of the present invention increase the oral bioavailability and circulating concns. of treprostinil when administered orally. Compds. of the present invention have formula (I) wherein, R1 is independently selected from the group consisting of H, substituted and unsubstituted benzyl groups, and groups wherein OR are substituted or unsubstituted glycolamide esters; R2 and R3 may be the same or different and are independently selected from the group consisting of H, phosphate and groups wherein OR2 and OR3 form esters of amino acids or proteins, with the proviso that all of R1, R2 and R3 are not H. The present methods can also comprise administering pharmaceutically effective amount of a p-glycoprotein inhibitor with the prostacyclin analogs.

IT 81846-19-7, Treprostinil
RL: BSU (Biological study, unclassified); PKT (Pharmacokinetics); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(compds. and methods for delivery of prostacyclin analogs for treatment of diseases such as pulmonary hypertension together with p-glycoprotein inhibitors)

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 830354-48-8
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); PRP

(Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compds. and methods for delivery of prostacyclin analogs for treatment of diseases such as pulmonary hypertension together with p-glycoprotein inhibitors)

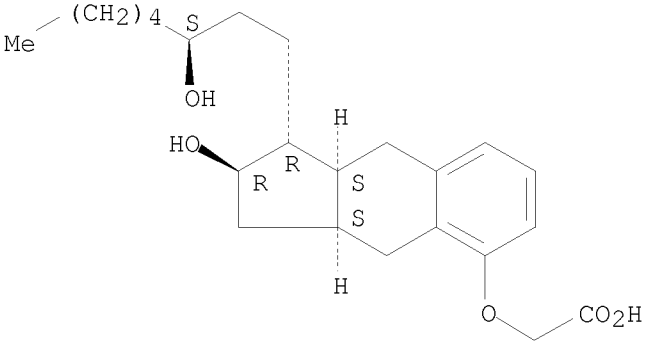
RN 830354-48-8 CAPLUS

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]-, compd. with 2,2'-iminobis[ethanol] (1:1) (CA INDEX NAME)

CM 1

CRN 81846-19-7
CMF C23 H34 O5

Absolute stereochemistry. Rotation (-).



CM 2

CRN 111-42-2
CMF C4 H11 N O2

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12334731	BATRA ET AL.
	Examiner	Art Unit
	Yevgeny Valenrod	1621

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
STN search	9/14/2011	YV
EAST search	9/14/2011	YV
inventor search	9/14/2011	YV
reviewed search report in counterpart PCT application	9/14/2011	YV

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

/YEVEGENY VALENROD/ Examiner.Art Unit 1621	

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12334731	BATRA ET AL.
	Examiner	Art Unit
	YEVEGENY VALENROD	1621

✓	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	09/14/2011								
	1	✓								
	2	✓								
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	27	✓								
	28	✓								

Atty. Dkt. No. 080618-0629

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.: 12/334,731

Filing Date: 12/15/2008

Examiner: Yevgeny Valenrod

Art Unit: 1621

Conf. No.: 8804

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

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

Sir:

Submitted herewith on Form PTO/SB/08 is a listing of documents known to Applicants in order to comply with Applicants' duty of disclosure pursuant to 37 CFR §1.56.

A copy of each non-U.S. patent document and each non-patent document is being submitted to comply with the provisions of 37 CFR §1.97 and §1.98.

The submission of any document herewith, which is not a statutory bar, is not intended as 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 which is determined to be a *prima facie* art reference against the claims of the present application.

10/13/2011 CCHAU1 00000022 12334731
01 FC:1806 180.00 OP

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(c), before the mailing date of any of a final action under 37 CFR §1.113, a notice of allowance under 37 CFR §1.311, or an action that otherwise closes prosecution in the application.

RELEVANCE OF EACH DOCUMENT

Any document listed on the attached PTO/SB/08 was cited as being relevant during the prosecution of the International Application No. PCT/US2011/38946, a copy of which is submitted herewith. An English-language abstract of foreign-language Document C4 is provided.

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.

FEE

A credit card payment form in the amount of $180.00 is enclosed to cover the fee associated with an information disclosure statement under 37 CFR §1.97(c).

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this submission under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741.

Respectfully submitted,

Date OCT 12 2011

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4632
Facsimile: (202) 672-5399

Alexey V. Saprigin
Attorney for Applicant
Registration No. 56,439

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
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: October 12, 2011

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	12/334,731
Filing Date	12/15/2008
First Named Inventor	Hitesh BATRA
Art Unit	1621
Examiner Name	Yevgeny Valenrod
Attorney Docket Number	080618-0629

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	2004/0176645 A1	09/09/2004	Moriarty et al.	
	C2	4,424,376 A	01/03/1984	Moniot et al.	
	C3	4,463,183 A	07/31/1984	Haslanger, Martin F.	

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]
	C4	EP 0 004 335 A2	10/03/1979	Hoechst AG		A
	C5	WO 2009/117095 A1	09/24/2009	Arena Pharmaceuticals, 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]

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.

This collection of information is required by 37 CFR 1.97 and 1.98. 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 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
STEPHEN B. MAEBIUS
FOLEY & LARDNER LLP
3000 K STREET, NW
SUITE 600
WASHINGTON, DC 20007

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 080618-0953	Date of mailing *(day/month/year)* 16 SEP 2011 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 11/38946	International filing date *(day/month/year)* 02 June 2011 (02.06.2011)
Applicant UNITED THERAPEUTICS CORPORATION	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 82 70

   For more detailed instructions, see *PCT Applicant's Guide*, International Phase, paragraphs 9.004 – 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. Following the expiration of 30 months from the priority date, these comments will also be made available to the public.

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer Lee W. Young PCT Helpdesk: 571-272-4300 Telephone No. PCT OSP: 571-272-7774

Form PCT/ISA/220 (July 2010)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 080618-0953	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 11/38946	International filing date *(day/month/year)* 02 June 2011 (02.06.2011)	(Earliest) Priority Date *(day/month/year)* 03 June 2010 (03.06.2010)
Applicant UNITED THERAPEUTICS CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

   c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☐ the text is approved as submitted by the applicant.

   ☒ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No. _____

   ☐ as suggested by the applicant.

   ☐ as selected by this Authority, because the applicant failed to suggest a figure.

   ☐ as selected by this Authority, because this figure better characterizes the invention.

   b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/38946

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

A method is disclosed for preparing a synthetic intermediate for treprostinil via a stereoselective alkyne addition reaction using a chiral inducing agent. Also described are methods of preparing treprostinil or a pharmaceutically acceptable salt thereof comprising the alkyne addition reaction as well as novel intermediates useful for synthesis prostacyclin derivatives. A functional alcohol protecting group protects the alcohol group from participating in reactions that are occurring in other parts of the molecule. The intermediate is later deprotected prior to conversion and hydrolyzing to obtain the final treprostinil product.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/38946

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07C 62/00, 65/00 (2011.01)
USPC - 562/466
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC- 562/466

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC- 514/569, 571, 573 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest (US Pat, PgPub, EPO, JPO), GoogleScholar (PL, NPL), FreePatentsOnline (US Pat, PgPub, EPO, JPO, WIPO, NPL); search terms: treprostinil, prostacylcin, epoprostanol, PGI2, remodulin, tyvaso, chiral, deprotect, protect, leave, hydrogenate, TBDMS, methyleneephedrin, tetrahydrofuranyl, stereoselec, benzyl, zinc

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2002/0173672 A1 (MORIARTY et al.) 21 November 2002 (21.11.2002) para [0006]-[0012], [0028], [0053], [0057], [0074]; pg 4-6	1-4, 10-19, 25-28 --- 7-9, 20-24, 29-30
X -- Y	US 2004/0176645 A1 (MORIARTY et al.) 09 September 2004 (09.09.2004), para [0006], [0027], [0032], [0047], [0048]	1, 5-6 --- 29-30
Y	WO 2009/117095 A1 (TRAN et al.) 24 September 2009 (24.09.2009) pg 2, ln 17 to pg 3, ln 24; pg 97, ln 24 to pg 98, ln 35; pg 106, ln 36 to pg 116, ln 8	7-9, 20-24
Y	US 4,463,183 A (HASLANGER) 31 July 1984 (31.07.1984) col 4-25	1-30
Y	US 4,424,376 A (MONIOT et al.) 03 January 1984 (03.01.1984) col 2-10	1-30
Y	EP 0 004 335 A2 (BARTMANN et al.) 14 March 1979 (14.03.1979) pg 1-25	1-30

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 September 2011 (06.09.2011)	16 SEP 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: STEPHEN B. MAEBIUS
FOLEY & LARDNER LLP
3000 K STREET, NW
SUITE 600
WASHINGTON, DC 20007

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	16 SEP 2011
Applicant's or agent's file reference 080618-0953	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 11/38946	02 June 2011 (02.06.2011)	03 June 2010 (03.06.2010)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C07C 62/00, 65/00 (2011.01)
USPC - 562/466

Applicant UNITED THERAPEUTICS CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1 *bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	06 September 2011 (06.09.2011)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (July 2011)

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      ☐ on paper

      ☐ in electronic form

   b. (time)

      ☐ in the international application as filed

      ☐ together with the international application in electronic form

      ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 11/38946

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	7-9, 20-24, 29-30	YES
	Claims	1-6, 10-19, 25-28	NO
Inventive step (IS)	Claims	none	YES
	Claims	1-30	NO
Industrial applicability (IA)	Claims	1-30	YES
	Claims	none	NO

2. Citations and explanations:

Claims 1-4, 10-19 and 25-28 lack novelty under PCT Article 33(2) as anticipated by US 2002/0173672 A1 to Moriarty et al. (hereinafter 'Moriarty '672').

Regarding Claims 1 and 10, Moriarty '672 discloses a method of preparing a compound represented by the following structural Formula (A) (para [0006]; pg 4, see intermediary 5):
P1 is an alcohol protecting group (para [0006], [0012], and [0053], see OR1, wherein R1 is RBDMS or THP);
R is -(CH2)nX; X is H, phenyl, -CN, -OR1 or COOR1; R1 is an alkyl, THP, TBDMS or a unsubstituted or substituted benzyl group; and n is 1,2 or 3 (para [0006]-[0010], see Z(CH2)nX, such that Z is O, R is -(CH2)nX, wherein X is OR9, n is 1, 2, or 3, and R9 is THP or TBDMS).

Regarding Claim 2, Moriarty '672 further discloses that R is (CH2)nCOOR1, wherein R1 is an alkyl (para [0006], [0008], and [0009], see Z(CH2)nX, such that Z is O, R is -(CH2)nX, wherein X is OR9, n is 1, 2, or 3, and R9 is THP or TBDMS) or a unsubstituted or substituted benzyl group.

Regarding Claim 3, Moriarty '672 further discloses that R1 is C1-C5 alkyl (para [0010]).

Regarding Claim 4, Moriarty '672 further discloses that R1 is benzyl (para [0008], see aryl.).

Regarding Claim 11, Moriarty '672 further discloses:
(1) reacting the compound of structural formula (A) with an alcohol protecting group to form a compound represented by structural formula (II) (pg 4-6);
(2) converting the compound of structural formula (II) to a tricyclic compound represented by structural formula (III) (pg 4-5);
(3) hydrogenating the tricyclic compound of structural formula (III) to form a hydrogenated tricyclic compound represented by structural formula (IV) (pg 4-6, See intermediary step 8);
(4) reacting the compound of structural formula (IV) with a reducing agent to form a compound represented by structural formula (V) (pg 4 -5);
(5) deprotecting the compound of structural represented by structural formula (VI) (pg 4-6);
(6) converting the compound represented by structural formula (VI) to a compound represented by structural formula (VII) (pg 4-6);
(7) reacting the compound represented by structural formula (VII) with X1(CH2)mCN to form a compound represented by structural formula (VIII) (pg 4-6, See intermediary step 9);
(8) hydrolyzing the compound of Structural Formula (VIII) to form the compound represented by Structural Formula (IX), wherein (pg 4-6).
P2 is an alcohol protecting group (para [0007] and 0012]);
m is 1,2 or 3 (para [0007]-[0009]); and
X1 is a leaving group (pg 6, see intemediary steps 15 to 16).

Regarding Claim 12, Moriarty '672 further discloses that R is (CH2)mCO2R1, wherein R1 is an alkyl (para [0006], [0008], and [0009], See Z(CH2)nX, such that Z is O, R is -(CH2)nX, wherein X is OR9, n is 1, 2, or 3, and R9 is THP or TBDMS) or a substituted or unsubstituted benzyl group.

Regarding Claim 13, Moriarty '672 further discloses:
(a) reacting the compound of structural formula (A) with a second alcohol protecting group to form a compound represented by structural formula (4) (pg 4-5; para [0006]-[0012] and [0053]); and
(b) converting the compound of structural formula (4) to a tricyclic compound 10 represented by structural formula (5) (pg 4-5; para [0006]-[0012] and [0053]).

Regarding Claim 14, Moriarty '672 further discloses that P2 is tert-butyldimethylsilyl (TBDMS) (para [0053]), tertiarybutyldiphenylsilyl (TBDPS), triethylsilyl (TES) or triphenylmethyl (trityl group).

Regarding Claim 15, Moriarty '672 further discloses that P2 is tert-butyldimethylsilyl (TBDMS) (para [0053]).

----------continued in Supplemental Box----------

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No. V 2. Citations and explanations:

Regarding Claim 16, Moriarty '672 further discloses that P1 is tetrahydrofuranyl (THP), benzyl, 2,4dinitrobenzyl, methoxymethyl (MOM), tertiarybutyldimethylsilyl (TBDMS) (para [0053]), tertiarybutyldiphenylsilyl (TBDPS) or triethylsilyl (TES).

Regarding Claim 17, Moriarty '672 further discloses that P1 is THP (para [0009]).

Regarding Claim 18, Moriarty '672 further discloses for the converting step (b), the compound of structural formula (4) is converted to the compound of structural formula (5) through a cobalt mediated cyclization reaction (para [0028]).

Regarding Claim 19, Moriarty '672 further discloses that the cobalt-mediated cyclization reaction is carried out in the presence of Co2(CO)8 (para [0028]).

Regarding Claim 25, Moriarty '672 further discloses that R1 is a substituted or unsubstituted benzyl group (para [0006]-[0012], See the aryl of Z.) and wherein the method further comprises: (c') hydrogenating the tricyclic compound of structural formula (5) to form a 10 hydrogenated tricyclic compound represented by structural formula (6'); and (d') converting the hydrogenated tricyclic compound represented by structural formula (6') to a compound represented by structural formula (IX) (pg 4-6).

Regarding Claim 26, Moriarty '672 further discloses that the hydrogenation reaction of step (c) is carried out in the presence of a base (para [0074]).

Regarding Claim 27, Moriarty '672 further discloses that the base is K2CO3 (para [0074]).

Regarding Claim 28, Moriarty '672 further discloses that R1 is an unsubstituted benzyl group (para [0008]).

Claims 1 and 5-6 lack novelty under PCT Article 33(2) as anticipated by US 2004/0176645 A1 to Moriarty et al. (hereinafter 'Moriarty '645').

Regarding Claim 1, Moriarty '645 discloses a method of preparing a compound represented by the following structural Formula (A) (para [0047], see intermediaries 20-23):
P1 is an alcohol protecting group (para [0006], [0027], [0032], and [0047], see OTHP);
R is -(CH2)nX; X is H, phenyl, -CN, -OR1 or COOR1; R1 is an alkyl, THP, TBDMS or a unsubstituted or substituted benzyl group; and n is 1,2 or 3 (para [0047], see OBn, such that R is -(CH2)nX, wherein X is H, R1 is an alkyl, and n is 1, 2, or 3).

Regarding Claim 5, Moriarty '645 further discloses that P1 is tert-butyldimethylsilyl (TBDMS) (para [0048]), tertiarybutyldiphenylsilyl (TBDPS), triethylsilyl (TES) or triphenylmethyl (trityl group).

Regarding Claim 6, Moriarty '645 further discloses that P1 is tert-butyldimethylsilyl (TBDMS) (para [0048]).

Claims 7-9 and 20-24 lack an inventive step under PCT Article 33(3) as obvious over Moriarty '672 in view of WO 2009/1170995 A1 to Tran et al. (hereinafter 'Tran').

Regarding Claims 7-9, Moriarty '672 discloses the method of Claim 1, but does not specifically disclose that:
- the reaction is carried out in the presence of chiral inducing agent (as in Claim 7);
- the chiral inducing ligand is (+)-N-methylephederin (as in Claim 8); or
- the reaction is carried out in the presence of a base and a zinc reagent (as in Claim 9). However, Tran discloses processes for producing intermediaries of cyclohexane derivatives (pg 2, ln 25 to pg 3, ln 24; pg 106, ln 36 to pg 116, ln 8), comprising:
a chiral resolving acid such as methylephedrin (pg 109, ln 29 to pg 110, ln 2), the reaction is carried out in the presence of a base and a metal cation reagent (pg 111, ln 1 to pg 112, ln 2), wherein the compound formed into a pharmaceutically acceptable salt metal cations such as zinc (pg 97, ln 24 to pg 98, ln 35). To a person of ordinary skill in the art, it would have been obvious to substitute the chiral resolving agent and metal cation as taught by Tran with the method as in Moriarty '672 in order to resolve desired chiral species of Formula (A), because Moriarty '672 and Tran are directed towards stereoselective intermediaries prostacyclin derivatives (Tran: pg 2, ln 17 -22).

----------continued in next Supplemental Box----------

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Prior Supplemental Box:

Regarding Claim 20, Moriarty '672 further discloses the method of Claim 13, wherein R1 is an alkyl group (para [0006]-[0012]), and wherein the method further comprises:
(c) hydrogenating the tricyclic compound of structural formula (5) to form a hydrogenated tricyclic compound represented by structural formula (6) (pg 4-6), but does not specifically disclose:
(d) converting the hydrogenated tricyclic compound represented by structural formula (6) to a compound represented by structural formula (IX); wherein said converting (d) accomplishes cleaving of the protective group PI and ester hydrolysis of R in a single pot. However, Tran discloses processes for producing intermediaries of cyclohexane derivatives (pg 2, ln 25 to pg 3, ln 24; pg 106, ln 36 to pg 116, ln 8), comprising:
a chiral resolving acid such as methylephedrin (pg 109, ln 29 to pg 110, ln 2), the reaction is carried out in the presence of a base and a metal cation reagent (pg 111, ln 1 to pg 112, ln 2), wherein the compound formed into a pharmaceutically acceptable salt metal cations such as zinc (pg 97, ln 24 to pg 98, ln 35) and protection/deprotection groups may be readily determined by one of ordinary skill in the art (pg 107, ln 20-25). To a person of ordinary skill in the art, it would have been obvious to substitute through routine experimentation to vary the species and location of protecting groups as taught by Tran with the method as in Moriarty '672 in order to resolve desired chiral species of Formula (A), because Moriarty '672 and Tran are directed towards stereoselective intermediaries prostacyclin derivatives (Tran: pg 2, ln 17-22).

Regarding Claim 21, Tran further teaches that the hydrogenation reaction of step (c) is carried out in the presence of a base (pg 97, ln 24 to pg 98, ln 35; pg 111, ln 1 to pg 113, ln 34).

Regarding Claim 22, Moriarty '672 further discloses that the base is K2CO3 (para [0074]).

Regarding Claim 23, Moriarty '672 further discloses that R1 is straight or branched C1-C5 alkyl (para [0010]).

Regarding Claim 24, Moriarty '672 further discloses that R1 is methyl (para [0010]).

Claims 29-30 lack an inventive step under PCT Article 33(3) as obvious over Moriarty '672 in view of Moriarty '645.

Regarding Claim 29, Moriarty '672 discloses the method of Claim 13, but does not specifically disclose reacting compound represented by formula (1) to form the compound represented by the structural formula OR(1), wherein m = 1 (as in Claim 29 and 30). However, Moriarty '645 discloses reacting compound represented by formula (1) to form the compound represented by the structural formula OR(1) (para [0047], See intermediaries 18a and 19). To a person of ordinary skill in the art, it would have been obvious to substitute the compound represented by formula (1) as taught by Moriarty '645 in the method as in Moriarty '672, in order to optimize formation of the alkyl group at OR, because Moriarty '672 and Moriarty '645 are directed towards stereoselective intermediaries prostacyclin derivatives.

Regarding Claim 30, Moriarty '672 further teaches that m = 1 (para [0057], see OMe.)

Claims 1-30 have industrial applicability as defined by PCT Article 33(4) because the subject matter could be made or used in industry.

Atty. Dkt. No. 080618-0629

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.: 12/334,731

Filing Date: 12/15/2008

Examiner: Karl J. PUTTLITZ

Art Unit: 1621

Conf. No.: 8804

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

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

Commissioner:

Submitted herewith on Form PTO/SB/08 is a listing of documents known to Applicants in order to comply with Applicants' duty of disclosure pursuant to 37 CFR §1.56.

A copy of each non-U.S. patent document and each non-patent document is being submitted to comply with the provisions of 37 CFR §1.97 and §1.98.

The submission of any document herewith, which is not a statutory bar, is not intended as 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 which is determined to be a *prima facie* art reference against the claims of the present application.

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(c), before the mailing date of any of a final action under 37 CFR §1.113, a notice of allowance under 37 CFR §1.311, or an action that otherwise closes prosecution in the application.

RELEVANCE OF EACH DOCUMENT

An English translation of foreign-language Documents D8 and D9 is provided. An English abstract is also provided with foreign-language Documents D8, D9 and D14. The absence of a full translation does not relieve the PTO from its duty to consider the submitted foreign language documents (37 CFR §1.98 and MPEP §609).

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.

FEE

A credit card payment form in the amount of $180.00 is enclosed to cover the fee associated with an information disclosure statement under 37 CFR §1.97(c).

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

Respectfully submitted,

Date MAR 12 2012

By _____

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

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

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: MAR 12 2012

(use as many sheets as necessary)

Sheet 1 of 3

Complete if Known	
Application Number	12/334,731
Filing Date	12/15/2008
First Named Inventor	Hitesh BATRA
Art Unit	1621
Examiner Name	Karl J. PUTTLITZ
Attorney Docket Number	080618-0629

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
	D1	2005/0101608 A1	05/12/2005	Santel, Donald J.	
	D2	2007/0078182 A1	04/05/2007	Phares et al.	
	D3	2009/0163738 A1	06/25/2009	Batra et al.	
	D4	4,544,764 A	10/01/1985	Aristoff, Paul A.	
	D5	4,668,814 A	05/26/1987	Aristoff, Paul A.	
	D6	4,683,330 A	07/28/1987	Aristoff, Paul A.	

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]
	D7	CA 2 710 726 A1	01/22/2012	Alphora Research Inc., CA		
	D8	CN 101891596 A	11/24/2010	Shanghai Techwell Biopharmaceutical Co. Ltd.		A✓
	D9	CN 101891715 A	11/24/2010	Shanghai Techwell Biopharmaceutical Co. Ltd.		A✓
	D10	EP 0 087 237 B1	05/14/1986	The Upjohn Company		
	D11	EP 0 159 784 B1	06/07/1989	The Upjohn Company		
	D12	EP 0 175 450 B1	03/22/1989	The Upjohn Company		
	D13	EP 0 496 548 A1	07/29/1992	Purdue Research Foundation		
	D14	WO 98/39337 A1	09/11/1998	Hoechst AG		A
	D15	WO 99/21830 A1	05/06/1999	United Therapeutics Corporation		
	D16	WO 03/070163 A2	08/28/2003	United Therapeutics Corporation		
	D17	WO 2005/007081 A2	01/27/2005	United Therapeutics Corporation		
	D18	WO 2008/100977 A2	08/21/2008	N.V. Organon		
	D19	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]
	D20	ALEXANDER et al., "The Synthesis of Benzindene Prostacyclin Analogs as Potential Antiulcer Agents," Prostaglandins, 1986, 32(5):647-653.	

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.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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(use as many sheets as necessary)

Sheet | 2 | of | 3

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	D21	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.	
	D22	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	
	D23	ARISTOFF et al., "Synthesis of Benzopyran Prostaglandins, Potent Stable Prostacyclin Analogs, Via an Intramolecular Mistunobu Reaction," Tetrahedron Letters, 1984, 25(36):3955-3958.	
	D24	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.	
	D25	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.	
	D26	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.	
	D27	CHUNG et al., "Promoters for the (Alkyne)hexacarbonyldicobalt-Based Cyclopentenone Synthesis," Organometallics, 1993, 12:220-223.	
	D28	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.	
	D29	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.	
	D30	HICKS et al., "A Practical Titanium-Catalyzed Synthesis of Bicyclic Cyclopentenones and Allylic Amines," J. Org. Chem., 1996, 61:2713-2718.	
	D31	JEONG et al., "Catalytic Version of the Intramolecular Pauson-Khand Reaction," J. Am. Chem. Soc., 1994, 116:3159-3160.	
	D32	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.	
	D33	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.	

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: MAR 12 2012

(use as many sheets as necessary)

Sheet 3 of 3

Complete if Known	
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Filing Date	12/15/2008
First Named Inventor	Hitesh BATRA
Art Unit	1621
Examiner Name	Karl J. PUTTLITZ
Attorney Docket Number	080618-0629

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]
	D34	MULZER et al., "Asymmetric Synthesis of Carbacyclin Precursors by Pauson-Khand Cyclization," Liebigs Ann. Chem., 1988, 891-897.	
	D35	NELSON, Norman A., "Prostaglandin Nomenclature," J. Med. Chem., September 1974, 17(9):911-918.	
	D36	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.	
	D37	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.	
	D38	PAULSON, Peter L., "The Khand Reaction," Tetrahedron, 1985, 41(24):5855-5860.	
	D39	SCHORE, Neil E., "Transition-Metal-Mediated Cycloaddition Reactions of Alkynes in Organic Synthesis," Chem. Rev., 1988, 88:1081-1119.	
	D40	SHAMBAYATI et al., "N-Oxide Promjoted Pauson-Khand Cyclizations at Room Temperature," Tetrahedron Letters, 1990, 31(37):5289-5292.	
	D41	SNELL et al., "Investigating the Effect of Impurities on Macromolecule Crystal Growth in Microgravity," Crystal Growth & Design, 2001, 1(2):151-158.	
	D42	TAKANO et al., "Enantiodivergent Synthesis of Both Enantiomers of Sulcatol and Matsutake Alcohol from (R)-Epichlorohydrin," Chemistry Letters, 1987, 2017-2020.	
	D43	VIEDMA, Cristobal, "Selective Chiral Symmetry Breaking during Crystallization: Parity Violation of Cryptochiral Environment in Control?" Crystal Growth & Design, 2007, 7(3):553-556.	
	D44	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		Date Considered	

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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.:	12/334,731
Filing Date:	12/15/2008
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	8804

REPLY UNDER 37 CFR § 1.111

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

Sir:

This paper responds to the Non-Final Office Action dated September 19, 2011. Applicants petition for an extension of time to make this response timely.

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

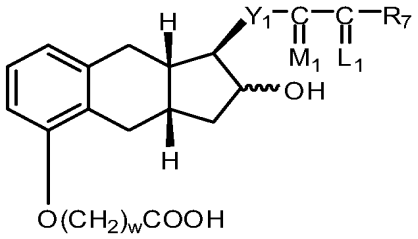
Remarks begin on page 10 of this document.

Amendments to the Claims:

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

Listing of Claims:

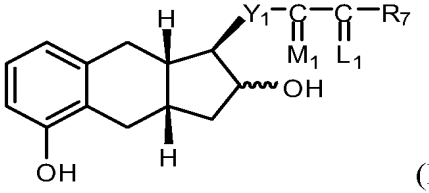
1. (Previously Presented) A process for the preparation of a compound of formula I



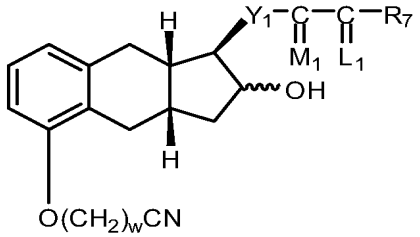
(I)

comprising

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



(II)



(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=$C(CH_3)_2$;

-$C(L_1)$-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

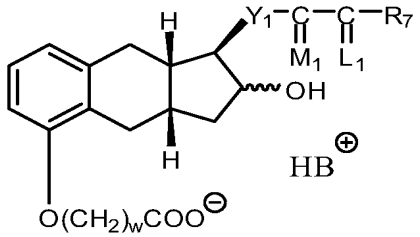
(4) 3-thienyloxymethyl;

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 formula III of step (a) with a base,

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



(I_s) and

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

2. (Previously Presented) The process according to claim 20, wherein the product of step (d) has the purity of compound of formula I of at least 90.0%.

3. (Original) The process according to claim 1, further comprising a step of isolating the salt of formula I_s.

4. (Original) The process according to claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.

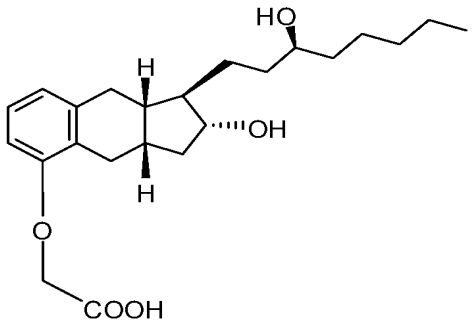
5. (Original) The process according to claim 1, wherein the base in step (b) is KOH or NaOH.

6. (Original) The process according to claim 1, wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

7. (Original) The process according to claim 1, wherein the acid in step (d) is HCl or H_2SO_4.

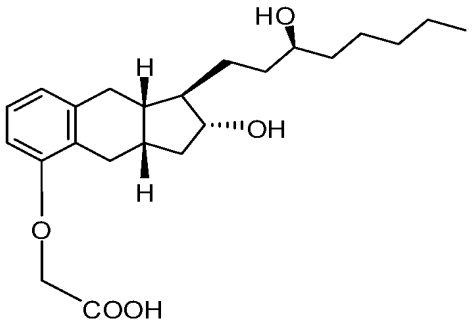
8. (Original) The process according to claim 1, wherein Y_1 is $–CH_2CH_2-$; M_1 is α-OH:β-H or α-H:β-OH; $-C(L_1)-R_7$ taken together is $–(CH_2)_4CH_3$; and w is 1.

9. (Original) The process according to claim 1, wherein the compound of formula I is a compound of formula IV.



(IV)

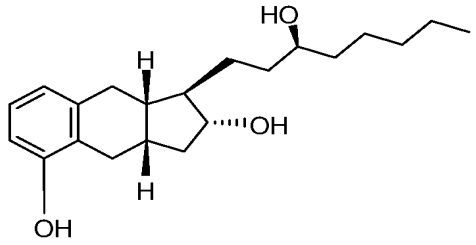
10. (Previously Presented) A process for the preparation of a compound having formula IV



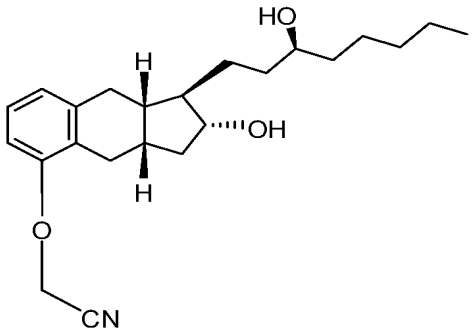
(IV)

comprising

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



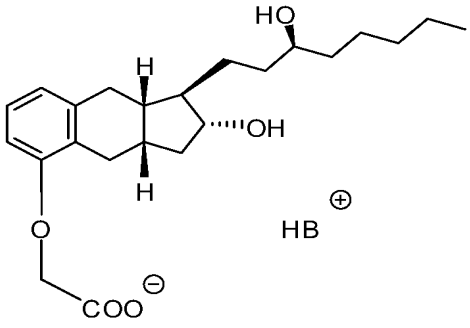
(V)



(VI)

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

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



(IV_s)

(d) reacting the salt formed in step (c) with an acid to form the compound of formula IV.

11. (Previously Presented) The process according to claim 22, wherein the product of step (d) has the purity of the compound of formula IV of at least 90.0%.

12. (Original) The process according to claim 10, further comprising a step of isolating the salt of formula IV_s.

13. (Original) The process according to claim 10, wherein the alkylating agent is $ClCH_2CN$.

14. (Original) The process according to claim 10, wherein the base in step (b) is KOH.

15. (Original) The process according to claim 10, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

16. (Original) The process according to claim 15, wherein the base B is diethanolamine.

17. (Original) The process according to claim 10, wherein the acid in step (d) is HCl.

18. (Canceled)

19. (Canceled)

20. (Previously Presented) The process of claim 1, which does not include purifying the compound of formula (III) produced in step (a).

21. (Previously Presented) The process of claim 20, wherein the product of step (d) has the purity of compound of formula I of at least 95%.

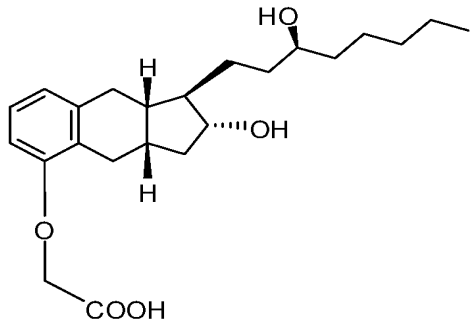
22. (Previously Presented) The process of claim 10, which does not include purifying the compound of formula (VI) produced in step (a).

23. (Previously Presented) The process of claim 22, wherein the product of step (d) has the purity of compound of formula I of at least 95%.

24. (Previously Presented) The process of claim 22, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

25. (Previously Presented) The process of claim 24, wherein the base B is diethanolamine.

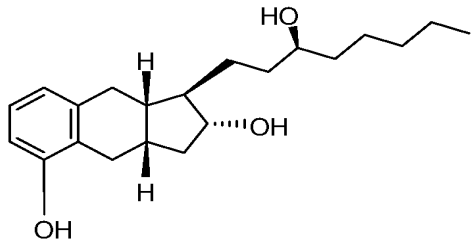
26. (Previously Presented) A process for the preparation of a compound having formula IV, or pharmaceutically acceptable salt thereof



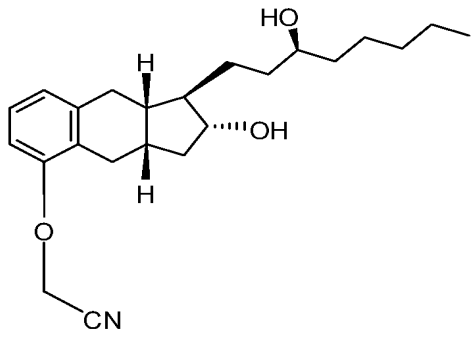
(IV)

comprising

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



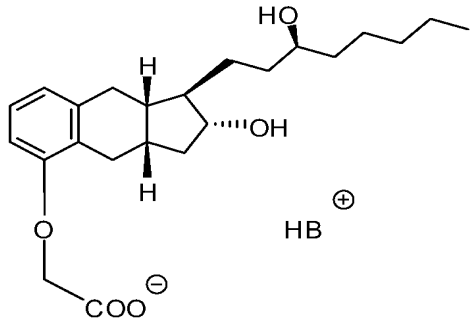
(V)



(VI)

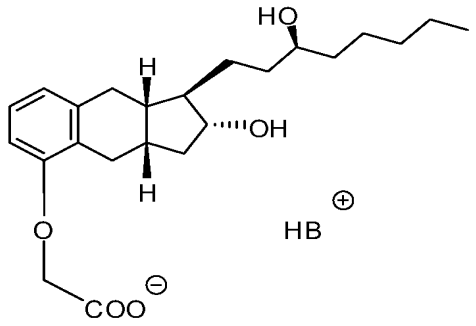
(b) hydrolyzing the product of formula VI of step (a) with a base, and

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



(IV_s), wherein the process does not comprise purifying the compound of formula (VI) produced in step (a).

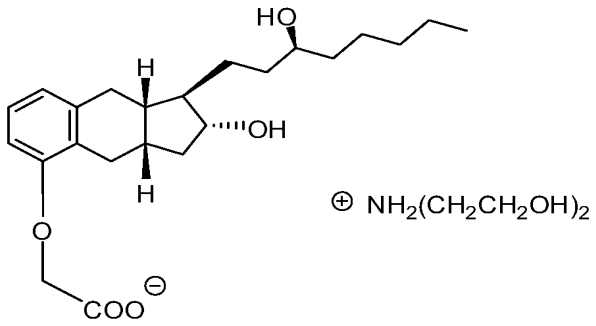
27. (Previously Presented) The process according to claim 26, wherein the base B in step (c) is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine and wherein the compound produced is a compound of the formula IV_s,



IV_s

wherein the base B is selected from a group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

28. (Previously Presented) The process according to claim 27, wherein the base B is diethanolamine and wherein the compound produced is a compound of the following formula:



.

29. (New) The process according to claim 1, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of

ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

30. (New) The process according to claim 10, wherein the base in step (b) is KOH or NaOH and wherein the base B in step (c) is selected from the group consisting of ammonia, N-methylglucamine, procaine, tromethanine, magnesium, L-lysine, L-arginine, triethanolamine, and diethanolamine.

REMARKS

Applicants respectfully request reconsideration and allowance of the present application.

CLAIMS STATUS

Applicants have added new claims 29-30. Support for the new claims may be found throughout the specification as filed and in particular, in original claims 5-6. No new matter has been added.

After the amendment, pending claims include a) examined claims 1-17 and 20-28 and b) new claims 29-30.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 1-17 and 20-28 stand rejected as obvious over Moriarty (US 2002/0173672) in view of Phares (US 2005/0085540). Applicants respectfully traverse.

The PTO failed to establish a *prima facie* case of obviousness at least because the PTO failed to make its obviousness analysis explicit.

In this regard, Applicants bring the PTO's attention to MPEP § 2142, which provide the following guidelines for an obviousness analysis by relying on the Supreme Court Decision *KSR International Co. v. Teleflex Inc*:

> **>The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007) noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of

obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). See also *KSR,* 550 U.S. at ___ , 82 USPQ2d at 1396

Applicants respectfully submit that the PTO relies on impermissible factually incorrect and conclusory assertions in arriving at its conclusion of obviousness. Applicants provide examples of the PTO's factually incorrect and conclusory statements below.

1) The PTO mischaracterizes Moriarty as teaching steps a), b) and d).

The PTO asserts on page 3 of the Office Action that "Moriarty et al. teach steps a), b) and d) of the instant claims." Applicants respectfully submit that the above cited PTO's assertion is factually incorrect. Applicants' understanding of the PTO's logic in the above cited assertion based on the PTO's citation of Moriarty's paragraphs 0078 and 0079 is follows:

i) The PTO treats alkylation of Moriarty's compound 14 with $ClCH_2CN$ in the presence of K_2CO_3 in acetone to produce Moriarty's compound 15 as step a) of the instant claims;

ii) The PTO treats addition of aqueous KOH to a stirred solution of Moriarty's compound 15 disclosed in the first sentence of Moriarty's paragraph 0079 as step b) of the instant claims;

iii) The PTO treats additions of HCl disclosed in the second and/or third sentences of Moriarty's paragraph 0079 as step d) of the instant claims.

If Applicants' understanding of the PTO's logic is incorrect, then Applicants respectfully request additional explanation on how the PTO interprets Moriarty in the next Office Action.

Applicants respectfully submit that one of ordinary skill in the art would not have interpreted Moriarty's additions of HCl disclosed in the second and/or third sentences of Moriarty's paragraph 0079 as step d of instant independent claim 1 or 10, which recite reacting the salt formed in step (c) with an acid. The salt formed in step (c) is a salt of the base B, which is different from the base recited in step b of the instant claims, see step c)

"contacting the product of step (b) with **a** base B." One of ordinary skill in the art would interpret the additions of HCl disclosed in the second and/or third sentences of Moriarty's paragraph 0079 only as reacting with an acid of the salt of the base recited in step b, which is different from the salt of the base B (the salt formed in step (c)). Applicants respectfully submit that claims 6, 15, 16, 24, 25, 29 and 30 further emphasize the differences between the claimed invention and Moriarty by providing particular examples of the base B.

In sum, Moriarty does not teach step d) of claims 1-25 and 29-30. Phares cannot remedy these deficiencies of Moriary at least because the PTO cites Phares only as teaching that "treprostinil diethanolamine can be crystallized". Thus, because Moriarty and Phares do not teach all the elements of the claimed invention, the PTO failed to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request withdrawal of the rejection.

2) The PTO's reasoning for combining Moriarty and Phares lacks the required articulated reasoning with rational underpinning.

The PTO formulates its reasoning for combining Moriarty and Phares on page 3 of the Office Action as follows:

> "One skilled in the art practicing the invention of Moriarty would have found it obvious to add a purification step in order to obtain a more pure product. Since Phares indicated that treprostinil diethanolamine can be [crystallized], one skilled in the art would have found it obvious to use this property of the diethanolamine salt in order to purify treprostinil via crystallization. As such in would have been obvious to convert the potassium salt of treprostinil obtained after step b), which is taught by Moriarty, into diethanolamine salt, purify said salt via crystallization followed by acidification as taught [by] Moriarty to recover treprostinil as a free acid. The instant invention amounts to addition of a purification step via crystallization. Since such a step has been taught in the art, at the time the instantly claimed invention was made one would have found it obvious to make the required modification. Motivation is

provided by desire to obtain a more pure product. Expectation of success is provided by Phares when a crystal form of the diethanolamine salt is disclosed."

Applicants identify at least the following deficiencies in the PTO's reasoning:

i) the PTO failed to articulate why one of ordinary skill in the art would choose purification by crystallization out of multiple other existing purification methods in order to obtain a product.

The PTO failed to articulate why of ordinary skill in the art would select purification by crystallization out of multiple other existing methods as a way to modify Moriarty's process in order to obtain a product. Simply stating that purification by crystallization has been taught in the art, as the PTO did in the Office Action, cannot serve as the required articulation with rational underpinning. Applicants respectfully submit that purification by silica gel chromatography that Moriarty uses in his process, see paragraph 0079, last sentence, is also known in the art. Thus, in order to justify its proposed addition of purification by crystallization, the PTO needs to provide its articulated reasoning with some rational underpinning on why one of ordinary skill in the art would select purification by crystallization among other known purification methods, such as Moriarty's silica gel chromatography, in order to obtain a product. In particular, since Moriarty already discloses one purification in his process, the PTO needs to provide its articulated reasoning with rational underpinning why one of ordinary skill in the art would expect that the use of a different purification by crystallization would result in a suitable product.

ii) the PTO failed to articulate why one of ordinary skill in the art would choose the particular version of purification by crystallization proposed by the PTO.

a) Besides failing to articulate its reasoning with the required rational underpinning for selecting purification by crystallization among other known purification techniques, the PTO failed to articulate its reasoning on why one of ordinary skill in the art would select the

particular purification by crystallization approach proposed by the PTO, purification by crystallization using treprostinil diethanolamine, which is performed after step b. For example, purification by crystallization could have been potentially applied at another stage, i.e., not after step b. For the record, Applicants respectfully submit that treprostinil *per se* can be crystallized, see e.g. page 3 of the enclosed MSDS for treprostinil, which states that treprostinil is delivered as a crystalline solid. Thus, one of ordinary skill in the art based on the PTO's logic could have used purification by crystallization using treprostinil *per se* after the Moriarty's process was complete. In sum, the PTO failed to establish a *prima facie* case of obviousness at least because the PTO did not provide any articulated reasoning on why one of ordinary skill in the art would be motivated to perform purification by crystallization after step b and would reasonably conclude that such purification would result in a suitable product.

b) The PTO did not articulate its reasoning with the required rational underpinning on why one of ordinary skill in the art would have selected treprostinil diethanolamine out of other treprostinil salts that can be crystallized to perform the PTO's proposed purification by crystallization. The only reason that the PTO provided for selecting treprostinil is based on the fact that Phares teaches that treprostinil diethanolamine can be crystallized. Applicants respectfully submit that the fact that treprostinil diethanolamine can be crystallized by itself cannot serve by itself as articulated reasoning with rational underpinning for selecting the PTO's proposed purification by crystallization using treprostinil diethanolamine at least because there are other salts treprostinil salts that can be crystallized. For example, treprostinil sodium, which is a salt of treprostinil used in a commercial product Remodulin ®, can also be crystallized. The PTO's failure to provide its articulated reasoning for selecting treprostinil diethanolamine demonstrates by itself the PTO's failure to establish a *prima facie* case of obviousness at least for claims 6, 15, 16, 24, 25 and 29-30.

iii) the PTO failed to articulate why one of ordinary skill in the art would have a reasonable expectation of success for either arriving at the claimed invention or for concluding that a suitable product should Moriarty's method be modified as proposed by the PTO.

According to MPEP § 2143.02, a reasonable expectation of success is required in order to support a conclusion of obviousness. Furthermore, each of the obviousness rationales from MPEP § 2143 includes a requirement regarding articulating a finding regarding predictability and/or reasonable expectation of success for modification of the prior art in order to arrive at the claimed invention. MPEP § 2143 emphasizes that if any of the findings required for a particular obviousness rationale cannot be made, then this rationale cannot be used to support a conclusion of obviousness.

In the Office Action, the PTO provides only the following comment regarding predictability/ reasonable expectation of success: "Expectation of success is provided by Phares when a crystal form of the diethanolamine salt is disclosed."

Applicants respectfully submit that the cited above PTO's comment cannot serve as the required articulated reasoning with rational underpinning at least for the following reasons:

a) Although Phares teaches that treprostinil diethanolamine can be crystallized, neither Phares, nor Moriarty teach that treprostinil diethanolamine can be transformed into treprostinil per se using acidification. Applicants respectfully submit that Moriarty's addition of HCl in the second and third sentences of Moriarty's paragraph can at most teach that potassium salt of treprostinil can be transformed in treprostinil per se. The PTO failed to articulate its reasoning with rational underpinning why one of ordinary skill in the art would extrapolate with a reasonable degree of success the reaction for Moriarty's potassium salt of treprostinil onto treprostinil diethanolamine.

b) The PTO failed to provide its articulated reasoning with the required rational underpinning on why one of ordinary skill in the art would have concluded based on Moriarty and Phares that the PTO proposed modification would predictably result in a suitable product. According to the PTO, the motivation for PTO's proposed modification is to obtain a more pure product. Applicants respectfully submit that one of ordinary skill in the art would not have such a motivation for the PTO's proposed modification unless he or she could conclude based on Moriarty and Phares that the PTO's proposed modification would predictably result in a product that is more pure than the one produced by Moriarty's process. Applicants respectfully submit that one of ordinary skill in the art would not have arrived at such conclusion based on the fact that Phares teaches that treprostinil diethanolamine can be

crystallized at least because Phares does not crystallize treprostinil diethanolamine under the same conditions and in the same environment as Moriarty performs his synthesis process. Applicants respectfully submit that crystallization does not necessarily result in purification of the crystallized material. For example, in some cases, impurities can incorporate into the lattice of the crystallized materials, hence, decreasing the level of purity of the crystal product, see e.g. the enclosed reference, Snell et al. Crystal Growth & Design 2001, vol. 1, 151-158, which provides documentary evidence of impurities incorporation into a lattice of a crystallized material. At least because Moriarty performs his synthesis under different conditions and in a different environment than those that Phares uses in his crystallization, one of ordinary skill in the art would not have concluded that applying the PTO's proposed crystallization of treprostinil diethanolamine would predictably result in purification of the product because one of ordinary skill in the art would not know whether or not impurities of Moriarty's process would incorporate themselves into treprostinil diethanolamine's lattice.

In sum, at least for the reasons discussed above, the PTO failed to establish a *prima facie* case of obviousness. Accordingly, Applicants request withdrawal of the rejection.

3) The PTO improperly disregards the purity elements of claims 2, 11, 21 and 22.

In the Office Action, the PTO relies on inherency theory for disregarding the purity elements of claims 2, 11, 21 and 22 by making the following assertions on page 4 of the Office Action:

> "Limitation directed to purity of the product are inherently met by the combination of Moriarty and Phares. Since the motivation to preform crystallization of the diethanolamine salt is to obtain a pure compound, it stands to reason that the purity of the product would be improved. The exact purity would inherently be same as instantly claimed because the same sequence of steps would be carried out."

Before addressing these assertions, Applicants respectfully bring the PTO's attention to MPEP § 2112.IV, which provides the following guidelines for supporting rejections based on inherency:

"IV. EXAMINER **MUST** PROVIDE RATION-ALE OR EVIDENCE TENDING TO SHOW INHERENCY" (Bold underlining added)

"The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)" (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence '**must make clear** that the missing descriptive matter is **necessarily** present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. **Inherency**, however, **may not be established by probabilities or possibilities**. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)" (Bold underlining added)

"In relying upon the theory of inherency, the examiner **must** provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (Bold underlining added)

In the present case, whether or not one of the ordinary skill in the art would arrive at the purity elements of claims 2, 11, 21 and 22 depends on whether or not one of ordinary skill in the art would arrive at the PTO's proposed modification of Moriarty and Phares. Applicants respectfully submit that the PTO's proposed modification of Moriarty and Phares **does not necessarily flow** from the teachings of Moriarty and Phares at least because for the reasons discussed in the sections above, such as that Moriarty and Phares do not teach step d) of claims 1-25 and 29-30. Thus, the PTO cannot rely on inherency in order to arrive at the purity elements of claims 2, 11, 21 and 22 because inherency cannot be established by probabilities or possibilities.

In sum, at least for the reasons discussed above, Applicants request withdrawal of the rejection as directed to claims 2, 11, 21 and 22.

CONCLUSION

Applicants believe that the present application is in condition for allowance. Favorable reconsideration 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.

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, Applicant hereby petitions 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 March 14, 2012

By_____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4632
Facsimile: (202) 672-5399

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

Electronic Patent Application Fee Transmittal

Application Number:	12334731
Filing Date:	15-Dec-2008
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN
First Named Inventor/Applicant Name:	Hitesh BATRA
Filer:	Alexey V. Saprigin
Attorney Docket Number:	080618-0629

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	2202	2	30	60
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 - 3 months with $0 paid	2253	1	635	635
Miscellaneous:				
			Total in USD ($)	**695**

Electronic Acknowledgement Receipt

EFS ID:	12299821
Application Number:	12334731
International Application Number:	
Confirmation Number:	8804
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
Filer Authorized By:	
Attorney Docket Number:	080618-0629
Receipt Date:	14-MAR-2012
Filing Date:	15-DEC-2008
Time Stamp:	12:08:50
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$695
RAM confirmation Number	10123
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 Letter	AmendmentTrans031412.pdf	33060 9b8167b0d187fa5c3632c839697ec5287959bf6e	no	2
Warnings:					
Information:					
2	Amendment/Req. Reconsideration-After Non-Final Reject	Amendment031412.pdf	85159 2588f24c1828d6f676fc758863e71cda4d6425ed	no	18
Warnings:					
Information:					
3	Non Patent Literature	MSDSTreprostinil.pdf	271355 95e7be3a8deaac90675c5a948b7cca136293677d	no	4
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	32383 e0d809d17e3457f1fac2cbc3a3c2c5ed018a5763	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	421957		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Hitesh BATRA et al.
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Appl. No.:	12/334,731
Filing Date:	12/15/2008
Examiner:	Yevgeny VALENROD
Art Unit:	1621
Confirmation Number:	8804

AMENDMENT TRANSMITTAL

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

Commissioner:

Transmitted herewith is an amendment in the above-identified application.

[**X**] Small Entity status under 37 C.F.R. § 1.9 and § 1.27 has been established by a previous assertion of Small Entity status.

[**X**] The fee required for additional claims is calculated below:

	Claims As Amended		Previously Paid For		Extra Claims Present		Rate		Additional Claims Fee
Total Claims:	28	-	26	=	2	x	$60.00	=	$120.00
Independent Claims:	3	-	3	=	0	x	$250.00	=	$0.00
							CLAIMS FEE TOTAL	=	$120.00

[**X**] Applicant hereby petitions for an extension of time under 37 C.F.R. §1.136(a) for the total number of months checked below:

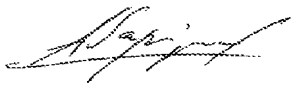
[X]	Extension for response filed within the third month:	$1,270.00	$1,270.00
		EXTENSION FEE TOTAL:	$1,270.00
		CLAIMS, EXTENSION AND DISCLAIMER FEE TOTAL:	$1,390.00
[X]		Small Entity Fees Apply (subtract ½ of above):	$695.00
		TOTAL FEE:	$695.00

The above-identified fees of $695.00 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.

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 extensions fees to Deposit Account No. 19-0741. Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

Respectfully submitted,



Date March 14, 2012

By _____

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Alexey V. Saprigin
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PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
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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	Filing Date	☐ To be Mailed
12/334,731	12/15/2008	

APPLICATION AS FILED – PART I

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

APPLICATION AS AMENDED – PART II

AMENDMENT	03/14/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 28	Minus	** 26	= 2	X $30 =	60	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $125 =	0	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	60	OR	TOTAL ADD'L FEE	

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

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

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

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

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

Legal Instrument Examiner:
/ANNETTE COWAN/

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 04/16/2012

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

EXAMINER
VALENROD, YEVGENY

ART UNIT	PAPER NUMBER
1621	

DATE MAILED: 04/16/2012

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/334,731	12/15/2008	Hitesh BATRA	080618-0629	8804

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$870	$300	$0	$1170	07/16/2012

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

22428 7590 04/16/2012
FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

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.
12/334,731	12/15/2008	Hitesh BATRA	080618-0629	8804

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	$870	$300	$0	$1170	07/16/2012

EXAMINER	ART UNIT	CLASS-SUBCLASS
VALENROD, YEVGENY	1621	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 credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/334,731	12/15/2008	Hitesh BATRA	080618-0629	8804

22428 7590 04/16/2012

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SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
VALENROD, YEVGENY	
ART UNIT	PAPER NUMBER
1621	

DATE MAILED: 04/16/2012

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 324 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 324 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No.	Applicant(s)	
	12/334,731	BATRA ET AL.	
	Examiner	Art Unit	
	YEVGENY VALENROD	1621	

-- 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 *remarks filed 3/14/12*.

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 *1-17 and 20-30*.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 10/12/11 and 3/12/12
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/YEVGENY VALENROD/
Examiner, Art Unit 1621

Issue Classification

Application/Control No.	Applicant(s)/Patent Under Reexamination
12334731	BATRA ET AL.
Examiner	**Art Unit**
YEVEGENY VALENROD	1621

ORIGINAL		INTERNATIONAL CLASSIFICATION	
CLASS	SUBCLASS	CLAIMED	NON-CLAIMED
562	466	C 0 7 C 62 / 00 (2006.01.01)	
CROSS REFERENCE(S)		C 0 7 C 65 / 00 (2006.01.01)	
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)		

☐ 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	17	17												
2	2	18	20												
3	3	19	21												
4	4	20	22												
5	5	21	23												
6	6	22	24												
7	7	23	25												
8	8	24	26												
9	9	25	27												
10	10	26	28												
11	11	27	29												
12	12	28	30												
13	13														
14	14														
15	15														
16	16														

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	28	
/YEVEGENY VALENROD/ Examiner.Art Unit 1621	04/13/2012	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12334731	BATRA ET AL.
	Examiner	Art Unit
	Yevgeny Valenrod	1621

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST search	4/13/2012	YV
inventor search	4/13/2012	YV

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner
SEE EAST		4/13/2012	YV

/YEVEGENY VALENROD/ Examiner.Art Unit 1621	

Atty. Dkt. No. 080618-0629

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.: 12/334,731

Filing Date: 12/15/2008

Examiner: Yevgeny Valenrod

Art Unit: 1621

Conf. No.: 8804

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

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

Sir:

Submitted herewith on Form PTO/SB/08 is a listing of documents known to Applicants in order to comply with Applicants' duty of disclosure pursuant to 37 CFR §1.56.

A copy of each non-U.S. patent document and each non-patent document is being submitted to comply with the provisions of 37 CFR §1.97 and §1.98.

The submission of any document herewith, which is not a statutory bar, is not intended as 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 which is determined to be a *prima facie* art reference against the claims of the present application.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /YV/

Atty. Dkt. No. 080618-0629

TIMING OF THE DISCLOSURE

The listed documents are being submitted in compliance with 37 CFR §1.97(c), before the mailing date of any of a final action under 37 CFR §1.113, a notice of allowance under 37 CFR §1.311, or an action that otherwise closes prosecution in the application.

RELEVANCE OF EACH DOCUMENT

Any document listed on the attached PTO/SB/08 was cited as being relevant during the prosecution of the International Application No. PCT/US2011/38946, a copy of which is submitted herewith. An English-language abstract of foreign-language Document C4 is provided.

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.

FEE

A credit card payment form in the amount of $180.00 is enclosed to cover the fee associated with an information disclosure statement under 37 CFR §1.97(c).

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this submission under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741.

Respectfully submitted,

Date OCT 12 2011

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4632
Facsimile: (202) 672-5399

Alexey V. Saprigin
Attorney for Applicant
Registration No. 56,439

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /YV/

PTO/SB/08A (09-06)
Approved for use through 03/31/2007. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: October 12, 2011

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	12/334,731
Filing Date	12/15/2008
First Named Inventor	Hitesh BATRA
Art Unit	1621
Examiner Name	Yevgeny Valenrod
Attorney Docket Number	080618-0629

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	2004/0176645 A1	09/09/2004	Moriarty et al.	
	C2	4,424,376 A	01/03/1984	Moniot et al.	
	C3	4,463,183 A	07/31/1984	Haslanger, Martin F.	

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]
	C4	EP 0 004 335 A2	10/03/1979	Hoechst AG		A
	C5	WO 2009/117095 A1	09/24/2009	Arena Pharmaceuticals, 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]

Examiner Signature	/Yevgeny Valenrod/	Date Considered	04/13/2012

*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.

This collection of information is required by 37 CFR 1.97 and 1.98. 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 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /YV/

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	4	((HITESH) near2 (BATRA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/04/13 15:41
L2	2	((SUDERSAN) near2 (TULADHAR)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/04/13 15:41
L3	15	((RAJU) near2 (PENMASTA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/04/13 15:41
L4	186	((DAVID) near2 (WALSH)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/04/13 15:41
L5	1	"6765117"	USPAT	OR	OFF	2012/04/13 15:41
L6	0	"20020173672"	USPAT	OR	OFF	2012/04/13 15:41
L7	1	("20020173672").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/04/13 15:41
L8	0	("2002/0173672").URPN.	USPAT	OR	OFF	2012/04/13 15:41
L9	1	("4306075").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/04/13 15:41
L10	1	("6441245").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/04/13 15:41
L11	1	("5387713").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/04/13 15:41
L12	1	("20050085540").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/04/13 15:41
L13	1	("20070078182").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/04/13 15:41
L14	1	("20070254032").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/04/13 15:41
L15	34	treprostinil diethanolamine	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2012/04/13 15:41
L16	1	("4845598").PN.	USPAT; USOCR	OR	OFF	2012/04/13 15:41

EAST Search History (Prior Art)

L17	1	("4485598").PN.	USPAT; USOCR	OR	OFF	2012/04/13 15:41
L18	1	("4486598").PN.	USPAT; USOCR	OR	OFF	2012/04/13 15:41
L19	1	("4486598").URPN.	USPAT	OR	OFF	2012/04/13 15:41
L20	41	treprostinil same diethanolamine	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2012/04/13 15:41
L21	7	L20 not L15	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2012/04/13 15:41
L22	184	L1 or L2 or L3 or L4	US-PGPUB; USPAT	OR	OFF	2012/04/13 15:41
L23	3	L22 and treprostinil	US-PGPUB; USPAT	OR	OFF	2012/04/13 15:41
L24	794	(562/466).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/04/13 15:46
L25	0	l24 and treprostinil	USPAT	OR	OFF	2012/04/13 15:47
L26	5	l24 and treprostinil	US-PGPUB; USPAT	OR	OFF	2012/04/13 15:47

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L27	0	(562/466).CCLS.	UPAD	OR	OFF	2012/04/13 15:48
L28	0	("treprostinil").PN.	UPAD	OR	OFF	2012/04/13 15:48
L29	1	((HITESH) near2 (BATRA)).INV.	USPAT; UPAD	OR	OFF	2012/04/13 15:48
L30	0	((SUDERSAN) near2 (TULADHAR)).INV.	USPAT; UPAD	OR	OFF	2012/04/13 15:48
L31	11	((RAJU) near2 (PENMASTA)).INV.	USPAT; UPAD	OR	OFF	2012/04/13 15:49
L32	124	((DAVID) near2 (WALSH)).INV.	USPAT; UPAD	OR	OFF	2012/04/13 15:49

Receipt date: 03/12/2012

12334731 GAU: 1621

PTO/SB/08A (09-06)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: MAR 12 2012

(use as many sheets as necessary)

Sheet 1 of 3

Complete if Known	
Application Number	12/334,731
Filing Date	12/15/2008
First Named Inventor	Hitesh BATRA
Art Unit	1621
Examiner Name	Karl J. PUTTLITZ
Attorney Docket Number	080618-0629

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
	D1	2005/0101608 A1	05/12/2005	Santel, Donald J.	
	D2	2007/0078182 A1	04/05/2007	Phares et al.	
	D3	2009/0163738 A1	06/25/2009	Batra et al.	
	D4	4,544,764 A	10/01/1985	Aristoff, Paul A.	
	D5	4,668,814 A	05/26/1987	Aristoff, Paul A.	
	D6	4,683,330 A	07/28/1987	Aristoff, Paul A.	

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]
	D7	CA 2 710 726 A1	01/22/2012	Alphora Research Inc., CA		
	D8	CN 101891596 A	11/24/2010	Shanghai Techwell Biopharmaceutical Co. Ltd.		A✓
	D9	CN 101891715 A	11/24/2010	Shanghai Techwell Biopharmaceutical Co. Ltd.		A✓
	D10	EP 0 087 237 B1	05/14/1986	The Upjohn Company		
	D11	EP 0 159 784 B1	06/07/1989	The Upjohn Company		
	D12	EP 0 175 450 B1	03/22/1989	The Upjohn Company		
	D13	EP 0 496 548 A1	07/29/1992	Purdue Research Foundation		
	D14	WO 98/39337 A1	09/11/1998	Hoechst AG		A
	D15	WO 99/21830 A1	05/06/1999	United Therapeutics Corporation		
	D16	WO 03/070163 A2	08/28/2003	United Therapeutics Corporation		
	D17	WO 2005/007081 A2	01/27/2005	United Therapeutics Corporation		
	D18	WO 2008/100977 A2	08/21/2008	N.V. Organon		
	D19	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]
	D20	ALEXANDER et al., "The Synthesis of Benzindene Prostacyclin Analogs as Potential Antiulcer Agents," Prostaglandins, 1986, 32(5):647-653.	

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.

This collection of information is required by 37 CFR 1.97 and 1.98. 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 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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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: MAR 12 2012

(use as many sheets as necessary)

Sheet 2 of 3

Complete if Known	
Application Number	12/334,731
Filing Date	12/15/2008
First Named Inventor	Hitesh BATRA
Art Unit	1621
Examiner Name	Karl J. PUTTLITZ
Attorney Docket Number	080618-0629

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]
	D21	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.	
	D22	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	
	D23	ARISTOFF et al., "Synthesis of Benzopyran Prostaglandins, Potent Stable Prostacyclin Analogs, Via an Intramolecular Mistunobu Reaction," Tetrahedron Letters, 1984, 25(36):3955-3958.	
	D24	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.	
	D25	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.	
	D26	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.	
	D27	CHUNG et al., "Promoters for the (Alkyne)hexacarbonyldicobalt-Based Cyclopentenone Synthesis," Organometallics, 1993, 12:220-223.	
	D28	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.	
	D29	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.	
	D30	HICKS et al., "A Practical Titanium-Catalyzed Synthesis of Bicyclic Cyclopentenones and Allylic Amines," J. Org. Chem., 1996, 61:2713-2718.	
	D31	JEONG et al., "Catalytic Version of the Intramolecular Pauson-Khand Reaction," J. Am. Chem. Soc., 1994, 116:3159-3160.	
	D32	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.	
	D33	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.	

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: MAR 12 2012

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Sheet 3 of 3

Complete if Known	
Application Number	12/334,731
Filing Date	12/15/2008
First Named Inventor	Hitesh BATRA
Art Unit	1621
Examiner Name	Karl J. PUTTLITZ
Attorney Docket Number	080618-0629

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]
	D34	MULZER et al., "Asymmetric Synthesis of Carbacyclin Precursors by Pauson-Khand Cyclization," Liebigs Ann. Chem., 1988, 891-897.	
	D35	NELSON, Norman A., "Prostaglandin Nomenclature," J. Med. Chem., September 1974, 17(9):911-918.	
	D36	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.	
	D37	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.	
	D38	PAULSON, Peter L., "The Khand Reaction," Tetrahedron, 1985, 41(24):5855-5860.	
	D39	SCHORE, Neil E., "Transition-Metal-Mediated Cycloaddition Reactions of Alkynes in Organic Synthesis," Chem. Rev., 1988, 88:1081-1119.	
	D40	SHAMBAYATI et al., "N-Oxide Promjoted Pauson-Khand Cyclizations at Room Temperature," Tetrahedron Letters, 1990, 31(37):5289-5292.	
	D41	SNELL et al., "Investigating the Effect of Impurities on Macromolecule Crystal Growth in Microgravity," Crystal Growth & Design, 2001, 1(2):151-158.	
	D42	TAKANO et al., "Enantiodivergent Synthesis of Both Enantiomers of Sulcatol and Matsutake Alcohol from (R)-Epichlorohydrin," Chemistry Letters, 1987, 2017-2020.	
	D43	VIEDMA, Cristobal, "Selective Chiral Symmetry Breaking during Crystallization: Parity Violation of Cryptochiral Environment in Control?" Crystal Growth & Design, 2007, 7(3):553-556.	
	D44	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	04/13/2012

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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12334731	BATRA ET AL.
	Examiner	Art Unit
	YEVEGENY VALENROD	1621

✓	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	09/14/2011	04/13/2012							
1	1	✓	=							
2	2	✓	=							
3	3	✓	=							
4	4	✓	=							
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25	27	✓	=							
26	28	✓	=							
27	29		=							
28	30		=							

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28	30		=							

Issue Classification

Application/Control No.	Applicant(s)/Patent Under Reexamination
12334731	BATRA ET AL.
Examiner	**Art Unit**
YEVEGENY VALENROD	1621

ORIGINAL		INTERNATIONAL CLASSIFICATION	
CLASS	SUBCLASS	CLAIMED	NON-CLAIMED
562	466	C 0 7 C 62 / 00 (2006.01.01)	
CROSS REFERENCE(S)		C 0 7 C 65 / 00 (2006.01.01)	
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)		

☐ 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	19	17												
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17	15														
18	16														

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 28	
/YEVEGENY VALENROD/ Examiner.Art Unit 1621 (Primary Examiner)	06/06/2012 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure none

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/334,731	12/15/2008	Hitesh BATRA	080618-0629	8804

22428 7590 06/08/2012

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SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
VALENROD, YEVGENY	
ART UNIT	PAPER NUMBER
1621	

MAIL DATE	DELIVERY MODE
06/08/2012	PAPER

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

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corrected ***Notice of Allowability***	**Application No.** 12/334,731	**Applicant(s)** BATRA ET AL.	
	Examiner YEVGENY VALENROD	**Art Unit** 1621	

-- 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 *RUSH dated 5/22/12*.
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 *1-17 and 20-30*.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☐ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/YEVGENY VALENROD/
Examiner, Art Unit 1621

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WASHINGTON, DC 20007

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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.
12/334,731	12/15/2008	Hitesh BATRA	080618-0629	8804

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	YES	~~$880~~ $1740	$300	$0	~~$1180~~ $2040	07/16/2012

EXAMINER	ART UNIT	CLASS-SUBCLASS
VALENROD, YEVGENY	1621	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, Maryland

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☒ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): (**Please first reapply any previously paid issue fee shown above**)
☐ A check is enclosed.
☒ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 19-0741 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
☒ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date JUL 13 2012

Typed or printed name Stephen B. Maebius Registration No. 35,264

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Electronic Patent Application Fee Transmittal

Application Number:	12334731
Filing Date:	15-Dec-2008
Title of Invention:	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:	080618-0629

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl issue fee	1501	1	1740	1740
Publ. Fee- early, voluntary, or normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2040**

Electronic Acknowledgement Receipt

EFS ID:	13244833
Application Number:	12334731
International Application Number:	
Confirmation Number:	8804
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:	080618-0629
Receipt Date:	13-JUL-2012
Filing Date:	15-DEC-2008
Time Stamp:	12:55:55
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$2040
RAM confirmation Number	10410
Deposit Account	
Authorized User	

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	135476 c42d4537385e85efda78163909a1a1d34493ca5d	no	1
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	32329 64407ee1ef62b79517aab883d1ba7575aeabae56	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	167805	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/334,731	08/14/2012	8242305	080618-0629	8804

22428 7590 07/25/2012

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

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 567 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Hitesh BATRA, Herndon, VA;
Sudersan M. TULADHAR, Silver Spring, MD;
Raju PENMASTA, Herndon, VA;
David A. WALSH, Palmyra, VA;

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®
Patent. No.:	8,242,305
Issue Date:	8/14/2012
Examiner:	Yevgeny VALENROD
Art Unit:	1621
Confirmation Number:	8804

REQUEST FOR CERTIFICATE OF CORRECTION PURSUANT TO 37 C.F.R. § 1.323

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

Commissioner:

Enclosed, in duplicate, is a Certificate of Correction, Form PTO-SB/44, for United States Patent Number 8,242,305 issued August 14, 2012.

Correction of the term"tromethanine" to "tromethamine" in five instances in the claims is requested.

Applicants submit that the noted errors do not constitute new matter, and correction thereof would not require reexamination.

Pursuant to 37 C.F.R. §1.323, Applicants request that the enclosed Certificate of Correction be approved.

Since the errors are not the fault of the Patent Office, payment is enclosed of the required fee of $100.00.

The above-identified fees 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.

Respectfully submitted,

Date JAN 08 2014

By _____

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

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

MODIFIED PTO/SB/44 (04-05)
Approved for use through 04/30/2007. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	:	8,242,305
APPLICATION NO.	:	12/334,731
DATED	:	8/14/2012
INVENTOR(S)	:	Hitesh BATRA; Sudersan M. TULADHAR; Raju PENMASTA; David A. WALSH

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Replace the term "tromethanine" with --tromethamine -- as follows:

Col. 19, claim 7, line 26;
Col. 21, claim 22, line 10;
Col. 22, claim 25, line 25;
Col. 23, claim 27, line 4; and
Col. 24, claim 28, line 2.

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Foley & Lardner LLP
3000 K Street, N.W., Suite 600
Washington, D.C. 20007-5143

Electronic Patent Application Fee Transmittal

Application Number:	12334731
Filing Date:	15-Dec-2008
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN
First Named Inventor/Applicant Name:	Hitesh BATRA
Filer:	Alexey V. Saprigin/Karen Walker
Attorney Docket Number:	080618-0629

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Certificate of Correction	1811	1	100	100
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**100**

Electronic Acknowledgement Receipt

EFS ID:	17851239
Application Number:	12334731
International Application Number:	
Confirmation Number:	8804
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:	080618-0629
Receipt Date:	08-JAN-2014
Filing Date:	15-DEC-2008
Time Stamp:	12:56:42
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$100
RAM confirmation Number	9363
Deposit Account	
Authorized User	

File Listing:

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

1	Request for Certificate of Correction	COC.pdf	92936 28c2cc82a7bf6fa9d6d4f366cc72258983455f7b	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30468 c4c28bb768d9553b5622efcaf1f313e589b656cf	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	123404	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 8,242,305 B2
APPLICATION NO.	: 12/334731
DATED	: August 14, 2012
INVENTOR(S)	: Hitesh Batra et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Replace the term "tromethanine" with --tromethamine-- as follows:

Col. 19, claim 17, line 26;
Col. 21, claim 22, line 10;
Col. 22, claim 25, line 25;
Col. 23, claim 27, line 4; and
Col. 24, claim 28, line 2.

Signed and Sealed this
Twenty-fifth Day of February, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Inventor Name:	Hitesh BATRA
Title:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
Patent. No.:	8,242,305
Issue Date:	8/14/2012
Examiner:	Yevgeny VALENROD
Art Unit:	1621
Confirmation Number:	8804

REQUEST FOR CERTIFICATE OF CORRECTION PURSUANT TO 37 C.F.R. § 1.323

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

Commissioner:

Enclosed is a Certificate of Correction, Form PTO-SB/44, for United States Patent Number 8,242,305 issued August 14, 2012.

Correction of the "αOR_1:β-R_5" with --αOR_2:β-R_5 -- in two instances in the specification, and in one instance in the claims, is requested.

Applicants submit that the noted errors do not constitute new matter, and correction thereof would not require reexamination.

Pursuant to 37 C.F.R. §1.323, Applicants request that the enclosed Certificate of Correction be approved.

Since the errors are not the fault of the Patent Office, payment is enclosed of the required fee of $100.00.

The above-identified fees 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.

Respectfully submitted,

Date JAN 06 2015

By _____

for Alexey V. Saprigin, Reg No. 35,264
Agent for Applicants
Registration No. 56,439

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

MODIFIED PTO/SB/44 (04-05)
Approved for use through 04/30/2007. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	:	8,242,305
APPLICATION NO.	:	12/334,731
DATED	:	8/14/2012
INVENTOR(S)	:	Hitesh BATRA; Sudersan M. TULADHAR; Raju PENMASTA; David A. WALSH

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Replace "αOR_1:β-R_5" with --αOR_2:β-R_5 – as follows:

Col. 2, line 60;
Col. 6, line 56; and
Claim 1, col. 18, line 55.

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Foley & Lardner LLP
3000 K Street, N.W., Suite 600
Washington, D.C. 20007-5109

4816-0467-3057.1

Electronic Patent Application Fee Transmittal

Application Number:	12334731
Filing Date:	15-Dec-2008
Title of Invention:	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:	080618-0629

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:				
Certificate of Correction	1811	1	100	100

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**100**

Electronic Acknowledgement Receipt

EFS ID:	21128302
Application Number:	12334731
International Application Number:	
Confirmation Number:	8804
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:	080618-0629
Receipt Date:	06-JAN-2015
Filing Date:	15-DEC-2008
Time Stamp:	12:29:22
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$100
RAM confirmation Number	9465
Deposit Account	
Authorized User	

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

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	COC.pdf	225153 8c092a714aeef4ffd08646ba97f1a6ef53060760	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30782 2e9ce8f8ac0730d00e591a6a0e857772704deecc	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	255935		

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.

SPE RESPONSE FOR CERTIFICATE OF CORRECTION

Paper No.:20150303

DATE : March 03, 2015

TO SPE OF : ART UNIT 1672

SUBJECT : Request for Certificate of Correction on Patent No.: 8242305

A response is requested with respect to the accompanying request for a certificate of correction.

Please complete this form and return with file, within **7** days to:
Certificates of Correction Branch - ST (South Tower) 9A22
Palm location **7590** - Tel. No. (703) 305-8309

With respect to the change(s) requested, correcting Office and/or Applicant's errors, should the patent read as shown in the certificate of correction? No new matter should be introduced, nor should the scope or meaning of the claims be changed.

Thank You For Your Assistance **Certificates of Correction Branch**

The request for issuing the above-identified correction(s) is hereby:

Note your decision on the appropriated box.

☒ **Approved** All changes apply.

☐ **Approved in Part** Specify below which changes **do not** apply.

☐ **Denied** State the reasons for denial below.

Comments:

/BRANDON FETTEROLF/
Supervisory Patent Examiner.Art Unit 1672

SPE RESPONSE FOR CERTIFICATE OF CORRECTION

Paper No.: _____

DATE : 3/3/2015

TO SPE OF : ART UNIT 1621

SUBJECT : Request for Certificate of Correction for Appl. No.: 12/334,731 Patent No.: 8,242,305

CofC mailroom date: 3/3/2015

Please respond to this request for a certificate of correction **within 7 days**.

FOR IFW FILES:

Please review the requested changes/corrections as shown in the **COCIN** document(s) in the IFW application image. No new matter should be introduced nor should the scope or meaning of the claims be changed.

Please complete the response (see below) and forward the completed response to scanning using document code **COCX**.

FOR PAPER FILES:

Please review the requested changes/corrections as shown in the attached certificate of correction. Please complete this form (see below) and forward it with the file to:

Certificates of Correction Branch (CofC)
Randolph Square – 9D10-A
Palm Location 7580

In particular note: **formulas (Clm 1) and Col. 2 & 6**

Ernest C. White 571 272-3385
Certificates of Correction Branch
703-756-1814

Thank You For Your Assistance

The request for issuing the above-identified correction(s) is hereby:
Note your decision on the appropriate box.

☐ **Approved**	**All** changes apply.
☐ **Approved in Part**	Specify below which changes **do not** apply.
☐ **Denied**	State the reasons for denial below.

Comments: _____

_____

_____

_____

_____ _____
SPE **Art Unit**

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 8,242,305 B2
APPLICATION NO.	: 12/334731
DATED	: August 14, 2012
INVENTOR(S)	: Hitesh Batra et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Replace "αOR_1:β-R_5" with --αOR_2:β-R_5-- as follows:

In the Specification
Col. 2, line 60;
Col. 6, line 56; and

In the Claims
Claim 1, col. 18, line 55.

Signed and Sealed this
Fourteenth Day of April, 2015

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office