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®

Prior Appl. No.: 12/334,731

Prior Appl. Filing Date: 12/15/2008

Examiner: Unassigned

Art Unit: Unassigned

CONTINUING PATENT APPLICATION TRANSMITTAL LETTER

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

Commissioner:

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

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

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

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

Enclosed are:

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

[**X**] Copy of Executed Declaration and Power of Attorney from prior application (4 pages).

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

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

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

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

The filing fee is calculated below:

	Number Filed		**Included in Basic Fee**		**Extra**		Rate		Fee Totals
Basic Filing Fee							$380.00	=	$380.00
Search Fee							$620.00		$620.00
Examination Fee							$250.00		$250.00
Size Fee	21	-	100	= 0		x	$310.00		$0.00
Total Claims:	21	-	20	= 1		x	$60.00	=	$60.00
Independent:	2	-	3	= 0		x	$250.00	=	$0.00
If any Multiple Dependent Claim(s) present:						+	$450.00	=	$0.00
Surcharge under 37 CFR 1.16(e) for late filing of Executed Declaration or late payment of filing fee						+	$130.00	=	$0.00
							SUBTOTAL:	=	$1310.00
[ ]							Small Entity Fees Apply (subtract ½ of above):	=	0
							Basic Filing Fee Reduction for Filing via EFS-Web		$0.00
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							Processing Fee (Track I) under 37 C.F.R. § 1.17 (i)		$0.00
							TOTAL FILING FEE:	=	$1310.00
Assignment Recordation Fee:						+	$40.00	=	$0.00
Processing Fee under 37 CFR 1.17(i) for Late Filing of English Translation of Application:						+	$130.00	=	$0.00
Publication Fee									$0.00
TOTAL FEE								=	$1310.00

The above-identified fees of $1310.00 are being paid by credit card via EFS-Web.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

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

Respectfully submitted,

Date JUL 13 2012

By _____

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

CROSS-REFERENCE TO RELATED APPLICATIONS

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

BACKGROUND

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

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

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

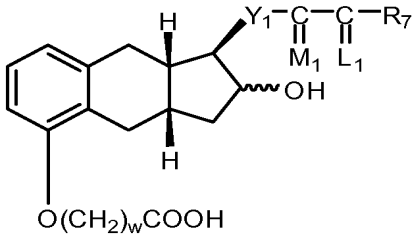
[0005] U.S. Patent No. 5,153,222 describes use of treprostinil for treatment of pulmonary hypertension. Treprostinil is approved for the intravenous as well as subcutaneous route, the latter avoiding septic events associated with continuous intravenous catheters. U.S. patents Nos. 6,521,212 and 6,756,033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

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

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

SUMMARY

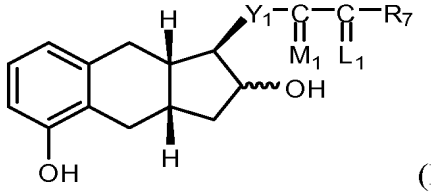
[0007] The present invention provides in one embodiment a process for the preparation of a compound of formula I, hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.



(I)

[0008] The process comprises the following steps:

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



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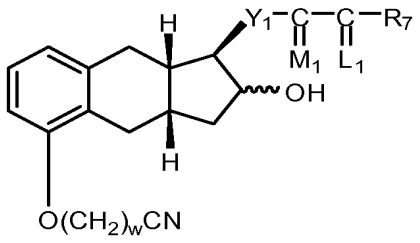


(III)

wherein

w= 1, 2, or 3;

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

R_7 is

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

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

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

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

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

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

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

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

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

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

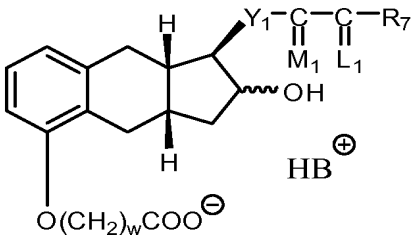
(4) 3-thienyloxymethyl;

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

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

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

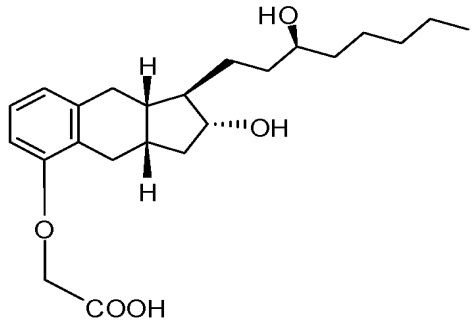
(c) contacting the product of step (b) with a base B to for a salt of formula I_s



(Is)

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

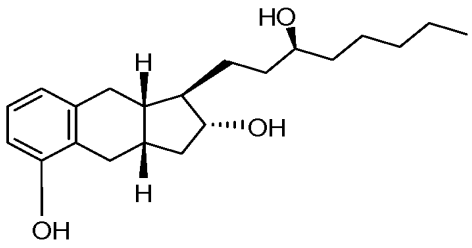
[0009] The present invention provides in another embodiment a process for the preparation of a compound of formula IV.



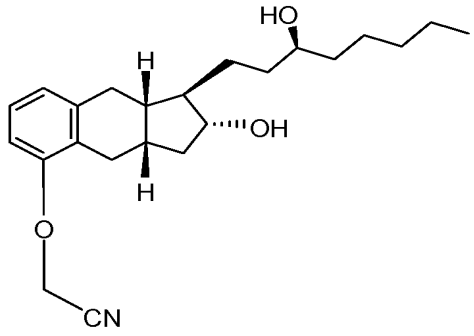
(IV)

[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,



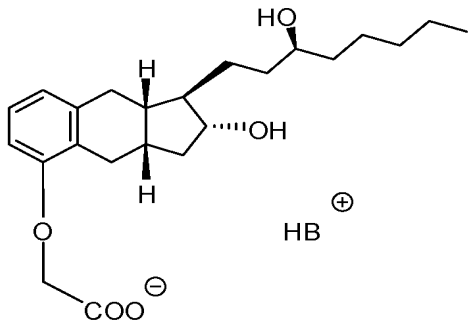
(V)



(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.

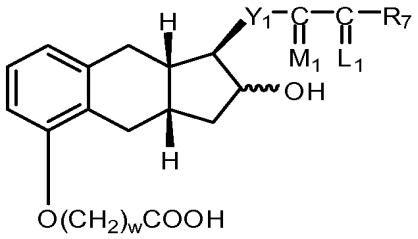
[0021] "Pharmaceutically acceptable salts" mean salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with organic and inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen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

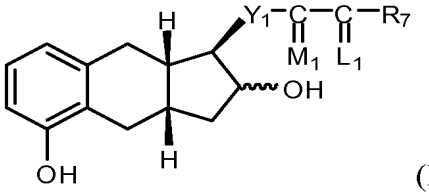
[0024] One embodiment of the present invention is a process for the preparation of a compound of formula I, or a hydrate, solvate, prodrug, or pharmaceutically acceptable salt thereof.



(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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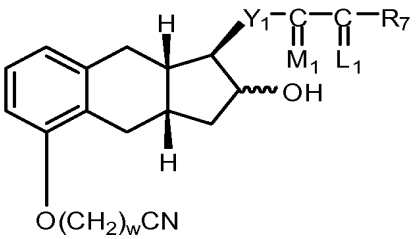


(III)

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

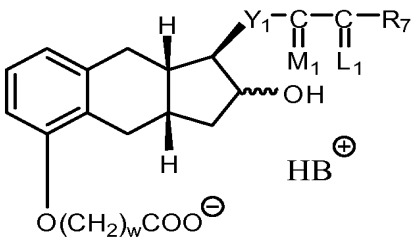
(4) 3-thienyloxymethyl;

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

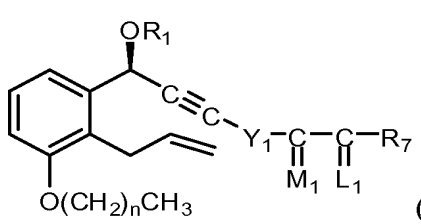


(I_s)

(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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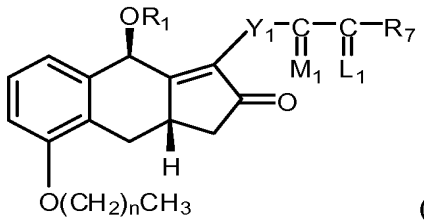
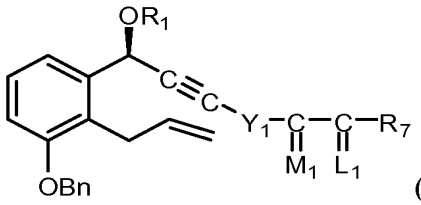


(XI)

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.



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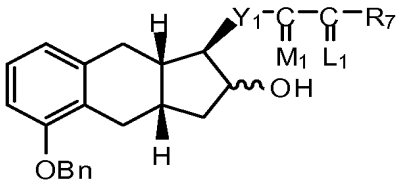
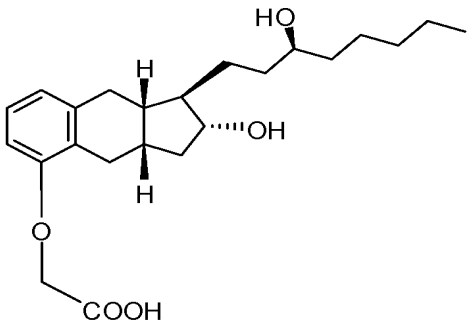


(XIII)

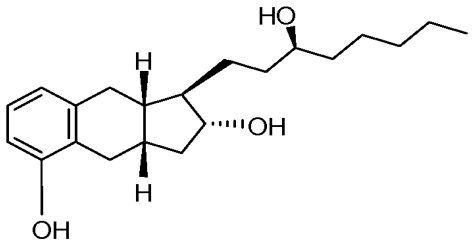
[0029] One embodiment of the present invention is a process for the preparation of a compound having formula IV, or a hydrate, solvate, or pharmaceutically acceptable salt thereof.



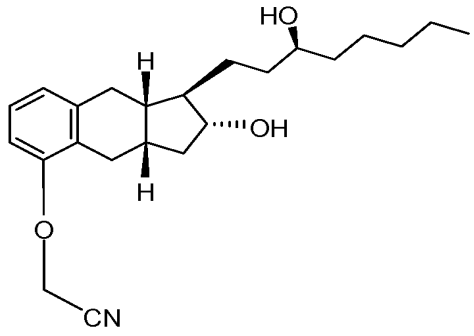
(IV)

[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,



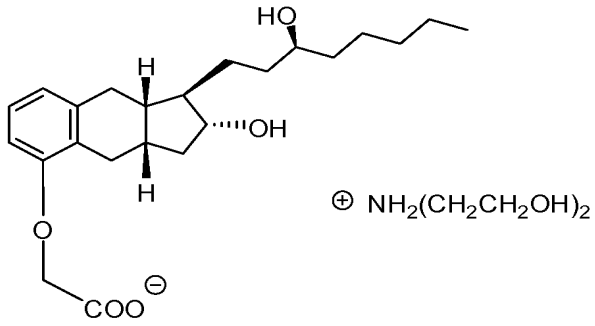
(V)



(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.

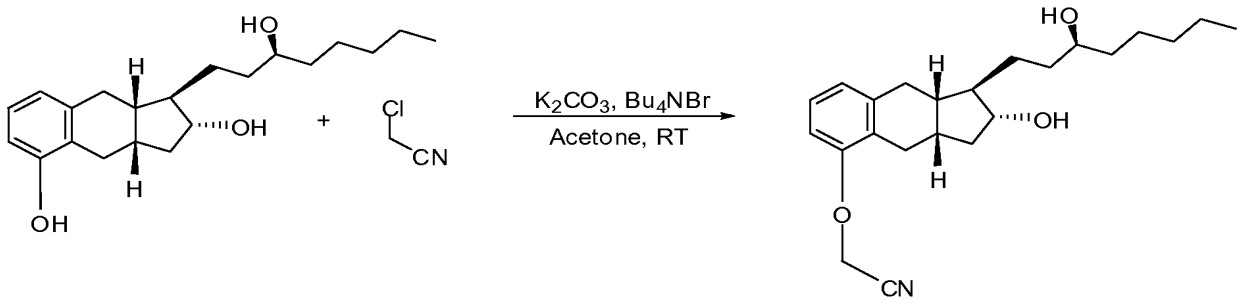
"AUC" means area under curve.

[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

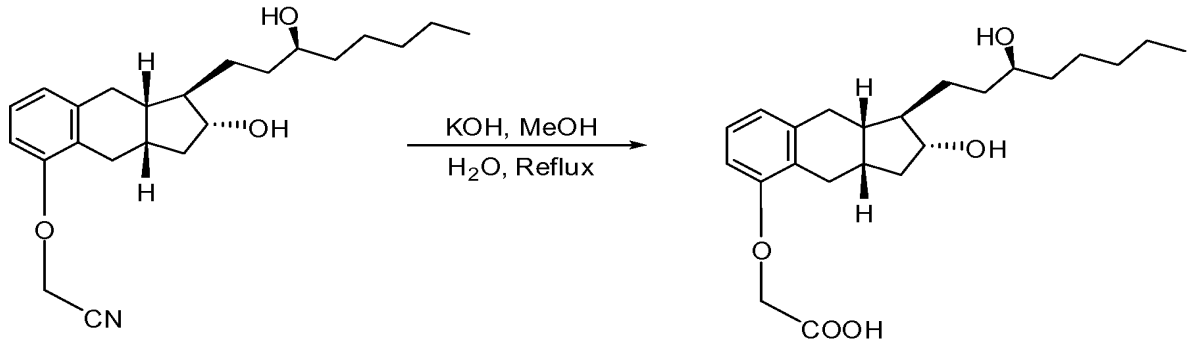
Example 1. Alkylation of Benzindene Triol



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.

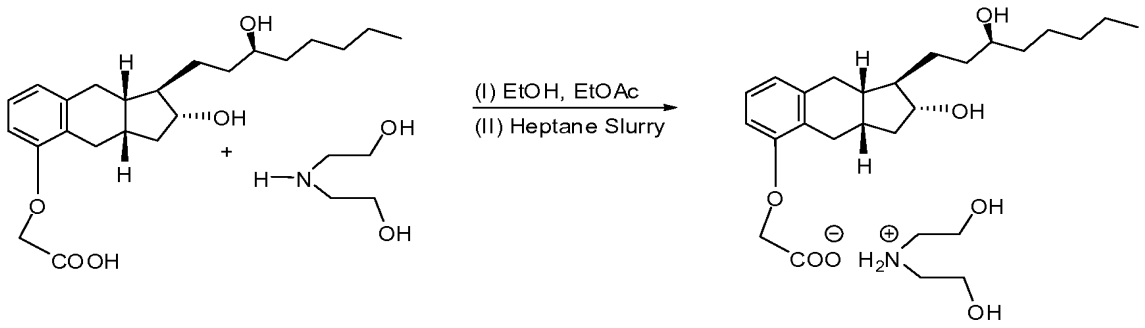
[0039] The aqueous layer was diluted with water (7-8 L) and extracted with ethyl acetate (2 × 6 L) to remove impurities soluble in ethyl acetate. To aqueous layer, ethyl acetate (22 L) was added and the pH of reaction mixture was adjusted to 1-2 by adding 3M HC1 (1.7 L) with stirring. The organic layer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

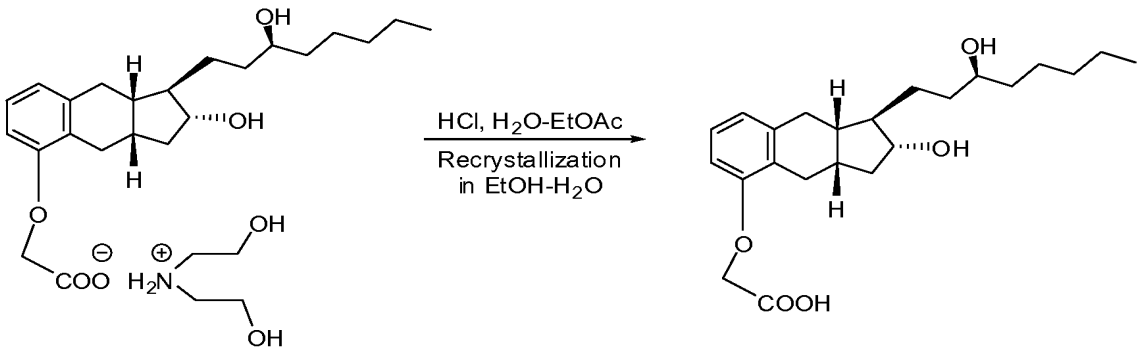
Name	Batch No.	Amount	Ratio
Treprostinil Diethanolamine Salt	2	3071 g	1
Heptane	--	36.0 L	12

[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.

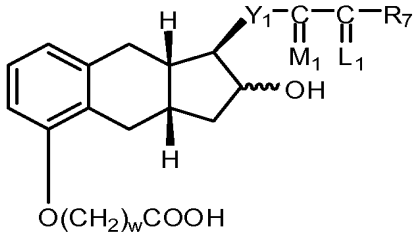
[0047] Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill

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.

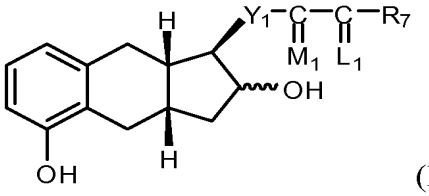
WHAT IS CLAIMED IS:

1. A product comprising a compound of formula I

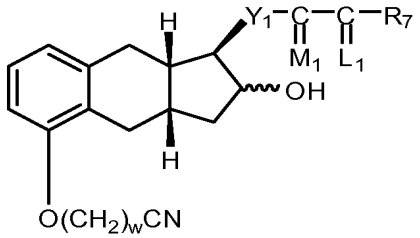


(I), wherein said product is prepared by a process comprising

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



(II)



(III)

wherein

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

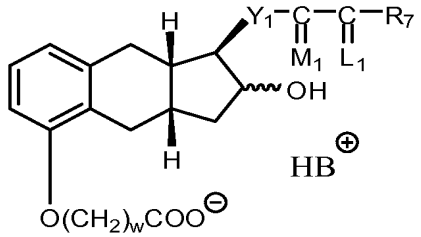
(4) 3-thienyloxymethyl;

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. The product of claim 1, wherein the purity of compound of formula I in said product isat least 99.5%.

3. The product of claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.

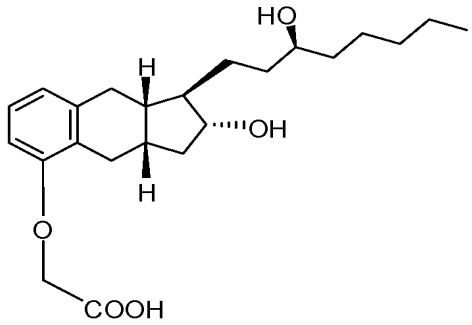
4. The product of claim 1, wherein the base in step (b) is KOH or NaOH.

5. The product of 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.

6. The product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4.

7. The product of 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.

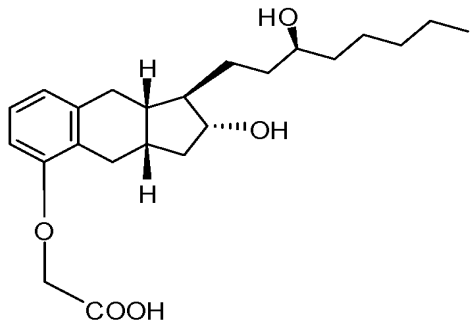
8. The product of claim 1, wherein the compound of formula I is a compound of formula IV.



(IV).

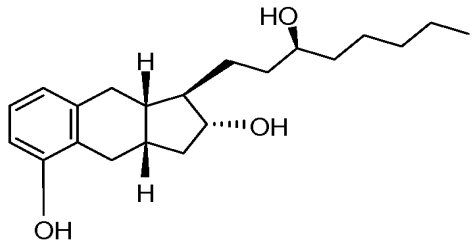
9. The product of claim 1, which the process does not include purifying the compound of formula (III) produced in step (a).

10. A product comprising a compound having formula IV

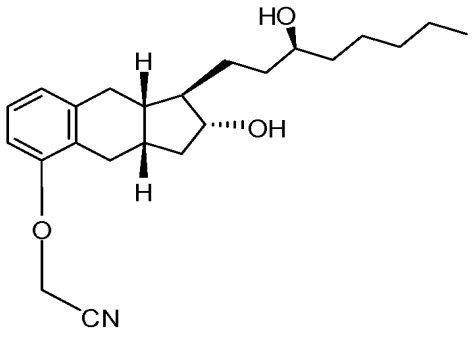


(IV), wherein the product is prepared by the process comprising

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



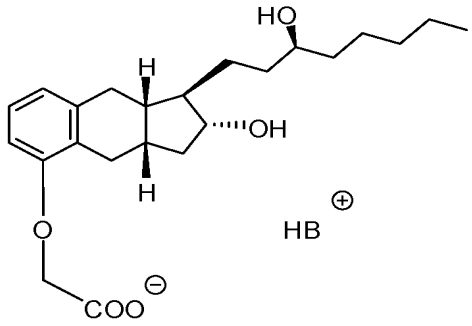
(V)



(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. The process of claim 10, wherein the product of step (d) has the purity of the compound of formula IV of at least 99.5%.

12. The product of claim 10, wherein the alkylating agent is $ClCH_2CN$.

13. The product of claim 10, wherein the base in step (b) is KOH.

14. The product of 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.

15. The product of claim 10, wherein the base B is diethanolamine.

16. The product of claim 10, wherein the acid in step (d) is HCl.

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

18. The product of claim 17, 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.

19. The product of claim 18, wherein the base B is diethanolamine.

20. The product of 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.

21. The product of 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.

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.

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.

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Date	1/13/09

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Date	1/13/09

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

Application Data Sheet

Application Information	
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::	080618-1162
Request for Early Publication?::	No
Request for Non-Publication?::	No
Suggested Drawing Figure::	
Total Drawing Sheets::	
Small Entity?::	No
Petition included?::	No
Secrecy Order in Parent Appl.?::	No

Applicant Information

Applicant Authority Type::	Inventor
Primary Citizenship Country::	India
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City of mailing address::	Herndon

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Postal or Zip Code of mailing address::	20171

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State or Province of mailing address::	MD
Postal or Zip Code of mailing address::	20904

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Postal or Zip Code of mailing address::	20171

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Primary Citizenship Country::	US
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Family Name::	WALSH
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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	Continuation of	12/334,731	12/15/2008

12/334,731	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

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Hitesh BATRA et al.

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

Appl. No.: Unassigned (CON of 12/334,731)

Filing Date: Herewith

Examiner: Unassigned

Art Unit: Unassigned

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

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

Commissioner:

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

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

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

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

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

TIMING OF THE DISCLOSURE

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

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

Respectfully submitted,

Date JUL 13 2012

By _____

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

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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: JUL 13 2012

(use as many sheets as necessary)

Sheet 1 of 4

Complete if Known	
Application Number	Unassigned
Filing Date	Herewith
First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	080618-1162

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	2002/0173672 A1	11/21/2002	Moriarty et al.	
	A2	2004/0176645 A1	09/09/2004	Moriarty et al.	
	A3	2005/0085540 A1	04/21/2005	Phares et al.	
	A4	2005/0101608 A1	05/12/2005	Santel, Donald J.	
	A5	2005/0165111 A1	07/28/2005	Wade et al.	
	A6	2005/0282903 A1	12/22/2005	Wade et al.	
	A7	2005/0282901 A1	12/22/2005	Phares et al.	
	A8	2007/0078182 A1	04/05/2007	Phares et al.	
	A9	2007/0078095 A1	04/05/2007	Phares et al.	
	A10	2008/0200449 A1	08/21/2008	Olschewski et al.	
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	A13	2009/0036465 A1	02/05/2009	Roscigno et al.	
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	A15	4,306,075 A	12/15/1981	Aristoff, Paul A.	
	A16	4,424,376 A	01/03/1984	Moniot et al.	
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	A34	7,417,070 B2	08/26/2008	Phares et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3] Number[4] Kind Code[5] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Documents	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]
	A35	CA 2 710 726 A1	01/22/2012	Alphora Research Inc., CA		

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.

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**	Unassigned
Date Submitted: JUL 13 2012				**Filing Date**	Herewith
				First Named Inventor	Hitesh BATRA
(use as many sheets as necessary)				Art Unit	Unassigned
				Examiner Name	Unassigned
Sheet	2	of	4	Attorney Docket Number	080618-1162

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]
	A36	CN 101891596 A	11/24/2010	Shanghai Techwell Biopharmaceutical Co. Ltd.		A ✓
	A37	CN 101891715 A	11/24/2010	Shanghai Techwell Biopharmaceutical Co. Ltd.		A ✓
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	A39	EP 0 087 237 B1	05/14/1986	The Upjohn Company		
	A40	EP 0 159 784 B1	06/07/1989	The Upjohn Company		
	A41	EP 0 175 450 B1	03/22/1989	The Upjohn Company		
	A42	EP 0 496 548 A1	07/29/1992	Purdue Research Foundation		
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	A44	WO 99/21830 A1	05/06/1999	United Therapeutics Corporation		
	A45	WO 03/070163 A2	08/28/2003	United Therapeutics Corporation		
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	A47	WO 2007/134292 A2	11/22/2007	United Therapeutics Corporation		
	A48	WO 2008/100977 A2	08/21/2008	N.V. Organon		
	A49	WO 2009/117095 A1	09/24/2009	Arena Pharmaceuticals, Inc.		
	A50	WO 2012/009816 A1	01/26/2012	Alphora Research Inc.		

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.) date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[6]
	A51	ALEXANDER et al., "The Synthesis of Benzindene Prostacyclin Analogs as Potential Antiulcer Agents," Prostaglandins, 1986, 32(5):647-653.	
	A52	ARISTOFF et al., "Synthesis and Structure-Activity Relationship of Novel Stable Prostacyclin Analogs," Advances in Prostaglandin, Thromboxane, and Leukotriene Research, Samuelsson et al., .Eds., 1983, 11:267-274	
	A53	ARISTOFF et al., "Synthesis of Benzopyran Prostaglandins, Potent Stable Prostacyclin Analogs, Via an Intramolecular Mistunobu Reaction," Tetrahedron Letters, 1984, 25(36):3955-3958.	
	A54	ARISTOFF et al., "Total Synthesis of a Novel Antiulcer Agent via a Modification of the Intramolecular Wadsworth-Emons-Wittig Reaction," J. Am. Chem. Soc., 1985, 107:7967-7974.	
	A55	BATRA et al., "Crystallization Process Development for a Stable Polymorph of Treprostinil Diethanolamine (UT-15C) by Seeding," Organic Process Research & Development, 2009, 13:242-249.	

Examiner Signature		Date Considered	

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

Substitute for form 1449/PTO				*Complete if Known*	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	Unassigned
Date Submitted: JUL 13 2012				**Filing Date**	Herewith
				First Named Inventor	Hitesh BATRA
(use as many sheets as necessary)				Art Unit	Unassigned
				Examiner Name	Unassigned
Sheet	3	of	4	Attorney Docket Number	080618-1162

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

Substitute for form 1449/PTO **INFORMATION DISCLOSURE STATEMENT BY APPLICANT** Date Submitted: JUL 13 2012 *(use as many sheets as necessary)*				***Complete if Known***	
				Application Number	Unassigned
				Filing Date	Herewith
				First Named Inventor	Hitesh BATRA
				Art Unit	Unassigned
				Examiner Name	Unassigned
Sheet	4	of	4	Attorney Docket Number	080618-1162

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]
	A70	PAULSON, Peter L., "The Khand Reaction," Tetrahedron, 1985, 41(24):5855-5860.	
	A71	SCHORE, Neil E., "Transition-Metal-Mediated Cycloaddition Reactions of Alkynes in Organic Synthesis," Chem. Rev., 1988, 88:1081-1119.	
	A72	SHAMBAYATI et al., "N-Oxide Promjoted Pauson-Khand Cyclizations at Room Temperature," Tetrahedron Letters, 1990, 31(37):5289-5292.	
	A73	SNELL et al., "Investigating the Effect of Impurities on Macromolecule Crystal Growth in Microgravity," Crystal Growth & Design, 2001, 1(2):151-158.	
	A74	Sorbera et al. "UT-15. Treatment of Pulmonary Hypertension Treatment of Peripheral Vascular Disease," *Drug of the Future*, 2001, 26(4), 364-374.	
	A75	TAKANO et al., "Enantiodivergent Synthesis of Both Enantiomers of Sulcatol and Matsutake Alcohol from (R)-Epichlorohydrin," Chemistry Letters, 1987, 2017-2020.	
	A76	VIEDMA, Cristobal, "Selective Chiral Symmetry Breaking during Crystallization: Parity Violation of Cryptochiral Environment in Control?" Crystal Growth & Design, 2007, 7(3):553-556.	
	A77	ZHANG et al., "A Nickel(0)-Catalyzed Process for the Transformation of Enynes to Bicyclic Cyclopentenones," J. Org. Chem., 1996, 61:4498-4499.	

Examiner Signature		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.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	AN IMPROVED PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Stephen Bradford Maebius/Karen Walker
Attorney Docket Number:	080618-1162

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility application filing	1011	1	380	380
Utility Search Fee	1111	1	620	620
Utility Examination Fee	1311	1	250	250
Pages:				
Claims:				
Claims in excess of 20	1202	1	60	60
Miscellaneous-Filing:				
Petition:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1310**

Electronic Acknowledgement Receipt

EFS ID:	13244906
Application Number:	13548446
International Application Number:	
Confirmation Number:	2092
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:	080618-1162
Receipt Date:	13-JUL-2012
Filing Date:	
Time Stamp:	13:00:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1310
RAM confirmation Number	10480
Deposit Account	
Authorized User	

File Listing:

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

1	Transmittal of New Application	Transmittal.pdf	98402 0d15a8ba4dc8e253cf5c161fcb6acd703d9903b8	no	3
Warnings:					
Information:					
2		Specification.pdf	233495 78ce548ef2e882aa2afaaa098e019bef1a437bce	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	Oath or Declaration filed	Declfromprior.pdf	172162 6d5b09fdfd00144bfaeb55e61acc8d6cc16d84c9	no	4
Warnings:					
Information:					
4	Application Data Sheet	ADS.pdf	63825 e6b6eaa0a08c8d18d7598119f522e77dcf999e84	no	4
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
5		IDS.pdf	555417 b297b7bd7d5776a029f5d2ceb5d22b123e568140	yes	6

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Transmittal Letter	1	2
	Information Disclosure Statement (IDS) Form (SB08)	3	6

Warnings:					
Information:					
6	Fee Worksheet (SB06)	fee-info.pdf	36853 9a2b705f4401f43366f35b420a420f7e05ed1fe8	no	2

Warnings:	
Information:	
Total Files Size (in bytes):	1160154

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.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/548,446

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	380
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	620
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	250
TOTAL CLAIMS (37 CFR 1.16(i))	21 minus 20 =	* 1			OR	x 60 =	60
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*				x 250 =	0.00
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						0.00
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	1310

APPLICATION AS AMENDED - PART II

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

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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United States Patent and Trademark Office
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/548,446	07/13/2012	1629	1310	080618-1162	21	2

CONFIRMATION NO. 2092

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

FILING RECEIPT

Date Mailed: 07/30/2012

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 application is a CON of 12/334,731 12/15/2008 PAT 8242305
which claims benefit of 61/014,232 12/17/2007

Foreign Applications (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.)

If Required, Foreign Filing License Granted: 07/25/2012

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/548,446**

Projected Publication Date: 11/08/2012

Non-Publication Request: No

Early Publication Request: No

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.

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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.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/548,446	07/13/2012	Hitesh Batra	080618-1162

CONFIRMATION NO. 2092

PUBLICATION NOTICE

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

OC000000057514237

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

Publication No.US-2012-0283470-A1
Publication Date:11/08/2012

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.

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Atty. Dkt. No. 080618-1162

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.: 13/548,446

Filing Date: 7/13/2012

Examiner: Yevgeny Valenrod

Art Unit: 1621

Conf. No.: 2092

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR §1.56

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

Commissioner:

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

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

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

TIMING OF THE DISCLOSURE

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

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

Respectfully submitted,

Date DEC 20 2012

By _____

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

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

PTO/SB/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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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: DEC 20 2012

(use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	13/548,446
Filing Date	7/13/2012
First Named Inventor	Hitesh BATRA
Art Unit	1621
Examiner Name	Yevgeny Valenrod
Attorney Docket Number	080618-1162

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	5,039,814 A	08/13/1991	Shuman et al.	
	B2	6,933,385 B2	08/23/2005	Westermann et al.	
	B3	7,999,007 B2	08/16/2011	Jeffs et al.	
	B4	2009/0124697 A1	05/14/2009	Cloutier et al.	
	B5	2009/0281189 A1	11/12/2009	Walsh, David A.	
	B6	2010/0076083 A1	03/25/2010	Olschewski	
	B7	2010/0282622 A1	11/11/2010	Phares, Kenneth R.	
	B8	2011/0092599 A1	04/21/2011	Wade et al.	
	B9	2011/0118213 A1	05/19/2011	Phares et al.	
	B10	2011/0144204 A1	06/16/2011	Jeffs et al.	
	B11	2011/0224236 A1	09/15/2011	Rothblatt et al.	
	B12	2011/0319641 A1	12/29/2011	Batra et al.	
	B13	2012/0004307 A1	01/05/2012	Wade et al.	
	B14	2012/0010159 A1	01/12/2012	Rothblatt et al.	

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	B15	13/409,685	03/01/2012	Sharma, Vijay	

FOREIGN PATENT DOCUMENTS

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

NON PATENT LITERATURE DOCUMENTS

Examiner 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: DEC 20 2012

(use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	13/548,446
Filing Date	7/13/2012
First Named Inventor	Hitesh BATRA
Art Unit	1621
Examiner Name	Yevgeny Valenrod
Attorney Docket Number	080618-1162

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]
	B16	COMINS et al., "Ortho Metalation Directed by α-Amino Alkoxides," J. Org. Chem., 1984, 49:1078-1083.	
	B17	COMINS et al., "Ortho Substitution of M-Anisaldehyde via α-Amino Alkoxide Directed Lithiation," J. Org. Chem., 1989, 54:3730-3732.	
	B18	COREY et al. "Novel Electronic Effects of Remote Substituents on the Oxazaborolidine-Catalyzed Enantioselective Reduction of Ketones," Tetrahedron Letters, 1995, 36(50):9153-9156.	
	B19	GREENE et al., "Protecting Groups," Protective Groups in Organic Synthesis, 2d. Ed., 1991, p. 1-11.	
	B20	PANSEGRAU et al., "The Oxazoline-Benzyne Route to 1,2,3-Trisubstituted Benzenes. Tandem Addition of Organolithiums, Organocuprates, and α-Lithionitriles to Benzynes," J. Am. Chem. Soc., 1988, 110:7178-7184.	
	B21	ROWLEY et al., "Application of the Pauson-Khand reaction to the synthesis of pentalenic acid," Journal of Organometallic Chemistry," 1991, 413:C5-C9.	

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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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/548,446	07/13/2012	Hitesh Batra	080618-1162	2092

22428 7590 01/03/2013

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
01/03/2013	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)	
	13/548,446	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 *13 July 2012*.

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) *1-21* 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) *1-21* is/are rejected.

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

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

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

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

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) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/13/12*.

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

4) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 102

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

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

Claims 1-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Moriarty et al. (*J. Org. Chem.* **2004**, *69(6)*, 1890-1902).

On Page 1892, column 1 Moriarty discloses compound 7 which has the same structure as the instantly claimed product. On page1902, paragraph bridging column 1 and 2, Moriarty disclose a method of preparing compound 7. In the second column 99.7% pure compound 7 is disclosed thereby meeting the purity limitations of claims 2 and 11. The instant claims are product by process. Since the product disclosed in the art is the same as the instantly claimed product, the patentability of the product is does not depend on the method of its production.

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from the product of the prior art, the claim is unpatentable even though the prior art product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (MPEP § 2113).

Conclusion

Claims 1-21 are pending

Claims 1-21 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, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1621

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: JUL 13 2012

(use as many sheets as necessary)

Sheet 1 of 4

Complete if Known	
Application Number	Unassigned
Filing Date	Herewith
First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	080618-1162

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (*if known*)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	A1	2002/0173672 A1	11/21/2002	Moriarty et al.	
	A2	2004/0176645 A1	09/09/2004	Moriarty et al.	
	A3	2005/0085540 A1	04/21/2005	Phares et al.	
	A4	2005/0101608 A1	05/12/2005	Santel, Donald J.	
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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]
	A35	CA 2 710 726 A1	01/22/2012	Alphora Research Inc., CA		

Examiner Signature		Date Considered	

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Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT				**Application Number**	Unassigned
Date Submitted: JUL 13 2012				**Filing Date**	Herewith
				First Named Inventor	Hitesh BATRA
(use as many sheets as necessary)				Art Unit	Unassigned
				Examiner Name	Unassigned
Sheet	2	of	4	Attorney Docket Number	080618-1162

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]
	A36	CN 101891596 A	11/24/2010	Shanghai Techwell Biopharmaceutical Co. Ltd.		A ✓
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	A50	WO 2012/009816 A1	01/26/2012	Alphora Research Inc.		

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

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: JUL 13 2012

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Sheet 3 of 4

Complete if Known	
Application Number	Unassigned
Filing Date	Herewith
First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
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NON PATENT LITERATURE DOCUMENTS

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Examiner Signature		Date Considered	

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Sheet 4 of 4

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First Named Inventor	Hitesh BATRA
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	080618-1162

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Examiner Signature	/Yevgeny Valenrod/	Date Considered	12/28/2012

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BIB DATA SHEET

CONFIRMATION NO. 2092

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/548,446	07/13/2012	~~562~~ 562/466	1621	080618-1162

APPLICANTS

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

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

This application is a CON of 12/334,731 12/15/2008 PAT 8,242,305
which claims benefit of 61/014,232 12/17/2007

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

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

07/25/2012

Foreign Priority claimed	❑ Yes ☑ No	❑ Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
35 USC 119(a-d) conditions met	☑ Yes ❑ No					
Verified and Acknowledged	/Y. Valenrod / Examiner's Signature	Initials	VA	0	21	2

ADDRESS

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

TITLE

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1310	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	❑ All Fees ❑ 1.16 Fees (Filing) ❑ 1.17 Fees (Processing Ext. of time) ❑ 1.18 Fees (Issue) ❑ Other _____ ❑ Credit

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	9	((HITESH) near2 (BATRA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L2	7	((SUDERSAN) near2 (TULADHAR)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L3	19	((RAJU) near2 (PENMASTA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L4	196	((DAVID) near2 (WALSH)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L5	4	"6765117"	USPAT	OR	OFF	2012/12/28 12:33
L6	0	"20020173672"	USPAT	OR	OFF	2012/12/28 12:33
L7	1	("20020173672").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L8	1	("2002/0173672").URPN.	USPAT	OR	OFF	2012/12/28 12:33
L9	1	("4306075").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L10	1	("6441245").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L11	1	("5387713").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L12	1	("20050085540").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L13	1	("20070078182").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L14	1	("20070254032").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L15	53	treprostinil diethanolamine	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2012/12/28 12:33
L16	1	("4845598").PN.	USPAT; USOCR	OR	OFF	2012/12/28 12:33

EAST Search History (Prior Art)

L17	1	("4485598").PN.	USPAT; USOCR	OR	OFF	2012/12/28 12:33
L18	1	("4486598").PN.	USPAT; USOCR	OR	OFF	2012/12/28 12:33
L19	2	("4486598").URPN.	USPAT	OR	OFF	2012/12/28 12:33
L20	63	treprostinil same diethanolamine	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2012/12/28 12:33
L21	10	L20 not L15	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2012/12/28 12:33
L22	195	L1 or L2 or L3 or L4	US-PGPUB; USPAT	OR	OFF	2012/12/28 12:33
L23	7	L22 and treprostinil	US-PGPUB; USPAT	OR	OFF	2012/12/28 12:33
L24	807	(562/466).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2012/12/28 12:33
L25	1	L24 and treprostinil	USPAT	OR	OFF	2012/12/28 12:33
L26	10	L24 and treprostinil	US-PGPUB; USPAT	OR	OFF	2012/12/28 12:33

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L27	0	(562/466).CCLS.	UPAD	OR	OFF	2012/12/28 12:33
L28	0	("treprostinil").PN.	UPAD	OR	OFF	2012/12/28 12:33
L29	2	((HITESH) near2 (BATRA)).INV.	USPAT; UPAD	OR	OFF	2012/12/28 12:33
L30	1	((SUDERSAN) near2 (TULADHAR)).INV.	USPAT; UPAD	OR	OFF	2012/12/28 12:33
L31	12	((RAJU) near2 (PENMASTA)).INV.	USPAT; UPAD	OR	OFF	2012/12/28 12:33
L32	127	((DAVID) near2 (WALSH)).INV.	USPAT; UPAD	OR	OFF	2012/12/28 12:33

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13548446	BATRA ET AL.
	Examiner	Art Unit
	YEVEGENY VALENROD	1621

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST	12/28/2012	YV
Inventor	12/28/2012	YV

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

	/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1621

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13548446	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	12/28/2012								
	1	✓								
	2	✓								
	3	✓								
	4	✓								
	5	✓								
	6	✓								
	7	✓								
	8	✓								
	9	✓								
	10	✓								
	11	✓								
	12	✓								
	13	✓								
	14	✓								
	15	✓								
	16	✓								
	17	✓								
	18	✓								
	19	✓								
	20	✓								
	21	✓								

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.:	13/548,446
Filing Date:	7/13/2012
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	2092

AMENDMENT & REQUEST FOR RECONSIDERATION UNDER 37 CFR § 1.111

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

Commissioner:

This paper responds to the Non-Final Office Action dated January 3, 2013.

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

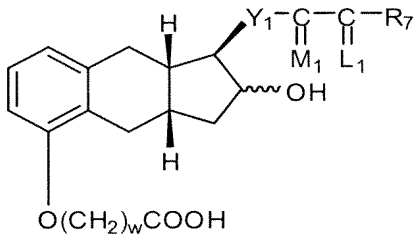
Remarks begin on page 9 of this document.

Amendments to the Claims:

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

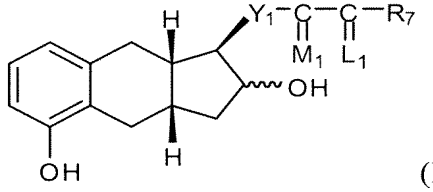
Listing of Claims:

1. (Currently Amended) A product comprising a compound of formula I

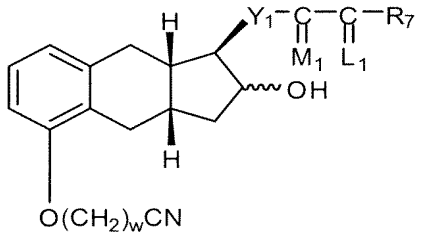


(I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising

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



(II)



(III)

wherein

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

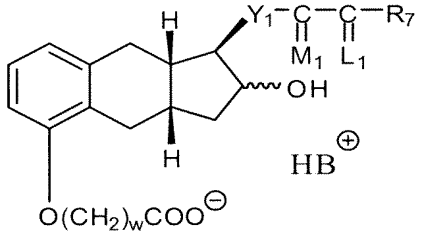
(4) 3-thienyloxymethyl;

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

2. (Currently Amended) The product of claim 1, wherein the purity of compound of formula I in said product ~~isat~~ is at least 99.5%.

3. (Original) The product of claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.

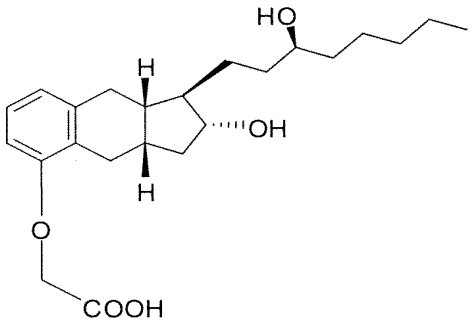
4. (Original) The product of claim 1, wherein the base in step (b) is KOH or NaOH.

5. (Original) The product of 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.

6. (Original) The product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4.

7. (Original) The product of 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.

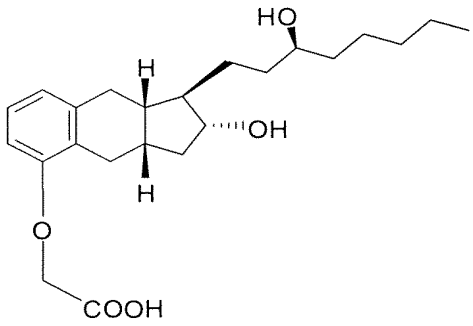
8. (Original) The product of claim 1, wherein the compound of formula I is a compound of formula IV.



(IV).

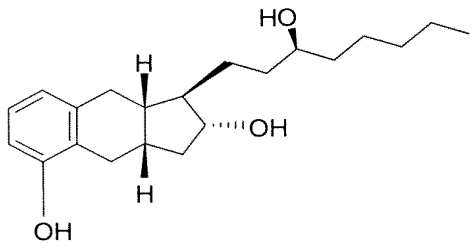
9. (Original) The product of claim 1, which the process does not include purifying the compound of formula (III) produced in step (a).

10. (Currently Amended) A product comprising a compound having formula IV

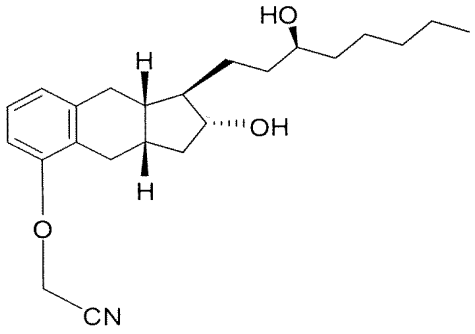


(IV) or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising

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



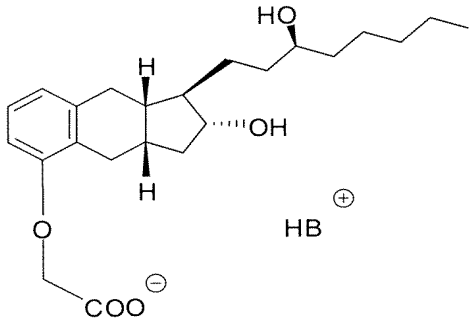
(V)



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

11. (Currently Amended) The process of claim 10, wherein the purity of product of step (d) ~~has the purity of the compound of formula IV of~~ is at least 99.5%.

12. (Original) The product of claim 10, wherein the alkylating agent is $ClCH_2CN$.

13. (Original) The product of claim 10, wherein the base in step (b) is KOH.

14. (Original) The product of 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.

15. (Original) The product of claim 10, wherein the base B is diethanolamine.

16. (Original) The product of claim 10, wherein the acid in step (d) is HCl.

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

18. (Original) The product of claim 17, 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.

19. (Original) The product of claim 18, wherein the base B is diethanolamine.

20. (Original) The product of 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.

21. (Original) The product of 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.

22. (New) The product of claim 1, wherein step (d) is performed.

23. (New) The product of claim 22, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d).

24. (New) A process of making a pharmaceutical product comprising treprostinil or a pharmaceutically acceptable salt thereof, said process comprising contacting a solution of treprostinil with a base to form a pharmaceutically acceptable salt of treprostinil, wherein the treprostinil in the solution has not been previously isolated.

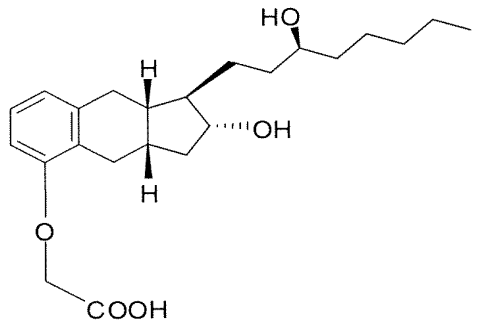
25. (New) The process of claim 24, further comprising isolating the pharmaceutically acceptable salt of treprostinil and adding a pharmaceutically acceptable carrier to form a pharmaceutical product.

26. (New) The process of claim 25, wherein the base is an inorganic base.

27. (New) The process of claim 26, wherein the salt formed by the inorganic base is a sodium salt of treprostinil.

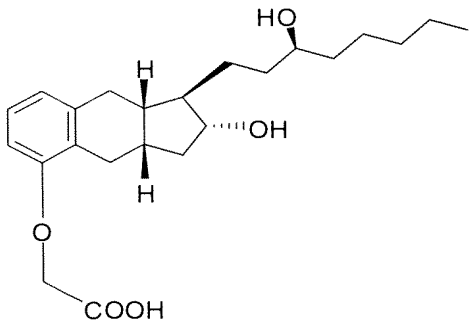
28. (New) The process of claim 26, wherein the salt formed by the inorganic base is a potassium salt of treprostinil.

29. (New) The process of claim 24, further comprising isolating the salt product followed by reacting the salt product with an acid to form a compound of the formula:



30. (New) The process of claim 29, wherein the salt product is a diethanolamine salt of treprostinil.

31. (New) The process of claim 30, further comprising adding a pharmaceutically acceptable carrier to the compound of the formula:



to form a pharmaceutical product.

REMARKS

Applicants respectfully request reconsideration and allowance of the present application.

CLAIM STATUS

Applicants have amended claims 1, 2, 10, and 11 without prejudice or disclaimer, to present the claimed subject matter in a clearer manner. Support for the amended claims may be found throughout the specification as filed. Additionally, claims 22-31 have been added, support for which can be found in paragraphs 46 ("the treprostinil salts can be synthesized from the solution of treprostinil without isolation"), 20 ("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"), 21 ("[b]ase addition salts may be formed with organic and inorganic bases, such as sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, choline and the like," and "[i]ncluded in the invention are pharmaceutically acceptable salts or compounds of any of the formulae herein"), as well as the working examples. No new matter has been added.

After the amendment, claims 1-31 are pending. Claims 1, 10, and 24 are independent.

CLAIM REJECTION UNDER 35 U.S.C. § 102(b)

Claims 1-21 stand rejected under 35 U.S.C. 102(b) over Moriarty et al. (J. Org. Chem. 2004, 69(6), 1890-1902). Applicants request reconsideration.

The product of Moriarty 2004 is physically different from the product of claims 1 and 10, in which a base addition salt is formed *in situ* with treprostinil that has not been previously isolated. Specifically, when a batch of treprostinil acid made by the type of process disclosed in Moriarty 2004 was analyzed by the applicants, it was found to contain small amounts of 4 different impurities (benzindene triol, treprostinil methyl ester, and 2 different stereoisomers of treprostinil). By contrast, not one of these four impurities was detectable in either a batch of treprostinil salt or a batch of treprostinil acid produced

according to claims 1 and 10. This physical difference in the product results directly from the steps recited in claims 1 and 10, in which a salt is formed *in situ* without previously isolating treprostinil. Since Moriarty does not teach a product of present claims 1 and 10, withdrawal of the rejection is requested.

Concerning new claims 24-31, the same argument above applies to these claims. When a salt is formed with treprostinil *in situ* without previously isolating the treprostinil as required by the steps of these claims, the impurities mentioned in the preceding paragraph resulting from the Moriarty 2004 steps are not detected. Thus, both the steps of the process for making pharmaceutical products recited in claims 24-31 and the products resulting from those steps are different than the process and product of Moriarty 2004 cited in the Office Action. Moriarty 2004 neither teaches nor suggests the advantages resulting from this difference, including the avoidance of the 4 impurities listed above in the product.

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 Feb. 8, 2013

By _____

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

Stephen B. Maebius
Agent for Applicants
Registration No. 55,264

Electronic Patent Application Fee Transmittal

Application Number:	13548446
Filing Date:	13-Jul-2012
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Stephen Bradford Maebius/Diana Meinecke
Attorney Docket Number:	080618-1162

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:				
Claims in excess of 20	1202	10	62	620
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**620**

Electronic Acknowledgement Receipt

EFS ID:	14916956
Application Number:	13548446
International Application Number:	
Confirmation Number:	2092
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Stephen Bradford Maebius/Diana Meinecke
Filer Authorized By:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1162
Receipt Date:	08-FEB-2013
Filing Date:	13-JUL-2012
Time Stamp:	16:30:34
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$620
RAM confirmation Number	3297
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	transmittal2-8-13.pdf	45393 334f796fcb79a1d176e6984cf300ec95850876ce	no	3
Warnings:					
Information:					
2		AmendRequest2-8-13.pdf	124837 8aff44c573671b9cb595066eaa7fe543438bcc11	yes	11

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	8
	Applicant Arguments/Remarks Made in an Amendment	9	11

Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30804 3306ede804040395105953e1d8fb8c5c4fd5f081	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	201034		

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.: 13/548,446

Filing Date: 07/13/2012

Examiner: Yevgeny Valenrod

Art Unit: 1621

Confirmation Number: 2092

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.

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

[ ] Assertion of Small Entity status is enclosed.

[**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:	31	-	21	=	10	x	$62.00	=	$620.00

Independent Claims:	3	-	3	=	0	x	$250.00	=	$0.00
First presentation of any Multiple Dependent Claims:						+	$460.00	=	$0.00
CLAIMS FEE TOTAL								=	$620.00

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

[ ] Extension for response filed within the first month:	$150.00	$0.00
[ ] Extension for response filed within the second month:	$570.00	$0.00
[ ] Extension for response filed within the third month:	$1,290.00	$0.00
[ ] Extension for response filed within the fourth month:	$2,010.00	$0.00
[ ] Extension for response filed within the fifth month:	$2,730.00	$0.00
EXTENSION FEE TOTAL:		$0.00
[ ] Statutory Disclaimer Fee under 37 C.F.R. 1.20(d):	$160.00	$0.00
CLAIMS, EXTENSION AND DISCLAIMER FEE TOTAL:		$620.00
[ ] Small Entity Fees Apply (subtract ½ of above):		$0.00
Extension Fees Previously Paid:		$0.00
TOTAL FEE:		$620.00

The above-identified fees of $620.00 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 Feb. 8, 2013 By _____

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

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

PTO/SB/06 (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
13/548,446	07/13/2012	

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 02/08/2013	(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))	* 31	Minus	** 21	= 10	X $ =		OR	X $62=	620
Independent (37 CFR 1.16(h))	* 3	Minus	***3	= 0	X $ =		OR	X $250=	0
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	**620**

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:
/SANDRA GARNETT/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/548,446	07/13/2012	Hitesh Batra	080618-1162	2092

22428 7590 05/15/2013
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
05/15/2013	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. 13/548,446	Applicant(s) BATRA ET AL.	
	Examiner YEVGENY VALENROD	Art Unit 1621	AIA (First Inventor to File) Status No

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

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* 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 *8 February 2013*.

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

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

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

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

Disposition of Claims

5)☒ Claim(s) *1-31* is/are pending in the application.

5a) Of the above claim(s) *24-31* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

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

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

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

Application Papers

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

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

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

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

Priority under 35 U.S.C. § 119

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

Certified copies:

a)☐ All b)☐ Some * c)☐ None of the:

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

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

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

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

Interim copies:

a)☐ All b)☐ Some c)☐ None of the: Interim copies of the priority documents have been received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/20/12*.

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

4) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Newly submitted claims 24-31 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 24-31 are directed to a process for making a pharmaceutical product while examined claims are directed to a product.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 24-31 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Maintained Claim Rejections - 35 USC § 102

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

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

Claims 1-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Moriarty et al. (*J. Org. Chem.* **2004**, *69(6)*, 1890-1902).

On Page 1892, column 1 Moriarty discloses compound 7 which has the same structure as the instantly claimed product. On page1902, paragraph bridging column 1 and 2, Moriarty disclose a method of preparing compound 7. In the second column

99.7% pure compound 7 is disclosed thereby meeting the purity limitations of claims 2 and 11. The instant claims are product by process. Since the product disclosed in the art is the same as the instantly claimed product, the patentability of the product is does not depend on the method of its production.

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from the product of the prior art, the claim is unpatentable even though the prior art product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (MPEP § 2113).

Reply to applicants' remarks

Applicants have traversed the above rejection on the grounds that the process by which the instantly claimed product is prepared results in a product that is different from the product of Moriarty. Specifically, applicants allege that treprostinil prepared by the process of Moriarty contains 4 different impurities (benzindene triol, treprostinil methyl ester and 2 different stereoisomers of treaprostinil), while the process in the instant claims results in a product where such impurities are not present. Upon a closer investigation of the Moriarty reference, Examiner has been unable to locate the description of the above mentioned impurities being present. Likewise, no comparative data demonstrating the difference between the two products has been found upon a closer review of the specification. As such, the evidence presented by the applicant

cannot be considered unless it is presented in a form of a declaration. Without such evidence, the product of Moriarty meets the limitations of the instant claims and the rejection of record is maintained.

Conclusion

Claims 1-31 are pending

Claims 1-23 are rejected

Claims 24-31 are withdrawn

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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

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

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1621

PTO/SB/08a (08-06)
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

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: DEC 20 2012

(use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	13/548,446
Filing Date	7/13/2012
First Named Inventor	Hitesh BATRA
Art Unit	1621
Examiner Name	Yevgeny Valenrod
Attorney Docket Number	080618-1162

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	5,039,814 A	08/13/1991	Shuman et al.	
	B2	6,933,385 B2	08/23/2005	Westermann et al.	
	B3	7,999,007 B2	08/16/2011	Jeffs et al.	
	B4	2009/0124697 A1	05/14/2009	Cloutier et al.	
	B5	2009/0281189 A1	11/12/2009	Walsh, David A.	
	B6	2010/0076083 A1	03/25/2010	Olschewski	
	B7	2010/0282622 A1	11/11/2010	Phares, Kenneth R.	
	B8	2011/0092599 A1	04/21/2011	Wade et al.	
	B9	2011/0118213 A1	05/19/2011	Phares et al.	
	B10	2011/0144204 A1	06/16/2011	Jeffs et al.	
	B11	2011/0224236 A1	09/15/2011	Rothblatt et al.	
	B12	2011/0319641 A1	12/29/2011	Batra et al.	
	B13	2012/0004307 A1	01/05/2012	Wade et al.	
	B14	2012/0010159 A1	01/12/2012	Rothblatt et al.	

UNPUBLISHED U.S. PATENT APPLICATION DOCUMENTS

Examiner Initials*	Cite No.[1]	U.S. Patent Application Document Serial Number-Kind Code[2] (*if known*)	Filing Date of Cited Document MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	B15	13/409,685	03/01/2012	Sharma, Vijay	

FOREIGN PATENT DOCUMENTS

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

NON PATENT LITERATURE DOCUMENTS

Examiner 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.

4811-8493-2114.1 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

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Date Submitted: DEC 20 2012

(use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	13/548,446
Filing Date	7/13/2012
First Named Inventor	Hitesh BATRA
Art Unit	1621
Examiner Name	Yevgeny Valenrod
Attorney Docket Number	080618-1162

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]
	B16	COMINS et al., "Ortho Metalation Directed by α-Amino Alkoxides," J. Org. Chem., 1984, 49:1078-1083.	
	B17	COMINS et al., "Ortho Substitution of M-Anisaldehyde via α-Amino Alkoxide Directed Lithiation," J. Org. Chem., 1989, 54:3730-3732.	
	B18	COREY et al. "Novel Electronic Effects of Remote Substituents on the Oxazaborolidine-Catalyzed Enantioselective Reduction of Ketones," Tetrahedron Letters, 1995, 36(50):9153-9156.	
	B19	GREENE et al., "Protecting Groups," Protective Groups in Organic Synthesis, 2d. Ed., 1991, p. 1-11.	
	B20	PANSEGRAU et al., "The Oxazoline-Benzyne Route to 1,2,3-Trisubstituted Benzenes. Tandem Addition of Organolithiums, Organocuprates, and α-Lithionitriles to Benzynes," J. Am. Chem. Soc., 1988, 110:7178-7184.	
	B21	ROWLEY et al., "Application of the Pauson-Khand reaction to the synthesis of pentalenic acid," Journal of Organometallic Chemistry," 1991, 413:C5-C9.	

Examiner Signature	/Yevgeny Valenrod/	Date Considered	05/06/2013

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

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /YV/

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13548446	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	12/28/2012	05/06/2013							
	1	✓	✓							
	2	✓	✓							
	3	✓	✓							
	4	✓	✓							
	5	✓	✓							
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	26		N							
	27		N							
	28		N							
	29		N							
	30		N							
	31		N							

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13548446	BATRA ET AL.
	Examiner	Art Unit
	YEVEGENY VALENROD	1621

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST	5/6/2013	YV
Inventor	5/6/2013	YV

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

	/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1621

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	9	((HITESH) near2 (BATRA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L2	7	((SUDERSAN) near2 (TULADHAR)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L3	19	((RAJU) near2 (PENMASTA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L4	198	((DAVID) near2 (WALSH)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L5	7	"6765117"	USPAT	OR	OFF	2013/05/06 15:29
L6	0	"20020173672"	USPAT	OR	OFF	2013/05/06 15:29
L7	1	("20020173672").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L8	1	("2002/0173672").URPN.	USPAT	OR	OFF	2013/05/06 15:29
L9	1	("4306075").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L10	1	("6441245").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L11	1	("5387713").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L12	1	("20050085540").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L13	1	("20070078182").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L14	1	("20070254032").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L15	58	treprostinil diethanolamine	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2013/05/06 15:29
L16	1	("4845598").PN.	USPAT; USOCR	OR	OFF	2013/05/06 15:29

EAST Search History (Prior Art)

L17	1	("4485598").PN.	USPAT; USOCR	OR	OFF	2013/05/06 15:29
L18	1	("4486598").PN.	USPAT; USOCR	OR	OFF	2013/05/06 15:29
L19	2	("4486598").URPN.	USPAT	OR	OFF	2013/05/06 15:29
L20	68	treprostinil same diethanolamine	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2013/05/06 15:29
L21	10	L20 not L15	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2013/05/06 15:29
L22	197	L1 or L2 or L3 or L4	US-PGPUB; USPAT	OR	OFF	2013/05/06 15:29
L23	8	L22 and treprostinil	US-PGPUB; USPAT	OR	OFF	2013/05/06 15:29
L24	811	(562/466).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/05/06 15:29
L25	2	L24 and treprostinil	USPAT	OR	OFF	2013/05/06 15:29
L26	12	L24 and treprostinil	US-PGPUB; USPAT	OR	OFF	2013/05/06 15:29

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L27	0	(562/466).CCLS.	UPAD	OR	OFF	2013/05/06 15:29
L28	0	("treprostinil").PN.	UPAD	OR	OFF	2013/05/06 15:29
L29	2	((HITESH) near2 (BATRA)).INV.	USPAT; UPAD	OR	OFF	2013/05/06 15:29
L30	1	((SUDERSAN) near2 (TULADHAR)).INV.	USPAT; UPAD	OR	OFF	2013/05/06 15:29
L31	12	((RAJU) near2 (PENMASTA)).INV.	USPAT; UPAD	OR	OFF	2013/05/06 15:29
L32	128	((DAVID) near2 (WALSH)).INV.	USPAT; UPAD	OR	OFF	2013/05/06 15:29

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.:	13/548,446
Filing Date:	7/13/2012
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	2092

REPLY UNDER 37 CFR § 1.116

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

Commissioner:

This paper responds to the outstanding Final Office Action dated May 15, 2013.

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

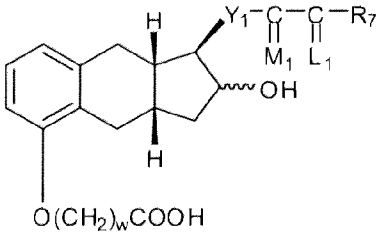
Remarks begin on page 7 of this document.

Amendments to the Claims:

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

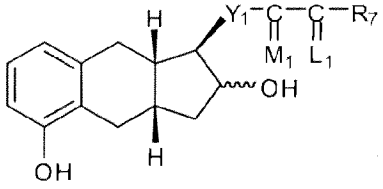
Listing of Claims:

1. (Previously Presented) A product comprising a compound of formula I

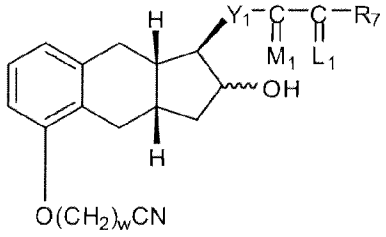


(I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising

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



(II)



(III)

wherein

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

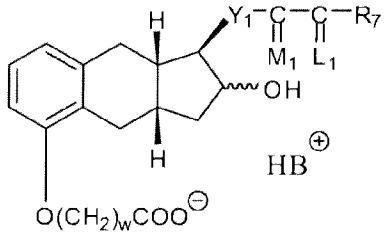
(4) 3-thienyloxymethyl;

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

2. (Previously Presented) The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.

3. (Original) The product of claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.

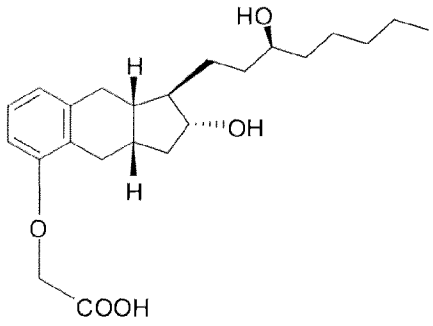
4. (Original) The product of claim 1, wherein the base in step (b) is KOH or NaOH.

5. (Original) The product of 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.

6. (Original) The product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4.

7. (Original) The product of 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.

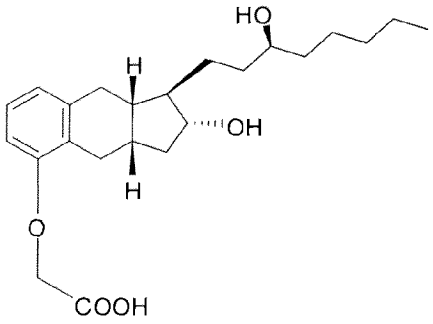
8. (Original) The product of claim 1, wherein the compound of formula I is a compound of formula IV.



(IV).

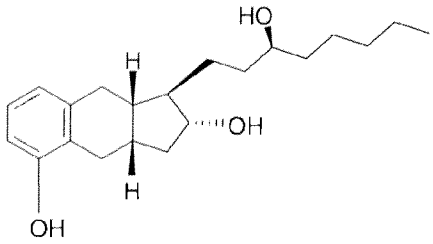
9. (Original) The product of claim 1, which the process does not include purifying the compound of formula (III) produced in step (a).

10. (Previously Presented) A product comprising a compound having formula IV

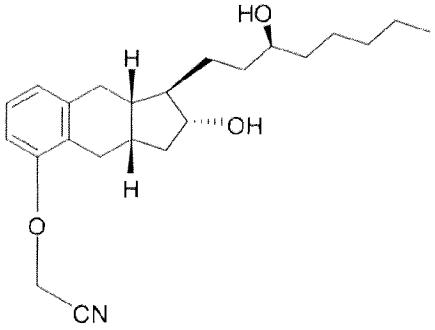


(IV) or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising

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



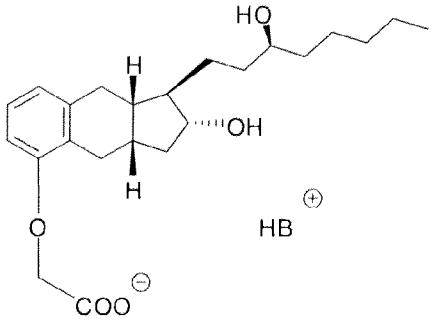
(V)



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

11. (Currently Amended) The ~~process~~ product of claim 10, wherein the purity of product of step (d) is at least 99.5%.

12. (Original) The product of claim 10, wherein the alkylating agent is $ClCH_2CN$.

13. (Original) The product of claim 10, wherein the base in step (b) is KOH.

14. (Original) The product of 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.

15. (Original) The product of claim 10, wherein the base B is diethanolamine.

16. (Original) The product of claim 10, wherein the acid in step (d) is HCl.

17. (Currently Amended) The product of claim 10, ~~which~~ wherein the process does not include purifying the compound of formula (VI) produced in step (a).

18. (Original) The product of claim 17, 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.

19. (Original) The product of claim 18, wherein the base B is diethanolamine.

20. (Original) The product of 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.

21. (Original) The product of 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.

22. (Previously Presented) The product of claim 1, wherein step (d) is performed.

23. (Previously Presented) The product of claim 22, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d).

24-31. (Canceled)

REMARKS

Applicants respectfully request reconsideration and allowance of the present application.

CLAIM STATUS

Applicants have amended claims 11 and 17 to correct inadvertent typographical errors. No new matter has been added.

Applicants have canceled claims 24-31, without prejudice or disclaimer. Applicants reserve the right to file one or more continuing application directed to the subject matter of the canceled claims.

After the amendment, claims 1-23 are pending. Claims 1 and 10 are independent.

CLAIM REJECTION UNDER 35 U.S.C. § 102(b)

Claims 1-21 stand rejected under 35 U.S.C. 102(b) over Moriarty et al. (J. Org. Chem. 2004, 69(6), 1890-1902). Applicants request reconsideration.

In the response filed February 8, 2013, Applicants submitted that the product of Moriarty 2004 is physically different from the product of claims 1 and 10, in which a base addition salt is formed *in situ* with treprostinil that has not been previously isolated. Specifically, Applicants noted that when a batch of treprostinil acid made by the type of process disclosed in Moriarty 2004 was analyzed by the applicants, it was found to contain small amounts of 4 different impurities (benzindene triol, treprostinil methyl ester, and 2 different stereoisomers of treprostinil). By contrast, not one of these four impurities was detectable in either a batch of treprostinil salt or a batch of treprostinil acid produced according to claims 1 and 10. In their February 8th response, Applicants explained that this physical difference in the product resulted directly from the steps recited in claims 1 and 10, in which a salt is formed *in situ* without previously isolating treprostinil.

In the Office Action, the PTO informed Applicants that "the evidence presented by the applicant cannot be considered unless it is presented in a form of a declaration," see sentence

bridging pages 3-4. The PTO decided to maintain the rejection because in the PTO's opinion, "[w]ithout such evidence, the product of Moriarty meets the limitations of the instant claims," see page 4.

To address the issue raised by the PTO, Applicants submit with the present response a declaration under 37 C.F.R. § 1.132 by Dr. David Walsh. In section 7 of his declaration, Dr. Walsh provides data from representative Certificates of Analysis with impurity profiles for treprostinil prepared according to the process corresponding to "Moriarty", treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 of the present application, and treprostinil as the free acid prepared according to the process specified in claim 1 or 10 of the present application. Based on the results provided, Dr. Walsh concludes "that each of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claimd 1 or 10 of the present application is physically different from treprostinil prepared according to the process of "Moriarty" at least because neither of them contains a detectable amount of any of benzindene triol, treprostinil methyl ester, 1AU90 treprostinil stereoisomer and 2AU90 treprostinil stereoisomer, each of which were present in detectable amounts in treprostinil produced according to the process of "Moriarty."

Since Dr. Walsh's declaration provides evidence that the product of present claims is physically difference than treprostinil produced according to the process of Moriarty, Moriarty cannot anticipate the present claims. Accordingly, Applicants request withdrawal of the rejection.

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 June 5, 2013

By [signature] for Alexey Saprigin Reg No 35,264

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

Agent for Applicants
Registration No. 56,439

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.:	13/548,446
Filing Date:	7/13/2012
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	2092

DECLARATION OF DAVID WALSH UNDER 37 C.F.R. 1.132

I, David A. Walsh, do hereby declare:

1. I am the Executive Vice President of Chemical Research and Development at the United Therapeutics Corporation.

2. I have extensive experience in the field of Pharmaceutical Chemistry as evidenced by my Ph.D. degree received in organic chemistry from the University of New Hampshire and over 39 years of professional experience. My Curriculum Vitae attached as Appendix A provides additional details on my qualifications and experience.

3. My employer, United Therapeutics Corporation, is the owner of the above identified application.

4. I am not receiving additional compensation for providing this Declaration beyond my normal compensation from my employer.

BAW 6/4/13

5. I am familiar with the Office Action dated May 15, 2013, as well as with Moriarty et al. (J. Org. Chem. 2004, 69(6), 1890-1902, "Moriarty") cited therein.

6. In my opinion, each of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 of the present application is physically different from treprostinil prepared according to the process of "Moriarty." In particular, each of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 differ from treprostinil prepared according to the process of "Moriarty" in their respective impurity profiles. In support, I provide the following data obtained from representative Certificates of Analysis with impurity profiles for treprostinil prepared according to the process of "Moriarty", treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 of the present application, and treprostinil as the free acid prepared according to the process specified in claim 1 or 10 of the present application, respectively.

Treprostinil free acid prepared according to "Moriarty"

Chromatographic Purity (HPLC) NB 1, PDR 16	1AU90:	Not more than 0.4%	ND
	2AU90:	Not more than 0.1%	< 0.05%
	97W86 (Benzindene Trial):	Not more than 0.2%	0.07%
	3AU90:	Not more than 1.0%	0.3%
	Treprostinil Methyl Ester:	Not more than 0.2%	< 0.05%
	Treprostinil Ethyl Ester:	Not more than 0.5%	0.1%
	750W93:	Not more than 0.5%	0.1%
	751W93:	Not more than 0.3%	0.07%
	Unidentified at:	Not more than 0.1% AUC each	ND
Total Related Substances NB 1, PDR 16	Not more than 3.0%		0.6%

6/14/13

Treprostinil diethanolamine prepared according to claims 1 or 10

	Com pound	Specifications	
Impurities (HPLC) [Known Impurities] (UTW-11-0327)	1AU90	Not more than 0.4 %	ND
	2AU90	Not more than 0.1 %	ND
	97W86	Not more than 0.2 %	ND
	3ALI9D	Not more than 0.5 %	< 0.05 % w/w
	Treprostinil Methyl Ester	Not more than 0.2 %	ND
	Treprostinil Ethyl Ester	Not more than 0.5 %	ND
	750W93	Not more than 0.5 %	ND
	751W93	Not more than 0.3 %	ND
Impurities (HPLC) [Unidentified Impurities] (UTW-11-0327)	Not more than 0.2 % AUC each		0.07 % AUC (RRT 0.26)
Impurities (HPLC) [Total Related Substances] (UTW-11-0327)	Not more than 1.5 %		0.1 % w/w

Treprostinil as the free acid prepared according to claims 1 or 10

	Compound	Specifications	
Impurities (HPLC)	1AU90	Not more than 0.40%	ND
	2AU90	Not more than 0.10%	ND
	3AU90	Not more than 1.00%	ND
	750W93	Not more than 0.50%	0.06 % w/w
	751W93	Not more than 0.30%	< 0.05 % w/w
	97W86 (Benzindene Triol)	Not more than 0.20%	ND
	Treprostinil Ethyl Ester	Not more than 0.50%	0.13 % w/w
	Treprostinil Methyl Ester	Not more than 0.20%	ND
Impurities (HPLC) [Unidentified Impurities]	Not more than 0.10% AUC each		ND
Impurities (HPLC) [Total Related Substances]	Not more than 3.00%		0.2 %

In each case, in the above tables, "ND" means not detected. The far right column represents the testing results for that product batch.

7. The impurity profiles shown above examine the following eight impurities: 1AU90, 2AU90 and 3AU90, each of which is a stereoisomer of treprostinil; triol; methyl ester of treprostinil and ethyl ester of treprostinil; 750W93 and 751W93, each of which is a dimer of treprostinil, in which the acid group of one treprostinil molecule esterifies with an alcohol group on another treprostinil molecule. According to the first profile above, treprostinil produced according to the process of "Moriarty" has 7 out of 8 impurities in detectable amounts. According to the second profile above, treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 of the present application has only one impurity, treprostinil stereoisomer 3A90, in a detectable amount. According to the third profile above, treprostinil as

the free acid prepared according to the process specified in claim 1 or 10 of the present application has only three impurities, treprostinil ethyl ester, treprostinil dimers 750W93 and 751W93.

8. Based on the results shown above, I conclude that each of treprostinil as the free acid and treprostinil diethanolamine prepared according to the process specified in claim 1 or 10 of the present application is physically different from treprostinil prepared according to the process of "Moriarty" at least because neither of them contains a detectable amount of any of benzindene triol, treprostinil methyl ester, 1AU90 treprostinil stereoisomer and 2AU90 treprostinil stereoisomer, each of which were present in detectable amounts in treprostinil produced according to the process of "Moriarty".

9. 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.

6/4/13

Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 4th day of JUNE, 2013.

David A. Walsh

David A. Walsh

Electronic Acknowledgement Receipt

EFS ID:	15957665
Application Number:	13548446
International Application Number:	
Confirmation Number:	2092
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN®
First Named Inventor/Applicant Name:	Hitesh Batra
Customer Number:	22428
Filer:	Stephen Bradford Maebius/Diana Meinecke
Filer Authorized By:	Stephen Bradford Maebius
Attorney Docket Number:	080618-1162
Receipt Date:	05-JUN-2013
Filing Date:	13-JUL-2012
Time Stamp:	15:34:28
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		116Reply.pdf	391887 37da8f5eb11ff49010ea1b16cae4d9a112177dba	yes	9

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment After Final	1	1
	Claims	2	6
	Applicant Arguments/Remarks Made in an Amendment	7	9

Warnings:					
Information:					
2	Miscellaneous Incoming Letter	DAWsigneddeclaration.pdf	147931 730f850fe95f504bd6b9ab1d587cd6e498023cd5	no	5
Warnings:					
Information:					
		Total Files Size (in bytes):	539818		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/548,446	Filing Date 07/13/2012	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	**380**
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	**380**

APPLICATION AS AMENDED – PART II

AMENDMENT **06/05/2013**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 23	Minus	** 31	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 2	Minus	***3	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	**0**

AMENDMENT

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

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

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22428 7590 06/12/2013

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EXAMINER
VALENROD, YEVGENY

ART UNIT	PAPER NUMBER
1621	

DATE MAILED: 06/12/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/548,446	07/13/2012	Hitesh Batra	080618-1162	2092

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN0

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$300	$0	$2080	09/12/2013

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

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 06/12/2013
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.
13/548,446	07/13/2012	Hitesh Batra	080618-1162	2092

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN0

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$300	$0	$2080	09/12/2013

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)

❑ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
❑ Applicant asserting small entity status. See 37 CFR 1.27	NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
❑ Applicant changing to regular undiscounted fee status.	NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/548,446	07/13/2012	Hitesh Batra	080618-1162	2092

22428 7590 06/12/2013

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

EXAMINER	
VALENROD, YEVGENY	

ART UNIT	PAPER NUMBER
1621	

DATE MAILED: 06/12/2013

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

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. 13/548,446	Applicant(s) BATRA ET AL.	
	Examiner YEVGENY VALENROD	Art Unit 1621	AIA (First Inventor to File) Status No

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

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *6/5/13*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-23*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

   Interim copies:

   a) ☐ All b) ☐ Some c) ☐ None of the: Interim copies of the priority documents have been received.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1621

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13548446	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	12/28/2012	05/06/2013	06/10/2013						
	1	✓	✓	=						
	2	✓	✓	=						
	3	✓	✓	=						
	4	✓	✓	=						
	5	✓	✓	=						
	6	✓	✓	=						
	7	✓	✓	=						
	8	✓	✓	=						
	9	✓	✓	=						
	10	✓	✓	=						
	11	✓	✓	=						
	12	✓	✓	=						
	13	✓	✓	=						
	14	✓	✓	=						
	15	✓	✓	=						
	16	✓	✓	=						
	17	✓	✓	=						
	18	✓	✓	=						
	19	✓	✓	=						
	20	✓	✓	=						
	21	✓	✓	=						
	22		✓	=						
	23		✓	=						
	24		N							
	25		N							
	26		N							
	27		N							
	28		N							
	29		N							
	30		N							
	31		N							

OK TO ENTER: /YV/

Atty. Dkt. No. 080618-1162
Appl. No. 13/548,446

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.:	13/548,446
Filing Date:	7/13/2012
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	2092

REPLY UNDER 37 CFR § 1.116

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

Commissioner:

This paper responds to the outstanding Final Office Action dated May 15, 2013.

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

Remarks begin on page 7 of this document.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13548446	BATRA ET AL.
	Examiner	Art Unit
	YEVEGENY VALENROD	1621

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
EAST	6/10/2013	YV
Inventor	6/10/2013	YV

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
562	466	6/10/2013	YV

	/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1621

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	9	((HITESH) near2 (BATRA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L2	7	((SUDERSAN) near2 (TULADHAR)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L3	19	((RAJU) near2 (PENMASTA)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L4	201	((DAVID) near2 (WALSH)).INV.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L5	7	"6765117"	USPAT	OR	OFF	2013/06/10 14:30
L6	0	"20020173672"	USPAT	OR	OFF	2013/06/10 14:30
L7	1	("20020173672").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L8	1	("2002/0173672").URPN.	USPAT	OR	OFF	2013/06/10 14:30
L9	1	("4306075").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L10	1	("6441245").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L11	1	("5387713").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L12	1	("20050085540").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L13	1	("20070078182").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L14	1	("20070254032").PN.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L15	59	treprostinil diethanolamine	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2013/06/10 14:30
L16	1	("4845598").PN.	USPAT; USOCR	OR	OFF	2013/06/10 14:30

EAST Search History (Prior Art)

L17	1	("4485598").PN.	USPAT; USOCR	OR	OFF	2013/06/10 14:30
L18	1	("4486598").PN.	USPAT; USOCR	OR	OFF	2013/06/10 14:30
L19	2	("4486598").URPN.	USPAT	OR	OFF	2013/06/10 14:30
L20	69	treprostinil same diethanolamine	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2013/06/10 14:30
L21	10	L20 not L15	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	ADJ	OFF	2013/06/10 14:30
L22	200	L1 or L2 or L3 or L4	US-PGPUB; USPAT	OR	OFF	2013/06/10 14:30
L23	8	L22 and treprostinil	US-PGPUB; USPAT	OR	OFF	2013/06/10 14:30
L24	811	(562/466).CCLS.	US-PGPUB; USPAT; USOCR	OR	OFF	2013/06/10 14:30
L25	2	L24 and treprostinil	USPAT	OR	OFF	2013/06/10 14:30
L26	12	L24 and treprostinil	US-PGPUB; USPAT	OR	OFF	2013/06/10 14:30

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L27	0	(562/466).CCLS.	UPAD	OR	OFF	2013/06/10 14:30
L28	0	("treprostinil").PN.	UPAD	OR	OFF	2013/06/10 14:30
L29	2	((HITESH) near2 (BATRA)).INV.	USPAT; UPAD	OR	OFF	2013/06/10 14:30
L30	1	((SUDERSAN) near2 (TULADHAR)).INV.	USPAT; UPAD	OR	OFF	2013/06/10 14:30
L31	12	((RAJU) near2 (PENMASTA)).INV.	USPAT; UPAD	OR	OFF	2013/06/10 14:30
L32	129	((DAVID) near2 (WALSH)).INV.	USPAT; UPAD	OR	OFF	2013/06/10 14:30

Issue Classification

Application/Control No.	Applicant(s)/Patent Under Reexamination
13548446	BATRA ET AL.
Examiner	**Art Unit**
YEVEGENY VALENROD	1621

CPC

Symbol				Type	Version
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CPC Combination Sets

Symbol				Type	Set	Ranking	Version
		/					
		/					

US ORIGINAL CLASSIFICATION		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)				

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 23
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1621 (Primary Examiner)	06/10/2013 (Date)	O.G. Print Claim(s): 1 — O.G. Print Figure: none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13548446	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1621

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	23	
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1621	06/10/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13548446	BATRA ET AL.
	Examiner	**Art Unit**
	YEVEGENY VALENROD	1621

☒ **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

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	23	
/YEVEGENY VALENROD/ Primary Examiner.Art Unit 1621	06/10/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	none

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 06/12/2013
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.
13/548,446	07/13/2012	Hitesh Batra	080618-1162	2092

TITLE OF INVENTION: PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN0

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$1780	$300	$0	$2080	09/12/2013

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, MD

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☒ Issue Fee
- ☒ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☒ Payment by credit card. Form PTO-2038 is attached.
- ☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or 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)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

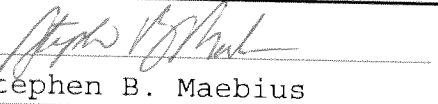
☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

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 JUN 18 2013

Typed or printed name Stephen B. Maebius Registration No. 35,264

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.:	13/548,446
Filing Date:	7/13/2012
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	2092

AMENDMENT UNDER 37 CFR 1.312

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

Commissioner:

Applicant acknowledges receipt of a Notice of Allowance in the above-captioned application. Prior to payment of the issue fee, please amend the application as follows:

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

Remarks/Arguments begin on page 7 of this document.

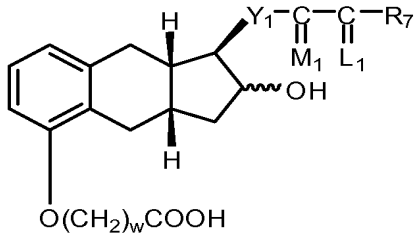
Please amend the application as follows:

Amendments to the Claims:

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

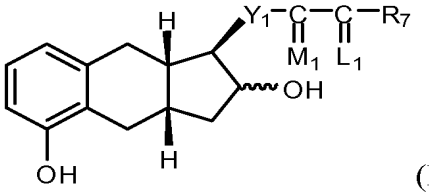
Listing of Claims:

1. (Previously Presented) A product comprising a compound of formula I

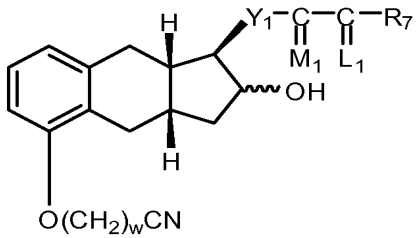


(I) or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising

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



(II)



(III)

wherein

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

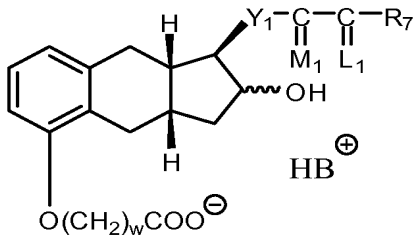
(4) 3-thienyloxymethyl;

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

2. (Previously Presented) The product of claim 1, wherein the purity of compound of formula I in said product is at least 99.5%.

3. (Original) The product of claim 1, wherein the alkylating agent is $Cl(CH_2)_wCN$, $Br(CH_2)_wCN$, or $I(CH_2)_wCN$.

4. (Original) The product of claim 1, wherein the base in step (b) is KOH or NaOH.

5. (Original) The product of 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.

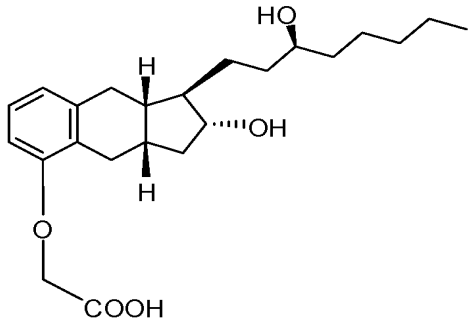
6. (Original) The product of claim 1, wherein the acid in step (d) is HCl or H_2SO_4.

7. (Original) The product of 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.

8. (Canceled)

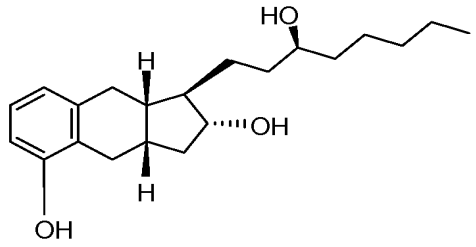
9. (Currently amended) The product of claim 1, ~~which~~ **wherein** the process does not include purifying the compound of formula (III) produced in step (a).

10. (Previously Presented) A product comprising a compound having formula IV

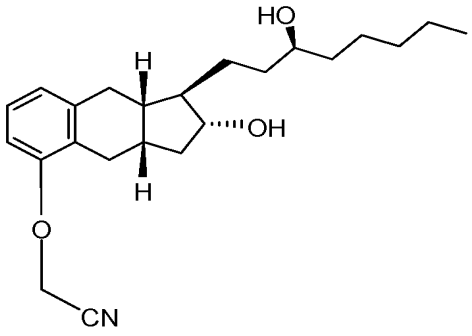


(IV) or a pharmaceutically acceptable salt thereof, wherein the product is prepared by the process comprising

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



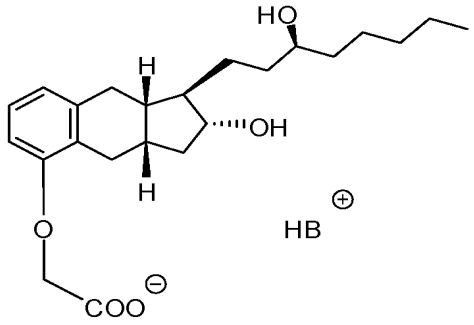
(V)



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

11. (Previously presented) The product of claim 10, wherein the purity of product of step (d) is at least 99.5%.

12. (Original) The product of claim 10, wherein the alkylating agent is $ClCH_2CN$.

13. (Original) The product of claim 10, wherein the base in step (b) is KOH.

14. (Original) The product of 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.

15. (Original) The product of claim 10, wherein the base B is diethanolamine.

16. (Original) The product of claim 10, wherein the acid in step (d) is HCl.

17. (Previously presented) The product of claim 10, wherein the process does not include purifying the compound of formula (VI) produced in step (a).

18. (Original) The product of claim 17, 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.

19. (Original) The product of claim 18, wherein the base B is diethanolamine.

20. (Original) The product of 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.

21. (Original) The product of 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.

22. (Previously Presented) The product of claim 1, wherein step (d) is performed.

23. (Previously Presented) The product of claim 22, wherein the product comprises a pharmaceutically acceptable salt formed from the product of step (d).

24-31. (Canceled)

REMARKS

This amendment is being filed prior to or concurrently with payment of the issue fee. Entry of the foregoing amendment is respectfully requested. The amendment is made to cancel claim 8 and to correct a minor typographical error in claim 9. The amendment does not change the scope of the claims. Accordingly, entry of the amendment is requested.

A detailed listing of all claims that are, or were, in the application is presented with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1-7 and 9-23 are now pending in this application.

It is believed that no fees are due in connection with this Rule 312 amendment. In the event this is not correct, the undersigned authorizes the Commissioner to charge Deposit Account No. 19-0741.

Respectfully submitted,

Date June 18, 2013

By /Stephen B. Maebius/

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

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

Electronic Patent Application Fee Transmittal

Application Number:	13548446
Filing Date:	13-Jul-2012
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN0
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Stephen Bradford Maebius/Karen Walker
Attorney Docket Number:	080618-1162

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	1780	1780
Publ. Fee- Early, Voluntary, or Normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2080**

Electronic Acknowledgement Receipt

EFS ID:	16073423
Application Number:	13548446
International Application Number:	
Confirmation Number:	2092
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN0
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:	080618-1162
Receipt Date:	18-JUN-2013
Filing Date:	13-JUL-2012
Time Stamp:	16:11:02
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$2080
RAM confirmation Number	3351
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	192726 6b0078d7521bf2d086d8bd0dce5a2de1ea4721db	no	2
Warnings:					
Information:					
2		312amend.pdf	125080 b4bf56b3dcdf81718bd3d27af749e1f4e7d3cbe7	yes	7

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment after Notice of Allowance (Rule 312)	1	1
	Claims	2	6
	Applicant Arguments/Remarks Made in an Amendment	7	7

Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32200 c03f4d01420ee49dbc42adbc1d8e95a2de483c18	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	350006		

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.

OK TO ENTER: /YV/

Atty. Dkt. No. 080618-1162

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.:	13/548,446
Filing Date:	7/13/2012
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	2092

AMENDMENT UNDER 37 CFR 1.312

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

Commissioner:

Applicant acknowledges receipt of a Notice of Allowance in the above-captioned application. Prior to payment of the issue fee, please amend the application as follows:

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

Remarks/Arguments begin on page 7 of this document.

Please amend the application as follows:

UNITED STATES PATENT AND TRADEMARK OFFICE

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

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/548,446	07/13/2012	Hitesh Batra	080618-1162	2092

22428 7590 06/26/2013
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
06/26/2013	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.

Response to Rule 312 Communication	Application No.	Applicant(s)
	13/548,446	BATRA ET AL.
	Examiner	Art Unit
	YEVGENY VALENROD	1621

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

1. ☒ The amendment filed on *18 June 2013* under 37 CFR 1.312 has been considered, and has been:

   a) ☒ entered.

   b) ☐ entered as directed to matters of form not affecting the scope of the invention.

   c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
   Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

   d) ☐ disapproved. See explanation below.

   e) ☐ entered in part. See explanation below.

/YEVGENY VALENROD/
Primary Examiner, Art Unit 1621

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.
13/548,446	07/30/2013	8497393	080618-1162	2092

22428 7590 07/10/2013

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 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Hitesh Batra, Herndon, VA;
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.:	8,497,393
Issue Date:	7/30/2013
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	2092

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 8,497,393 issued July 30, 2013.

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 noted 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 _____

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

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

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.	:	8,497,393
APPLICATION NO.	:	13/548,446
DATED	:	7/30/2013
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 5, line 38;
Col. 20, claim 13, line 55;
Col. 20., claim 17, line 66;
Col. 21, claim 19, line 6; and
Col. 21, claim 20, line 11.

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

4845-0325-0455.1

Electronic Patent Application Fee Transmittal

Application Number:	13548446
Filing Date:	13-Jul-2012
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN0
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Alexey V. Saprigin/Karen Walker
Attorney Docket Number:	080618-1162

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:	17851300
Application Number:	13548446
International Application Number:	
Confirmation Number:	2092
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN0
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:	080618-1162
Receipt Date:	08-JAN-2014
Filing Date:	13-JUL-2012
Time Stamp:	13:00:28
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	9398
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	90316 d354fa5bd08d430444455be9f704488c9a157b99	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30441 02179a308a3eb11527002940bb150e617296aeac	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	120757	

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.	: 8,497,393 B2
APPLICATION NO.	: 13/548446
DATED	: July 30, 2013
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 5, line 38;
Col. 20, claim 13, line 5;
Col. 20, claim 17, line 66;
Col. 21, claim 19, line 6; and
Col. 21, claim 20, line 11.

Signed and Sealed this
Eighteenth Day of March, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 8,497,393 B2
APPLICATION NO.	: 13/548446
DATED	: July 30, 2013
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 5, line 38;
Col. 20, claim 13, line 55;
Col. 20, claim 17, line 66;
Col. 21, claim 19, line 6; and
Col. 21, claim 20, line 11.

This certificate supersedes the Certificate of Correction issued March 18, 2014.

Signed and Sealed this
Twenty-seventh Day of May, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:14–cv–05498–PGS–LHG	9/2/2014	TRENTON, NJ

PLAINTIFF	DEFENDANT
UNITED THERAPEUTICS CORPORATION	TEVA PHARMACEUTICALS USA, INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 US 6,765,117 B2	July 20, 2004	United Therapeutic Corporation
2 US 8,497,393 B2	July 30, 2013	United Therapeutics Corporation
3 US 7,999,007 B2	August 16, 2011	United Therapeutics Corporation
4 US 8,653,137 B2	February 18, 2014	United Therapeutics Corporation
5 US 8,658,694 B2	February 25, 2014	United Therapeutics Corporation

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ Marlene Kalbach	9/2/2014

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8** **Director of the U.S. Patent and Trademark Office** **P.O. Box 1450** **Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
____ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:14–cv–05499–PGS–LHG	9/2/2014	TRENTON, NJ

PLAINTIFF	DEFENDANT
UNITED THERAPEUTICS CORPORATION	SANDOZ, INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 US 8,497,393 B2	July 30, 2013	United Therapeutics Corporation
2		
3		
4		
5		

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY
	___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ Marlene Kalbach	9/2/2014

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

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.:	8,497,393
Issue Date:	7/30/2013
Examiner:	Yevgeny Valenrod
Art Unit:	1621
Confirmation Number:	2092

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 8,497,393 issued July 30, 2013.

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 noted 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 _____

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

Alexey V. Saprigin Reg No 35,264
Agent for Applicants
Registration No. 56,439

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.	:	8,497,393
APPLICATION NO.	:	13/548,446
DATED	:	7/30/2013
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 62;
Col. 6, line 55; and
Claim 1, col. 19, line 4.

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

Electronic Patent Application Fee Transmittal

Application Number:	13548446
Filing Date:	13-Jul-2012
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN0
First Named Inventor/Applicant Name:	Hitesh Batra
Filer:	Stephen Bradford Maebius/Karen Walker
Attorney Docket Number:	080618-1162

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:	21128519
Application Number:	13548446
International Application Number:	
Confirmation Number:	2092
Title of Invention:	PROCESS TO PREPARE TREPROSTINIL, THE ACTIVE INGREDIENT IN REMODULIN0
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:	080618-1162
Receipt Date:	06-JAN-2015
Filing Date:	13-JUL-2012
Time Stamp:	12:40:07
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	9595
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	219304 8f6217f5f07757996dabdd311e81e44ff4defd94	no	3
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	30681 8d5a7ee1647890b53650938d1f8a978e578f1a4e	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	249985		

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. : 8,497,393 B2
APPLICATION NO. : 13/548446
DATED : July 30, 2013
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 62;
Col. 6, line 55; and

In the Claims:
Claim 1, col. 19, line 4.

Signed and Sealed this
Thirty-first Day of March, 2015

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office

AO 120 (Rev. 08/10)

TO:	**Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313–1450**	**REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK**

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the **U.S. District Court for the District of New Jersey** on the following:
___ Trademarks or **X** Patents. (____ the patent action involves 35 U.S.C. § 292.)

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
3:15–cv–05723–PGS–LHG	7/23/2015	TRENTON, NJ

PLAINTIFF	DEFENDANT
UNITED THERAPEUTICS CORPORATION	WATSON LABORATORIES, INC.

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 US 6,521,212 B1	2/18/2003	UNITED THERAPEUTICS CORPORATION
2 US 6,756,033 B2	6/29/2004	UNITED THERAPEUTICS CORPORATION
3 US 8,497,393 B2	7/30/2013	UNITED THERAPEUTICS CORPORATION
4		
5		

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ___ Amendment ___ Answer ___ Cross Bill ___ Other Pleading	
PATENT OR TRADEMARK NO.	**DATE OF PATENT OR TRADEMARK**	**HOLDER OF PATENT OR TRADEMARK**
1		
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE
William T. Walsh	s/ JAWEIA CAMPBELL	7/23/2015

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court CENTRAL DISTRICT OF CALIFORNIA on the following

☑ Trademarks or ☐ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	7/23/2015	CENTRAL DISTRICT OF CALIFORNIA

PLAINTIFF	DEFENDANT
SPIRIT CLOTHING COMPANY, a California corporation	PANDA APPAREL, LLC, a limited liability company

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	4,280,977	1/23/2013	SPIRIT CLOTHING COMPANY
2			
3			
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5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy