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मैं, अधोहस्ताक्षरी जो पेटेंट अधिनियम, 1970 की धारा 73(3) के तहत महानियंत्रक एकस्व, अभिकल्प एवं व्यापार चिह्न की ओर से प्रमाणपत्र हस्ताक्षर व जारी करने के लिए प्राधिकृत अधिकारी हूँ, एतद्वारा यह प्रमाणित करता/ती हूँ कि निम्नलिखित पेटेंट आवेदन के संबंध में फाइल दस्तावेज़(जों) की सही प्रतिलिपि इसके साथ संलग्न है:

I, the undersigned, being an officer duly authorized to sign and issue the certificate on behalf of the Controller General of Patents, Designs and Trademarks in accordance with the provisions of Section 73(3) of the Patents Act, 1970, hereby certify that annexed hereto is a True Copy of the document(s) as filed in connection with the following Patent Application:

क) आवेदन संख्या / a) Application Number: **202221045237**

ख) फाइल करने की तारीख / b) Date of Filing: **08/08/2022**

ग) अनुरोधित दस्तावेज़(जों) का नाम / C) Name of the document(s) requested:

1) Application for Grant of Patent (Form-1)

2) Complete Specification filed on 08/08/2022

यह प्रमाणपत्र पेटेंट अधिनियम, 1970 की धारा 147(1) के अधीन मुझमें निहित शक्तियों के तहत जारी किया गया है।

This certificate is issued under the powers vested in me U/S 147(1) of The Patents Act, 1970.

दिनांक/Dated this 28th day of AUGUST, 2023.


(SAPNA NARVARIYA)

सहायक नियंत्रक पेटेंट व डिजाइन / Assistant Controller of Patents and Designs

(प्राधिकृत हस्ताक्षरी/ Authorized Signatory)

FORM 1 THE PATENTS ACT 1970 (39 OF 1970) AND The Patents Rules, 2003 APPLICATION FOR GRANT OF PATENT (See section 7, 54 and 135 and sub-rule (I) of rule 20)				(FOR OFFICE USE ONLY)	
				Application No:	
				Filing Date:	
				Amount of Fee Paid:	
				CBR No:	
				Signature:	
1. APPLICANT'S REFERENCE / IDENTIFICATION NO. (AS ALLOTTED BY OFFICE):					
2. TYPE OF APPLICATION [Please tick (✓) at the appropriate category]:					
☒ Ordinary (✓)		☐ Convention ()		☐ PCT-NP ()	
☐ Divisional ()	☐ Patent of Addition ()	☐ Divisional ()	☐ Patent of Addition ()	☐ Divisional ()	☐ Patent of Addition ()
3A. APPLICANT(S):					
Name in Full		Nationality	Country of Residence	Address of the Applicant	
CIPLA LIMITED		Indian Company incorporated under the Companies Act, 1956	Indian	House No.	Cipla House, Peninsula Business Park,
				Street	Ganpatrao Kadam Marg, Lower Parel,
				City	Mumbai
				State	Maharashtra
				Country	India
				Pin code	400013
3B. CATEGORY OF APPLICANT [Please tick (✓) at the appropriate category]					
☐ Natural Person ()		☐ Other than Natural Person			
		☐ Small Entity ()	☐ Startup ()	☐ Educational Institution ()	☒ Others (✓)
4. INVENTOR(S) [Please tick (✓) at the appropriate category]					
Are all the inventor(s) same as the applicant(s) named above?			☐ Yes ()	☒ No (✓)	
If "No", furnish the details of the inventor(s)					
Name in Full		Nationality	Country of Residence	Address of the Inventors	
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			Street	Chogm Road
			City	Porvorim
			State	Goa
			Country	India
			Pin code	403521
SAWANT, Ashwini	India	Indian	House No.	B- 605, Akruti Elegance,
			Street	90 Feet Road, Gawanpada, Mulund (East),
			City	Mumbai
			State	Maharashtra
			Country	India
			Pin code	400081
5. TITLE OF THE INVENTION: “AN IMPROVED PROCESS FOR PREPARING ANTIVIRAL PHOSPHONATE ANALOGUES”				
6. AUTHORISED REGISTERED PATENT AGENT(S):	IN/PA No.		IN/PA 509	
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	Name		Dr. P. Aruna Sree	
	IN/PA No.		IN/PA 2338	
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	IN/PA No.		IN/PA 2725	
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	IN/PA No.		IN/PA 2761	
	Name		Manish Chemburkar	
	IN/PA No.		IN/PA 2917	
	Name		Bina Dandekar	
	IN/PA No.		IN/PA 3565	
	Name		Ms. Vanija Verma	
	IN/PA No.		IN/PA 3226	
	Name		Mr. Umeshkumar Ku	
7. ADDRESS FOR SERVICE OF APPLICANT IN INDIA	Name		Gnanlex Associates LLP	
	Postal Address		335, 3rd floor, V Mall, Asha Nagar, Near Saidham, Thakur Complex Kandivali East, Mumbai - 400101,	

		Maharashtra, India.			
	Telephone No.	91-22-40895454			
	Mobile No.	09821152272			
	Fax No.				
	E-mail ID	<u>ipr@gnanlex.net</u> <u>gopanair@gnaipr.net</u>			

8. IN CASE OF APPLICATION CLAIMING PRIORITY OF APPLICATION FILED IN CONVENTION COUNTRY, PARTICULARS OF CONVENTION APPLICATION:

Country	Application Number	Filing Date	Name of the Applicant	Title of the Invention	IPC (as classified in the convention country)
-	-	-	-	-	-

9. IN CASE OF PCT NATIONAL PHASE APPLICATION, PARTICULARS OF INTERNATIONAL APPLICATION FILED UNDER PATENT CO-OPERATION TREATY (PCT):

International application number	International filing date as allotted by the receiving office
-	-

10. IN CASE OF DIVISIONAL APPLICATION FILED UNDER SECTION 16, PARTICULARS OF ORIGINAL (FIRST) APPLICATION:

Original (first) application number	Date of filing of Original (first) application
-	-

11. IN CASE OF PATENT OF ADDITION FILED UNDER SECTION 54, PARTICULARS OF MAIN APPLICATION OR PATENT

Main application/patent Number	Date of filing of main application
-	-

12. DECLARATIONS:

(i) Declaration by the inventor(s):

(In case the applicant is an assignee: the inventor(s) may sign herein below or the applicant may upload the assignment or enclose the assignment with this application for patent or send the assignment by post/electronic transmission duly authenticated within the prescribed period).

We, the above named inventors are the true and first inventors for this invention and declare that the applicant herein is our assignee or legal representative.

(a) Date : **8th August, 2022**

(b) Signature of the inventor: _____

(c) Name : **DAS, Arijit**

(a) Date : **8th August, 2022**

(b) Signature of the inventor: _____

(c) Name : **SAWANT, Ashwini**

(ii) Declaration by the applicant(s) in the convention country:

(In case the applicant in India is different than the applicant in the convention country: the applicant in the convention country may sign herein below or applicant in India may upload the assignment from the applicant in the convention country or enclose the said assignment with this application for patent or send the assignment by post/electronic transmission duly authenticated within the prescribed period)

I/We, the applicant(s) in the convention country declare that the applicant(s) herein is/are my/our assignee or legal representative.

N/A

(ii) Declaration by the applicant(s):

We, the applicant(s) hereby declare(s) that:-

- ☒ We are in possession of the above-mentioned invention.
- ☒ The Complete specification relating to the invention is filed with this application.
- ☒ The invention as disclosed in the specification uses the biological material from India and the necessary permission from the competent authority shall be submitted by me/us before the grant of Patent to me/us.
- ☒ There is no lawful ground of objection to the grant of the Patent to us.
- ☒ We are the assignee or legal representative of true & first inventors.
- ☒ The application or each of the applications, particulars of which are given in Paragraph 8 was the first application in convention country/countries in respect of my/our invention.
- ☒ I/We claim the priority from the above mentioned application(s) filed in convention country/countries and state that no application for protection in respect of the invention had been made in a convention country before that date by me/us or by any person from which I/we derive the title.
- ☒ My/Our application in India is based on International application under Patent

Cooperation Treaty (PCT) as mentioned in Paragraph – 9.

- ☒ The application is divided out of my/our application particulars of which are given in Paragraph 10 and Pray that this application may be treated as deemed to have been filed on (DD/MM/YYYY) under section 16 of the Act.
- ☒ The said invention is an improvement in or modification of the invention particulars of which are given in Paragraph 11.

13. FOLLOWING ARE THE ATTACHMENTS WITH THE APPLICATION:

(a) Complete specification (Total No. of sheets 27; Total no. of Claims 17)

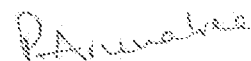
Item	Details	Fee	Remarks
Complete/ ~~provisional~~ specification)#	No. of pages: 21	Rs.8000/-	
No. of Claim(s)	No. of pages: 05 No. of claims: 17	Rs.11,200/-	7 extra claims
Abstract	No. of pages: 01		
Drawings	No. of pages: 00 No. of Drawing: 00		

#In case of a complete specification, if the applicant desires to adopt the drawings filed with his provisional specification as the drawings or part of the drawings for the complete specification under rule 13(4), the number of such pages filed with the provisional specification are required to be mentioned here.

- (b) Statement and undertaking on Form 3;
(c) Declaration of Inventorship on Form 5
(d) Certified true copy of Power of Attorney (Original Power of Attorney submitted with application no. 202121041687)
(e) Online payment of Application Fee **19200/-**;

We hereby declare that to the best of our knowledge, information and belief the fact and matters stated herein are correct and We request that a patent may be granted to me/us for the said invention.

Dated this 8th day of August, 2022



Dr. P. Aruna Sree
(Regn.No.: IN/PA 998)
Agent for the Applicant
Gnanlex Associates LLP

To,
The Controller of Patents
The Patent office, At Mumbai.

Note: -

- * Repeat boxes in case of more than one entry.
- * To be signed by the applicant(s) or by authorized registered patent agent otherwise where mentioned.
- * Tick (✓) /cross (x) whichever is applicable/not applicable in declaration in paragraph-12.
- * Name of the inventor and applicant should be given in full, family name in the beginning.
- * Strike out the portion which is/are not applicable.
- * For fee: See First Schedule";

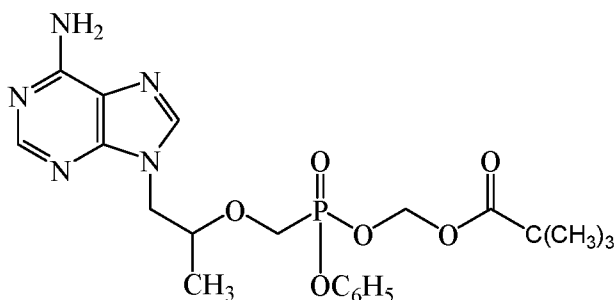
FORM 2 THE PATENTS ACT, 1970 (39 of 1970) AND The Patents Rules, 2003 COMPLETE SPECIFICATION (See section 10 and rule 13)
1. TITLE OF THE INVENTION: “AN IMPROVED PROCESS FOR PREPARING ANTIVIRAL PHOSPHONATE ANALOGUES”
2. APPLICANT: (a) NAME: CIPLA LIMITED (b) NATIONALITY: Indian Company incorporated under the Companies Act, 1956 (c) ADDRESS: Cipla House, Peninsula Business Park, Ganpatrao Kadam Marg, Lower Parel, Mumbai 400013, Maharashtra, India.
3. PREAMBLE TO THE DESCRIPTION:
The following specification particularly describes the invention and the manner in which it is to be performed.

FIELD OF THE INVENTION:

This invention relates to an improved process for preparation of (((1-(6-amino-9H-purin-9-yl)propan-2-yloxy)methyl)(phenoxy)phosphoryloxy)methyl pivalate or its pharmaceutically acceptable salts thereof, as well as pharmaceutical compositions comprising the same and methods of treatment using the same.

RELATED BACKGROUND ART:

The compound (((1-(6-amino-9H-purin-9-yl)propan-2-yloxy)methyl)(phenoxy)phosphoryloxy)methyl pivalate of Formula (1) and its pharmaceutically acceptable salts thereof is disclosed in US 9,227,990 B2.



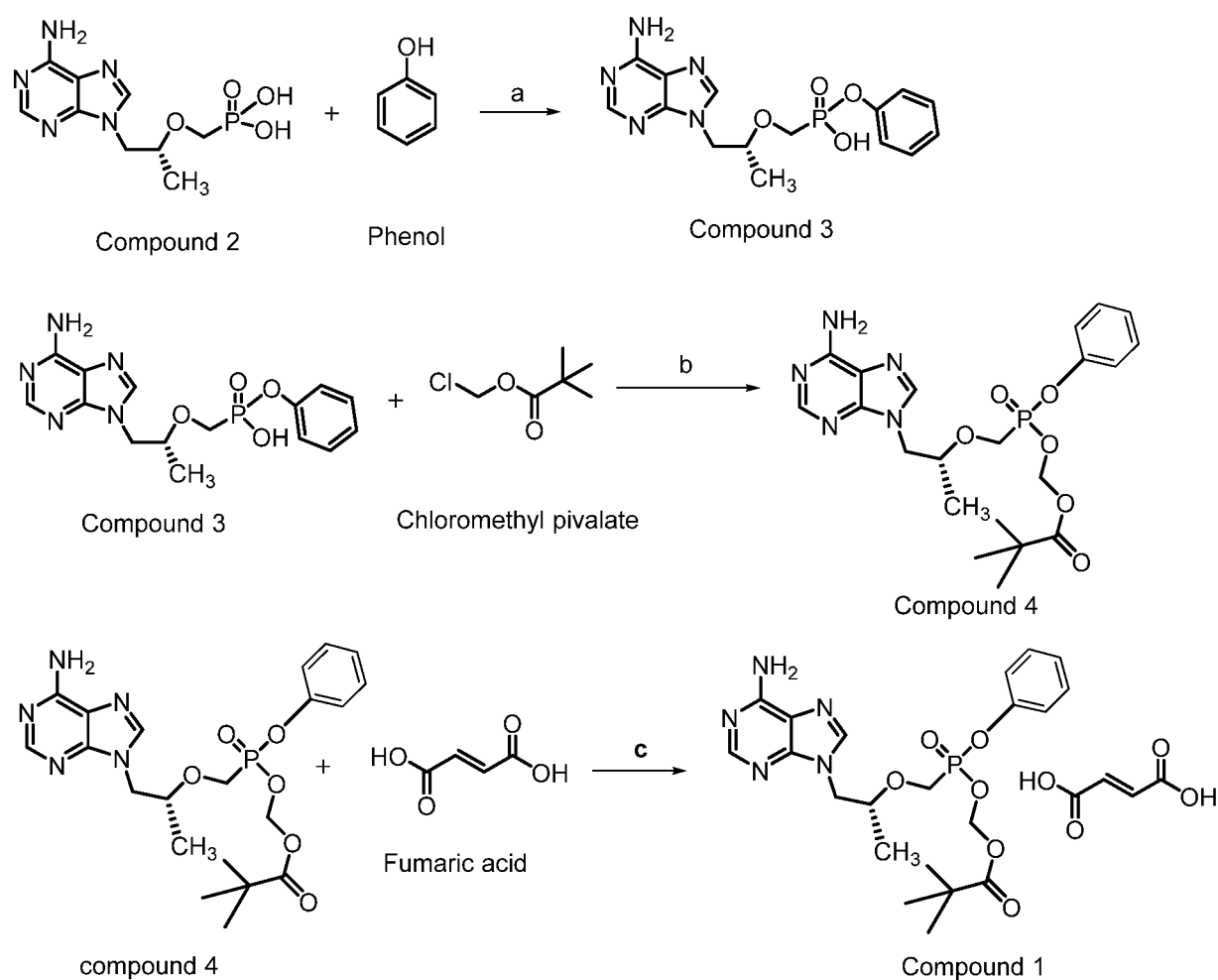
Formula (1)

The compound (((1-(6-amino-9H-purin-9-yl)propan-2-yloxy)methyl)(phenoxy)phosphoryloxy)methyl pivalate of Formula (I) may exist as a diastereomer having either the (R,R), (S,S), (R,S) or (S,R) configuration. Preferably, the compound of formula (I) or the acid salt thereof is in the form of the (R,R) diastereomer. Accordingly, salts of the present invention also include all diastereomers occurring in the salts.

Valuable pharmacological properties are attributed to this compound. It can be used, for example, as a nucleotide reverse transcriptase inhibitor useful in therapy for diseases which respond to inhibition of protein kinase activity.

The earliest known synthesis of Compound (1), by Phull et al., is described in US Patent 9,227,990 B2. The synthetic method employed is depicted in the following reaction Scheme 1.

Scheme 1



Starting from (R)-9-(2-Phosphonomethoxypropyl) adenine (PMPA /Compound 2) a literature procedure was used to prepare Compound (3) via a coupling reaction using N,N-dicyclohexylcarbodiimide as a coupling agent and phenol as reactant in solvent N-methyl pyrrolidone. Compound (3) was isolated and reacted with

chloromethyl pivalate in solvent N-methyl pyrrolidone and Compound (1) was isolated as a fumarate salt.

While the synthesis provided by U.S. Patent US 9,227,990 B2 is the best known to date, it nevertheless, suffers from certain drawbacks associated with manufacturing higher quantity of this active pharmaceutical ingredient.

The main disadvantages for the synthesis of Compound (1) that had to be addressed before the scale-up were the following:

1. N-methyl pyrrolidone was used as solvent in Step a and Step b. N-methyl pyrrolidone is a high boiling solvent and known to human & environmental hazard, and is difficult to remove completely and hence replacement of this solvent was necessary.
2. Reaction mechanism to be studied to control impurity formation and eventually increasing yield.
3. Lower yield in each stage, inconsistency in reaction conversion demanded to a quality by design approach for scale up of Compound 1.

These problems combined to decrease the efficiency of larger scale processes. There is thus a pressing need in the art for a better low cost and high-yields synthesis for Compound (1), suitable for industrial scale.

The process of the present invention provides large scale synthesis of Compound (1), and its salts having high degree of chromatographic and diastereomeric purity and low residual solvent content. Such improved processes may provide higher yields, be easier to perform, or use less costly or toxic reagents than currently available processes.

OBJECT OF THE INVENTION:

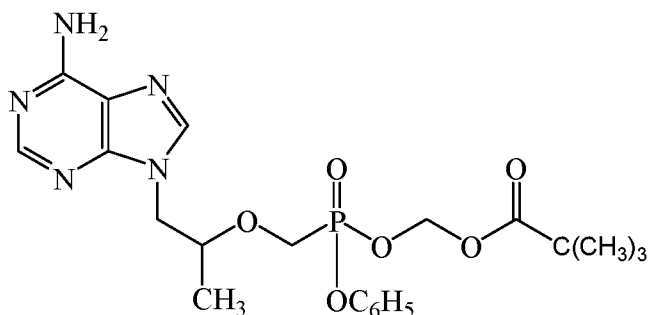
The object of the present invention is to provide an improved process for preparing Compound (1) or pharmaceutically acceptable salts thereof in high diastereomeric purity.

Yet another object of the present invention is to provide an improved process for preparing Compound (3).

Yet another object of the present invention is to provide a green process for the synthesis of Compound (1) or pharmaceutically acceptable salts thereof which is simple, economical and suitable for industrial scale-up.

SUMMARY OF THE INVENTION:

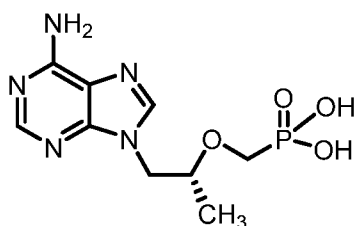
The present invention provides an improved process for preparing Compound (1) or pharmaceutically acceptable salts thereof;



Compound (1)

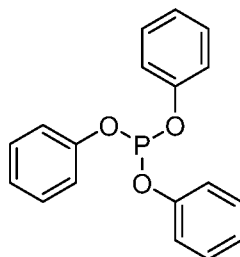
comprising;

- a. reacting Compound (2)



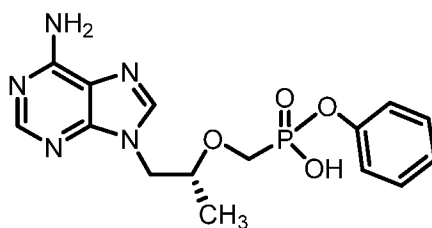
Compound 2

with triphenylphosphite



triphenyl phosphite

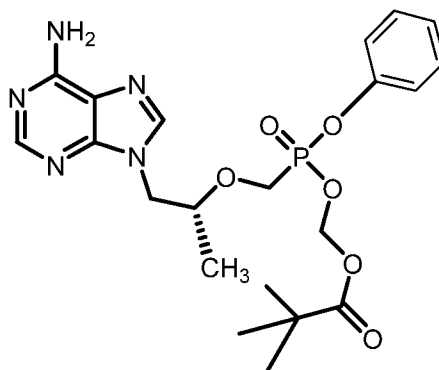
in the presence of a suitable base, in a polar aprotic solvent or non- polar aprotic solvents or in a mixture thereof to yield Compound (3)



Compound 3

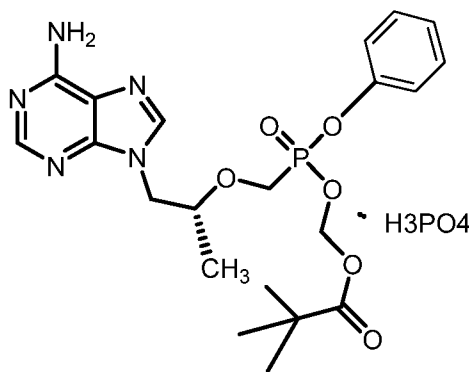
;

- b. reacting Compound (3) with chloromethyl pivalate in the presence of a suitable phase transfer catalyst and a suitable organic base in an aprotic organic solvent, or water or in a mixture of aprotic organic solvent or water thereof to yield Compound (4)



Compound 4

c. optionally, isolating Compound (4) as a phosphate salt (Compound 5a)



Compound 5a

and;

d. optionally, converting phosphate salt Compound (5a) to an acid addition salt of Compound (1), either by first isolating the free base Compound (1) or without isolating the free base Compound (1).

Further, the present invention provides (((1-(6-amino-9H-purin-9-yl)propan-2-yloxy)methyl) (phenoxy) phosphoryloxy) methyl pivalate Compound (1) or pharmaceutically acceptable salts thereof; prepared according to the process described above, having a purity of more than about 95%, preferably at least 99%, more preferably at least 99.5% by HPLC.

The invention is further directed to pharmaceutical compositions comprising:

- (a) an acid salt of (((1-(6-amino-9H-purin-9-yl)propan-2-yloxy)methyl) (phenoxy) phosphoryloxy) methyl pivalate Compound (1) (which may be present in crystalline or amorphous form), or solvate or hydrate thereof prepared according to the process of the present invention; and
- (b) at least one pharmaceutically acceptable excipient.

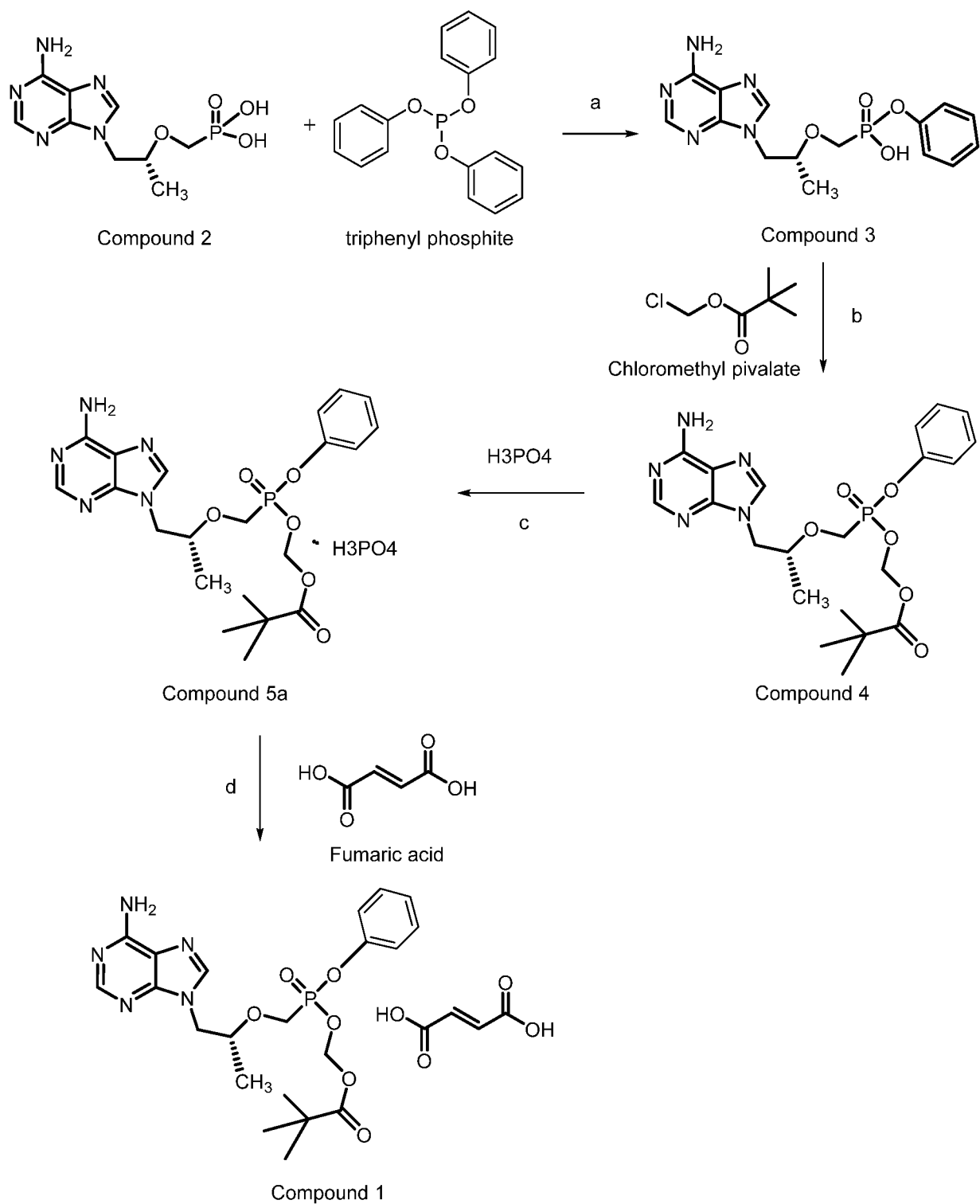
The present invention is also directed to a method of treating a disease which responds to an inhibition of nucleotide reverse transcriptase activity, such as HIV and/or AIDS, comprising the step of administering to a subject in need of such treatment a therapeutically effective amount of an acid salt of (((1-(6-amino-9H-purin-9-yl)propan-2-yloxy)methyl) (phenoxy) phosphoryloxy) methyl pivalate) Compound (1) or a solvate or hydrate thereof, prepared according to the process of the present invention.

Detailed Description of the Invention

In an embodiment of the present invention, there is provided an improved synthesis of

(((1-(6-amino-9H-purin-9-yl)propan-2-yloxy)methyl) (phenoxy) phosphoryloxy) methyl pivalate Compound (1) or pharmaceutically acceptable salts thereof; as depicted below in reaction scheme 2.

Scheme 2



In an embodiment Compound (3) is an important synthetic intermediate that is useful for preparing Compound (1).

In an embodiment Compound (2) is reacted with triphenylphosphite in the presence of a suitable base in presence of a polar aprotic solvent, non-polar aprotic solvents or in a mixture thereof to yield Compound (3).

A suitable base used for the reaction may be an organic base. Organic bases may be aliphatic or aromatic and may be selected from, but not limited to triethylamine, di-isopropyl amine, diethyl amine, pyridine, picoline, piperidine, 2-methylimidazole, dimethylaminopyridine (DMAP), N,N-diisopropylethylamine, 1,5-diazobicyclo[4.3.0]non-5-ene (DBN), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or a mixture thereof.

Preferably, the reaction is carried out in the presence of mixture of bases selected from amine bases such as triethylamine, di-isopropyl amine, diethyl amine, and 4-N, N-dimethylaminopyridine (DMAP); most preferably a mixture of triethylamine and DMAP.

In a preferred embodiment, the reaction is conducted in a mixture of polar aprotic solvent and non-polar aprotic solvents selected from the comprising of ketone, C₁ to C₅ nitriles, C₄ to C₇ ethers, C₅ to C₈ cyclic ethers, C₂ to C₇ esters, C₁ to C₆ halogenated hydrocarbons, C₆ to C₁₄ aromatic hydrocarbons, and the like.

Preferably, the polar aprotic solvent is selected from the group comprising of acetone, methyl ethyl ketone, acetonitrile, propionitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, dimethylformamide, dimethylsulfoxide, or a mixture thereof. In a preferred embodiment, the polar aprotic solvent is selected from acetonitrile and propionitrile.

Preferably, the non-polar aprotic solvent is selected from the group comprising of toluene, xylene, cyclohexane, dichloromethane, chloroform, dioxane, tetrahydrofuran, diethyl ether, diisopropyl ether, methyl tert-butylether or mixtures thereof. In a preferred embodiment, the non-polar aprotic solvent is selected from toluene and cyclohexane.

In an embodiment w/v ratio of compound (2) to the solvent/s varies from 1: 1 to 1: 5.

In a most preferred embodiment, the reaction is conducted in a mixture of acetonitrile and toluene.

In an embodiment v/v ratio of acetonitrile to toluene is 1:1.

Preferably, the reaction is carried out at a temperature in the range of from about 25°C to about 120°C for about 10 hours to about 50 hours. More preferably the reaction step is carried out at a temperature in the range from about 40°C to about 110°C, for about 20 hours to about 45 hours. Most preferably the reaction step is carried out at a temperature in the range from about 60°C to about 100°C, for about 30 hours to about 40 hours.

In one specific embodiment, use of biphasic solvent in the reaction has certain advantages over prior art process.

The prior art teaches use of N-methyl pyrrolidone which is a high boiling solvent and known to human & environmental hazard. Also traces of N-methyl pyrrolidone is found difficult to remove completely from the reaction mass, leading to the loss of yield and hence replacement of this solvent was necessary.

Inventor of the present invention found that by carrying reaction in a biphasic solvent mixture not only led to a scalable, but economically feasible green process as well. This forms one aspect of the present invention.

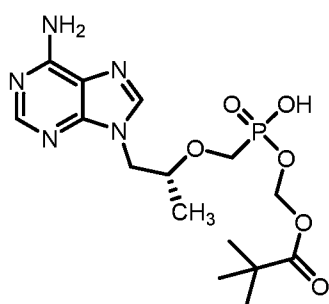
Further, in the prior art process after completion of the reaction, solvent is distilled from the reaction mass and then the reaction mass is again treated with by addition of biphasic solvents. Whereas in the process of present invention, after completion of the reaction, organic and aqueous phases are separated and thus avoids solvent distillation as reported in the prior art. This forms another aspect of the present invention.

Further, in the prior art process, aqueous phase, is seeded with 0.05% of Compound (3), whereas in the process of the present invention seeding with Compound (3) of aqueous phases, is not necessary. This forms yet another aspect of the present invention.

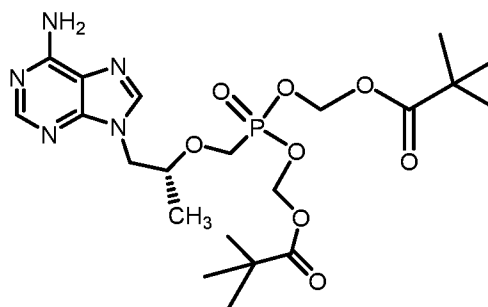
In an embodiment, in the process of the present invention after completion of reaction, aqueous phases are separated, optionally washed with organic solvents to remove organic impurities and acidified and the Compound (3) is isolated, for example by filtration.

In an embodiment, Compound (3) is reacted with chloromethyl pivalate in the presence of a suitable phase transfer catalyst and a suitable organic base in an aprotic organic solvent, water or in a mixture of aprotic organic solvent and water thereof to yield Compound (4).

Conversion of Compound (3) to Compound (1) is a crucial step. When reaction was monitored closely, it is observed that during reaction, Compound (3) partially degrades back to Compound (2), which in turn couples with chloromethyl pivalate and leads to the formation of dipivalate impurities, namely Compound (4a) and Compound (4b) as depicted below .



4a



4b

These impurities were difficult to remove, impacting on the conversion rate and leading to lesser yield.

Further, the prior art teaches use of dipolar aprotic solvent like N-methyl pyrrolidone. N-methyl pyrrolidone, being a high boiling solvent and not green because of its detrimental effects on human health and hazards to the natural environment caused by its inescapable toxicity as well as large wastewater streams and high-energy-input requirements. Further, traces of N-methyl pyrrolidone are found difficult to remove completely from the reaction mass, leading to the loss of yield and hence replacement of this solvent was necessary. Therefore, minimizing and avoiding the use of such solvents has become one of the most important facets of green chemistry.

Preferably, the reaction is carried out in the presence of an aprotic organic solvent, wherein aprotic organic solvent is preferably selected from the group comprising of C₁ to C₅ nitriles, C₂ to C₇ ester, carbonic esters, C₄ to C₇ ethers, C₅ to C₈ cyclic ethers, and water or mixtures thereof.

Preferably, the aprotic organic solvent is selected from the group comprising of acetonitrile, propionitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, dimethyl carbonate, ethylene carbonate, propylene carbonate, dioxane, tetrahydrofuran, dimethylacetamide, dimethylformamide, dimethylsulfoxide, and water or mixtures thereof. Preferred solvents for the reaction are acetonitrile, dioxane, dimethyl carbonate, ethylene carbonate, propylene

carbonate, dimethylacetamide, dimethylformamide, and water or mixtures thereof; most preferably acetonitrile, dioxane or dimethyl carbonate.

A suitable base used for the reaction may be an organic base. Organic bases may be aliphatic or aromatic amines and may be selected from, but not limited to triethyl amine, di-isopropyl amine, pyridine, picoline, diethyl amine, DBU, piperidine, N, N-diisopropylethylamine. More preferably, bases are selected from triethyl amine, N, N-diisopropylethylamine, and DBU. Most preferably, the base is N, N-diisopropylethylamine.

The reaction is preferably carried out at a temperature of about 30°C to about 90°C, preferably about 40°C to about 80°C, more preferably about 55°C to about 65°C.

Preferably, the reaction is maintained for about 1 hours or more, for example about 10 hours or more or about 20 hours or more. More preferably, the reaction is maintained for about 2 hours to about 8 hours. Most preferably, the reaction is maintained for about 3 hours to about 6 hours

Optionally, coupling is carried out in the presence of a phase transfer catalyst selected from tetrabutyl ammonium bromide, benzyltriethylammonium chloride, methyltricaprylammonium chloride, methyltributylammonium chloride, tetramethyl ammonium bromide, trimethylpropyl ammonium bromide benzyltributylammonium chloride and tetraethyl ammonium bromide or mixture thereof. Most preferably, the phase transfer catalyst is tetrabutyl ammonium bromide.

Inventor of the present invention found that by carrying reaction in an aprotic organic solvent or mixture of aprotic organic solvents not only led to a scalable, but economically feasible green process as well. This forms one aspect of the present invention.

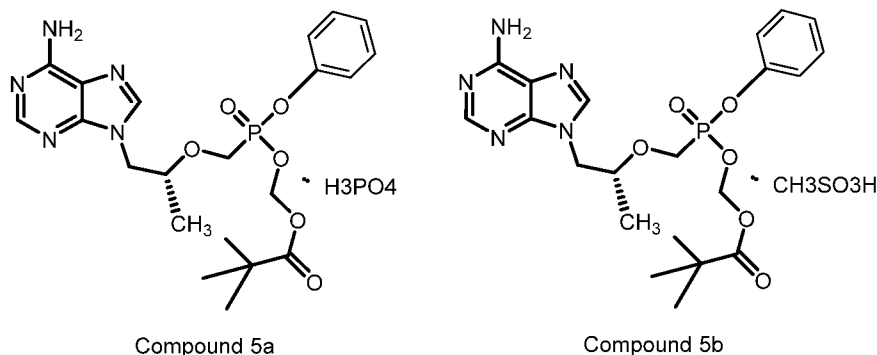
Further, the amount of dipivalate impurities, such as Compound (4a) and Compound (4b) reduced below detection limit leading to better conversion and improved yield of Compound (4). This forms another aspect of the present invention.

Compound (4) obtained by the process of present invention may be converted to an acid addition salt of pure Compound (1), either by first isolating the free base or without isolating the free base.

In one aspect, Compound (4) is not isolated, i.e. the free base is converted to an acid salt *in situ*.

In one embodiment Compound (4) is isolated as phosphate salt (Compound 5a).

In an alternative embodiment Compound (4) is isolated as methane sulfonate salt (Compound 5b)



In one aspect, Compound (4) is dissolved in a suitable solvent to facilitate formation of the acid salt. Suitable solvents include, but are not limited to the organic solvent preferably selected from the group comprising of ketone, C₂ to C₇ ester, C₄ to C₇ ethers, C₁ to C₅ alcohol, aliphatic hydrocarbon, C₆-C₁₀ substituted aromatic hydrocarbons, and C₁-C₅ halogenated hydrocarbons or mixtures thereof. Preferably, the organic solvent is selected from the group comprising of acetone, methyl isobutyl ketone, acetonitrile, dimethylformamide, dimethylsulfoxide, N-methyl-2-pyrrolidone, ethyl acetate, toluene, xylene, dichloromethane, chloroform, dioxane,

tetrahydrofuran, diethyl ether, methanol, ethanol, isopropanol, n-propanol, tert-butanol, tert-amyl alcohol or combinations thereof. Preferred solvents are acetone, methyl isobutyl ketone, N-methyl-2-pyrrolidone, dimethylformamide, alcohols or combinations thereof; most preferably a mixture of methanol and ethyl acetate or a mixture of methanol and acetone.

The solution containing Compound (4) is treated with either phosphoric acid or methane sulfonic acid. The acid may be in the form of a solution or solid. The resulting acid addition salt may be isolated as a solid by any known technique, including but not limited to, cooling, chilling, completely or partially distilling solvents, and/or filtering.

Alternatively, acid addition salts of pure Compound (1), may be prepared in accordance with the present invention by a salt interconversion method. This process involves reacting an acid salt of Compound (4) with a suitable base to form the free base of pure Compound (1), and thereafter converting the free base so formed into an acid salt form of pure Compound (1), (by addition of an acid).

Examples of the pharmaceutically acceptable acid addition salt of pure Compound (1) include, but are not limited to, inorganic acid salts such as hydrochloric acid salt, sulfuric acid salt, nitric acid salt, hydrobromic acid salt, hydroiodic acid salt and phosphoric acid salt, organic carboxylic acid salts such as acetic acid salt, lactic acid salt, citric acid salt, oxalic acid salt, glutaric acid salt, malic acid salt, tartaric acid salt, fumaric acid salt, mandelic acid salt, maleic acid salt, benzoic acid salt and phthalic acid salt; and organic sulfonic acid salts such as methanesulfonic acid salt, ethane sulfonic acid salt, benzenesulfonic acid salt, p-toluene sulfonic acid salt and camphorsulfonic acid salt. Among these, fumaric acid, tartaric acid, citric acid, salicylic acid, acetic acid, succinic acid, d(-)-tartaric acid, oxalic acid, and methane sulfonic acid are more preferred, but the acid addition salt is not restricted thereto. In a preferred embodiment Compound (1) is converted to the fumarate salt.

Advantage of the process is that it removes unreacted starting materials as well as undesired impurities formed in both stages. The process of the invention is advantageous as the isolated salt has purity of more than 98%. This forms one aspect of the present invention

Further, salts and more specifically phosphate salt (compound 5a) and mesylate salt (compound 5b), are easy to purify, handle and store on large scale. Hence, suitable for industrial synthesis. This forms another aspect of the present invention.

Further, the isolated salts are not hygroscopic and are readily soluble in physiologically acceptable solvents. This forms yet another aspect of the present invention.

The salts of the present invention may be crystalline or noncrystalline.

In certain aspects, the acid salts and polymorphic forms described herein may potentially exhibit improved properties. For example, in certain aspects, the acid salts and polymorphic forms described herein may potentially exhibit improved stability, improved pharmacokinetic properties and/or potentially improved bioavailability. Such improved stability could have a potentially beneficial impact on the manufacture of the Compound (1), such as for example offering the ability to store process intermediate for extended periods of time. Improved stability could also potentially benefit a composition or pharmaceutical composition of the Compound (1). In further aspects, the salts and polymorphic forms described herein may also potentially result in improved yield of the Compound (1), or potentially result in an improvement of the quality of the Compound (1).

The following examples, which include preferred aspects, will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for purpose of illustrative discussion of preferred aspects of the invention.

EXAMPLES

Example-1 Preparation of Phenyl hydrogen (((R)-1-(6-amino-9H-purin-9-yl)propan-2-yloxy)methyl phosphonate (Compound 3):

PMPA (100gm, 0.348mmol) 1,4-dioxane (350ml, 1.2V), Phenol (62.2gms, 0.661 mmol) and triethylamine (42.22gm, 0.418mmol) were added to a 2 L reaction vessel equipped with a mechanical stirrer. The contents of reactor were agitated at 80-85°C to give a solution. To this solution was charged solution of N, N-dicyclohexyl carbodiimide (111.25gms, 0.540mmol) in 1,4-dioxane (50ml, 0.5V) at 80-85 °C. The reactor contents were then heated to 100-105°C to give a complete solution. The reactor contents were agitated at 100-105°C for 5hrs. Reaction mass was sampled and monitored by HPLC. After reaction completion, water (200ml) was charged to reaction solution, to obtain slurry. Reaction mixture was agitated at 25-30°C for 1hr. and filtered at 25-30°C to remove inorganics. The pH of the clear filtrate was adjusted to 11-12 using 25% sodium hydroxide solution (25ml), stirring continued for 15 mins at 25-30°C. To this basic solution, ethyl acetate (200ml, 2V) was added and stirred for 15 mins at 25-30°C. The aqueous layer was separated in 2litre reactor and pH of the aqueous layer was adjusted to 2.3-3 using conc. Hydrochloric acid (30ml). Reaction mixture was agitated for 8-10 hrs at 25-30°C to ensure complete precipitation. The solids were isolated by filtration, slurred in methanol (1000ml, 10V) at 25-30 °C, filtered, washed with Methanol (250ml, 2.5V). Solid obtained was dried at 50-55 °C for 8-10 hrs till kf NMT 1.0% to yield 75gms of compound 3.

Example-2 Preparation of Phenyl hydrogen (((R)-1-(6-amino-9H-purin-9-yl)propan-2-yloxy)methyl phosphonate (Compound 3):

PMPA (100gm, 0.348mmol), Acetonitrile (150ml, 1.5V), Triphenylphosphite (162.2gms, 0.5226 mmol), 4-N,N-dimethylaminopyridine (42.56gms, 0.3484 mmol), Toluene (150ml, 1.5V) and triethylamine (7.05gm, 0.6969mmol) were added to a 2 L reaction vessel equipped with a mechanical stirrer. The reactor contents were then heated to 80-85°C to give a complete solution. The reactor

contents were agitated at 80-85°C for 40 hrs. Reaction mass was sampled and monitored by HPLC. After reaction completion, Toluene (200ml, 2V) and Water (200ml, 2V) was charged to reaction solution, to obtain slurry. Reaction mixture was agitated at 25-30°C for 30mins. The aqueous layer was separated in 2litre reactor and washed with Toluene (200ml, 2V). The aqueous layer was separated in 2litre reactor and pH of the aqueous layer was adjusted to. 2-2.5 using conc. Hydrochloric acid (30ml). The Reaction mixture was agitated for 1 hr at 25-30°C to ensure complete precipitation, further chilled to 2-8°C. The solids were isolated by filtration, slurred in methanol (1000ml, 10V) at 25-30°C, filtered, washed with Methanol (250ml, 2.5V). Solid obtained was dried at 50-55 °C for 8-10 hrs till kf NMT 1.0% to yield 106 gms of compound 3.

Example-3 Preparation of (((1-(6-amino-9H-purin-9-yl)propan-2-yloxy)methyl) (phenoxy) phosphoryloxy) methyl pivalate phosphate (Compound 5a):

Phenyl hydrogen (((R)-1-(6-amino-9H-purin-9-yl)propan-2-yloxy)methyl phosphonate (Compound 3) (100gm,0.275mmol), N,N-diisopropyl ethylamine (72ml, 52.12gm, 0.404mmol), Tetrabutyl ammonium bromide (30gms, 30%, 0.0930mmol) and dimethyl carbonate (500ml, 5V) were charged to 3 L four-neck flask provided with a thermometer, a dropping funnel and a mechanical stirrer. The contents were agitated at 25-30°C to give a slurry mixture. To this mixture were charged Chloromethyl pivalate (62gms, 0.4133mmol) at 25-30°C. The reactor contents were then heated to 55-60°C to give a complete solution. The reactor contents were agitated at 55-60°C for 5hrs. The reaction was sampled and monitored by HPLC. The solvents were evaporated under vacuum to yield 120gms of Compound (4) as an oil. The reactor contents were cooled to 25-30°C and dissolved in dichloromethane (500ml, 5V). Organic layer was washed with 10% Sodium dihydrogen orthophosphate (200ml, 2V, twice). The layers were settled and separated. The organic layer was evaporated under vacuum at 40-45°C to yield Compound (4) as an oil. The oil was stirred in isopropyl alcohol (500ml, 5V). The reactor jacket was cooled to 25-30°C. Charged O-phosphoric acid (32.5gms, 0.3316

mmol) to Isopropyl alcohol solution and reactor contents were agitated at 25-30°C for 30 mins. The reactor jacket was heated to 70-75°C and reaction mixture was stirred at 70-75°C for 15mins to obtain a clear solution. The reactor jacket was cooled to 25-30°C, reaction solution was stirred at 25-30°C for 2hrs to obtain slurry. The reactor contents were filtered, and the cake was washed with isopropyl alcohol (100ml, 1V). The wet cake (160gms) was used as such for purification. To a 2-litre reactor, the wet cake was charged along with Methanol (200ml) and Acetone (500ml) at 25-30°C. The reactor jacket was heated at 65-70°C and reaction mixture was stirred at 65-70°C for 15 mins to get a clear solution. The reactor jacket was then cooled to 25-28°C and stirred for 2 hrs at 25-28°C. The solid were isolated by filtration was washed with acetone (100ml, 1V) and dried in vacuum tray drying at temperature below 45°C to yield 100 gms of Compound 5a. Analysis of Compound 4' on HPLC showed Impurity 4a and Impurity 4b less than 0.5%.

Example-4 Preparation of (((1-(6-amino-9H-purin-9-yl)propan-2-yloxy)methyl) (phenoxy) phosphoryloxy) methyl pivalate fumarate (Compound 1):

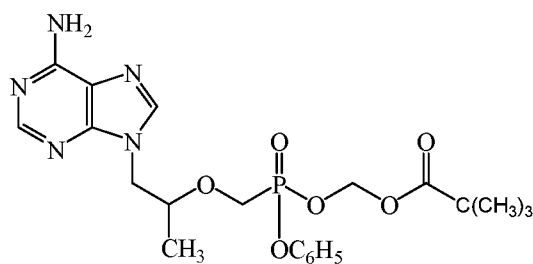
Compound 5b, (100gms, 0.173mmol) along with dichloromethane (500ml) and water (200ml) were charged to four necked 2 L reactor with mechanistic stirrer and . The reaction mixture was allowed to stir at 20-25°C to obtain clear solution. Liquor ammonia (100ml, 1V) was charged to reaction solution at 25°C under stirring. After stirring the solution for 30mins, layers allowed to separate. Product was extracted in organic dichloromethane layer; aqueous layer was discarded. Organic layer was washed with 10% sodium dihydrogen phosphate solution (200ml, 2V), organic layer was collected, dried over sodium sulfate and solvent was evaporated under vacuum below 40°C to obtain oil. Residue oil was dissolved in mixture of Isopropyl alcohol (500ml, 5V) and water (1000ml, 2V). To this solution was charged Fumaric acid (18.15gms,0.156mmol) and the obtained slurry was heated at 45-50°C under stirring for 30 minutes. Solution was further cooled to 0-5°C and stirred at this temperature for 2hrs. Solids were isolated by filtration at 0-5°C, washed with water

(200ml, 2V) and further dried in vacuum oven below 45°C for 5hrs, to yield 60gms of Compound 1 having purity as per HPLC: 99.5% and LOD : < 1%.

Example-5 Preparation of (((1-(6-amino-9H-purin-9-yl)propan-2-yloxy)methyl) (phenoxy) phosphoryloxy) methyl pivalate methane sulfonate (Compound 5b): Compound 5a (20gms, 0.034mmol) along with dichloromethane (200ml) and water (100ml) were charged to four necked 2 L reactor with mechanistic stirrer and the reaction mixture was allowed to stir at 20-25°C to obtain clear solution. Liquor ammonia (20ml, 1V) was charged to reaction solution at 25°C under stirring. After stirring the solution for 30mins, layers allowed to separate. Product was extracted in organic dichloromethane layer; aqueous layer was discarded. Organic layer was washed with 10% sodium dihydrogen phosphate solution (40ml, 2V), organic layer was collected, dried over sodium sulfate and solvent was evaporated under vacuum below 40°C to obtain oil. Residue oil was dissolved in mixture of ethyl acetate (100ml, 5V), and cooled to 15-20°C. To this solution, charged Methane sulfonic acid (3.5gms, 0.0364mmol) and slurry initially stirred at 15-2°C and then at 25-30°C for 30 minutes. The solids were isolated by filtration at 25-30°C, washed with ethyl acetate (20ml, 1V) and dried in vacuum oven below 40°C or 5hrs, to yield 15gms of Compound 5b, having purity as per HPLC: 99.5% and LOD : < 1%.

We claim,

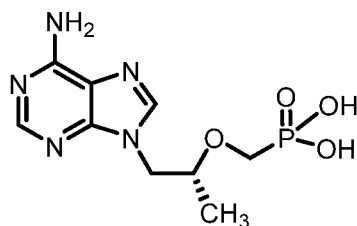
1. A process for the preparation of Compound (1) or pharmaceutically acceptable salts thereof;



Compound (1)

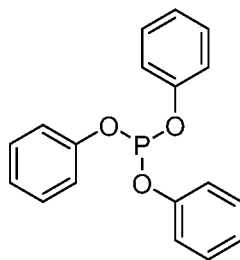
comprising;

- d. reacting Compound (2)



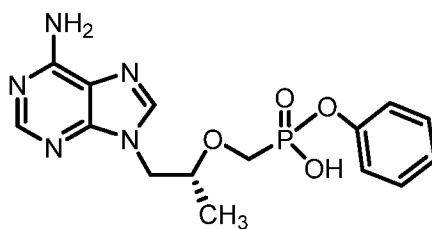
Compound 2

with triphenylphosphite



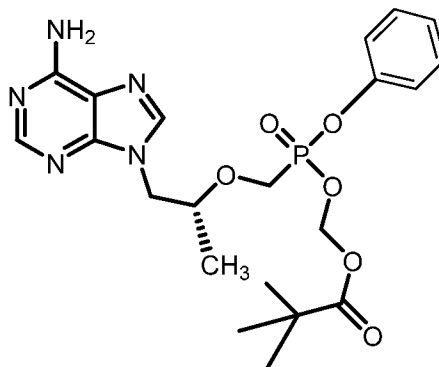
triphenyl phosphite

in the presence of a suitable base, in a polar aprotic solvent or non- polar aprotic solvents or in a mixture thereof to yield Compound (3)



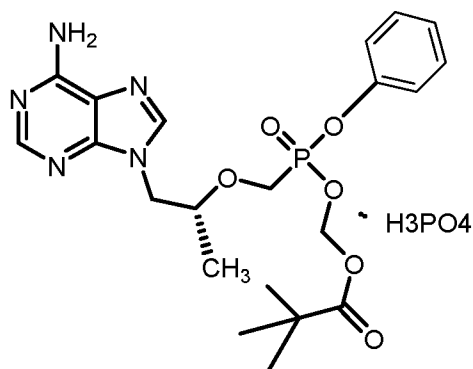
Compound 3

- e. reacting Compound (3) with chloromethyl pivalate in the presence of a suitable phase transfer catalyst and a suitable organic base, in an aprotic organic solvent or water or in a mixture of aprotic organic solvent or water, thereof to yield Compound (4)



Compound 4

- f. optionally, isolating Compound (4) as a phosphate salt (Compound 5a)



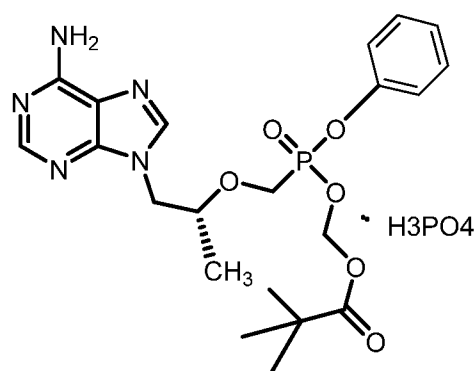
Compound 5a

and;

d. optionally, converting phosphate salt Compound (5a) to an acid addition salt of Compound (1), either by first isolating the free base Compound (1) or without isolating the free base Compound (1).

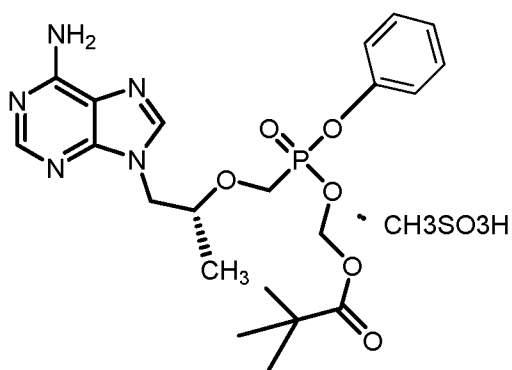
2. The process according to claim 1, wherein compound (1) is having a purity of more than about 95%, preferably at least 99%, more preferably at least 99.5% by HPLC.
3. The process according to claim 1, wherein Compound (2) is treated with triphenylphosphite in the presence of triethylamine and dimethylaminopyridine in a suitable mixture of a polar aprotic solvent or non-polar aprotic solvent to provide Compound (3).
4. The process according to claim 3, wherein the volume ratio of Compound (2) to solvent varies from 1:1 to 1:5.
5. The process according to claim 3, wherein Compound (2) is treated with triphenylphosphite in the presence of triethylamine and dimethylaminopyridine in a mixture of acetonitrile and toluene at a temperature in the range of about 60°C to about 100°C, to provide Compound (3).
6. The process according to claim 5, wherein the volume ratio of acetonitrile to toluene is 1:1.
7. The process according to claim 1, wherein aprotic organic solvent is selected from acetonitrile, propionitrile, ethyl acetate, methyl acetate, propyl acetate, isopropyl acetate, dimethyl carbonate, ethylene carbonate, propylene carbonate, dioxane, tetrahydrofuran, imethylacetamide, dimethylformamide, and dimethylsulfoxide.
8. The process according to claim 8, wherein aprotic organic solvent is selected from acetonitrile, dioxane and dimethyl carbonate.
9. The process according to claim 1, organic base is selected from, but not limited to triethyl amine, di-isopropyl amine, pyridine, picoline, diethyl amine, DBU, piperidine, N, N-diisopropylethylamine.

10. The process according to claim 1, wherein a phase transfer catalyst is selected from tetrabutyl ammonium bromide, benzyltriethylammonium chloride, methyltricaprylammonium chloride, methyltributylammonium chloride, tetramethyl ammonium bromide, trimethylpropyl ammonium bromide, benzyltributylammonium chloride and tetraethyl ammonium bromide or mixture thereof.
11. The process according to claim 1, wherein Compound (3) is treated with chloromethyl pivalate at about 55°C to about 65°C, for about 3 hours to about 6 hours.
12. The process according to claim 1, wherein Compound (4) is converted to phosphate salt (compound 5a)



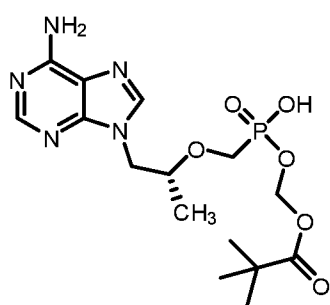
Compound 5a

13. The process according to claim 1, wherein Compound (4) is converted to mesylate salt (compound 5b).

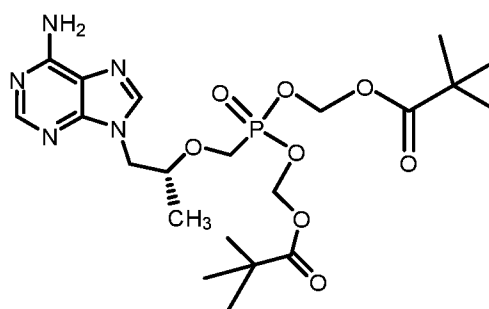


Compound 5b

14. The process according to claim 12 or 13, wherein the resulting phosphate salt (compound 5a) or mesylate salt (compound 5b) is extracted and basified to provide solution of pure Compound (1).
15. The process according to claim 15, wherein the Compound (1) is not isolated and converted to the fumarate salt.
16. The process according to claim 15, wherein fumarate salt of Compound (1) contains less than about 0.5% of dipivalate impurities, namely Compound (4a) and Compound (4b)



4a



4b

17. The process according to claim 16, wherein the fumarate salt of Compound (1) contains HPLC purity of more than 99%.

Dated this 8th day of August, 2022

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“AN IMPROVED PROCESS FOR PREPARING ANTIVIRAL PHOSPHONATE ANALOGUES”

Abstract

The present invention relates to an improved process for the preparation of (((1-(6-amino-9H-purin-9-yl)propan-2-yloxy)methyl)(phenoxy)phosphoryloxy)methyl pivalate Compound (1) or its pharmaceutically acceptable salts thereof. The compound is useful as nucleotide reverse transcriptase inhibitor in therapy for diseases which respond to inhibition of protein kinase activity in humans in need thereof.