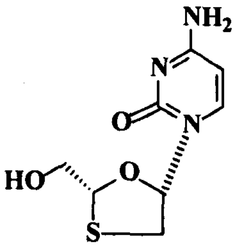
ABSTARCT

The present invention relates to an improved process for preparing pure Lamivudine of Formula I, which comprises treating Lamivudine (I) with hydrochloric acid to give Lamivudine hydrochloride salt (VIII); optionally isolating Lamivudine hydrochloride salt (VIII), desalifying the Lamivudine hydrochloride salt (VIII) to give Lamivudine; and isolating pure Lamivudine (I).

We Claim:

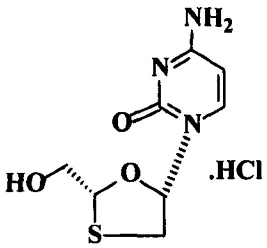
1. An improved process for the preparation of pure Lamivudine of Formula I,



Formula I

which comprises:

(a) treating Lamivudine (I) with hydrochloric acid to give Lamivudine hydrochloride salt of Formula VIII;



Formula VIII

(b) optionally isolating Lamivudine hydrochloride salt (VIII);

(c) desalifying the Lamivudine hydrochloride salt of Formula VIII to give Lamivudine (I).

2. The process according to claim 1, the desalification in step (c) is carried out in presence of a base.

3. The process according to claim 2, the base comprises sodium hydroxide (NaOH), potassium hydroxide (KOH), magnesium hydroxide ($Mg(OH)_2$), and calcium hydroxide ($Ca(OH)_2$), triethylamine (TEA), tetrabutylamine (TBA), diisopropy ethylamine (DIPEA), ethylamine, butylamine, ammonia or mixtures thereof.

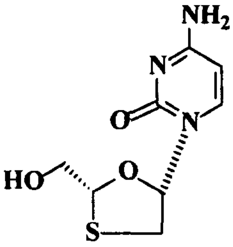
4. The process according to claim 1, the desalification in step (c) is carried out in presence of an anion resin.

5. The process according to claim 4, the anion resin comprises Amberlite IRA 96, Amberlite IRA 96RF, Amberlite IRA 96SB, Amberlite IRA 67, Amberlite IRA 67RF, Amberlite IRA 70RF, Amberlite CR5550, Dowex 66, Dowex 66RF.

6. The process according to claim 1, wherein Lamivudine hydrochloride salt obtained is anhydrous.

7. The process according to claim 1, wherein Lamivudine hydrochloride salt obtained has moisture content less than 0.5%.

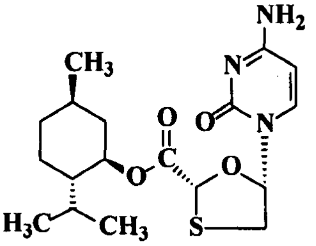
8. An improved process for the preparation of pure Lamivudine of Formula I,



Formula I

which comprises:

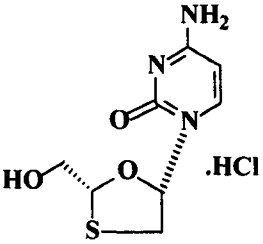
a) reducing Lamivudine coupled ester (VI),



Formula VI

to produce Lamivudine (I);

b) treating Lamivudine (I) *in-situ* with concentrated hydrochloric acid to give Lamivudine hydrochloride salt of Formula VIII;



Formula VIII

c) optionally isolating Lamivudine hydrochloride salt (VIII);

d) desalifying the Lamivudine hydrochloride salt of Formula VIII to give Lamivudine (I).

9. The process according to claim 8, wherein the reducing agent used in step (a) comprises sodium borohydride, potassium borohydride, sodium hydride, lithium borohydride, lithium aluminium hydride, diisobutylaluminium hydride.

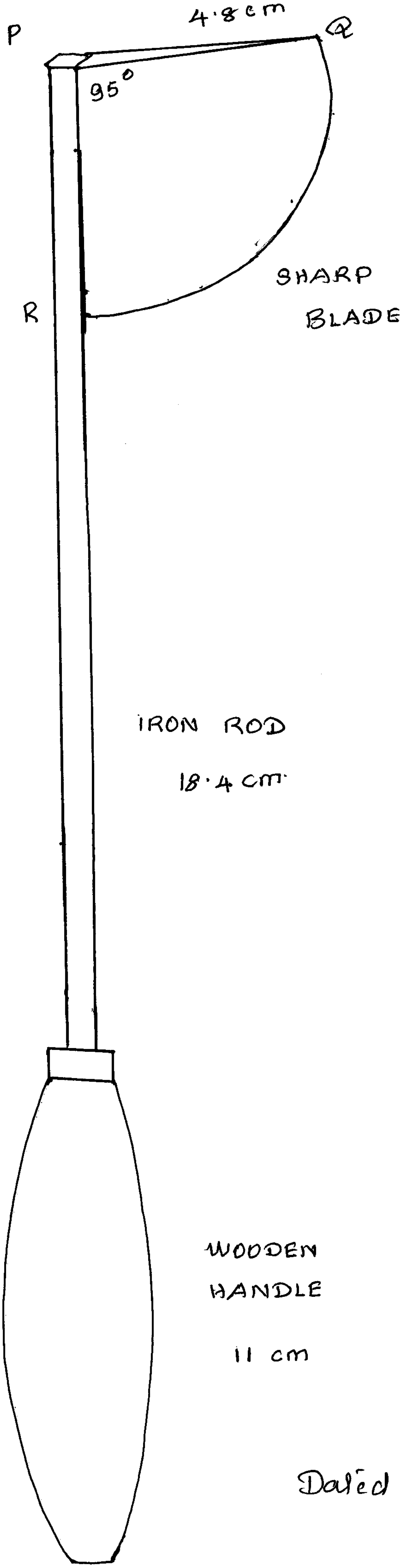
10. The process according to claim 8, the reduction step (a) is carried out in a solvent comprises water, methanol, ethanol, isopropanol, acetone, ethyl acetate, toluene or mixtures thereof.

Dated this the 28th **day of** August, **2014.**

Dr. M. SIVAKUMARAN
DIRECTOR

FIGURE 1

KNIFE FOR IUT TAPPING OF RUBBER TREE BY INCISION



Dated 2nd ~~31st~~ of September ~~August~~ 2013

Thankamma

L. Thankamma

FIGURE 2

MARKING OF THE TREE FOR TAPPING USING IUT SYSTEM BY INCISION

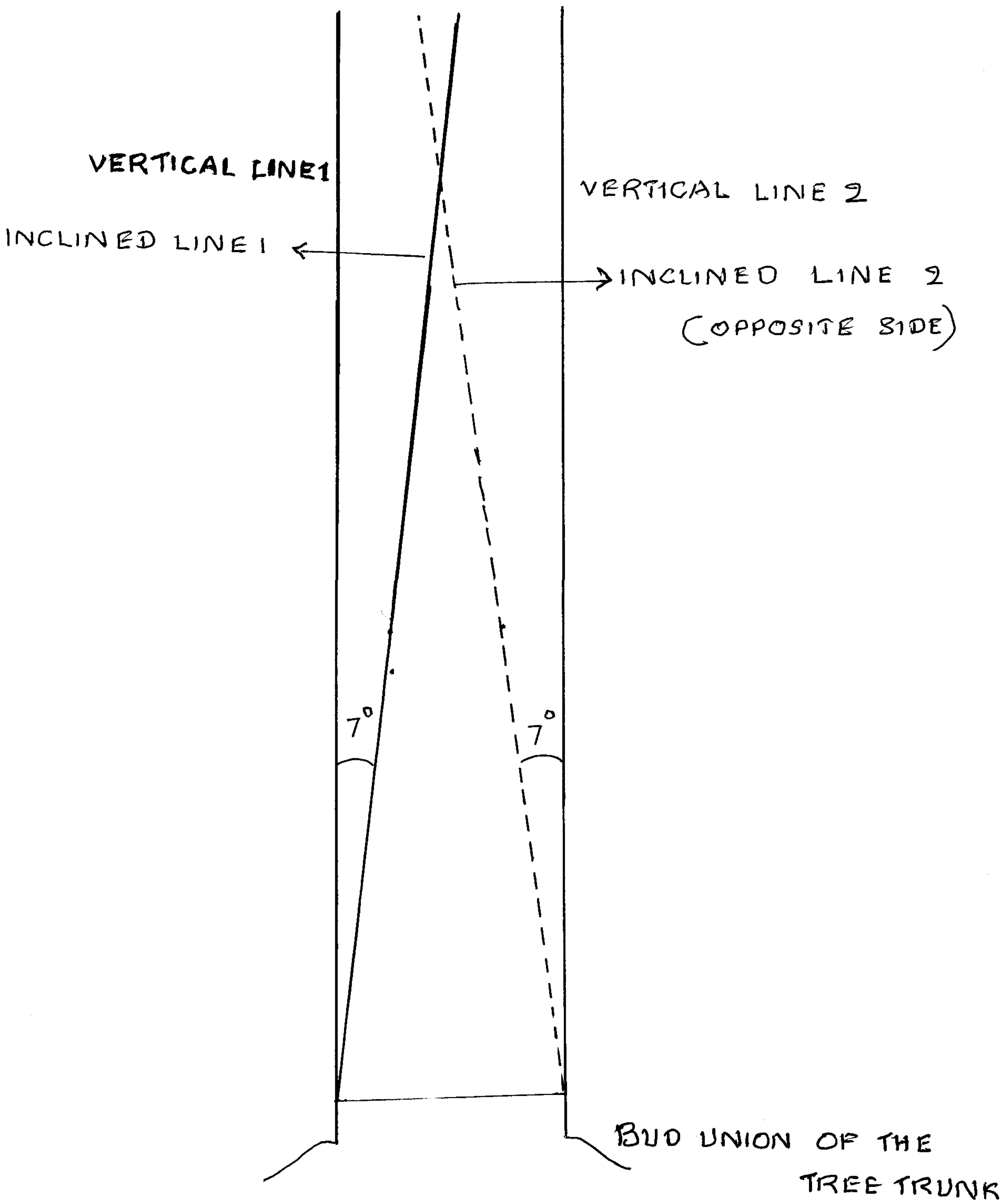


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FIGURE 3

AREA MARKED FOR 50 TAPPINGS

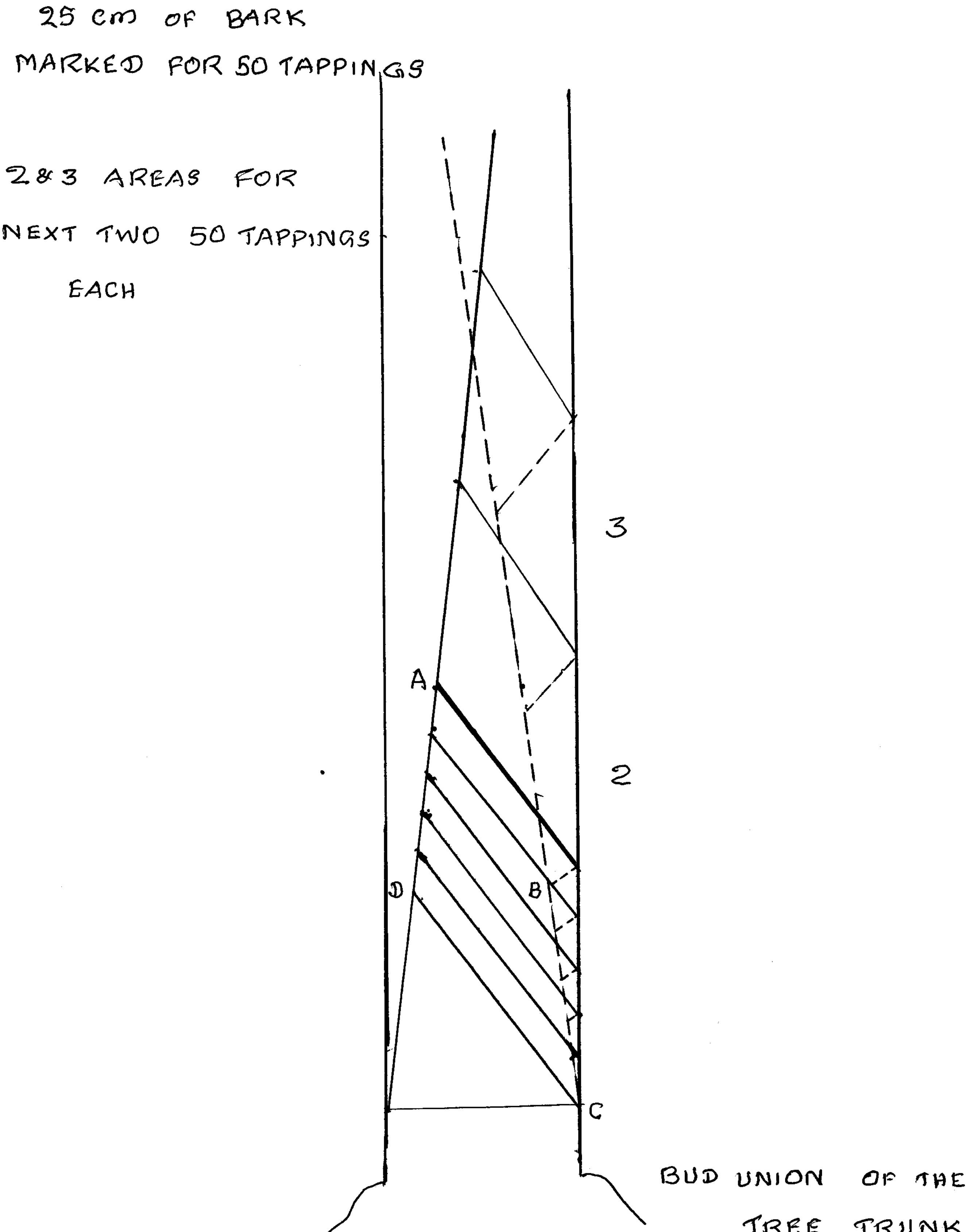

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FIGURE 4

AREA MARKED FOR FIRST FIFTY TAPPINGS ENLARGED

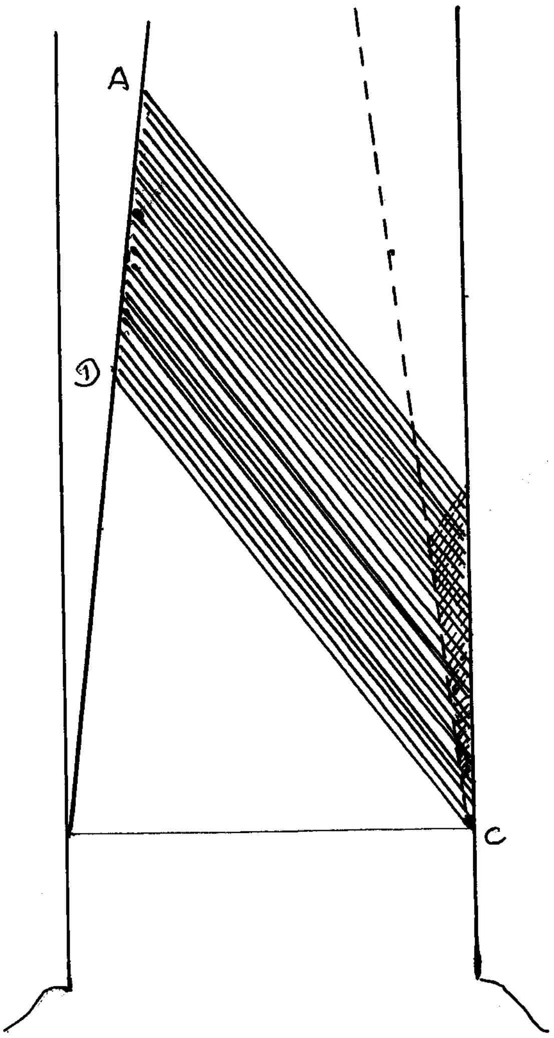

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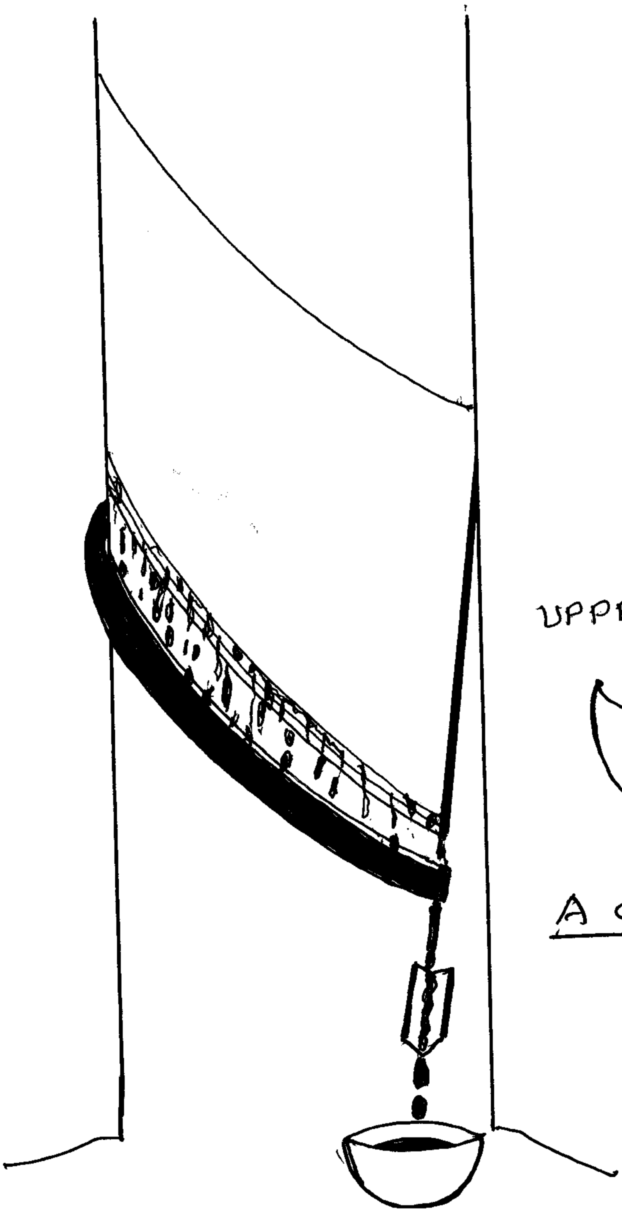
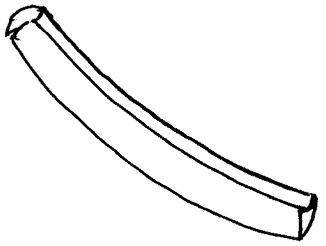
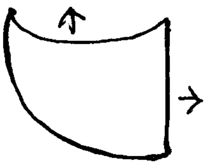
FIGURE. 5

TAPPING PANEL MARKED FOR FIRST 50 DAYS.
THREE TAPPINGS CARRIED OUT
L.S.P.D IS FIXED TO GUIDE LATEX
INTO THE CUP.





A BIT OF L.S.P.D



A CROSS SECTION OF LSPD

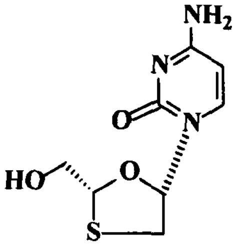
Dated ~~31st August~~ 2nd September 2013

Thaokamma. J.

L. Thaokamma.

FIELD OF THE INVENTION

The present invention relates to a novel and stereo selective synthetic process for the preparation of Lamivudine of Formula I,



Formula I

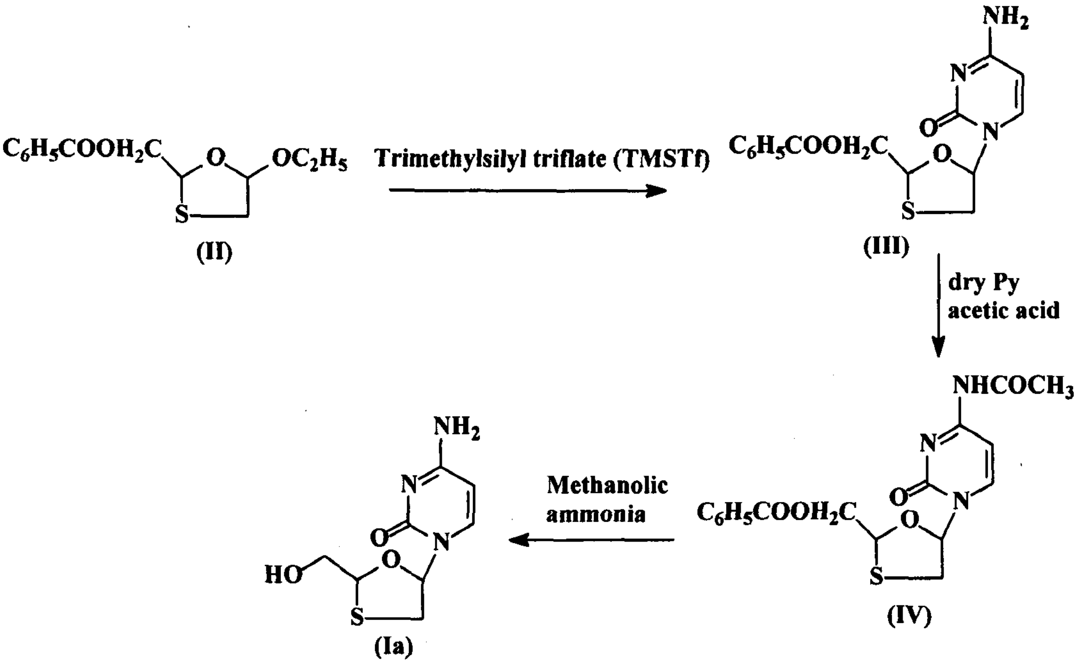
BACKGROUND OF INVENTION

Cis-Nucleoside derivatives Lamivudine (3TC) and Emtricitabine (FTC) are useful in the treatment of retroviral infections caused by Human immuno deficiency virus (HIV), Hepatitis B virus (HBV) and Human T-Lymotropic virus (HTLV).

Lamivudine (3-TC) is presently marketed by Glaxo SmithKline and is available as "EPIVIR" and is disclosed first in US 5,047,407.

US 5,047,407 and US 6,903,224 B2 disclose the preparation of Lamivudine as a racemic mixture i.e. (±) 3-TC. The process comprises, reacting silylated cytosine with 2-benzoyloxymethyl-5-ethoxy-1,3-oxathiolane (II) in presence of trimethylsilyl triflate (TMSTf) for three days under reflux to yield glycosidated product (III). Glycosidated product (III) is isolated after chromatography as a mixture of cis and trans isomers (1:1). The isomeric mixture obtained after chromatography is acetylated and the acetylated mass was again subjected to chromatography for separating cis and trans isomers. Thereafter the diprotected cis or trans derivative (IV) is deprotected in basic medium (methanolic ammonia) to yield racemic Lamivudine (Ia). As evident, this is not the industrially desired condition where the glycosidation reaction is carried out for three days at reflux temperature, the reaction results in isomeric mixture (1:1) and the reaction product requires extra acetylation step for isomeric separation, involves repeated chromatographic separation and as a result of all these gives a very low overall yield of the racemic product.

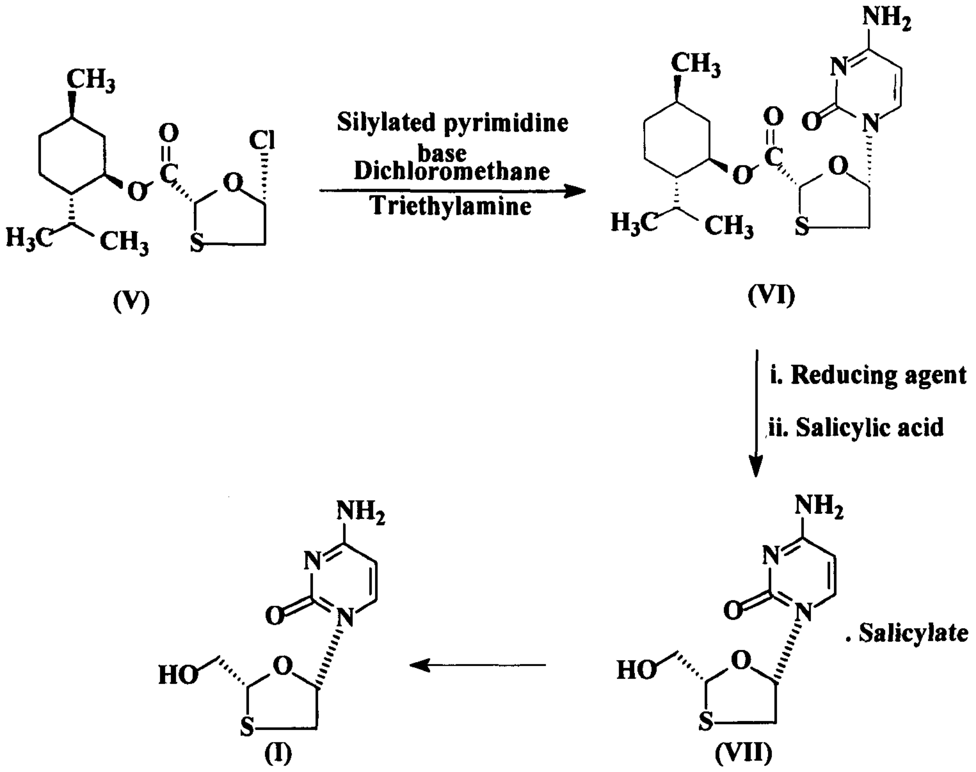
The process is as shown in Scheme-I below:



Scheme I

US 6,051,709 discloses a process for the preparation of Oxathiolane compound including Lamivudine by reacting (2R,5S)-5-chloro-[1,3]oxathiolane-2-carboxylic acid (V) with silylated pyrimidine base in presence of dichloromethane and triethylamine to produce (2R,5S)-5-(4-amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]-oxathiolane-2-carboxylicacid,2S,isopropyl-5R-methyl-1R-cyclohexylester (Lamivudine coupled ester) (VI). Lamivudine coupled ester is reduced using a reducing agent, followed by treated with salicylic acid to produce Lamivudine salicylate (VII), which is further converted to Lamivudine (I).

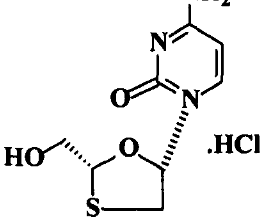
The process is as shown in Scheme-II below:



Scheme II

In US '709 before isolating Lamivudine free base (I), the Lamivudine (I) is converted to Salicylate salt (VII). This salicylate preparation makes the process inefficient as it leads to lot of effluents in the commercial production, which is not suitable for large-scale industrial production.

Crystal Engineering Communications 2012, 14, pp 2373-2376 discloses Lamivudine inorganic salts such as hydrochloric acid. Further, this journal also discloses that Lamivudine hydrochloric acid (VIII) exists as anhydrate and monohydrate.



Formula VIII

In this journal, the anhydrous Lamivudine hydrochloride salt (VIII) is prepared using three component system such as Lamivudine (I), 0.28 mol L-1 solution of hydrochloric acid in water, whereas monohydrate is prepared using two component system such as Lamivudine and the same water solution of hydrochloric acid. In this journal hydrochloric salts of Lamivudine (I) has been described, however doesn't disclose the conversion or use of hydrochloride salt (VIII) in the preparation of Lamivudine (I).

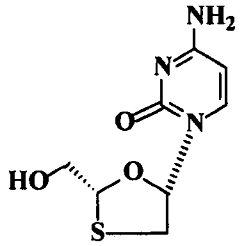
Therefore, there is currently a need for cost effective, large scale/commercial production of pure Lamivudine (I) with less or no effluents.

OBJECTIVE

The main objective of the present invention is to provide an improved process to prepare Lamivudine, which is useful in commercial production with less or no effluents, industrially applicable and economically viable.

SUMMARY OF THE INVENTION

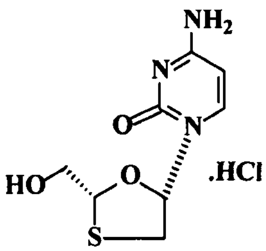
The present invention relates to an improved process for the preparation of pure Lamivudine of Formula I,



Formula I

which comprises:

a) treating Lamivudine (I) with hydrochloric acid to give Lamivudine hydrochloride salt of Formula VIII;

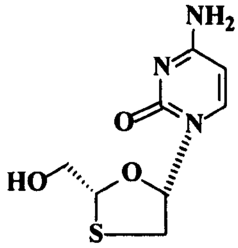


Formula VIII

b) optionally isolating Lamivudine hydrochloride salt (VIII);

c) desalifying the Lamivudine hydrochloride salt (VIII) to give Lamivudine (I).

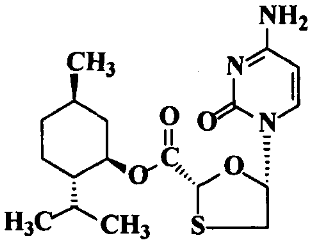
In another embodiment, the present invention relates to an improved process to prepare pure Lamivudine of Formula I,



Formula I

which comprises:

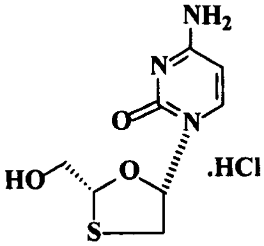
a) reducing Lamivudine coupled ester (VI)



Formula VI

to produce Lamivudine (I);

b) treating Lamivudine (I) *in-situ* with hydrochloric acid to give Lamivudine hydrochloride salt of Formula VIII;



Formula VIII

c) optionally isolating Lamivudine hydrochloride salt (VIII);

d) desalifying the Lamivudine hydrochloride salt (VIII) to give Lamivudine (I).

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the present invention provides an improved process for the preparation of Lamivudine (I) or a pharmaceutically acceptable salt thereof.

The process comprises, Lamivudine (I) is treated with hydrochloric acid, preferably concentrated hydrochloric acid in a solvent comprises water, methanol, ethanol, isopropanol, acetone, ethyl acetate, toluene or mixtures thereof at a temperature ranging from 15-35°C to give Lamivudine hydrochloride salt (VIII).

The compound (VIII) is subjected to purification either by column chromatography or crystallization.

In another embodiment, Lamivudine hydrochloride salt (VIII) obtained is anhydrous and has moisture content less than 0.5% (by Karl Fischer).

In another embodiment, desalification of Lamivudine hydrochloride salt (VIII) is carried out in two different methods.

In another embodiment, desalification of Lamivudine hydrochloride salt (VIII) is carried out using a base comprises sodium hydroxide (NaOH), potassium hydroxide (KOH), magnesium hydroxide ($Mg(OH)_2$), and calcium hydroxide ($Ca(OH)_2$), triethylamine (TEA), tetrabutylamine (TBA), diisopropy ethylamine (DIPEA), ethylamine, butylamine, ammonia at room temperature to give Lamivudine (I).

In another embodiment, desalification of Lamivudine hydrochloride salt (VIII) is carried out by passing aqueous solution of Lamivudine hydrochloride salt (VIII) through an anion resin comprises to Amberlite IRA 96, Amberlite IRA 96RF, Amberlite IRA 96SB, Amberlite IRA 67, Amberlite IRA 67RF, Amberlite IRA 70RF, Amberlite CR5550, Dowex 66, Dowex 66RF at room temperature and concentrating the obtained solution to give Lamivudine (I).

In still another embodiment of the present invention, the Compound (I) is optionally purified by known methods, for example recrystallization by dissolving in a solvent comprises acetone, acetonitrile, hexane, heptane, methanol, ethanol, isopropanol, dimethyl formamide (DMF), dimethyl acetamide (DMAc) and dimethyl sulfoxide (DMSO), water, and mixtures thereof; precipitating pure crystalline Compound (I) by cooling the solution or by adding an anti solvent comprises ketone, ether and esters, acetone, THF or ethyl acetate.

Further, the present inventors have prepared Lamivudine through Lamivudine hydrochloride and Lamivudine salicylate and observed that the purity of the product obtained by both salts were same and is as shown below:

TEST	**LAMIVUDINE HYDROCHLORIDE**	**LAMIVUDINE SALICYLATE**
DIASTEREOISOMER	NMT 0.7	NMT 0.3
LAMIVUDINE ACID	NMT 0.7	NMT 0.5
CYTOSINE	NMT 0.1	NMT 0.5
PURITY	NLT 98.5	NLT 98.5

In another embodiment, the present invention provides an improved process for the preparation of pure Lamivudine (I) or a pharmaceutically acceptable salt thereof.

The process comprises Lamivudine coupled ester (III) is reduced to produce Lamivudine (I).

The reduction of Lamivudine coupled ester (VI) is carried out using reducing agent comprises sodium borohydride, potassium borohydride, sodium hydride, lithium borohydride, lithium aluminium hydride or diisobutylaluminium hydride.

The reduction is carried out in a solvent comprises water, methanol, ethanol, isopropanol, acetone, ethyl acetate, toluene or mixtures thereof; at a temperature ranging from 15-35°C.

Lamivudine (I) is used as such without isolating in the next step or optionally isolated by conventional methods such as by removing the solvent under reduced pressure, filtration and drying the product.

In another embodiment, Lamivudine (I) is treated with hydrochloric acid, preferably concentrated hydrochloric acid in a solvent comprises water, methanol, ethanol, isopropanol, acetone, ethyl acetate, toluene or mixtures thereof at a temperature ranging from 15-35°C to give Lamivudine hydrochloride salt (VIII).

The compound (VIII) is optionally subjected to purification either by column chromatography or crystallization.

In another embodiment, Lamivudine hydrochloride salt (VIII) obtained is anhydrous and has moisture content less than 0.5% (by Karl Fischer).

In another embodiment, desalification of Lamivudine hydrochloride salt (VIII) is carried out in two different methods.

In another embodiment, desalification of Lamivudine hydrochloride salt (VIII) is carried out using a base comprises sodium hydroxide (NaOH), potassium hydroxide (KOH), magnesium hydroxide ($Mg(OH)_2$), and calcium hydroxide ($Ca(OH)_2$), triethylamine (TEA), tetrabutylamine (TBA), diisopropy ethylamine (DIPEA), ethylamine, butylamine, ammonia at room temperature to give Lamivudine (I).

In another embodiment, desalification of Lamivudine hydrochloride salt (VIII) is carried out by passing aqueous solution of Lamivudine hydrochloride salt (VIII) through an anion resin comprises to Amberlite IRA 96, Amberlite IRA 96RF, Amberlite IRA 96SB, Amberlite IRA 67, Amberlite IRA 67RF, Amberlite IRA 70RF, Amberlite CR5550, Dowex 66, Dowex 66RF at room temperature and concentrating the obtained solution to give Lamivudine (I).

In still another embodiment of the present invention, the Compound (I) is optionally purified by known methods, for example recrystallization by dissolving in a solvent comprises acetone, acetonitrile, hexane, heptane, methanol, ethanol, isopropanol, dimethyl formamide (DMF), dimethyl acetamide (DMAc) and dimethyl sulfoxide (DMSO), water, and mixtures thereof; precipitating pure crystalline Compound (I) by cooling the solution or by adding an anti solvent comprises ketone, ether and esters, acetone, THF or ethyl acetate.

In another embodiment, Lamivudine coupled ester (VI) is prepared by the processes known in the prior-art or through process described in Aurobindo's pending applications IN 118/CHE/2009 and IN 1237/CHE/2009.

The invention is illustrated with the following examples, which are provided by way of illustration only and should not be construed to limit the scope of the invention.

EXAMPLE 1

PREPARATION OF LAMIVUDINE HYDROCHLORIDE

Dipotassiumhydrogenortho phosphate (200g) was added to a mixture of ethanol (1300 ml), methanol (100 ml) and DM water (260 ml) at 25-30°C. The mixture was heated to 40-45°C and stirred for 30 minutes. Thereafter the contents were cooled to 20-25°C and Lamivudine coupled ester [(2R,5S)-5-(4-Amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]-oxathiolane-2-carboxylicacid,2S,isopropyl-5R-methyl-1R-cyclohexyl ester] (200 g) was added at 20-25°C. Thereafter sodium borohydride solution (prepared by dissolving sodium hydroxide (0.3 g) in DM water (260 ml) and cooling the solution to 15-20°C, adding sodium borohydride (40g) and stirred to get clear solution) was added to the reaction mass in 30 min by maintaining temperature at 20-25°C. The reaction mixture was stirred for 5 hours and monitored the completion of reaction by HPLC. After completion of reaction, concentrated hydrochloric acid was added at 15-20°C to precipitate Lamivudine hydrochloride. The product was filtered and dried to isolate title compound.

Yield: 120.0 g

Chromatographic purity (by HPLC): 98.0%

EXAMPLE 2

PREPARATION OF LAMIVUDINE

Lamivudine hydrochloride (100gm) was dissolved in water (1000 ml) at 25-30°C and passed through weak base anion exchange resin. Carbon was added to the reaction solution, filtered through hyflo and washed with DM water (300 ml). The water was distilled out under reduced pressure at 50-100 mm Hg at 55-60°C and product was obtained. The product was dried under reduced pressure 50-100 mm Hg till moisture content <0.1% to yield Lamivudine.

Yield: 80.0 g

Chromatographic purity (by HPLC): 99.6%

EXAMPLE 3

PREPARATION OF LAMIVUDINE

Ethanol was added to Lamivudine hydrochloride (150 g). Thereafter, triethylamine (75.0 g) was added over a period of 3 hrs and stirred to yield title compound. The obtained product was filtered and dried at 45°C at reduced pressure.

Yield: 122 g

Chromatographic purity (by HPLC): 99.70%

EXAMPLE 4

PREPARATION OF LAMIVUDINE HYDROCHLORIDE

Mixture of potassium dihydrogen phosphate (42.5 g) and dipotassium hydrogenortho phosphate (125.0 g) was added to a mixture of ethanol (1300 ml), methanol (100 ml) and DM water (260 ml) at 25-30°C. The mixture was heated to 40-45°C and stirred for 30 minutes. Thereafter the contents were cooled to 20-25°C and Lamivudine coupled ester [(2R,5S)-5-(4-Amino-2-oxo-2H-pyrimidin-1-yl)-[1,3]-oxathiolane-2-carboxylicacid,2S,isopropyl-5R-methyl-1R-cyclohexylester] (200 g) was added at 20-25°C. Thereafter sodium borohydride solution (prepared by dissolving sodium hydroxide (0.3 g) in DM water (260 ml) and cooling the solution to 15-20°C, adding sodium borohydride (40g) and stirred to get clear solution) was added to the reaction mass in 30 min by maintaining temperature at 20-25°C. The reaction mixture was stirred for 5 hours. The reaction was monitored by HPLC. After completion of reaction, concentrated hydrochloric acid was added at 15-20°C to precipitate Lamivudine hydrochloride. The product was filtered and dried to isolate title compound.

Yield: 120.0 g

Chromatographic purity (by HPLC): 98.0%

EXAMPLE 5

PREPARATION OF LAMIVUDINE

Lamivudine hydrochloride (100gm) was dissolved in water (1000 ml) at 25-30°C and passed through anion resin Amberlite IRA 67. Carbon was added to the reaction solution, filtered through hyflo and washed with DM water (300 ml). The water was distilled out under reduced pressure at 50-100 mmHg at 55-60°C and the product obtained was crystallized in ethanol (150 ml) then filtered and dried under reduced pressure 50-100 mm Hg till moisture content <0.1% to yield Lamivudine.

Yield: 75.0 g

Chromatographic purity (by HPLC): 99.50%

EXAMPLE 6

PREPARATION OF LAMIVUDINE

Ethanol was added to Lamivudine hydrochloride (150 g). Thereafter, triethylamine (85.0 g) was added over a period of 3 hrs and stirred to yield title compound. The obtained product was filtered and dried at 45°C at reduced pressure.

Yield: 118 g

Chromatographic purity (by HPLC): 99.60%