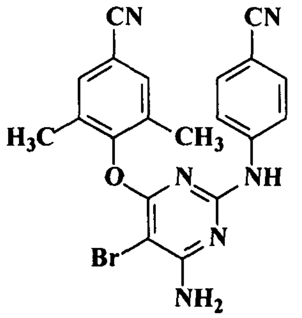
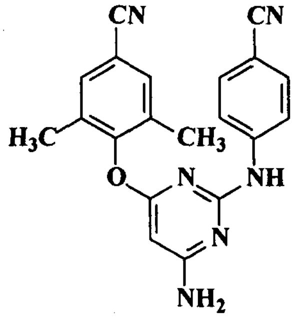
ABSTRACT:

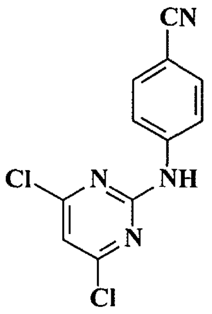
The present invention relates to an improved process for the preparation of Etravirine (I) and its intermediates, wherein Des-bromo Etravirine (XI) is purified and this purified form as such used in the next step for the preparation of Etravirine (I). The present invention also relates to purification of Etravirine (I) from an aqueous solvent.



Formula I



Formula XI



Formula IX

wherein, the base is not N,N-dimethyl aniline; and

(ii) converting compound of formula (IX) to Etravirine (I).

9. A process according to claim 8, wherein the chlorinating agent used in step (i) is phosphorous oxychloride ($POCl_3$), thionyl chloride ($SOCl_2$), sulfuryl chloride (SO_2Cl_2), methyl chloride or a mixture thereof.

10. A process according to claim 8, wherein the base used in step (i) is organic base comprises, triethylamine, diisopropylethylamine, dimethylamine, diethylamine, methylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo [4.3.0]non-5-ene (DBN), 1,4-diaza-bicyclo[2.2.2]octane (DABCO), pyridine or 4-(dimethylamino) pyridine (DMAP) or inorganic base comprises, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate or a mixture thereof, with the proviso that the base is not N,N-dimethyl aniline.

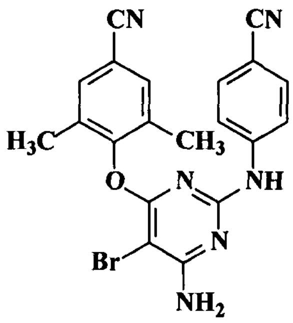
Dated this 19th day of December 2013.

For Aurobindo Pharma Limited

Dr. M. Sivakumaran
Director

FIELD OF THE INVENTION

The present invention relates to an improved process for the preparation of Etravirine of formula (I).



Formula I

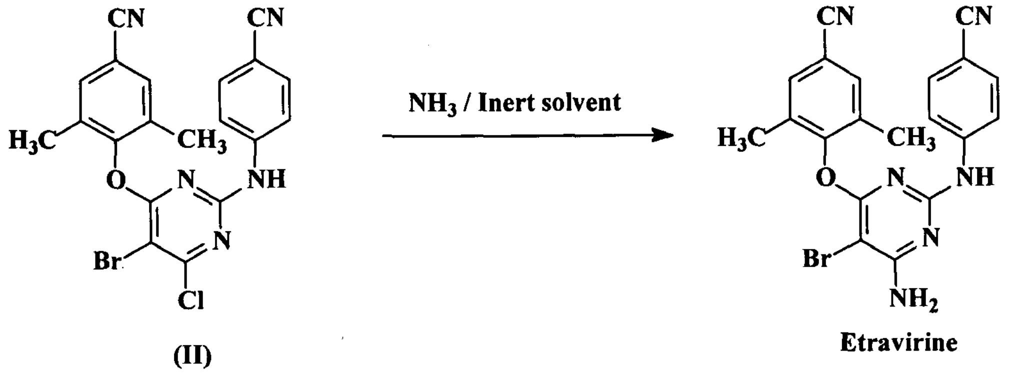
BACKGROUND OF THE INVENTION

Etravirine is chemically known as 4-[[6-amino-5-bromo-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile. Etravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type-1 (HIV-1). It binds directly to reverse transcriptase (RT) and blocks the RNA dependent and DNA dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site.

Etravirine is marketed under the brand name of Intelence®. It has been approved in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Etravirine is disclosed in US 7,037,917. This patent also discloses a process for the preparation of Etravirine. The process disclosed in US '917 comprises reacting 4-[[6-chloro-5-bromo-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile (II) with ammonia in presence of inert solvent such as 1,4-dioxane to produce Etravirine.

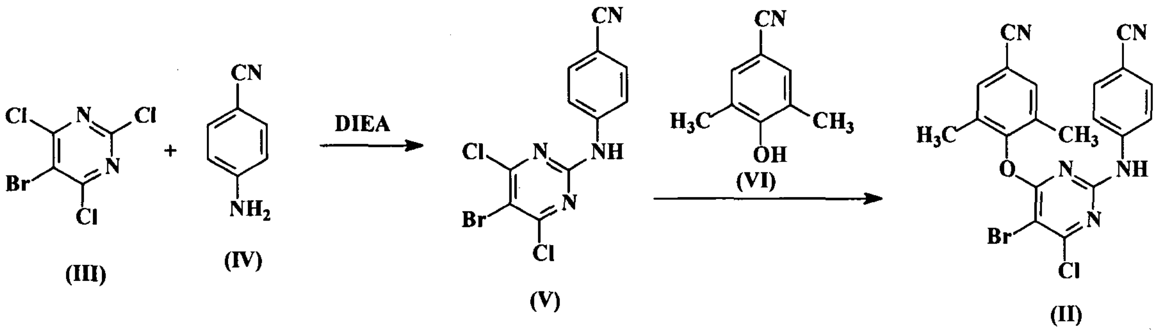
The process as shown below:



Scheme-I

Drugs of the Future 2005, 30(5): 462-468, discloses a process for the preparation of 4-[[6-chloro-5-bromo-2[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile (II), by reacting 5-bromo-2,4,6-trichloropyrimidine (III) with 4-aminobenzonitrile (IV) in presence of diisopropylethylamine (DIEA) to produce 4-(5-bromo-4,6-dichloropyrimidin-2-ylamino)benzonitrile (V), which is then reacted with 4-hydroxy-3,5-dimethylbenzonitrile (VI) to produce 4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-6-chloro-2-pyrimidinyl]amino]benzonitrile (II).

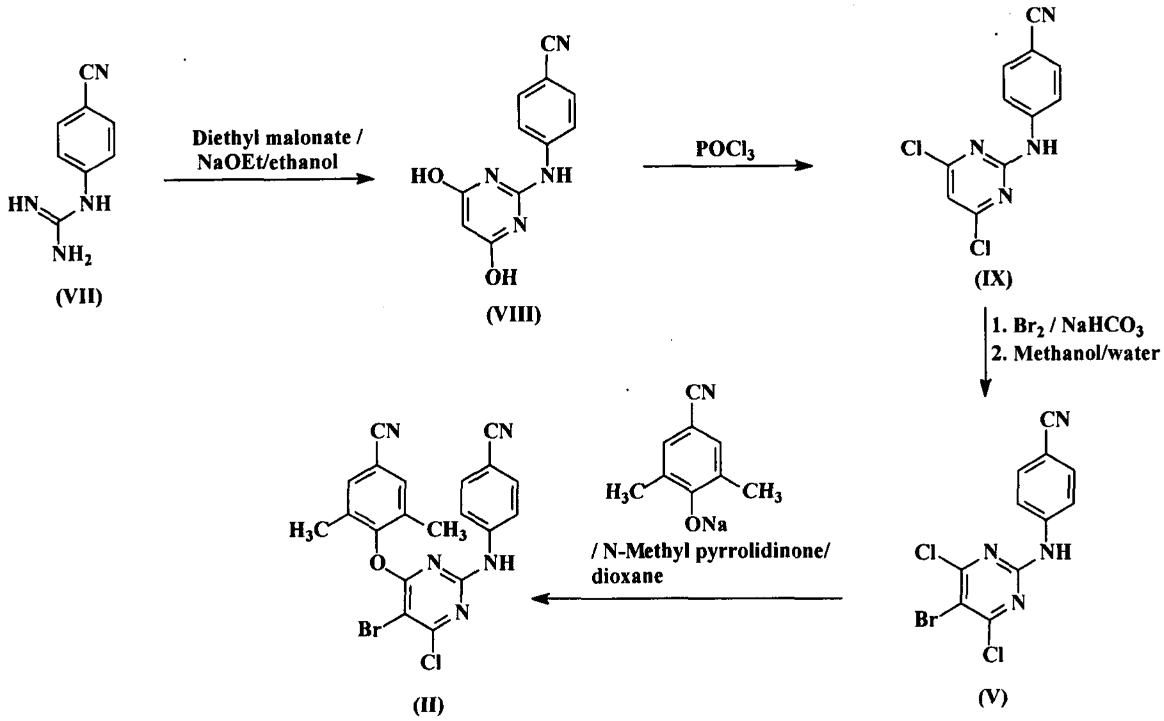
The process as shown below:



Scheme-II

The above article also discloses another variant process for the preparation of 4-[[6-chloro-5-bromo-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile (II) by reacting 4-cyanophenyl guanidine (VII) with diethylmalonate in the presence of sodium ethoxide to produce 4-(4,6-dihydroxypyrimidine-2-ylamino)benzonitrile (VIII), which upon treatment with $POCl_3$ to produce corresponding di-chloro derivative namely 4-(4,6-dichloropyrimidine-2-ylamino)benzonitrile (IX). Compound (IX) is brominated using bromine in the presence of sodium bicarbonate in aqueous methanol to produce 4-(5-bromo-4,6-dichloropyrimidin-2-ylamine)benzonitrile (V), which is further condensed with sodium salt of cyano-2,6-dimethylphenolate in presence of N-methylpyrrolidone and dioxane gives 4-[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-6-chloro-2-pyrimidinyl]amino] benzonitrile (II).

The process as shown below:

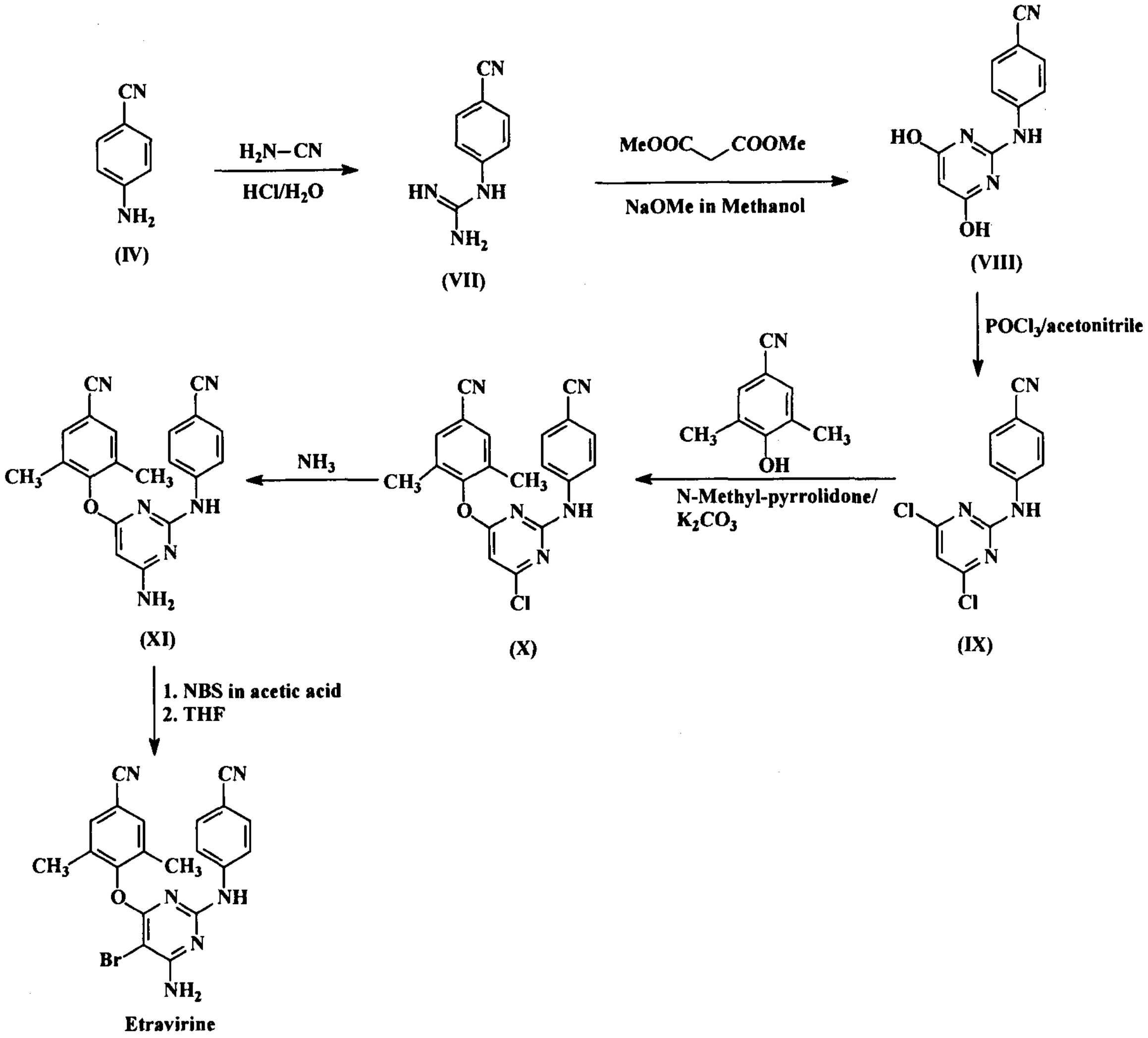


Scheme-III

The major disadvantage with the above processes is that the critical step of aminolysis of Compound (II) with ammonia at high pressure was not satisfactory because of lower yield (41%) and long reaction time of approximately 4 days. The low yield and long reaction period could be attributed to the presence of the bromine atom situated adjacent to the amination site.

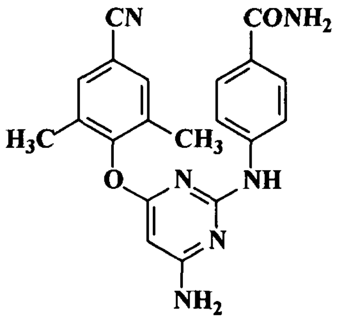
US 7,935,711 discloses a process for the preparation of Etravirine, which comprises reacting 4-aminobenzonitrile (IV) with cyanamide to produce 4-cyanophenyl guanidine (VII), which is treated with malonic ester to produce 4-(4,6-dihydroxy-2-pyrimidinyl-amino)cyanobenzene (VIII), which is further treatment with POCl$_3$ in acetonitrile to produce the corresponding dichloro derivative namely 4-(4,6-dichloropyrimidine-2-ylamino)benzonitrile (IX). Compound (IX) is reacted with 3,5-dimethyl-4-hydroxy benzonitrile (VI) to produce 4-[[6-chloro-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5–dimethyl benzonitrile (X), which undergoes aminolysis to produce Des-bromo Etravirine (XI). Finally bromination of Compound (XI) is carried out in the presence of NBS in THF gives Etravirine.

The process as shown below:



Scheme-IV

The major disadvantage with the above process is that the formation of undesired desbromo Etravirine amide impurity (XII) and other unwanted impurities during amination step. Removal of these impurities was found to be difficult and carried forward in subsequent reaction steps and results in Etravirine (I) with poor quality and requires additional purification step for desbromo Etravirine.



Formula XII

WO 2010/150279 discloses a process for the preparation of Etravirine, wherein bromination of 4-[[6-amino-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethyl benzonitrile (XI) is carried out using liquid bromine in MDC followed by treating with aqueous NaOH to produce Etravirine.

The disadvantage with the above process is that the use of NaOH in bromination step leads to the formation of undesired desbromo Etravirine, which is difficult to remove and required repeated purification steps.

WO 2012/001695 discloses a process for the preparation of Etravirine, which comprises reacting 4-cyanophenyl guanidine (VII) with malonic ester to produce 4-(4,6-dihydroxy-2-pyrimidinyl-amino)cyanobenzene (VIII), which is further treatment with $POCl_3$ in N,N-dimethyl aniline to produce the corresponding dichloro derivative namely 4-(4,6-dichloro pyrimidine-2-ylamino)benzonitrile (IX), which is further converted to Etravirine.

The disadvantage with the above process is that the use of N,N-dimethyl aniline in chlorination step, which is genotoxic and has to be controlled in Etravitrine to a undetectable limit.

Hence, there is a need to have simple, easy to handle and cost effective process for the preparation of Etravirine and its intermediates with high chemical purity and higher yields.

The present invention is specifically directed towards purification process, which provides Des-bromo Etravirine (XI) in pure form. This pure Compound (XI) as such used in the next step, which reduces the un-required impurities and produces Etravirine with higher yield and purity.

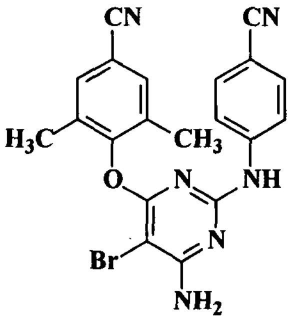
The present invention also specifically directed towards purification process of Etravirine (I).

OBJECTIVE OF THE INVENTION

The main objective of the present invention is to provide a simple, cost effective and an improved process for the preparation of Etravirine (I) on commercial scale.

SUMMARY OF THE INVENTION

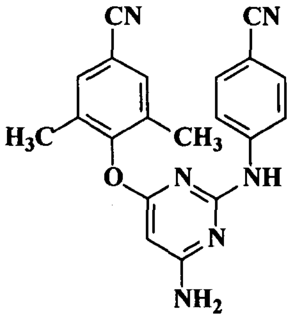
In one of the embodiments, the present invention provides an improved process for the preparation of Etravirine of formula I,



Formula I

which comprises:

(i) purifying 4-[[6-amono-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethyl benzonitrile (Des-bromo Etravirine) of formula XI,



Formula XI

from a solvent or a mixture thereof,

(ii) brominating a compound of formula XI to obtain Etravirine (I),

(iii) optionally, purifying Etravirine (I).

In another embodiment, the present invention provides a process for the preparation of Etravirine (I):

which comprises:

(i) brominating a compound of formula XI;

(ii) treating the reaction mixture of step (i) with a base;

(iii) isolating Etravirine (I);

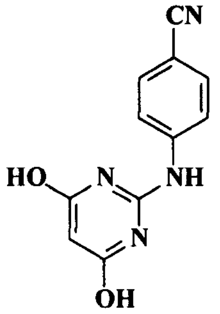
(iv) optionally, purifying Etravirine (I).

In another embodiment, the present invention provides purification of Etravirine (I), which comprises:

(i) treating Etravirine (I) with an aqueous solvent;
(ii) isolating Etravirine (I).

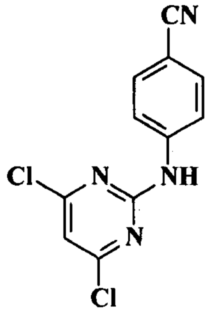
In another embodiment, the present invention provides a process for the preparation of Etravirine (I), which comprises:

(i) reacting 4-(4,6-dihydroxypyrimidine-2-ylamino)benzonitrile of formula VIII,



Formula VIII

with a chlorinating agent in presence of a base to produce 4-(4,6-dichloropyrimidine-2-ylamino)benzonitrile of formula IX; and



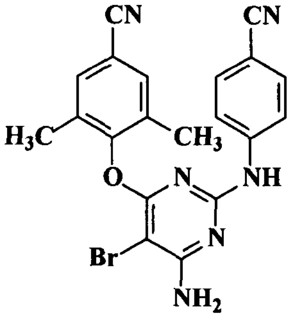
Formula IX

wherein, the base is not N,N-dimethyl aniline.

(ii) converting compound of formula (IX) to Etravirine (I).

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to an improved process for the preparation of Etravirine of formula I:



Formula I

The process comprises, treating 4-(4,6-dihydroxypyrimidine-2-ylamino)benzonitrile of formula VIII with a chlorinating agent in presence of a base to produce 4-(4,6-dichloropyrimidine-2-ylamino)benzonitrile of formula IX.

The chlorinating agent is phosphorous oxychloride ($POCl_3$), thionyl chloride ($SOCl_2$), sulfuryl chloride (SO_2Cl_2), methyl chloride, preferably phosphorous oxychloride ($POCl_3$) used as a chlorinating agent. The base used is organic base such as triethylamine, diisopropylethylamine, dimethylamine, diethylamine, methylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo [4.3.0]non-5-ene (DBN), 1,4-diaza-bicyclo[2.2.2]octane (DABCO), pyridine or 4-(dimethylamino) pyridine (DMAP) or inorganic base such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, preferably triethylamine is used as a base, with the proviso that the base is not N,N-dimethyl aniline.

The reaction is performed at a temperature ranging from 20-80°C based on the base/solvent used for the reaction. The sufficient period of time necessary for obtaining the compound (IX) will depend on the parameters of the reaction. Preferably, maintaining the reaction mixture for 1 to 3 hours.

Compound (IX) is converted to Des-bromo Etravirine (XI) by the process as disclosed in US 7,935,711. The process comprises; reacting Compound (IX) with 3,5-dimethyl-4-hydroxy benzonitrile (VI) to produce 4-[[6-chloro-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5–dimethyl benzonitrile (X), which undergoes aminolysis to produce Des-bromo Etravirine (XI).

Des-bromo Etravirine (XI) is purified from a solvent or a mixture thereof. The solvent used for the purification is polar solvent comprises, tetrahydrofuran (THF), dichloromethane, ethyl acetate, acetone, dimethylformamide (DMF), acetonitrile, dimethyl sulfoxide (DMSO), formic acid, n-butanol, isopropanol, n-propanol, ethanol, methanol, acetic acid, water or a mixture thereof. Preferably, mixture of THF and ethanol are used in the purification.

Des-bromo Etravirine (XI) is brominated by a halogen donor compounds. This bromination reaction is preferably carried out in a suitable inert solvent comprises chlorinated hydrocarbons or ether. The reaction is performed at a temperature about 25-50°C, preferably at 25-30°C.

After completion of the reaction, the reaction mixture of bromination step is treated with an organic base comprises triethylamine, diisopropylethylamine, dimethylamine, diethylamine, methylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo [4.3.0]non-5-ene (DBN), 1,4-diaza-bicyclo[2.2.2]octane (DABCO), preferably triethylamine. Solvent is added to the resulting reaction mass to isolate Etravirine.

The solvent used is tetrahydrofuran (THF), dichloromethane, ethyl acetate, acetone, dimethylformamide (DMF), acetonitrile, dimethyl sulfoxide (DMSO), formic acid, n-butanol, isopropanol, n-propanol, ethanol, methanol, acetic acid, water or a mixture thereof. Preferably, acetone is used as a solvent.

Purification of Etravirine is carried out using aqueous solvent to obtain pure Etravirine. The purification step is carried out by suspending Etravirine in an organic solvent and water later heated to 40 to 80°C to obtain a clear solution. Optionally, adding the resulting solution with carbon enoanticromos. Pure Etravirine is isolated by the conventional methods, such as concentrating the solvent completely or partially or by cooling the mass.

The organic solvent used is acetone, methanol, ethanol, isopropanol, preferably acetone and aqueous solvent used for purification is selected from aqueous acetone.

The following examples illustrate the nature of the invention and are provided for illustrative purposes only and should not be construed to limit the scope of the invention.

EXAMPLES

EXAMPLE - 1

Stage-I: PREPARATION OF (4-CYANOPHENYL)GUANIDINE:

4-Aminobenzonitrile (300g) was suspended in DM water (600 ml) at 25-30°C. The suspension was heated to 40-45°C. 50% w/w Aqueous cyanamide (641g) and hydrochloric acid (~32% w/w, 870 g) were added simultaneously over a period of ~5hrs at 40-50°C. Stirring was continued at 45-50°C till 4-aminobenzonitrile was left unreacted is ≤ 8% by qualitative HPLC analysis. Thereafter, the resulting suspension was cooled to 0-5°C and stirring was continued at this temperature for 2hrs. The product was filtered and washed the wet cake with pre-cooled ethanol (absolute alcohol, 300 ml, 0-5°C). The above filtered mass (~ 450 g) was suspended in pre-heated DM water (3.75 Lt, 45-50°C) at 45-50°C and stirring was continued at this temperature for 15 min to obtain a solution. Aqueous sodium hydroxide solution (prepared by dissolving 80.25 g of sodium hydroxide in 750 ml of DM water) was added at 45-50°C in ~30 min. Thereafter, the suspension was continued stirring at this temperature for 30 min. The product was filtered and washed with DM water (750 ml, 25-30°C). The product was dried at 95-100°C under reduced pressure (~10 mmHg) to obtain 270 g of the title compound.

Stage-II: PREPARATION OF 4-(4,6-DIHYDROXYPYRIMIDIN-2-YLAMINO) BENZONITRILE:

(4-Cyanophenyl)guanidine (225 g) was dissolved in ethanol (absolute alcohol, 1.69 Lt) at 25-30°C. Diethylmalonate (529 g) was added at 25-30°C and sodium ethoxide (250 g) was added in six equal lots over a period of ~1h at 25-50°C. Thereafter, contents were stirred at 50-55°C till completion of the reaction. DM water (2.25 Lt) was added at 50-55°C. The reaction mass was concentrated under reduced pressure (100-150 mm Hg) at 40-55°C to collect ~1.93 Lt of the distillate. Thereafter, DM water (1.125 Lt) and by ethyl acetate (675 ml) were added at 40-55°C. The suspension was cooled to 0-5°C and continued stirring at this temperature for 1h. The product was filtered and washed with pre-cooled

DM water (2.25 Lt, 0-5°C) followed by ethyl acetate (450 ml, 25-30°C). The product was dried at 95-100°C under reduced pressure (~10 mmHg) to obtain 309 g of the title compound.

Stage-III: PREPARATION OF 4-(4,6-DICHLOROPYRIMIDIN-2-YLAMINO) BENZONITRILE:

4-(4,6-Dihydroxypyrimidin-2-ylamino)benzonitrile (250 g) was added in small lots in phosphorous oxychloride (1.25 Lt) at 25-60°C in ~60 min. Triethylamine (151.70 g) was added slowly in ~ 30 min at 50-80°C. Thereafter, the reaction mass was stirred at 80-85°C till completion of the reaction. The hot (80-85°C) reaction mass was poured slowly in pre-heated DM water (10 Lt, 50-80°C) at 50-80°C in ~3h. The slurry was cooled to 40-45°C. The product was filtered and washed with DM water (6.25 Lt). The product was dried at 70-75°C under reduced pressure (~10 mm Hg) to obtain 245 g of the title compound.

Stage-IV: PREPARATION OF 4-[6-CHLORO-2-[(4-CYANOPHENYL)AMINO]-4-PYRIMIDINYL]OXY]-3,5-DIMETHYLBENZONITRILE :

4-(4,6-Dichloropyrimidin-2-ylamino)benzonitrile (200 g) was added in acetone (2 Lt) at 25-30°C. 4-Hydroxy-3,5-dimethylbenzonitrile (110 g) was added to the resulting mass followed by anhydrous potassium carbonate (135 g) at 25-30°C. Thereafter, the contents were heated to reflux at 55-60°C till completion of the reaction. Thereafter, the reaction mass was cooled to 45-50°C and DM water (200 ml) was added at this temperature in ~15 min. The slurry was cooled to 0-5°C and stirring was continued at this temperature for 1h. The product was filtered and washed with DM water (4 Lt, 45-50°C). Thereafter, filtrate was washed with pre-cooled acetone (400 ml, 0-5°C). The product was dried at 70-75°C under reduced pressure to obtain 240 g of the title compound.

Stage-V: PREPARATION OF 4-[[6-AMINO-2-[(4-CYANOPHENYL)AMINO]-4-PYRIMIDINYL]OXY]-3,5-DIMETHYL BENZONITRILE :

4-[[6-Chloro-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethyl benzonitrile (200 g) was suspended in 1,4-dioxane (3 Lt) at 25-30°C in a pressure vessel. Aqueous ammonia (1.20 Lt) was added at 25-30°C. The contents were heated to 125-135°C (in-built pressure 12-14 Kg). Thereafter, stirring was continued at 130-135°C till completion of the reaction. Thereafter, the reaction mass was cooled to 25-30°C and DM water (600 ml) was added at this temperature in ~30 min. Stirring was continued at 25-30°C for 15h. The slurry was cooled to 0-5°C and stirring was continued at this temperature for 2 hrs. The product was filtered and slurry washed with DM water (4 Lit). Thereafter, the product (Desbromo etravirine) was washed with pre-cooled ethanol (absolute alcohol, 200 ml, 0-5°C).

PURIFICATION OF 4-[[6-AMINO-2-[(4-CYANOPHENYL)AMINO]-4-PYRIMIDINYL]OXY]-3,5-DIMETHYL BENZONITRILE :

Filtered mass (desbromo etravirine wet as obtained above) was suspended in tetrahydrofuran (1120 ml) at 25-35°C. The solution was concentrated at atmospheric pressure at 64-66°C to collect ~800 ml of the distillate. The resulting slurry was cooled to 55-60°C and ethanol (absolute alcohol, 960 ml) was added at the same temperature. Concentration was continued at atmospheric pressure to collect ~640 ml of the distillate. The slurry was cooled to 0-5°C and stirring was continued at 0-5°C for 1h. The product was filtered and washed with pre-cooled ethanol (absolute alcohol, 160 ml, 0-5°C). The product was dried at 70-75°C under reduced pressure to obtain 145 g of the title compound.

Stage-VI: PREPARATION OF 4-[[6-AMINO-5-BROMO-2-[(4-CYANOPHENYL) AMINO]-4-PYRIMIDINYL]OXY]-3,5-DIMETHYLBENZONITRILE [ETRAVIRINE]:

4-[[6-Amino-2-[(4-cyanophenyl)amino]-4-pyrimidinyl]oxy]-3,5-dimethyl benzonitrile (Deabromo etravirine, 100 g) was suspended in methylene chloride (800 ml) at 25-30°C. The solution was cooled to 0-5°C and a solution of liquid bromine in methylene chloride (prepared by mixing 47.20 g of liquid bromine in 100 ml of methylene chloride) was added at 0-10°C in ~ 1h. Thereafter, stirring was continued at 0-10°C till completion of the reaction. Thereafter, the reaction mass was cooled to -5 to -10°C. Triethylamine (34 g) was added at -5 to -10°C in ~ 30 min. Thereafter, stirring was continued at -5 to -10°C for 15 min. Acetone (400 ml) was added at -5 to -10°C and stirring was continued at this temperature for 90 min. The product was filtered and washed it with pre-cooled 1:1 v/v aqueous acetone (200 ml, prepared by mixing 100 ml of acetone with 100 ml of DM water, 0-5°C). The product was dried at 70-75°C under reduced pressure to obtain 110 g of the title compound.

PURIFICATION OF ETRAVIRINE CRUDE:

Etravirine crude (100 g) was suspended in a mixture of acetone (1900 ml) and DM water (100 ml) at 25-30°C. The contents were heated to reflux at 52-55°C to obtain a clear solution. The solution was cooled to 40-45°C and carbon enoanticromos (10 g) were added at this temperature. Thereafter, the contents were heated to reflux at 52-55°C and stirring was continued at this temperature for 30 min. The reaction mass was cooled to 40-45°C. The carbon was filtered and the residue was washed with pre-heated acetone (200 ml, 45-50°C). The filtrate (~ 2.25 Lt) was concentrated at atmospheric pressure at 50-60°C to a volume of ~800 ml. (Distillate volume ~1.3 Lt). The resulting slurry was cooled to 40-45°C. DM water (100 ml) was added at 40-45°C. Thereafter, the slurry was cooled to 0-5°C and stirring was continued at this temperature for 1h. The product was filtered and washed it with pre-cooled 1:1 v/v aqueous acetone (200 ml, 0 to 5°C). The product was dried at 70-75°C under reduced pressure to obtain 93 g of the title compound.