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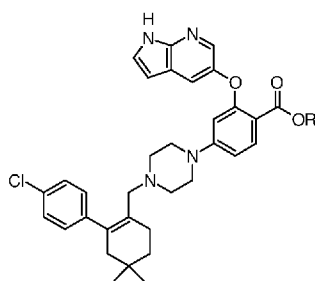
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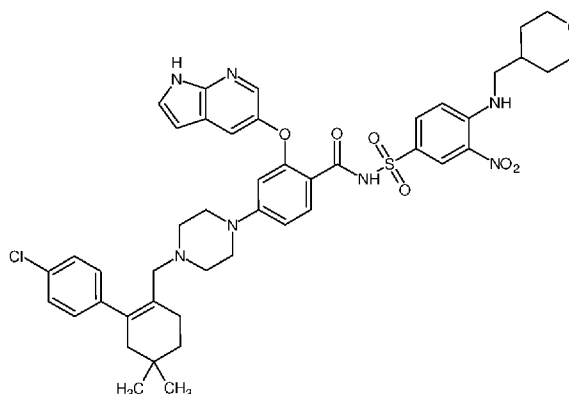
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(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF VENETOCLAX



Formula I



Formula V

(57) Abstract: An improved process for the preparation of Venetoclax. The present invention also relates to an improved process for the preparation of a compound of formula I or its salts, (I) wherein R is C₁₋₄ alkyl; and its use for the preparation of the compound of formula V. (v)

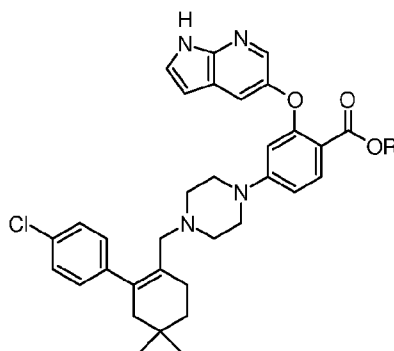
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AN IMPROVED PROCESS FOR THE PREPARATION OF VENETOCLAX

FIELD OF THE INVENTION

The present invention relates to an improved process for the preparation of a compound
 5 of formula I or its salt,

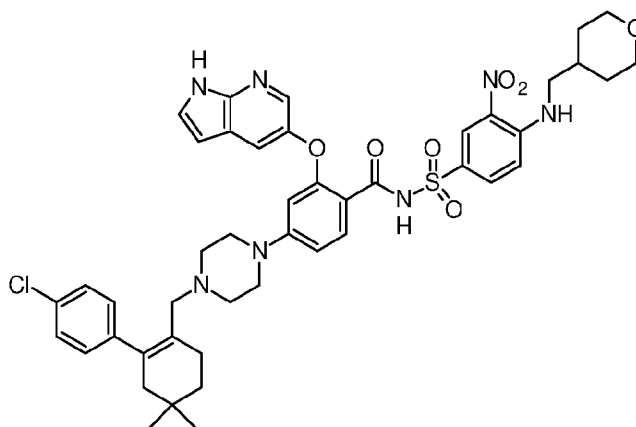


Formula I,

wherein R is C₁₋₄ alkyl.

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The present invention further relates to an improved process for the conversion of compound of formula I to a compound of formula V,

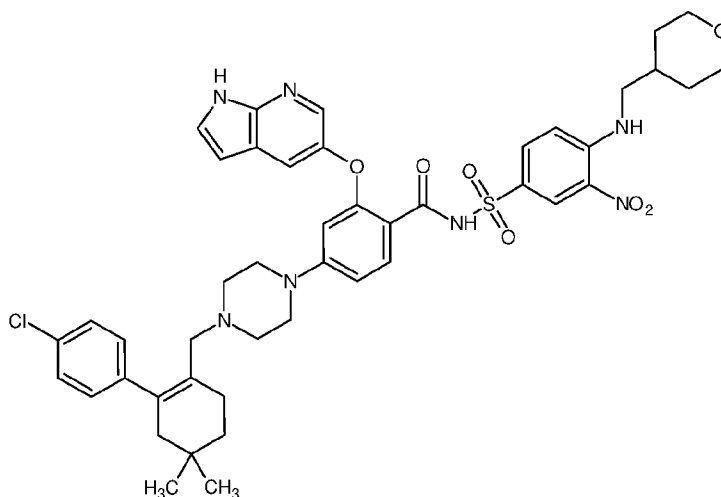


Formula V (Venetoclax)

15 The present invention also relates to an improved process for the preparation of the compound of formula V.

BACKGROUND OF THE INVENTION

Venetoclax, 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl) piperazin-1-yl)-*N*-({3-nitro-4[(tetrahydro-2*H*-pyran-4ylmethyl)amino]phenyl} sulfonyl)-2-(1*H*-pyrrolo[2,3-*b*]pyridin-5-yloxy)benzamide) is represented by a compound of formula V.



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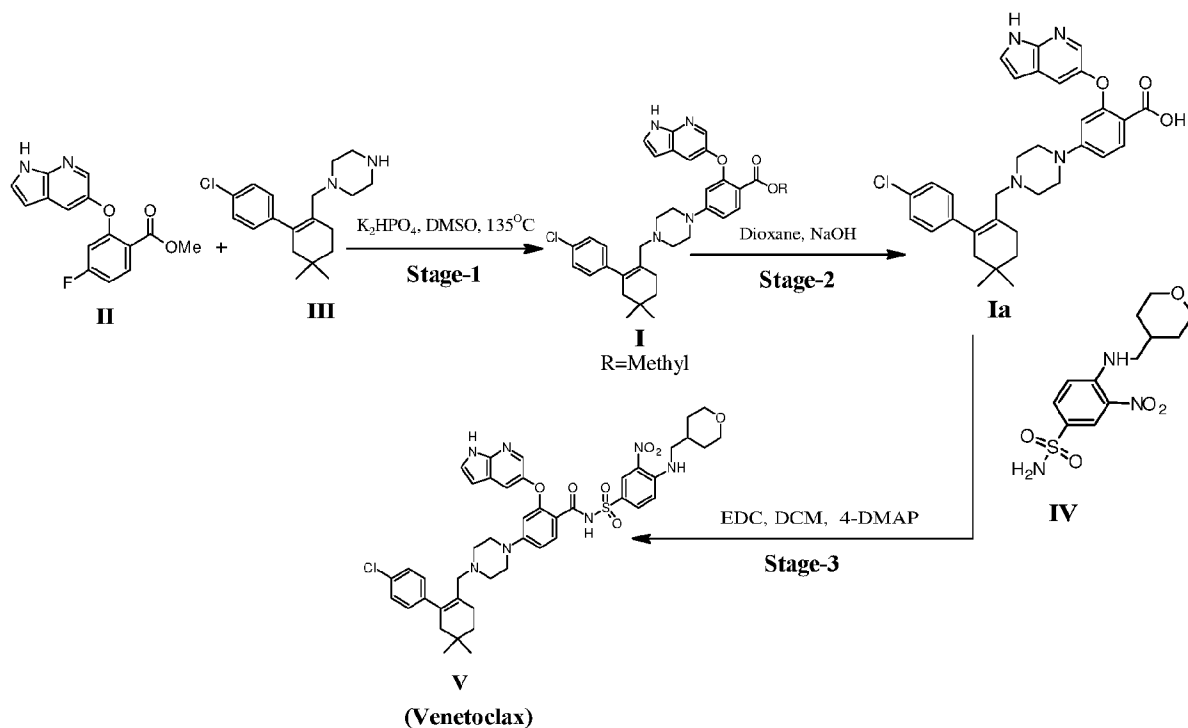
Formula V

Venetoclax (marketed under the trade name Venclexta, Abbvie Inc.) is an inhibitor of anti-apoptotic Bcl-2 proteins. It is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL).

- 10 Venetoclax, as represented by formula V, is disclosed in WO 2011/149492. Various processes for the preparation of venetoclax have been disclosed in literature.

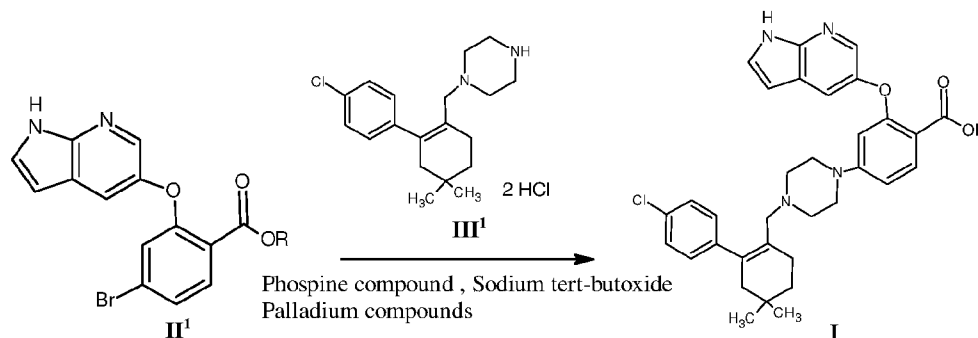
WO 2011/149492 and Bioconjugate Chemistry 2014, 2081 describe a process for the preparation of compound of formula V as depicted in scheme-1:

15



- 5 In stage-1, a reaction of the compound of formula II with the compound of formula III is carried out in the presence of dipotassium hydrogen phosphate (K_2HPO_4) at a temperature of 135 degree Celsius with stirring for about 24 hours. The compound of formula I obtained at stage-1, is purified by silica gel chromatography. The yield is ca. 37%. Purity is not reported.
- 10 In stage-2, the compound of formula I is hydrolysed to obtain a compound of formula Ia in the presence of sodium hydroxide and dioxane as a solvent.
- Subsequently, the compound of formula Ia is coupled with a compound of formula IV
- 15 to obtain the compound of formula V (stage-3).
- In stage-3, coupling of the compound of formula Ia with the compound of formula IV is performed in the presence of 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride (EDC-HCl) and 4-dimethylaminopyridine in dichloromethane. The obtained compound of formula V is purified by silica gel chromatography. The yield is
- 20 ca. 32%. Purity is not reported.

Another process for the synthesis of the compound of formula I is disclosed in WO 2014/165044,



Scheme-2

wherein R=t-Butyl

5

In WO 2014/165044, the preparation of the compound of formula I involves use of a phosphine compound and a palladium compound. The reaction of a compound of formula II¹ with a compound of formula III¹ is carried out in the presence of a phosphine compound, sodium tert-butoxide and Pd₂dba₃ at 55 to 75 degree Celsius to give the compound of formula I.

10

Sodium tert-butoxide and the compound of formula II¹ in toluene solution were combined in tetrahydrofuran in a suitable reactor and sparged with nitrogen for NLT 45 min.

15

Pd₂dba₃, phosphine and the compound of formula III¹ were combined in a second suitable reactor and purged with nitrogen until oxygen level was NMT 40 ppm.

Using nitrogen pressure, the solution containing the compound of formula II¹ and sodium tert-butoxide in toluene/tetrahydrofuran was added through a 0.45 µm inline filter to the second reactor.

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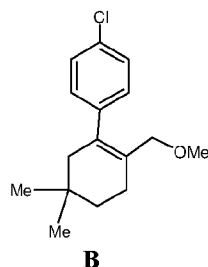
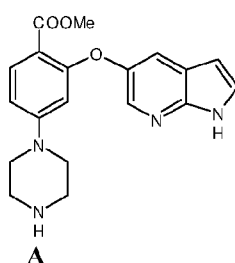
The compound of formula I was isolated by solvent-extractions using large volumes of solvents such as tetrahydrofuran, heptane and cyclohexane.

The process also requires use of amino acids such as L-cysteine. The product was crystallized by seeding. Thereby, the process disclosed in WO 2014/165044 is quite lengthy and complicated.

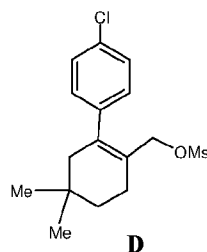
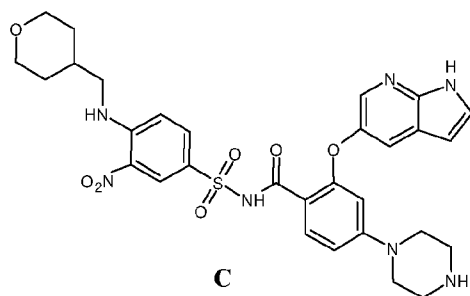
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There are other patent applications, such as CN 2014/10582048, CN 2017/1271772, WO 2017/156398 and WO2018/029711 which disclose the synthesis of the compound of formula I, used in the synthesis of the compound of formula V.

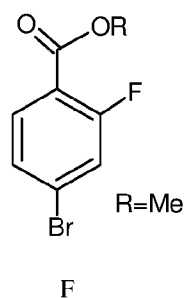
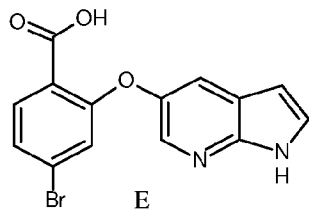
- 5 Chinese application CN 2014/10582048 discloses the synthesis of the compound of formula I, using intermediates of formula A and B,



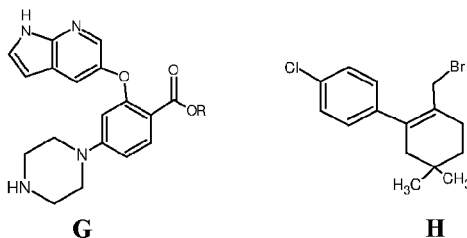
- 10 Chinese application CN 2017/1271772 discloses the synthesis of the compound of formula V using intermediates of formula C and D,



- 15 In WO 2017/156398, the authors disclose a process for the preparation of the compound of formula V by using intermediates of formula E and formula F,



In WO2018/029711, the compound of formula I is prepared using different intermediates of formula G and H.



5 wherein, R is C₁₋₄ alkyl.

From the forgoing, it is apparent that the reported methods for the preparation of the compound of formula V, require stringent operational conditions which are not only tedious but also result in significant yield loss. These processes require use of silica gel chromatography for purification. The work-up procedure also involves tedious solvent exchange methods for the isolation of compound of formula I. Moreover, use of palladium ligands in the synthesis of formula I makes it difficult to control the palladium content in the drug product within the recommended ICH limit i.e. <10 ppm.

Therefore, there remains a need to formulate an efficient, simple and industrially viable synthetic process which can overcome the drawbacks of the prior art as well as provide
15 the compound of formula V i.e. venetoclax and its intermediates in high yield and purity.

OBJECT OF THE INVENTION

It is an object of the present invention to overcome the above-mentioned drawbacks of
20 the prior art.

It is another objective of the present invention to provide a process for the synthesis of a compound of formula I.

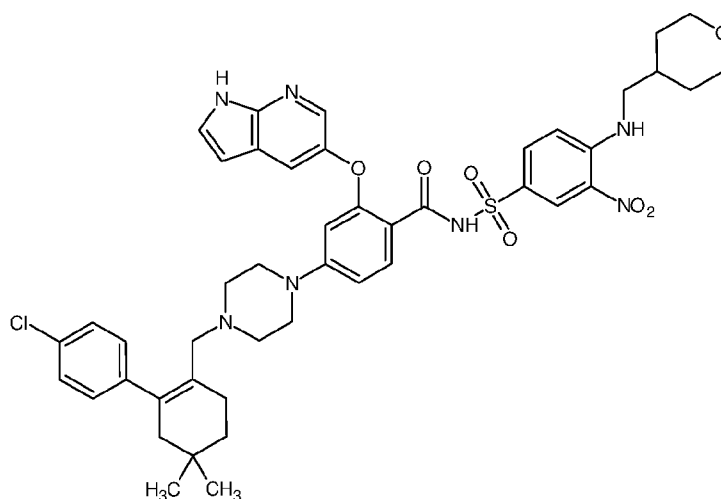
25 It is another objective of the present invention to avoid tedious and long work-up process for the synthesis of the compound of formula I or its salts.

It is yet another objective of the present invention to provide a process for the conversion of the compound of formula I or its salts to the compound of formula V.

- 5 It is further objective of the present invention to provide an improved and commercially viable process for the synthesis of the compound of formula V.

SUMMARY OF THE INVENTION

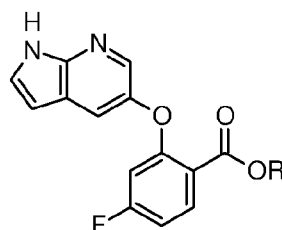
In first aspect, the present invention relates to a process for the preparation of the
10 compound of formula V,



Formula V

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comprising the reaction of a compound of formula II,

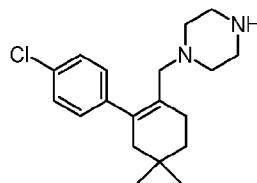


Formula II

wherein R is C₁₋₄ alkyl;

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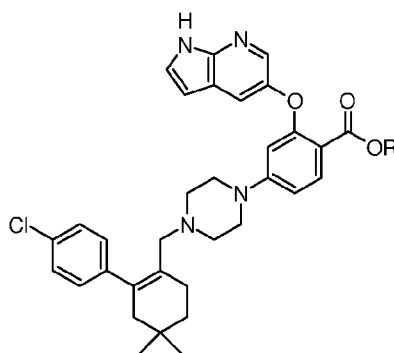
with a compound of formula III,



Formula III

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in the presence of an alkyl amine to obtain a compound of formula I or its salts,



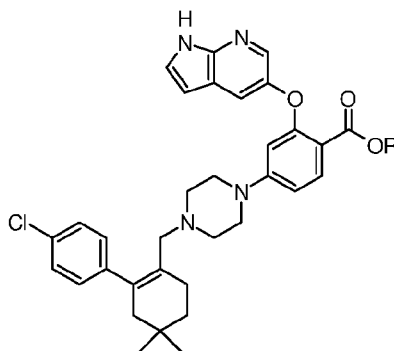
Formula I

10

wherein R is C₁₋₄ alkyl;

and converting the compound of formula I or its salts to the compound of formula V.

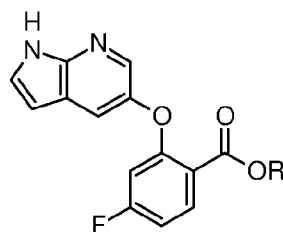
Another aspect of the present invention is to provide a process for the preparation of
15 compound of formula I or its salts,



Formula I

20

comprising the reaction of a compound of formula II,

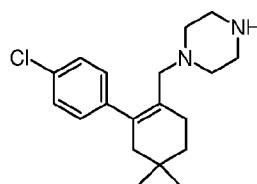


Formula II

5

wherein R is C₁₋₄ alkyl;

with a compound of formula III,



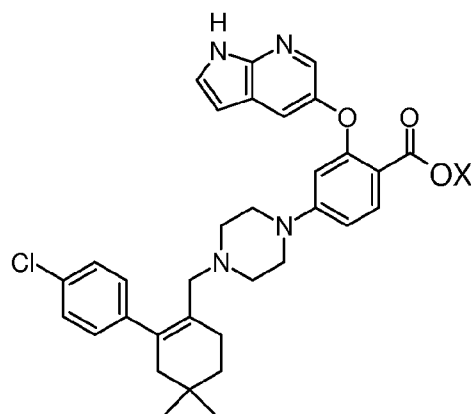
Formula III

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in the presence of an alkyl amine.

Another aspect of the present invention is to provide a compound of formula Ib.

15

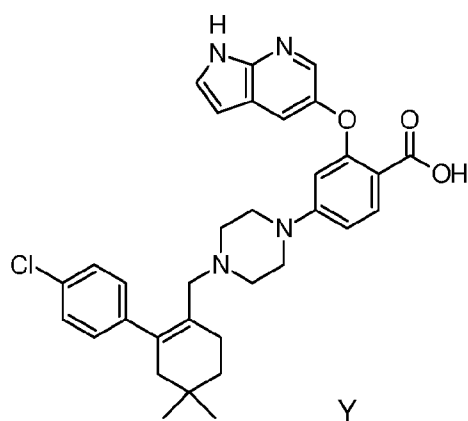


Formula Ib

wherein X= K, Na, Li

20

Another aspect of the present invention is to provide salts of the formula Ia represented as a compound of formula Ia¹,

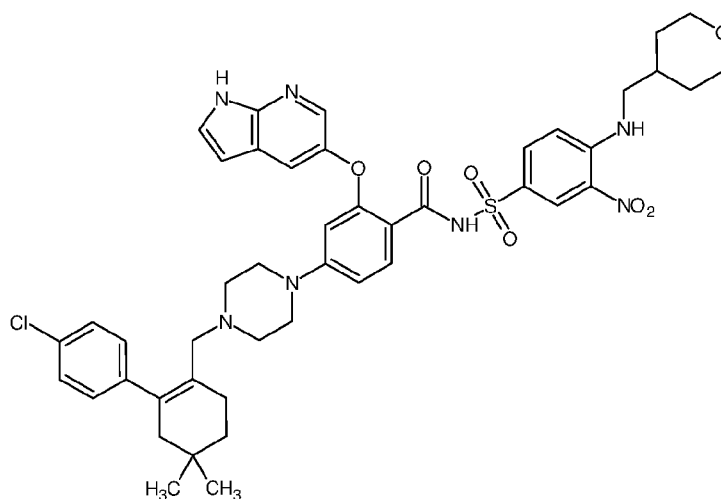
**Formula Ia¹**

- 5 wherein Y is hydrochloric acid, sulphuric acid, p-toluenesulphonic acid, trifluoroacetic acid, oxalic acid, dicyclohexylamine;

and to provide a process for their preparation.

10 DETAILED DESCRIPTION OF THE INVENTION

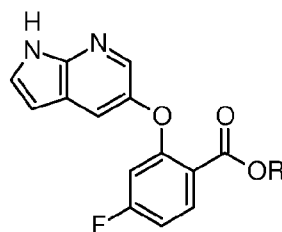
In one aspect, the present invention relates to a process for the preparation of a compound of formula V,

**Formula V**

15

comprising the steps of:

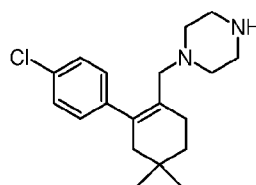
a) reacting a compound of formula II,



Formula II

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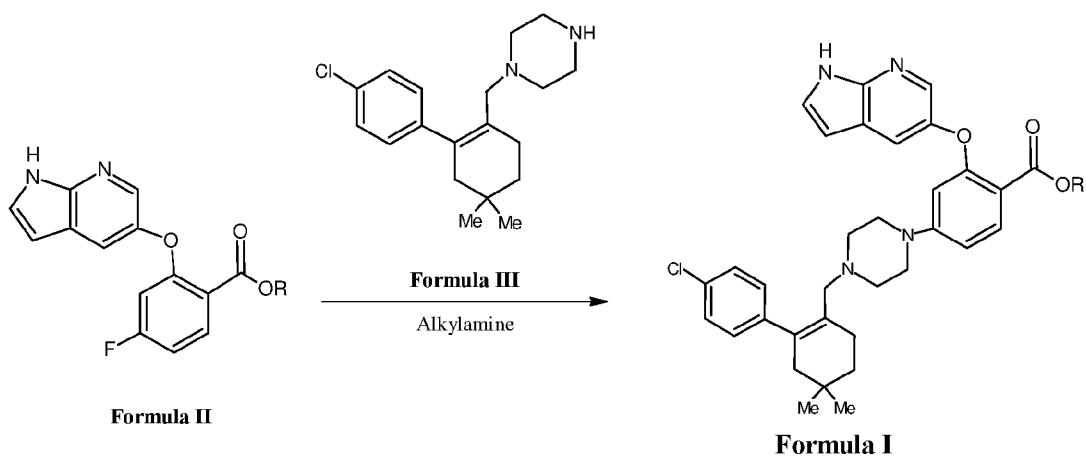
with a compound of formula III,



Formula III

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in the presence of an alkyl amine to obtain a compound of formula I or its salts,



Sc

heme-3

15

wherein R is C₁₋₄ alkyl;

b) converting the compound of formula I or its salts to a compound of formula V.

The C₁₋₄ alkyl is selected from methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl and t-butyl, preferably methyl.

20

The alkylamine may be selected from the group consisting of N,N-diisopropylethylamine (DIPEA), trimethylamine (Me₃N), triethylamine (Et₃N), N,N-dimethylaniline (DMA), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5-Diazabicyclo [4.3.0]non-5-ene (DBN),
5 preferably N,N-diisopropylethyl amine (DIPEA).

The reaction is preferably carried out in the presence of an aprotic solvent selected from the group consisting of dichloromethane, dimethylsulphoxide, chloroform, acetone,
10 acetonitrile, tetrahydrofuran, dimethylformamide, N-methyl pyrrolidine, dioxane, nitromethane, pyridine, 2-methyltetrahydrofuran and mixtures thereof. Most preferably, the reaction is carried out in dimethylsulphoxide (DMSO).

The reaction is preferably carried out at 90 to 120 degree Celsius, more preferably at 95
15 to 105 degree Celsius.

In a preferred embodiment, the compound of formula II, wherein R is methyl, is reacted with the compound of formula III, in the presence of a suitable alkylamine such as N,N-diisopropylethylamine and a suitable solvent such as dimethylsulphoxide. Preferably,
20 the reaction is carried out at 90 to 115 degree Celsius, more preferably at 95 to 105 degree Celsius. The reaction mixture is stirred for 24-28 hours at the same temperature to obtain the compound of formula I.

The salt of the compound of formula I is typically prepared by reacting the compound
25 of formula I with an acid selected from the group consisting of hydrochloric acid, sulphuric acid, p-toluenesulphonic acid, trifluoroacetic acid and oxalic acid. Preferably, the salt of the compound of formula I is the hydrochloride salt.

The salt of the compound of formula I is preferably prepared in the presence of a
30 solvent selected from methanol, ethanol, water, ethyl acetate, acetone and dichloromethane or a mixture thereof, more preferably methanol.

In a preferred embodiment, the salt of the compound of formula I is prepared by reacting the compound of formula I with a suitable acid such as concentrated

hydrochloric acid in a suitable solvent such as methanol to give the hydrochloride salt of the compound of formula I.

The methods for the preparation of the compound of formula I as reported in the prior arts such as WO 2011/149492 involve the use of palladium reagents which require long and tedious work-up procedures for the isolation and purification of the product. Other processes such as disclosed in WO 2014/165044 involve the use of silica gel column chromatography for purifications which result in significant yield loss.

10 The inventors of the present invention found that using an alkylamine such as diisopropylethyl amine (DIPEA) in the preparation of the compound of formula I, surprisingly improves the yield at the first stage and the high yield of the compound of formula I or its salts, effects the further stages of the synthesis of venetoclax and as a result venetoclax is obtained in significantly higher yield and purity without
15 cumbersome isolation or chromatographic purifications.

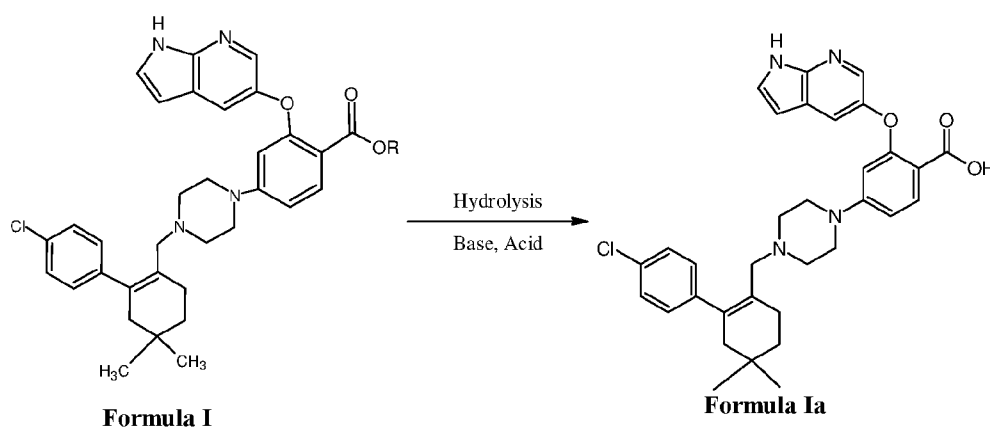
In some embodiments, the yield of the compound of formula I or a salt thereof is 60% or greater, e.g., 70% or greater, 80% or greater, or 90% or greater. In other embodiments, the yield of the compound of formula I or a salt thereof is 95% or less,
20 e.g., 85% or less, 75% or less, or 65% or less. In yet other embodiments, the yield of the compound of formula I or a salt thereof is in a range of any of the forgoing values, e.g., 60%-95%, 60%-85%, 60%-75%, 70%-95%, 70%-85%, or 80%-95%.

The invention also provides the compound of formula I or a salt thereof in a highly purified form. In some embodiments, the purity of the compound of formula I or a salt thereof is 95% or greater, e.g., 97% or greater, 99.0% or greater, 99.4% or greater, or
25 99.8% or greater. In other embodiments, the purity of the compound of formula I or a salt thereof is 99.9% or less, e.g., 99.6% or less, 99.3% or less, 98.5% or less, or 97.5% or less. In yet other embodiments, the purity of the compound of formula I or a salt thereof is in a range of any of the forgoing values, e.g., 95%-99.3%, 97%-98.5%, 97%-
30 99.9%, 99.0%-99.6%, 99.0%-99.9%, or 99.4%-99.9%. In a particularly preferred embodiment, the yield of the hydrochloride salt of the compound of formula I is 74.14% and the purity 99.3%.

The compound of formula I or its salts can be further converted to the compound of formula V by processes well known in the prior art.

In the same aspect, the present invention relates to the conversion of the compound of formula I or its salts to the compound of formula V.

In an embodiment, the compound of formula I or its salt is hydrolyzed to the compound of formula Ia,



Scheme-4

wherein R is C₁₋₄ alkyl

The hydrolysis of the compound of formula I or its salts is preferably carried out in presence of a base selected from potassium hydroxide, lithium hydroxide and sodium hydroxide or a mixture thereof, preferably potassium hydroxide.

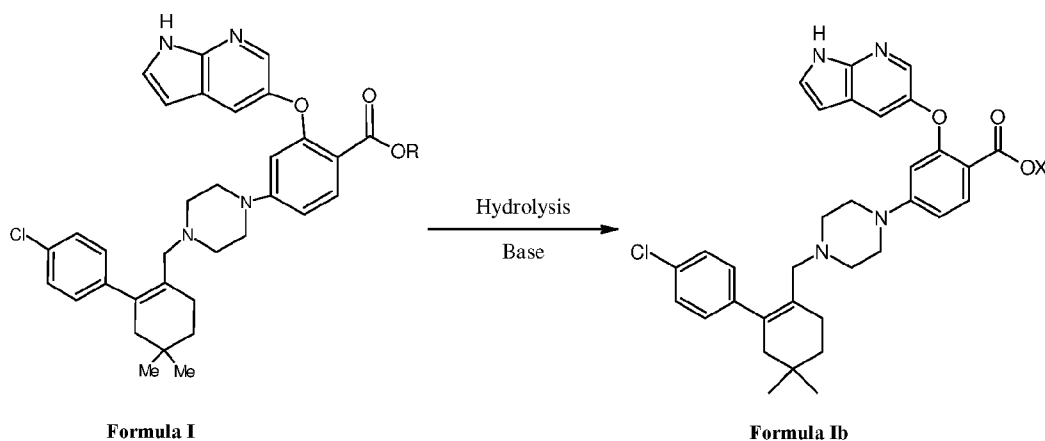
The compound of formula I or its salts is preferably hydrolyzed in presence of a solvent selected from methanol, ethanol, water, ethyl acetate and dichloromethane or a mixture thereof, preferably methanol.

The acid is preferably selected from the group consisting of hydrochloric acid, sulphuric acid, p-toluenesulphonic acid, trifluoroacetic acid and oxalic acid, more preferably hydrochloric acid.

The compound of formula I or its salts is preferably hydrolyzed at a temperature of 55-80 degree Celsius.

In a preferred embodiment, the compound of formula I or its salts is hydrolyzed in the presence of a suitable base such as aqueous potassium hydroxide and a suitable solvent such as methanol and a suitable acid such as hydrochloric acid to obtain the compound of formula Ia at a temperature of 60-75 degree Celsius.

In an embodiment, the hydrolysis of the compound of formula I to the compound of
10 formula Ia comprises reacting compound of formula I or its salts
with a base in a solvent to obtain a compound of formula Ib.



Scheme-5

wherein X= K, Na, Li

The base is preferably selected from potassium hydroxide, lithium hydroxide and sodium hydroxide or a mixture thereof, more preferably potassium hydroxide.

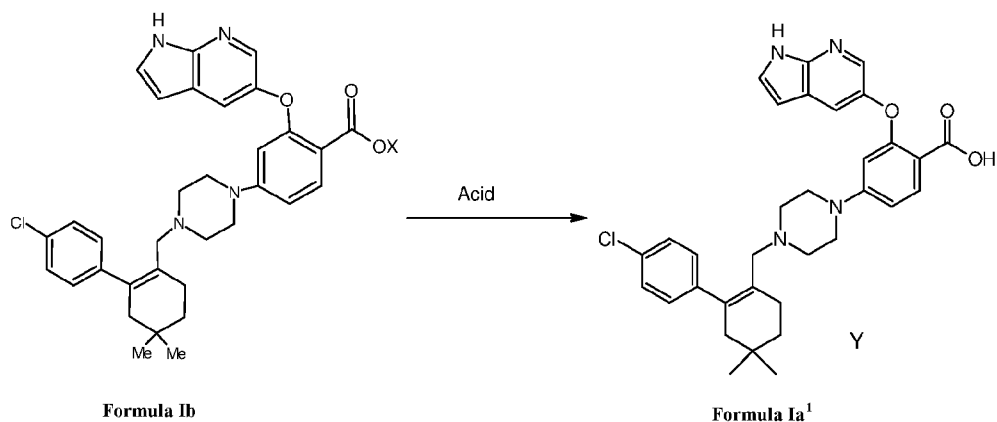
The solvent is preferably selected from methanol, ethanol, water, ethyl acetate and dichloromethane or a mixture thereof, more preferably methanol.

The compound of formula Ib wherein X is Na can also prepared by treating the
25 compound of formula Ia with sodium 2-ethylhexenoate.

In a preferred embodiment, the compound of formula I or its salts is hydrolyzed in the presence of a suitable base such as potassium hydroxide and a suitable solvent such as methanol to obtain the compound of formula Ib, wherein X is potassium.

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In another embodiment, the compound of formula Ib is isolated and converted to the compound of formula Ia¹ by treating with an acid,



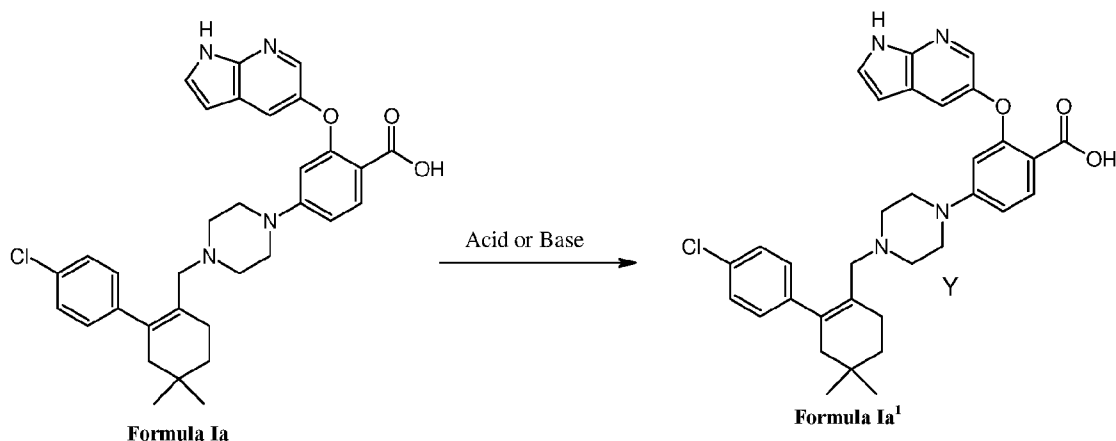
Scheme-6

wherein X= K, Na, Li and Y is hydrochloric acid, sulphuric acid, p-toluenesulphonic acid, trifluoroacetic acid, oxalic acid, dicyclohexylamine

15 The acid is preferably selected from the group consisting of hydrochloric acid, sulphuric acid, p-toluenesulphonic acid, trifluoroacetic acid and oxalic acid, more preferably hydrochloric acid.

In a preferred embodiment, the compound of formula Ib is isolated and treated with a
20 suitable acid such as hydrochloric acid to obtain the compound of formula Ia¹, wherein
Y is hydrochloric acid.

In another embodiment, the compound of formula Ia is converted into the compound of formula Ia¹ by treating with an acid or a base, typically in the presence of a solvent,

**Scheme-7**

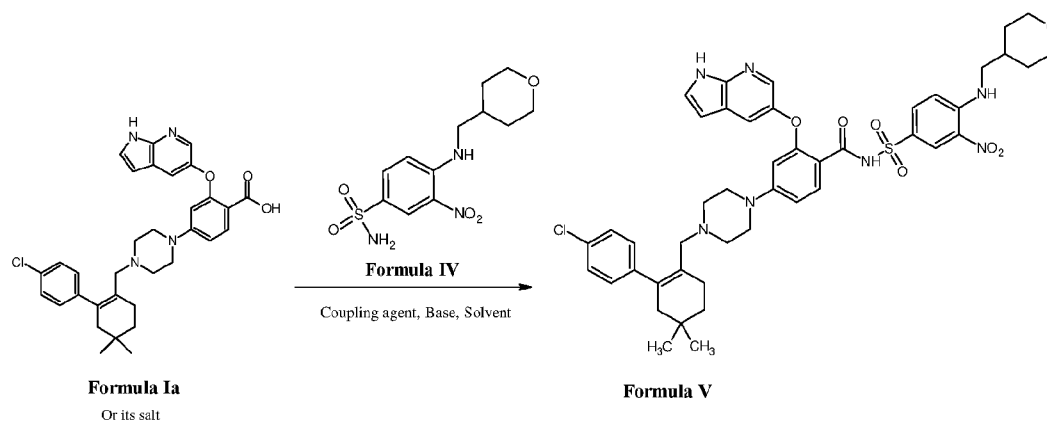
wherein Y is hydrochloric acid, sulphuric acid, p-toluenesulphonic acid trifluoroacetic
 5 acid, oxalic acid, dicyclohexylamine.

- The acid is preferably selected from hydrochloric acid, sulphuric acid, p-toluenesulphonic acid, trifluoroacetic acid and oxalic acid.
- 10 The base is preferably dicyclohexylamine.

- The solvent is preferably selected from ethyl acetate, acetone, methanol, water or a mixture thereof. More preferably, the solvent is methanol.
- 15 In a preferred embodiment, the compound of formula Ia is treated with a suitable acid such as hydrochloric acid to obtain its hydrochloride salt.

- In an embodiment, the compound of formula Ia or its salt is reacted with a compound of formula IV,

20



Scheme-5

The reaction is typically carried out in presence of a suitable coupling agent.

5

The suitable coupling agent may be selected from the group consisting of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC HC1), dicyclohexylcarbodiimide (DCC), O-benzotriazole-N,N',N'-tetramethyl uronium hexafluoro phosphate (HBTU) and benzotriazol-1-yloxypyrrolidinophosphonium hexafluorophosphate (PyBOP), preferably 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC HC1).

10

The reaction is carried out in presence of a suitable base.

The suitable base may be selected from the group consisting of triethylamine, N,N-diisopropylethylamine, 4-dimethylaminopyridine, N,N dimethylethylenediamine or mixture thereof.

15

The reaction is preferably carried out in presence of a suitable solvent.

20

The suitable solvent may be selected from the group consisting of dichloromethane, chloroform, acetone, acetonitrile, tetrahydrofuran, dimethylformamide, N-methyl pyrrolidine, dioxane, nitromethane, pyridine and 2-methyltetrahydrofuran, preferably dichloromethane.

25

The compound of formula Ia or its salts is preferably reacted with a compound of formula IV at a temperature of 20-35 degree Celsius.

In a preferred embodiment, the compound of formula Ia or its salts is reacted with a compound of formula IV in presence of a suitable base such as triethylamine, 4-dimethylaminopyridine and N,N dimethylethylenediamine and a suitable coupling agent
5 such as N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC-HCl), preferably in presence of a suitable solvent such as dichloromethane, preferably at a temperature of 25-30 degree Celsius.

10 Thus, in one aspect, the invention provides the compound of formula I in significantly high yield and purity as compared to the prior art methods without using complicated isolation and purification processes and in a further aspect, the compound of formula I is converted to the compound of formula V in high yield and purity with ease of procedure and less complexity.

15

In some embodiments, the yield of the compound of formula V is 60% or greater, e.g., 70% or greater, 80% or greater, or 90% or greater. In other embodiments, the yield of the compound of formula V is 95% or less, e.g., 85% or less, 75% or less, or 65% or less. In yet other embodiments, the yield of the compound of formula V is in a range of
20 any of the forgoing values, e.g., 60%-95%, 60%-85%, 60%-75%, 70%-95%, 70%-85%, or 80%-95%.

The invention also provides the compound of formula V in a highly purified form. In some embodiments, the purity of the compound of formula V is 95% or greater, e.g., 97% or greater, 99.0% or greater, 99.4% or greater, or 99.8% or greater. In other
25 embodiments, the purity of the compound of formula V is 99.9% or less, e.g., 99.6% or less, 99.3% or less, 98.5% or less, or 97.5% or less. In yet other embodiments, the purity of the compound of formula V is in a range of any of the forgoing values, e.g., 95%-99.3%, 97%-98.5%, 97%-99.9%, 99.0%-99.6%, 99.0%-99.9%, or 99.4%-99.9%. In a particularly preferred embodiment, the yield of the compound of formula V is
30 70.0%, and the purity is 99.7%.

The process of the present invention is advantageous in the respect that it is economical, industrially viable and commercially favourable. Further, the process of the present invention does not involve use of palladium, hence making the process more attractive.

5

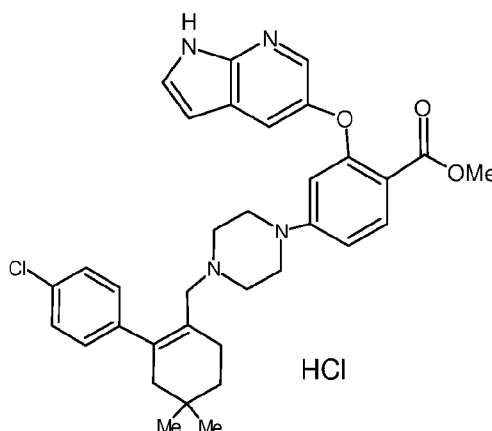
EXPERIMENTAL

Detailed experimental parameters according to the present invention are provided by the following examples, which are intended to be illustrative and not limiting of all possible embodiments of the invention.

Examples

Example-1

Preparation of methyl 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-benzoate. HCl.



A mixture of methyl 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-fluorobenzoate (500.0 g), 1-((4'-Chloro-5,5-dimethyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)-methyl)piperazine (1114.0 g) and N,N-diisopropylethylamine (225.8 g) in dimethylsulphoxide (1500 mL) was heated to 90 to 105 degree Celsius for 26h. The reaction mixture was diluted with ethyl acetate (2500 ml) and washed with water (2500 mL). The organic layer was concentrated under vacuum. The residue was taken up in methanol (2500 mL) at 60 to 65 degree Celsius and cooled to 20 to 30 degree Celsius

and stirred for 4h, followed by 0 to 5 degree Celsius for 3h. The resulting slurry was filtered and washed with cold methanol (500 mL). The filtered solid was treated with concentrated hydrochloric acid (218.3 g) in methanol (3200 mL) followed by addition of water (1600 mL). The resulting slurry was cooled to 0 to 5 degree Celsius, filtered and washed with a 2:1 mixture of methanol-water and the solid dried under vacuum at 50 to 60 degree Celsius for 16 h to provide methyl 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-benzoate. HCl.

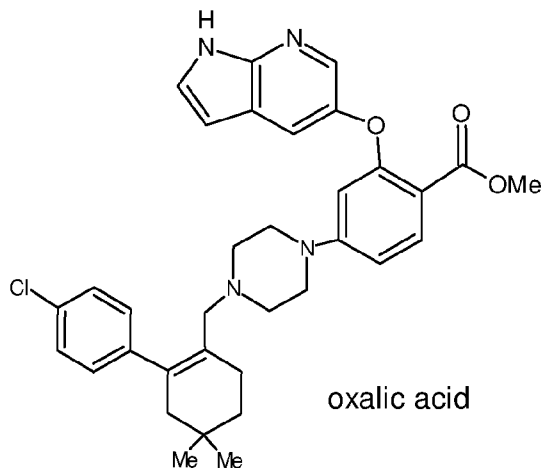
Yield: 74.14% (805g)

HPLC Purity: ~99.3%

¹H NMR data-(DMSO-d₆): δ 0.942 (s, 6H), 1.444 (t, J=6.4 Hz, 2H), 2.014 (s, 2H), 2.366 (t, br, 2H), 2.723 (d, 2H), 3.281 (m, 4H), 3.702 (m, 2H), (m, d, J=12.8 Hz, 8H), 3.542 (s, 2H), 3.659 (s, 3H), 6.385 (dd, J= 1.6, 2.0, 3.2, 3.6Hz, 1H), 6.414-6.420 (d, J=2.4Hz, 1H), 6.776 (dd, J=2.4, 9.2Hz, 1H), 7.105 (d, J=8.4Hz, 2H), 7.395 (d, J=8.4Hz, 2H), 7.438 (d, J=2.0, 1H), 7.483 (t, J=2.8Hz, 1H), 7.781 (d, J=9.2Hz, 1H), 7.999 (d, J=2.8Hz, 1H), 10.752 (s, br, 1H), 11.666 (s, 1H).

Example-1a

Preparation of methyl 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-benzoate. oxalic acid salt.



A mixture of methyl 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-benzoate (5.0 g) in acetone (50 mL) was treated with oxalic acid solution (1.53 g oxalic acid in 50 mL of acetone) and stirred at 30-35 degree Celsius for 2-3h followed by 20-30 degree Celsius for 4-5h. The resulting slurry was filtered, washed with acetone (25 mL) and the solid dried under vacuum at 40-45 degree Celsius for 16 h to furnish the oxalate salt of methyl 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-benzoate. oxalic acid salt.

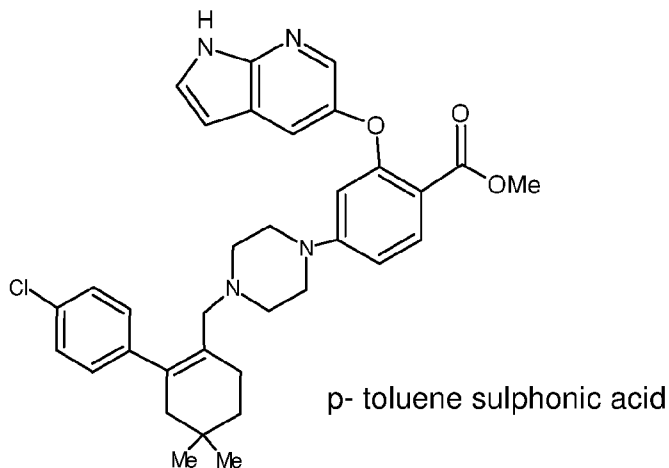
Yield: 29.46% (1.7g)

HPLC Purity: 77.24%

¹H NMR (DMSO-d₆): δ 0.93 (s, 6H), 1.41 (t, J=5.6 Hz, 2H), 1.98 (s, 2H), 2.18 (t, br, 2H), 2.42 (m, 4H), 2.97 (s, 2H), 3.21 (m, 4H), 3.65 (s, 3H), 6.37 (dd, J=1.6, 3.2 Hz, 2H), 6.74 (dd, J=2.0, 2.4 Hz, 1H), 7.08 (m, 2H), 7.34 (m, 2H), 7.42 (d, J=2.8 Hz, 1H), 7.47 (t, J=2.8, 2.4 Hz, 1H), 7.74 (d, J=8.8 Hz, 1H), 7.99 (d, J=2.4 Hz, 1H), 11.63 (s, 1H, NH).

Example-1b

Preparation of methyl 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-benzoate. p-toluenesulfonic acid salt.



A mixture of methyl 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-benzoate (1.0 g) in acetone (10 mL) was treated with p-toluenesulfonic acid monohydrate (0.65 g) and stirred at 20-30 degree Celsius for 4-5h. The resulting slurry was filtered, washed with acetone (10 mL) and the solid dried under vacuum at 45-50 degree Celsius for 16 h to furnish the methyl 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-benzoate. p-toluenesulfonic acid salt.

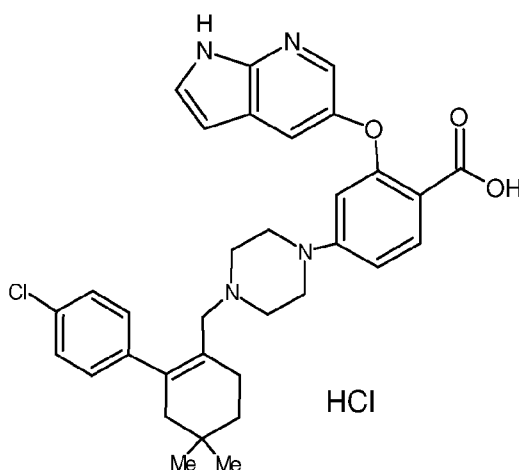
Yield: 91.05 % (1.12 g)

HPLC Purity: 98.08%

¹H NMR (DMSO-d₆): δ 0.95 (s, 6H), 1.44 (t, 2H), 1.99 (s, 1H), 2.03 (s, 2H), 2.21 (t, br, 2H), 2.29 (s, 6H), 2.75 (m, 2H), 3.08 (m, 2H), 3.28 (m, 2H), 3.60 (m, 2H), 3.66 (s, 3H), 3.74 (m, 2H), 6.36 (dd, J=2.0 Hz, 2H), 6.77 (dd, J=2.4 Hz, 1H), 7.08 (m, 6H), 7.39 (d, J=8.0 Hz, 2H), 7.49 (m, 5H), 7.78 (d, J=9.2 Hz, 1H), 7.99 (d, J=2.8 Hz, 1H), 11.68 (s, 1H, NH).

Example-2

2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)benzoic acid HCl.



A mixture of methanol (2.0 L), methyl 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl) piperazin-1-yl)-

benzoate hydrochloride (200.0 g), potassium hydroxide (106.2 g) and water (400 mL) was heated to 65 to 75 degree Celsius for 9h. The reaction mixture was diluted with water and the product was extracted with dichloromethane (2.0 L). The dichloromethane layer was then diluted with acetone (1.0 L) and was treated with concentrated hydrochloric acid (67.0 g) and stirred at 20 to 30 degree Celsius. The resulting slurry was filtered and the solid cake was successively washed with 2:1 mixture of dichloromethane-acetone (300mL), water (3.0 L) and acetone (200 mL). The solid was dried under vacuum at 50 to 60 degree Celsius for 16 h to provide 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)benzoic acid hydrochloride.

Yield: 92.08% (180g)

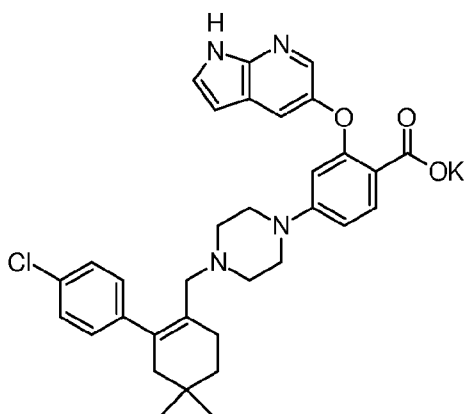
HPLC Purity: ~99.36 %

15 ¹H NMR data-(DMSO-d₆): δ 0.947 (s, 6H), 1.452 (t, J=6.4Hz, 2H), 2.020 (s, 2H),
2.337 (t, br, 2H), 2.743 (d, 2H), 3.301 (m, 4H), 3.670 (m, 2H), 3.559 (d, J=4.0Hz, 2H),
6.378 (dd, J=1.6, 2.0, 3.2, 3.6Hz, 1H), 6.408 (d, J=2.0Hz, 1H), 6.761 (dd, J=2.4, 8.8Hz,
1H) 7.106 (d, J=8.8Hz, 2H), 7.40 (d, J=8.4Hz, 2H), 7.406 (s, 1H), 7.476 (t, J=2.8,
3.2Hz, 1H), 7.778 (d, J=9.2Hz, 1H), 7.985 (d, J=2.4Hz, 1H), 10.431 (s, br, 1H), 11.634
20 (s, 1H), 12.266 (s, br, 1H).

Example-2a

Preparation of Potassium 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)benzoate.

25



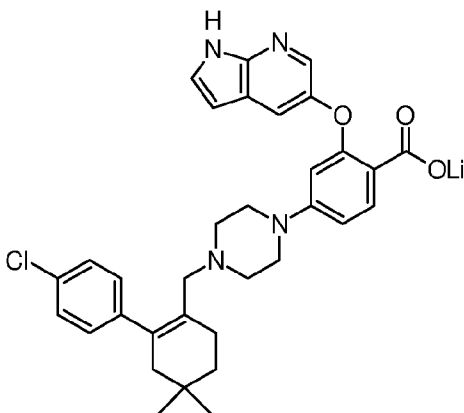
A mixture of methanol (130.0 L), methyl 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-benzoate. HCl (10.0 g), potassium hydroxide (10.6 g) and distilled water (20 mL) was heated to 60-70 degree Celsius for 3h. The reaction mixture was diluted with distilled water (40 ml) and extracted the product with dichloromethane (60.0 L). The dichloromethane layer was distilled out completely followed by slurry formation in acetone (80.0 L). The resulting slurry was filtered and the solid cake was washed with acetone (20mL). The solid was dried under vacuum at 30-35 degree Celsius for 17 h to furnish Potassium 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)benzoate.

Yield: 78.9% (4.10 g).

HPLC Purity: 94.0%

15 Example-2b

Preparation of Lithium 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)benzoate.



20

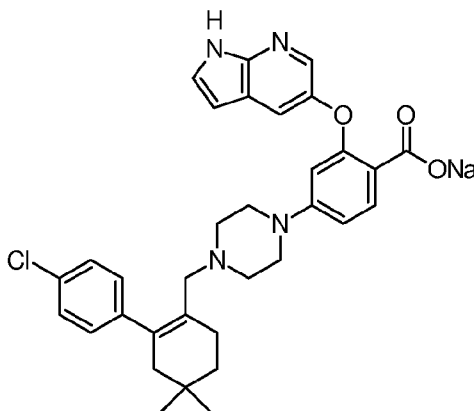
A mixture of methanol (65.0 L), methyl 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)-benzoate. HCl (5.0 g), lithium hydroxide (3.37 g) and distilled water (10 mL) was heated to 60-70 degree Celsius for 3h. The reaction mixture was diluted with distilled water (40 ml) and extracted the product with dichloromethane (60.0 L). The dichloromethane layer was distilled out completely followed by slurry formation in acetone (50.0 L). The resulting slurry was filtered and the solid cake was washed with

acetone (10mL). The solid was dried under vacuum at 35-40 degree Celsius for 17 h to furnish Lithium 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)benzoate.

5 Yield: 64.2 % (1.58 g)

Example-2c

Preparation of Sodium 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)benzoate.



10

A solution of sodium-2-ethylhexenoate (0.32 g) in ethyl acetate (5 mL) was added to a mixture of 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)benzoic acid (1.0 g) in ethyl acetate (5 mL) and stirred at 20-30 degree Celsius. The resulting slurry was filtered, washed with ethyl acetate (5 mL) and the solid was dried under vacuum at 50-55 degree Celsius for 16 h to furnish sodium 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)benzoate.

20

Yield: 57.80% (0.6g)

HPLC Purity: 96.97%

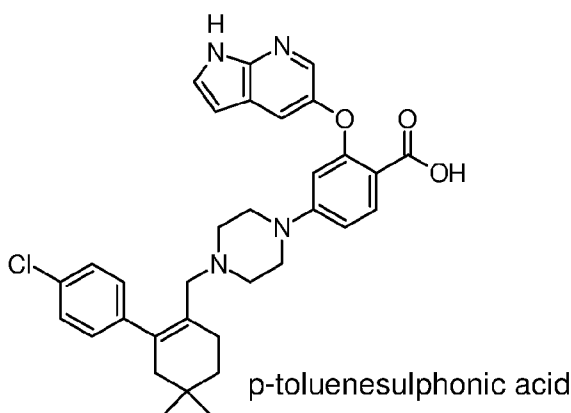
25

¹H NMR (DMSO-d₆): δ 0.93 (s, 6H), 1.37 (t, J= 6.4 Hz, 2H), 1.96 (s, 2H), 2.16 (t, br, 2H), 2.21 (m, 4H), 2.73 (s, 2H), 2.97 (s, 4H), 6.26 (dd, J=2.0, 1.2 Hz, 2H), 6.57 (dd, J=1.6, 2.0, Hz, 1H), 7.05 (d, J=8.4, 2H), 7.29 (d, J=2.8 Hz, 1H), 7.34 (d, J=8.4 Hz, 2H),

7.38 (t, J=2.8 Hz, 1H), 7.45 (d, J=8.8 Hz, 1H), 7.94 (d, J=2.8 Hz, 1H), 11.49 (s, 1H, NH).

5 Example-2d

Preparation of 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)benzoic acid. p - toluenesulfonic acid salt.



10

A mixture of 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)benzoic acid (2.0 g) in acetone (20 mL) was treated with p-toluenesulfonic acid monohydrate (1.33 g) and stirred at 20-30 degree Celsius for 4-5h. The resulting slurry was filtered, washed with acetone (10 mL) and the solid was dried under vacuum at 45-50 degree Celsius for 16 h to furnish 2-((1H-pyrrolo [2,3-b] pyridin-5-yl)oxy)-4 -(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-bi phenyl]-2-yl) methyl)piperazin-1-yl) benzoic acid. p - toluenesulfonic acid salt.

20 Yield: 86.92 % (2.26 g)

HPLC Purity: 97.88%

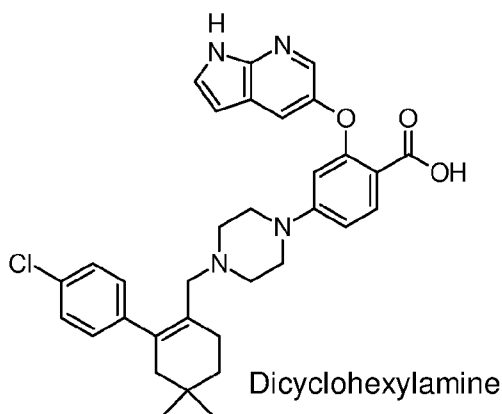
¹H NMR (DMSO-d₆): δ 0.95 (s, 6H), 1.43 (t, J=2.0, 2.4 Hz, 2H), 2.03 (s, 2H), 2.21 (t, br, 2H), 2.29 (s, 6H), 2.77 (m, 2H), 3.09 (m, 2H), 3.29 (m, 2H), 3.61 (m, 2H), 3.74 (m, 2H), 6.42 (m, 2H), 6.76 (dd, J=2.0 Hz, 2H), 7.09 (m, 6H), 7.39 (d, J=8.4 Hz, 2H), 7.50 (t, 5H), 7.78 (d, J=9.2 Hz, 1H), 8.03 (d, J=2.4 Hz, 1H), 11.74 (s, 1H, NH).

25

Example-2e

Preparation of 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)benzoic acid dicyclohexylamine salt.

5



A mixture of (7:3) acetone-methanol (3 mL), 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)benzoic acid (0.5 g) and dicyclohexylamine (0.19 g) was stirred at 20-30 degree Celsius for 3-4h. The resulting slurry was filtered, washed with (7:3) acetone-methanol (2 mL) and the solid was dried under vacuum at 40-50 degree Celsius for 16 h to furnish 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)benzoic acid dicyclohexylamine salt.

15

Yield: 60.6 % (0.4 g)

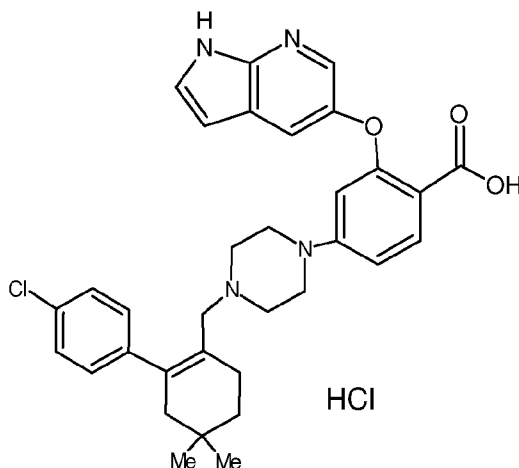
HPLC Purity: 97.2 %

¹H NMR (DMSO-d₆): δ 0.93 (s, 6H), 1.08 (m, 6H), 1.15 (m, 4H), 1.39 (t, J=6.0, 6.4 Hz, 2H), 1.50 (d, J=12.4 Hz, 2H), 1.60 (d, J=13.2 Hz, 4H), 1.77 (d, J=10.8 Hz, 4H), 2.16 (m, br, 6H), 2.58 (m, 2H), 2.73 (s, 2H), 3.04 (s, 4H), 6.31 (d, J=2.8 Hz, 2H), 6.64 (d, J=7.6, Hz, 1H), 7.04 (d, J=8.0 Hz, 2H), 7.33 (d, J=8.0 Hz, 3H), 7.41 (s, 1H), 7.60 (d, J=8.8 Hz, 1H), 7.95 (d, J=2.0 Hz, 1H), 11.55 (s, 1H, NH)

25

Example-3

Preparation of 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)benzoic acid. HCl.



5

A mixture of dichloromethane (30.0 L), Potassium 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)benzoate (3.0 g) and acetone (15 mL) was treated with conc. hydrochloric acid (1.0 g) and stirred at 20-30 degree Celsius. The resulting slurry was filtered and the solid cake was successively washed with 2:1 mixture of dichloromethane -acetone (9mL), distilled water (51.0 L) and acetone (3.0mL). The solid was dried under vacuum at 50-60 degree Celsius for 16 h to furnish the 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro 1,1'-biphenyl]-2-yl)methyl)piperazin-1-yl)benzoic acid. HCl.

Yield: 91.3 % (2.72 g)

20

Example-4

Preparation of 4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}-piperazin-1-yl)-N-({3-nitro-4[(tetrahydro-2H-pyran-4yl)methyl]amino}-phenyl)sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide (Compound of

25 **Formula V)**

A mixture of dichloromethane (12.0 L), 2-((1H-pyrrolo[2,3-b]pyridin-5-yl)oxy)-4-(4-((4'-chloro-5,5-dimethyl-3,4,5,6-tetrahydro[1,1'-biphenyl]-2-yl)methyl) piperazin-1-yl)benzoic acid hydrochloride (600.0 g), triethylamine (299.79 g), 4-dimethylaminopyridine (180.97 g), 3-nitro-4-(((tetrahydro-2H-pyran-4-yl)methyl)amino)benzenesulfonamide (342.56 g) and N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (283.97 g) was stirred at 25 to 30 degree Celsius for 8h. The reaction mixture was treated with N,N-dimethylethylenediamine (217.63 g) at 20 to 30 degree Celsius and stirred for 4h. The organic layer was washed with water (6.0 L) and concentrated under vacuum. The residue was dissolved in dichloromethane-methanol mixture (1:5) (7.2 L) and treated with acetic acid-methanol mixture (415.11 g acetic acid and 600 mL methanol) and stirred at 20 to 30 degree Celsius. The resulting slurry was cooled to 0 to 5 degree Celsius, filtered and washed with methanol (600 mL). The solid was dissolved in (9:1) mixture of dichloromethane-methanol (4.8 L) at 35 to 45 degree Celsius, diluted with methanol (1680 mL) and stirred for 8h at 20 to 30 degree Celsius. The resulting slurry was cooled to 0 to 5 degree Celsius, filtered, washed with methanol (600 mL) and the solid was dried under vacuum at 60 to 65 degree Celsius for 18 h to provide 4-(4-([2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl})-piperazin-1-yl)-N-({3-nitro-4[(tetrahydro-2H-pyran-4ylmethyl)amino]-phenyl} sulfonyl)-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy)benzamide.

20

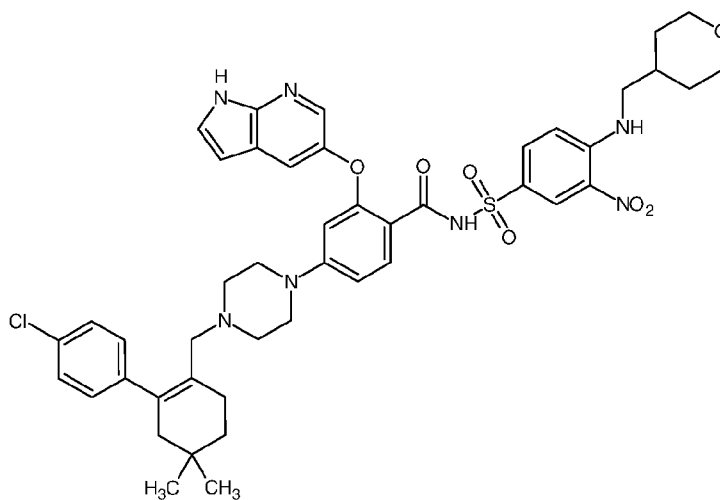
Yield: 70.0% (600g)

HPLC Purity: ~99.9%

¹H NMR data-(DMSO-d₆): δ 0.921 (s, 6H), 1.204-1.308, 1.598-1.626 (m, d, J=11.2Hz, 4H), 1.382 (t, J=6.4Hz, 4H), 1.883 (m, 1H), 1.951 (s, 2H), 2.144 (t, br, 2H), 2.199 (s, br, 4H), 2.754 (s, 2H), 3.073 (s, br, 4H), 3.237-3.291, 3.829-3.865 (m, dd, J=2.8, 3.2, 11.2, 11.6Hz, 6H), 6.189 (d, J=2.0Hz, 1H), 6.388 (dd, J=2.0, 3.6Hz, 1H), 6.678 (d, J=2.0, 2.4, 9.2, 9.6Hz, 1H), 7.037 (d, J=8.8Hz, 2H) 7.11 (d, J=9.2Hz, 1H), 7.34 (d, J=8.0Hz, 2H), 7.495 (m, 2H), 7.535 (d, J=2.4Hz, 1H), 7.801 (dd, J=2.0, 2.4, 8.8, 9.2Hz, 1H), 8.038 (d, J=2.0Hz, 1H), 8.558 (d, J=2.4Hz, 1H), 8.598 (t, 1H), 11.366 (s, br, 1H), 11.679 (s, 1H).

WE CLAIM:

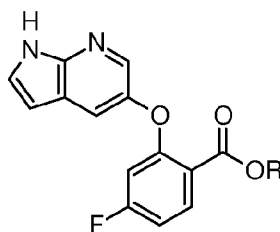
1. A process for the preparation of a compound of formula V,



Formula V

comprising the steps of:

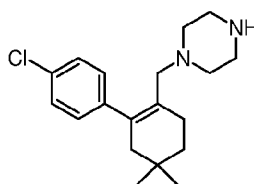
- a) reacting a compound of formula II,



Formula II

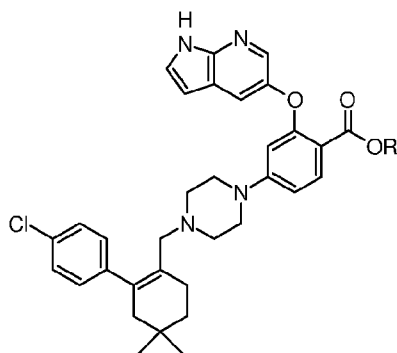
wherein R is C₁₋₄ alkyl;

with a compound of formula III,



Formula III

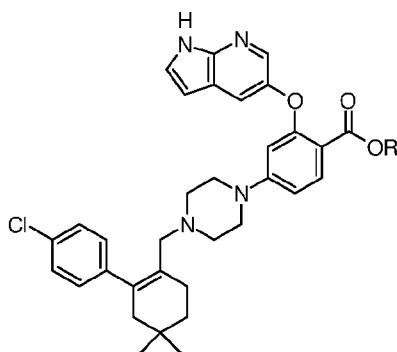
in the presence of an alkyl amine to obtain a compound of formula I or its salts,

**Formula I**

wherein R is C₁₋₄ alkyl;

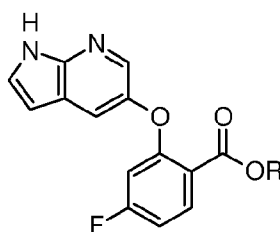
5 b) converting the compound of formula I or its salts to the compound of formula V.

2. A process for the preparation of a compound of formula I or its salts,

**Formula I**

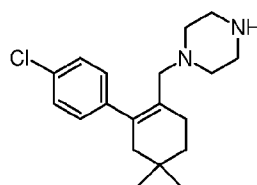
wherein R is C₁₋₄ alkyl;

comprising the reaction of a compound of formula II,

**Formula II**

wherein R is C₁₋₄ alkyl;

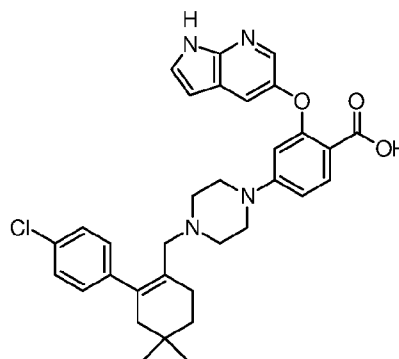
with a compound of formula III,

**Formula III**

5 in the presence of an alkyl amine.

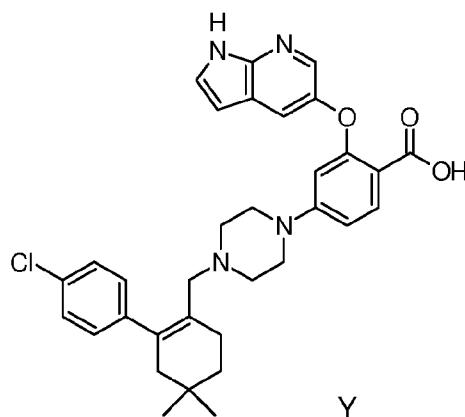
3. The process according to claim 1, wherein the conversion of step b) comprises the steps of:

10 b1) hydrolyzing the compound of formula I or its salt to a compound of formula Ia,

**Formula Ia**

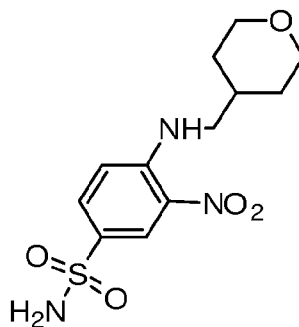
or its salt of the compound of formula Ia¹,

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**Formula Ia¹**

wherein Y is hydrochloric acid, sulphuric acid, p-toluenesulphonic acid, trifluoroacetic acid, oxalic acid, or dicyclohexylamine;

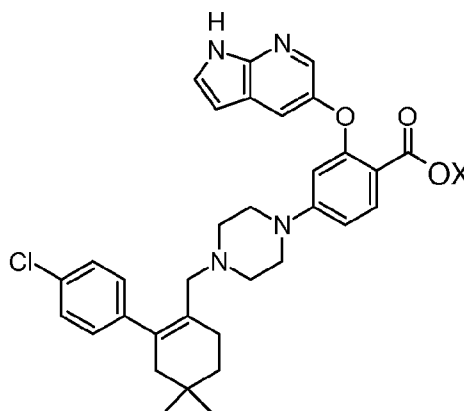
- b2) reacting the compound of formula Ia or the compound of the formula Ia¹ with a compound of formula IV,



Formula IV

to obtain the compound of Formula V.

4. The process according to claim 3, wherein the conversion of step b1) comprises the steps of:
- b11) optionally isolating a compound of formula Ib,

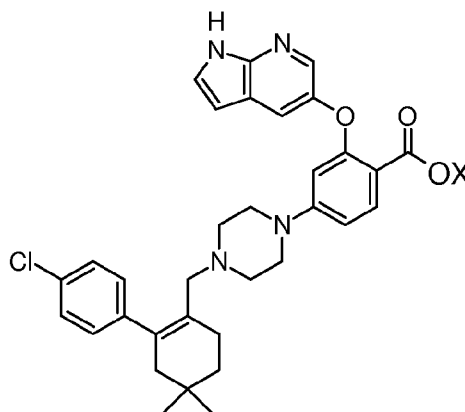


Formula Ib

wherein X= K, Na, Li

- b12) converting the compound of formula Ib to a compound of formula Ia or its salt Ia¹.

5. A compound of formula Ib,

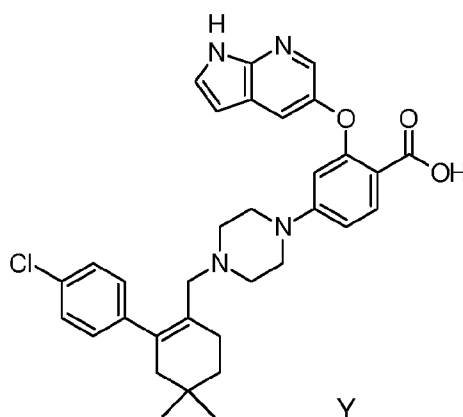
**Formula Ib**

wherein X= K, Na, Li

5

6. The process according to any one of claims 1 to 4, wherein the alkyl amine is selected from the group consisting of N,N-diisopropylethylamine (DIPEA), trimethylamine (Me₃N), triethylamine (Et₃N), N,N-dimethylaniline (DMA), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,5-Diazabicyclo [4.3.0]non-5-ene (DBN), preferably N,N-diisopropylethylamine (DIPEA).
7. The process according to any one of claims 1 to 4 or 6, wherein the reaction of the compound of formula II with the compound of formula III is carried out in the presence of an aprotic solvent selected from the group consisting of dichloromethane, dimethylsulphoxide, chloroform, acetone, acetonitrile, tetrahydrofuran, dimethylformamide, N-methyl pyrrolidine, dioxane, nitromethane, pyridine, 2-methyltetrahydrofuran or mixture thereof.
8. The process according to claim 7, wherein the solvent is dimethylsulphoxide.
9. The process according to any one of claims 1 to 4 or 6 to 8, wherein the salt of the compound of formula I is prepared by reacting the compound of formula I with an acid selected from hydrochloric acid, sulphuric acid, p-toluenesulphonic acid, trifluoroacetic acid and oxalic acid.
10. The process according to any one of claims 1 to 4 or 6 to 9, wherein the salt of the compound of formula I is the hydrochloride salt.

11. The process according to claim 9 or 10, wherein the salt of the compound of formula I is prepared in the presence of a solvent selected from methanol, ethanol, acetone, dioxane, water, ethyl acetate and dichloromethane or a mixture thereof.
12. The process according to claim 3 or 4, wherein the hydrolysis is carried out in presence of a base selected from potassium hydroxide, lithium hydroxide and sodium hydroxide or mixture thereof.
13. The process according to claim 3, 4 or 12, wherein the hydrolysis is carried out in presence of a solvent selected from methanol, ethanol, acetone, dioxane, water, and dichloromethane or a mixture thereof.
14. The process according to claim 4, wherein the compound of formula Ib is converted to a compound of formula Ia¹ by reacting with an acid selected from hydrochloric acid, sulphuric acid, p-toluenesulphonic acid, trifluoroacetic acid and oxalic acid, preferably hydrochloric acid.
15. The process according to claim 3 or 4, wherein the salt of formula Ia¹ is prepared by reacting the compound of formula Ia with an acid selected from hydrochloric acid, sulphuric acid, p-toluenesulphonic acid, trifluoroacetic acid and oxalic acid or with dicyclohexylamine as base.
16. A compound of formula Ia¹,

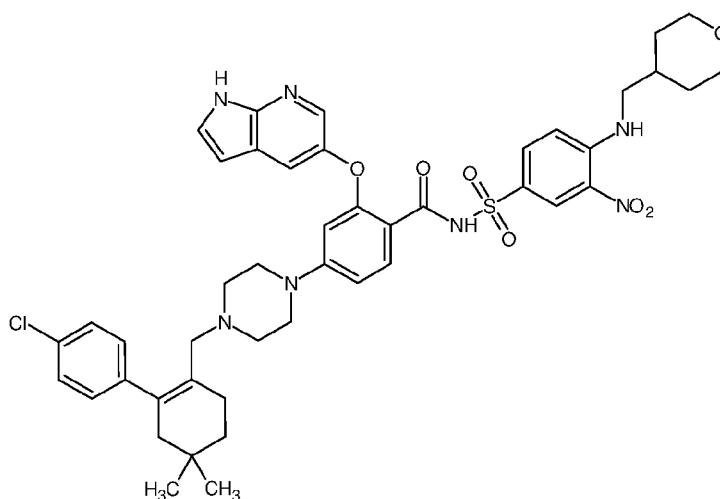


Formula Ia¹

wherein Y is hydrochloric acid, sulphuric acid, p-toluenesulphonic acid, trifluoroacetic acid, oxalic acid, or dicyclohexylamine.

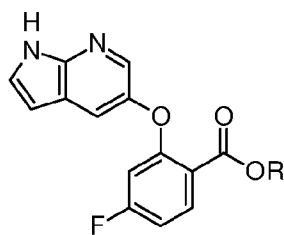
- 5 17. The process according to claim 3 or 4, wherein step b3) is carried out in the presence of a coupling agent selected from the group consisting of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC HC1), dicyclohexylcarbodiimide (DCC), O-benzotriazole-N,N',N'-tetramethyl uronium hexafluoro phosphate (HBTU) and benzotriazol-1-yloxypyrrolidinophosphonium
- 10 hexafluorophosphate (PyBOP), preferably 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC HC1).
18. The process according to claim 3, 4 or 17, wherein step b3) is carried out in the presence of a solvent selected from the group consisting of dichloromethane,
- 15 chloroform, acetone, acetonitrile, tetrahydrofuran, dimethylformamide, N-methyl pyrrolidine, dioxane, nitromethane, pyridine and 2-methyltetrahydrofuran, preferably dichloromethane.
19. The process according to claim 3, 4, 17 or 18, wherein step b3) is carried out in the presence of a base selected from triethylamine, N,N-diisopropylethylamine,
- 20 N,N-dimethylethylenediamine, 4-(dimethylamino)pyridine or mixture thereof.

20. A process for the preparation of a compound of formula V,

**Formula V**

comprising the steps of:

a) reacting a compound of formula II,

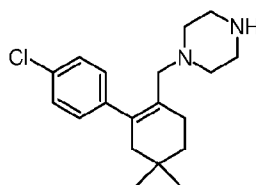


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Formula II

wherein R is C₁₋₄ alkyl;

with a compound of formula III,

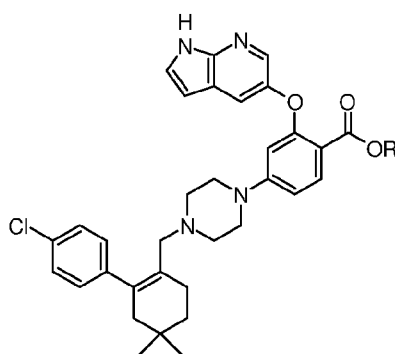


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Formula III

in the presence of diisopropylethylamine to obtain a compound of formula I or its salts,

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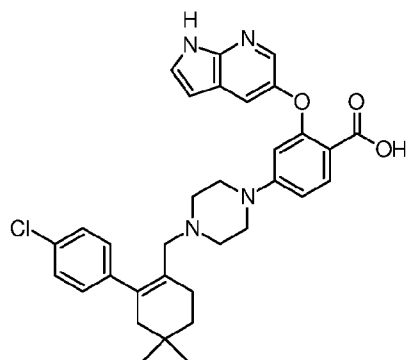


Formula I

wherein R is C₁₋₄ alkyl;

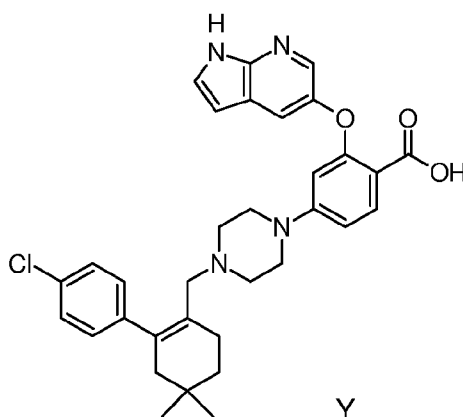
20

b) hydrolyzing the compound of formula I or its salts to a compound of formula Ia,

**Formula Ia**

c) converting the compound of formula Ia to its salt of formula Ia¹,

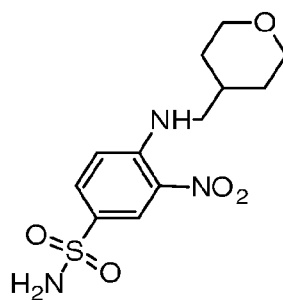
5

**Formula Ia¹**

wherein Y is hydrochloric acid

10

d) reacting the compound of formula Ia¹ with a compound of formula IV,

**Formula IV**

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in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride, triethylamine, 4-dimethylaminopyridine, N, N-dimethylethylenediamine, and dichloromethane to obtain the compound of Formula V.

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INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2019/055578

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07D471/04
 ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2011/149492 A1 (ABBOTT LAB [US]; BRUNCKO MILAN [US] ET AL.) 1 December 2011 (2011-12-01) Page 293 Examples 3I Page 294 Example 3K Page 298 Example 5J Page 299 Example 5L -----	1,2, 6-11,20
Y	WO 2014/165044 A1 (ABBVIE INC [US]) 9 October 2014 (2014-10-09) Page 28 Scheme 5 pages 37-38 Example 8 -----	1,2, 6-11,20
X,P	WO 2018/225043 A1 (LUPIN LTD [IN]) 13 December 2018 (2018-12-13) claims 20, 25, 26, 27; examples 1, 2 -----	1,2, 6-11,20



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

3 September 2019

Date of mailing of the international search report

13/11/2019

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040,
 Fax: (+31-70) 340-3016

Authorized officer

Sotoca Usina, E

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2019/055578

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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			ES 2683378 T3 26-09-2018

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2019/055578

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		JP 2016514137 A	19-05-2016
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		UA 118667 C2	25-02-2019
		UY 35394 A	30-09-2014
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WO 2018225043	A1	13-12-2018	NONE

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2019/055578

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

2, 6-11(completely); 1, 20(partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 2, 6-11(completely); 1, 20(partially)

Process for the preparation of a compound of formula I

2. claims: 12-15(completely); 3, 4, 20(partially)

Process for the preparation of a compound of formulae Ia or Ia'

3. claims: 5(completely); 4(partially)

Intermediate of formula Ib and process for the preparation of a compound of formula Ib

4. claims: 17-19(completely); 1, 3(partially)

Process for the preparation of a compound of formula V

5. claims: 16(completely); 20(partially)

Intermediate of Formula Ia1
