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- with international search report (Art. 21(3))

(54) Title: A PROCESS FOR PREPARING HALOGENATED AZAINDOLE COMPOUNDS USING BOROXINE

(57) Abstract: A process for preparing halogenated azaindole compounds makes use of stable reagents including a brominating reagent, a boroxine and a sulfonic anhydride to enhance the selectivity and yield of the final product. In addition, the process is associated with various other advantages, including the ability to recycle reagents, cost reduction, and improved manufacturability.



WO 2016/100625 A1

A PROCESS FOR PREPARING HALOGENATED AZAINDOLE COMPOUNDS USING BOROXINE

CROSS REFERENCE TO RELATED APPLICATION

5 This application claims the priority of U.S. Provisional Application Serial No. 62/093,645 filed December 18, 2014 which is herein incorporated by reference in its entirety.

FIELD OF THE INVENTION

10 The present invention relates to a process for preparing halogenated azaindole compounds which are used in obtaining HIV attachment inhibitor compounds useful as antivirals. In particular, the invention provides methods of making the piperazine prodrug compound identified as 1-benzoyl-4-[2-[4-methoxy-7-(3-methyl-1*H*-1,2,4-triazol-1-yl)-1-[(phosphonooxy)methyl]-1*H*-pyrrolo[2,3-*c*]pyridin-3-yl]-1,2-dioxoethyl]-piperazine, as
15 well as certain intermediates thereof. The invention also relates to the compounds produced by the processes herein.

BACKGROUND OF THE INVENTION

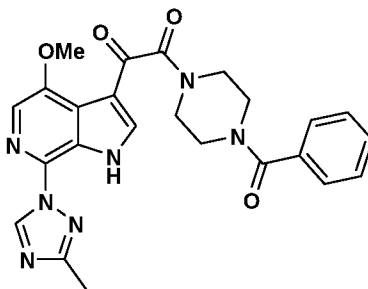
 HIV-1 (human immunodeficiency virus -1) infection remains a major medical
20 problem, with tens of millions of people still infected worldwide at the end of 2011. The number of cases of HIV and AIDS (Acquired Immuno Deficiency Syndrome) has risen rapidly. In 2005, for example, approximately 5 million new infections were reported and 3.1 million people died from AIDS. Despite continued advances in HIV treatment options, the development of new antiretroviral drugs and regimens continues to represent
25 an important area of unmet medical need due to long-term tolerability concerns and the emergence of viral strains resistant to current therapies. To date, the approved therapies to treat HIV infection fall into 4 general classes: (1) reverse-transcriptase inhibitors, (2) protease inhibitors, (3) integrase inhibitors and (4) entry inhibitors. Examples of available drugs for the treatment of HIV include nucleoside reverse transcriptase (RT)
30 inhibitors or approved single pill combinations: zidovudine (or AZT or RETROVIR®), didanosine (or VIDEX®), stavudine (or ZERIT®), lamivudine (or 3TC or EPIVIR®), zalcitabine (or DDC or HIVID®), abacavir succinate (or ZIAGEN®), Tenofovir disoproxil

fumarate salt (or VIREAD[®]), emtricitabine (or FTC or EMTRIVA[®]), COMBIVIR[®] (contains -3TC plus AZT), TRIZIVIR[®] (contains abacavir, lamivudine, and zidovudine), EPZICOM[®] (contains abacavir and lamivudine), TRUVADA[®] (contains VIREAD[®] and EMTRIVA[®]); non-nucleoside reverse transcriptase inhibitors: nevirapine (or
5 VIRAMUNE[®]), delavirdine (or RESCRIPTOR[®]) and efavirenz (or SUSTIVA[®]), ATRIPLA[®] (TRUVADA[®] + SUSTIVA[®]), and etravirine, and peptidomimetic protease inhibitors or approved formulations: saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, KALETRA[®] (lopinavir and Ritonavir), darunavir, atazanavir (REYATAZ[®]), and tipranavir (APTIVUS[®]), and integrase inhibitors such as raltegravir
10 (ISENTRESS[®]), and entry inhibitors such as enfuvirtide (T-20) (FUZEON[®]) and maraviroc (SELZENTRY[®]).

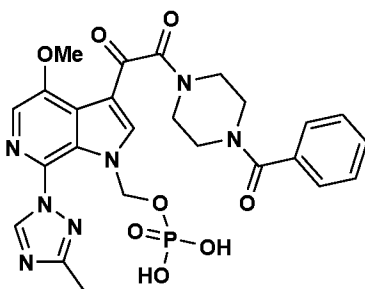
The identification of potent, orally active antiretrovirals with a unique mechanism of action led to HIV attachment inhibitors a novel subclass of antiviral compounds that
15 bind to the HIV surface glycoprotein gp120, and interfere with the interaction between the surface protein gp120 and the host cell receptor CD4. Thus, they prevent HIV from attaching to the human CD4 T-cell, and block HIV replication in the first stage of the HIV life cycle. The properties of HIV attachment inhibitors have been improved in an effort to obtain compounds with maximized utility and efficacy as antiviral agents.

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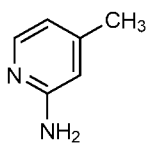
One HIV attachment inhibitor compound, in particular, has now shown considerable prowess against HIV. This compound is identified as 1-(4-benzoyl-piperazin-1-yl)-2-[4-methoxy-7-(3-methyl-[1,2,4] triazol-1-yl)-1H-pyrralo [2,3-c] pyridine-3-yl]-ethane-1,2-dione, and is set forth and described in U.S. 7,354,924, which is
25 incorporated herein in its entirety. The compound is represented by the formula below:



The above compound is the parent compound of the prodrug known as 1-benzoyl-4-[2-[4-methoxy-7-(3-methyl-1*H*-1,2,4-triazol-1-yl)-1-[(phosphonoxy)methyl]-1*H*-pyrrolo[2,3-*c*]pyridin-3-yl]-1,2-dioxoethyl]-piperazine. It is set forth and described in U.S. Patent No. 7,745,625, which is incorporated by reference herein in its entirety. The compound is represented by the formula below:



Various methods for making this prodrug compound have been set forth, including those detailed in the '625 reference. In particular, the '625 reference includes various methods for acylation, alkylation and phosphorylation. Another patent reference, U.S. Patent No. 8,436,168 entitled "Methods of Making HIV Attachment Inhibitor Prodrug Compound and Intermediates", also details various procedures for making the piperazine prodrug compound. These include a multi-step process which uses the



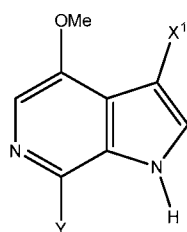
compound as a starting material, which is subsequently brominated, and then nitrated. Further on, a triazolyl moiety is added to the compound before further attaching the piperazine moiety separated by dual carbonyl groups. Yet another patent reference, U.S. Patent No. 8,889,869 filed February 6, 2013, entitled "Methods for the Preparation of HIV Attachment Inhibitor Piperazine Prodrug Compound", also details procedures for making the compound. These include a multi-step process which uses the compound *N*-sulfonylated pyrrole as a starting material, which is subsequently subjected to a Friedel-Crafts acylation reaction, Pictet-Spengler cyclization, two oxidation reactions followed by bromination, deprotection and a second Friedel-Crafts acylation. Further on, the piperazine moiety is incorporated by amidation of the dual carbonyl groups followed by the copper catalyzed reaction to install the triazolyl moiety.

What is now needed in the art are new methods of making the halogenated azaindole compounds so as to prepare piperazine prodrug compounds which are useful against HIV. The methods should be economical and also be able to produce the halogenated azaindole in high yield and selectivity.

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SUMMARY OF THE INVENTION

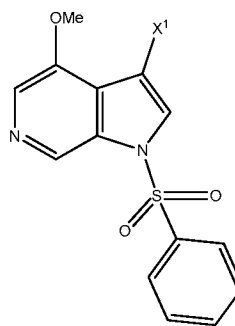
In a first embodiment, the invention provides a process for preparing a compound of formula I,



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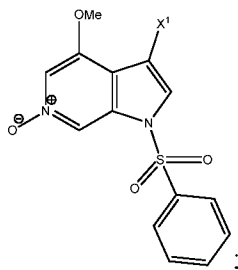
(I)

said process comprising the steps of:



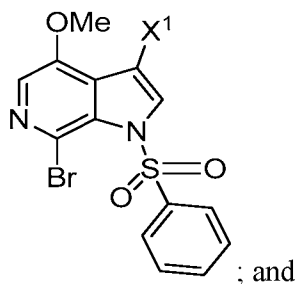
(a) performing an oxidation reaction on the compound

to yield the



compound

- (b) performing a bromination reaction in the presence of one or more boroxine compounds on the compound obtained in step (a) to obtain the compound

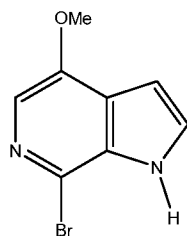


- (c) performing a deprotection reaction on the compound obtained in step (b) to prepare the compound of formula I above;

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wherein X¹ is selected from the group of H, and , and Y is Br.

In another embodiment, the present invention provides a process for preparing a compound of formula II

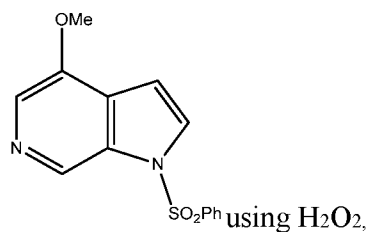


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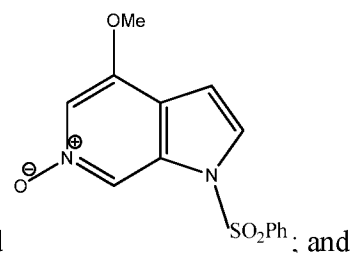
(II)

said process comprising the steps of:

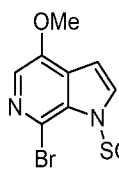
(a) performing an oxidation reaction on the compound



phthalic anhydride, and solvent to yield the compound



(b) performing a bromination reaction on the compound obtained in step (a) using one or more boroxine compounds along with a bromide source and an activating agent to

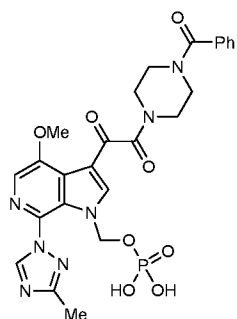


5 obtain the compound

(c) performing a deprotection reaction on the compound obtained in step (b) using either substantially pure toluene or toluene in combination with a solvent, followed by crystallization, to prepare the compound of formula II or its salts thereof.

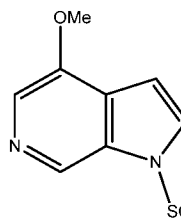
In a further embodiment, the present invention provides a method of making a

10 compound of formula III

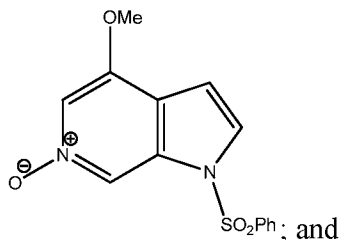


(III),

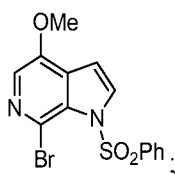
said process comprising the steps of:



- (a) performing an oxidation reaction on the compound
phthalic anhydride and dichloromethane to yield the compound

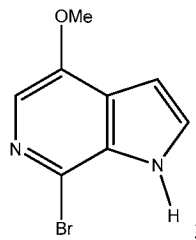


- (b) performing a bromination reaction on the compound obtained in step (a) using one or
5 more boroxine compounds along with a bromide source and an activating agent to



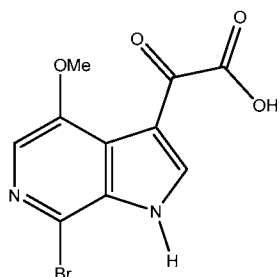
obtain the compound

- (c) performing a deprotection reaction on the compound obtained in step (b) using either
substantially pure toluene or toluene in combination with a solvent, followed by

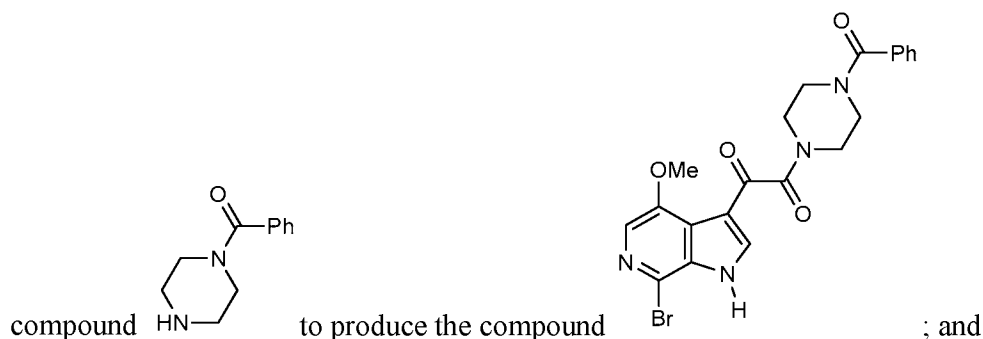


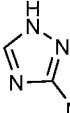
crystallization, to obtain the compound

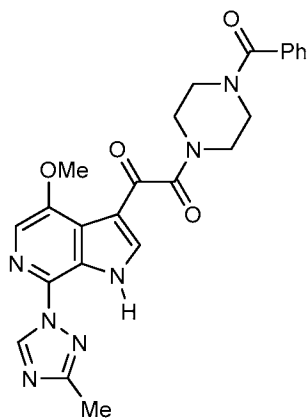
(d) reacting the compound obtained in step (c) to obtain the compound



followed by an activation reaction and coupling with the



(e) adding the triazolyl compound  in the presence of Cu ion and a ligand



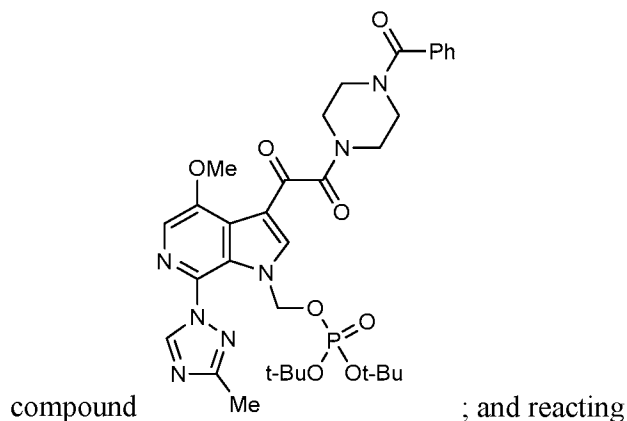
5

to obtain the compound ;

10

wherein said ligand is selected from the group of 1,2-diaminocyclohexane, *trans*-1,2-diaminocyclohexane, *cis*-/*trans*-diaminocyclohexane, *cis*-*N,N'*-dimethyl-1,2-diaminocyclohexane, *trans*-*N,N'*-dimethyl-1,2-diaminocyclohexane, *cis*-/*trans*-*N,N'*-dimethyl-1,2-diaminocyclohexane, 1,2-diaminoethane, *N,N'*-dimethyl-1,2-diaminoethane, 1,10-phenanthroline, 4,7-diphenyl-1,10-phenanthroline, 5-methyl-1,10-phenanthroline, 5-chloro-1,10-phenanthroline, and 5-nitro-1,10-phenanthroline; and

(f) reacting the compound obtained in step (e) with $(t\text{-BuO})_2\text{POOCH}_2\text{Cl}$ to produce the



(g) the compound obtained in step (f) with an acid, such as acetic acid, to yield the compound of formula III above.

5

The invention in further embodiments is also directed to each of the compounds of formulas I, II and III herein which are produced by the processes herein set forth.

The present invention is directed to these, as well as other important ends,
10 hereinafter described.

DETAILED DESCRIPTION OF THE EMBODIMENTS

It will be understood that any given exemplary embodiment can be combined with one or more additional exemplary embodiments. As used herein, the singular forms “a”,
15 “an”, and “the” include plural reference unless the context clearly dictates otherwise.

Unless otherwise specifically set forth, many reagents have been identified herein by their commonly accepted letter abbreviations in the art for ease of reference.

20 In addition, unless otherwise specifically set forth elsewhere in the application, the following terms may be used herein, and shall have the following meanings:

An “alkyl” group refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms
25 (whenever a numerical range; e.g., “1-20”, is stated herein, it means that the group, in this

case the alkyl group may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up to and including 20 carbon atoms). More preferably, it is a medium size alkyl having 1 to 10 carbon atoms. Most preferably, it is a lower alkyl having 1 to 4 carbon atoms. The alkyl group may be substituted or unsubstituted.

5

The term "C₁₋₆ alkyl" as used herein and in the claims means straight or branched chain alkyl groups with up to and including 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, amyl, hexyl and the like.

10

An "aryl" "Aryl" or "Ar" group refers to an all carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, naphthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted.

15

The abbreviations used in the present application are well-known to those skilled in the art. Some of the abbreviations used are as follows:

Ac₂O: acetic anhydride

20 Boroxines: General term to refer to cyclic trimeric boronic acid anhydrides; these will include the trialkylboroxines such as trimethylboroxine, and also the triarylboroxines such as triphenylboroxine

t-Bu: *tert*-butyl; K₃PO₄: potassium phosphate tribasic

DCM: dichloromethane

25 HCl: Hydrochloric acid

H₂O₂: Hydrogen peroxide

IPA: isopropyl alcohol

*m*CPBA: *m*-Chloroperbenzoic acid

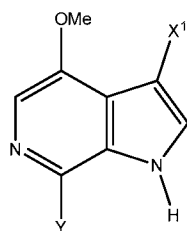
Ms₂O: methanesulfonic anhydride

30 NaOH: sodium hydroxide

Oct₄NBr: Tetraoctylammonium bromide

Tris: 2-amino-2-(hydroxymethyl)propane-1,3-diol

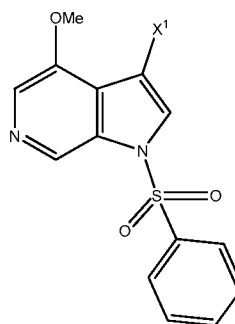
In a first aspect, the present invention provides a process for preparing a compound of formula I,



(I)

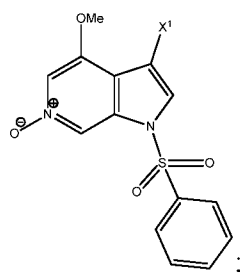
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said process comprising the steps of:



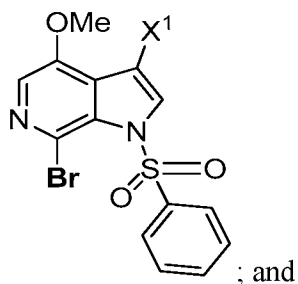
(a) performing an oxidation reaction on the compound

to yield the



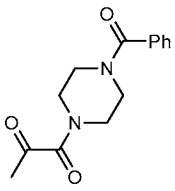
compound

10 (b) performing a bromination reaction in the presence of one or more boroxine compounds on the compound obtained in step (a) to obtain the compound



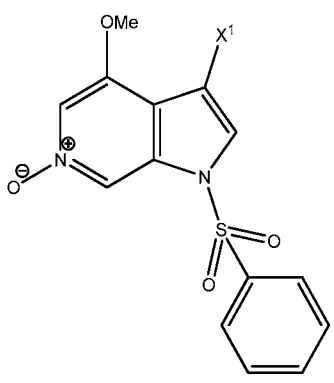
; and

(c) performing a deprotection reaction on the compound obtained in step (b) to obtain the compound of formula I above;

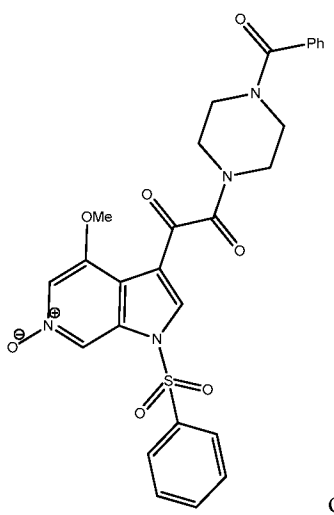
wherein X^1 is selected from the group of H,  and , and Y is Br.

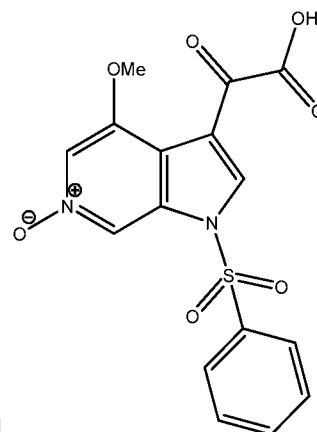
In a first embodiment of the first aspect, the oxidation reaction is carried out using
 5 oxidizing agents selected from the group of catalytic methyltrioxorhenium (MTO) and hydrogen peroxide urea complex (UHP), *m*-CPBA (*m*-chloroperoxybenzoic acid), a mixture of Ac_2O and H_2O_2 , and a mixture of phthalic anhydride and H_2O_2 .

In a second embodiment of the first aspect, the compound

 obtained in step (a) is treated with aqueous Na_2SO_3 followed
 10 by the addition of aqueous K_3PO_4 .

In a third embodiment of the first aspect, the compound

 obtained in step (a) is a crystalline solid with about 85 % yield
 and > about 99 % purity.



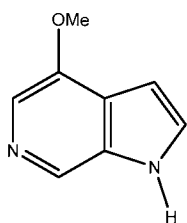
In a third embodiment of the first aspect, the compound obtained in step (a) is a crystalline solid which is not isolated.

In a fourth embodiment of the first aspect, the bromination is carried out in the presence of a bromide source such as tetrabutyl ammonium bromide, an activating agent such as methanesulfonic anhydride, and a boroxine compound such as triphenylboroxine.

In a fifth embodiment of the first aspect, the deprotection reaction is carried out using toluene in conjunction with isopropyl alcohol (IPA).

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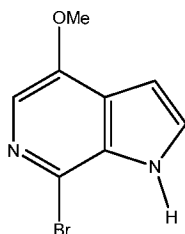
In a sixth embodiment of the first aspect, the compound of formula I



is obtained with a yield ranging from about 67.1 % to 70.3 %, and purity ranging from about 98.5 to 99.7%.

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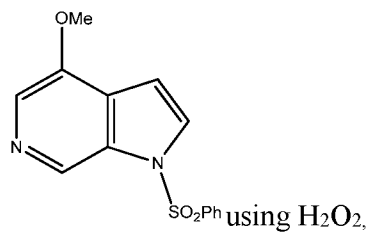
In a second aspect, the present invention provides a process for preparing a compound of formula II



(II)

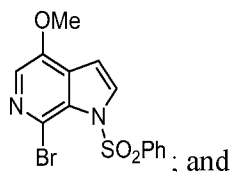
said process comprising the steps of:

(a) performing an oxidation reaction on the compound



5 phthalic anhydride, and a solvent to yield the compound

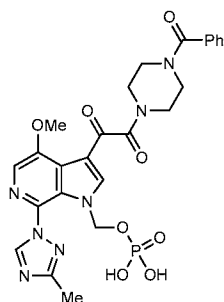
(b) performing a bromination reaction on the compound obtained in step (a) using one or more boroxine compounds, along with a bromide source and an activating agent to



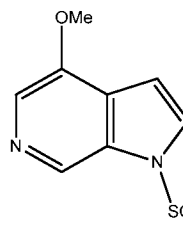
obtain the compound

(c) performing a deprotection reaction on the compound obtained in step (b) using either
 10 pure toluene or toluene in combination with a solvent, followed by crystallization, to prepare the compound of formula II or its salts thereof.

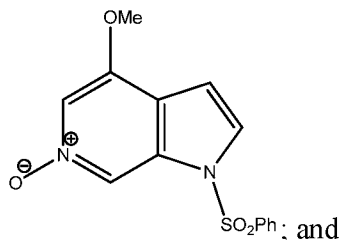
In a third aspect, the present invention provides a method of making a compound of formula III

**(III),**

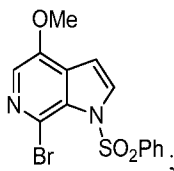
said process comprising the steps of:



- (a) performing an oxidation reaction on the compound
phthalic anhydride and dichloromethane to yield the compound

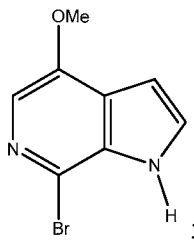


- (b) performing a bromination reaction on the compound obtained in step (a) using one
5 or more boroxine compounds, along with a bromide source and an activating agent,



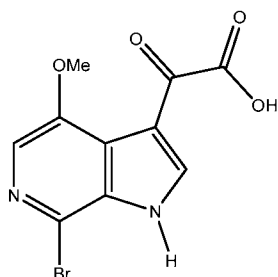
to obtain the compound

- (c) performing a deprotection reaction on the compound obtained in step (b) using
either pure toluene or toluene in combination with a solvent, followed by

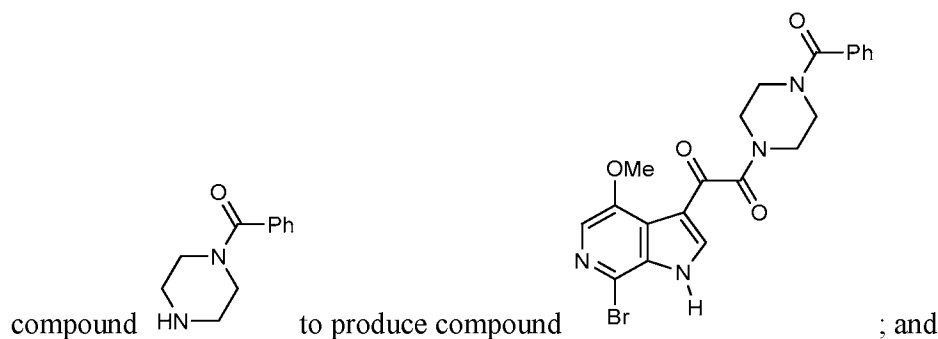


crystallization, to obtain the compound

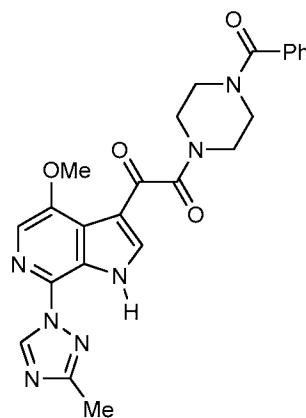
(d) reacting the compound obtained in step (c) to obtain the compound



followed by an activation reaction and coupling with



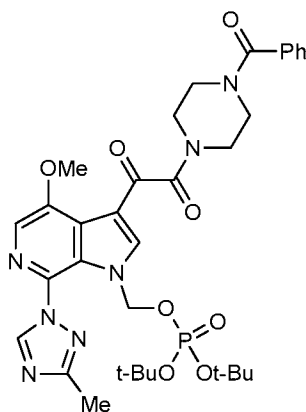
(e) adding the triazolyl compound  in the presence of Cu ion and a



5 ligand to obtain compound

wherein said ligand is selected from the group of 1,2-diaminocyclohexane, trans-1,2-diaminocyclohexane, *cis*-/trans-diaminocyclohexane, *cis*-*N,N'*-dimethyl-1,2-diaminocyclohexane, *trans*-*N,N'*-dimethyl-1,2-diaminocyclohexane, *cis*-/trans-*N,N'*-dimethyl-1,2-diaminocyclohexane, 1,2-diaminoethane, *N,N'*-dimethyl-1,2-diaminoethane, 1,10-phenanthroline, 4,7-diphenyl-1,10-phenanthroline, 5-methyl-1,10-phenanthroline, 5-chloro-1,10-phenanthroline, and 5-nitro-1,10-phenanthroline; and

(f) reacting the compound obtained in step (e) with $(t\text{-BuO})_2\text{POOCH}_2\text{Cl}$ to



produce the compound ; and reacting compound obtained in step (f) with an acid, such as acetic acid, to yield the compound of formula III above.

5

EXAMPLES

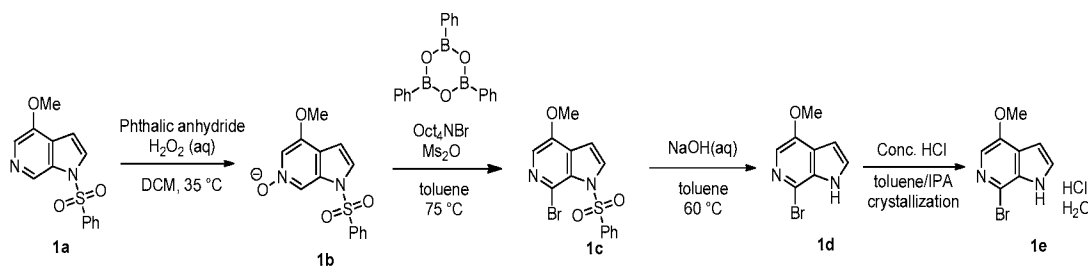
The present invention will now be described in connection with certain embodiments which are not intended to limit its scope. On the contrary, the present invention covers all alternatives, modifications, and equivalents as can be included within the scope of the claims. Thus, the following examples, which include specific embodiments, will illustrate one practice of the present invention, it being understood that the examples are for the purposes of illustration of certain embodiments and are presented to provide what is believed to be the most useful and readily understood description of its procedures and conceptual aspects.

The compounds of the present invention may be prepared using the reactions and techniques described in this section, as well as, other synthetic methods which may be available to those of ordinary skill in the art. The reactions are performed in solvents appropriate to the reagents and materials employed and suitable for the transformation being affected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvents, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and

reactions proposed. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

5

In a preferred embodiment of the invention, the synthesis of the halogenated azaindole compounds can be set forth in the following non-limiting schematic representation – Scheme I.



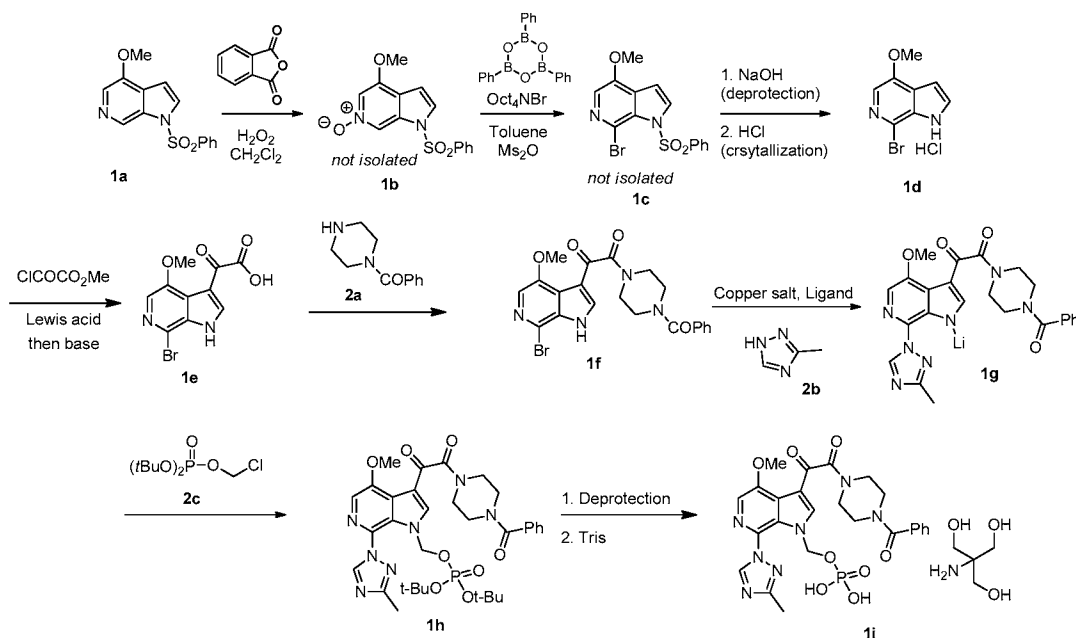
10

All reagents were used as received without further purification. Reaction progress and final product purity was monitored using HPLC conditions, Table 1, using an Ascentis Express C18, 2.7 μ m 4.6 x 150 mm column at 25 °C. Mobile Phase A: 0.01M NH₄OAc in H₂O:MeOH (80:20), Mobile phase B: 0.01 NH₄OAc in H₂O:MeCN:MeOH (5:75:20),
1.0 mL/min. Gradient:

15

Table 1: HPLC Conditions

Time (minutes)	Mobile Phase Composition		Gradient Profile
	% A	% B	
0.0	100.0	0.0	Initial
5.0	70.0	30.0	Linear
20.0	55.0	45.0	Linear
25.0	0.0	100.0	Linear
30.0	0.0	100.0	Hold



7-Bromo-4-methoxy-1*H*-pyrrolo[2,3-*c*]pyridine hydrochloride monohydrate (**1d**), CH_2Cl_2 (2660 L), Compound **1a** (190 kg, 1.0 equiv) and phthalic anhydride (127.3 kg, 1.3 equiv) were charged to an 8000 L glass lined vessel, and the resulting mixture was heated to 35 °C. A 30% w/w aqueous solution of hydrogen peroxide (76.8 kg, 1.2 equiv) was added via pump over 2 hours. The resulting suspension was stirred at 35-37 °C for an additional 2 hours, then sampled and analyzed by HPLC to determine the reaction progress. Once the oxidation reaction was deemed complete, the mixture was cooled to 10 °C. The reaction was quenched by controlled addition of a solution of sodium sulfite (85.5 kg, 1 equiv) in water (1330 kg) such that the internal temperature remained below 20 °C. The resulting biphasic mixture was stirred vigorously at 20 °C for 2 hours to ensure complete reduction of any residual oxidant. A solution of K_3PO_4 (353 kg) in water (1330 kg) was then added to the quenched reaction mixture and the biphasic mixture stirred at 20 °C for 2 hours. The top aqueous phase was discarded and the lower product-rich organic phase was washed with water (1330 kg). The bottom product-rich organic phase was transferred to a clean 8000 L reactor.

Toluene (1900 L) was added, and the batch was concentrated at ≤ 0.075 MPa while maintaining the jacket temperature below 40 °C to a final volume of 3000 L. Toluene was added (1900 L) two more times with similar concentrations to volume batch volume of 3000 L in order to meet the specifications for KF (<200 ppm) and DCM

(dichloromethane) (< 1 wt%). The batch was cooled to 20 °C and toluene (1900 L) was added. Tetraoctylammonium bromide (450.4 kg, 1.25 equiv) and triphenylboroxine (267 kg, 1.3 equiv) were added, and the mixture was agitated for 1 h. Methanesulfonic anhydride (275.5 kg, 2.4 equiv) and toluene (413 kg) were then added and the mixture
5 agitated for 30 min. The slurry was heated to 75 °C for 10 h, then sampled and analyzed. During this time the reaction mixture transformed from a thick slurry to a homogenous solution. After completion of the bromination reaction, the batch was concentrated at ≤ 0.075 MPa while maintaining the jacket temperature below 40 °C to a final volume of 3000 L. The resulting slurry was cooled to 25 °C and acetonitrile (1200 kg) was added
10 and agitated for 2 h. The slurry was filtered and the solids were rinsed with acetonitrile (450 kg). The solids were triphenylboroxine, and can be dried (50 °C under vacuum) and re-used in subsequent bromination reactions. Expected recovery is 60-70% of the input quantity of the triphenylboroxine. To the product-rich filtrate a solution of potassium phosphate tribasic (560 kg, 4 equiv) in water (1678 kg) was added to the reactor at such a
15 rate that the internal temperature was maintained below 35 °C. The resulting biphasic mixture was then heated to 40 °C for 2 hours. The batch was cooled to 20 °C, the phases were allowed to split and were separated, and the aqueous layer was discarded. To the resulting mixture was added sodium hydroxide (106.4 kg, 4.0 equiv) in water (532 kg), and the mixture was then heated to 60 °C for 4 hours. After reaction completion the batch
20 was cooled to 20 °C, and water (950 kg) was added to dissolve solids. The biphasic mixture was polish filtered (1 μ m) and then the phases were allowed to split and were separated. The top phase (product-rich) was sequentially washed with: a solution of NaOH (106.4 g, 4 equiv) in water (532 kg), a solution of KH₂PO₄ (105.9 kg) in water (950 kg), and water (950 kg).

25

The organic stream was transferred to an 8000 L glass lined vessel and toluene (950 L) was added. The mixture was then concentrated ($T \leq 50$ °C, 40-90 mbar) to a final volume of 1300 L, at which point the water content of the toluene solution was <1.0 wt. Isopropanol (450 kg) was added and the batch was heated to 40 °C. Aqueous HCl (162.5
30 kg, 35 w/w %, 2.5 equiv) was then added over 3 hours with high agitation. The resulting suspension was cooled to 20 °C over 1 hour and then stirred for 2 hours. The product was collected by centrifugation, washed with a mixture of toluene (400 L) and isopropanol (171 L), a mixture of toluene (752 L) and isopropanol (293 L), and toluene (570 L), and

dried at 50 °C at <0.1 MPa to afford the brominated azaindole **1d** as an off-white solid, 129.5 kg (99.64 AP, 99.79 wt%, 69.7% corrected yield).

Thus, the halogenated azaindole compounds and the reactions described above
5 can be used in the production of the piperazine prodrug compound as shown further along in the scheme above. Also, in the scheme above, particularly **1e** may be converted to **1i** using the schemes described in PCT application number PCT/US2013/024880 filed February, 6, 2013, entitled "Methods for the Preparation of HIV Attachment Inhibitor Piperazine Prodrug Compound", and incorporated herein in its entirety.

10 A Friedel-Crafts acylation followed by hydrolysis and amidation produced intermediate **1f**. The triazole substituent was then incorporated via a copper-catalyzed Ullmann-Goldberg-Buchwald cross-coupling reaction of **1f** and **2b** leading to the formation of **1g**. Attachment of the phosphate pro-drug by alkylation with **2c** followed by
15 hydrolysis and crystallization affords the drug substance **1i**.

The effective preparation of the brominated intermediate **1d** is an important step for the effective synthesis of compound **1i**. The bromination process uses readily available and stable reagents such as triphenylboroxine, Oct₄NBr and Ms₂O and has
20 several advantages. It provides high selectivity for the desired brominated azaindole and reduces the number of undesired impurities. This translates into higher yields and increased purity (average of 99 wt%). The ability to recycle and reuse the triphenylboroxine (~60 %) reagent results in a reduction of the cost of the overall process, and increases the sustainability of the manufacturing process. Initial cost estimations have
25 shown that this process can be ~20-35% less expensive than other preparations of compound **1e**.

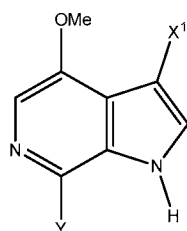
It will be evident to one skilled in the art that the present invention is not limited
30 to the foregoing disclosure and that it can be embodied in other specific forms without departing from the essential attributes thereof. It is therefore desired that the instant disclosure be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing disclosure, and all changes

which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

CLAIMS

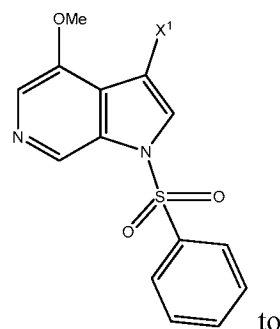
What is claimed is:

1. A process for preparing a compound of formula I,

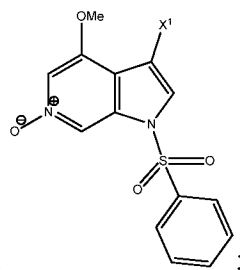


(I)

said process comprising the steps of:

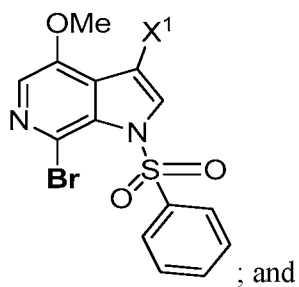


- (a) performing an oxidation reaction on the compound



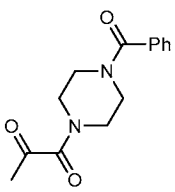
yield the compound

- (b) performing a bromination reaction in the presence of one or more boroxine compounds on the compound obtained in step (a) to obtain the compound

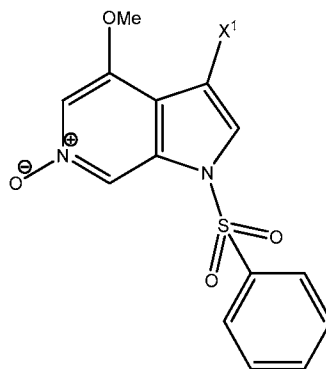


; and

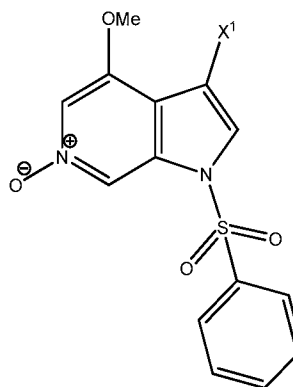
- (c) performing a deprotection reaction on the compound obtained in step (b) to obtain the compound of formula I above;

wherein X^1 is selected from the group of H,  and , and Y is Br.

2. The process of claim 1, wherein said oxidation reaction is carried out using oxidizing agents selected from the group of catalytic methyltrioxorhenium (MTO) and hydrogen peroxide urea complex (UHP), *m*-CPBA, a mixture of Ac_2O and H_2O_2 , and a mixture of phthalic anhydride and H_2O_2 .

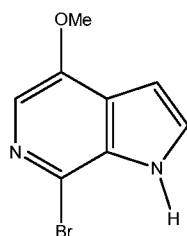


3. The process of claim 1, wherein the compound obtained in step (a) is treated with aqueous Na_2SO_3 followed by addition of aqueous K_3PO_4 .



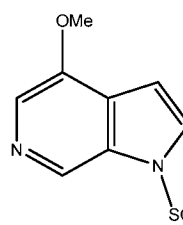
4. The process of claim 1, wherein the compound obtained in step (a) is a crystalline solid with about 85 % yield and > about 99 % purity.

5. The process of claim 1, wherein said bromination is carried out in the presence of a bromide source such as tetrabutyl ammonium bromide, an activating agent such as methanesulfonic anhydride and a boroxine compound such as triphenylboroxine.
6. The process of claim 1, wherein said deprotection reaction is carried out using either substantially pure toluene, or toluene in combination with a solvent.
7. The process of claim 1, wherein the compound of formula I is obtained with a yield ranging from about 67.1 % to 70.3 % and purity ranging from about 98.5 to 99.7%.
8. A process for preparing a compound of formula II

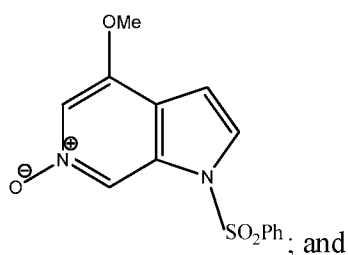


(II)

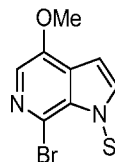
said process comprising the steps of:



- (a) performing an oxidation reaction on the compound H_2O_2 , phthalic anhydride, and a solvent to yield the compound



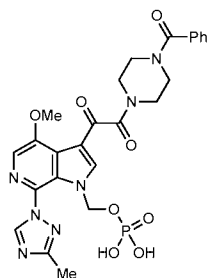
- (b) performing a bromination reaction on the compound obtained in step (a) using one or more boroxine compounds along with a bromide source and an



activating agent to obtain the compound

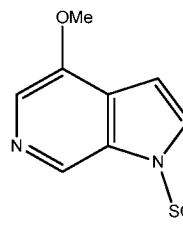
- (c) performing a deprotection reaction on the compound obtained in step (b) using either substantially pure toluene, or toluene in combination with a solvent, followed by crystallization, to prepare the compound of formula II or its salts thereof.

9. A method of making a compound of formula III

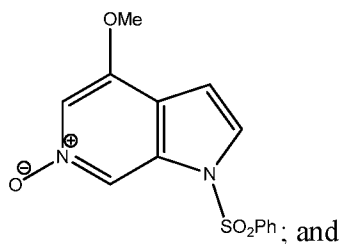


(III),

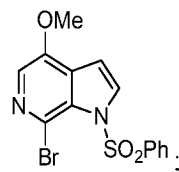
said process comprising the steps of:



- (a) performing an oxidation reaction on the compound H_2O_2 , phthalic anhydride and dichloromethane to yield the compound

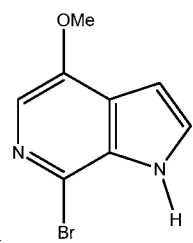


- (b) performing a bromination reaction on the compound obtained in step (a) using one or more boroxine compounds, along with a bromide source and an



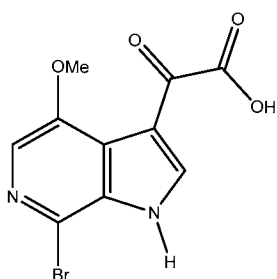
activating agent, to obtain the compound

- (c) performing a deprotection reaction on the compound obtained in step (b) using either substantially pure toluene or toluene in combination with a solvent,

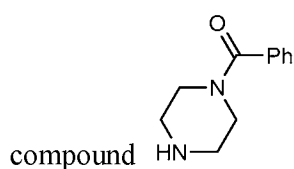


followed by crystallization, to obtain the compound

- (d) reacting the compound obtained in step (c) to obtain the compound



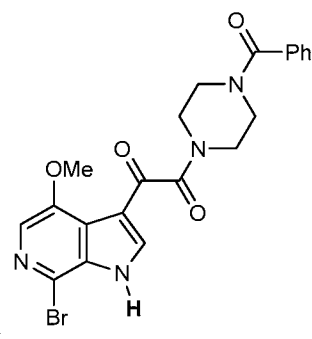
followed by an activation reaction and coupling with



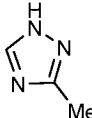
compound

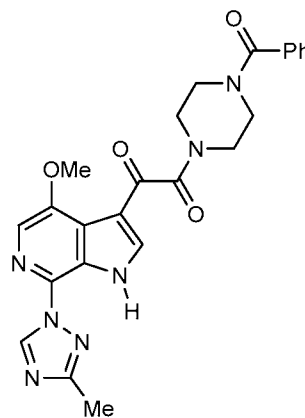
and

to produce the compound



;

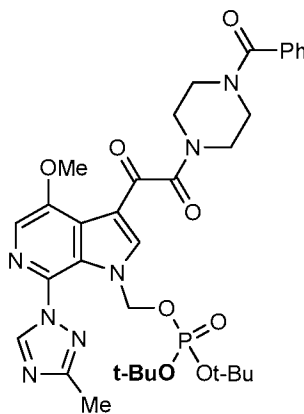
- (e) adding the triazolyl compound  in the presence of Cu ion and a



ligand to obtain the compound ;

wherein said ligand is selected from the group of 1,2-diaminocyclohexane, *trans*-1,2-diaminocyclohexane, *cis*-/*trans*-diaminocyclohexane, *i*-dimethyl-1,2-diaminocyclohexane, *trans*-*N,N'*-dimethyl-1,2-diaminocyclohexane, *cis*-/*trans*-*N,N'*-dimethyl-1,2-diaminocyclohexane, 1,2-diaminoethane, *i*-dimethyl-1,2-diaminoethane, 1,10-phenanthroline, 4,7-diphenyl-1,10-phenanthroline, 5-methyl-1,10-phenanthroline, 5-chloro-1,10-phenanthroline, and 5-nitro-1,10-phenanthroline; and

- (f) reacting the compound obtained in step (e) with $(t\text{-BuO})_2\text{POOCH}_2\text{Cl}$ to



produce the compound

; and reacting the

compound obtained in step (f) with an acid to yield the compound of formula III.

10. The method of claim 9, wherein said bromination is carried out in the presence of a bromide source which is tetraoctyl ammonium bromide, an activating agent which is methanesulfonic anhydride, and a boroxine compound which is triphenylboroxine.
11. The method of claim 10, wherein said acid is acetic acid.
12. The method of claim 11, wherein in step c) said solvent is isopropyl alcohol.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/066299

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D471/04 C07F9/09 A61K31/437 A61P31/18
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 C07F

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)

EP0-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2013/119625 A1 (SQUIBB BRISTOL MYERS CO [US]) 15 August 2013 (2013-08-15) claim 16 and page 15 -----	1-12
A	WO 2007/127731 A1 (SQUIBB BRISTOL MYERS CO [US]; BACHAND CAROL [CA]; DEON DANIEL H [CA];) 8 November 2007 (2007-11-08) compound E1 in page 59 -----	1-12
A	WO 2009/158394 A1 (SQUIBB BRISTOL MYERS CO [US]; WANG TAO [US]; UEDA YASUTSUGU [US]; HAMA) 30 December 2009 (2009-12-30) compound J-In-2 in p. 88 ----- -/--	1-12



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

1 March 2016

Date of mailing of the international search report

09/03/2016

Name and mailing address of the ISA/

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

Authorized officer

Sahagún Krause, H

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/066299

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	KE CHEN ET AL: "Synthesis of the 6-Azaindole Containing HIV-1 Attachment Inhibitor Pro-Drug, BMS-663068", THE JOURNAL OF ORGANIC CHEMISTRY, vol. 79, no. 18, 19 September 2014 (2014-09-19), pages 8757-8767, XP055251332, US ISSN: 0022-3263, DOI: 10.1021/jo5016008 the whole document -----	1-12
Y	SARAH E. WENGRYNIUK ET AL: "Regioselective Bromination of Fused Heterocyclic N -Oxides", ORGANIC LETTERS, vol. 15, no. 4, 15 February 2013 (2013-02-15), pages 792-795, XP055251397, US ISSN: 1523-7060, DOI: 10.1021/ol3034675 whole document, specially figure 1(C) -----	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2015/066299

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013119625 A1	15-08-2013	CA 2864087 A1 CN 104080785 A EA 201491446 A1 EP 2812332 A1 JP 2015508071 A US 2013203992 A1 US 2015038709 A1 US 2015038710 A1 US 2015038711 A1 US 2015038712 A1 US 2015038716 A1 US 2015038717 A1 WO 2013119625 A1	15-08-2013 01-10-2014 28-11-2014 17-12-2014 16-03-2015 08-08-2013 05-02-2015 05-02-2015 05-02-2015 05-02-2015 05-02-2015 05-02-2015 05-02-2015 15-08-2013
WO 2007127731 A1	08-11-2007	EP 2013170 A1 US 2007249624 A1 WO 2007127731 A1	14-01-2009 25-10-2007 08-11-2007
WO 2009158394 A1	30-12-2009	CN 102131810 A EP 2303876 A1 ES 2462403 T3 JP 5433690 B2 JP 2011526283 A US 2010009993 A1 US 2011212971 A1 WO 2009158394 A1	20-07-2011 06-04-2011 22-05-2014 05-03-2014 06-10-2011 14-01-2010 01-09-2011 30-12-2009