(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 September 2013 (12.09.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/131255 A1

(51) International Patent Classification:
C07D 213/75 (2006.01) *C07C 43/235* (2006.01)
C07D 213/74 (2006.01) *C07C 43/164* (2006.01)

(21) International Application Number:
PCT/CN2012/072020

(22) International Filing Date:
7 March 2012 (07.03.2012)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) Title: PREPARATION METHOD OF ROFLUMILAST

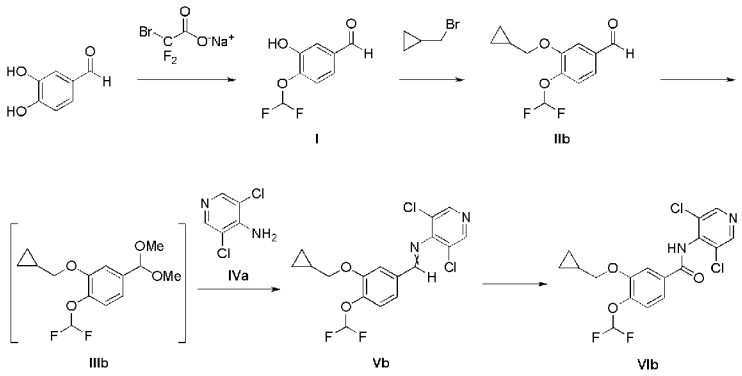


Fig. 2

(57) Abstract: The present invention provides novel processes for the preparation of N-substituted benzamides having the formula VIc: (formula) In some embodiments, the invention provides a process for preparation of roflumilast and other pharmaceutically active species. Novel compounds, including intermediates for the synthesis of roflumilast, are also provided.

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A NOVEL PROCESS FOR THE PREPARATION OF ROFLUMILAST

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] NOT APPLICABLE

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] NOT APPLICABLE

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK

[0003] NOT APPLICABLE

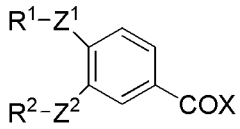
BACKGROUND OF THE INVENTION

[0004] Phosphodiesterases (PDEs) are a family of enzymes that metabolize 3′,5′ cyclic nucleotides to 5′ nucleoside monophosphates, thereby terminating cyclic adenosine monophosphate (cAMP) second messenger activity. Phosphodiesterase-4 (PDE4), a high affinity, cAMP-specific type IV PDE, has generated interest as a potential target for the development of novel anti-asthmatic and anti-inflammatory compounds. PDE4 is known to exist in at least four isoforms, each of which is encoded by a distinct gene. Each of the four known PDE4 gene products is believed to play varying roles in over forty allergic and/or inflammatory responses. It is thus believed that the inhibition of PDE4, and in particular the inhibition of specific isoforms that produce detrimental responses, can beneficially affect allergy and inflammation symptoms. Practical and economical methods providing novel PDE4 inhibitors are therefore highly desirable.

[0005] Roflumilast (CAS 162401-32-3) is a member of a class of fluoroalkoxy-substituted benzamides developed by BYK Gulden Lomberg Chemische Fabrik GmbH (see, for example, U.S. Patent No. 5,712,298). The chemical name of roflumilast is 3-(cyclopropylmethoxy)-N-(3,5-dichloro-pyridin-4-yl)-4-(difluoromethoxy)benzamide. The compound is indicated to be useful as a PDE4 inhibitor.

[0006] WO 95/01338 describes the preparation of dialkyl-substituted benzamides, including roflumilast, and the use thereof as PDE4 inhibitors. Such compounds are also proposed for the treatment of certain disorders of the skin such as dermatoses. WO 2004/033430 describes the preparation of a dialkoxy-substituted benzoyl compound which can be further converted to dialkoxy-substituted benzamides.

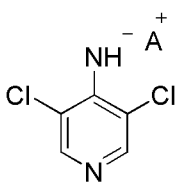
[0007] WO 94/02465 and WO 93/25517 describe the preparation of dialkoxy-substituted benzamides. The compounds are obtained by reacting activated benzoic acid derivatives of the general formula:



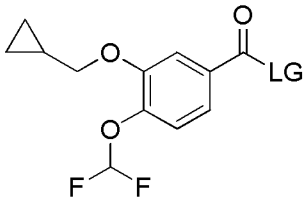
with amines of the general formula R^3NH_2. The disclosed benzoic acid derivatives are acid halides, especially acid chlorides, and anhydrides. The reaction takes place in the presence of a base (e.g. an organic base such as triethylamine, N-methylmorpholine, or pyridine; or an alkali metal hydride, such as sodium hydride) in an inert solvent.

[0008] WO 2004/080967 describes the preparation of dialkoxy-substituted benzamides from dialkoxy-substituted benzoic acid and the anion of 4-amino-3,5-dichloropyridine. Roflumilast is prepared using the anion of 4-amino-3,5-dichloropyridine (Scheme 1, Formula **1**, below) and an activated derivative of 3-cyclopropylmethoxy-4-difluoromethoxybenzoic acid that contains a suitable leaving group (Scheme 1, Formula **2**, below). The use of a strong base, such as KO^tBu, NaO^tBu, or LiO^tBu, is necessary to prepare the anion **1**. The reaction temperature must be maintained between 15 and 30°C. The preparation of benzoic acid derivative **2**, where LG is a chloride leaving group, requires 1-4 equivalents of thionyl chloride for reaction with 3-cyclopropylmethoxy-4-difluoromethoxybenzoyl acid at 70-90°C. The coupling of **1** and **2** is carried out at 20-30°C in DMF.

Scheme 1



1



2

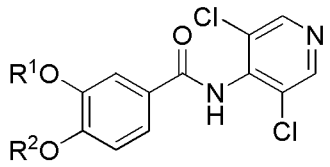
[0009] WO 2004/033430 describes the preparation of a dialkoxy-substituted benzoyl compound which can be further converted to dialkoxy-substituted benzamides, including

roflumilast, using carbonylation technology. The key intermediates, including 3-cyclopropyl methoxy-4-difluoromethoxybenzoic acid and its derivatives (as disclosed in WO 2004/080967), are derived via carbonylation of l-halo-3-cyclopropylmethoxy-4-difluoromethoxybenzene.

[0010] Although processes for roflumilast preparation have been disclosed as discussed above, none of the known methods are environmentally friendly. The known processes are either environmentally unfriendly or use harsh conditions. WO 95/01338, for example, describes the preparation of dialkyl-substituted benzamides using thionyl chloride, reaction of which can produce dangerous gases, and pyrophoric strong bases such as sodium hydride. Meanwhile, WO 2004/080967 describes the preparation of roflumilast using combustible potassium *tert*-butoxide (KO^tBu). Therefore, there is still an unmet need for a simple and safe process for industrial preparation of roflumilast and similar benzamides. The practical and economical processes disclosed herein address this need and other needs.

BRIEF SUMMARY OF THE INVENTION

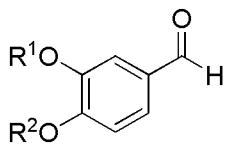
[0011] In one aspect, the present invention provides a process for the preparation of a compound of formula **VIc**:



VIc

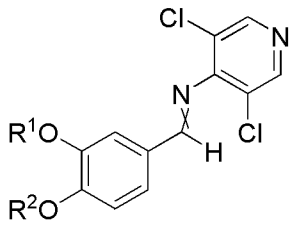
The process includes:

a) converting a compound of formula **IIc**



IIc

to a compound of formula **Vc**



Vc

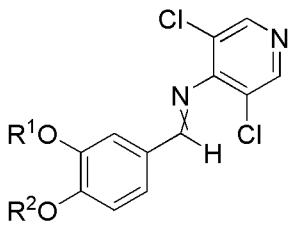
in a one-pot reaction; and

b) oxidizing the compound of formula **Vc** under conditions suitable to provide the compound of formula **VIc**;

wherein

R^1 and R^2 are independently selected from the group consisting of H; C_{1-6} alkyl; C_{3-7} cycloalkyl; C_{3-7} cycloalkylmethyl; and C_{1-4} alkyl which is partially or completely substituted with fluorine.

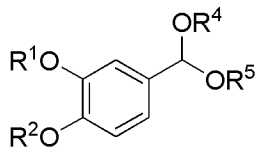
[0012] In a second aspect, the present invention provides a compound of formula **Vc**



Vc ,

wherein the 'crossed' imine bond indicates cis, trans or a mixture of cis and trans isomers,

as well as a compound of formula **IIIc**



IIIc ;

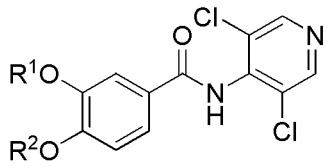
wherein:

R^1 are R^2 independently selected from the group consisting of H; C_{1-6} alkyl; C_{3-7} cycloalkyl; C_{3-7} cycloalkylmethyl; and C_{1-4} alkyl which is partially or completely substituted with fluorine; and

R^4 and R^5 are independently selected from the group consisting of C_{1-6} alkyl and acyl; or

R^4 and R^5 are taken together to form an optionally substituted 5-7 member cyclic ring.

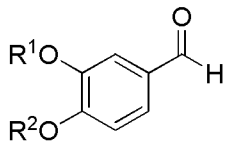
[0013] In a third aspect, the present invention provides a process for the preparation of a compound of structure **VIc**



VIc

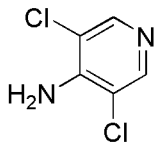
The process includes:

a) contacting a compound of formula **IIc**



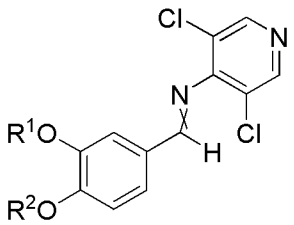
IIc

with a compound of formula **IVa**



IVa

under conditions sufficient to provide a compound of formula **V**



Vc ; and

b) oxidizing the compound of formula **Vc** under conditions suitable to provide the compound of formula **VIc**;

wherein

R^1 are R^2 independently selected from the group consisting of H; C_{1-6} alkyl; C_{3-7} cycloalkyl; C_{3-7} cycloalkylmethyl; and C_{1-4} alkyl which is partially or completely substituted with fluorine.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Figure 1 shows the schematic for the synthesis of *N*-(3,5-dichloro-pyridin-4-yl)-3,4-dimethoxy-benzamide from 3,4-dimethoxybenzaldehyde.

[0015] Figure 2 shows the schematic for the synthesis of roflumilast from 3-cyclopropyl methoxy-4-difluoromethoxybenzaldehyde.

DETAILED DESCRIPTION OF THE INVENTION

I. General

[0016] The present invention provides a process for preparation of substituted benzamides from substituted benzaldehydes. The novel one-pot methods have been discovered to be mild, safe, economically efficient, and environmentally friendly. The inventive process eliminates the need for caustic or dangerous reagents such as thionyl chloride and sodium hydride.

II. Definitions

[0017] As used herein, the term "contacting" refers to the process of bringing into contact at least two distinct species such that they can react. It should be appreciated, however, that the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents which can be produced in the reaction mixture.

[0018] As used herein, the term "alkyl" by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain hydrocarbon radical. Alkyl substituents, as well as other hydrocarbon substituents, may contain number designators indicating the number of carbon atoms in the substituent (*i.e.* C_1-C_8 means one to eight carbons), although such designators may be omitted. Unless otherwise specified, the alkyl groups of the present invention contain 1 to 12 carbon atoms. For example, an alkyl group can contain 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 1-11, 1-12, 2-3, 2-4, 2-5, 2-6, 3-4, 3-5, 3-6, 4-5, 4-6 or 5-6 carbon atoms. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like.

[0019] As used herein, the term "acyl" refers to an alkyl radical as described above, wherein the carbon atom attached to the remainder of a molecule is substituted with an oxo group so as to form a C=O bond. Examples of acyl groups include, but are not limited to, acetyl, propionyl, and butyryl.

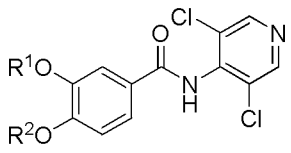
[0020] As used herein, the term "cycloalkyl" refers to an alkyl group as described above, wherein the carbon chain is a cyclic carbon chain. The cycloalkyl groups of the present invention contain at least 3 carbon atoms.

[0021] As used herein, the term "one-pot reaction" refers to a reaction in which a starting material undergoes at least two sequential chemical transformations in a single reaction vessel. In general, compounds formed as intermediates in the sequence are not isolated from a one-pot reaction mixture. Reagents necessary to effect the transformation sequence may be added together at the beginning of the sequence, or they may be added one after another as the sequence progresses.

[0022] As used herein, the term "protecting reagent" refers to a reagent capable of reacting with a functional moiety to form a protecting group that renders the functional moiety unreactive. The protecting group is also removable so as to restore the functional moiety to its original state. A protecting reagent can be an "aldehyde protecting reagent" wherein the protected functional moiety is an aldehyde. Such reagents are capable of reacting with aldehydes to form protecting groups including acetals, monothioacetals, dithioacetals, and hydrazones. Various protecting groups and protecting reagents, including aldehyde protecting reagents, are well known to one of ordinary skill in the art and include compounds that are disclosed in *Protective Groups in Organic Synthesis*, 4th edition, T. W. Greene and P. G. M. Wuts, John Wiley & Sons, New York, 2006, which is incorporated herein by reference in its entirety.

III. Embodiments of the Invention

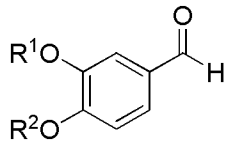
[0023] The present invention provides a process for the preparation of substituted benzamides from substituted benzaldehydes. In one aspect, the invention provides a process for the preparation of a compound of formula **VIc**:



VIc

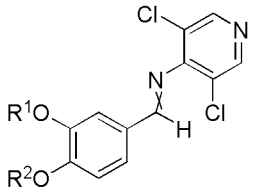
The process includes:

a) converting a compound of formula **IIc**



IIc

to a compound of formula **Vc**



Vc

in a one-pot reaction; and

b) oxidizing the compound of formula **Vc** under conditions suitable to provide the compound of formula **VIc**;

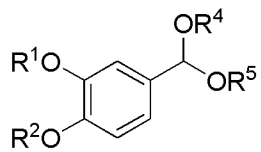
wherein:

R^1 and R^2 are independently selected from the group consisting of H; C_{1-6} alkyl; C_{3-7} cycloalkyl; C_{3-7} cycloalkylmethyl; and C_{1-4} alkyl which is partially or completely substituted with fluorine.

[0024] Throughout the specification, the use of a crossed imine double bond is meant to indicate *cis*, *trans*, or a mixture of *cis* and *trans* orientations about the double bond.

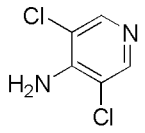
[0025] In some embodiments, a substituted benzaldehyde **IIc** is activated by converting it to a substituted benzaldehyde acetal. The substituted benzaldehyde acetal then reacts with 4-amino-3,5-dichloropyridine providing a substituted phenyl imine. The substituted phenyl imine is then oxidized to provide a substituted benzamide. In some embodiments, the one-pot reaction of step a), discussed above, comprises:

i) converting a compound of formula (IIc) under conditions sufficient to provide a compound of formula (IIIc)



IIIc ; and

ii) contacting the compound of formula IIIc with a compound of formula IVa



IVa

under conditions suitable to form the compound of formula **Vc**;

wherein:

R^4 and R^5 are independently selected from the group consisting of C_{1-6} alkyl and acyl; or

R^4 and R^5 are taken together to form an optionally substituted 5-7 member cyclic ring.

[0026] Preferably, the one-pot reaction converting **IIc** to **Vc** is conducted in a non-polar organic solvent under acidic conditions with or without an aldehyde protecting reagent. In some embodiments the invention provides a method for the preparation of a compound of formula **VIc** as described above, wherein: 1. the conversion of aldehyde **IIc** to benzacetal **IIIc** is conducted in a non-polar organic solvent in the presence of an acid; and 2. the one-pot conversion optionally includes an aldehyde protecting reagent. The organic solvent can be selected from suitable solvents including, but not limited to, toluene, xylene, and mixtures thereof. Acidic conditions can be maintained by using an acid such as *p*-toluenesulfonyl acid (PTSA), camphorsulfonic acid, acetic acid, and the like. In some embodiments the inventive process includes a one-pot reaction as described above, wherein the non-polar organic solvent is selected from the group consisting of toluene and xylene. In some embodiments the inventive process includes a one-pot reaction as described above, wherein the acid is selected from the group consisting of *p*-toluenesulfonic acid, camphorsulfonic acid, and acetic acid.

[0027] Any suitable aldehyde protecting reagent may be used in the methods of the present invention. Suitable reagents are capable of reacting with aldehydes to form protecting groups, including but not limited to acetals, monothioacetals, dithioacetals, and hydrazones. Such protecting groups can be removed to restore the aldehyde moiety. In some embodiments the inventive process includes a one-pot reaction as described above, wherein the aldehyde protecting reagent is selected from the group consisting of trimethyl orthoformate (TMOF), triethyl orthoformate, triethyl orthoacetate, trimethyl orthoacetate, acetic anhydride, ethylene glycol, and propylene glycol. One of skill in the art will appreciate that still other aldehyde protecting reagents may be useful in the inventive process.

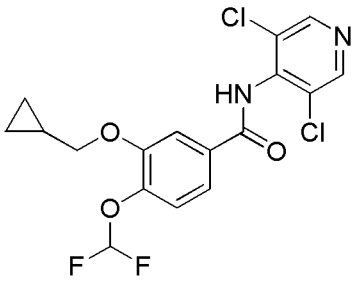
[0028] The oxidative conversion of **Vc** to **VIc** can be conducted under any suitable conditions. In particular, the present invention provides a process for preparing substituted benzamides via imine oxidation using aqueous conditions requiring neither strong bases nor

dangerous acid derivatives. The process is safe, energy efficient, and environmentally friendly. In some embodiments, benzamide oxidation is conducted using a mixture of tetrahydrofuran and water. In some embodiments the inventive process includes the oxidation of **Vc** as described above, wherein the oxidation step includes an oxidant selected from the group consisting of a chlorite, a transition metal catalyst, nickel peroxide, *meta*-chloroperoxybenzoic acid (*m*-CPBA), *tert*-butyl hydroperoxide (TBHP), potassium peroxomonosulfate (Oxone), or mixtures thereof. In some embodiments, the chlorite is selected from the group consisting of chlorous acid, magnesium chlorite, sodium chlorite, and potassium chlorite. The oxidation step can be conducted in a buffered solution. In some embodiments, the oxidation step is conducted with a chlorite that is buffered with an electrolyte selected from the group consisting of HCl/sodium citrate, citric acid/sodium citrate, acetic acid/sodium citrate, potassium dihydrogen phosphate, dipotassium phosphate/sodium dihydrogen phosphate, and disodium phosphate mixtures.

[0029] In some embodiments the present invention provides a process for preparing an *N*-substituted (3,4-dimethoxy)benzamide from a (3,4-dimethoxy)benzaldehyde, wherein the (3,4-dimethoxy)benzaldehyde is activated by converting it to a (3,4-dimethoxy)benzacetal (as shown, for example, in **Figure 1**). The (3,4-dimethoxy)benzacetal then reacts with 4-amino-3,5-dichloropyridine, resulting in an *N*-substituted (3,4-dimethoxy)benzylimine. The *N*-substituted (3,4-dimethoxy)benzylimine is then oxidized under conditions suitable to provide the *N*-substituted (3,4-dimethoxy)benzamide.

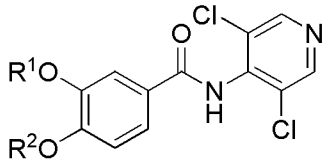
[0030] In some embodiments the present invention provides a process for preparing an *N*-substituted (3-cyclopropylmethoxy-4-difluoromethoxy)benzamide from a (3-cyclopropylmethoxy-4-difluoromethoxy)benzaldehyde, wherein the (3-cyclopropylmethoxy-4-difluoromethoxy)benzaldehyde is activated by converting it to a (3-cyclopropylmethoxy-4-difluoromethoxy)benzacetal (as shown, for example, in **Figure 2**). The (3-cyclopropylmethoxy-4-difluoromethoxy)benzacetal then reacts with a substituted amine (for example, 4-amino-3,5-dichloropyridine), resulting in an *N*-substituted (3-cyclopropylmethoxy-4-difluoromethoxy)benzylimine. One of skill in the art will understand that a variety of substituted amines can be used in this process. The *N*-substituted (3-cyclopropylmethoxy-4-difluoromethoxy)benzylimine is then oxidized to afford the *N*-substituted (3-cyclopropylmethoxy-4-difluoromethoxy)benzamide. In some embodiments, the *N*-substituted (3-cyclopropylmethoxy-4-difluoromethoxy)benzamide is roflumilast.

[0031] In some embodiments the present invention provides a process for preparing substituted benzamides as described above, wherein the compound of formula **VIc** is:



VIb

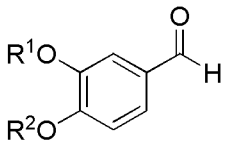
[0032] In a related aspect, the present invention provides a process for the preparation of a compound of structure **VIc**



VIc

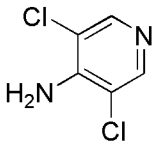
The process includes:

a) contacting a compound of formula **IIc**



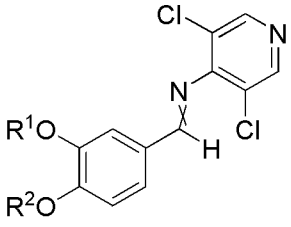
IIc

with a compound of formula **IVa**



IVa

under conditions sufficient to provide a compound of formula **Vc**



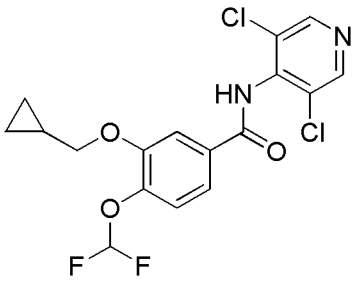
Vc ; and

b) oxidizing the compound of formula **Vc** under conditions suitable to provide the compound of formula **VIc**;

wherein

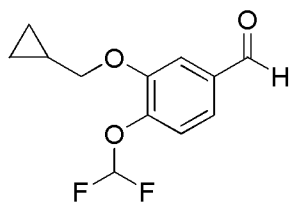
R^1 are R^2 independently selected from the group consisting of H; C_{1-6} alkyl; C_{3-7} cycloalkyl; C_{3-7} cycloalkylmethyl; and C_{1-4} alkyl which is partially or completely substituted with fluorine.

[0033] In general, the reaction conditions, oxidants, and buffering agents contemplated for use in this related aspect are as described above. In some embodiments, the conversion of **Vc** to **VIc** is conducted in a mixture of tetrahydrofuran and water. In some embodiments, the compound of formula **VIc** is:



VIb

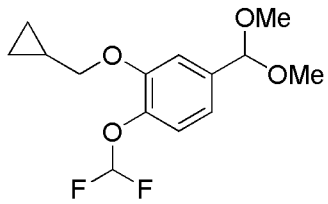
[0034] In some embodiments, the present invention provides a process for preparing an *N*-substituted 3-cyclopropylmethoxy-4-difluoromethoxy benzamide by oxidation of the *N*-substituted imine obtained from a benzaldehyde and an aminopyridine. The molar ratio of the benzaldehyde to the aminopyridine is from 1:1 to 1:1.2. The amount of aminopyridine required is dramatically reduced as compared to known methods. For example, WO 2004/080967 requires a molar ratio of 1:1.8 to 1:2.7 for a benzaldehyde derivative and an aminopyridine. Therefore, the inventive process as presently disclosed is more economically efficient. In some embodiments, the invention provides a process for the conversion of a compound of formula **IIb**, below, to a compound of formula **VIb**, i.e. roflumilast. The compound of formula **IIb** can be made according to WO 2008/15226.



IIb

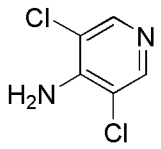
[0035] In some embodiments, the conversion process includes:

a) converting a compound of formula **IIb** in a one-pot reaction under conditions sufficient to provide a compound of formula **IIIb**



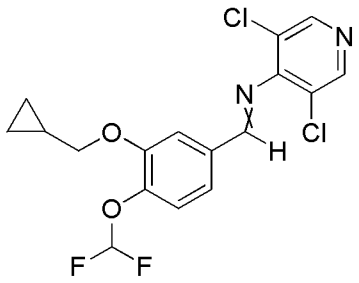
IIIb ; and

b) reacting the compound of formula **IIIb** with a compound of formula **IVa**



IVa

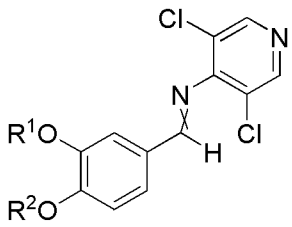
in the one-pot reaction under conditions suitable to form a compound of formula **Vb**



Vb ; and

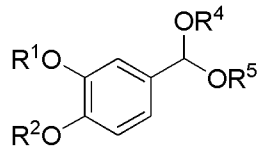
c) oxidizing the compound of formula **Vb** to provide the compound of formula **VIb**.

[0036] In another aspect, the present invention provides a compound of formula **Vc**



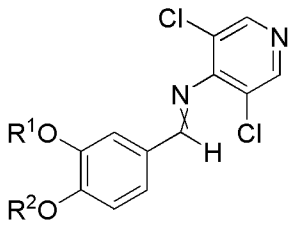
Vc ,

as well as a compound of formula **IIIc**



IIIc

[0037] In some embodiments, the invention provides a compound of formula **Vc**:



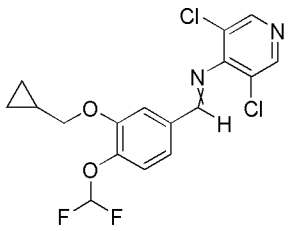
Vc ;

wherein:

R^1 and R^2 are independently selected from the group consisting of H; C_{1-6} alkyl; C_{3-7} cycloalkyl; C_{3-7} cycloalkylmethyl; and C_{1-4} alkyl which is partially or completely substituted with fluorine.

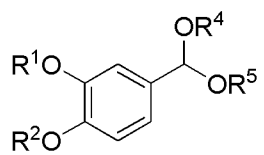
[0038] In some embodiments, the invention provides a compound of formula **Vc** wherein R^1 and R^2 are independently selected from the group consisting of C_{3-7} cycloalkylmethyl and C_{1-4} alkyl which is partially or completely substituted with fluorine.

[0039] In some embodiments, the compound of formula **Vc** has the formula:



Vb

[0040] In some embodiments, the invention provides a compound of formula **IIIc**:



IIIc ;

wherein:

R^1 are R^2 independently selected from the group consisting of H; C_{1-6} alkyl; C_{3-7} cycloalkyl; C_{3-7} cycloalkylmethyl; and C_{1-4} alkyl which is partially or completely substituted with fluorine; and

R^4 and R^5 are independently selected from the group consisting of C_{1-6} alkyl and acyl; or

R^4 and R^5 are taken together to form an optionally substituted 5-7 member cyclic ring.

[0041] In some embodiments, the invention provides a compound of formula **IIIc**, wherein:

R^1 and R^2 are independently selected from the group consisting of C_{1-6} alkyl; C_{3-7} cycloalkylmethyl; and C_{1-4} alkyl which is partially or completely substituted with fluorine; and

R^4 and R^5 are independently selected from the group consisting of C_{1-6} alkyl groups.

IV. Examples

[0042] The following examples are presented to describe the invention in further detail. However, the present invention is by no means restricted to the specific embodiments described herein.

Example 1

Synthesis of 3,5-dichloro-N-(3,4-dimethoxy)benzylidene)pyridin-4-amine(Va)

[0043] To a solution of 3,4-dimethoxybenzaldehyde (5 g, 30 mmol, 1.2 eq.) in toluene (25 mL) were added PTSA (103 mg, 0.6 mmol, 0.02 eq.) and TMOF (3.6 mL, 33 mmol, 1.32 eq.). The reaction mixture was heated to reflux for 2 hours and then cooled to 65 ± 5°C. 4-Amino-3,5-dichloropyridine (4.1 g, 25 mmol, 1.0 eq.) and additional PTSA (413 mg, 2 mmol, 0.08 eq.) were added and the reaction mixture was then heated to 120°C and refluxed for 15 hours. The mixture was cooled to room temperature and *n*-heptane (40 mL) was added. The precipitate was filtered, and the crude product was recrystallized from DCM/*n*-heptane to give 2.8 g of the imine as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 2H), 8.23 (s, 1H), 7.64 (s, 1H), 7.38 (d, 1H, J = 8.4 Hz), 6.98 (d, 1H, J = 8.4 Hz), 3.99 (s, 3H), 3.98 (s, 3H).

Example 2

Synthesis of *N*-(3,5-dichloro-pyridin-4-yl)-3,4-dimethoxy-benzamide (VIa)

[0044] The imine **Va** of Example 1 (311 mg, 1.0 mmol, 1.0 eq) was dissolved in a mixture of THF (5 mL) and 2-methylbut-2-ene (1.1 mL, 10.0 mmol, 10.0 eq). $NaClO_2$ (452 mg, 5.0

mmol, 5.0 eq) was then added to the solution. The reaction mixture was vigorously stirred while an aqueous solution of NaH_2PO_4 (3.3 M, 1.5 mL, 5.0 mmol, 5.0 eq) was added dropwise. When the reaction was complete as assessed by TLC, the reaction mixture was diluted with DCM (30 mL) and washed with water, 10% aqueous $Na_2S_2O_3$, and brine (10 mL each). The organic layer was dried over $MgSO_4$ and solvents were evaporated to afford the crude benzamide (283 mg). ^1H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 2H), 7.69 (s, 1H), 7.54-7.52 (m, 3H), 6.97 (d, 1H, J = 9.0 Hz), 6.97 (s, 6H).

Example 3

Synthesis of 3,5-dichloro-N-(3-(cyclopropylmethoxy)-4-(difluoromethoxy) benzylidene) pyridin-4-amine (Vb)

[0045] To a solution of **IIb** (5.0 g, 20.6 mmol, 1.0 eq) in toluene (25 mL) were added PTSA (71 mg, 0.41 mmol, 0.02 eq) and TMOF (2.4 g, 22.6 mmol, 1.1 eq). The reaction mixture was heated to reflux for 2 hours. Then additional TMOF (2.4 g, 22.6 mmol, 1.1 eq) and PTSA (142 mg, 0.82 mmol, 0.04 eq) were added and heating was continued for 1 hour, after which the reaction was finished as assessed by TLC. The reaction temperature was lowered to 70-80°C, and **IVa** (2.5 g, 15.3 mmol, 0.75 eq) and PTSA (142 mg, 0.82 mmol, 0.04 eq) were added. The mixture again was heated to reflux. After 15 hours, additional PTSA (355 mg, 2.05 mmol, 0.1 eq) and **IVa** (1.8 g, 11 mmol, 0.54 eq) were added and heating was continued for another 15 hours. Then, the mixture was cooled to room temperature and solvents were removed by evaporation. The residue was dissolved in dichloromethane and then washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated. The crude mixture was purified by column chromatography to afford 1.8 g (23% yield) of **Vb** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 2H), 8.26 (s, 1H), 7.68 (s, 1H), 7.39-7.26 (m, 2H), 7.00-6.51 (t, 1H, J = 75 Hz), 4.00 (d, 2H, J = 6.9 Hz), 1.33 (m, 1H), 0.71-0.65 (m, 2H), 0.42-0.38 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.38, 153.31, 150.98, 147.85, 144.15, 132.78, 124.23, 122.99, 122.29, 117.81 (CF_2, J_{CF} = 260 Hz), 115.74 (CF_2), 113.66 (CF_2), 112.51, 74.01, 9.99, 3.22. ^{19}F NMR (282 MHz, $CDCl_3$) δ - 82.24, - 82.51.

Example 3

Synthesis of 3-(cyclopropylmethoxy)-N-(3,5-dichloro-pyridin-4-yl)-4-(difluoromethoxy) benzamide, (VIb; roflumilast).

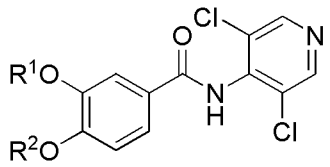
[0046] 3-(cyclopropylmethoxy)-N-(3,5-dichloro-pyridin-4-yl)-4-(difluoromethoxy) benzamide (VIb). Vb (387 mg, 1.0 mmol, 1.0 eq) was dissolved in a mixture of THF (5 mL) and 2-methylbut-2-ene (1.1 mL, 10.0 mmol, 10.0 eq), and then $NaClO_2$ (452 mg, 5.0 mmol, 5.0 eq) was added to the solution. The reaction mixture was vigorously stirred while an aqueous solution of NaH_2PO_4 (3.3 M, 1.5 mL, 5.0 mmol, 5.0 eq) was added dropwise. Upon reaction completion as assessed by TLC, the reaction mixture was diluted with EtOAc (30 mL) and washed with water, 10% aqueous $Na_2S_2O_3$, and brine (10 mL each). The organic layer was dried over $MgSO_4$ and solvents were evaporated to afford crude roflumilast **VIb** (400 mg).

[0047] Recrystallization of roflumilast. Crude roflumilast, IPA (6 mL), and purified water (2.1 mL) were added to a 25 mL flask. The mixture was stirred and heated to 75 ± 5°C to dissolve all material, and then the clear solution was cooled to the cloud point (55°C). The mixture was then held at the same temperature for 30 minutes. The mixture was cooled to 25 ± 5°C and continuously stirred at this temperature for 2 hours. The crystals were collected by filtration. The filter cake was washed with purified water and dried at 50 ± 5°C under reduced pressure to yield 230 mg (57% yield) of roflumilast as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 2H), 7.66 (s, 1H), 7.59 (d, 1H, J = 2.1 Hz), 7.49 (dd, 1H, J = 2.1, 8.4 Hz), 7.31 (d, 1H, J = 8.4 Hz), 7.00-6.50 (t, 1H, J = 74.7 Hz), 3.98 (d, 2H, J = 6.9), 1.4-1.2 (m, 1H), 0.70-0.67 (m, 2H), 0.39-0.37 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.70, 150.99, 148.38, 143.94, 139.70, 130.88, 128.91, 122.36, 119.93, 117.76 (CF_2, J_{CF} = 261 Hz), 115.68 (CF_2), 114.32, 113.66 (CF_2), 74.26, 10.02, 3.29. ^{19}F NMR (282 MHz, $CDCl_3$) δ -82.35, -82.62.

[0048] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference. Where a conflict exists between the instant application and a reference provided herein, the instant application shall dominate.

WHAT IS CLAIMED IS:

1. A process for the preparation of a compound of formula **VIc**

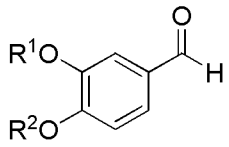


VIc

,

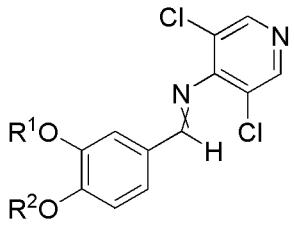
the process comprising:

a) converting a compound of formula **IIc**



IIc

to a compound of formula **Vc**



Vc

in a one-pot reaction; and

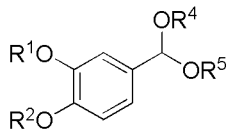
b) oxidizing the compound of formula **Vc** under conditions suitable to provide the compound of formula **VIc**;

wherein

R^1 and R^2 are independently selected from the group consisting of H; C_{1-6} alkyl; C_{3-7} cycloalkyl; C_{3-7} cycloalkylmethyl; and C_{1-4} alkyl which is partially or completely substituted with fluorine.

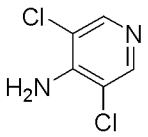
2. The process of claim **1**, wherein the one-pot reaction of step a) comprises:

i) converting a compound of formula **IIc** under conditions sufficient to provide a compound of formula **IIIc**



IIIc ; and

ii) contacting the compound of formula **IIIc** with a compound of formula **IVa**



IVa

under conditions suitable to form the compound of formula **Vc**;

wherein:

R^4 and R^5 are independently selected from the group consisting of C_{1-6} alkyl and acyl; or

R^4 and R^5 are taken together to form an optionally substituted 5-7 member cyclic ring.

3. The process of claim **2**, wherein:

step i) is conducted in a non-polar organic solvent in the presence of an acid; and

the one-pot reaction optionally comprises an aldehyde protecting reagent.

4. The process of claim **3,** wherein the non-polar organic solvent is selected from the group consisting of toluene and xylene.

5. The process of claim **3**, wherein the acid is selected from the group consisting of *p*-toluenesulfonic acid, camphorsulfonic acid, and acetic acid.

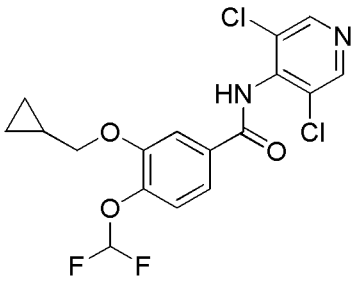
6. The process of claim **3**, wherein the aldehyde protecting reagent is selected from the group consisting of trimethyl orthoformate, triethyl orthoformate, triethyl orthoacetate, trimethyl orthoacetate, acetic anhydride, and ethylene glycol.

7. The process of claim **1**, wherein step b) comprises an oxidant selected from the group consisting of a chlorite, a transition metal catalyst, nickel peroxide, *m*-CPBA, TBHP, potassium peroxomonosulfate, and mixtures thereof.

8. The process of claim **7**, wherein the chlorite is selected from the group consisting of chlorous acid, magnesium chlorite, sodium chlorite, and potassium chlorite.

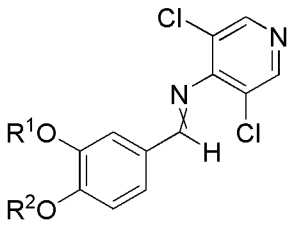
9. The process of claim **7**, wherein the chlorite is buffered with an electrolyte selected from the group consisting of HCl/sodium citrate, citric acid/sodium citrate, acetic acid/sodium citrate, potassium dihydrogen phosphate, dipotassium phosphate/sodium dihydrogen phosphate, and disodium phosphate.

10. The process of claim **1**, wherein the compound of formula **VIc** is:



VIb .

11. A compound of formula (Vc):



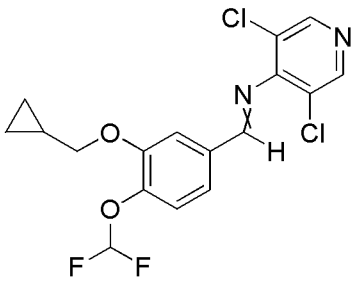
Vc ;

wherein

R^1 and R^2 are independently selected from the group consisting of H; C_{1-6} alkyl; C_{3-7} cycloalkyl; C_{3-7} cycloalkylmethyl; and C_{1-4} alkyl which is partially or completely substituted with fluorine.

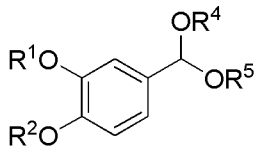
12. The compound of claim **11**, wherein R^1 and R^2 are independently selected from the group consisting of C_{3-7} cycloalkylmethyl and C_{1-4} alkyl which is partially or completely substituted with fluorine.

13. A compound of claim **11**, wherein the compound of formula **Vc** has the formula:



Vb .

14. A compound of formula **IIIc**:



IIIc ;

wherein:

R^1 and R^2 are independently selected from the group consisting of H; C_{1-6} alkyl; C_{3-7} cycloalkyl; C_{3-7} cycloalkylmethyl; and C_{1-4} alkyl which is partially or completely substituted with fluorine; and

R^4 and R^5 are independently selected from the group consisting of C_{1-6} alkyl and acyl; or

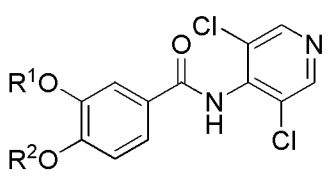
R^4 and R^5 are taken together to form an optionally substituted 5-7 membered cyclic ring.

15. The compound of claim **14**, wherein

R^1 and R^2 are independently selected from the group consisting of C_{1-6} alkyl; C_{3-7} cycloalkylmethyl; and C_{1-4} alkyl which is partially or completely substituted with fluorine; and

R^4 and R^5 are independently selected from the group consisting of C_{1-6} alkyl groups.

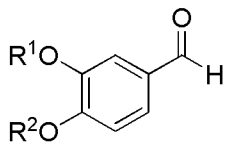
16. A process for the preparation of a compound of structure **VIc**



VIc ,

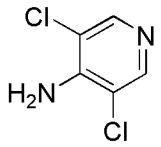
the process comprising:

a) contacting a compound of formula **IIc**



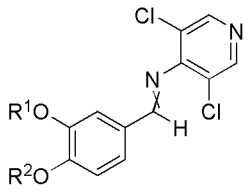
IIc

with a compound of formula **IVa**



IVa

under conditions sufficient to provide a compound of formula **Vc**



Vc ; and

b) oxidizing the compound of formula **Vc** under conditions suitable to provide the compound of formula **VIc**;

wherein

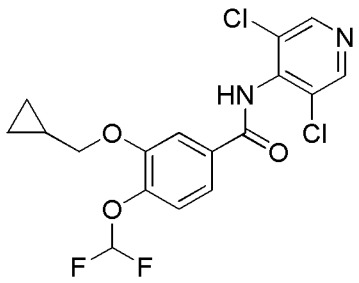
R^1 and R^2 are independently selected from the group consisting of H; C_{1-6} alkyl; C_{3-7} cycloalkyl; C_{3-7} cycloalkylmethyl; and C_{1-4} alkyl which is partially or completely substituted with fluorine.

17. The process of claim **16** wherein step b) comprises an oxidant selected from the group consisting of a buffered chlorite, a transition metal catalyst, nickel peroxide, *m*-CPBA, TBHP, potassium peroxomonosulfate, and mixtures thereof.

18. The process of claim **17**, wherein the chlorite is selected from the group consisting of chlorous acid, magnesium chlorite, sodium chlorite, and potassium chlorite.

19. The process of claim **17**, wherein the chlorite is buffered with an electrolyte selected from the group consisting of HCl/sodium citrate, citric acid/sodium citrate, acetic acid/sodium citrate, potassium dihydrogen phosphate, dipotassium phosphate/sodium dihydrogen phosphate, and disodium phosphate.

20. The process of claim **16**, wherein the compound of formula **VIc** is:



VIb .

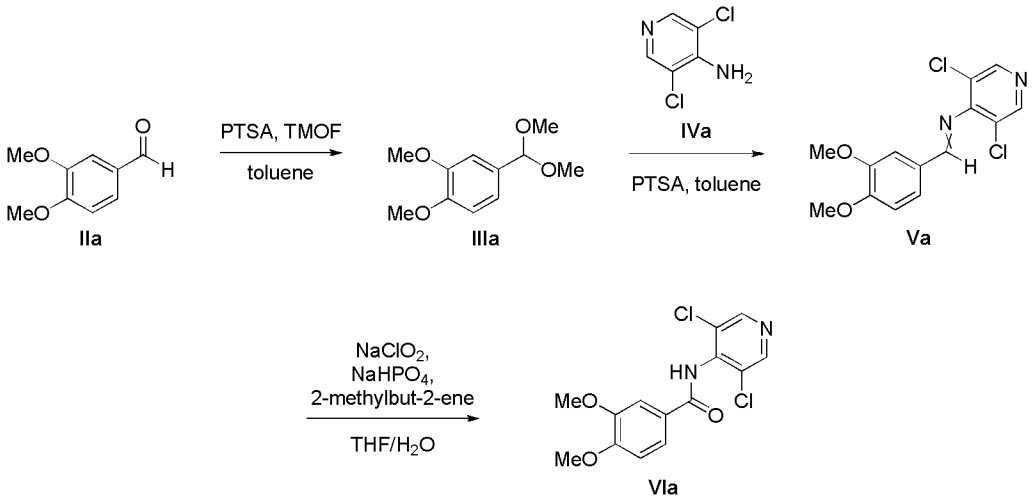

MeO
MeO
O
H
IIa
PTSA, TMOF
toluene
MeO
MeO
OMe
OMe
IIIa
Cl
N
NH2
Cl
IVa
PTSA, toluene
Cl
N
N
H
Cl
MeO
MeO
Va
NaClO2,
NaHPO4,
2-methylbut-2-ene
THF/H2O
Cl
N
HN
Cl
O
MeO
MeO
VIa

Fig. 1

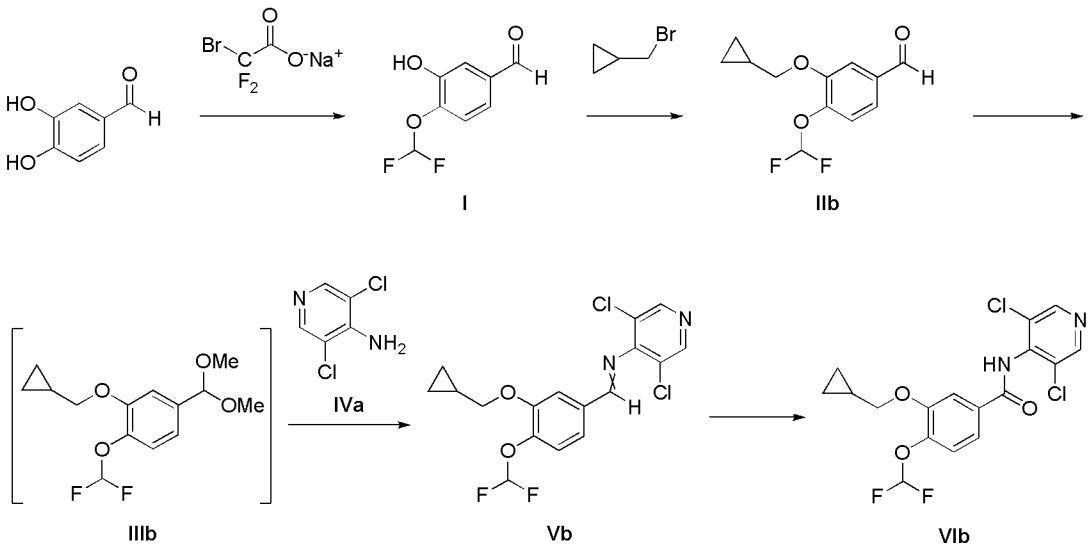

HO
HO
O
H
Br
C
F2
O
O-Na+
HO
O
H
O
F F
I
Br
O
O
H
O
F F
IIb
OMe
OMe
O
O
F F
IIIb
N
Cl
NH2
Cl
IVa
Cl
N
N
H
O
F F
Cl
Vb
Cl
N
HN
O
Cl
O
O
F F
VIb

Fig. 2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2012/072020

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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)

IPC: C07D 213, C07C 43

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)

WPI, EPODOC, CNPAT, CNKI, CAS

pyridine, pyridinyl, amino, amido, benzamide, roflumilast, prepare, intermediate, [162401-32-3]

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/080967 A1 (ALTANA PHARMA AG et al.), 23 Sep. 2004 (23.09.2004), see the whole document, especially claims 1-14	1-20
A	CN 102336703 A (BEIJING SECOND PHARM CO LTD), 01 Feb. 2012 (01.02.2012), see the whole document	1-20
A	CN 102351787 A (TIANJIN HANKANG PHARM BIOTECHNOLOGY CO L), 15 Feb. 2012 (15.02.2012), see the whole document	1-20

☐ 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	Date of mailing of the international search report
29 Nov. 2012 (29.11.2012)	**13 Dec. 2012 (13.12.2012)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer CHANG, Xiaoyu Telephone No. (86-10)62084403

Form PCT/ISA /210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2012/072020

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:

In this international application, there is no same or corresponding technical feature between cliams 14-15 and the other claims. The subject-matter of claims 14-15 are compound IIIc, and the other claims relate to the preparation method of compound VIc and its intermediate compound Vc. Compound IIIc is also a kind of intermediate for compound VIc, but it is not the intermediate of the final step, which is not like compound Vc. Thus, it has no common or corresponding special technical feature between the present claims 14-15 and the other claims. Thus, the application does not meet the requirements of unity of invention as defined in Rule 13.1 PCT.

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 fee.

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.:

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.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2012/072020

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
WO 2004/080967 A1	23.09.2004	AU 2004220357 A1	23.09.2004
		MXPA 04008070 A	01.01.2005
		BRPI 0406427 A	04.10.2005
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		JP 2006519818 A	31.08.2006
		NZ 539542 A	28.09.2007
		US 7470791 B2	30.12.2008
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		DE 602004023921 E	17.12.2009
		NO 329301 B	27.09.2010
		AU 2004220357 B	30.09.2010
		IL 168170 A	30.12.2010
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		IS 2723 B	15.03.2011
		AR 043531 A	03.08.2005
		HR 20050399 A	31.08.2006

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2012/072020

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
		RS 20050669 A	04.04.2008
		EA 009985 B	28.04.2008
		AT 447555 T	15.11.2009
		HK 1085480 A	11.12.2009
		PT 1606261 E	11.01.2010
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		SI 1606261 T	31.03.2010
		US 2012294942 A	22.11.2012
CN 102336703 A	01.02.2012	none	
CN 102351787 A	15.02.2012	none	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2012/072020

A. CLASSIFICATION OF SUBJECT MATTER

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

C07D 213/75 (2006.01)i
C07D 213/74 (2006.01)i
C07C 43/235 (2006.01)i
C07C 43/164 (2006.01)i