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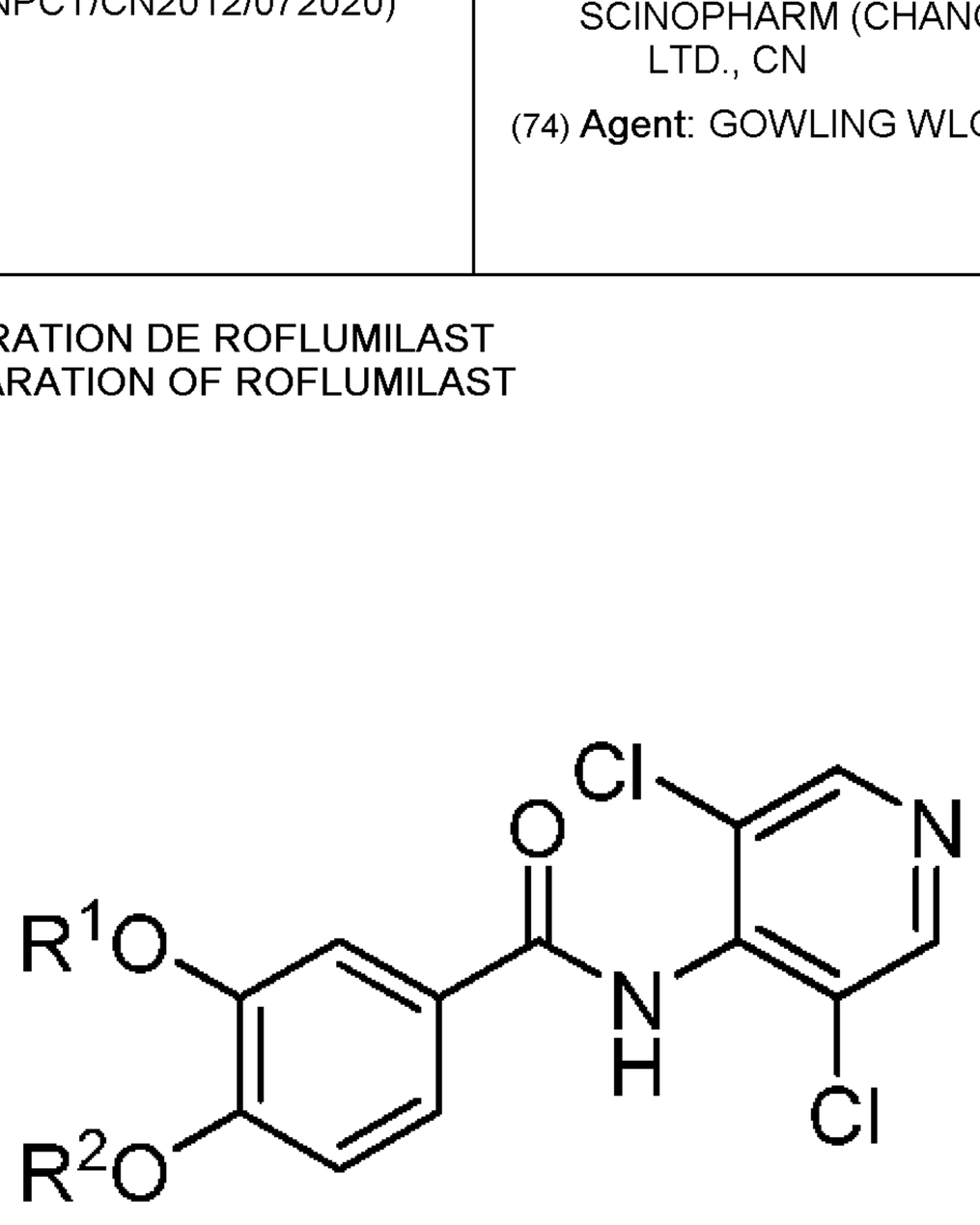
(54) Title: PROCESS FOR PREPARATION OF ROFLUMILAST




**VIc**

(57) Abrégé/Abstract:
The present invention provides novel processes for the preparation of N-substituted benzamides having the formula (VIc). 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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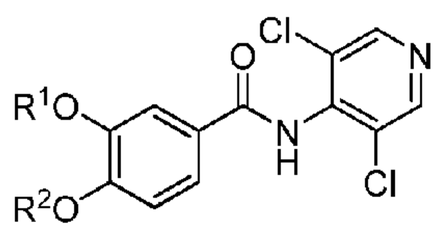



(VIc)

(57) **Abstract**: The present invention provides novel processes for the preparation of N-substituted benzamides having the formula (VIc). 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.

WO 2013/131484 A1

# PROCESS FOR PREPARATION OF ROFLUMILAST

**[0001]**

**[0002]**

**[0003]**

## BACKGROUND OF THE INVENTION

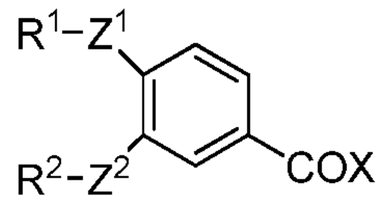
**[0004]** Phosphodiesterases (PDEs) are a family of enzymes that metabolize 3′,5′ cyclic nucleotides to 5′ nucleoside monophosphates, thereby regulating the activity of second messengers such as cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). Phosphodiesterase type 4 (PDE4), which is a subfamily of cAMP-specific PDE, has generated interest as a 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. 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.

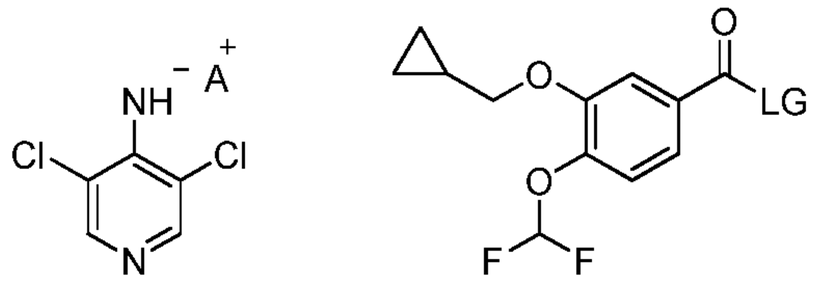
**[0007]** WO 94/02465 and WO 93/25517 describe the preparation of dialkoxy-substituted benzamides. The compounds are obtained by reacting activated benzoic acid derivatives of the general formula:




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**, and 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**



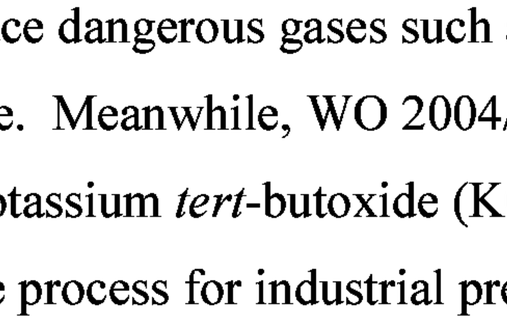

1 2

**[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 harmful or used in harsh conditions. WO 95/01338, for example, describes the preparation of dialkyl-substituted benzamides by making use of thionyl chloride, which is corrosive, explosive and may produce dangerous gases such as sulfur dioxide, and pyrophoric strong bases such as sodium hydride. Meanwhile, WO 2004/080967 describes the preparation of roflumilast by using combustible potassium *tert*-butoxide ($KO^tBu$). Accordingly, there remains 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

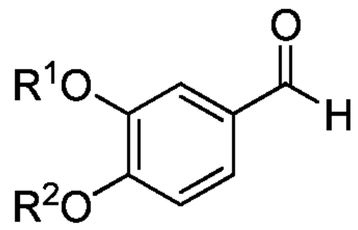
**[0011]** In one aspect, the present invention provides a process for the preparation of a compound of formula **VIc**:




**VIc**

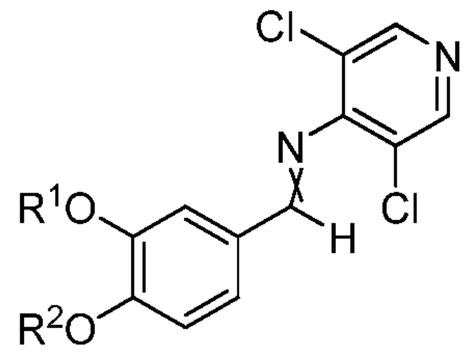
The process includes:

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



**IIc**

to a compound of formula **Vc**



**Vc**

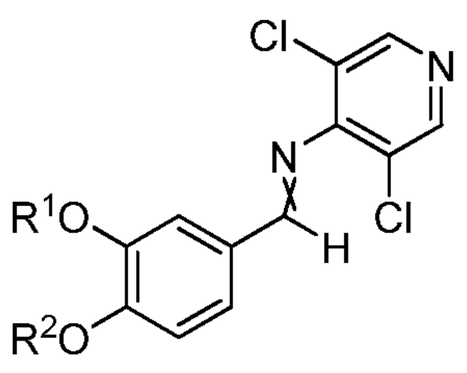
in a one-pot reaction; and

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**

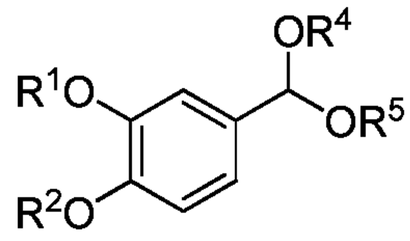


**Vc**

,

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** ;

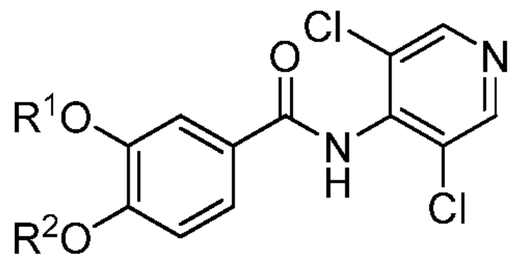
wherein:

$R^1$ 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 member cyclic ring.

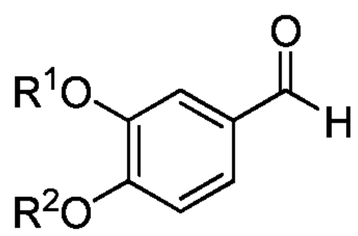
**[0013]** In a third aspect, the present invention provides a process for the preparation of a compound of structure **VIc**



**VIc** .

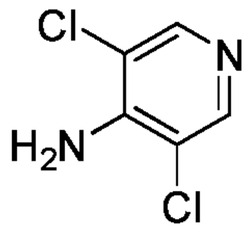
The process includes:

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



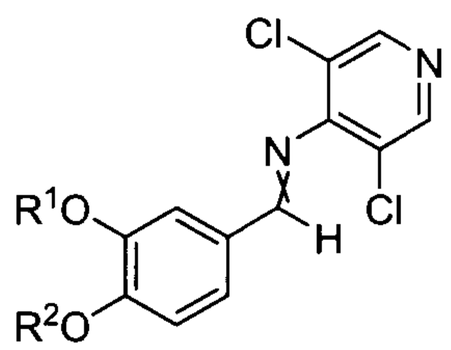
**IIc**

with a compound of formula **IVa**



**IVa**

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

## 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.

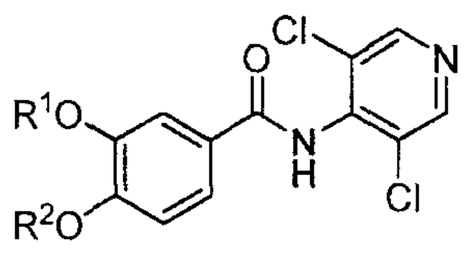
**[0021]** As used herein, the term "one-pot reaction" refers to a reaction in which a starting material undergoes at least two sequential chemical transformations in a single reaction vessel. In general, compounds formed as intermediates in the sequence are not isolated from a one-pot reaction mixture. Reagents necessary to affect 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 Wilcy & Sons, New York, 2006.

## III. Embodiments of the Invention

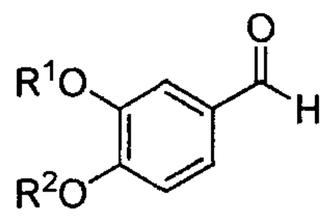
**[0023]** The present invention provides a process for the preparation of substituted benzamides from substituted benzaldehydes. In one aspect, the invention provides a process for the preparation of a compound of formula **VIc**:



**VIc**

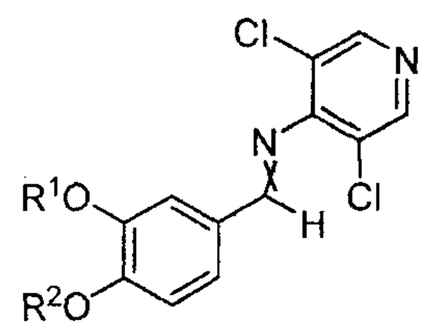
The process includes:

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**;

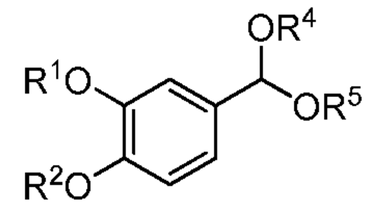
wherein:

$R^1$ 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.

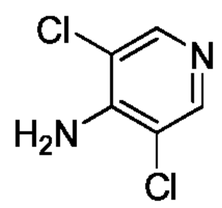
**[0025]** In some embodiments, a substituted benzaldehyde **IIc** is activated by converting it to a substituted benzaldehyde acetal. The substituted benzaldehyde acetal then reacts with 4-amino-3,5-dichloropyridine providing a substituted phenyl imine. The substituted phenyl imine is then oxidized 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, polymeric resin based sulfonic 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.

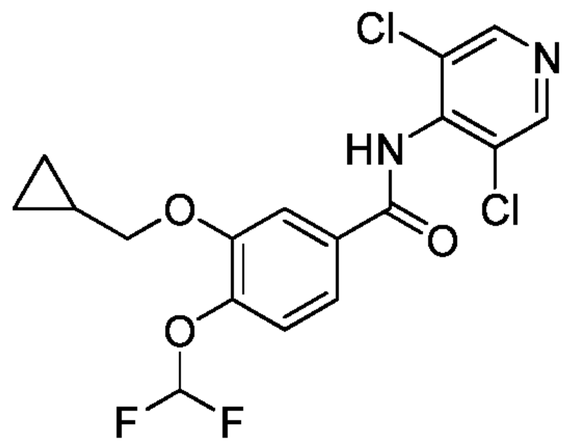
**[0028]** The oxidative conversion of **Vc** to **VIc** can be conducted under any suitable conditions. In particular, the present invention provides a process for preparing substituted benzamides via imine oxidation using aqueous conditions requiring neither strong bases nor dangerous acid derivatives.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

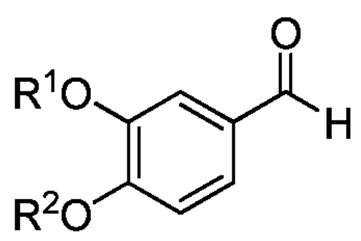
**[0030]** In some embodiments the present invention provides a process for preparing an *N*-substituted (3-cyclopropylmethoxy-4-difluoromethoxy)benzamide from a (3-cyclopropylmethoxy-4-difluoromethoxy)benzaldehyde, wherein the (3-cyclopropylmethoxy-4-difluoromethoxy)benzaldehyde is activated by converting 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:



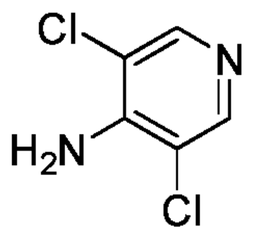
**VIb**

**[0032]** In some embodiments, the one-pot reaction converting **IIc** to **Vc** is conducted in conditions without using an aldehyde protecting reagent, wherein the one-pot reaction of step a) as discussed above, comprises contacting the compound of formula **IIc**



**IIc**

with a compound of formula **IVa**

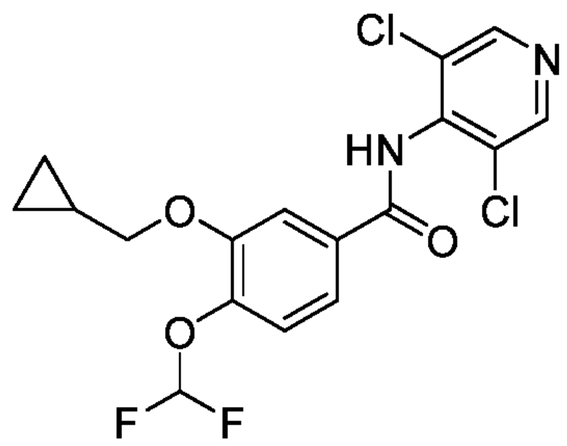


**IVa**

in the presence of a catalyst and/or reaction promoter to form the compound of formula **Vc**

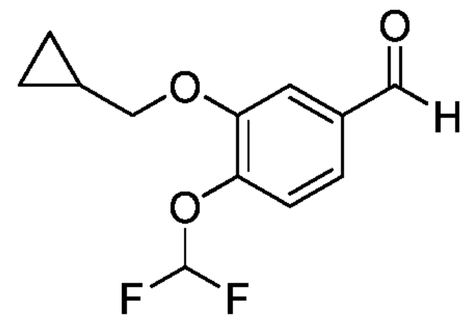
**[0033]** In some embodiments, the aforesaid process is conducted in the presence of a catalyst such as Lewis acid and reaction promoter like silylation reagent. In some embodiments the inventive process as described above, wherein the Lewis acid including, but not limited to trimethylsilyl trifluoromethanesulfonate (TMSOTf), trimethylsilyl chloride (TMSCl), *p*-toluenesulfonic acid (PTSA), trifluoromethanesulfonic acid (TfOH), methanesulfonic acid (MSA), Trifluoroacetic acid (TFA) and mixture thereof and/or the silylation reagent is selected from N,O-Bis(trimethylsilyl)trifluoroacetamide (BSTFA), Bis(trimethylsilyl)acetamide (BSA) and mixture thereof.

**[0034]** 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

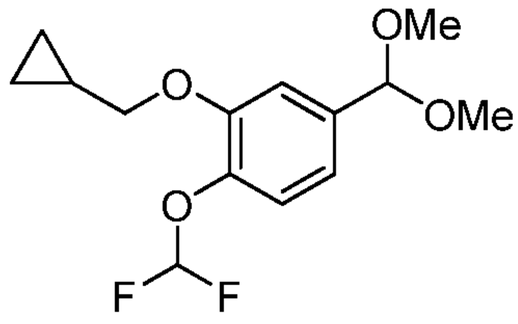
**[0035]** In some embodiments, the present invention provides a process for preparing an *N*-substituted 3-cyclopropylmethoxy-4-difluoromethoxy benzamide by oxidation of the *N*-substituted imine obtained from a benzaldehyde and an aminopyridine. The molar ratio of the benzaldehyde to the aminopyridine 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 2008/006509.



**IIb**

**[0036]** 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**

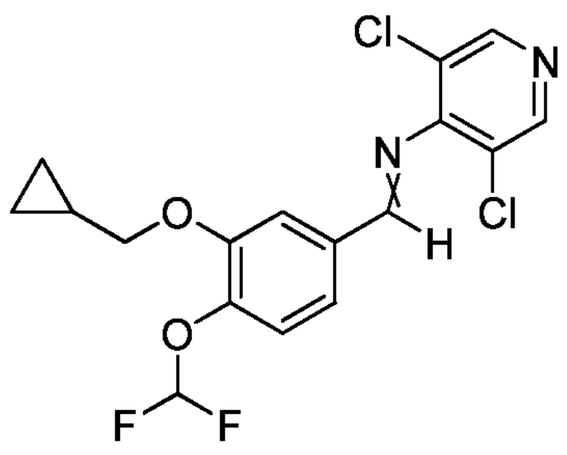


**IIIb** ; and

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**

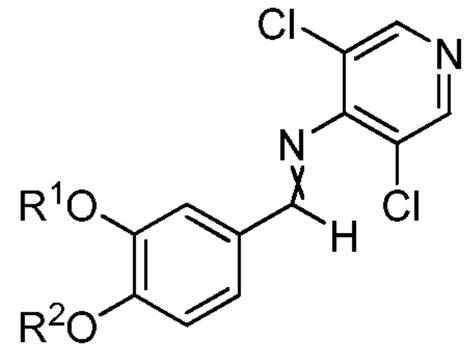


**Vb**

; and

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

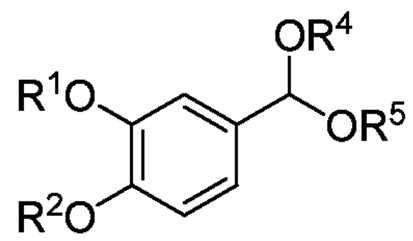
**[0037]** In another aspect, the present invention provides a compound of formula **Vc**



**Vc**

,

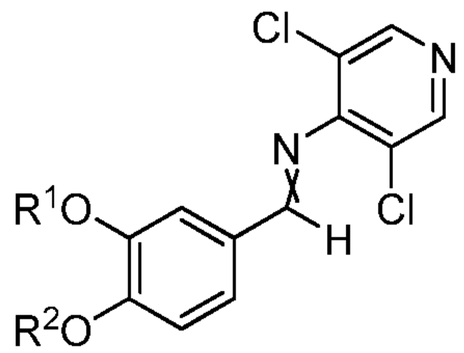
as well as a compound of formula **IIIc**



**IIIc**

.

**[0038]** In some embodiments, the invention provides a compound of formula **Vc**:



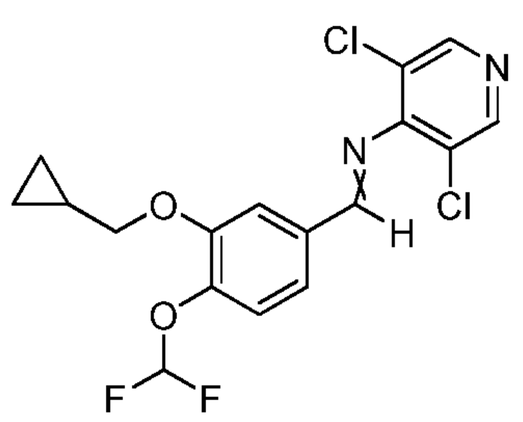
Vc ;

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.

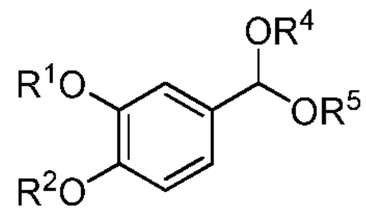
**[0039]** In some embodiments, the invention provides a compound of formula **Vc** wherein $R^1$ and $R^2$ are independently selected from the group consisting of $C_{3-7}$ cycloalkylmethyl and $C_{1-4}$ alkyl which is partially or completely substituted with fluorine.

**[0040]** In some embodiments, the compound of formula **Vc** has the formula:



Vb .

**[0041]** 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.

**[0042]** 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

**[0043]** 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)**

**[0044]** 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)**

**[0045]** 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)**

**[0046]** To a solution of **IIb** (30 g, 123.9 mmol, 1.0 eq) in toluene (150 mL) at 20-30 °C under $N_2$ atmosphere were added trimethyl orthoformate (TMOF, 46.0 g, 433.7 mmol, 3.5 eq) and Amberlyst 15 wet (9.0 g, 30% w/w). The mixture was heated to reflux then kept refluxing until reaction completed. The solvent and excess TMOF were removed under reduced pressure at 50-60 °C to obtain **IIIb**. Toluene (150 mL) was added to the mixture and followed by the addition of **IVa** (21.2 g, 130.1 mmol, 1.05 eq) and TFA (2.8 g, 24.8 mmol, 0.2 eq) at a temperature of 40-50 °C. The flask was connected with condenser and receiver, and the mixture was again heated to 110 °C and distillation was continued until the reaction was completed. The mixture was cooled to 50-60 °C, then filtered and the solid was washed with toluene (30 mL). The filtrate was washed by saturated $NaHCO_3$ (60 mL) and water (60 mL), respectively. The organic phase was removed under reduced pressure (30-50 mmHg). The flask was charged with 95% EtOH (150 mL) and then 75 mL of solvent was distilled under reduced pressure at 50 °C. Repeatedly, 75 mL of 95% EtOH was charged to the residue then 75 mL of solvent was distilled to afford **Vb** in EtOH solution. The mixture was cooled to 25 °C then additional 95% EtOH was charged to the residue to 210 mL followed by $H_2O$ (90 mL) at the same temperature. The suspended solution was allowed to stirred for 30 min then cooled 0-5 °C then stirred for 1 hour. The slurry was filtered and the filter cake was washed with $H_2O$ (30 mL) and dried under reduced pressure at 40 °C for 2 hours to obtain **Vb** (35 g, 73% yield).

MS *m/z* (M+1): 387.1;

IR (KBr): 3000, 2940, 1635, 1550, 1270, 1550 $^{-1}$cm.

$^1H$ 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 4

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

**[0047]** **Vb** (24 g, 62.0 mmol, 1.0 eq.) was dissolved in a mixture of $CH_3CN$ (96 mL) and 2-methyl-2-butene (17.5 g, 248.2 mmol, 4.0 eq.). Then 25% aqueous $NaClO_2$ [28.0 g (80% solid, 249 mmol) in 84 mL $H_2O$ (4.0 eq)] was added in one portion. The mixture was placed into an ice-water bath. A solution of aqueous $CH_3COOH$ [$CH_3COOH$ (11.2 g, 186 mmol) diluted in $H_2O$ (48 mL, 3.0 eq).] was added and the temperature was maintained below 25 °C. The reaction mixture was vigorously stirred at 20-30 °C while product precipitated slowly as the reaction progressed. The reaction was stirred for 2 hours, 96 mL of $H_2O$ was added and stirring was continued for 1 hour. The resulting slurry was filtered and the filter cake was washed with $H_2O$ (36 mL). The product was dried under reduced pressure at 40 °C for 3 hours to obtain crude **VIb**, roflumilast (22.4 g, 92.4% yield with 98.0% purity).

**[0048] Recrystallization of roflumilast.**

Crude roflumilast (10 g, 24.8 mmol) and $CH_3CN$ (45 mL) were placed in a 250-mL reactor. The mixture was stirred and heated 65 °C to dissolve material. Insoluble material was removed by hot filtration. The mixture was heated to 70 °C then $H_2O$ (22.3 mL) was added to the solution at the same temperature, then cooled down to 68 ± 2°C and held at that temperature for 2 hours. The mixture was cooled to 25 ± 3 °C and continuously stirred at this temperature for 12 hours. The resulting crystals were collected by filtration, and the filter cake washed with $H_2O$ (10 mL), dried at 40 ± 2 °C under reduced pressure for 4 hours to get roflumilast (8.2 g, 82% yield with 99.7% purity).

MS *m/z* (M+1): 403.0

IR (KBr): 3445, 3262, 1651, 1503, 1156 $^{-1}$cm.

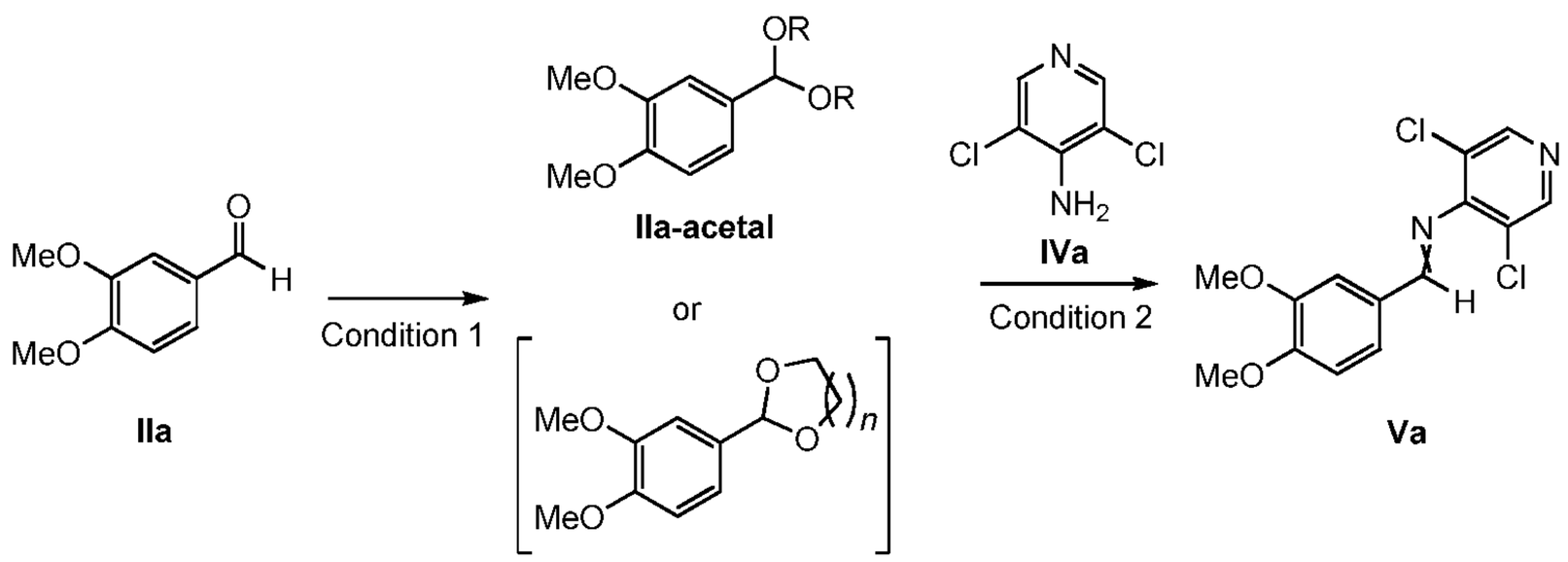
$^1$H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 2H), 7.66 (s, 1H), 7.59 (d, 1H, $J$ = 2.1 Hz), 7.49 (dd, 1H, $J$ = 2.1, 8.4 Hz), 7.31 (d, 1H, $J$ = 8.4 Hz), 7.00-6.50 (t, 1H, $J$ = 74.7 Hz), 3.98 (d, 2H, $J$ = 6.9), 1.4-1.2 (m, 1H), 0.70-0.67 (m, 2H), 0.39-0.37 (m, 2H).

$^{13}C$ 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.

## Example 5

**Synthesis of N-(3,5-dichloro-pyridin-4-yl)-3,4-dimethoxy-benzamide (Va) via different acetals.**




**[0049]** The compound of formula **Va** can be prepared from 3,4-dimethoxybenzaldehyde via different acetals. The experimental procedure in Example 1 is applied. The details of reagent and the results are summarized in Table 1.

**Table 1**

| Entry | **IIa** to **IIa-acetal or cyclic acetal** | | **IIa-acetal or IIa-cyclic acetal** to **Va** | |
|---|---|---|---|---|
| | Condition 1 | Result | Condition 2 | Result |
| 1 | **IIa-acetal: R = Ac**<br>**IIa ,** Acetic anhydride, $I_2$, $CH_2Cl_2$ | Reaction was completed. | **IVa**, PTSA · $H_2O$, reflux | 43% of **Va** and 54% of **IIa-acetal** by HPLC |
| 2 | **IIa-acetal: R = Et**<br>**IIa**, TEOF, $NH_4Cl$, EtOH, reflux | Reaction was completed. | **IVa**, PTSA · $H_2O$, reflux | 87% of **Va** and 13% of **IIa-acetal** by HPLC |
| 3 | **IIa- cyclic acetal**: n = 2<br>**IIa**, propane-1,3-diol, PTSA · $H_2O$, toluene, reflux | Reaction was completed. | **IVa**, PTSA · $H_2O$, reflux for 33 hours | 5 % of **Va** by LCMS |
| 4 | **IIa- cyclic acetal**: n = 1<br>**IIa**, ethane-1,2-diol, PTSA · $H_2O$, toluene, reflux | Reaction was completed. | **IVa**, PTSA · $H_2O$, reflux for 30 hours | 5% of **Va** by LCMS |

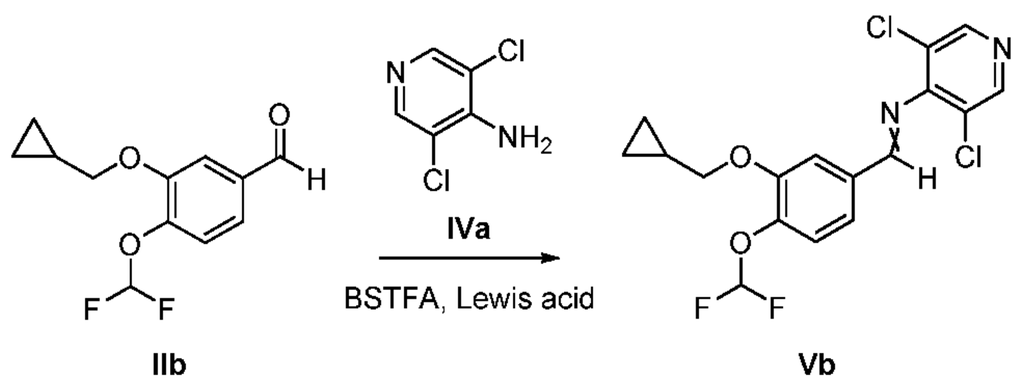
## Example 6

**Synthesis of N-(3,5-dichloro-pyridin-4-yl)-3,4-dimethoxy-benzamide (Va) without via acetal intermediates.**

**[0050]** 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 4-Amino-3,5-dichloropyridine (4.1 g, 25 mmol, 1.0 eq.). The reaction mixture was heated to reflux for 30 days. 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 2.24 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 7

**Synthesis of 3,5-dichloro-N-(3-(cyclopropylmethoxy)-4-(difluoromethoxy) benzylidene) pyridin-4-amine (Vb) without an acetal intermediate.**




**[0051]** As is evident from the embodiment, the synthesis of the compound of formula **IIb** to the compound of formula **Vb** directly can be carried out with various Lewis acids in the presence of *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA). **Table 2** shows the result using TMSOTf, TMSCl, PTSA, TfOH, MSA and TFA. The percentage of the convergence is observed via HPLC. The reaction is operated under conventional conditions in the presence of 0.2 equivalent of the Lewis acid. The reaction duration is from 3 to 48 hours.

**Table 2**

| Entry | Condition & materials | **Vb HPLC purity** |
|---|---|---|
| 1 | **IVa**, BSTFA, TMSOTf, $CH_3CN$, reflux for 3h | **60%** |
| 2 | **IVa**, BSTFA, TMSCl, $CH_3CN$, reflux for 24h | **23%** |

| | | |
|---|---|---|
| 3 | **IVa**, BSTFA, PTSA, $CH_3CN$, reflux for 48h | **70%** |
| 4 | **IVa**, BSTFA, TfOH, $CH_3CN$, reflux for 5h | **62%** |
| 5 | **IVa**, BSTFA, MSA, $CH_3CN$, reflux for 20h | **70%** |
| 6 | **IVa**, BSTFA, TFA, $CH_3CN$, reflux for 18h | **25%** |

## Example 8

**Synthesis of *N*-(3,5-dichloro-pyridin-4-yl)-3,4-dimethoxy-benzamide (VIa) using different oxidation conditions.**

**[0052]** As is evident from the embodiment, the oxidation of the compound of formula **Va** to the compound of formula **VIa** can be carried out with various oxidants. **Table 3** shows the result using $KMnO_4$, *m*-CPBA, Oxone and TBHP. The percentage of the convergence is observed via HPLC. The reaction is operated under conventional oxidation conditions in the presence of 1-2 equivalents of oxidant. The reaction duration is from 1 to 24 hours.

**Table 3**

| Entry | Oxidant | Result | |
|---|---|---|---|
| | | Observed **VIa** by HPLC | Percentage (by HPLC) |
| 1 | $KMnO_4$ | √ | 27.5% |
| 2 | *m*-CPBA | √ | <2% |
| 3 | Oxone | √ | <2% |
| 4 | TBHP | √ | 9.7% |

## Example 9

**3-(cyclopropylmethoxy)-N-(3,5-dichloro-pyridin-4-yl)-4-(difluoromethoxy) benzamide (VIb) using different oxidation conditions.**

**[0053]** As is evident from the embodiment, the oxidation of the compound of formula **Vb** to the compound of formula **VIb** can be carried out with various oxidants. **Table 4** shows the result using $KMnO_4$, *m*-CPBA, Oxone and TBHP. The percentage of the convergence is observed via HPLC. The reaction is operated under conventional oxidation conditions in the presence of 1-2 equivalents of oxidant. The reaction duration is from 1 to 24 hours.

**Table 4**

| Entry | Condition & materials | Isolation yield |
|---|---|---|

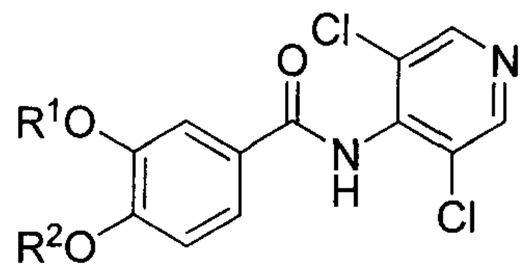
| | | |
|---|---|---|
| 1 | *m*-CPBA, $BF_3$•$Et_2O$,$CHCl_3$, rt | 28% |
| 2 | Oxone, $BF_3$-$Et_2O$, DMF | 32% |
| 3 | $KMnO_4$ (5.9 mmol), $CH_3CN/H_2O$, 50 °C | 65% |
| 4 | TBHP | < 2% by HPLC |

**[0054]** 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.

Where a conflict exists between the instant application and a reference provided herein, the instant application shall dominate.

**CLAIMS:**

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

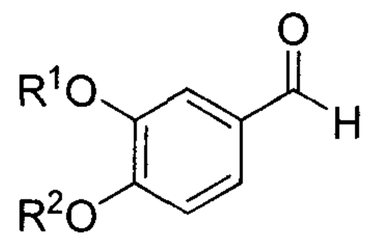


**VIc**

,

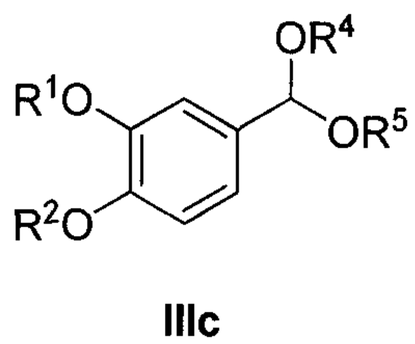
the process comprising:

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



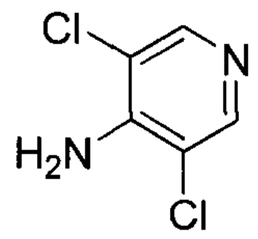
**IIc**

to a compound of formula **IIIc**



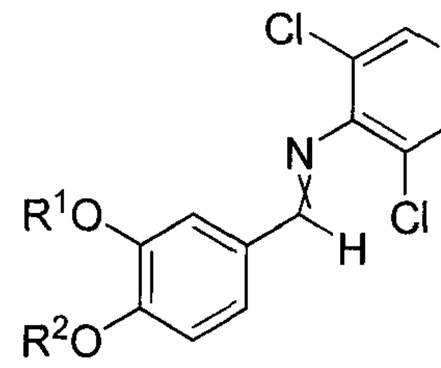
**IIIc** ; and

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



**IVa**

to form a compound of formula **Vc**



**Vc**

in a one-pot reaction; and

b) oxidizing the compound of formula **Vc** 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;

$R^4$ 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; and

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

**2**. The process of claim **1**, wherein:

step a) 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.

**3**. The process of claim **2,** wherein the non-polar organic solvent is selected from the group consisting of toluene and xylene.

**4**. The process of claim **2**, wherein the acid is selected from the group consisting of *p*-toluenesulfonic acid, camphorsulfonic acid, polymeric resin based sulfonic acid and acetic acid.

**5**. The process of claim **2**, 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.

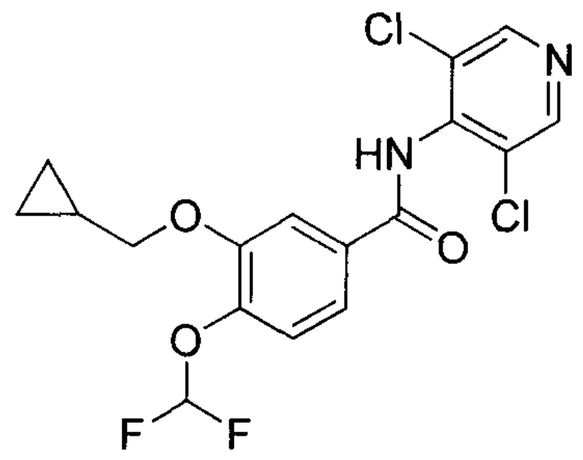
**6**. The process of claim **1**, wherein step b) comprises an oxidant selected from the group consisting of a chlorite, a transition metal catalyst, nickel peroxide, *m*-CPBA, TBHP, potassium peroxomonosulfate and mixtures thereof.

**7**. The process of claim **6**, wherein the chlorite is selected from the group consisting of chlorous acid, magnesium chlorite, sodium chlorite and potassium chlorite.

**8**. The process of claim **6**, wherein the chlorite is buffered with an electrolyte selected from the group consisting of HCl/sodium citrate, citric acid/sodium citrate, acetic

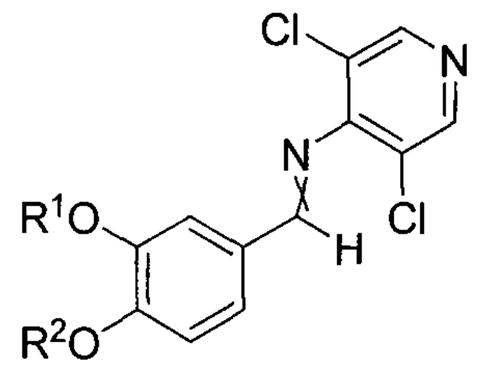
acid/sodium citrate, potassium dihydrogen phosphate, dipotassium phosphate/sodium dihydrogen phosphate, acetic acid and disodium phosphate.

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



**VIb**

**10**. A compound of formula **Vc**:



**Vc** ;

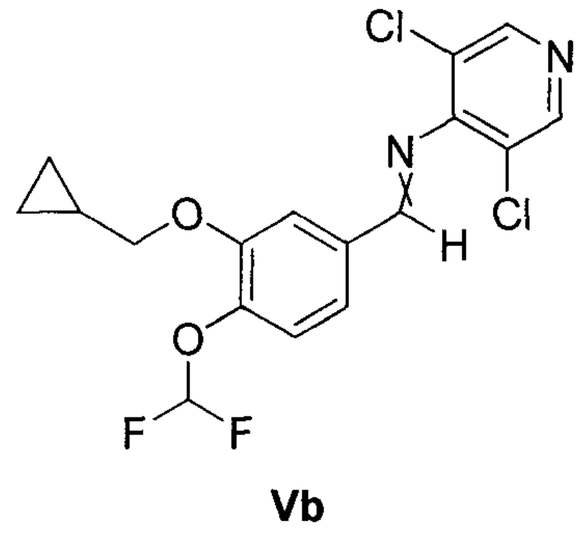
wherein

$R^1$ 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; and

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

**11**. The compound of claim **10**, 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.

**12**. A compound of claim **10**, wherein the compound of formula **Vc** has the formula:




**Vb** ;

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

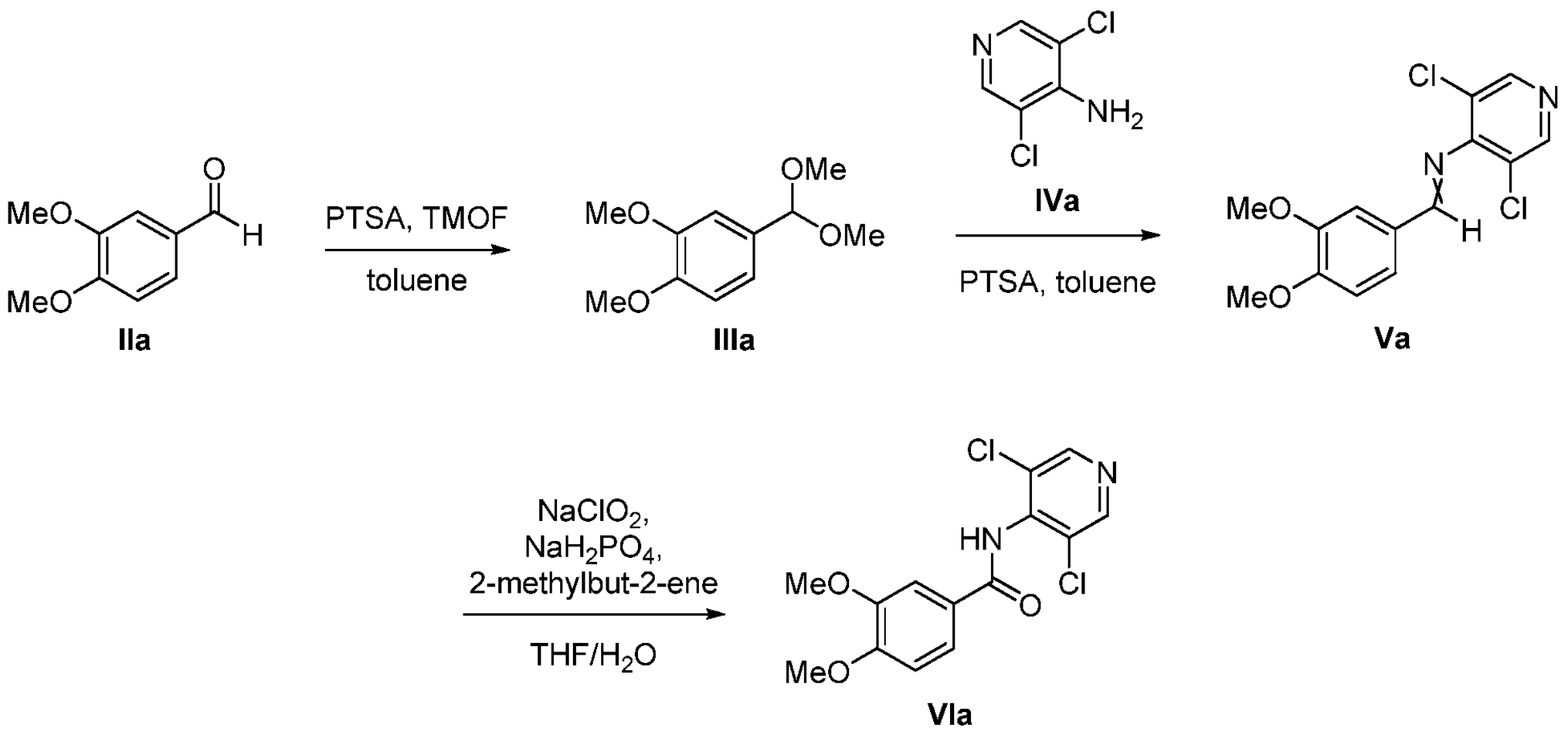



**Figure 1**

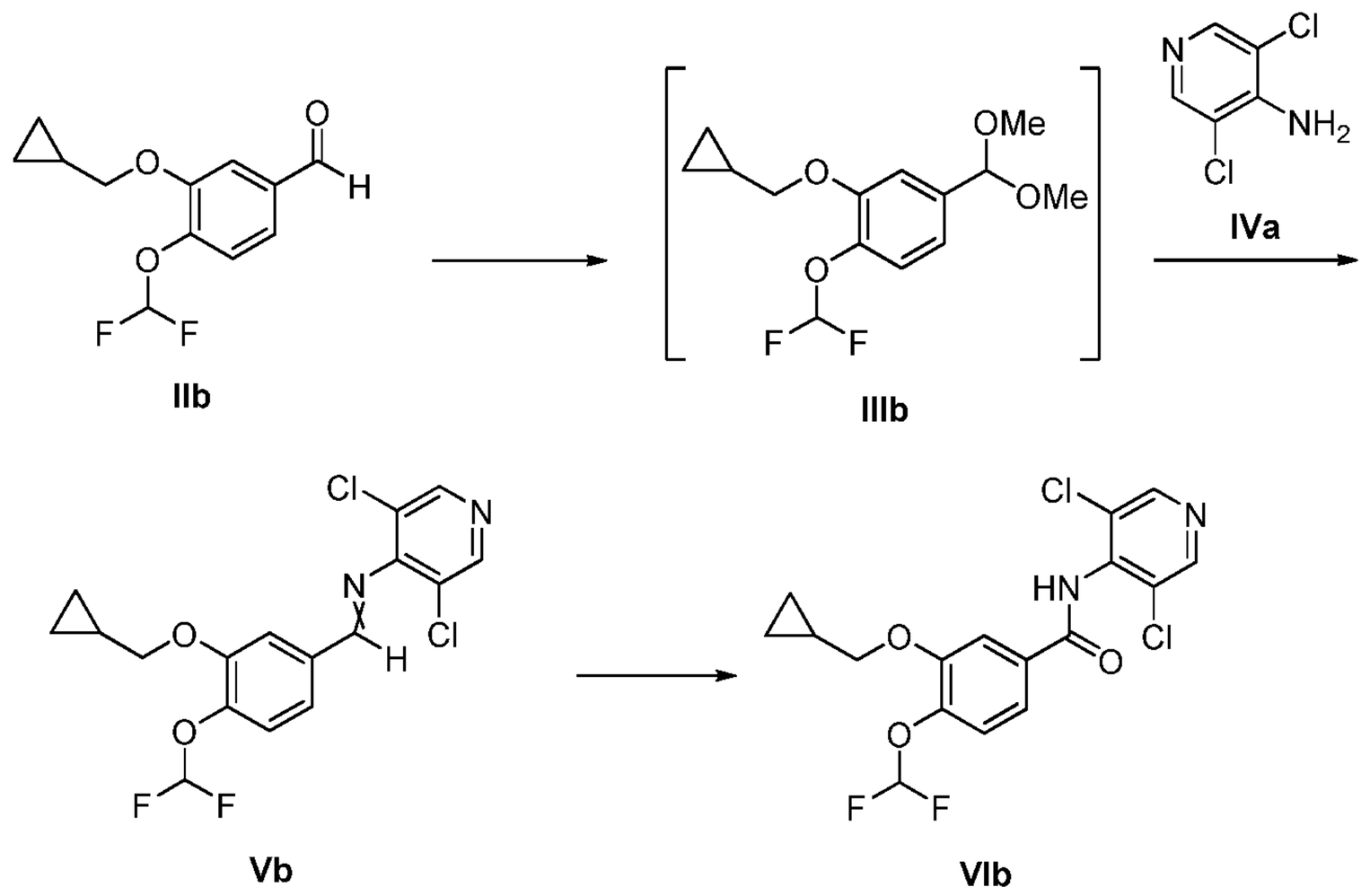
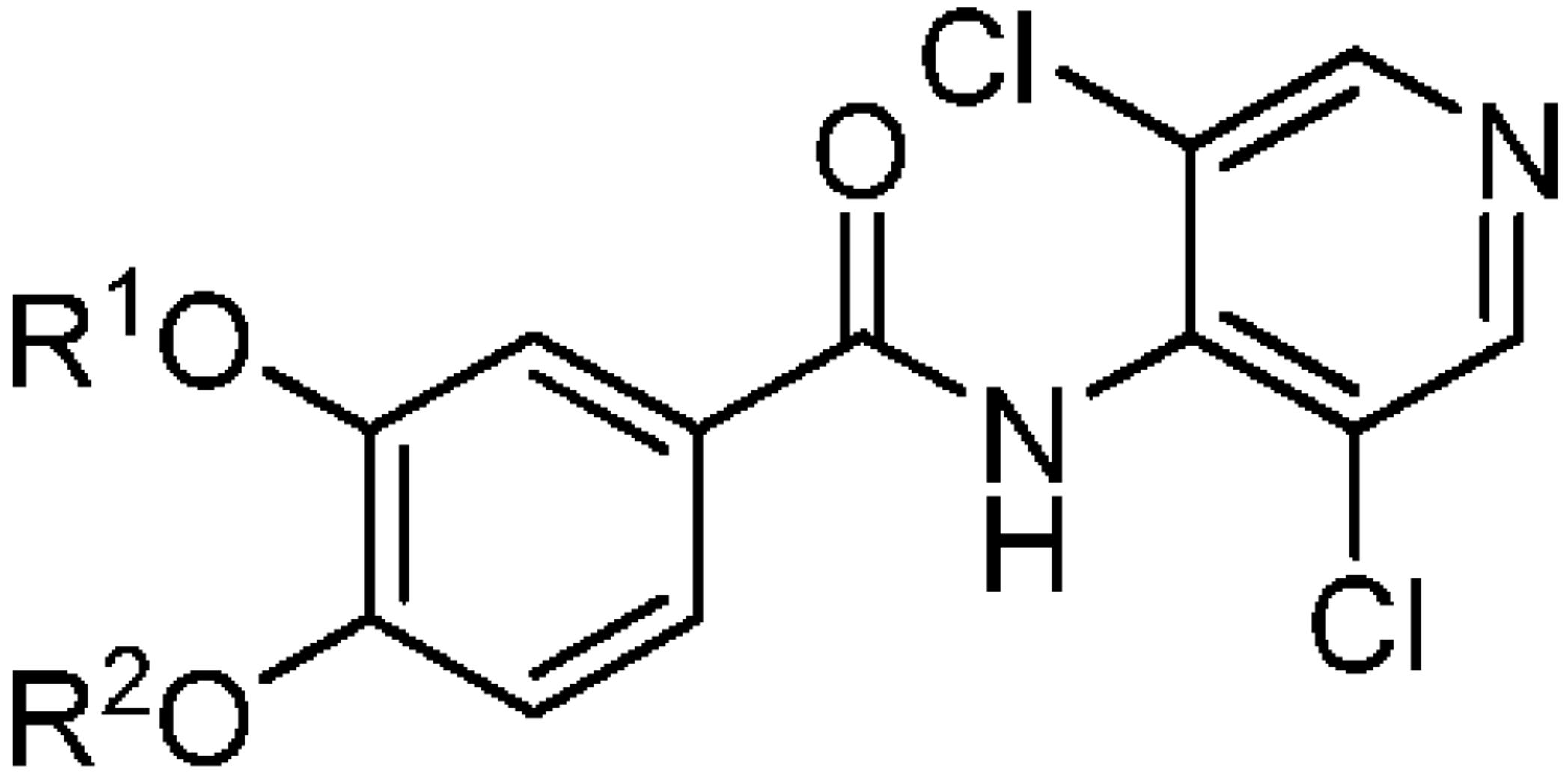



**Figure 2**




**VIc**