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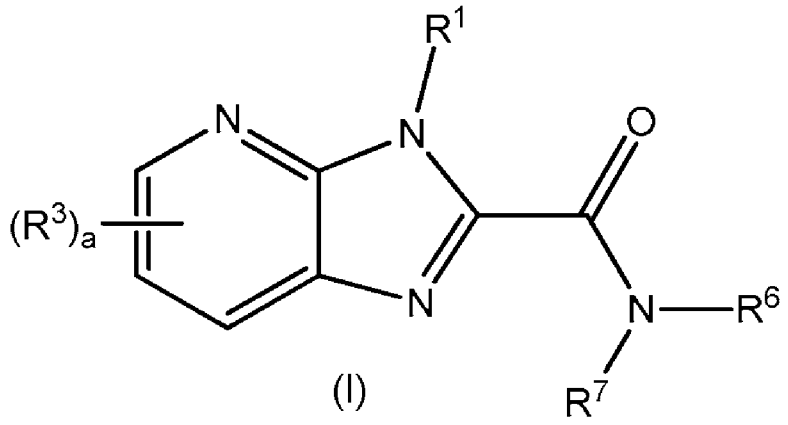
(54) Title: AZABENZIMIDAZOLE COMPOUNDS AS INHIBITORS OF PDE4 ISOZYMES FOR THE TREATMENT OF CNS AND OTHER DISORDERS



(I)

(57) Abstract: The present invention is directed to compounds of formula (I): or a pharmaceutically acceptable salt thereof, wherein the substituents are as defined 5 herein. The compounds of formula I are useful as inhibitors of PDE4 for the treatment of CNS and other disorders.

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AZABENZIMIDAZOLE COMPOUNDS AS INHIBITORS OF PDE4 ISOZYMES FOR THE TREATMENT OF CNS AND OTHER DISORDERS

Field of the Invention

The present invention relates to azabenzimidazole compounds of formula I, which are inhibitors of PDE4 isozymes, especially with a binding affinity for the PDE4B isoform, and to the use of such compounds in methods for treating certain central nervous system (CNS), metabolic, autoimmune and inflammatory diseases or disorders.

Background of the Invention

Phosphodiesterases (PDEs) are a class of intracellular enzymes involved in the hydrolysis of the nucleotide cyclic adenosine monophosphate (cAMP) into adenosine 5'-monophosphate (AMP). The cyclic nucleotide cAMP is synthesized by adenylyl cyclase, and serves as a secondary messenger in various cellular pathways.

cAMP functions as a second messenger regulating many intracellular processes within the body. An example is in the neurons of the central nervous system, where the activation of cAMP-dependent kinases and the subsequent phosphorylation of proteins is involved in acute regulation of synaptic transmission as well as neuronal differentiation and survival. The complexity of cyclic nucleotide signaling is indicated by the molecular diversity of the enzymes involved in the synthesis and degradation of cAMP. There are at least ten families of adenylyl cyclases, and eleven families of phosphodiesterases. Furthermore, different types of neurons are known to express multiple isozymes of each of these classes, and there is good evidence for compartmentalization and specificity of function for different isozymes within a given neuron.

A principal mechanism for regulating cyclic nucleotide signaling is via phosphodiesterase-catalyzed cyclic nucleotide catabolism. The 11 known families of PDEs are encoded by 21 different genes; each gene typically yields multiple splice variants that further contribute to the isozyme diversity. The PDE families are distinguished functionally based on cyclic nucleotide substrate specificity, mechanism(s) of regulation, and sensitivity to inhibitors. Furthermore, PDEs are differentially expressed throughout the organism, including in the central nervous system. As a result of these distinct enzymatic activities and localization, different PDEs' isozymes can serve distinct physiological functions. Furthermore, compounds that can selectively inhibit distinct PDE isozymes may offer particular therapeutic effects, fewer side effects, or both (Deninno, M., *Future Directions in*

Phosphodiesterase Drug Discovery. Bioorganic and Medicinal Chemistry Letters 2012, 22, 6794-6800).

The present invention relates to compounds having a binding affinity for the fourth family of PDEs (i.e., PDE4A, PDE4B, PDE4C, and PDE4D), and, in particular, a binding affinity for the PDE4B isoform. In addition to affinity for the PDE4B isoform, the compounds of the present invention also have affinity for the PDE4A and PDE4C isoforms.

The PDE4 isozymes are characterized by selective, high-affinity hydrolytic degradation of the second messenger cyclic adenosine 3',5'-monophosphate (cAMP), and by sensitivity to inhibition by Rolipram™ (Schering AG); beneficial pharmacological effects resulting from that inhibition have been shown in a variety of disease models. A number of other PDE4 inhibitors have been discovered in recent years. For example, Roflumilast (Daliresp®), marketed by Forest Pharmaceuticals, Inc., is approved for severe chronic obstructive pulmonary disease (COPD) to decrease the number of flare-ups or the worsening of COPD symptoms (exacerbations). Apremilast (Celgene Corp.) is in Phase III development and clinical trials have shown apremilast to be effective for the treatment of psoriasis (Papp, K. et al., *Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomized controlled trial.* Lancet 2012; 380(9843):738-46).

While beneficial pharmacological activity of PDE4 inhibitors has been shown, a common side-effect of these treatments has been the induction of gastrointestinal side effects such as nausea, emesis, and diarrhea, which is currently believed to be associated with inhibition of the PDE4D isoform. Attempts were made to develop compounds with an affinity for the PDE4B isoform over the PDE4D isoform (See: Donnell, A. F. et al., *Identification of pyridazino[4,5-b]indolizines as selective PDE4B inhibitors.* Bioorganic & Medicinal Chemistry Letters 2010; 20:2163-7; and Naganuma, K. et al., *Discovery of selective PDE4B inhibitors.* Bioorganic & Medicinal Chemistry Letters 2009; 19:3174-6). However, there remains a need to develop PDE4 inhibitors, especially those having an affinity for the PDE4B isoform. In particular, there remains a need to develop compounds that have enhanced binding affinity for the PDE4B isoform over the PDE4D isoform for the treatment of various diseases and disorders of the central nervous system (CNS). The discovery of selected compounds of the present invention addresses this continued need, and provides additional therapies for the treatment of various diseases and disorders of the central nervous system (CNS), as well as metabolic, autoimmune and inflammatory diseases or disorders. Such diseases and disorders include, but are not limited to, neurodegenerative or psychiatric disorders, including psychosis, impaired cognition,

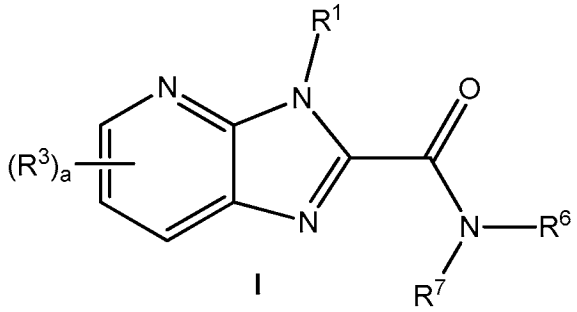
schizophrenia, anxiety, depression (e.g., major depressive disorder), dementia, Alzheimer's disease, Huntington's disease, multiple sclerosis, muscular dystrophy, sickle cell disease and diabetes.

Treatment with the PDE4B inhibitors of the present invention may also lead to a decrease in gastrointestinal side effects (e.g., nausea, emesis and diarrhea) believed to be associated with inhibition of the PDE4D isoform (Robichaud, A. et al., *Deletion of Phosphodiesterase 4D in Mice Shortens α2-Adrenoreceptor-Mediated Anesthesia, A Behavioral Correlate of Emesis.* Journal of Clinical Investigation 2002, Vol. 110, 1045-1052).

In addition to the development of compounds having affinity for the PDE4B isoform, there remains a need to develop compounds having an affinity for the PDE4A and PDE4C isoforms. The discovery of selected compounds of the present invention having affinity for the PDE4A and PDE4C isoforms also provides for the treatment of various diseases and disorders of the central nervous system (CNS), as well as treatment for various metabolic, autoimmune and inflammatory diseases or disorders.

Summary of the Invention

The present invention is directed to compounds of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is represented by a substituent selected from the group consisting of (C_3-C_{10})cycloalkyl, a (4- to 10-membered)heterocycloalkyl, (C_6-C_{10})aryl, and a (5- to 10-membered) heteroaryl; wherein said (C_3-C_{10})cycloalkyl, (C_6-C_{10})aryl and (5- to 10-membered)heteroaryl are optionally substituted with $(R^2)_b$; and said (4- to 10-membered)heterocycloalkyl is optionally substituted at one to five carbon atoms with a substituent independently selected from the group consisting of halogen, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_1-C_6)alkylthio, -C(O)NR^4R^5, hydroxy, and cyano, and optionally substituted at each available nitrogen with (C_1-C_6)alkyl;

R^2 is represented by a substituent independently selected from the group consisting of halogen, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkylthio; $-C(O)NR^4R^5$, hydroxy, and cyano;

R^3, if present, at each occurrence is represented by a substituent independently selected from the group consisting of halogen, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkylthio, $-C(O)NR^4R^5$, hydroxy, and cyano;

R^4 and R^5 are each represented by a substituent independently selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, and $(C_3\text{-}C_6)$cycloalkyl;

R^6 and R^7 are each represented by a substituent independently selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, $-(CH_2)_m\text{-}(C_3\text{-}C_{10})$cycloalkyl, $-(CH_2)_m$-(4- to 10-membered) heterocycloalkyl, $-(CH_2)_m\text{-}(C_6\text{-}C_{10})$aryl, and $-(CH_2)_m$-(5- to 10-membered)heteroaryl; wherein said $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, $(C_6\text{-}C_{10})$aryl, and (5- to 10-membered)heteroaryl are optionally substituted with one to five substituents independently selected from the group consisting of halogen, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkylthio, $-C(O)NR^4R^5$, hydroxy, and cyano; and said (4- to 10-membered)heterocycloalkyl is optionally substituted at one to five carbon atoms with a substituent independently selected from the group consisting of halogen, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkylthio, $-C(O)NR^4R^5$, hydroxy, and cyano, and optionally substituted at each available nitrogen with $(C_1\text{-}C_6)$alkyl; or R^6 and R^7 taken together with the nitrogen to which they are attached form a (4- to 10-membered)heterocycloalkyl, wherein said (4- to 10-membered)heterocycloalkyl is optionally substituted at one to five carbon atoms with a substituent independently selected from the group consisting of halogen, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkylthio, $-C(O)NR^4R^5$, hydroxy, and cyano;

a is represented by an integer selected from 0, 1, 2 or 3;

b is represented by an integer selected from 0, 1, 2, 3, 4 or 5; and

m is represented by an integer selected from 0, 1, 2, or 3.

Compounds of the invention include Examples 1-92 or a pharmaceutically acceptable salt thereof as described herein.

The compounds of formula I are inhibitors of the PDE4B isoform.

In addition, the compounds of formula I are inhibitors of the PDE4A and PDE4C isoforms.

The compounds of formula I are useful for treating or preventing neurodegenerative or psychiatric disorders, including, but not limited to, cognitive dysfunction, psychosis, schizophrenia, depression, dementia, anxiety, bipolar affective disorder, Parkinson's disease, Alzheimer's disease (AD), Huntington's disease (HD), multiple sclerosis (MS), and neuroinflammatory disorders as well as a host of other diseases or disorders in a mammal associated with PDE4B isoform activity. Additional diseases and disorders include, but are not limited to, pain, cancer, immunodeficiency diseases (e.g., psoriasis and arthritis), inflammation, asthma, chronic obstructive pulmonary disease (COPD), diabetes, muscular dystrophy, sickle cell disease, cardiovascular diseases, cerebral vascular disease, stroke and allergic conjunctivitis.

The present invention is also directed to the use of a compound of the present invention, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment or prevention of a condition amenable to modulation of the PDE4B gene family (i.e., PDE4B enzymes) which consists of various splice variants such as PDE4B1, B2, B3, PDE4B4, and B5 protein. Examples of conditions include, but are not limited to, cognitive dysfunction, psychosis, schizophrenia, depression, dementia, anxiety, bipolar affective disorder, Parkinson's disease, Alzheimer's disease (AD), Huntington's disease (HD), multiple sclerosis (MS), and neuroinflammatory disorders as well as a host of other diseases or disorders in a mammal associated with PDE4B isoform activity, such as, but not limited to, pain, cancer, immunodeficiency diseases (e.g., psoriasis and arthritis), inflammation, asthma, chronic obstructive pulmonary disease (COPD), diabetes, muscular dystrophy, sickle cell disease, cardiovascular diseases, cerebral vascular disease, stroke and allergic conjunctivitis.

The present invention is also directed to pharmaceutically acceptable formulations containing an admixture of a compound(s) of the present invention and at least one excipient formulated into a pharmaceutical dosage form. Examples of such dosage forms include tablets, capsules, solutions/suspensions for injection, aerosols for inhalation and solutions/suspensions for oral ingestion.

Detailed Description of the Invention

The headings within this document are only being utilized to expedite its review by the reader. They should not be construed as limiting the invention or claims in any manner.

Definitions and Exemplifications

As used throughout this application, including the claims, the following terms have the meanings defined below, unless specifically indicated otherwise. The plural and singular should be treated as interchangeable, other than the indication of number:

"(C_1-C_6)alkyl" as used herein, refers to a branched- or straight-chain alkyl group containing from 1 to 6 carbon atoms, such as, but not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, and *n*-hexyl.

"halo" or "halogen" as used herein, refers to a chlorine, fluorine, bromine, or iodine atom.

"halo(C_1-C_6)alkyl" as used herein, refers to a (C_1-C_6)alkyl group, as defined above, wherein at least one hydrogen atom is replaced with a halogen, as defined above. Representative examples of a halo(C_1-C_6)alkyl include, but are not limited to, chloromethyl, 2-fluoroethyl, trifluoromethyl, pentafluoroethyl, and 2-chloro-3-fluoropentyl.

"(C_1-C_6)alkoxy" as used herein, refers to a (C_1-C_6)alkyl group, as defined above, attached to the parent molecular moiety through an oxygen atom. Representative examples of a (C_1-C_6)alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, *tert*-butoxy, pentyloxy, and hexyloxy.

"halo(C_1-C_6)alkoxy" as used herein, refers to a (C_1-C_6)alkoxy group, as defined above, wherein at least one hydrogen atom is replaced with a halogen, as defined above. Representative examples of a halo(C_1-C_6)alkoxy include, but are not limited to, chloromethoxy, 2-fluoroethoxy, trifluoromethoxy, and pentafluoroethoxy.

"thio" as used herein, means –S (sulfur).

"(C_1-C_6)alkylthio" as used herein, means a (C_1-C_6)alkyl group, as defined herein, attached to the parent molecular moiety through a sulfur atom. Representative examples of a (C_1-C_6)alkylthio include, but are not limited to, methylthio, ethylthio, propylthio, and butylthio.

"(C_3-C_{10})cycloalkyl" as used herein, refers to a saturated or partially saturated monocyclic, bicyclic, bridged bicyclic or tricyclic alkyl radical wherein the cyclic framework has 3 to 10 carbons. Examples of monocyclics include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl and cyclodecyl. Alternatively, a cycloalkyl may be a bicyclic ring such as a bicycloalkyl. The bicycloalkyl may be a fused system, such as bicyclo[1.1.0]butane, bicyclo[2.1.0]pentane, bicyclo[2.2.0]hexane, bicyclo[3.1.0]hexane,

bicyclo[3.2.0]heptane, and bicyclo[3.3.0]octane. The term "bicycloalkyl" also includes bridged bicycloalkyl systems such as, but not limited to, bicyclo[2.2.1]heptane and bicyclo[1.1.1]pentane. The cycloalkyl may also be a bicyclic ring such that a monocyclic ring is fused to an aryl or heteroaryl ring. In this case, a group having such a fused cycloalkyl group as a substituent is bound to a carbon atom of the saturated or partially saturated ring. For example, a cycloalkyl moiety may include, but is not limited to, 2,3-dihydro-1*H*-inden-2-yl.

"heterocycloalkyl," as used herein, refers to a substituent obtained by removing a hydrogen from a saturated or partially saturated ring structure, wherein at least one of the ring atoms is a heteroatom selected from oxygen, nitrogen or sulfur. For example, as used herein, the term "(4- to 6-membered)heterocycloalkyl" means the substituent contains a total of 4 to 6 ring atoms. A "(4- to 10-membered)heterocycloalkyl" means the substituent contains a total of 4 to 10 ring atoms. A heterocycloalkyl may be a single ring with up to 10 total members. Alternatively, a heterocycloalkyl as defined above may comprise 2 or 3 rings fused together, wherein at least one such ring contains a heteroatom as a ring atom (i.e., nitrogen, oxygen, or sulfur). In a group that has a heterocycloalkyl substituent, the ring atom of the heterocycloalkyl substituent that is attached to the group may be the at least one heteroatom, or it may be a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom. Similarly, if the heterocycloalkyl substituent is in turn substituted with a group or substituent, the group or substituent may be bound to the at least one heteroatom, or it may be bound to a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom.

The term "heterocycloalkyl" also includes substituents that are fused to a C_6-C_{10} aromatic ring or a (5- to 10-membered)heteroaromatic ring, wherein a group having such a fused heterocycloalkyl group as a substituent is bound to a heteroatom of the heterocycloalkyl group or to a carbon atom of the heterocycloalkyl group. When such a fused heterocycloalkyl group is substituted with one or more substituents, the one or more substituents, unless otherwise specified, are each bound to a heteroatom of the heterocycloalkyl group or to a carbon atom of the heterocycloalkyl group. The fused C_6-C_{10} aromatic ring or a (5- to 10-membered)heteroaromatic ring may be optionally substituted with halogen, (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, (C_1-C_6)alkoxy or =O. Examples of heterocycloalkyl substituents include, but are not limited to, tetrahydroquinolyl, dihydrobenzofuryl and the like. Other heterocycloalkyl rings include: azetidinyl,

dihydrofuranyl, tetrahydropyranyl, dihydrothiophenyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl, piperidinyl, piperazinyl, azepane, azocane, morpholinyl, isochromyl, tetrahydrotriazine, tetrahydropyrazole, dihydro-1*H*-isoindole, tetrahydro-oxazolyl, tetrahydro-oxazinyl, thiomorpholinyl, tetrahydropyrimidinyl, octahydrobenzofuranyl, octahydrobenzimidazolyl, and octahydrobenzothiazolyl.

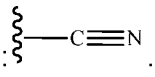
"(C_6-C_{10})aryl" refers to an aromatic substituent containing from 6 to 10 carbon atoms, including one ring or two fused rings such as phenyl, or naphthyl,. The term "aryl" also includes substituents such as phenyl and naphthyl that are fused to a (C_4-C_6)cycloalkyl or (C_4-C_{10})heterocycloalkyl, wherein a group having such a fused aryl group as a substituent is bound to an aromatic carbon of the aryl group. When such an aryl group is substituted with one or more substituents, the one or more substituents, unless otherwise specified, are each bound to an aromatic carbon of the fused aryl group. The fused (C_3-C_6)cycloalkyl or (C_4-C_{10})heterocycloalkyl ring may be optionally substituted with halogen, (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, or = O. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, indanyl (e.g., 2,3-dihydro-1*H*-inden-5-yl), indenyl and dihydrobenzofuranyl (e.g., 1,3-dihydro-2-benzofuran-5-yl), .

"(5- to 10-membered)heteroaryl" refers to an aromatic ring having from 5 to 10 ring atoms in which at least one of the ring atoms is a heteroatom (i.e., oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. A heteroaryl may be a single ring or 2 or 3 fused rings. In a group that has a heteroaryl substituent, the ring atom of the heteroaryl substituent that is bound to the group may be the at least one heteroarom, or it may be a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom or where the ring carbon atom may be in a different ring from the at least one heteroatom. Similarly, if the heteroaryl substituent is in turn substituted with a group or substituent, the group or substituent may be bound to the at least one heteroarom, or it may be bound to a ring carbon atom, where the ring carbon atom may be in the same ring as the at least one heteroatom, or where the ring carbon atom may be in a different ring from the at least one heteroatom.

The term "heteroaryl" also includes substituents such as pyridyl and triazolyl that are fused to a (C_4-C_{10})cycloalkyl group, or to a (4- to 10-membered)heterocycloalkyl group, wherein a group having such a fused heteroaryl group as a substituent is bound to an aromatic carbon of the heteroaryl group or to a heteroatom of the heteroaryl group. When such a fused heteroaryl group is substituted with one or more substituents, the one or more substituents, unless otherwise specified, are each bound to an aromatic carbon of the

heteroaryl group or to a heteroatom of the heteroaryl group. The fused (C_4-C_{10})cycloalkyl group or (4- to 10-membered)heterocycloalkyl group may be optionally substitued with halogen, (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, or =O. Examples of heteroaryls include, but are not limited to, 6-membered ring substituents such as pyridyl, pyrazyl, pyrimidinyl and pyridazinyl; 5-membered heteroaryls such as triazolyl, imidazolyl, furanyl, isoxazolyl, isothiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl, oxazolyl, thiophenyl, thiazolyl, and pyrazolyl. Representative examples of bicyclic heteroaryls include, but are not limited to, benzimidazolyl, benzofuranyl, benzothienyl, benzoxadiazolyl, benzothiazolyl (e.g., 1,3-benzothiazol-6-yl and 2-methyl-1,3-benzothiazol-6-yl), benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, 1,4-benzoxazinyl, cinnolinyl, furopyridinyl, indazolyl, indolyl, isoquinolinyl, naphthyridinyl, purinyl, quinolinyl, quinazolinyl, 5,6,7,8-tetrahydroquinolinyl, thienopyridinyl, and triazolopyridinyl (e.g., 5,6,7,8-tetrahydro[1,2,4]triazolo[1,5-*a*]pyridin-2-yl).

"hydroxy" or "hydroxyl" as used herein, means an -OH group.

"cyano" as used herein, means a -CN group, which also may be depicted:  .

"optionally substituted" as used herein, means that substitution is optional and therefore includes both unsubstituted and substituted atoms and moieties. A "substituted" atom or moiety indicates that any hydrogen on the designated atom or moiety can be replaced with a selection from the indicated substituent group (up to and including that every hydrogen atom on the designated atom or moiety is replaced with a selection from the indicated substituent group), provided that the normal valency of the designated atom or moiety is not exceeded, and that the substitution results in a stable compound. For example, if a methyl group (i.e., CH_3) is optionally substituted, then up to 3 hydrogen atoms on the carbon atom can be replaced with substituent groups.

As used herein, unless specified, the point of attachment of a substituent can be from any suitable position of the substituent. For example, pyridinyl (or pyridyl) can be 2-pyridinyl (or pyridin-2-yl), 3-pyridinyl (or pyridin-3-yl), or 4-pyridinyl (or pyridin-4-yl).

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any of the ring-forming atoms in that ring that are substitutable (i.e., bonded to one or more hydrogen atoms). For example, as shown in formula Ia below, R^2 may be bonded to any ring-forming atom that is substitutable (i.e., bonded to one or more hydrogen atoms).

"Therapeutically effective amount" refers to that amount of the compound being administered which will relieve to some extent one or more of the symptoms of the disorder being treated.

"Patient" refers to warm blooded animals such as, for example, pigs, cows, chickens, horses, guinea pigs, mice, rats, gerbils, cats, rabbits, dogs, monkeys, chimpanzees, and humans.

"Treating" or "treat", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, unless otherwise indicated, refers to the act of treating as "treating" is defined immediately above. The term "treating" also includes adjuvant and neo-adjuvant treatment of a subject.

"Pharmaceutically acceptable" indicates that the substance or composition must be compatible, chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

"Isoform" means any of several different forms of the same protein.

"Isozyme" or "isoenzyme" means a closely related variant of an enzyme that differs in amino acid sequence but catalyzes the same chemical reaction.

"Isomer" means "stereoisomer" and "geometric isomer" as defined below.

"Stereoisomer" refers to compounds that possess one or more chiral centers, which may each exist in the R or S configuration. Stereoisomers include all diastereomeric, enantiomeric and epimeric forms as well as racemates and mixtures thereof.

"Geometric isomer" refers to compounds that may exist in cis, trans, anti, *entgegen* (E), and *zusammen* (Z) forms as well as mixtures thereof.

This specification uses the terms "substituent," "radical," and "group" interchangeably.

If substituents are described as being "independently selected" from a group, each instance of a substituent is selected independent of the other. Each substituent therefore may be identical to or different from the other substituent(s).

As used herein the terms "formula I" and "formula Ia" may be hereinafter referred to as a "compound(s) of the invention." Such terms are also defined to include all forms of the

compound of formulas I, and Ia, including hydrates, solvates, isomers, crystalline and non-crystalline forms, isomorphs, polymorphs, and metabolites thereof. For example, the compounds of the invention, or pharmaceutically acceptable salts thereof, may exist in unsolvated and solvated forms. When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound, as in channel solvates and hygroscopic compounds, the water/solvent content will be dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the norm.

The compounds of the invention may exist as clathrates or other complexes. Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the compounds of the invention containing two or more organic and/or inorganic components, which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionized, partially ionized, or non-ionized. For a review of such complexes, see J. Pharm. Sci., 64 (8), 1269-1288 by Haleblian (August 1975).

The compounds of the invention have asymmetric carbon atoms. The carbon-carbon bonds of the compounds of the invention may be depicted herein using a solid line (———), a solid wedge (), or a dotted wedge (). The use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers (e.g., specific enantiomers, racemic mixtures, etc.) at that carbon atom are included. The use of either a solid or dotted wedge to depict bonds to asymmetric carbon atoms is meant to indicate that the stereoisomer shown is present. When present in racemic compounds, solid and dotted wedges are used to define relative stereochemistry, rather than absolute stereochemistry. Racemic compounds possessing such indicated relative stereochemistry are marked with (+/-). For example, unless stated otherwise, it is intended that the compounds of the invention can exist as stereoisomers, which include cis and trans isomers, optical isomers such as R and S enantiomers, diastereomers, geometric isomers, rotational isomers, conformational isomers, atropoisomers, and mixtures thereof (such as racemates and diastereomeric pairs). The compounds of the invention may exhibit more than one type of isomerism. Also included are acid addition or base addition salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

When any racemate crystallizes, crystals of two different types are possible. The first type is the racemic compound (true racemate) referred to above wherein one homogeneous

form of crystal is produced containing both enantiomers in equimolar amounts. The second type is the racemic mixture or conglomerate wherein two forms of crystal are produced in equimolar amounts each comprising a single enantiomer.

The compounds of this invention may be used in the form of salts derived from inorganic or organic acids. Depending on the particular compound, a salt of the compound may be advantageous due to one or more of the salt's physical properties, such as enhanced pharmaceutical stability in differing temperatures and humidities, or a desirable solubility in water or oil. In some instances, a salt of a compound also may be used as an aid in the isolation, purification, and/or resolution of the compound.

Where a salt is intended to be administered to a patient (as opposed to, for example, being used in an in vitro context), the salt preferably is pharmaceutically acceptable. The term "pharmaceutically acceptable salt" refers to a salt prepared by combining a compound of the present invention with an acid whose anion, or a base whose cation, is generally considered suitable for human consumption. Pharmaceutically acceptable salts are particularly useful as products of the methods of the present invention because of their greater aqueous solubility relative to the parent compound.

Suitable pharmaceutically acceptable acid addition salts of the compounds of the present invention when possible include those derived from inorganic acids, such as, but not limited to, hydrochloric, hydrobromic, hydrofluoric, boric, fluoroboric, phosphoric, meta-phosphoric, nitric, carbonic, sulfonic, and sulfuric acids, and organic acids such as acetic, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, trifluoromethanesulfonic, succinic, toluenesulfonic, tartaric, and trifluoroacetic acids. Suitable organic acids generally include but are not limited to aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids.

Specific examples of suitable organic acids include but are not limited to acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartrate, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilate, stearate, salicylate, *p*-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, toluenesulfonate, 2-hydroxyethanesulfonate, sufanilate, cyclohexylamino-ulfonate, algenic acid, β-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, heptanoate, hexanoate, nicotinate, 2-naphthalene-

sulfonate, oxalate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, thiocyanate, and undecanoate.

Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts. In another embodiment, base salts are formed from bases which form non-toxic salts, including aluminum, arginine, benzathine, choline, diethylamine, diolamine, glycine, lysine, meglumine, olamine, tromethamine and zinc salts.

Organic salts may be made from secondary, tertiary or quaternary amine salts, such as tromethamine, diethylamine, *N,N'*-dibenzylethylenediamine, chloroprocaine, choline, diethanol- amine, ethylenediamine, meglumine (*N*-methylglucamine), and procaine. Basic nitrogen- containing groups may be quaternized with agents such as lower alkyl (C_1-C_6) halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g., decyl, lauryl, myristyl, and stearyl chlorides, bromides, and iodides), arylalkyl halides (e.g., benzyl and phenethyl bromides), and others.

In one embodiment, hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

Certain compounds of the invention may exist as geometric isomers. The compounds of the invention may possess one or more asymmetric centers, thus existing as two, or more, stereoisomeric forms. The present invention includes all the individual stereoisomers and geometric isomers of the compounds of the invention and mixtures thereof. Individual enantiomers can be obtained by chiral separation or using the relevant enantiomer in the synthesis.

In addition, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention. The compounds may also exist in one or more crystalline states, i.e., polymorphs, or they may exist as amorphous solids. All such forms are encompassed by the claims.

Also within the scope of the present invention are so-called “prodrugs” of the compound of the invention. Thus, certain derivatives of the compound of the invention that

may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into the compound of the invention having the desired activity, for example, by hydrolytic cleavage. Such derivatives are referred to as "prodrugs." Further information on the use of prodrugs may be found in "Pro-drugs as Novel Delivery Systems, Vol. 14, ACS Symposium Series (T. Higuchi and W. Stella) and "Bioreversible Carriers in Drug Design," Pergamon Press, 1987 (ed. E. B. Roche, American Pharmaceutical Association). Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of the present invention with certain moieties known to those skilled in the art as "pro-moieties" as described, for example, in "Design of Prodrugs" by H. Bundgaard (Elsevier, 1985).

This invention also encompasses compounds of the invention containing protective groups. One skilled in the art will also appreciate that compounds of the invention can also be prepared with certain protecting groups that are useful for purification or storage and can be removed before administration to a patient. The protection and deprotection of functional groups is described in "Protective Groups in Organic Chemistry", edited by J. W. F. McOmie, Plenum Press (1973) and "Protective Groups in Organic Synthesis", 3rd edition, T. W. Greene and P. G. M. Wuts, Wiley-Interscience (1999).

The present invention also includes all pharmaceutically acceptable isotopically-labeled compounds, which are identical to those recited in formulas I and Ia, wherein one or more atoms are replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature. Examples of isotopes suitable for inclusion in the compounds of the present invention include, but are not limited to, isotopes of hydrogen, such as ^{2}H, ^{3}H; carbon, such as ^{11}C, ^{13}C, and ^{14}C; chlorine, such as ^{36}Cl; fluorine, such as ^{18}F; iodine, such as ^{123}I and ^{125}I; nitrogen, such as ^{13}N and ^{15}N; oxygen, such as ^{15}O, ^{17}O, and ^{18}O; phosphorus, such as ^{32}P; and sulfur, such as ^{35}S. Certain isotopically-labeled compounds of the present invention, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies (e.g., assays). The radioactive isotopes tritium, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with heavier isotopes such as deuterium, i.e., ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C, ^{15}F, ^{15}O and ^{13}N, can be useful in positron emission tomography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of the present invention can

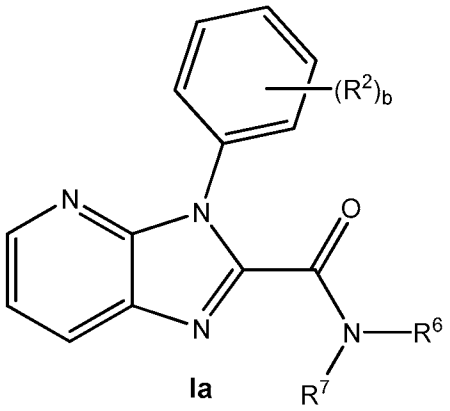
generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Schemes and/or in the Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed. Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g., D_2O, acetone-d_6, or DMSO-d_6. Compounds of formula I and formula 1a, as well as the compounds exemplified in Examples 1-92 described below, include isotopically-labeled versions of these compounds, such as, but not limited to, the deuterated and tritiated isotopes and all other isotopes discussed above.

Compounds

The present invention is directed to azabenzimidazole compounds of formula I as described above. In certain embodiments, the pyridine ring of the imidazopyridine core does not contain any substitutions on the ring. In these instances the "a" of the $(R^3)_a$ substituent is represented by the integer 0.

To further elucidate the compounds of the present invention, the following subgenus is described below.

Formula Ia depicted below is a subset of formula I as depicted, wherein R^1 is represented by a phenyl optionally substituted with $(R^2)_b$; and a is represented by the integer 0. In formula Ia, b is represented by an integer selected from 0, 1, 2, or 3; each R^2, if present, is represented by a substituent independently selected from the group consisting of fluoro, chloro, cyano, methyl, trifluoromethyl, methylthio, methoxy, and trifluoromethoxy; R^6 and R^7 are each independently selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, $-(CH_2)_m$-$(C_3$-$C_{10})$cycloalkyl, and $-(CH_2)_m$-(5- to 10-membered)heteroaryl, wherein said $(C_1$-$C_6)$alkyl, $(C_3$-$C_{10})$cycloalkyl, and (5 to 10-membered)heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of halogen, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylthio, $-C(O)NR^4R^5$, hydroxy, and cyano; or R^6 and R^7 taken together with the nitrogen to which they are attached form a (4- to 6-membered)heterocycloalkyl, wherein said heterocycloalkyl is optionally substituted at one to three carbon atoms with a substituent independently selected from the group consisting of halogen, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylthio, $-C(O)NR^4R^5$, hydroxy, and cyano; wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and $(C_1$-$C_6)$alkyl; and m is represented by an integer 0, 1, or 2:



Ia

In certain embodiments of the invention, in formula Ia as depicted above, b is represented by an integer selected from 0, 1, 2, or 3; each R^2, if present, is represented by a substituent independently selected from the group consisting of chloro, fluoro, methyl and cyano; one of R^6 and R^7 is represented by hydrogen, and the other is represented by a substituent selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $-(CH_2)_m\text{-}(C_3\text{-}C_{10})$cycloalkyl, and $-(CH_2)_m$-(5- to 10-membered)heteroaryl, wherein said $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_{10})$cycloalkyl, and (5 to 10-membered)heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of halogen, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkylthio, $-C(O)NR^4R^5$, hydroxy, and cyano.

In certain embodiments of the invention, in formula Ia as depicted above, b is an integer selected from 0, 1, 2, or 3; each R^2, if present, is represented by a substituent independently selected from the group consisting of chloro, fluoro, methyl, and cyano; one of R^6 and R^7 is represented by hydrogen, and the other is represented by $(C_1\text{-}C_6)$alkyl optionally substituted with one to three substituents independently selected from the group consisting of halogen, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkylthio, hydroxy, and cyano. In certain embodiments, one of R^6 and R^7 is represented by hydrogen, and the other is represented by a substituent selected from the group consisting of ethyl and propyl. In certain embodiments, one of R^6 and R^7 is represented by hydrogen, and the other is represented by propyl.

In certain other embodiments of the invention, in formula Ia as depicted above, b is represented by an integer selected from 0, 1, 2, or 3; each R^2, if present, is represented by a substituent independently selected from the group consisting of chloro, fluoro, methyl, and cyano; one of R^6 and R^7 is represented by hydrogen, and the other is represented by $-(CH_2)_m\text{-}(C_3\text{-}C_{10})$cycloalkyl optionally substituted with one to three substituents independently selected from the group consisting of halogen, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkylthio, hydroxy, and cyano; and m is represented by an integer

selected from 0, 1, or 2. In certain embodiments, one of R^6 and R^7 is represented by hydrogen, and the other is represented by cyclopropyl.

In certain other embodiments of the invention, in formula Ia as depicted above, b is represented by an integer selected from 0, 1, 2, or 3; each R^2, if present, is represented by a substituent independently selected from the group consisting of chloro, fluoro, methyl, and cyano; one of R^6 and R^7 is represented by hydrogen, and the other is represented by -$(CH_2)_m$-(5- to 10-membered)heteroaryl optionally substituted with one to three substituents independently selected from the group consisting of halogen, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylthio, hydroxy, and cyano, wherein m is represented by an integer selected from 0, 1, or 2. In certain embodiments, one of R^6 and R^7 is represented by hydrogen, and the other is represented by pyrazolyl optionally substituted by a $(C_1$-$C_6)$alkyl. In certain embodiments, one of R^6 and R^7 is represented by hydrogen, and the other is represented by *N*-methylpyrazolyl (e.g., *N*-methylpyrazol-3-yl).

In certain embodiments of the invention, in formula Ia, b is represented by an integer selected from 0, 1, 2, or 3; each R^2, if present, is represented by a substituent independently selected from the group consisting of fluoro, chloro, cyano, methyl, trifluoromethyl, methylthio, methoxy, and trifluoromethoxy; R^6 and R^7 taken together with the nitrogen to which they are attached form a (4- to 6-membered)heterocycloalkyl optionally substituted at one to three carbon atoms with a substituent independently selected from the group consisting of halogen, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylthio, -C(O)NR^4R^5, hydroxy, and cyano, wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and $(C_1$-$C_6)$alkyl.

In certain other embodiments of the invention, in formula Ia as depicted above, b is represented by an integer selected from 0, 1, 2, or 3; each R^2, if present, is represented by a substituent independently selected from the group consisting of chloro, fluoro, methyl and cyano; and R^6 and R^7 taken together with the nitrogen to which they are attached form an azetidine ring optionally substituted with one to three halogen. In certain embodiments R^6 and R^7 taken together with the nitrogen to which they are attached form 3-fluoro-azetidin-1-yl.

In another embodiment, selected compounds of the present invention may be useful for treating a PDE4B-mediated disorder, comprising administering to a mammal (preferably a human) in need thereof a therapeutically effective amount of a compound of the invention effective in inhibiting PDE4B activity; more preferably, administering an amount of a compound of the invention having improved binding affinity for PDE4B while at the same

time possessing less inhibitory activity toward PDE4D.

In another embodiment, selected compounds of the present invention may be useful for treating a PDE4A-mediated disorder, comprising administering to a mammal (preferably a human) in need thereof a therapeutically effective amount of a compound of the invention effective in inhibiting PDE4A activity.

In yet another embodiment, selected compounds of the present invention may be useful for treating a PDE4C-mediated disorder, comprising administering to a mammal (preferably a human) in need thereof a therapeutically effective amount of a compound of the invention effective in inhibiting PDE4C activity.

In certain other embodiments, selected compounds of the present invention may exhibit a binding affinity for the PDE4A, PDE4B and PDE4C isoforms or combinations thereof.

In certain embodiments, the compounds of the present invention have an enhanced binding affinity for the PDE4B isoform over the PDE4D isoform such that the compounds display about a 2-fold to about a 120-fold binding affinity for the PDE4B isoform over the PDE4D isoform. In certain other embodiments, the compounds of the present invention display about a 35-fold to about a 75-fold binding affinity for the PDE4B isoform over the PDE4D isoform. In certain embodiments, the compounds of the present invention display at least about a 2-fold binding affinity for the PDE4B isoform over the PDE4D isoform. In certain embodiments, the compounds of the present invention display at least about a 5-fold binding affinity for the PDE4B isoform over the PDE4D isoform. In certain embodiments, the compounds of the present invention display at least about a 10-fold binding affinity for the PDE4B isoform over the PDE4D isoform. In certain embodiments, the compounds of the present invention display at least about a 20-fold binding affinity for the PDE4B isoform over the PDE4D isoform. In certain other embodiments, the compounds of the present invention display at least about a 40-fold binding affinity for the PDE4B isoform over the PDE4D isoform. In certain other embodiments, the compounds of the present invention display at least about a 50-fold binding affinity for the PDE4B isoform over the PDE4D isoform. The binding affinities of the compounds of the present invention for the PDE4B and PDE4D isoforms are shown in Table 4 of the Experimental Section below.

In another embodiment, the present invention provides a pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, in admixture with at least one pharmaceutically acceptable excipient.

In yet another embodiment, administration of the compounds of the present invention to a patient in need thereof may also lead to a decrease in gastrointestinal discomfort such as emesis, diarrhea, and nausea, which is currently believed to be associated with administration of compounds having binding affinity for other PDE4 isoforms, especially the PDE4D isoform, resulting in an increase in patient compliance as well as overall treatment outcome.

In another embodiment, the present invention provides a method of treating central nervous system (CNS), metabolic, autoimmune and inflammatory diseases or disorders. comprising administering to the mammal, particularly a human, in need of such treatment a therapeutically effect amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

In another embodiment, the present invention provides the use of a compound of the present invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating central nervous system (CNS), autoimmune and inflammatory diseases or disorders.

Pharmacology

Phosphodiesterases (PDEs) of the PDE4 family are characterized by selective, high-affinity hydrolytic degradation of the second messenger cyclic nucleotide, adenosine 3',5'-cyclic monophosphate (cAMP). The PDE4A, PDE4B and PDE4D subtypes are known to be widely expressed throughout the brain, with regional and intracellular distribution for the PDE4A, PDE4B and PDE4D subtypes being distinct, whereas the PDE4C subtype is expressed at lower levels throughout the central nervous system (See; Siuciak, J. A. et al., *Antipsychotic profile of rolipram: efficacy in rats and reduced sensitivity in mice deficient in the phosphodiesterase-4B (PDE4B) enzyme*, Psychopharmacology (2007) 192:415-424). The location of the PDE4 subtypes makes them an interesting target for exploring new treatments for central nervous system diseases and disorders. For example, PDE4B has been identified as a genetic susceptibility factor for schizophrenia (See: Millar, J. K. et al., *Disrupted in schizophrenia 1 and phosphodiesterase 4B: towards an understanding of psychiatric illness*, J. Physiol. 584 (2007) pp. 401-405).

The PDE4 inhibitor rolipram has been shown to be useful in treating or reversing Aβ-induced memory deficits via the attenuation of neuronal inflammation and apoptosis-mediated cAMP/CREB signaling, and is a potential target for treatment of cognitive deficits associated with AD. (See: Wang, C. et al., *The phosphodiesterase-4 inhibitor rolipram*

reverses Aβ-induced cognitive impairment and neuroinflammatory and apoptotic responses in rats, International Journal of Neuropsychopharmacology (2012), 15, 749-766).

PDE4 inhibitors have also been shown to possess antidepressant effects by decreasing brain levels of PDE4 in individuals with major depressive disorder (MDD) (See: Fujita, M. et al., *C-(R-)-Rolipram Positron Emission Tomography in Major Depressive Disorder*, Biological Psychiatry, 71, 2012, 548-554).

Furthermore, PDE4 inhibitors have been shown to possess therapeutic activity with implications for the treatment of multiple sclerosis (See: Sun, X. et al., *Rolipram promotes remyelination possibly via MEK-ERK signal pathway in cuprizone-induced demyelination mouse*, Experimental Neurology 2012; 237:304-311).

In view of the above, in certain embodiments, the compounds of the present invention have a wide range of therapeutic applications for the treatment of conditions or diseases of the central nervous system including, but not limited to, Niemann-Pick type C; Batten Disease; neurological disorders (such as headache, migraine; epilepsy; Alzheimer's disease; Parkinson's disease; brain injury (TBI); stroke; cerebrovascular diseases (including cerebral arteriosclerosis, cerebral amyloid angiopathy, hereditary cerebral hemorrhage, and brain hypoxia-ischemia); cognitive disorders (including amnesia, senile dementia, HIV-associated dementia, Alzheimer's disease, Huntington's disease, Lewy body dementia, vascular dementia, drug-related dementia, tardive dyskinesia, myoclonus, dystonia, delirium, Pick's disease, Creutzfeldt-Jacob disease, HIV disease, Gilles de la Tourette's syndrome, epilepsy, muscular spasms and disorders associated with muscular spasticity or weakness including tremors, and mild cognitive impairment); mental deficiency (including spasticity, Down syndrome and fragile X syndrome); sleep disorders (including hypersomnia, circadian rhythm sleep disorder, insomnia, parasomnia, and sleep deprivation) and psychiatric disorders such as anxiety (including acute stress disorder, generalized anxiety disorder, social anxiety disorder, panic disorder, post-traumatic stress disorder, agoraphobia, and obsessive-compulsive disorder); factitious disorders (including acute hallucinatory mania); impulse control disorders (including compulsive gambling and intermittent explosive disorder); mood disorders (including bipolar I disorder, bipolar II disorder, mania, mixed affective state, major depression, chronic depression, seasonal depression, psychotic depression, premenstrual syndrome (PMS) premenstrual dysphoric disorder (PDD), and postpartum depression); psychomotor disorders; psychotic disorders (including schizophrenia, schizoaffective disorder, schizophreniform, and delusional disorder); drug dependence and abuse (including narcotic dependence, alcoholism, amphetamine and

methamphetamine dependence, opioid dependence, cocaine addiction, nicotine dependence, and drug withdrawal syndrome, and relapse prevention); eating disorders (including anorexia, bulimia, binge eating disorder, hyperphagia, obesity, compulsive eating disorders and pagophagia); sexual dysfunction disorders, urinary incontinence (e.g., bladder overactivity); neuronal damage disorders (including ocular damage, retinopathy or macular degeneration of the eye, tinnitus, hearing impairment and loss, and brain edema) and pediatric psychiatric disorders (including attention deficit disorder, attention deficit/hyperactive disorder, conduct disorder, and autism) in a mammal, preferably a human, comprising administering to said mammal a therapeutically effective amount of a compound of the present invention or a pharmaceutically acceptable salt thereof.

In certain embodiments, the present invention is directed to methods for the treatment of schizophrenia by administration of a therapeutically effective amount of an azabenzimidazole compound of the present invention to a patient in need thereof.

In certain other embodiments, the invention is further directed to a method for the treatment of cognitive impairment associated with schizophrenia by administration of a therapeutically effective amount of an azabenzimidazole compounds of the present invention to a patient in need thereof.

In addition to the central nervous system disorders mentioned above, there is extensive literature in the art describing the effects of PDE inhibitors on various inflammatory cell responses, which in addition to cAMP increase, include inhibition of superoxide production, degranulation, chemotaxis and tumor necrosis factor (TNF) release in eosinophils, neutrophils and monocytes. Therefore, the azabenzimidazole compounds of the present invention may be useful for treating autoimmune and Inflammatory diseases. (See: Schett, G. et al., *Apremilast: A novel PDE4 Inhibitor in the Treatment of Autoimmune and Inflammatory Diseases*, Ther. Adv. Musculoskeletal Dis. 2010; 2(5):271-278). For example, the compounds of the present invention may be useful for treatment of oral ulcers associated with Behçet's disease (Id.). The compounds of the present invention may also be useful for the treatment of pain associated with arthritis (See: Hess, A. et al., *Blockade of TNF-α rapidly inhibits pain responses in the central nervous system,* PNAS, vol. 108, no. 9, 3731-3736 (2011) or for the treatment of psoriasis or psoriatic arthritis (See: Schafer, P., *Apremilast mechanism of action and application to psoriasis and psoriatic arthritis*, Biochem. Pharmacol. (2012), 15;83(12):1583-90). Accordingly, the azabenzimidazole compounds of the present invention may also be useful for treatment of ankylosing spondylitis [see: Patan, E. et al., *Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in ankylosing spondylitis*, Ann. Rheum. Dis. (Sep. 14, 2102)]. Other conditions treatable by

administration of the compounds of the present invention include, but are not limited to, multiple sclerosis, burns, sepsis, asthma, chronic or acute bronchoconstriction, chronic bronchitis, bronchiectasis, small airways obstruction, emphysema, obstructive or inflammatory airways diseases, pneumoconiosis, seasonal allergic rhinitis or perennial allergic rhinitis or sinusitis, allergic conjunctivitis, acute respiratory distress syndrome (ARDS), acute lung injury (ALI), arthritis (e.g., rheumatoid arthritis and osteoarthritis) gout, and fever and pain associated with inflammation, eosinophil-related disorders, dermatitis or eczema, urticaria, conjunctivitis, uveitis, psoriasis, inflammatory bowel disease, Crohn's disease, septic shock, liver injury, pulmonary hypertension, bone loss disease, neuropathy, and infection.

In yet another embodiment, the compounds of the present invention may be useful for treating cancer and tumors. For example, the compounds of the present invention may be useful for treatment of brain cancer (e.g., medulloblastoma) (See: Schmidt, A. L., *BDNF and PDE4, but not GRPR, Regulate Viability of Human Medulloblastoma Cells*, J. Mol. Neuroscience (2010) 40:303-310). The compounds of the present invention may also be useful for treating melanoma (See: Marquette, A. et al., *ERK and PDE4 cooperate to induce RAF isoform switching in melanoma,* Nature Structural & Molecular Biology, vol. 18, no. 5, 584-91, 2011). In certain embodiments, the compounds of the present invention may be useful for treating leukemia, e.g., chronic lymphocytic leukemia, (See: Kim, D. H. et al., *Type 4 Cyclic Adenosine Monophosphate Phosphodiesterase as a Therapeutic Target in Chronic Lymphocytic Leulemia*, Blood Journal of The American Society of Hematology, October 1, 1998, vol. 92, no. 7 2484-2494).

In certain other embodiments, the compounds of the present invention may be useful for treating diabetes or conditions associated with diabetes (See: Vollert, S. et al., *The glucose-lowering effects of the PDE4 inhibitors roflumilast and roflumilast-N-Oxide in db/db mice*, Diabetologia (2012) 55:2779-2788. Wouters, E. F. M. et al., *Effect of the Phosphodiesterase 4 Inhibitor Roflumilast on Glucose Metabolism in Patients with Treatment-Naïve, Newly Diagnosed Type 2 Diabetes Mellitus,* Journal of Clinical Endocrinology and Metabolism 2012, 97, 1720-1725). In certain embodiments, the compounds of the present invention may be useful for treating diabetic macular edema (DME) and diabetic neuropathy (DN).

Formulations

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or

sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

In another embodiment, the compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

In another embodiment, the compounds of the invention may also be formulated such that administration topically to the skin or mucosa (i.e., dermally or transdermally) leads to systemic absorption of the compound. In another embodiment, the compounds of the invention can also be formulated such that administration intranasally or by inhalation leads to systemic absorption of the compound. In another embodiment, the compounds of the invention may be formulated such that administration rectally or vaginally leads to systemic absorption of the compound.

The dosage regimen for the compounds and/or compositions containing the compounds is based on a variety of factors, including the type, age, weight, sex and medical condition of the patient; the severity of the condition; the route of administration; and the activity of the particular compound employed. Thus the dosage regimen may vary widely. Dosage levels of the order from about 0.01 mg to about 100 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions. In one embodiment, the total daily dose of a compound of the invention (administered in single or divided doses) is typically from about 0.01 to about 100 mg/kg. In another embodiment, the total daily dose of the compound of the invention is from about 0.1 to about 50 mg/kg, and in another embodiment, from about 0.5 to about 30 mg/kg (i.e., mg compound of the invention per kg body weight). In one embodiment, dosing is from 0.01 to 10 mg/kg/day. In another embodiment, dosing is from 0.1 to 1.0 mg/kg/day. Dosage unit compositions may contain such amounts or submultiples thereof to make up the daily dose. In many instances, the administration of the compound will be repeated a plurality of times in a day (typically no greater than 4 times). Multiple doses per day typically may be used to increase the total daily dose, if desired.

For oral administration, the compositions may be provided in the form of tablets containing 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 75.0, 100, 125, 150, 175, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment

of the dosage to the patient. A medicament typically contains from about 0.01 mg to about 500 mg of the active ingredient, or in another embodiment, from about 1 mg to about 100 mg of active ingredient. Intravenously, doses may range from about 0.1 to about 10 mg/kg/minute during a constant rate infusion.

Suitable subjects according to the present invention include mammalian subjects. Mammals according to the present invention include, but are not limited to, canine, feline, bovine, caprine, equine, ovine, porcine, rodents, lagomorphs, primates, and the like, and encompass mammals in utero. In one embodiment, humans are suitable subjects. Human subjects may be of either gender and at any stage of development.

In another embodiment, the invention comprises the use of one or more compounds of the invention for the preparation of a medicament for the treatment of the conditions recited herein.

For the treatment of the conditions referred to above, the compounds of the invention can be administered as compound per se. Alternatively, pharmaceutically acceptable salts are suitable for medical applications because of their greater aqueous solubility relative to the parent compound.

In another embodiment, the present invention comprises pharmaceutical compositions. Such pharmaceutical compositions comprise a compound of the invention presented with a pharmaceutically acceptable carrier. The carrier can be a solid, a liquid, or both, and may be formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from 0.05% to 95% by weight of the active compounds. A compound of the invention may be coupled with suitable polymers as targetable drug carriers. Other pharmacologically active substances can also be present.

The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The active compounds and compositions, for example, may be administered orally, rectally, parenterally, or topically.

Oral administration of a solid dose form may be, for example, presented in discrete units, such as hard or soft capsules, pills, cachets, lozenges, or tablets, each containing a predetermined amount of at least one compound of the present invention. In another embodiment, the oral administration may be in a powder or granule form. In another embodiment, the oral dose form is sub-lingual, such as, for example, a lozenge. In such solid dosage forms, the compounds of the present invention are ordinarily combined with

one or more adjuvants. Such capsules or tablets may contain a controlled-release formulation. In the case of capsules, tablets, and pills, the dosage forms also may comprise buffering agents or may be prepared with enteric coatings.

In another embodiment, oral administration may be in a liquid dose form. Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (e.g., water). Such compositions also may comprise adjuvants, such as wetting, emulsifying, suspending, flavoring (e.g., sweetening), and/or perfuming agents.

In another embodiment, the present invention comprises a parenteral dose form. "Parenteral administration" includes, for example, subcutaneous injections, intravenous injections, intraperitoneal injections, intramuscular injections, intrasternal injections, and infusion. Injectable preparations (i.e., sterile injectable aqueous or oleaginous suspensions) may be formulated according to the known art using suitable dispersing, wetting, and/or suspending agents.

In another embodiment, the present invention comprises a topical dose form. "Topical administration" includes, for example, transdermal administration, such as via transdermal patches or iontophoresis devices, intraocular administration, or intranasal or inhalation administration. Compositions for topical administration also include, for example, topical gels, sprays, ointments, and creams. A topical formulation may include a compound that enhances absorption or penetration of the active ingredient through the skin or other affected areas. When the compounds of this invention are administered by a transdermal device, administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibers, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, Finnin and Morgan, J. Pharm. Sci., 88 (10), 955-958 (1999).

Formulations suitable for topical administration to the eye include, for example, eye drops wherein the compound of this invention is dissolved or suspended in a suitable carrier. A typical formulation suitable for ocular or aural administration may be in the form of drops of a micronized suspension or solution in isotonic, pH-adjusted, sterile saline. Other formulations suitable for ocular and aural administration include ointments,

biodegradable (e.g., absorbable gel sponges, collagen) and non-biodegradable (e.g., silicone) implants, wafers, lenses and particulate or vesicular systems, such as niosomes or liposomes. A polymer such as crossed-linked polyacrylic acid, polyvinyl alcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelan gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

For intranasal administration or administration by inhalation, the active compounds of the invention are conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant. Formulations suitable for intranasal administration are typically administered in the form of a dry powder (either alone; as a mixture, for example, in a dry blend with lactose; or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrohydrodynamics to produce a fine mist), or nebulizer, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

In another embodiment, the present invention comprises a rectal dose form. Such rectal dose form may be in the form of, for example, a suppository. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Other carrier materials and modes of administration known in the pharmaceutical art may also be used. Pharmaceutical compositions of the invention may be prepared by any of the well-known techniques of pharmacy, such as effective formulation and administration procedures. The above considerations in regard to effective formulations and administration procedures are well known in the art and are described in standard textbooks. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania, 1975; Liberman et al., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe et al., Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington, 1999.

The compounds of the present invention can be used, alone or in combination with other therapeutic agents, in the treatment of various conditions or disease states. The

compound(s) of the present invention and other therapeutic agent(s) may be administered simultaneously (either in the same dosage form or in separate dosage forms) or sequentially. An exemplary therapeutic agent may be, for example, a metabotropic glutamate receptor agonist.

The administration of two or more compounds "in combination" means that the two compounds are administered closely enough in time that the presence of one alters the biological effects of the other. The two or more compounds may be administered simultaneously, concurrently or sequentially. Additionally, simultaneous administration may be carried out by mixing the compounds prior to administration or by administering the compounds at the same point in time but at different anatomic sites or using different routes of administration.

The phrases "concurrent administration," "co-administration," "simultaneous administration," and "administered simultaneously" mean that the compounds are administered in combination.

The present invention includes the use of a combination of a PDE4 inhibitor compound of the present invention and one or more additional pharmaceutically active agent(s). If a combination of active agents is administered, then they may be administered sequentially or simultaneously, in separate dosage forms or combined in a single dosage form. Accordingly, the present invention also includes pharmaceutical compositions comprising an amount of: (a) a first agent comprising a compound of the present invention or a pharmaceutically acceptable salt of the compound; (b) a second pharmaceutically active agent; and (c) a pharmaceutically acceptable carrier, vehicle or diluent.

Various pharmaceutically active agents may be selected for use in conjunction with the compounds of the present invention, depending on the disease, disorder, or condition to be treated. Pharmaceutically active agents that may be used in combination with the compositions of the present invention include, without limitation:

(i) acetylcholinesterase inhibitors, such as donepezil hydrochloride (ARICEPT, MEMAC), physostigmine salicylate (ANTILIRIUM), physostigmine sulfate (ESERINE), metrifonate, neostigmine, ganstigmine, pyridostigmine (MESTINON), ambenonium (MYTELASE), demarcarium, Debio 9902 (also known as ZT-1; Debiopharm), rivastigmine (EXELON), ladostigil, NP-0361, galantamine hydrobromide (RAZADYNE, RIMINYL, NIVALIN), tacrine (COGNEX), tolserine, velnacrine maleate, memoquin, huperzine A (HUP-A; NeuroHitech), phenserine, edrophonium (ENLON, TENSILON), and INM-176;

(ii) amyloid-ß (or fragments thereof), such as $A\beta_{1-15}$ conjugated to pan HLA DR-binding epitope (PADRE), ACC-001 (Elan/Wyeth), ACI-01, ACI-24, AN-1792, Affitope AD-01, CAD106, and V-950;

(iii) antibodies to amyloid-ß (or fragments thereof), such as ponezumab, solanezumab, bapineuzumab (also known as AAB-001), AAB-002 (Wyeth/Elan), ACI-01-Ab7, BAN-2401, intravenous Ig (GAMMAGARD), LY2062430 (humanized m266; Lilly), R1450 (Roche), ACU-5A5, huC091, and those disclosed in International Patent Publication Nos WO04/032868, WO05/025616, WO06/036291, WO06/069081, WO06/118959, in US Patent Publication Nos US2003/0073655, US2004/0192898, US2005/0048049, US2005/0019328, in European Patent Publication Nos EP0994728 and 1257584, and in US Patent No 5,750,349;

(iv) amyloid-lowering or -inhibiting agents (including those that reduce amyloid production, accumulation and fibrillization) such as dimebon, davunetide, eprodisate, leuprolide, SK-PC-B70M, celecoxib, lovastatin, anapsos, oxiracetam, pramiracetam, varenicline, nicergoline, colostrinin, bisnorcymserine (also known as BNC), NIC5-15 (Humanetics), E-2012 (Eisai), pioglitazone, clioquinol (also known as PBT1), PBT2 (Prana Biotechnology), flurbiprofen (ANSAID, FROBEN) and its *R*-enantiomer tarenflurbil (FLURIZAN), nitroflurbiprofen, fenoprofen (FENOPRON, NALFON), ibuprofen (ADVIL, MOTRIN, NUROFEN), ibuprofen lysinate, meclofenamic acid, meclofenamate sodium (MECLOMEN), indomethacin (INDOCIN), diclofenac sodium (VOLTAREN), diclofenac potassium, sulindac (CLINORIL), sulindac sulfide, diflunisal (DOLOBID), naproxen (NAPROSYN), naproxen sodium (ANAPROX, ALEVE), ARC031 (Archer Pharmaceuticals), CAD-106 (Cytos), LY450139 (Lilly), insulin-degrading enzyme (also known as insulysin), the gingko biloba extract EGb-761 (ROKAN, TEBONIN), tramiprosate (CEREBRIL, ALZHEMED), eprodisate (FIBRILLEX, KIACTA), compound W (3,5-bis(4-nitrophenoxy)benzoic acid), NGX-96992, neprilysin (also known as neutral endopeptidase (NEP)), scyllo-inositol (also known as scyllitol), atorvastatin (LIPITOR), simvastatin (ZOCOR), KLVFF-(EEX)3, SKF-74652, ibutamoren mesylate, BACE inhibitors such as ASP-1702, SCH-745966, JNJ-715754, AMG-0683, AZ-12304146, BMS-782450, GSK-188909, NB-533, E2609 and TTP-854; gamma secretase modulators such as ELND-007; and RAGE (receptor for advanced glycation end-products) inhibitors, such as TTP488 (Transtech) and TTP4000 (Transtech), and those disclosed in US Patent No 7,285,293, including PTI-777;

(v) alpha-adrenergic receptor agonists, such as guanfacine (INTUNIV, TENEX), clonidine (CATAPRES), metaraminol (ARAMINE), methyldopa (ALDOMET, DOPAMET, NOVOMEDOPA), tizanidine (ZANAFLEX), phenylephrine (also known as neosynephrine),

methoxamine, cirazoline, guanfacine (INTUNIV), lofexidine, xylazine, modafinil (PROVIGIL), adrafinil, and armodafinil (NUVIGIL);

(vi) beta-adrenergic receptor blocking agents (beta blockers), such as carteolol, esmolol (BREVIBLOC), labetalol (NORMODYNE, TRANDATE), oxprenolol (LARACOR, TRASACOR), pindolol (VISKEN), propanolol (INDERAL), sotalol (BETAPACE, SOTALEX, SOTACOR), timolol (BLOCADREN, TIMOPTIC), acebutolol (SECTRAL, PRENT), nadolol (CORGARD), metoprolol tartrate (LOPRESSOR), metoprolol succinate (TOPROL-XL), atenolol (TENORMIN), butoxamine, and SR 59230A (Sanofi);

(vii) anticholinergics, such as amitriptyline (ELAVIL, ENDEP), butriptyline, benztropine mesylate (COGENTIN), trihexyphenidyl (ARTANE), diphenhydramine (BENADRYL), orphenadrine (NORFLEX), hyoscyamine, atropine (ATROPEN), scopolamine (TRANSDERM-SCOP), scopolamine methylbromide (PARMINE), dicycloverine (BENTYL, BYCLOMINE, DIBENT, DILOMINE), tolterodine (DETROL), oxybutynin (DITROPAN, LYRINEL XL, OXYTROL), penthienate bromide, propantheline (PRO-BANTHINE), cyclizine, imipramine hydrochloride (TOFRANIL), imipramine maleate (SURMONTIL), lofepramine, desipramine (NORPRAMIN), doxepin (SINEQUAN, ZONALON), trimipramine (SURMONTIL), and glycopyrrolate (ROBINUL);

(viii) anticonvulsants, such as carbamazepine (TEGRETOL, CARBATROL), oxcarbazepine (TRILEPTAL), phenytoin sodium (PHENYTEK), fosphenytoin (CEREBYX, PRODILANTIN), divalproex sodium (DEPAKOTE), gabapentin (NEURONTIN), pregabalin (LYRICA), topirimate (TOPAMAX), valproic acid (DEPAKENE), valproate sodium (DEPACON), 1-benzyl-5-bromouracil, progabide, beclamide, zonisamide (TRERIEF, EXCEGRAN), CP-465022, retigabine, talampanel, and primidone (MYSOLINE);

(ix) antipsychotics, such as lurasidone (LATUDA, also known as SM-13496; Dainippon Sumitomo), aripiprazole (ABILIFY), chlorpromazine (THORAZINE), haloperidol (HALDOL), iloperidone (FANAPTA), flupentixol decanoate (DEPIXOL, FLUANXOL), reserpine (SERPLAN), pimozide (ORAP), fluphenazine decanoate, fluphenazine hydrochloride, prochlorperazine (COMPRO), asenapine (SAPHRIS), loxapine (LOXITANE), molindone (MOBAN), perphenazine, thioridazine, thiothixine, trifluoperazine (STELAZINE), ramelteon, clozapine (CLOZARIL), norclozapine (ACP-104), risperidone (RISPERDAL), paliperidone (INVEGA), melperone, olanzapine (ZYPREXA), quetiapine (SEROQUEL), talnetant, amisulpride, ziprasidone (GEODON), blonanserin (LONASEN), and ACP-103 (Acadia Pharmaceuticals);

(x) calcium channel blockers such as lomerizine, ziconotide, nilvadipine (ESCOR, NIVADIL), diperdipine, amlodipine (NORVASC, ISTIN, AMLODIN), felodipine (PLENDIL), nicardipine (CARDENE), nifedipine (ADALAT, PROCARDIA), MEM 1003 and its parent compound nimodipine (NIMOTOP), nisoldipine (SULAR), nitrendipine, lacidipine (LACIPIL, MOTENS), lercanidipine (ZANIDIP), lifarizine, diltiazem (CARDIZEM), verapamil (CALAN, VERELAN), AR-R 18565 (AstraZeneca), and enecadin;

(xi) catechol *O*-methyltransferase (COMT) inhibitors, such as nitecapone, tolcapone (TASMAR), entacapone (COMTAN), and tropolone;

(xii) central nervous system stimulants, such as atomoxetine, reboxetine, yohimbine, caffeine, phenmetrazine, phendimetrazine, pemoline, fencamfamine (GLUCOENERGAN, REACTIVAN), fenethylline (CAPTAGON), pipradol (MERETRAN), deanol (also known as dimethylaminoethanol), methylphenidate (DAYTRANA), methylphenidate hydrochloride (RITALIN), dexmethylphenidate (FOCALIN), amphetamine (alone or in combination with other CNS stimulants, e.g., ADDERALL (amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate)), dextroamphetamine sulfate (DEXEDRINE, DEXTROSTAT), methamphetamine (DESOXYN), lisdexamfetamine (VYVANSE), and benzphetamine (DIDREX);

(xiii) corticosteroids, such as prednisone (STERAPRED, DELTASONE), prednisolone (PRELONE), predisolone acetate (OMNIPRED, PRED MILD, PRED FORTE), prednisolone sodum phosphate (ORAPRED ODT), methylprednisolone (MEDROL); methylprednisolone acetate (DEPO-MEDROL), and methylprednisolone sodium succinate (A-METHAPRED, SOLU-MEDROL);

(xiv) dopamine receptor agonists, such as apomorphine (APOKYN), bromocriptine (PARLODEL), cabergoline (DOSTINEX), dihydrexidine, dihydroergocryptine, fenoldopam (CORLOPAM), lisuride (DOPERGIN), terguride spergolide (PERMAX), piribedil (TRIVASTAL, TRASTAL), pramipexole (MIRAPEX), quinpirole, ropinirole (REQUIP), rotigotine (NEUPRO), SKF-82958 (GlaxoSmithKline), cariprazine, pardoprunox and sarizotan;

(xv) dopamine receptor antagonists, such as chlorpromazine, fluphenazine, haloperidol, loxzpine, resperidone, thioridazine, thiothixene, trifluoperazine, tetrabenazine (NITOMAN, XENAZINE), 7-hydroxyamoxapine, droperidol (INAPSINE, DRIDOL, DROPLETAN), domperidone (MOTILIUM), L-741742, L-745870, raclopride, SB-277011A, SCH-23390, ecopipam, SKF-83566, and metoclopramide (REGLAN);

(xvi) dopamine reuptake inhibitors such as bupropion, safinamide, nomifensine maleate (MERITAL), vanoxerine (also known as GBR-12909) and its decanoate ester DBL-583, and amineptine;

(xvii) gamma-amino-butyric acid (GABA) receptor agonists, such as baclofen (LIORESAL, KEMSTRO), siclofen, pentobarbital (NEMBUTAL), progabide (GABRENE), and clomethiazole;

(xviii) histamine 3 (H3) antagonists such as ciproxifan, tiprolisant, S-38093, irdabisant, pitolisant, GSK-239512, GSK-207040, JNJ-5207852, JNJ-17216498, HPP-404, SAR-110894, trans-3-fluoro-3-(3-fluoro-4-pyrrolidin-1-ylmethyl-phenyl)-cyclobutane carboxylic acid ethylamide (PF-3654746 and those disclosed in US Patent Publication Nos US2005-0043354, US2005-0267095, US2005-0256135, US2008-0096955, US2007-1079175, and US2008-0176925; International Patent Publication Nos WO2006/136924, WO2007/063385, WO2007/069053, WO2007/088450, WO2007/099423, WO2007/105053, WO2007/138431, and WO2007/088462; and US Patent No 7,115,600);

(xix) immunomodulators such as glatiramer acetate (also known as copolymer-1; COPAXONE), MBP-8298 (synthetic myelin basic protein peptide), dimethyl fumarate, fingolimod (also known as FTY720), roquinimex (LINOMIDE), laquinimod (also known as ABR-215062 and SAIK-MS), ABT-874 (human anti-IL-12 antibody; Abbott), rituximab (RITUXAN), alemtuzumab (CAMPATH), daclizumab (ZENAPAX), and natalizumab (TYSABRI);

(xx) immunosuppressants such as methotrexate (TREXALL, RHEUMATREX), mitoxantrone (NOVANTRONE), mycophenolate mofetil (CELLCEPT), mycophenolate sodium (MYFORTIC), azathioprine (AZASAN, IMURAN), mercaptopurine (PURI-NETHOL), cyclophosphamide (NEOSAR, CYTOXAN), chlorambucil (LEUKERAN), cladribine (LEUSTATIN, MYLINAX), alpha-fetoprotein, etanercept (ENBREL), and 4-benzyloxy-5-((5-undecyl-2H-pyrrol-2-ylidene)methyl)-2,2'-bi-1H-pyrrole (also known as PNU-156804);

(xxi) interferons, including interferon beta-1a (AVONEX, REBIF) and interferon beta-1b (BETASERON, BETAFERON);

(xxii) levodopa (or its methyl or ethyl ester), alone or in combination with a DOPA decarboxylase inhibitor (e.g., carbidopa (SINEMET, CARBILEV, PARCOPA), benserazide (MADOPAR), α-methyldopa, monofluromethyldopa, difluoromethyldopa, brocresine, or *m*-hydroxybenzylhydrazine);

(xxiii) *N*-methyl-D-aspartate (NMDA) receptor antagonists, such as memantine (NAMENDA, AXURA, EBIXA), amantadine (SYMMETREL), acamprosate (CAMPRAL), besonprodil, ketamine (KETALAR), delucemine, dexanabinol, dexefaroxan, dextromethorphan, dextrorphan, traxoprodil, CP-283097, himantane, idantadol, ipenoxazone, L-701252 (Merck), lancicemine, levorphanol (DROMORAN), LY-233536 and LY-235959 (both Lilly), methadone, (DOLOPHINE), neramexane, perzinfotel, phencyclidine, tianeptine (STABLON), dizocilpine (also known as MK-801), EAB-318 (Wyeth), ibogaine, voacangine, tiletamine, riluzole (RILUTEK), aptiganel (CERES0TAT), gavestinel, and remacimide;

(xxiv) monoamine oxidase (MAO) inhibitors, such as selegiline (EMSAM), selegiline hydrochloride (l-deprenyl, ELDEPRYL, ZELAPAR), dimethylselegilene, brofaromine, phenelzine (NARDIL), tranylcypromine (PARNATE), moclobemide (AURORIX, MANERIX), befloxatone, safinamide, isocarboxazid (MARPLAN), nialamide (NIAMID), rasagiline (AZILECT), iproniazide (MARSILID, IPROZID, IPRONID), CHF-3381 (Chiesi Farmaceutici), iproclozide, toloxatone (HUMORYL, PERENUM), bifemelane, desoxypeganine, harmine (also known as telepathine or banasterine), harmaline, linezolid (ZYVOX, ZYVOXID), and pargyline (EUDATIN, SUPIRDYL);

(xxv) muscarinic receptor (particularly M1 subtype) agonists, such as cevimeline, levetiracetam, bethanechol chloride (DUVOID, URECHOLINE), itameline, pilocarpine (SALAGEN), NGX267, arecoline, L-687306 (Merck), L-689660 (Merck), furtrethonium iodide (FURAMON, FURANOL), furtrethonium benzensulfonate, furtrethonium *p*-toluenesulfonate, McN-A-343, oxotremorine, sabcomeline, AC-90222 (Acadia Pharmaceuticals), and carbachol (CARBASTAT, MIOSTAT, CARBOPTIC);

(xxvi) neuroprotective drugs such as bosutinib, condoliase, airmoclomol, lamotrigine, perampanel, aniracetam, minaprime, viluzole 2,3,4,9-tetrahydro-1*H*-carbazol-3-one oxime, desmoteplase, anatibant, astaxanthin, neuropeptide NAP (e.g., AL-108 and AL-208; both Allon Therapeutics), neurostrol, perampenel, ispronicline, bis(4-β-D-glucopyranosyloxybenzyl)-2-β-D-glucopyranosyl-2-isobutyltartrate (also known as dactylorhin B or DHB), formobactin, xaliproden (XAPRILA), lactacystin, dimeboline hydrochloride (DIMEBON), disufenton (CEROVIVE), arundic acid (ONO-2506, PROGLIA, CEREACT), citicoline (also known as cytidine 5'-diphosphocholine), edaravone (RADICUT), AEOL-10113 and AEOL-10150 (both Aeolus Pharmaceuticals), AGY-94806 (also known as SA-450 and Msc-1), granulocyte-colony stimulating factor (also known as AX-200), BAY-38-7271 (also known as KN-387271; Bayer AG), ancrod (VIPRINEX, ARWIN), DP-b99 (D-Pharm Ltd), HF-0220 (17-ß-hydroxyepiandrosterone; Newron Pharmaceuticals), HF-0420

(also known as oligotropin), pyridoxal 5'-phosphate (also known as MC-1), microplasmin, S-18986, piclozotan, NP031112, tacrolimus, L-seryl-L-methionyl-L-alanyl-L-lysyl-L-glutamyl-glycyl-L-valine, AC-184897 (Acadia Pharmaceuticals), ADNF-14 (National Institutes of Health), stilbazulenyl nitrone, SUN-N8075 (Daiichi Suntory Biomedical Research), and zonampanel;

(xxvii) nicotinic receptor agonists, such as epibatidine, bupropion, CP-601927, varenicline, ABT-089 (Abbott), ABT-594, AZD-0328 (AstraZeneca), EVP-6124, R3487 (also known as MEM3454; Roche/Memory Pharmaceuticals), R4996 (also known as MEM63908; Roche/Memory Pharmaceuticals), TC-4959 and TC-5619 (both Targacept), and RJR-2403;

(xxviii) norepinephrine (noradrenaline) reuptake inhibitors, such as atomoxetine (STRATTERA), doxepin (APONAL, ADAPIN, SINEQUAN), nortriptyline (AVENTYL, PAMELOR, NORTRILEN), amoxapine (ASENDIN, DEMOLOX, MOXIDIL), reboxetine (EDRONAX, VESTRA), viloxazine (VIVALAN), maprotiline (DEPRILEPT, LUDIOMIL, PSYMION), bupropion (WELLBUTRIN), and radaxafine;

(xxix) phosphodiesterase (PDE) inhibitors, including but not limited to, (a) PDE1 inhibitors (e.g., vinpocetine (CAVINTON, CERACTIN, INTELECTOL) and those disclosed in US Patent No 6,235,742, (b) PDE2 inhibitors (e.g., erythro-9-(2-hydroxy-3-nonyl)adenine (EHNA), BAY 60-7550, and those described in US Patent No. 6,174,884), (c) PDE3 inhibitors (e.g., anagrelide, cilostazol, milrinone, olprinone, parogrelil, and pimobendan), (d) PDE4 inhibitors (e.g., apremilast, ibudilastroflumilast, rolipram, Ro 20-1724, ibudilast (KETAS), piclamilast (also known as RP73401), CDP840, cilomilast (ARIFLO), roflumilast, tofimilast, oglemilast (also known as GRC 3886), tetomilast (also known as OPC-6535), lirimifast, theophylline (UNIPHYL, THEOLAIR), arofylline (also known as LAS-31025), doxofylline, RPR-122818, or mesembrine), and (e) PDE5 inhibitors (e.g., sildenafil (VIAGRA, REVATIO), tadalafil (CIALIS), vardenafil (LEVITRA, VIVANZA), udenafil, avanafil, dipyridamole (PERSANTINE), E-4010, E-4021, E-8010, zaprinast, iodenafil, mirodenafil, DA-8159, and those disclosed in International Patent Applications WO2002/020521, WO2005/049616, WO2006/120552, WO2006/126081, WO2006/126082, WO2006/126083, and WO2007/122466), (f) PDE7 inhibitors; (g) PDE8 inhibitors; (h) PDE9 inhibitors (e.g., BAY 73-6691 (Bayer AG) and those disclosed in US Patent Publication Nos US2003/0195205, US2004/0220186, US2006/0111372, US2006/0106035, and USSN 12/118,062 (filed May 9, 2008)), (i) PDE10 inhibitor such as 2-[4-(1-Methyl-4-pyridin-4-yl-1H-pyrazol-3-yl)phenoxymethyl]quinoline (PF-2545920), and SCH-1518291; and (j) PDE11 inhibitors;

(xxx) quinolines, such as quinine (including its hydrochloride, dihydrochloride, sulfate, bisulfate and gluconate salts), chloroquine, sontoquine, hydroxychloroquine (PLAQUENIL), mefloquine (LARIAM), and amodiaquine (CAMOQUIN, FLAVOQUINE);

(xxxi) β-secretase inhibitors, such as ASP-1702, SCH-745966, JNJ-715754, AMG-0683, AZ-12304146, BMS-782450, GSK-188909, NB-533, LY-2886721, E-2609, HPP-854, (+)-phenserine tartrate (POSIPHEN), LSN-2434074 (also known as LY-2434074), KMI-574, SCH-745966, Ac-rER (N^2-acetyl-D-arginyl-L-arginine), loxistatin (also known as E64d), and CA074Me;

(xxxii) γ-secretase inhibitors and modulators, such as BMS-708163 (Avagacest), WO20060430064 (Merck), DSP8658 (Dainippon), ITI-009, L-685458 (Merck), ELAN-G, ELAN-Z, 4-chloro-*N*-[2-ethyl-1(S)-(hydroxymethyl)butyl]benzenesulfonamide;

(xxxiii) serotonin (5-hydroxytryptamine) 1A ($5\text{-}HT_{1A}$) receptor antagonists, such as spiperone, *levo*-pindolol, BMY 7378, NAD-299, *S*(-)-UH-301, NAN 190, lecozotan;

(xxxiv) serotonin (5-hydroxytryptamine) 2C (5-HT2c) receptor agonists, such as vabicaserin, and zicronapine;

(xxxv) serotonin (5-hydroxytryptamine) 4 ($5\text{-}HT_4$) receptor agonists, such as PRX-03140 (Epix);

(xxxvi) serotonin (5-hydroxytryptamine) 6 ($5\text{-}HT_6$) receptor antagonists, such as A-964324, AVI-101, AVN-211, mianserin (TORVOL, BOLVIDON, NORVAL), methiothepin (also known as metitepine), ritanserin, ALX-1161, ALX-1175, MS-245, LY-483518 (also known as SGS518; Lilly), MS-245, Ro 04-6790, Ro 43-68544, Ro 63-0563, Ro 65-7199, Ro 65-7674, SB-399885, SB-214111, SB-258510, SB-271046, SB-357134, SB-699929, SB-271046, SB-742457 (GlaxoSmithKline), Lu AE58054 (Lundbeck A/S), and PRX-07034 (Epix);

(xxxvii) serotonin (5-HT) reuptake inhibitors such as alaproclate, citalopram (CELEXA, CIPRAMIL), escitalopram (LEXAPRO, CIPRALEX), clomipramine (ANAFRANIL), duloxetine (CYMBALTA), femoxetine (MALEXIL), fenfluramine (PONDIMIN), norfenfluramine, fluoxetine (PROZAC), fluvoxamine (LUVOX), indalpine, milnacipran (IXEL), paroxetine (PAXIL, SEROXAT), sertraline (ZOLOFT, LUSTRAL), trazodone (DESYREL, MOLIPAXIN), venlafaxine (EFFEXOR), zimelidine (NORMUD, ZELMID), bicifadine, desvenlafaxine (PRISTIQ), brasofensine, vilazodone, cariprazine, neuralstem and tesofensine;

(xxxviii) trophic factors, such as nerve growth factor (NGF), basic fibroblast growth factor (bFGF; ERSOFERMIN), neurotrophin-3 (NT-3), cardiotrophin-1, brain-derived neurotrophic factor (BDNF), neublastin, meteorin, and glial-derived neurotrophic factor (GDNF), and agents that stimulate production of trophic factors, such as propentofylline, idebenone, PYM50028 (COGANE; Phytopharm), and AIT-082 (NEOTROFIN);

(xxxix) Glycine transporter-1 inhibitors such as paliflutine, ORG-25935, JNJ-17305600, and ORG-26041;

(xl) AMPA-type glutamate receptor modulators such as perampanel, mibampator, selurampanel, GSK-729327, *N*-{(3*S*,4*S*)-4-[4-(5-cyanothiophen-2-yl)phenoxy]tetrahydro-furan-3-yl}propane-2-sulfonamide, and the like.

The present invention further comprises kits that are suitable for use in performing the methods of treatment described above. In one embodiment, the kit contains a first dosage form comprising one or more of the compounds of the present invention and a container for the dosage, in quantities sufficient to carry out the methods of the present invention.

In another embodiment, the kit of the present invention comprises one or more compounds of the invention.

The compounds of the invention, or their pharmaceutically acceptable salts, may be prepared by a variety of methods that are analogously known in the art. The reaction schemes described below, together with synthetic methods known in the art of organic chemistry, or modifications and derivatizations that are familiar to those of ordinary skill in the art, illustrate six (6) methods for preparing the compounds. Others, including modifications thereof, will be readily apparent to one skilled in the art.

The starting materials used herein are commercially available or may be prepared by routine methods known in the art (such as those methods disclosed in standard reference books such as the COMPENDIUM OF ORGANIC SYNTHETIC METHODS, Vol. I-XII (published by Wiley-Interscience)). Preferred methods include, but are not limited to, those described below.

During any of the following synthetic sequences, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This can be achieved by means of conventional protecting groups, such as those described in T. W. Greene, Protective Groups in Organic Chemistry, John Wiley & Sons, 1981; T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons,

1991; and T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley & Sons, 1999, which are hereby incorporated by reference.

Compounds of the present invention or their pharmaceutically acceptable salts of said compounds or tautomers and radioisotopes, can be prepared according to the reaction Schemes discussed herein below. Unless otherwise indicated, the substituents in the Schemes are defined as above. Isolation and purification of the products is accomplished by standard procedures, which are known to a chemist of ordinary skill.

One skilled in the art will recognize that in some cases, the compounds in Schemes 1 through 6 will be generated as a mixture of diastereomers and/or enantiomers; these may be separated at various stages of the synthetic schemes using conventional techniques or a combination of such techniques, such as, but not limited to, crystallization, normal-phase chromatography, reversed phase chromatography and chiral chromatography, to afford the single enantiomers of the invention.

It will be understood by one skilled in the art that the various symbols, superscripts and subscripts used in the schemes, methods and examples are used for convenience of representation and/or to reflect the order in which they are introduced in the schemes, and are not intended to necessarily correspond to the symbols, superscripts or subscripts in the appended claims. The schemes are representative of methods useful in synthesizing the compounds of the present invention. They are not to constrain the scope of the invention in any way.

Scheme 1 below illustrates one synthesis sequence for the preparation of compounds of formula **I**. The initial step in the synthesis, as depicted, utilizes 2-chloro-3-nitropyridine of formula **1** as an initial starting material. The 2-chloro-3-nitropyridine **1** undergoes S_NAr reactions with amine nucleophiles of formula **2** such as anilines, in the presence of base as a proton scavenger, at temperatures from room temperature to 200°C, to give aminonitropyridines of formula **II**. During the initial S_NAr reaction step the R^1 substituent on the amine nucleophiles of formula **2** should be represented by the same moiety as is desired in the final product, or a protected variation thereof. For example, the final product of Example 1 (*N*-cyclopropyl-3-(3-fluoro-4-methylphenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide*)* can be prepared utilizing reaction scheme 1, wherein R^1 of the amine nucleophile of formula **2** is represented by 3-fluoro-4-methylphenyl.

The next step of the reaction is the reduction of the nitro group of formula **II** to the amine to give the diaminopyridine compounds of formula **III**. This step can be effected

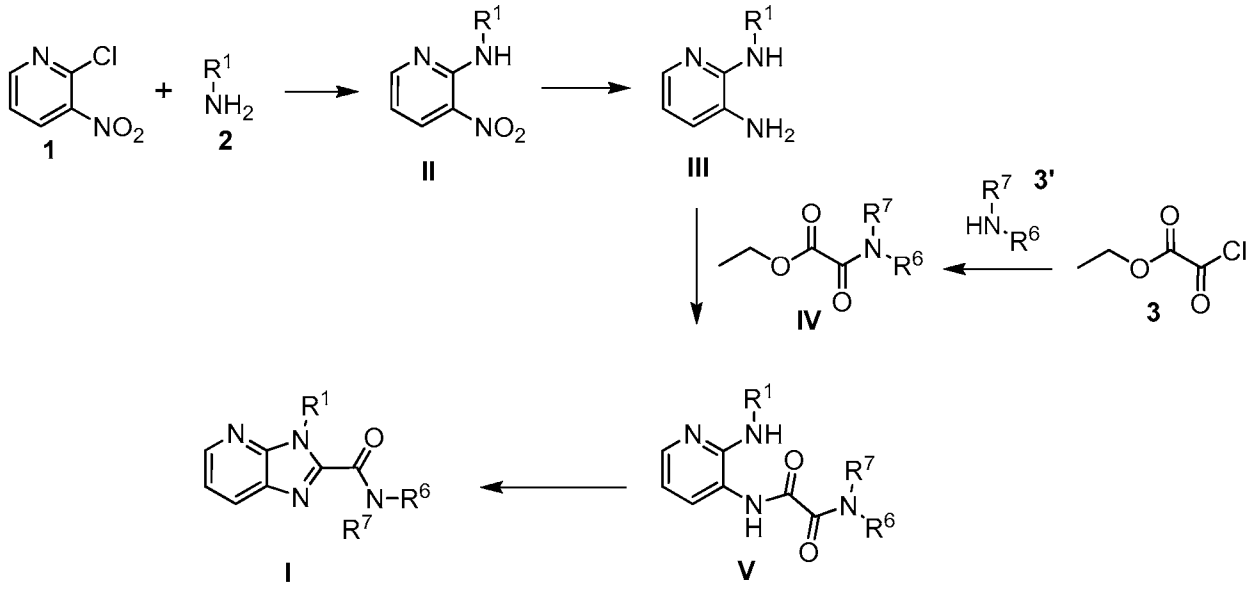
through palladium or nickel reduction in the presence of a hydrogen source or through stoichiometric metal reductions, such as iron and zinc in the presence of mild acid.

In the next step, the half ester oxalamides of formula **IV** can be generated from amines of formula **3'** (i.e., HNR^6R^7) displacement on a half ester of oxalyl chloride of formula **3**. During the amine displacement step, the R^6 and R^7 substituents on the amines of formula **3'** should be represented by the same moiety as is desired in the final product, or a protected variation thereof. For example, for the final product of Example 1 mentioned above, one of R^6 and R^7 of the amines of formula **3'** is represented by hydrogen and the other is represented by cyclopropyl.

Following the amine displacement step, the compounds of formula **V** can be prepared by condensation of the diaminopyridines of formula **III** and the compounds of formula **IV** under thermal conditions, with reaction rates being increased under basic conditions.

In the final step of scheme 1, conversion of the compounds of formula **V** to the compounds of formula **I** can be accomplished under dehydrating conditions such as heat, treatment with a Lewis acid, or amide coupling conditions.

Scheme 1

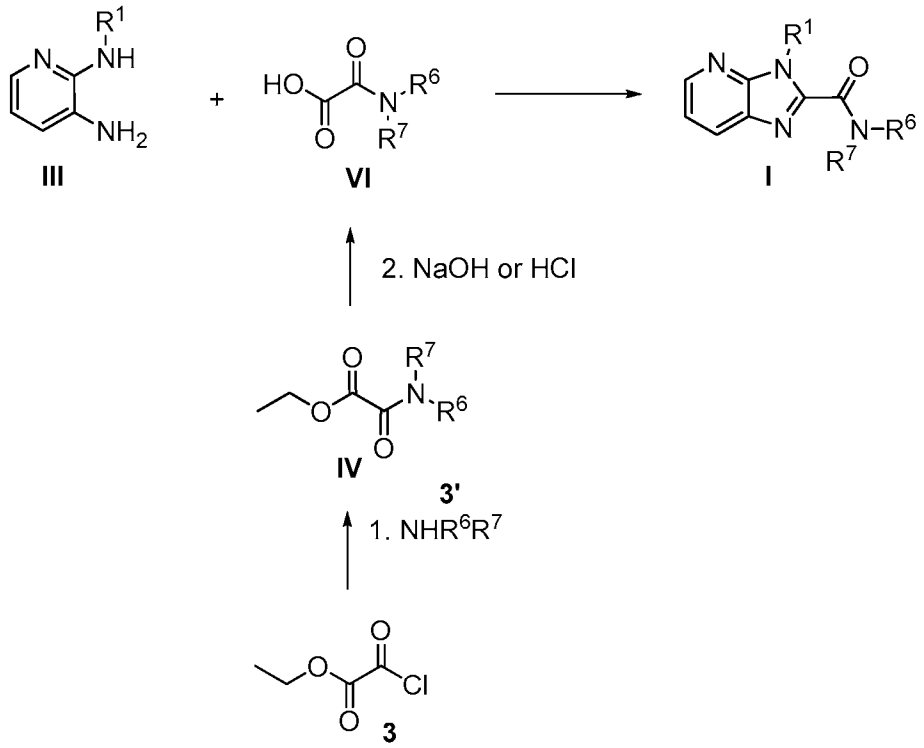


Scheme 2 below describes an alternative synthetic sequence for the preparation of compounds of formula **I**. Oxalic acids of formula **VI** can be generated in two steps from the treatment of half esters of oxalyl chloride of formula **3** with an amine of formula **3'** in the presence of base, usually at room temperature or below. The resultant half ester

oxalamides of formula **IV** can be hydrolyzed to the oxalic acids of formula **VI** by treatment under acidic or basic aqueous conditions at temperatures from 0 °C to 150 °C.

Next, the diaminopyridines of formula **III** can be mixed with the oxalic acids of formula **VI** in the presence of amide coupling/dehydrating reagents, such as 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU), dicyclohexylcarbodiimide (DCC), etc., at temperatures ranging from -20 °C to 100 °C; subsequent heating up to 200 °C generates compounds of formula **I**.

Scheme 2

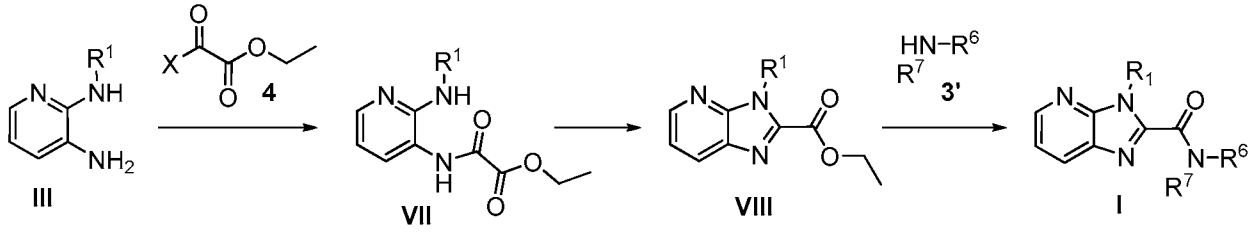


Scheme 3 below illustrates an alternative synthetic sequence for the preparation of compounds of formula **I**. Diaminopyridines of formula **III** can be acylated by the nucleophilic displacement of a leaving group on an ester-oxalate of formula **4** (wherein x is represented by chloride, alkoxy, succinimide, etc.) to generate the aminopyridine aminooxoacetate compounds of formula **VII**.

In the next step the compounds of formula **VII** can be cyclized under dehydrating conditions such as heat, treatment with a Lewis acid, or amide coupling conditions such as 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU), dicyclohexylcarbodiimide (DCC), etc., to generate the imidazopyridine esters of formula **VIII**.

Next, the conversion of imidazopyridine esters of formula **VIII** to amides of formula **I** may be carried out via addition of an amine of formula **3'** to imidazopyridine esters of formula **VIII** at temperatures from 20 °C to 200 °C in the presence or absence of solvent. Additionally, this transformation can be accomplished through the addition of a base or Lewis acid to the mixture of amine and imidazopyridine esters of formula **VIII** at temperatures ranging from 20 °C to 200 °C or under microwave irradiation at applicable temperatures.

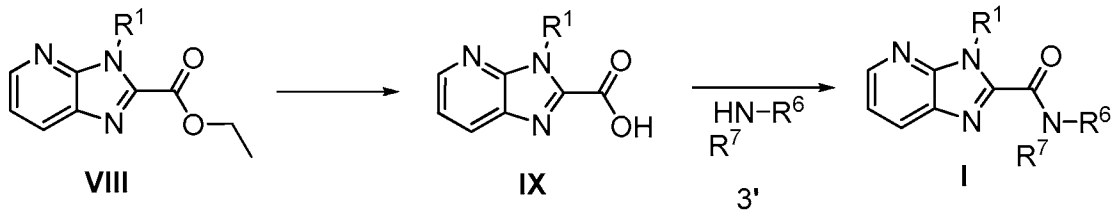
Scheme 3



Scheme 4 below illustrates another alternative synthetic sequence for preparation of the compounds of formula **I** from the esters of formula **VIII**. In an initial step, esters of formula **VIII** can be hydrolyzed to the corresponding imidazopyridine carboxylic acids of formula **IX** under basic or acidic aqueous conditions. During the initial step, the R^1 substituent on the esters of formula **VIII** should be represented by the same moiety as is desired in the final product, or a protected variation thereof.

Next, the imidazopyridine acids of formula **IX** can be reacted with an appropriate amine of formula **3'** using any of a variety of amide coupling reagents such as 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU), dicyclohexylcarbodiimide (DCC), etc., to provide the compounds of formula **I**.

Scheme 4

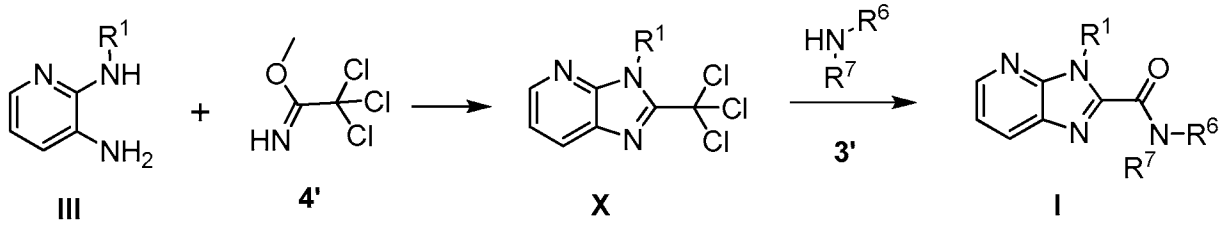


Scheme 5 below illustrates another alternative synthetic sequence for the preparation of compounds of formula **I** from the diaminopyridine compounds of formula **III**. In the initial step, compounds of formula **III** can be treated with methyl 2,2,2-trichloroacetimidate of formula **4'**

in the presence of mild acid to form trichloromethyl-substituted imidazo[4,5-*b*]pyridines of formula **X** (see Venable, J. et al., *Journal of Medicinal Chemistry* **2005**, *48*, 8289).

Next, the compounds of formula **X** can be treated with amines of formula **3'** under mild basic aqueous conditions to provide compounds of formula **I**.

Scheme 5



Scheme 6 below illustrates another synthetic sequence for the prepratation of the compounds of formula **I** wherein R^1 is optionally substituted aryl.

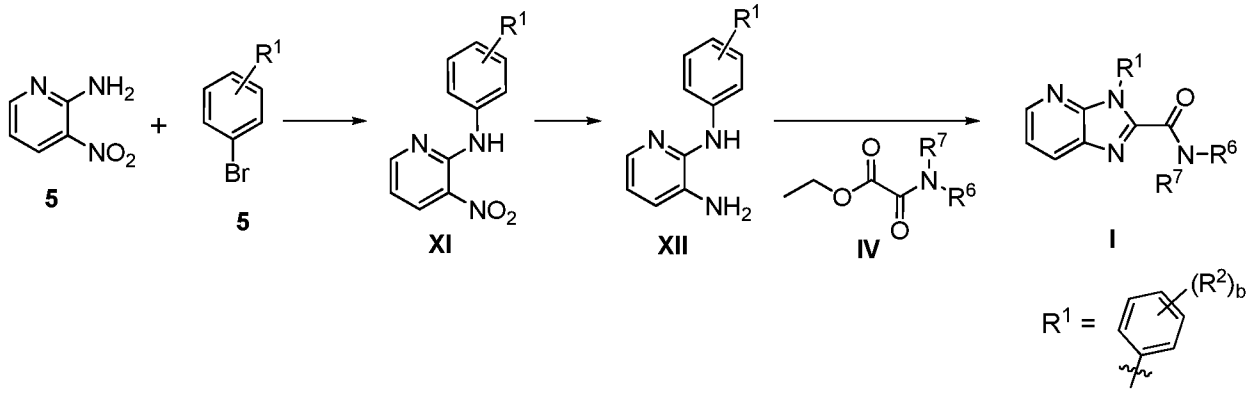
In a first step, 2-amino-3-nitropyridine is coupled with a haloaryl compound of formula **5** in the presence of a metal catalyst (palladium, copper, rhodium, etc.), a ligand, and a base at temperatures ranging from room temperature to ~200 °C, to generate anilinopyridine structures of formula **XI**. This general reaction is sometimes referred to as the Buchwald-Hartwig amination. Similar couplings have been described previously (WO2008/4117 A1 and *Org. Lett.* **2009**, *11*, 5502-5505). During this reaction, the R^1 substituent on the haloaryl compound of formula **5** should be represented by the same moiety as is desired in the final product, or a protected variation thereof. For example, the final product of Example 7 [3-(4-cyano-3-fluorophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide] can be prepared utilizing reaction scheme 6, wherein R^1 of the diaminopyridine is represented by 4-cyano-3-fluorophenyl.

In the next step, reduction of the nitro group to an amine to give the compounds of formula **XII** can occur through palladium or nickel reduction in the presence of a hydrogen source, or through stoichiometric metal reductions, such as iron and zinc in the presence of mild acid.

Next, compounds of formula **XII** can be converted to compounds of formula **I** through reaction of compounds of formula **XII** and a compound of formula **IV** (Scheme 2) under basic conditions, at temperatures ranging from room temperature to 200 °C followed by the room temperature addition of a dehydrating reagent/amide coupling reagent 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P), *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU), dicyclohexylcarbodiimide (DCC), etc., and

subsequent reaction via appropriate heating (room temperature to 200 °C) to generate compounds of formula I wherein R^1 is optionally substituted aryl, wherein the optional substituent is represented by $(R^2)_b$.

Scheme 6



Experimental Procedures and Working Examples

The following illustrate the synthesis of various compounds of the present invention. Additional compounds within the scope of this invention may be prepared using the methods illustrated in these Examples, either alone or in combination with techniques generally known in the art.

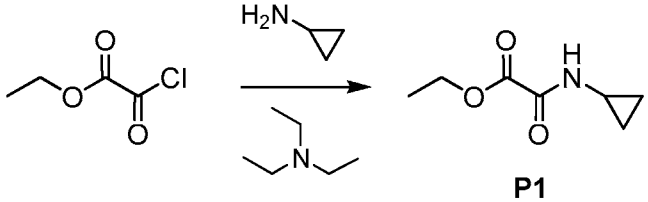
Experiments were generally carried out under inert atmosphere (nitrogen or argon), particularly in cases where oxygen- or moisture-sensitive reagents or intermediates were employed. Commercial solvents and reagents were generally used without further purification. Anhydrous solvents were employed where appropriate (generally Sure-Seal™ products from the Aldrich Chemical Company, Milwaukee, Wisconsin, or solvents that had been dried and distilled using procedures familiar to those skilled in the art). Products were generally dried under vacuum before being carried on to further reactions or submitted for biological testing. Mass spectrometry data is reported from either liquid chromatography-mass spectrometry (LCMS), atmospheric pressure chemical ionization (APCI) or gas chromatography-mass spectrometry (GCMS) instrumentation. Chemical shifts for nuclear magnetic resonance (NMR) data are expressed in parts per million (ppm, δ) referenced to residual peaks from the deuterated solvents employed.

For syntheses referencing procedures in other Examples or Methods, reaction conditions (length of reaction and temperature) may vary. In general, reactions were followed by thin layer chromatography or mass spectrometry, and subjected to work-up

when appropriate. Purifications may vary between experiments: in general, solvents and the solvent ratios used for eluents/gradients were chosen to provide appropriate R_fs or retention times.

Preparation P1

*Ethyl (cyclopropylamino)(oxo)acetate (**P1**).*

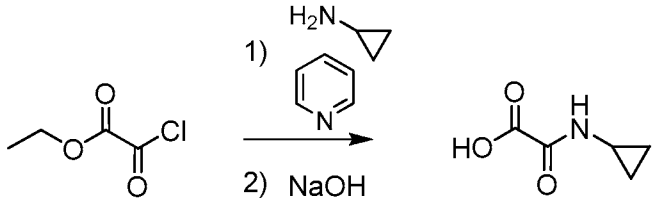


P1

A mixture of cyclopropylamine (1.39 g, 24.3 mmol) and triethylamine (3.5 g, 35 mmol) was added drop-wise to a 0 °C solution of ethyl chloro(oxo)acetate (3.5 g, 26 mmol) in tetrahydrofuran (25 mL). The reaction mixture was stirred at 0 °C for 10 minutes and filtered; the filtrate was concentrated *in vacuo* to afford the product as a yellow solid. Yield: 3.0 g, 19 mmol, 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (br s, 1H), 4.34 (q, *J*=7.2 Hz, 2H), 2.78-2.86 (m, 1H), 1.38 (t, *J*=7.2 Hz, 3H), 0.83-0.90 (m, 2H), 0.59-0.65 (m, 2H).

Preparation P2

(Cyclopropylamino)(oxo)acetic acid (**P2**)



P2

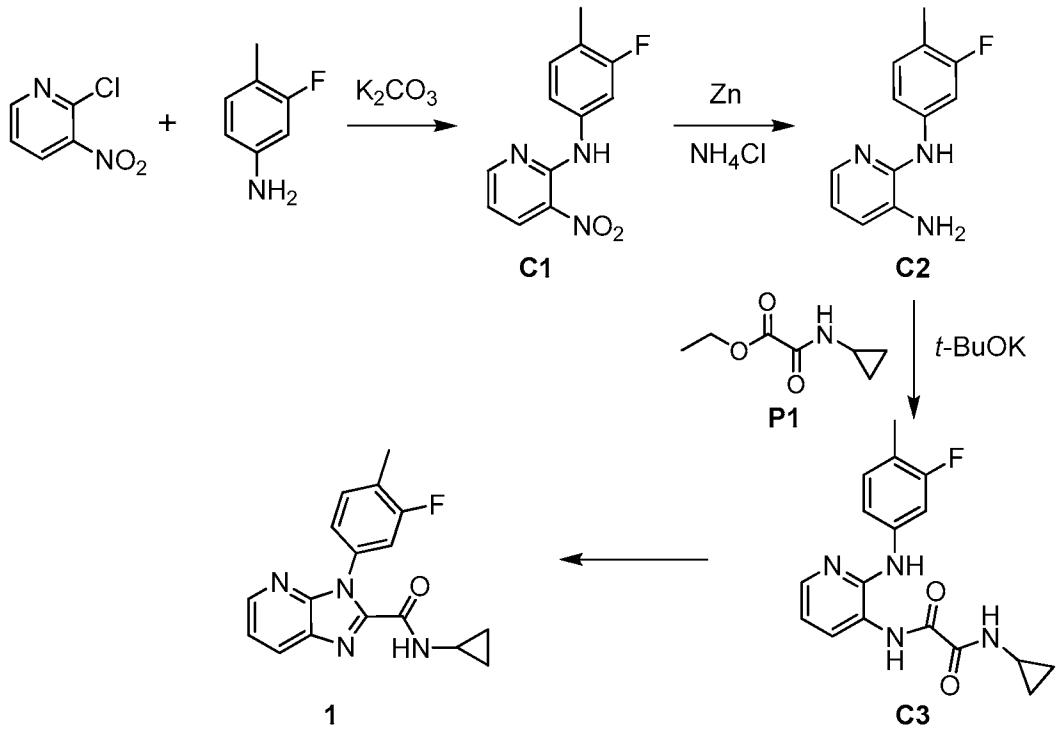
Ethyl chloro(oxo)acetate (96 mL, 0.86 mol) was added over 10 minutes to a −20 °C solution of cyclopropylamine (60 mL, 0.86 mol) and pyridine (70 mL, 0.86 mol) in dichloromethane (740 mL), and the reaction mixture was stirred at 0 °C for 1 hour, then at 20 °C for 20 hours. The reaction mixture was washed with aqueous hydrochloric acid (1 M, 3 x 185 mL), then the organic layer was stirred with aqueous sodium hydroxide solution (1 M, 930 mL, 0.93 mol) for 30 minutes. The resulting aqueous layer was acidified to pH 1 with concentrated hydrochloric acid (78 mL), treated with sodium chloride (100 g), and extracted with dichloromethane (6 x 500 mL) and ethyl acetate (6 x 500 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*; the resulting solid was mixed with ethyl acetate (150 mL) and warmed to reflux. After cooling to room temperature over 16 hours with stirring, the solid was collected via filtration and washed with ethyl acetate, affording the product as a sparkling white solid. Yield: 67.8 g, 0.525 mol, 61%.

LCMS *m/z* 130.0 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 13.73 (br s, 1H), 8.83 (br d, *J*=4.0 Hz, 1H), 2.68-2.77 (m, 1H), 0.61-0.68 (m, 2H), 0.54-0.61 (m, 2H).

Examples

Example 1

N-*Cyclopropyl-3-(3-fluoro-4-methylphenyl)-3*H-*imidazo[4,5*-b*]pyridine-2-carboxamide (**1**)*



Step 1. Synthesis of N-*(3-fluoro-4-methylphenyl)-3-nitropyridin-2-amine (**C1**).*

A mixture of 2-chloro-3-nitropyridine (4.76 g, 30.0 mmol), 3-fluoro-4-methylaniline (3.75 g, 30.0 mmol) and potassium carbonate (8.29 g, 60.0 mmol) in dimethyl sulfoxide (30 mL) was stirred at 140 °C for 40 minutes. The reaction mixture was then cooled to room temperature, diluted with water, and extracted with ethyl acetate. The combined organic layers were washed with water, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford the product as a black solid. Yield: 6.78 g, 27.4 mmol, 91%. ^1H NMR (400 MHz, $CDCl_3$) δ 10.11 (br s, 1H), 8.54 (dd, *J*=8.3, 1.8 Hz, 1H), 8.51 (dd, *J*=4.6, 1.8 Hz, 1H), 7.59-7.64 (m, 1H), 7.15-7.21 (m, 2H), 6.86 (dd, *J*=8.4, 4.6 Hz, 1H), 2.28 (d, *J*=2.0 Hz, 3H).

Step 2. Synthesis of N^2-*(3-fluoro-4-methylphenyl)pyridine-2,3-diamine (**C2**).*

Zinc dust (14.3 g, 219 mmol) was added to a stirring mixture of *N*-(3-fluoro-4-methylphenyl)-3-nitropyridin-2-amine (**C1**) (6.78 g, 27.4 mmol) and ammonium chloride (11.7 g, 219 mmol) in tetrahydrofuran (55 mL) and water (55 mL), which caused the temperature

of the mixture to rise to 45 °C. The reaction mixture was stirred for 10 minutes, and then filtered through a pad of Celite, rinsing with ethyl acetate. The organic layer from the filtrate was further diluted with ethyl acetate, washed with aqueous ammonium chloride solution and with saturated aqueous sodium chloride solution, dried over magnesium sulfate, and filtered. The filtrate was concentrated *in vacuo* to afford the product as a black solid (6.6 g), the bulk of which was taken directly to the following step. LCMS *m/z* 218.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$), characteristic product peaks: δ 7.84 (dd, *J*=4.9, 1.6 Hz, 1H), 7.01 (dd, *J*=7.6, 1.6 Hz, 1H), 6.82 (br dd, *J*=8, 2 Hz, 1H), 6.77 (dd, *J*=7.6, 4.9 Hz, 1H), 2.20 (d, *J*=2 Hz, 3H).

Step 3. Synthesis of N-*cyclopropyl*-N'-*{2-[(3-fluoro-4-methylphenyl)amino]pyridin-3-yl}ethanediamide (**C3**).*

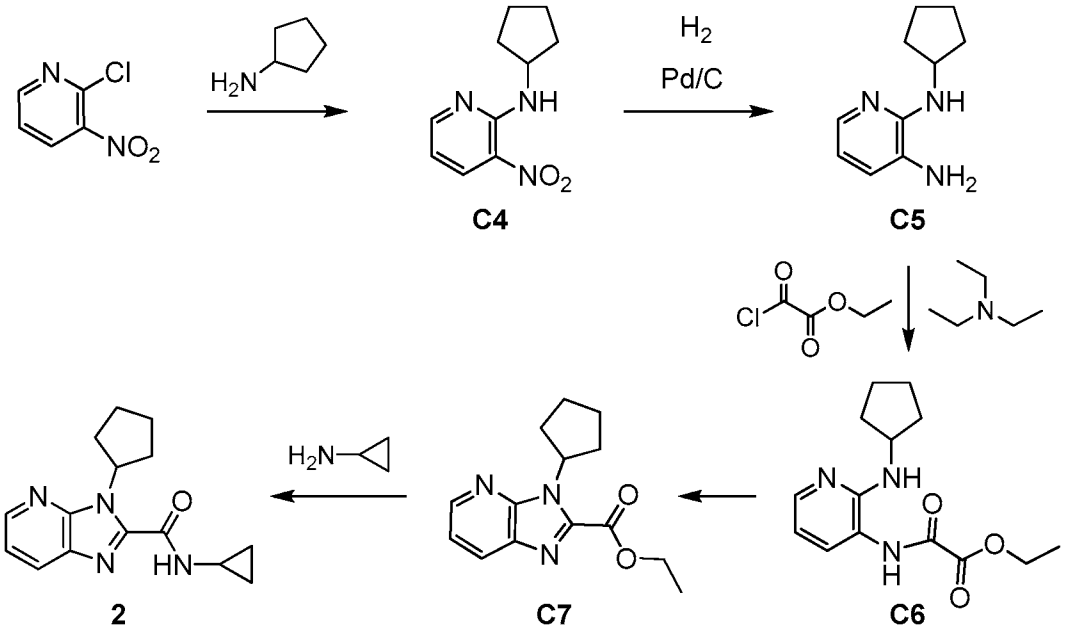
Potassium *tert*-butoxide (4.54 g, 40.5 mmol) was added to a solution of N^2-(3-fluoro-4-methylphenyl)pyridine-2,3-diamine (**C2**) (from the previous step, 5.87 g, ≤24.4 mmol) and ethyl (cyclopropylamino)(oxo)acetate (**P1**) (6.36 g, 40.5 mmol) in 1-methylpyrrolidin-2-one (27 mL). The reaction mixture was heated at 120 °C for 10 minutes, cooled to room temperature and diluted with aqueous ammonium chloride solution. Tetrahydrofuran was added to assist solubilization, followed by ethyl acetate. The organic layer was washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to provide the crude product (13.0 g). A portion of this material was used directly in the following step. LCMS *m/z* 329.0 $[M+H]^+$.

Step 4. Synthesis of N-*cyclopropyl-3-(3-fluoro-4-methylphenyl)-3*H-*imidazo[4,5-*b*]pyridine-2-carboxamide (**1**).*

A mixture of *N*-cyclopropyl-*N'*-{2-[(3-fluoro-4-methylphenyl)amino]pyridin-3-yl}ethanediamide (**C3**) (from the preceding step, 8.86 g, ≤16.6 mmol) and ethane-1,2-diol (27 mL) was stirred at 200 °C for 1 hour. After cooling to room temperature, the reaction mixture was diluted with water (100 mL) and aqueous sodium hydroxide solution (1 M, 100 mL), then extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification using silica gel chromatography (Gradient: 5% to 50% ethyl acetate in heptane) was followed by recrystallization from 3:1 toluene / heptane, to afford the product as a solid. Yield: 2.52 g, 8.12 mmol, 49% over three steps. LCMS *m/z* 311.0 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (dd, *J*=4.7, 1.5 Hz, 1H), 8.13 (dd, *J*=8.1, 1.5 Hz, 1H), 7.68 (br s, 1H), 7.37 (dd, *J*=8.1, 4.7 Hz, 1H), 7.34-7.40 (m, 1H), 7.10-7.15 (m, 2H), 2.83-2.90 (m, 1H), 2.37 (br d, *J*=2 Hz, 3H), 0.83-0.89 (m, 2H), 0.67-0.72 (m, 2H).

Example 2

*3-Cyclopentyl-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide (**2**)*



Step 1. Synthesis of N*-cyclopentyl-3-nitropyridin-2-amine (**C4**).*

Cyclopentanamine (2.7 g, 32 mmol) was added to a solution of 2-chloro-3-nitropyridine (5.0 g, 32 mmol) in tetrahydrofuran (200 mL), and the reaction mixture was stirred at reflux for 18 hours. After removal of solvent under reduced pressure, the residue was purified via silica gel chromatography to give the product as a yellow solid. Yield: 5.5 g, 26 mmol, 81%. ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (dd, half of ABX pattern, *J*=8.3, 1.8 Hz, 1H), 8.40 (dd, half of ABX pattern, *J*=4.5, 1.8 Hz, 1H), 6.69 (dd, *J*=8.3, 4.5 Hz, 1H), 4.51-4.59 (m, 1H), 2.07-2.17 (m, 2H), 1.62-1.85 (m, 4H), 1.51-1.62 (m, 2H)

Step 2. Synthesis of N^2*-cyclopentylpyridine-2,3-diamine (**C5**).*

To a solution of *N*-cyclopentyl-3-nitropyridin-2-amine (**C4**) (4.7 g, 23 mmol) in methanol (100 mL) was added palladium on carbon (0.5 g), and the mixture was degassed with hydrogen. After stirring under hydrogen at room temperature for 4 hours, the reaction mixture was filtered; the filtrate was concentrated *in vacuo* to afford the product as a black solid. Yield: 3.6 g, 20 mmol, 87%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 (dd, *J*=5, 1 Hz, 1H), 6.63 (dd, *J*=7.3, 1.0 Hz, 1H), 6.30 (dd, *J*=7.3, 5.0 Hz, 1H), 5.31 (br d, *J*=6.3 Hz, 1H), 4.69 (br s, 2H), 4.18-4.28 (m, 1H), 1.88-2.00 (m, 2H), 1.61-1.75 (m, 2H), 1.36-1.60 (m, 4H).

*Step 3. Synthesis of ethyl {[2-(cyclopentylamino)pyridin-3-yl]amino}(oxo)acetate (**C6**).*

To a solution of N^2-cyclopentylpyridine-2,3-diamine (**C5**) (1.78 g, 10.0 mmol) and triethylamine (1.52 g, 15.0 mmol) in dichloromethane (100 mL) was added ethyl chloro(oxo)acetate (1.49 g, 10.9 mmol), and the reaction mixture was stirred at room

temperature for 18 hours. Removal of volatiles *in vacuo* afforded the crude product (2 g) as a brown solid, which was used in the next step without further purification.

*Step 4. Synthesis of ethyl 3-cyclopentyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxylate (**C7**).*

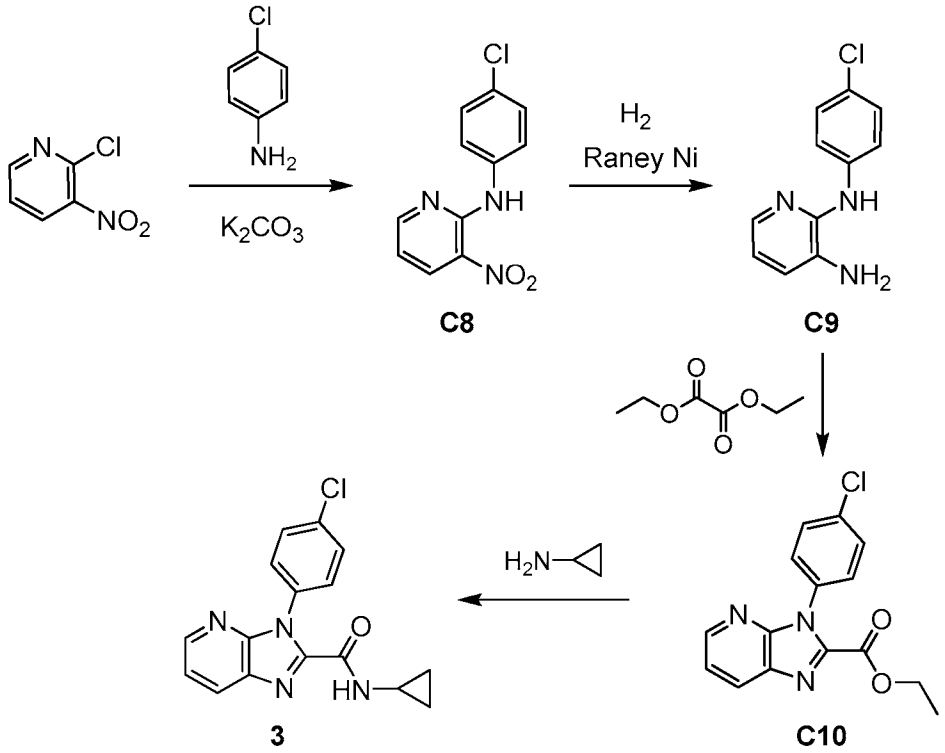
A solution of crude ethyl {[2-(cyclopentylamino)pyridin-3-yl]amino}(oxo)acetate (**C6**) (from the previous step, 2 g) in toluene (100 mL) was stirred at reflux for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified using silica gel chromatography (Gradient: 9% to 50% ethyl acetate in petroleum ether) to provide the product as a brown solid. Yield: 0.70 g, 2.7 mmol, 27% over 2 steps. ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (dd, *J*=4.6, 1.4 Hz, 1H), 8.14 (dd, *J*=8.2, 1.4 Hz, 1H), 7.40 (dd, *J*=8.2, 4.7 Hz, 1H), 5.79-5.89 (m, 1H), 4.51 (q, *J*=7.1 Hz, 2H), 2.48-2.61 (m, 2H), 2.07-2.20 (m, 4H), 1.70-1.83 (m, 2H), 1.46 (t, *J*=7.2 Hz, 3H).

*Step 5. Synthesis of 3-cyclopentyl-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide (**2**).*

To a solution of ethyl 3-cyclopentyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxylate (**C7**) (0.12 g, 0.46 mmol) in ethanol (10 mL) was added cyclopropylamine (0.55 g, 9.6 mmol), and the reaction mixture was stirred at room temperature for 18 hours. After concentration *in vacuo*, purification was effected via preparative thin layer chromatography on silica gel (Eluent: 5:1 petroleum ether / ethyl acetate) to afford the product as a yellow solid. Yield: 36 mg, 0.13 mmol, 28%. LCMS *m/z* 270.9 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (dd, *J*=4.6, 1.5 Hz, 1H), 8.02 (br d, *J*=8 Hz, 1H), 7.85 (br s, 1H), 7.27 (dd, *J*=8.2, 4.6 Hz, 1H, assumed; partially obscured by solvent peak), 6.16-6.27 (m, 1H), 2.89-2.97 (m, 1H), 2.51-2.64 (m, 2H), 2.06-2.19 (m, 4H), 1.69-1.81 (m, 2H), 0.87-0.95 (m, 2H), 0.69-0.76 (m, 2H).

Example 3

*3-(4-Chlorophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide (**3**)*



Step 1. Synthesis of N*-(4-chlorophenyl)-3-nitropyridin-2-amine (**C8**).*

To a solution of 2-chloro-3-nitropyridine (15.4 g, 97.1 mmol) in *N,N*-dimethylformamide (100 mL) were added 4-chloroaniline (12.4 g, 97.2 mmol) and potassium carbonate (20 g, 140 mmol). The reaction mixture was stirred at 100 °C for 18 hours, and then poured into ice-water (200 mL). The precipitate was collected via filtration and washed with water (3 x 30 mL) to provide the product as a black solid. Yield: 15 g, 60 mmol, 62%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.97 (br s, 1H), 8.47-8.57 (m, 2H), 7.69 (d, *J*=8.8 Hz, 2H), 7.41 (d, *J*=8.8 Hz, 2H), 7.01 (dd, *J*=8.2, 4.6 Hz, 1H).

Step 2. Synthesis of N^2*-(4-chlorophenyl)pyridine-2,3-diamine (**C9**).*

To a solution of *N*-(4-chlorophenyl)-3-nitropyridin-2-amine (**C8**) (2.68 g, 10.7 mmol) in ethyl acetate (100 mL) was added Raney nickel (1.5 g), and the mixture was degassed with hydrogen. After 6 hours of hydrogenation at room temperature, the reaction mixture was filtered; concentration of the filtrate *in vacuo* afforded the product as a black solid. Yield: 1.8 g, 8.2 mmol, 77%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (br s, 1H), 7.67 (d, *J*=8.9 Hz, 2H), 7.50 (br d, *J*=4 Hz, 1H), 7.25 (d, *J*=8.9 Hz, 2H), 6.91 (br d, *J*=7.5 Hz, 1H), 6.64 (dd, *J*=7.3, 4.8 Hz, 1H), 5.08 (br s, 2H).

*Step 3. Synthesis of ethyl 3-(4-chlorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxylate (**C10**).*

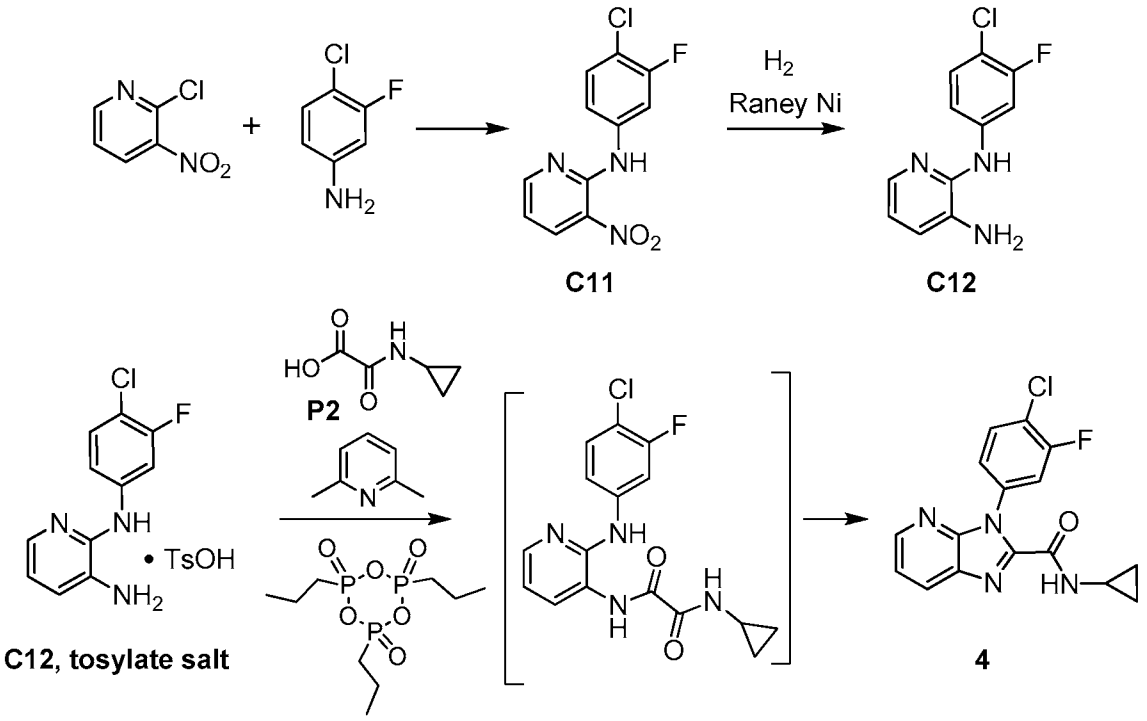
A mixture of N^2-(4-chlorophenyl)pyridine-2,3-diamine (**C9**) (1.8 g, 8.2 mmol) and diethyl ethanedioate (18 g, 123 mmol) was stirred at 140 °C for 18 hours. Purification using silica gel chromatography (Gradient: 16% to 50% ethyl acetate in petroleum ether) provided the product as a brown solid, containing approximately 30% of a contaminant by ^{1}H NMR analysis. Yield: 250 mg, 0.83 mmol, 10%. ^{1}H NMR (400 MHz, CD_3OD), product peaks only: δ 8.49 (dd, *J*=4.8, 1.5 Hz, 1H), 8.31 (dd, *J*=8.2, 1.4 Hz, 1H), 7.61 (br d, *J*=8.9 Hz, 2H), 7.52 (dd, *J*=8.2, 4.6 Hz, 1H), 7.49 (br d, *J*=8.9 Hz, 2H), 4.34 (q, *J*=7.2 Hz, 2H), 1.25 (t, *J*=7.2 Hz, 3H).

*Step 4. Synthesis of 3-(4-chlorophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide (**3**).*

Ethyl 3-(4-chlorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxylate (**C10**) was converted to the product using the method described for synthesis of **2** in Example 2. The product was obtained as an off-white solid. Yield: 34.5 mg, 0.110 mmol, 28%. LCMS *m/z* 312.9 $[M+H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (dd, *J*=4.8, 1.5 Hz, 1H), 8.24 (dd, *J*=8.2, 1.4 Hz, 1H), 7.58 (br d, *J*=8.8 Hz, 2H), 7.43-7.49 (m, 3H), 2.76-2.83 (m, 1H), 0.77-0.84 (m, 2H), 0.63-0.69 (m, 2H).

Example 4

*3-(4-Chloro-3-fluorophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide (**4**)*



Step 1. Synthesis of N-*(4-chloro-3-fluorophenyl)-3-nitropyridin-2-amine (**C11**).*

4-Chloro-3-fluoroaniline (10.0 g, 68.7 mmol) was heated to 180 °C in an oil bath. 2-Chloro-3-nitropyridine (11.0 g, 69.4 mmol) was added, and the resulting mixture was stirred at 180 °C for 10 minutes. The reaction mixture was then cooled to 15 °C and washed with petroleum ether, providing the product as a salmon-pink solid. Yield: 15 g, 56 mmol, 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.20 (br s, 1H), 8.57 (dd, *J*=8.3, 1.6 Hz, 1H), 8.54 (dd, *J*=4.6, 1.7 Hz, 1H), 7.90 (dd, *J*=11.3, 2.4 Hz, 1H), 7.38 (dd, *J*=8.5, 8.3 Hz, 1H), 7.23-7.28 (m, 1H, assumed; partially obscured by solvent peak), 6.94 (dd, *J*=8.3, 4.5 Hz, 1H).

Step 2. Synthesis of N^2*-(4-chloro-3-fluorophenyl)pyridine-2,3-diamine (**C12**).*

A mixture of *N*-(4-chloro-3-fluorophenyl)-3-nitropyridin-2-amine (**C11**) (5.0 g, 19 mmol) and Raney nickel (3 g) in ethyl acetate (400 mL) was degassed three times with hydrogen. The reaction mixture was then hydrogenated at room temperature for 20 hours. After removal of the catalyst via filtration, the filtrate was concentrated *in vacuo*. Purification via silica gel chromatography afforded the product as a gray solid. Yield: 3.1 g, 13 mmol, 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J*=4.9, 1.6 Hz, 1H), 7.38 (dd, *J*=11.5, 2.5 Hz, 1H), 7.24 (dd, *J*=8.5, 8.4 Hz, 1H), 7.06 (dd, *J*=7.6, 1.6 Hz, 1H), 6.92 (ddd, *J*=8.7, 2.5, 1.0 Hz, 1H), 6.82 (dd, *J*=7.6, 4.9 Hz, 1H), 6.37 (br s, 1H), 3.38 (br s, 2H).

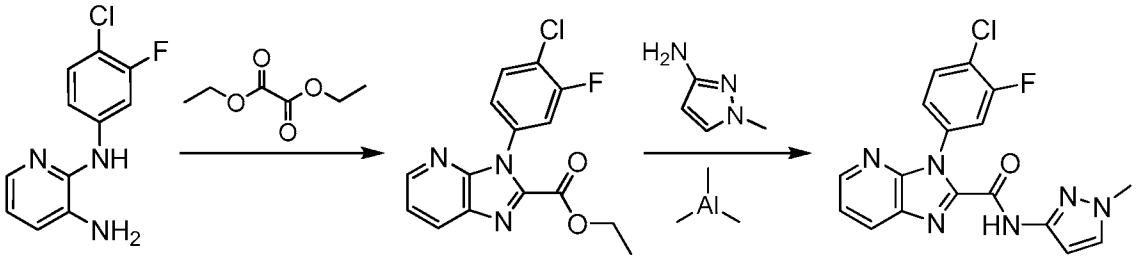
*Step 3. Synthesis of 3-(4-chloro-3-fluorophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide (**4**).*

A mixture of the mono-tosylate salt of *N*^{2}-(4-chloro-3-fluorophenyl)pyridine-2,3-diamine (**C12**) [prepared via treatment of **C12** with *p*-toluenesulfonic acid monohydrate (1.5 equivalents) in ethanol at 80 °C, followed by cooling to room temperature and isolation via filtration] (1.003 g, 2.447 mmol), (cyclopropylamino)(oxo)acetic acid (**P2**) (0.304 g, 2.35 mmol), 2,6-dimethylpyridine (0.91 mL, 0.84 g, 7.8 mmol), and 2-methyltetrahydrofuran (10 mL) was cooled to −10 °C and treated with 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (50 weight% solution in ethyl acetate, 4.3 mL, 4.6 g, 7.2 mmol). The reaction mixture was warmed to 0 °C and held for 1 hour, heated at reflux for 20 hours, and then cooled to 0 °C and filtered, rinsing with 2-methyltetrahydrofuran. The filtrate was sequentially washed with water (10 mL, 5 mL), with aqueous ammonium hydroxide solution (15%, 3 x 5 mL), with aqueous hydrochloric acid (0.1 M, 10 mL, 5 mL), and with water (10 mL). The organic layer was distilled to a volume of approximately 4 mL, diluted with 2-methyltetrahydrofuran (13 mL), and again distilled to approximately 4 mL, whereupon it was cooled to 50 °C and treated with heptane (3 mL). The resulting slurry was stirred at 50 °C for 2 hours, cooled to 20 °C, and stirred for 12 hours. The solid was collected via filtration and washed with a mixture of heptane and 2-methyltetrahydrofuran (2:1, 5 mL). The resulting

material (0.488 g) was reslurried in a mixture of 2-propanol and ethyl acetate (9:1, 4.9 mL), warmed to 40 °C, cooled to 20 °C, and stirred for 16 hours. Filtration and washing with 2-propanol (3 mL) afforded the product as an off-white solid. Yield: 410 mg, 1.24 mmol, 53%. LCMS *m/z* 330.9, 332.9 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (d, *J*=4.8 Hz, 1H), 8.45 (d, *J*=4.5 Hz, 1H), 8.27 (d, *J*=8.0 Hz, 1H), 7.71-7.80 (m, 2H), 7.47 (dd, *J*=8.0, 4.8 Hz, 1H), 7.40 (br d, *J*=8.5 Hz, 1H), 2.77-2.86 (m, 1H), 0.65-0.69 (m, 4H).

Example 5

3-(4-Chloro-3-fluorophenyl)-N-*(1-methyl-1*H*-pyrazol-3-yl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide (**5**)*



C12 **C13** **5**

*Step 1. Synthesis of ethyl 3-(4-chloro-3-fluorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxylate (**C13**).*

Conversion of N^2-(4-chloro-3-fluorophenyl)pyridine-2,3-diamine (**C12**) to the product was effected using the method described for synthesis of **C10** in Example 3. The product was obtained as a brown solid. Yield: 700 mg, 2.2 mmol, 17%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (dd, *J*=4.6, 1.4 Hz, 1H), 8.29 (dd, *J*=8.2, 1.4 Hz, 1H), 7.61 (dd, *J*=8.3, 8.0 Hz, 1H), 7.42 (dd, *J*=8.2, 4.8 Hz, 1H), 7.29 (dd, *J*=8.9, 2.3 Hz, 1H, assumed; partially obscured by solvent peak), 7.18-7.22 (m, 1H), 4.44 (q, *J*=7.2 Hz, 2H), 1.41 (t, *J*=7.1 Hz, 3H).

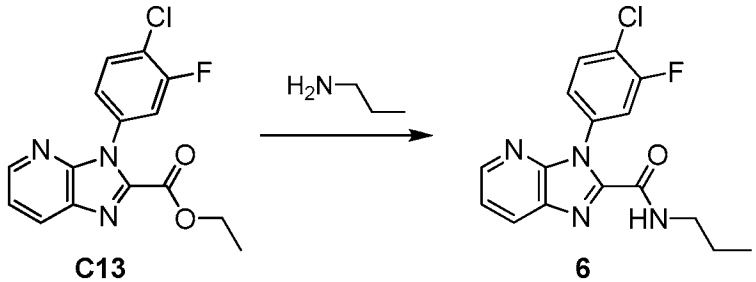
Step 2. Synthesis of 3-(4-chloro-3-fluorophenyl)-N-*(1-methyl-1*H*-pyrazol-3-yl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide (**5**).*

To a solution of ethyl 3-(4-chloro-3-fluorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxylate (**C13**) (32 mg, 0.10 mmol) and 1-methyl-1*H*-pyrazol-3-amine (29 mg, 0.30 mol) in toluene (3 mL) was added trimethylaluminum (2 M solution in toluene, 0.3 mL, 0.6 mmol) at room temperature. The reaction mixture was irradiated in a microwave reactor at 150 °C for 1 hour, whereupon it was partitioned between water (20 mL) and ethyl acetate (50 mL). The organic layer was washed with saturated aqueous sodium chloride solution (20 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via reversed phase HPLC (Column: Agella Venusil ASB-C18, 5 µm; Mobile phase A: 0.225% formic acid in water; Mobile phase B: 0.225% formic acid in acetonitrile; Gradient: 33% to 63% B)

afforded the product as a yellow solid. Yield: 2.0 mg, 5.4 µmol, 5%. LCMS *m/z* 371.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.47 (br d, *J*=4.6 Hz, 1H), 8.32 (br d, *J*=8 Hz, 1H), 7.69 (dd, *J*=8, 8 Hz, 1H), 7.48-7.56 (m, 3H), 7.35 (br d, *J*=8 Hz, 1H), 6.52-6.55 (m, 1H), 3.83 (s, 3H).

Example 6

3-(4-Chloro-3-fluorophenyl)-N-*propyl-3*H-*imidazo[4,5*-b*]pyridine-2-carboxamide (**6**)*

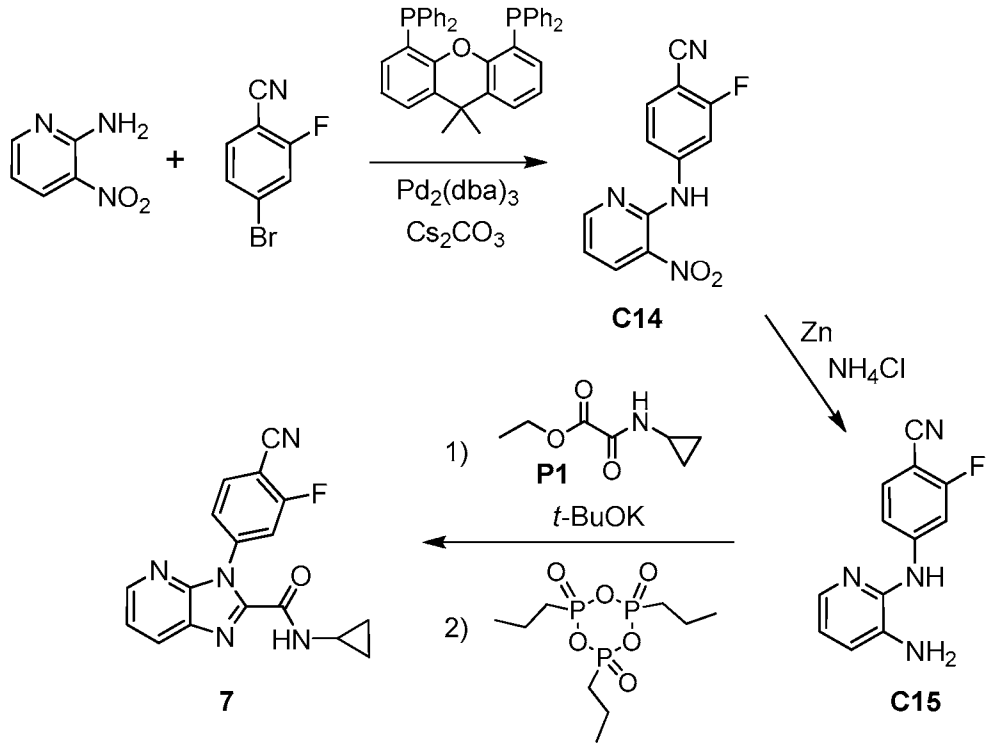


C13 **6**

n-Propylamine (148 mg, 2.5 mol) was added to a solution of ethyl 3-(4-chloro-3-fluorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxylate (**C13**) (80 mg, 0.25 mmol) in ethanol (5 mL) and the reaction mixture was stirred at room temperature for 18 hours. After concentration under reduced pressure, the residue was purified by preparative thin layer chromatography on silica gel (Eluent: 1:1 petroleum ether / ethyl acetate) to provide the product as a pale yellow solid. Yield: 28 mg, 84 µmol, 34%. LCMS *m/z* 332.9 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.43 (dd, *J*=4.8, 1.4 Hz, 1H), 8.26 (dd, *J*=8.2, 1.5 Hz, 1H), 7.67 (dd, *J*=8.4, 8.2 Hz, 1H), 7.45-7.50 (m, 2H), 7.30 (ddd, *J*=8.5, 2.3, 1.2 Hz, 1H), 3.28-3.34 (m, 2H, assumed; partially obscured by solvent peak), 1.58-1.68 (m, 2H), 0.96 (t, *J*=7.4 Hz, 3H).

Example 7

*3-(4-Cyano-3-fluorophenyl)-N-cyclopropyl-3H-imidazo[4,5-b]pyridine-2-carboxamide (**7**)*



*Step 1. Synthesis of 2-fluoro-4-[(3-nitropyridin-2-yl)amino]benzonitrile (**C14**).*

A mixture of 3-nitropyridin-2-amine (3.44 g, 24.7 mmol), 4-bromo-2-fluorobenzonitrile (4.95 g, 24.7 mmol), tris(dibenzylideneacetone)dipalladium(0) (226 mg, 0.247 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos, 286 mg, 0.494 mmol) and cesium carbonate (32.3 g, 99.0 mmol) in 1,4-dioxane (124 mL) was degassed, placed under nitrogen and stirred at 100 °C for 30 minutes. The reaction mixture was filtered through a pad of Celite using tetrahydrofuran, and the filtrate was concentrated *in vacuo*. A 1:1 mixture of heptane and ethyl acetate was added to the residue, and the mixture was cooled in an ice/water bath. The solid was collected via filtration and washed with cold 1:1 heptane / ethyl acetate to afford the product as a gray solid. Yield: 6.2 g, 24 mmol, 97%. LCMS *m/z* 259.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 10.46 (br s, 1H), 8.60-8.63 (m, 2H), 8.16 (dd, *J*=11.8, 2.1 Hz, 1H), 7.59 (dd, *J*=8.5, 7.2 Hz, 1H), 7.40 (br dd, *J*=8.6, 2 Hz, 1H), 7.05-7.09 (m, 1H).

*Step 2. Synthesis of 4-[(3-aminopyridin-2-yl)amino]-2-fluorobenzonitrile (**C15**).*

To a solution of 2-fluoro-4-[(3-nitropyridin-2-yl)amino]benzonitrile (**C14**) (5.4 g, 21 mmol) in a 1:1 mixture of tetrahydrofuran and water (40 mL) was added ammonium chloride (8.9 g, 170 mmol), followed by zinc (10.8 g, 165 mmol). The mixture was stirred at 60 °C for 30 minutes, whereupon it was filtered through a pad of Celite. The organic layer from the filtrate was diluted with ethyl acetate, washed with saturated aqueous ammonium chloride

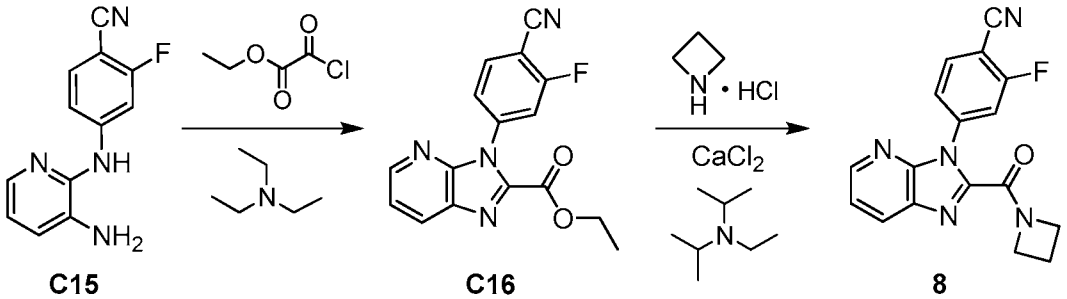
solution, dried over sodium sulfate, filtered, and concentrated *in vacuo;* the residue was washed with heptane to afford the product as a brown solid. Yield: 4.2 g, 18 mmol, 86%. LCMS *m/z* 229.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.68 (br s, 1H), 7.82 (dd, *J*=13.6, 2.0 Hz, 1H), 7.66 (dd, *J*=8.4, 8.3 Hz, 1H), 7.61 (dd, *J*=4.8, 1.6 Hz, 1H), 7.37 (dd, *J*=8.8, 2.0 Hz, 1H), 7.03 (dd, *J*=7.8, 1.6 Hz, 1H), 6.82 (dd, *J*=7.8, 4.8 Hz, 1H), 5.24 (br s, 2H).

*Step 3. Synthesis of 3-(4-cyano-3-fluorophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide (**7**).*

To a mixture of 4-[(3-aminopyridin-2-yl)amino]-2-fluorobenzonitrile (**C15**) (3.9 g, 17 mmol) and ethyl (cyclopropylamino)(oxo)acetate (**P1**) (4.03 g, 25.6 mmol) in 1-methylpyrrolidin-2-one (17 mL) was added potassium *tert*-butoxide (2.88 g, 25.7 mmol). The reaction mixture was stirred at 120 °C for 30 minutes, cooled to room temperature, and treated with 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P) (~50% weight solution, 20.3 mL, 32 mmol). After the reaction mixture had been stirred at 120 °C for 18 hours, it was allowed to cool. Water (10 mL) was added and stirring was continued for 10 minutes. Saturated aqueous sodium bicarbonate solution (20 mL) was introduced, and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution, filtered, and concentrated *in vacuo.* Silica gel chromatography (Gradient: 10% to 50% ethyl acetate in petroleum ether) afforded the product as a white solid. Yield: 2.29 g, 7.13 mmol, 42%. LCMS *m/z* 322.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (dd, *J*=4.7, 1.4 Hz, 1H), 8.17 (dd, *J*=8.2, 1.5 Hz, 1H), 7.79-7.85 (m, 1H), 7.69 (br s, 1H), 7.38-7.45 (m, 3H), 2.83-2.90 (m, 1H), 0.87-0.93 (m, 2H), 0.68-0.73 (m, 2H).

Example 8

*4-[2-(Azetidin-1-ylcarbonyl)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]-2-fluorobenzonitrile (**8**)*



*Step 1. Synthesis of ethyl 3-(4-cyano-3-fluorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxylate (**C16**).*

To a 0 °C solution of 4-[(3-aminopyridin-2-yl)amino]-2-fluorobenzonitrile (**C15**) (300 mg, 1.31 mmol) and triethylamine (270 mg, 2.67 mmol) in dichloromethane (20 mL) was

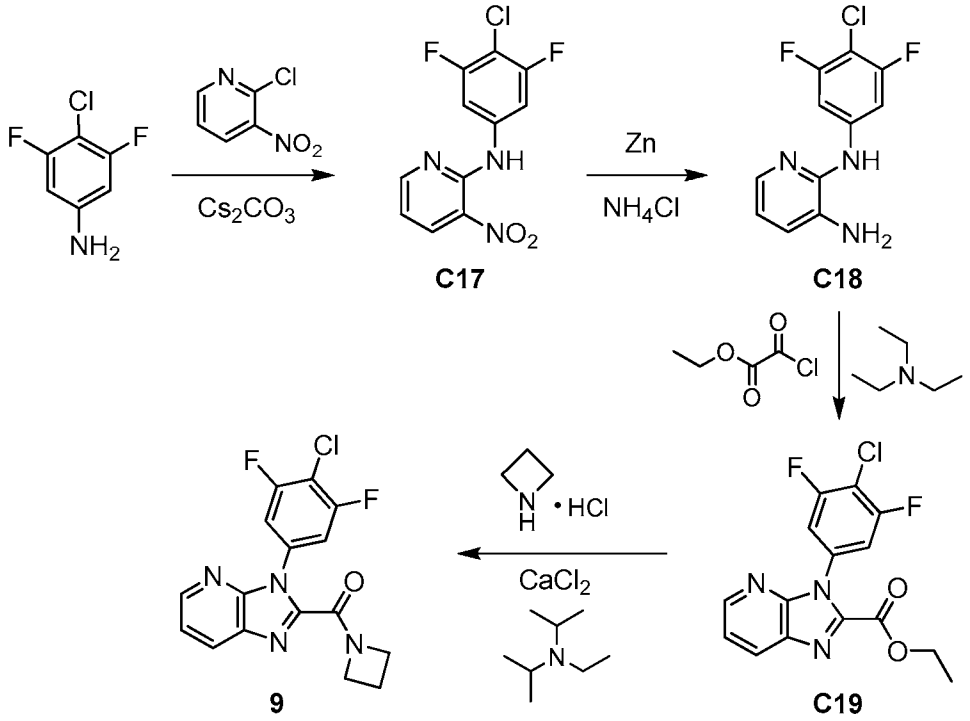
added ethyl chloro(oxo)acetate (220 mg, 1.61 mmol), and the solution was stirred at 0 °C for 2 hours. After addition of water (20 mL), the mixture was extracted with dichloromethane (3 x 20 mL); the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL), dried over sodium sulfate, filtered, concentrated under reduced pressure and purified by preparative thin layer chromatography on silica gel (Eluent: 10:1 dichloromethane / methanol) to afford the product as a yellow solid. Yield: 40 mg, 0.13 mmol, 10%. ^{1}H NMR (400 MHz, $CDCl_3$), characteristic peaks: δ 8.55 (d, *J*=5 Hz, 1H), 4.46 (q, *J*=7 Hz, 2H), 1.43 (t, *J*=7 Hz, 3H).

*Step 2. Synthesis of 4-[2-(azetidin-1-ylcarbonyl)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]-2-fluorobenzonitrile (**8**).*

A mixture of azetidine hydrochloride (120 mg, 1.3 mmol) and *N,N*-diisopropylethylamine (168 mg, 1.30 mmol) in methanol (2 mL) was stirred at room temperature for 1 hour. At this point, ethyl 3-(4-cyano-3-fluorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxylate (**C16**) (40 mg, 0.13 mmol) and calcium chloride (15 mg, 0.13 mmol) were added, and the reaction mixture was stirred at room temperature for an additional 2 hours. After removal of solvents *in vacuo*, the residue was purified by reversed phase HPLC (Column: DIKMA Diamonsil C18(2), 5 µm; Mobile phase A: 0.225% formic acid in water; Mobile phase B: 0.225% formic acid in acetonitrile; Gradient: 15% to 45% B) to provide the product as a yellow solid. Yield: 4.0 mg, 12 µmol, 9%. LCMS *m/z* 322.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (dd, *J*=4.8, 1.3 Hz, 1H), 8.20 (dd, *J*=8.2, 1.4 Hz, 1H), 7.77-7.82 (m, 1H), 7.36-7.43 (m, 3H), 4.80-4.89 (m, 2H), 4.18-4.26 (m, 2H), 2.39-2.50 (m, 2H).

Example 9

*Azetidin-1-yl[3-(4-chloro-3,5-difluorophenyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]methanone (**9**)*



Step 1. Synthesis of N-*(4-chloro-3,5-difluorophenyl)-3-nitropyridin-2-amine (**C17**).*

A mixture of 4-chloro-3,5-difluoroaniline (1.64 g, 10.0 mmol), 2-chloro-3-nitropyridine (1.56 g, 9.84 mmol) and cesium carbonate (6.56 g, 20.1 mmol) in *N,N*-dimethylformamide (30 mL) was stirred at 80 °C for 36 hours. The reaction mixture was cooled to room temperature, diluted with water (200 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (5 x 50 mL), dried over sodium sulfate, filtered, concentrated *in vacuo* and purified by chromatography on silica gel (Gradient: 0% to 5% ethyl acetate in petroleum ether) to provide the product as a yellow solid. Yield: 200 mg, 0.70 mmol, 7%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (br s, 1H), 8.55-8.61 (m, 2H), 7.52 (br d, *J*=9 Hz, 2H), 6.96-7.01 (m, 1H).

Step 2. Synthesis of N^2*-(4-chloro-3,5-difluorophenyl)pyridine-2,3-diamine (**C18**).*

To a solution of *N*-(4-chloro-3,5-difluorophenyl)-3-nitropyridin-2-amine (**C17**) (100 mg, 0.35 mmol) in a 1:1 mixture of tetrahydrofuran and water (20 mL) was added ammonium chloride (148 mg, 2.77 mmol) followed by zinc (182 mg, 2.78 mmol), and the reaction mixture was stirred at room temperature for 2 hours. It was then diluted with water (10 mL) and extracted with ethyl acetate (3 x 20 mL); the combined organic layers were washed with saturated aqueous sodium chloride solution (20 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford the product as a yellow solid. This material was used directly in the following step. Yield: 80 mg, 0.31 mmol, 89%.

*Step 3. Synthesis of ethyl 3-(4-chloro-3,5-difluorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxylate (**C19**).*

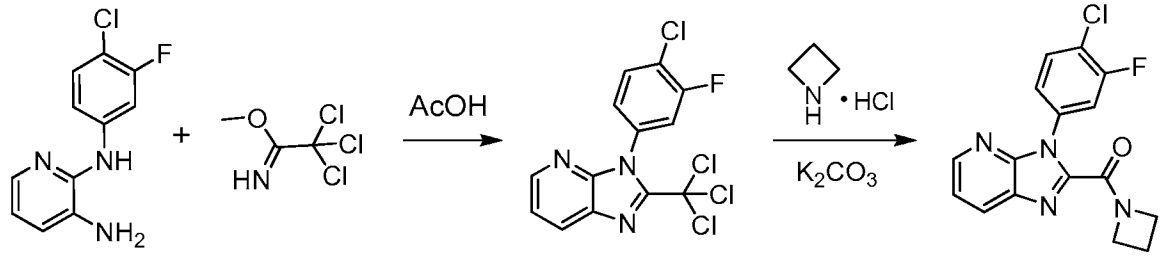
N^2-(4-Chloro-3,5-difluorophenyl)pyridine-2,3-diamine (**C18**) was converted to the product using the method described for synthesis of **C16** in Example 8. The product was obtained as a yellow solid. Yield: 40 mg, 0.12 mmol, 41%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (dd, *J*=4.7, 1.3 Hz, 1H), 8.30 (dd, *J*=8.1, 1.5 Hz, 1H), 7.44 (dd, *J*=8.2, 4.7 Hz, 1H), 7.11-7.15 (m, 2H), 4.46 (q, *J*=7.2 Hz, 2H), 1.43 (t, *J*=7.2 Hz, 3H).

*Step 4. Synthesis of azetidin-1-yl[3-(4-chloro-3,5-difluorophenyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]methanone (**9**).*

Ethyl 3-(4-chloro-3,5-difluorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxylate (**C19**) was converted to the product using the method described for synthesis of **8** in Example 8. The product was obtained as a yellow solid. Yield: 7.9 mg, 23 μmol, 39%. LCMS *m/z* 349.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (dd, *J*=4.7, 1.4 Hz, 1H), 8.19 (dd, *J*=8.1, 1.4 Hz, 1H), 7.39 (dd, *J*=8.1, 4.7 Hz, 1H), 7.10-7.15 (m, 2H), 4.80-4.85 (m, 2H), 4.19-4.25 (m, 2H), 2.40-2.49 (m, 2H).

Example 10

*Azetidin-1-yl[3-(4-chloro-3-fluorophenyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]methanone (**10**)*



C12 **C20** **10**

*Step 1. Synthesis of 3-(4-chloro-3-fluorophenyl)-2-(trichloromethyl)-3*H*-imidazo[4,5-*b*]pyridine (**C20**).*

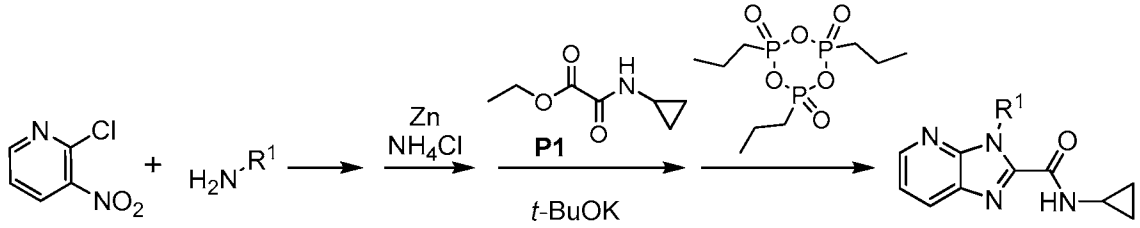
Methyl 2,2,2-trichloroethanimidoate (0.743 mL, 6.00 mmol) was added to a solution of N^2-(4-chloro-3-fluorophenyl)pyridine-2,3-diamine (**C12**) (951 mg, 4.00 mmol) in acetic acid (4 mL), and the reaction mixture was stirred at room temperature for 5 hours. After concentration *in vacuo*, the residue was purified via chromatography on silica gel (Gradient: 5% to 100% ethyl acetate in heptane) to afford the product as a white solid. Yield: 1.04 g, 2.85 mmol, 71%. LCMS *m/z* 366.0 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (dd, *J*=4.7, 1.5 Hz, 1H), 8.27 (dd, *J*=8.1, 1.5 Hz, 1H), 7.64 (ddd, *J*=8.5, 7.8, 0.3 Hz, 1H), 7.42 (dd, *J*=8.1, 4.7 Hz, 1H), 7.39 (ddd, *J*=8.8, 2.4, 0.2 Hz, 1H), 7.32 (ddd, *J*=8.5, 2.4, 1.3 Hz, 1H).

*Step 2. Synthesis of azetidin-1-yl[3-(4-chloro-3-fluorophenyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]methanone (**10**).*

3-(4-Chloro-3-fluorophenyl)-2-(trichloromethyl)-3*H*-imidazo[4,5-*b*]pyridine (**C20**) (50 mg, 0.14 mmol) was dissolved in a 3:1 mixture of acetonitrile and water (1.4 mL). Azetidine hydrochloride (25.6 mg, 0.274 mmol) was added, followed by an aqueous solution of potassium carbonate (4 M, 0.15 mL, 0.60 mmol), and the reaction mixture was heated at 50 °C for 22 hours, then at 80 °C for 3 hours, and finally at 100 °C for 18 hours. The layers were separated, and the organic layer was concentrated *in vacuo*; purification via reversed phase HPLC (Column: Waters Sunfire C18, 5 µm; Mobile phase A: 0.05% trifluoroacetic acid in water (v/v); Mobile phase B: 0.05% trifluoroacetic acid in acetonitrile (v/v); Gradient: 30% to 50% B) afforded the product. Yield: 17 mg, 51 µmol, 36%. LCMS *m/z* 331.1, 333.1 $[M+H]^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.45 (dd, *J*=4.6, 1.5 Hz, 1H), 8.30 (dd, *J*=7.9, 1.3 Hz, 1H), 7.76 (dd, *J*=8.3, 8.3 Hz, 1H), 7.73 (dd, *J*=10.1, 2.2 Hz, 1H), 7.46 (dd, *J*=8.1, 4.6 Hz, 1H), 7.40-7.43 (m, 1H), 4.64-4.68 (m, 2H), 4.02-4.07 (m, 2H), 2.29-2.35 (m, 2H).

Method A

Synthesis of Examples from 2-Chloro-3-nitropyridine and Amines

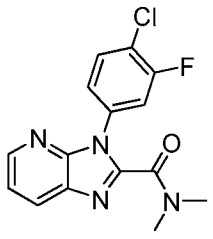


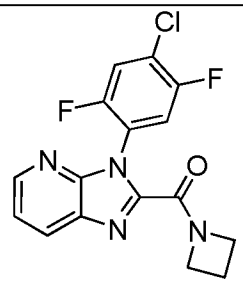
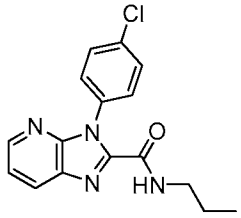
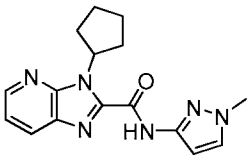
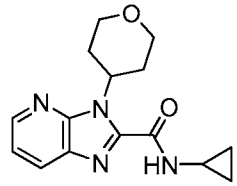
The requisite amine (0.20 mmol) was combined with a solution of 2-chloro-3-nitropyridine (31.7 mg, 0.200 mmol) in tetrahydrofuran (0.1 mL) and polyethylene glycol 400 (PEG 400, 0.1 mL); if an amine salt was used, triethylamine (28 µL, 0.20 mmol) was also added. The reaction mixture was shaken at 150 °C for 1 – 1.5 hours, then cooled to room temperature. To this was added tetrahydrofuran (0.4 mL) and a solution of ammonium chloride (85.6 mg, 1.60 mmol) in water (0.4 mL), followed by zinc (approximately 105 mg, 1.6 mmol). The reaction mixture was shaken at 65 °C for 1.5 hours, then partitioned between water (1 mL) and ethyl acetate (2.5 mL). The organic layer was eluted through a 6 mL solid phase extraction cartridge filled with sodium sulfate (approximately 1 g). This extraction was repeated twice, and the combined eluates from the cartridge were concentrated *in vacuo*. To the crude residue was added a solution of ethyl (cyclopropylamino)(oxo)acetate (**P1**) (47 mg, 0.30 mmol) in 1-methylpyrrolidin-2-one (0.2 mL) and a solution of potassium *tert*-butoxide in tetrahydrofuran (1 M, 0.3 mL, 0.3 mmol); this reaction mixture was shaken at 120 °C for 30 minutes, then cooled to room temperature and treated with acetic acid (18 µL, 0.31 mmol).

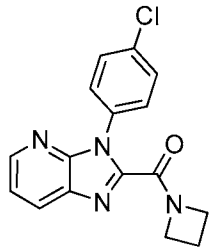
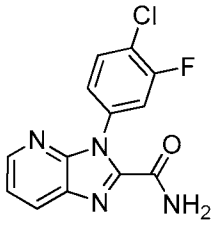
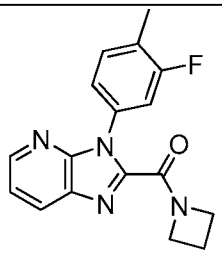
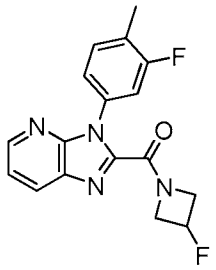
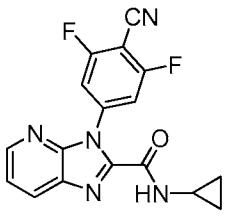
2,4,6-Tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P, 50% weight solution in ethyl acetate, 254 mg, 0.40 mmol) was added, and the reaction mixture was shaken at 120 °C for 24 hours. The reaction mixture was then partitioned between ethyl acetate (2.5 mL) and aqueous sodium hydroxide solution (1 M, 1.5 mL); the organic layer was eluted through a 6 mL solid phase extraction cartridge filled with sodium sulfate (approximately 1 g). This extraction was repeated twice, and the combined eluates from the cartridge were concentrated *in vacuo* and purified via reversed phase HPLC using one of the following systems: 1) Column: Waters XBridge C18, 5 µm; Mobile phase A: 0.03% ammonium hydroxide in water (v/v); Mobile phase B: 0.03% ammonium hydroxide in acetonitrile (v/v); Gradient: 20% to 60% B or 10% to 100% B; 2) Column: Waters Sunfire C18, 5 µm; Mobile phase A: 0.05% trifluoroacetic acid in water (v/v); Mobile phase B: 0.05% trifluoroacetic acid in acetonitrile (v/v); Gradient: 10% to 100% B.

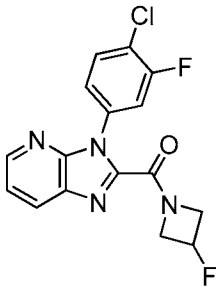
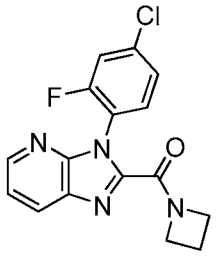
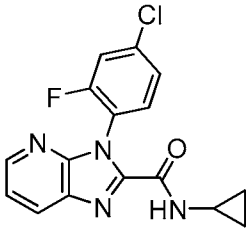
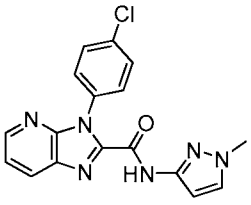
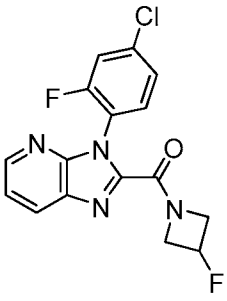
Using the methodology described above for Examples 1-10, the compounds in Table 1 and Table 2 were also made (See Tables 1 and 2 for characterization data).

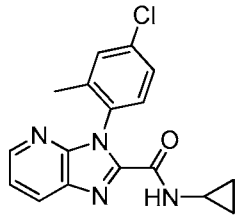
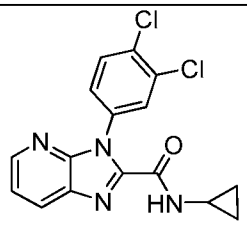
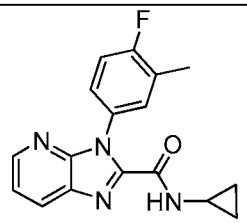
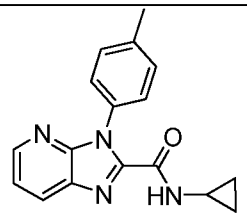
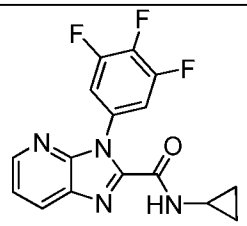
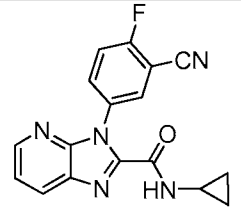
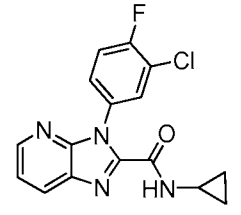
Table 1

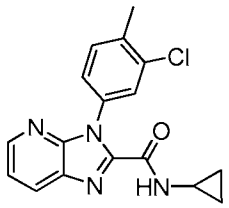
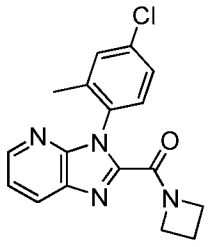
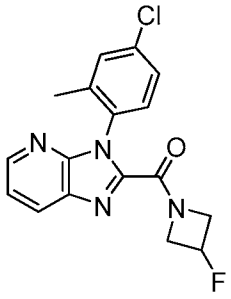
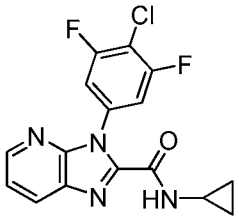
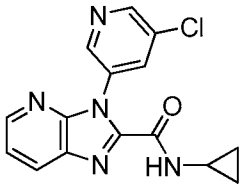
Example Number	Structure	Method of Preparation; Non-commercial Starting Materials	^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm); Mass spectrum, observed ion *m/z* $[M+H]^+$ or HPLC retention time[1] (minutes); Mass spectrum *m/z* $[M+H]^+$ (unless otherwise indicated)
11		Example 1[2]; **C12**	^{1}H NMR (600 MHz, DMSO-d_6), δ 8.46 (dd, *J*=4.6, 1.5 Hz, 1H), 8.28 (dd, *J*=8.1, 1.5 Hz, 1H), 7.81 (dd, *J*=8.3, 8.3 Hz, 1H), 7.74 (dd, *J*=10.1, 2.2 Hz, 1H), 7.47 (dd, *J*=8.1, 4.6 Hz, 1H), 7.41-7.44 (m, 1H), 3.15 (s, 3H), 2.98 (s, 3H); 319.0, 321.0

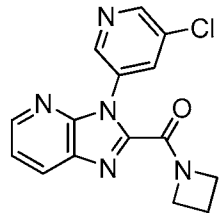
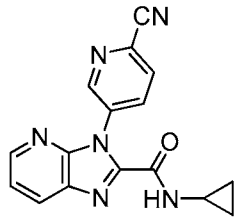
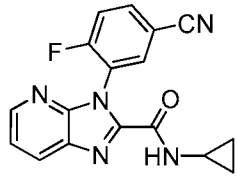
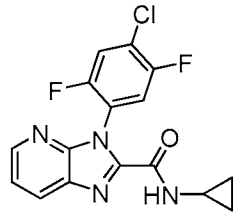
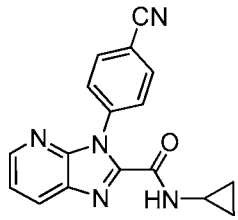
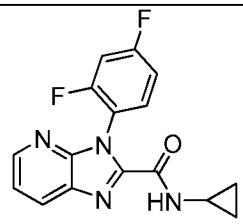
12	 • CF_3COOH	Example 10	^{1}H NMR (600 MHz, DMSO-d_6), δ 8.46-8.49 (m, 1H), 8.32-8.36 (m, 1H), 7.90-7.96 (m, 2H), 7.47-7.51 (m, 1H), 4.71 (dd, *J*=7.7, 7.7 Hz, 2H), 4.06 (dd, *J*=7.7, 7.4 Hz, 2H), 2.30-2.37 (m, 2H); 349.1, 351.1
13		Example 6; **C10**	characteristic peaks: 8.46-8.53 (m, 1H), 8.15 (br d, *J*=8 Hz, 1H), 7.63-7.73 (br m, 1H), 7.53 (br d, *J*=8 Hz, 2H), 7.39 (br d, *J*=8 Hz, 2H), 3.33-3.43 (m, 2H), 0.99 (t, *J*=7.3 Hz, 3H); 314.8
14		**C7**[3]	10.09 (br s, 1H), 8.49 (dd, *J*=4.6, 1.5 Hz, 1H), 8.07 (dd, *J*=8.2, 1.5 Hz, 1H), 7.32 (d, *J*=2.3 Hz, 1H), 7.29 (dd, *J*=8.2, 4.6 Hz, 1H), 6.78 (d, *J*=2.3 Hz, 1H), 6.22-6.33 (m, 1H), 3.87 (s, 3H), 2.55-2.67 (m, 2H), 2.08-2.21 (m, 4H), 1.70-1.83 (m, 2H); 311.0
15		Example 2	^{1}H NMR (400 MHz, CD_3OD), δ 8.47 (dd, *J*=4.7, 1.4 Hz, 1H), 8.09 (dd, *J*=8.2, 1.4 Hz, 1H), 7.36 (dd, *J*=8.2, 4.6 Hz, 1H), 5.68 (tt, *J*=12, 4 Hz, 1H), 4.13 (dd, *J*=11.5, 4.5 Hz, 2H), 3.60 (ddd, *J*=12.4, 11.8, 1.5 Hz, 2H), 3.03-3.15 (m, 2H), 2.89-2.96 (m, 1H), 1.81-1.89 (m, 2H), 0.83-0.90 (m, 2H), 0.69-0.76 (m, 2H); 286.9

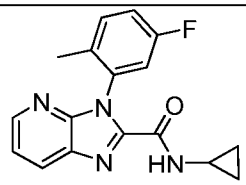
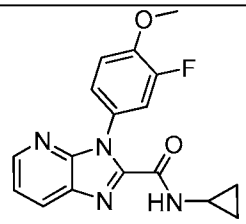
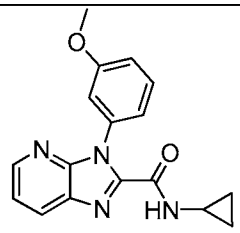
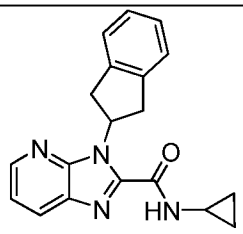
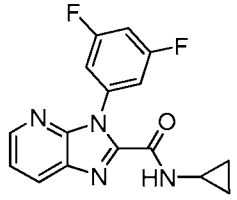
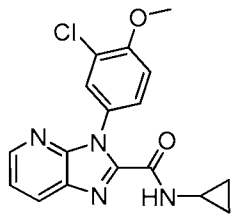
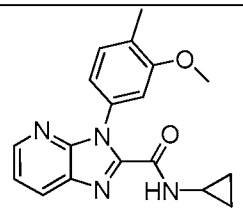
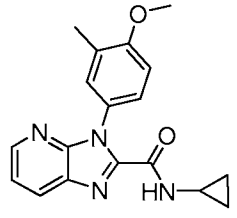
16		Example 10; **C9**	^{1}H NMR (600 MHz, DMSO-d_6), δ 8.44 (dd, *J*=4.7, 1.3 Hz, 1H), 8.28 (dd, *J*=8.1, 1.3 Hz, 1H), 7.56 (br AB quartet, J_{AB}=8.7 Hz, $\Delta\nu_{AB}$=39.2 Hz, 4H), 7.45 (dd, *J*=8.1, 4.7 Hz, 1H), 4.63 (dd, *J*=7.8, 7.7 Hz, 2H), 4.04 (dd, *J*=7.8, 7.7 Hz, 2H), 2.28-2.35 (m, 2H); 313.1, 315.1
17		Example 7; **C12**	8.52 (dd, *J*=4.7, 1.3 Hz, 1H), 8.19 (dd, *J*=8.2, 1.3 Hz, 1H), 7.59 (dd, *J*=8.2, 8.2 Hz, 1H), 7.41 (dd, *J*=8.1, 4.7 Hz, 1H), 7.28-7.32 (m, 1H), 7.20-7.24 (m, 1H); 290.8
18		Example 3[4]	8.49 (d, *J*=4.4 Hz, 1H), 8.15 (d, *J*=7.6 Hz, 1H), 7.31-7.38 (m, 2H), 7.10-7.16 (m, 2H), 4.73-4.80 (m, 2H), 4.16-4.24 (m, 2H), 2.36 (s, 3H), 2.36-2.45 (m, 2H); 311.0
19		Example 3[4]	8.45 (dd, *J*=4.8, 1.3 Hz, 1H), 8.30 (dd, *J*=8.2, 1.1 Hz, 1H), 7.38-7.49 (m, 3H), 7.23-7.27 (m, 1H), 5.49 (br d, J_{HF}=57 Hz, 1H), 4.93-5.05 (m, 1H), 4.63-4.76 (m, 1H), 4.32-4.44 (m, 1H), 4.04-4.16 (m, 1H), 2.33 (s, 3H); 329.0
20		Example 7	8.50 (dd, *J*=4.7, 1.5 Hz, 1H), 8.17 (dd, *J*=8.2, 1.5 Hz, 1H), 7.67 (br d, 1H), 7.44 (dd, *J*=8.1, 4.7 Hz, 1H), 7.21-7.25 (m, 2H), 2.83-2.90 (m, 1H), 0.88-0.94 (m, 2H), 0.69-0.74 (m, 2H); 340.1

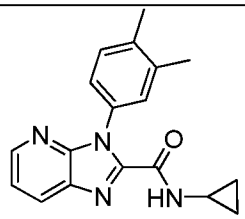
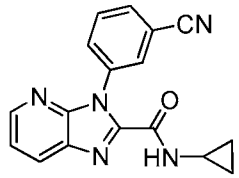
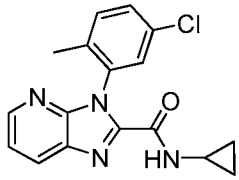
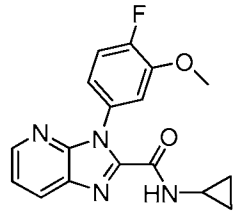
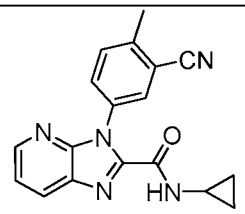
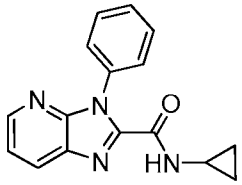
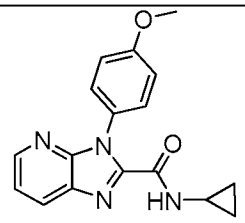
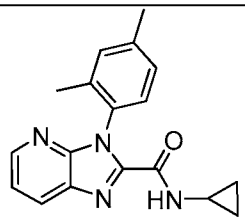
21		Example 3[4]	8.51 (dd, *J*=4.6, 1.2 Hz, 1H), 8.19 (dd, *J*=8.2, 1.1 Hz, 1H), 7.57 (dd, *J*=8.3, 8.0 Hz, 1H), 7.39 (dd, *J*=8.2, 4.6 Hz, 1H), 7.27 (dd, *J*=8.8, 2.3 Hz, 1H), 7.16-7.22 (m, 1H), 5.33-5.54 (m, J_{HF}=57 Hz, 1H), 5.08-5.20 (m, 1H), 4.85-4.98 (m, 1H), 4.40-4.52 (m, 1H), 4.23-4.36 (m, 1H); 348.9
22		Example 3[4]	8.49 (dd, *J*=4.7, 1.4 Hz, 1H), 8.18 (dd, *J*=8.2, 1.4 Hz, 1H), 7.47 (dd, *J*=8.4, 7.4 Hz, 1H), 7.37 (dd, *J*=8.1, 4.8 Hz, 1H), 7.28-7.35 (m, 2H), 4.69-4.96 (br m, 2H), 4.16-4.26 (m, 2H), 2.37-2.47 (m, 2H); 331.0
23		Example 3[4]	8.50 (dd, *J*=4.8, 1.5 Hz, 1H), 8.15 (dd, *J*=8.1, 1.4 Hz, 1H), 7.66 (br s, 1H), 7.45 (dd, *J*=9.0, 7.4 Hz, 1H), 7.40 (dd, *J*=8.1, 4.7 Hz, 1H), 7.31-7.37 (m, 2H), 2.83-2.89 (m, 1H), 0.84-0.91 (m, 2H), 0.68-0.73 (m, 2H); 330.9
24		Example 5; **C10**	characteristic peaks: 9.94 (br s, 1H), 8.52 (dd, *J*=4.8, 1.5 Hz, 1H), 8.20 (dd, *J*=8.2, 1.4 Hz, 1H), 7.56 (br d, *J*=8.8 Hz, 2H), 7.43 (br d, *J*=8.7 Hz, 2H), 7.40 (dd, *J*=8.2, 4.6 Hz, 1H), 6.68 (d, *J*=2.1 Hz, 1H), 3.85 (s, 3H); 352.9
25		Example 3[4]	8.51 (dd, *J*=4.8, 1.4 Hz, 1H), 8.20 (dd, *J*=8.2, 1.4 Hz, 1H), 7.46 (dd, *J*=8.4, 7.9 Hz, 1H), 7.39 (dd, *J*=8.2, 4.8 Hz, 1H), 7.29-7.37 (m, 2H), 5.33-5.54 (m, J_{HF}=57 Hz, 1H), 4.8-5.3 (v br m, 2H), 4.40-4.54 (m, 1H), 4.23-4.37 (m, 1H); 348.9

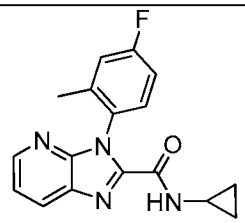
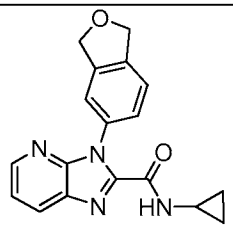
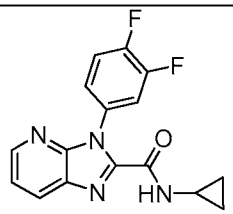
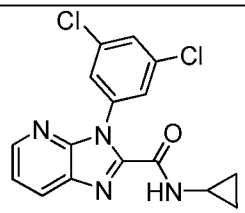
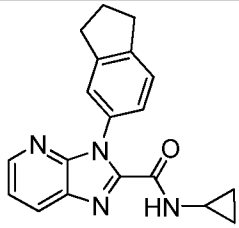
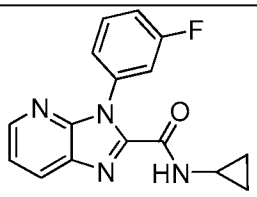
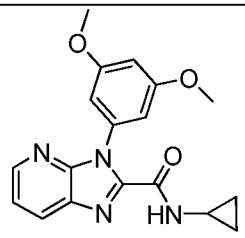
26		Example 3[4]	8.49 (dd, *J*=4.8, 1.1 Hz, 1H), 8.15 (dd, *J*=7.9, 1.1 Hz, 1H), 7.66 (br s, 1H), 7.32-7.43 (m, 3H), 7.19 (d, *J*=8.2 Hz, 1H), 2.81-2.89 (m, 1H), 1.98 (s, 3H), 0.83-0.89 (m, 2H), 0.66-0.71 (m, 2H); 327.0
27		Method A	2.97 minutes; 347.0, 349.0
28		Method A	2.59 minutes; 311.1
29		Method A	2.51 minutes; 293.1
30	 • CF_3COOH	Method A	2.70 minutes; 333.0
31		Method A	2.46 minutes; 322.1
32		Method A	2.53 minutes; 331.0, 333.0

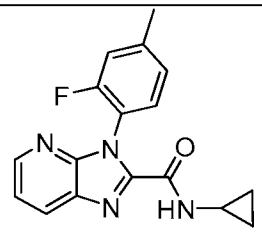
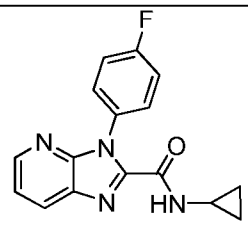
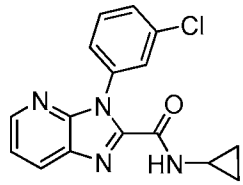
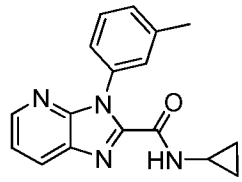
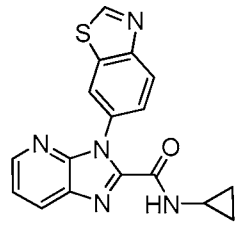
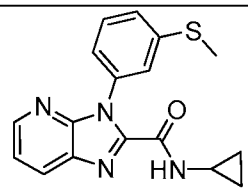
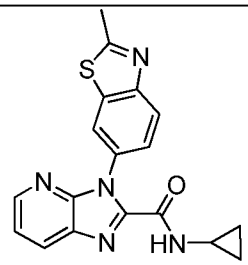
33		Method A	2.90 minutes; 327.0, 329.0
34		Example 3[4]	8.48 (dd, *J*=4.8, 1.5 Hz, 1H), 8.18 (dd, *J*=8.2, 1.4 Hz, 1H), 7.30-7.40 (m, 3H), 7.17 (d, *J*=8.3 Hz, 1H), 4.75-4.92 (m, 2H), 4.15-4.22 (m, 2H), 2.36-2.46 (m, 2H), 1.99 (s, 3H); 327.0
35		Example 3[4]	presumed to be a mixture of rotamers; 8.50 (dd, *J*=4.6, 1.4 Hz, 1H), 8.20 (br d, *J*=8.0 Hz, 1H), 7.31-7.42 (m, 3H), 7.14-7.19 (m, 1H), 5.32-5.52 (m, J_{HF}=57 Hz, 1H), 5.04-5.26 (m, 1H), 4.82-5.03 (m, 1H), 4.38-4.50 (m, 1H), 4.21-4.34 (m, 1H), 1.99 and 1.97 (2 s, total 3H); 345.0
36		Example 9	8.51 (dd, *J*=4.6, 1.5 Hz, 1H), 8.15 (dd, *J*=8.2, 1.5 Hz, 1H), 7.68 (br s, 1H), 7.41 (dd, *J*=8.2, 4.8 Hz, 1H), 7.11-7.16 (m, 2H), 2.82-2.90 (m, 1H), 0.86-0.92 (m, 2H), 0.68-0.73 (m, 2H); 349.1
37		Example 2[5]	8.72 (d, *J*=2.0 Hz, 1H), 8.60 (d, *J*=2.1 Hz, 1H), 8.51 (dd, *J*=4.6, 1.4 Hz, 1H), 8.16 (dd, *J*=8.2, 1.4 Hz, 1H), 7.86 (dd, *J*=2.1, 2.0 Hz, 1H), 7.69 (br s, 1H), 7.42 (dd, *J*=8.3, 4.6 Hz, 1H), 2.83-2.91 (m, 1H), 0.86-0.92 (m, 2H), 0.68-0.73 (m, 2H); 314.1, 316.0

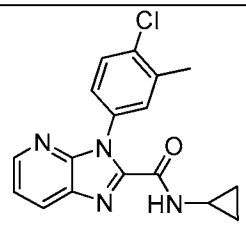
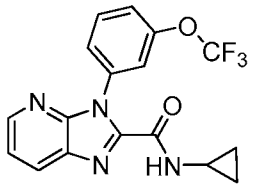
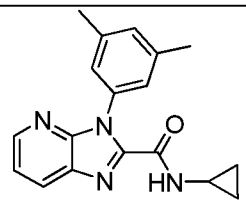
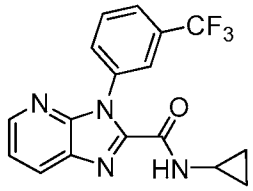
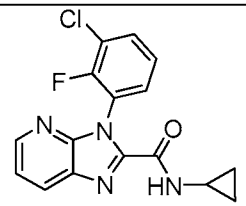
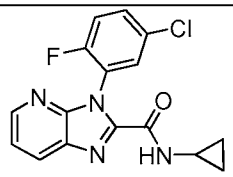
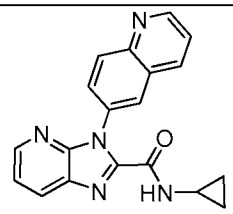
38		Example 37	8.69 (d, *J*=2.3 Hz, 1H), 8.56 (d, *J*=1.9 Hz, 1H), 8.50 (dd, *J*=4.6, 1.3 Hz, 1H), 8.20 (dd, *J*=8.1, 1.3 Hz, 1H), 7.85-7.88 (m, 1H), 7.40 (dd, *J*=8.2, 4.6 Hz, 1H), 4.82-4.87 (m, 2H), 4.19-4.25 (m, 2H), 2.39-2.49 (m, 2H); 313.9, 315.9
39		Example 7[6]	8.84 (br d, *J*=2.4 Hz, 1H), 8.50 (dd, *J*=4.7, 1.4 Hz, 1H), 8.18 (dd, *J*=8.2, 1.4 Hz, 1H), 8.03 (dd, half of ABX pattern, *J*=8.3, 2.4 Hz, 1H), 7.91 (dd, half of ABX pattern, *J*=8.3, 0.5 Hz, 1H), 7.72 (br s, 1H), 7.44 (dd, *J*=8.2, 4.8 Hz, 1H), 2.82-2.90 (m, 1H), 0.87-0.93 (m, 2H), 0.68-0.73 (m, 2H); 305.1
40		Example 7	8.50 (dd, *J*=4.9, 1.4 Hz, 1H), 8.17 (dd, *J*=8.3, 1.3 Hz, 1H), 7.81-7.87 (m, 2H), 7.68 (br s, 1H), 7.39-7.45 (m, 2H), 2.82-2.89 (m, 1H), 0.86-0.92 (m, 2H), 0.68-0.74 (m, 2H); 322.2
41		Example 7[7]	8.51 (dd, *J*=4.6, 1.5 Hz, 1H), 8.16 (dd, *J*=8.0, 1.3 Hz, 1H), 7.64 (br s, 1H), 7.32-7.43 (m, 3H), 2.83-2.90 (m, 1H), 0.85-0.92 (m, 2H), 0.68-0.74 (m, 2H); 349.1
42		Method A	2.32 minutes; 304.1
43		Method A	2.47 minutes; 315.1

44		Method A	2.54 minutes; 311.1
45		Method A	2.44 minutes; 327.1
46		Method A	2.34 minutes; 309.1
47		Method A	3.25 minutes; 319.1
48		Method A	2.55 minutes; 315.0
49		Method A	2.66 minutes; 343.0, 345.0
50		Method A	2.60 minutes; 323.1
51		Method A	2.60 minutes; 323.1

52		Method A	2.71 minutes; 307.1
53		Method A	2.30 minutes; 304.1
54		Method A	2.85 minutes; 327.1, 329.1
55		Method A	2.40 minutes; 327.1
56		Method A	2.52 minutes; 318.1
57		Method A	2.13 minutes; 279.1
58		Method A	2.33 minutes; 309.1
59		Method A	2.74 minutes; 307.1

60		Method A	2.55 minutes; 311.1
61		Method A	2.10 minutes; 321.1
62		Method A	2.52 minutes; 315.0
63		Method A	3.06 minutes; 347.0, 349.0
64		Method A	2.83 minutes; 319.1
65		Method A	2.39 minutes; 297.1
66		Method A	2.46 minutes; 339.1

67		Method A	2.69 minutes; 311.1
68		Method A	2.35 minutes; 297.1
69		Example 7[8]	8.50 (dd, *J*=4.8, 1.3 Hz, 1H), 8.14 (dd, *J*=8.2, 1.1 Hz, 1H), 7.69 (br s, 1H), 7.47-7.53 (m, 2H), 7.45 (br s, 1H), 7.33-7.41 (m, 2H), 2.83-2.90 (m, 1H), 0.83-0.90 (m, 2H), 0.67-0.73 (m, 2H); 312.9
70		Method A	2.48 minutes; 293.1
71		Method A	2.13 minutes; 336.0
72		Method A	2.65 minutes; 325.0
73		Method A	2.27 minutes; 350.0

74		Method A	2.85 minutes; 327.1, 329.0
75		Method A	2.95 minutes; 363.0
76		Method A	2.71 minutes; 307.1
77		Method A	2.88 minutes; 347.0
78	 • CF_3COOH	Method A	2.79 minutes; 331.0, 333.0
79	 • CF_3COOH	Method A	2.76 minutes; 331.0, 333.0
80	 • CF_3COOH	Method A	1.59 minutes; 330.1

1. Conditions for analytical HPLC. Column: Waters Atlantis dC18, 4.6 x 50 mm, 5 µm; Mobile phase A: 0.05% trifluoroacetic acid in water (v/v); Mobile phase B: 0.05% trifluoroacetic

acid in acetonitrile (v/v); Gradient: 5.0% to 95% B, linear over 4.0 minutes; Flow rate: 2 mL/minute.

2. Ethyl (dimethylamino)(oxo)acetate was employed in place of ethyl (cyclopropylamino)(oxo)acetate (**P1**).

3. Hydrolysis of **C7** with lithium hydroxide afforded the corresponding carboxylic acid; this was condensed with 1-methyl-1*H*-pyrazol-3-amine using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride and 1*H*-benzotriazol-1-ol.

4. *N,N*-Diisopropylethylamine was utilized in the final step.

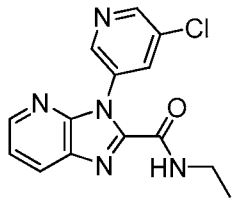
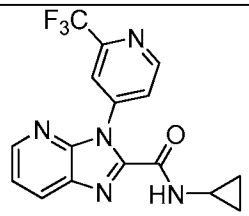
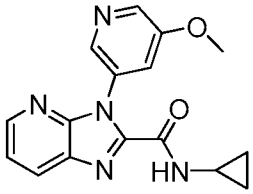
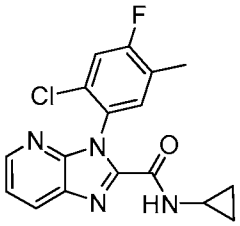
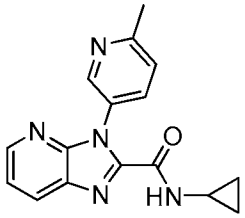
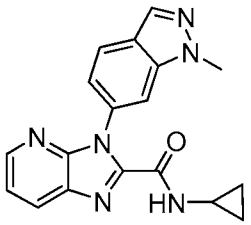
5. The requisite N^2-(5-chloropyridin-3-yl)pyridine-2,3-diamine was prepared via reaction of 2-chloro-3-nitropyridine with 5-chloropyridin-3-amine using palladium(II) acetate and 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, followed by treatment with Raney nickel.

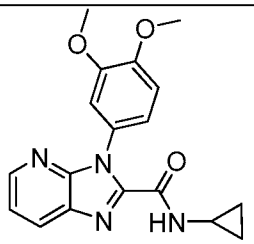
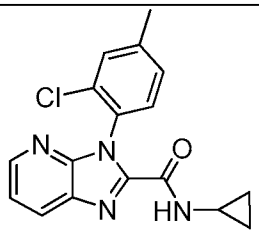
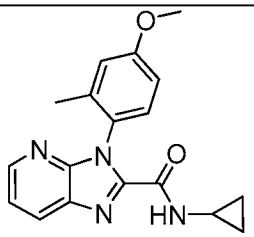
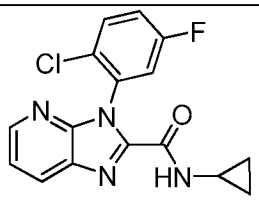
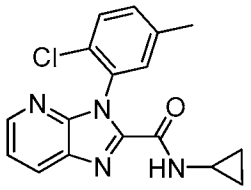
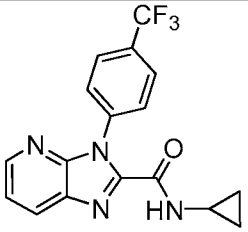
6. 5-[(3-Nitropyridin-2-yl)amino]pyridine-2-carbonitrile was prepared by the method used for synthesis of **C17** in Example 9.

7. *N*-(4-Chloro-2,5-difluorophenyl)-3-nitropyridin-2-amine was prepared by the method used for synthesis of **C17** in Example 9.

8. *N*-(3-Chlorophenyl)-3-nitropyridin-2-amine was prepared by heating 2-chloro-3-nitropyridine with 3-chloroaniline at 150 °C.

Table 2

Example Number	Structure	Method of Preparation; Non-commercial Starting Materials	Mass spectrum, observed ion *m/z* $[M+H]^+$
81		Example 2[1]	302.0
82		Example 7[2]	348.2
83		Example 7	309.9
84		Method A	345.0, 347.0
85		Method A	294.1
86		Method A	333.1

87		Method A	339.1
88		Method A	327.1, 329.0
89		Method A	323.1
90		Method A	331.0, 333.0
91		Method A	327.1, 329.0
92		Method A	347.1

1. See footnote 5 in Table 1.

2. 3-Nitro-*N*-[2-(trifluoromethyl)pyridin-4-yl]pyridin-2-amine was prepared from 2-chloro-3-nitropyridine and 2-(trifluoromethyl)pyridin-4-amine using the method for synthesis of **C17** in Example 9.

The binding affinity of the compounds in Examples 1-92 for the PDE4B isoform is shown in column 2 of Table 3 below, and the affinity of these compounds for the PDE4D isoform is shown in column 3. A review of the data shows that selected compounds have an enhanced binding affinity for the PDE4B isoform over the PDE4D isoform. For example, the

data for Examples 2, 15, 17, 81, 82, 83, 85, 90 and 91 shows that these compounds display at least about a 2-fold selectivity over the PDE4D isoform. The data for Examples 13, 14, 21, 25, 35, 40, 47, 77, 88, 89 and 92 shows that these compounds display at least about a 5-fold selectivity over the PDE4D isoform. The data for Examples 19, 20, 33, 38, 41, 44, 49, 57, 61, 72, 75, 79 and 87 shows that these compounds display at least about a 10-fold to selectivity over the PDE4D isoform. The data for Examples 6, 9, 10, 11, 12, 22, 27, 31, 34, 37, 39, 43, 56, 59, 60, 63, 66, 69, 70, 73, 74, 78 and 80 shows that these compounds display at least about a 20-fold selectivity over the PDE4D isoform. The data for Examples 4, 7, 18, 36, 46, 62, 67 and 71 shows that these compounds display at least about a 40-fold selectivity over the PDE4D isoform. The data for Examples 1, 3, 8, 16, 23, 26, 28, 30, 32, 33, 42, 45, 48, 50, 51, 52, 54, 55, 58, 64, 65, 68 and 76 shows that these compounds display at least about a 50-fold selectivity over the PDE4D isoform.

The PDE4B and PDE4D binding affinity for the compounds of the present invention was determined utilizing the following biological assay(s):

Biological Assays

A portion of the human PDE4D3 coding sequence (amino acids 50 to 672 from the sequence with accession number Q08499-2) was cloned into the baculovirus expression vector pFastBac (Invitrogen) engineered to include a C-terminal His6 affinity tag to aid in purification as described in Seeger, T. F. et al., Brain Research 985 (2003) 113-126. The recombinant Bacmid was isolated and used to transfect insect cells to generate a viral stock. To generate cell paste for purification, insect cells were infected and cells were harvested 72 hours after infection. Insect cell paste was lysed and after centrifugation, the supernatant was chromatographed on Ni-NTA agarose (Qiagen) as described in Seeger, T. F. et al., Brain Research 985 (2003) 113-126. Ni-NTA agarose eluting fractions containing PDE4 were pooled, diluted with Q Buffer A (50 mM Tris HCl pH 8, 4% glycerol, 100 mM NaCl, 1 mM TCEP, Protease inhibitors EDTA-free (Roche)) to reduce NaCl to ~200 mM, and loaded on a Q Sepharose (GE Healthcare) column. After washing with Q buffer A to baseline, PDE4D was eluted with a gradient from 10% to 60% of Buffer B (50 mM Tris HCl pH 8, 1 M NaCl, 4% glycerol, 1 mM TCEP). PDE4D fractions were analyzed by SDS-PAGE Coomassie blue staining, pooled based on purity, frozen and stored at −80 °C.

Human PDE4B1 coding sequence (amino acids 122 to 736 from the sequence with accession number Q07343) with the mutations resulting in the amino acid substitutions S134E, S654A, S659A, and S661A was cloned into the baculovirus expression vector pFastBac (Invitrogen) engineered to include a N-terminal His6 affinity tag to aid in

purification followed by a thrombin cleavage site. The recombinant Bacmid was isolated and used to transfect insect cells to generate a viral stock. To generate cell paste for purification, insect cells were infected with the virus stock and cells were harvested 72 hours after infection as described in Seeger, T. F. et al., Brain Research 985 (2003) 113-126. Insect cell paste was lysed and after centrifugation, the supernatant was chromatographed on Ni-NTA agarose (Qiagen) as described in Seeger, T. F. et al., Brain Research 985 (2003) 113-126. Ni-NTA agarose eluting fractions containing PDE4 were pooled, diluted with Q buffer A (20 mM Tris HCl pH 8, 5% glycerol, 1 mM TCEP) to reduce NaCl to ~100 mM and loaded on a Source 15Q (GE Healthcare) column. After washing with Q buffer A/10% buffer B to baseline, PDE4D was eluted with a gradient from 10% to 60% of Buffer B (20 mM Tris HCl pH 8, 1 M NaCl, 5% glycerol, 1 mM TCEP). PDE4D fractions were analyzed by SDS-PAGE Coomassie blue staining, pooled based on purity, frozen and stored at −80 °C.

The PDE4B and 4D assays use scintillation proximity assay (SPA) technology to measure the inhibition of human recombinant PDE4B and PDE4D enzyme activity by compounds in vitro. The PDE4B and 4D assays are run in parallel using identical parameters, except for the concentration of enzyme (~32 pM PDE4B and ~16 pM PDE4D). The assays are performed in a 384-well format with 50 µL assay buffer (50 mM Tris pH 7.5; 1.3 mM $MgCl_2$; 0.01% Brij) containing enough PDE4B and PDE4D to convert ~20% of substrate (1 µM cAMP consisting of 20 nM ^{3}H-cAMP + 980 µM cold cAMP) and a range of inhibitors. Reactions are incubated for 30 min at 25 °C. The addition of 20 µL of 8 mg/mL yitrium silicate SPA beads (PerkinElmer) stops the reaction. The plates are sealed (TopSeal, PerkinElmer) and the beads are allowed to settle for 8 hrs, after which they are read on the Trilux Microbeta overnight.

Table 3

Example Number	Human PDE4B FL; IC_{50} (nM)[a]	Human PDE4D FL; IC_{50} (μM)[a]	IUPAC Name
1	31.8[b]	2.21[b]	*N*-Cyclopropyl-3-(3-fluoro-4-methylphenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
2	426	1.27[b]	3-Cyclopentyl-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
3	131[b]	7.95[b]	3-(4-Chlorophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
4	18.4[b]	0.908[b]	3-(4-Chloro-3-fluorophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
5	54.1	5.64	3-(4-Chloro-3-fluorophenyl)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
6	38.1[b]	0.778[b]	3-(4-Chloro-3-fluorophenyl)-*N*-propyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
7	40.8[b]	1.88[b]	3-(4-Cyano-3-fluorophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
8	16.0	0.910	4-[2-(Azetidin-1-ylcarbonyl)-3*H*-imidazo[4,5-*b*]pyridin-3-yl]-2-fluorobenzonitrile
9	14.2[b]	0.420[b]	Azetidin-1-yl[3-(4-chloro-3,5-difluorophenyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]methanone
10	15.2[b]	0.567[b]	Azetidin-1-yl[3-(4-chloro-3-fluorophenyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]methanone
11	405	9.64	3-(4-Chloro-3-fluorophenyl)-*N,N*-dimethyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
12	99.4	1.52	Azetidin-1-yl[3-(4-chloro-2,5-difluorophenyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]methanone, trifluoroacetate salt
13	944	6.64[b]	3-(4-Chlorophenyl)-*N*-propyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide

14	822	4.38	3-Cyclopentyl-*N*-(1-methyl-1*H*-pyrazol-3-yl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
15	1730	6.90	*N*-Cyclopropyl-3-(tetrahydro-2*H*-pyran-4-yl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
16	196	5.50	Azetidin-1-yl[3-(4-chlorophenyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]methanone
17	8510	>30.0	3-(4-Chloro-3-fluorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
18	48.7	2.14	Azetidin-1-yl[3-(3-fluoro-4-methylphenyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]methanone
19	281	5.28	(3-Fluoroazetidin-1-yl)[3-(3-fluoro-4-methylphenyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]methanone
20	13.8	0.262[b]	3-(4-Cyano-3,5-difluorophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
21	42.6	0.316	[3-(4-Chloro-3-fluorophenyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl](3-fluoroazetidin-1-yl)methanone
22	273	5.59	Azetidin-1-yl[3-(4-chloro-2-fluorophenyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]methanone
23	632	>30.0	3-(4-Chloro-2-fluorophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
24	211	>24.1	3-(4-Chlorophenyl)-*N*-(1-methyl-1*H*-pyrazol-3-yl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
25	910	5.84	[3-(4-Chloro-2-fluorophenyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl](3-fluoroazetidin-1-yl)methanone
26	319	>17.9	3-(4-Chloro-2-methylphenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
27	12.2[b]	0.511[b]	*N*-Cyclopropyl-3-(3,4-dichlorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
28	114	8.23	*N*-Cyclopropyl-3-(4-fluoro-3-methylphenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
29	225	>28.0[b]	*N*-Cyclopropyl-3-(4-methylphenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide

30	5.77	0.333	*N*-Cyclopropyl-3-(3,4,5-trifluorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide, trifluoroacetate salt
31	87.5	2.55	3-(3-Cyano-4-fluorophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
32	15.7	0.886	3-(3-Chloro-4-fluorophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
33	15.9	1.23[b]	3-(3-Chloro-4-methylphenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
34	399	10.2	Azetidin-1-yl[3-(4-chloro-2-methylphenyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]methanone
35	1130	8.28	[3-(4-Chloro-2-methylphenyl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl](3-fluoroazetidin-1-yl)methanone
36	5.65	0.255	3-(4-Chloro-3,5-difluorophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
37	409	10.7	3-(5-Chloropyridin-3-yl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
38	466	6.67	Azetidin-1-yl[3-(5-chloropyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridin-2-yl]methanone
39	363	10.2	3-(6-Cyanopyridin-3-yl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
40	1710	15.2	3-(5-Cyano-2-fluorophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
41	100	1.17	3-(4-Chloro-2,5-difluorophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
42	276[b]	>22.4[b]	3-(4-Cyanophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
43	927	>26.6	*N*-Cyclopropyl-3-(2,4-difluorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
44	1660	>29.0	*N*-Cyclopropyl-3-(5-fluoro-2-methylphenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
45	205	14.8	*N*-Cyclopropyl-3-(3-fluoro-4-methoxyphenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
46	329	13.8	*N*-Cyclopropyl-3-(3-methoxyphenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide

47	1260	6.39	*N*-Cyclopropyl-3-(2,3-dihydro-1*H*-inden-2-yl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
48	88.9	4.82	*N*-Cyclopropyl-3-(3,5-difluorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
49	629	12.3	3-(3-Chloro-4-methoxyphenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
50	339	>30.0	*N*-Cyclopropyl-3-(3-methoxy-4-methylphenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
51	207	13.2	*N*-Cyclopropyl-3-(4-methoxy-3-methylphenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
52	271	25.8	*N*-Cyclopropyl-3-(3,4-dimethylphenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
53	287	3.40	3-(3-Cyanophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
54	329	19.2	3-(5-Chloro-2-methylphenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
55	304	>23.7	*N*-Cyclopropyl-3-(4-fluoro-3-methoxyphenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
56	167	4.85	3-(3-Cyano-4-methylphenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
57	1160	>19.7	*N*-Cyclopropyl-3-phenyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
58	506	>30.0	*N*-Cyclopropyl-3-(4-methoxyphenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
59	1020	>30.0	*N*-Cyclopropyl-3-(2,4-dimethylphenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
60	1200	>30.0	*N*-Cyclopropyl-3-(4-fluoro-2-methylphenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
61	1580	>30.0	*N*-Cyclopropyl-3-(1,3-dihydro-2-benzofuran-5-yl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
62	34.9	1.49[b]	*N*-Cyclopropyl-3-(3,4-difluorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
63	68.0	2.55	*N*-Cyclopropyl-3-(3,5-dichlorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
64	206	15.7	*N*-Cyclopropyl-3-(2,3-dihydro-1*H*-inden-5-yl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide

65	188	10.9	*N*-Cyclopropyl-3-(3-fluorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
66	759	19.4	*N*-Cyclopropyl-3-(3,5-dimethoxyphenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
67	619	>30.0	*N*-Cyclopropyl-3-(2-fluoro-4-methylphenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
68	219	11.9	*N*-Cyclopropyl-3-(4-fluorophenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
69	70.9[b]	1.91[b]	3-(3-Chlorophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
70	421	14.9	*N*-Cyclopropyl-3-(3-methylphenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
71	155	6.34	3-(1,3-Benzothiazol-6-yl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
72	40.9	0.753	*N*-Cyclopropyl-3-[3-(methylsulfanyl)phenyl]-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
73	516	12.6	*N*-Cyclopropyl-3-(2-methyl-1,3-benzothiazol-6-yl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
74	58.8	1.99	3-(4-Chloro-3-methylphenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
75	389	3.98	*N*-Cyclopropyl-3-[3-(trifluoromethoxy)phenyl]-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
76	374	>18.8	*N*-Cyclopropyl-3-(3,5-dimethylphenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
77	1150	8.64	*N*-Cyclopropyl-3-[3-(trifluoromethyl)phenyl]-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
78	387	11.4	3-(3-Chloro-2-fluorophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide, trifluoroacetate salt
79	106	1.76	3-(5-Chloro-2-fluorophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide, trifluoroacetate salt
80	1470	>30.0	*N*-Cyclopropyl-3-(quinolin-6-yl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide, trifluoroacetate salt

81	8270	>30.0	3-(5-Chloropyridin-3-yl)-*N*-ethyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
82	6070	17.5	*N*-Cyclopropyl-3-[2-(trifluoromethyl)pyridin-4-yl]-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
83	13600	>29.3	*N*-Cyclopropyl-3-(5-methoxypyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
84	16600	>30.0	3-(2-Chloro-4-fluoro-5-methylphenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
85	7730	>30.0	*N*-Cyclopropyl-3-(6-methylpyridin-3-yl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
86	24500	>30.0	*N*-Cyclopropyl-3-(1-methyl-1*H*-indazol-6-yl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
87	2720	>30.0	*N*-Cyclopropyl-3-(3,4-dimethoxyphenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
88	3700	>30.0	3-(2-Chloro-4-methylphenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
89	3520	>30.0	*N*-Cyclopropyl-3-(4-methoxy-2-methylphenyl)-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
90	9230	>30.0	3-(2-Chloro-5-fluorophenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
91	9420	>30.0	3-(2-Chloro-5-methylphenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide
92	3110	>30.0	*N*-Cyclopropyl-3-[4-(trifluoromethyl)phenyl]-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide

a. Values represent the geometric mean of 2 - 6 determinations.

b. Value represents the geometric mean of ≥7 determinations.

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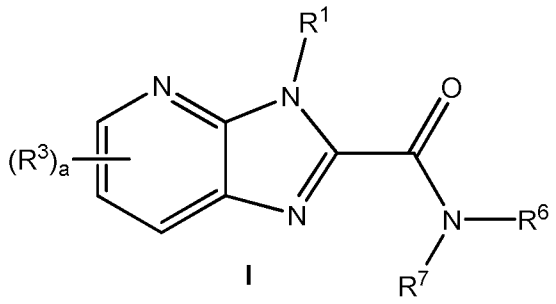
What is claimed:

1. A compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is represented by a substituent selected from the group consisting of (C_3-C_{10})cycloalkyl, a (4- to 10-membered)heterocycloalkyl, (C_6-C_{10})aryl, and a (5- to 10-membered) heteroaryl; wherein said (C_3-C_{10})cycloalkyl, (C_6-C_{10})aryl and (5- to 10-membered)heteroaryl are optionally substituted with $(R^2)_b$; and said (4- to 10-membered)heterocycloalkyl is optionally substituted at one to five carbon atoms with a substituent independently selected from the group consisting of halogen, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_1-C_6)alkylthio, -C(O)NR^4R^5, hydroxy, and cyano, and optionally substituted at each available nitrogen with (C_1-C_6)alkyl;

R^2 is represented by a substituent independently selected from the group consisting of halogen, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_1-C_6)alkylthio; -C(O)NR^4R^5, hydroxy, and cyano;

R^3, if present, at each occurrence is represented by a substituent independently selected from the group consisting of halogen, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_1-C_6)alkylthio, -C(O)NR^4R^5, hydroxy, and cyano;

R^4 and R^5 are each represented by a substituent independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, and (C_3-C_6)cycloalkyl;

R^6 and R^7 are each represented by a substituent independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, -$(CH_2)_m$-(C_3-C_{10})cycloalkyl, -$(CH_2)_m$-(4- to 10-membered)- heterocycloalkyl, -$(CH_2)_m$-(C_6-C_{10})aryl, and -$(CH_2)_m$-(5- to 10-membered)heteroaryl; wherein said (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, (C_6-C_{10})aryl, and (5- to 10-membered)heteroaryl are optionally substituted with one to five substituents independently selected from the group consisting of halogen, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_1-C_6)alkylthio, -C(O)NR^4R^5, hydroxy, and cyano; and said (4- to 10-membered)heterocycloalkyl is optionally substituted at one to five carbon

atoms with a substituent independently selected from the group consisting of halogen, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_1-C_6)alkylthio, -C(O)NR^4R^5, hydroxy, and cyano, and optionally substituted at each available nitrogen with (C_1-C_6)alkyl; or R^6 and R^7 taken together with the nitrogen to which they are attached form a (4- to 10-membered)heterocycloalkyl, wherein said (4- to 10-membered) heterocycloalkyl is optionally substituted at one to five carbon atoms with a substituent independently selected from the group consisting of halogen, (C_1-C_6)alkyl, halo(C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, (C_1-C_6)alkylthio, -C(O)NR^4R_5, hydroxy, and cyano;

a is represented by an integer selected from 0, 1, 2 or 3;

b is represented by an integer selected from 0, 1, 2, 3, 4 or 5; and

m is represented by an integer selected from 0, 1, 2, or 3.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein a is represented by the integer 0.

3. The compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^1 is represented by a (5 to 10-membered)heteroaryl, optionally substituted with one to three R^2.

4. The compound according to claim 3, or a pharmaceutically acceptable salt thereof, wherein R^1 is represented by pyridinyl; wherein said pyridinyl is optionally substituted with one to three R^2 independently selected from the group consisting of chloro, fluoro, methyl, methoxy, trifluoromethyl, trifluoromethoxy, cyano, and methylthio.

5. The compound according to claim 4, or a pharmaceutically acceptable salt thereof, wherein R^1 is represented by the group consisting of 5-chloropyridin-3-yl, 6-methylpyridin-3-yl, 5-methoxypyridin-3-yl, 2-trifluoromethylpyridin-4-yl, and 6-cyanopyridin-3-yl.

6 The compound according to claim 3, or a pharmaceutically acceptable salt thereof, wherein R^1 is represented by 1-methyl-1*H*-indazol-5-yl, quinolin-6-yl, 1,3-benzothiazol-6-yl, and 2-methyl-1,3-benzothiazol-6-yl.

7. The compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^1 is represented by (C_3-C_{10})cycloalkyl, optionally substituted with one to three R^2.

8. The compound according to claim 7, or a pharmaceutically acceptable salt thereof, wherein R^1 is represented by cyclopentyl; wherein said cyclopentyl is optionally substituted with one to three R^2 independently selected from the group consisting of chloro, fluoro, methyl, methoxy, trifluoromethyl, trifluoromethoxy, cyano, and methylthio.

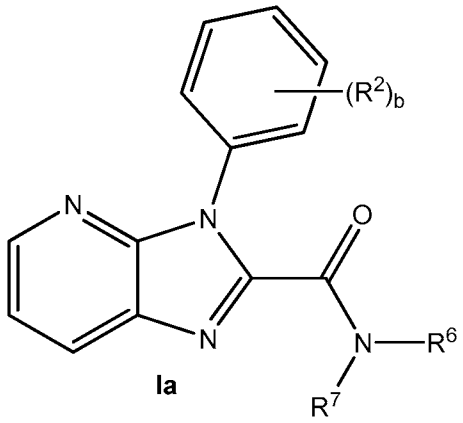
9. The compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^1 is represented by a (4 to 10-membered)heterocycloalkyl optionally substituted at one to three carbon atoms with one to three R^2 independently selected from the group consisting of halogen, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkylthio, $-C(O)NR^4R^5$, hydroxy, and cyano, and optionally substituted at each available nitrogen with a $(C_1\text{-}C_6)$alkyl.

10. The compound according to claim 9 or a pharmaceutically acceptable salt thereof, wherein R^1 is represented by tetrahydropyranyl; in which up to three carbon atoms of said tetrahydropyranyl is optionally substituted with one to three R^2 independently selected from the group consisting of chloro, fluoro, methyl, methoxy, trifluoromethyl, trifluoromethoxy, cyano, and methylthio.

11. The compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^1 is represented by $(C_6\text{-}C_{10})$aryl, optionally substituted with one to three R^2 independently selected from the group consisting of halogen, $(C_1\text{-}C_6)$alkyl, halo$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, halo$(C_1\text{-}C_6)$alkoxy, $(C_1\text{-}C_6)$alkylthio, $-C(O)NR^4R^5$, hydroxy, and cyano.

12. The compound of claim 11, wherein said $(C_6\text{-}C_{10})$aryl is selected from the group consisting of and 2,3-dihydro-1*H*-inden-5-yl and 1,3-dihydro-2-benzofuran-5-yl.

13. A compound of formula Ia:



Ia

or a pharmaceutically acceptable salt thereof, wherein:

b is represented by an integer selected from 0, 1, 2, or 3;

each R^2, if present, is represented by a substituent independently selected from the group consisting of fluoro, chloro, cyano, methyl, trifluoromethyl, methylthio, methoxy, and trifluoromethoxy;

R^6 and R^7 are each independently selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, $-(CH_2)_m$-$(C_3$-$C_{10})$cycloalkyl, and $-(CH_2)_m$-(5- to 10-membered)heteroaryl; wherein said $(C_1$-$C_6)$alkyl, $(C_3$-$C_{10})$cycloalkyl, and (5- to 10-membered)heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of halogen, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylthio, hydroxy, and cyano; or R^6 and R^7 taken together with the nitrogen to which they are attached form a (4 to 6-membered)heterocycloalkyl, in which up to three carbon atoms of said heterocycloalkyl are optionally substituted with a substituent independently selected from the group consisting of halogen, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, halo$(C_1$-$C_6)$alkoxy, $(C_1$-$C_6)$alkylthio, $-C(O)NR^4R^5$, hydroxy, and cyano,

wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and $(C_1$-$C_6)$alkyl;

and m is represented by an integer selected from 0, 1, or 2.

14. The compound according to claim 13, or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 taken together with the nitrogen to which they are attached form a (4- to 6-membered)heterocycloalkyl optionally substituted at one to three carbon atoms with halogen.

15. The compound of claim 14, wherein R^6 and R^7 taken together with the nitrogen to which they are attached form azetidinyl, optionally substituted with one to three halogen.

16. The compound according to claim 15, wherein said azetidinyl is selected from azetidin-1-yl or 3-fluoroazetidin-1-yl.

17. The compound according to claim 13, or a pharmaceutically acceptable salt thereof, wherein b is represented by an integer selected from 0, 1, 2, or 3; each R^2, if present, is represented by a substituent independently selected from the group consisting of fluoro, chloro, cyano, methyl, trifluoromethyl, methylthio, methoxy, and trifluoromethoxy; one of R^6 and R^7 is represented by hydrogen and the other represented by a substituent selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, $-(CH_2)_m$-$(C_3$-$C_6)$cycloalkyl, and $-(CH_2)_m$-(5- to 10-membered)heteroaryl, wherein said $(C_1$-$C_6)$alkyl, $(C_3$-$C_{10})$cycloalkyl, and (5- to 10-membered)heteroaryl are optionally substituted with one to three substituents independently selected from the group consisting of halogen, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$, $(C_1$-$C_6)$alkoxy,

halo(C_1-C_6)alkoxy, (C_1-C_6)alkylthio, hydroxy, and cyano; wherein R^4 and R^5 are each independently selected from the group consisting of hydrogen and (C_1-C_6)alkyl; and m is represented by an integer selected from 0, 1, or 2.

18. The compound according to claim 17, or a pharmaceutically acceptable salt thereof, wherein b is represented by an integer selected from 0, 1, 2, or 3; and each R^2, if present, is represented by a substituent independently selected from the group consisting of chloro, fluoro, methyl, and cyano; and one of R^6 and R^7 is represented by hydrogen and the other is represented by (C_1-C_6)alkyl.

19. The compound according to claim 18, or a pharmaceutically acceptable salt thereof, wherein one of R^6 and R^7 is represented by hydrogen and the other is represented by the group consisting of ethyl or propyl.

20. The compound according to claim 13, or a pharmaceutically acceptable salt thereof, wherein b is represented by an integer selected from 0, 1, 2, or 3; and each R^2, if present, is represented by a substituent independently selected from the group consisting of chloro, fluoro, methyl, and cyano; and one of R^6 and R^7 is represented by hydrogen and the other is represented by -$(CH_2)_m$-(C_3-C_6)cycloalkyl.

21. The compound according to claim 20, or a pharmaceutically acceptable salt thereof, wherein one of R^6 and R^7 is represented by hydrogen and the other is represented by cyclopropyl.

22. The compound according to claim 13, or a pharmaceutically acceptable salt thereof, wherein b is represented by an integer selected from 0, 1, 2, or 3; and each R^2, if present, is represented by a substituent independently selected from the group consisting of chloro, fluoro, methyl, and cyano; and one of R^6 and R^7 is represented by hydrogen and the other is represented by -$(CH_2)_m$-(5 -to 10-membered)heteroaryl optionally substituted by a (C_1-C_6)alkyl.

23. The compound according to claim 22, or a pharmaceutically acceptable salt thereof, wherein R^6 is represented by pyrazolyl optionally substituted by methyl.

24. The compound according to claim 23, or a pharmaceutically acceptable salt thereof, wherein one of R^6 and R^7 is represented by hydrogen and the other is represented by *N*-1-methyl-1H-pyrazol-3-yl.

25. A method of treating a patient suffering from a disease or condition mediated by the PDE4B isoform, comprising administering to said patient in need of said treatment a

therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

26. The method of claim 25wherein said disease is selected from the group consisting of schizophrenia, depression, anxiety, Alzheimer's disease, Parkinson's disease, multiple sclerosis, chronic obstructive pulmonary disease, inflammation, stroke, asthma, cerebral vascular disease, and allergic conjunctivitis.

27. A pharmaceutical composition comprising a compound according to any of claims 1-24, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

28. Use of a compound as defined according to any of claims 1-24, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of schizophrenia, depression, anxiety, Alzheimer's disease, Parkinson's disease, multiple sclerosis, chronic obstructive pulmonary disease, inflammation, stroke, asthma, cerebral vascular disease, and allergic conjunctivitis.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/058840

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437 A61K31/444 A61P25/16 A61P25/18
A61P25/22 A61P25/24 A61P25/28 A61P37/08
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ISMET DORANGE ET AL: "Discovery of novel pyrrolopyridazine scaffolds as transient receptor potential vanilloid (TRPV1) antagonists", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 22, no. 22, 1 November 2012 (2012-11-01), pages 6888-6895, XP055107781, ISSN: 0960-894X, DOI: 10.1016/j.bmcl.2012.09.059	1,2,11, 13
A	table 2; compound 13 First two paragraphs	3-10,12, 14-28

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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
17 March 2014	25/03/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Sarakinos, Georgios

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/058840

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 08 295667 A (TAKEDA CHEM IND LTD) 12 November 1996 (1996-11-12) The two products synthesized in paragraph [0139]: first product with RN 185332-11-0 and second product with RN 185332-12-1 claim 1 paragraph [0127] paragraph [0129] -----	1-28
X	WO 2008/033739 A2 (NEUROGEN CORP [US]; CHANDRASEKHAR JAYARAMAN [US]; GUO QIN [US]; IHLE D) 20 March 2008 (2008-03-20) claims 1, 23, 29-32 -----	1-28
A	WO 2006/050976 A1 (SANOL ARZNEI SCHWARZ GMBH [DE]; GMEINER PETER [DE]; SCHLOTTER KARIN [D) 18 May 2006 (2006-05-18) the whole document -----	1-28

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2014/058840

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 08295667 A	12-11-1996	---	
WO 2008033739 A2	20-03-2008	NONE	
WO 2006050976 A1	18-05-2006	AU 2005303904 A1	18-05-2006
		BR PI0517846 A	21-10-2008
		CA 2575668 A1	18-05-2006
		CN 101056878 A	17-10-2007
		DE 102004054634 A1	18-05-2006
		EA 200700909 A1	28-12-2007
		EP 1771448 A1	11-04-2007
		JP 2008519797 A	12-06-2008
		KR 20070083843 A	24-08-2007
		US 2007299091 A1	27-12-2007
		WO 2006050976 A1	18-05-2006
		ZA 200700252 A	27-05-2009

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代理人 安琪 张晓威
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A61K 31/444(2006.01)
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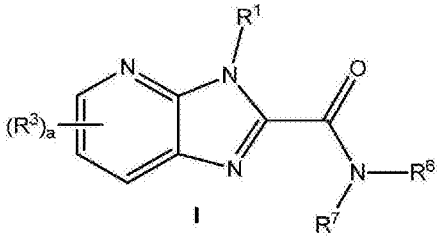
A61P 25/18(2006.01)
A61P 25/22(2006.01)
A61P 25/24(2006.01)
A61P 25/28(2006.01)
A61P 37/08(2006.01)

权利要求书4页 说明书58页

(54)发明名称

作为PDE4亚型抑制剂用于治疗CNS和其他病症的氮杂苯并咪唑化合物

(57)摘要

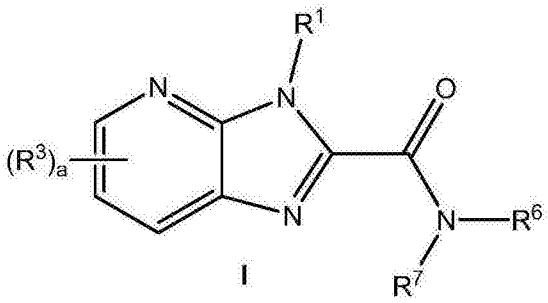


I

本发明涉及式I的化合物或其药学上可接受的盐，其中取代基如本文中所定义。所述式I的化合物用作PDE4抑制剂用于治疗CNS和其他病症。

CN 105121439 A

1. 式 I 的化合物或其药学上可接受的盐，



I

其中：

R^1由选自以下的取代基表示：(C_3-C_{10}) 环烷基、(4 至 10 元) 杂环烷基、(C_6-C_{10}) 芳基和 (5 至 10 元) 杂芳基；其中所述 (C_3-C_{10}) 环烷基、(C_6-C_{10}) 芳基和 (5 至 10 元) 杂芳基任选地被 $(R^2)_b$取代；并且所述 (4 至 10 元) 杂环烷基任选地在 1 至 5 个碳原子处被独立地选自以下的取代基取代：卤素、(C_1-C_6) 烷基、卤代 (C_1-C_6) 烷基、(C_1-C_6) 烷氧基、卤代 (C_1-C_6) 烷氧基、(C_1-C_6) 烷硫基、-C(O)NR^4R^5、羟基和氰基，并且任选地在每一可用的氮处被 (C_1-C_6) 烷基取代；

R^2由独立地选自以下的取代基表示：卤素、(C_1-C_6) 烷基、卤代 (C_1-C_6) 烷基、(C_1-C_6) 烷氧基、卤代 (C_1-C_6) 烷氧基、(C_1-C_6) 烷硫基；-C(O)NR^4R^5、羟基和氰基；

R^3若存在，则在每次出现时由独立地选自以下的取代基表示：卤素、(C_1-C_6) 烷基、卤代 (C_1-C_6) 烷基、(C_1-C_6) 烷氧基、卤代 (C_1-C_6) 烷氧基、(C_1-C_6) 烷硫基、-C(O)NR^4R^5、羟基和氰基；

R^4和 R^5各自由独立地选自以下的取代基表示：氢、(C_1-C_6) 烷基和 (C_3-C_6) 环烷基；

R^6和 R^7各自由独立地选自以下的取代基表示：氢、(C_1-C_6) 烷基、-$(CH_2)_m$-(C_3-C_{10}) 环烷基、-$(CH_2)_m$-(4 至 10 元) 杂环烷基、-$(CH_2)_m$-(C_6-C_{10}) 芳基和 -$(CH_2)_m$-(5 至 10 元) 杂芳基；其中所述 (C_1-C_6) 烷基、(C_3-C_{10}) 环烷基、(C_6-C_{10}) 芳基和 (5 至 10 元) 杂芳基任选地被 1 至 5 个独立地选自以下的取代基取代：卤素、(C_1-C_6) 烷基、卤代 (C_1-C_6) 烷基、(C_1-C_6) 烷氧基、卤代 (C_1-C_6) 烷氧基、(C_1-C_6) 烷硫基、-C(O)NR^4R^5、羟基和氰基；并且所述 (4 至 10 元) 杂环烷基任选地在 1 至 5 个碳原子处被独立地选自以下的取代基取代：卤素、(C_1-C_6) 烷基、卤代 (C_1-C_6) 烷基、(C_1-C_6) 烷氧基、卤代 (C_1-C_6) 烷氧基、(C_1-C_6) 烷硫基、-C(O)NR^4R^5、羟基和氰基，并且任选地在每一可用的氮处被 (C_1-C_6) 烷基取代；或者 R^6和 R^7与其所连接的氮一起形成 (4 至 10 元) 杂环烷基，其中所述 (4 至 10 元) 杂环烷基任选地在 1 至 5 个碳原子处被独立地选自以下的取代基取代：卤素、(C_1-C_6) 烷基、卤代 (C_1-C_6) 烷基、(C_1-C_6) 烷氧基、卤代 (C_1-C_6) 烷氧基、(C_1-C_6) 烷硫基、-C(O)NR^4R^5、羟基和氰基；

a 由选自 0、1、2 或 3 的整数表示；

b 由选自 0、1、2、3、4 或 5 的整数表示；且

m 由选自 0、1、2 或 3 的整数表示。

2. 权利要求 1 的化合物或其药学上可接受的盐，其中 a 由整数 0 表示。

3. 权利要求 1 或 2 的化合物或其药学上可接受的盐，其中 R^1由任选地被 1-3 个 R^2取代的 (5 至 10 元) 杂芳基表示。

4. 权利要求 3 的化合物或其药学上可接受的盐，其中 R^1由吡啶基表示；其中所述吡啶

基任选地被 1-3 个独立地选自以下的 R^2 取代 :氯、氟、甲基、甲氧基、三氟甲基、三氟甲氧基、氰基和甲硫基。

5. 权利要求 4 的化合物或其药学上可接受的盐,其中 R^1 由 5- 氯吡啶 -3- 基、6- 甲基吡啶 -3- 基、5- 甲氧基吡啶 -3- 基、2- 三氟甲基吡啶 -4- 基和 6- 氰基吡啶 -3- 基表示。

6. 权利要求 3 的化合物或其药学上可接受的盐,其中 R^1 由 1- 甲基 -1H- 吲唑 -5- 基、喹啉 -6- 基、1,3- 苯并噻唑 -6- 基和 2- 甲基 -1,3- 苯并噻唑 -6- 基表示。

7. 权利要求 1 或 2 的化合物或其药学上可接受的盐,其中 R^1 由任选地被 1-3 个 R^2 取代的 (C_3-C_{10}) 环烷基表示。

8. 权利要求 7 的化合物或其药学上可接受的盐,其中 R^1 由环戊基表示 ;其中所述环戊基任选地被 1-3 个独立地选自以下的 R^2 取代 :氯、氟、甲基、甲氧基、三氟甲基、三氟甲氧基、氰基和甲硫基。

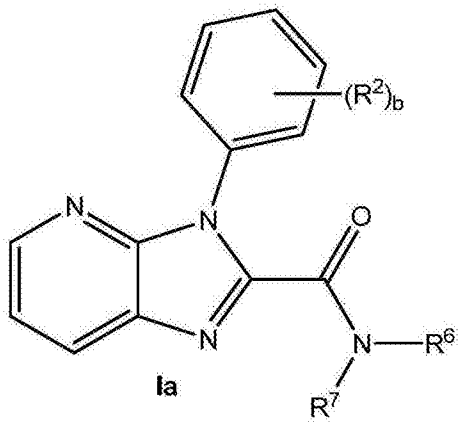
9. 权利要求 1 或 2 的化合物或其药学上可接受的盐,其中 R^1 由 (4 至 10 元) 杂环烷基表示,所述 (4 至 10 元) 杂环烷基任选地在 1 至 3 个碳原子处被 1 至 3 个独立地选自以下的 R^2 取代 :卤素、(C_1-C_6) 烷基、卤代 (C_1-C_6) 烷基、(C_1-C_6) 烷氧基、卤代 (C_1-C_6) 烷氧基、(C_1-C_6) 烷硫基、$-C(O)NR^4R^5$、羟基和氰基,并且任选地在每一可用的氮处被 (C_1-C_6) 烷基取代。

10. 权利要求 9 的化合物或其药学上可接受的盐,其中 R^1 由四氢吡喃基表示 ;其中所述四氢吡喃基的至多 3 个碳原子任选地被 1 至 3 个独立地选自以下的 R^2 取代 :氯、氟、甲基、甲氧基、三氟甲基、三氟甲氧基、氰基和甲硫基。

11. 权利要求 1 或 2 的化合物或其药学上可接受的盐,其中 R^1 由 (C_6-C_{10}) 芳基表示,所述 (C_6-C_{10}) 芳基任选地被 1 至 3 个独立地选自以下的 R^2 取代 :卤素、(C_1-C_6) 烷基、卤代 (C_1-C_6) 烷基、(C_1-C_6) 烷氧基、卤代 (C_1-C_6) 烷氧基、(C_1-C_6) 烷硫基、$-C(O)NR^4R^5$、羟基和氰基。

12. 权利要求 11 的化合物,其中所述 (C_6-C_{10}) 芳基选自 2,3- 二氢 -1H- 茚 -5- 基和 1,3- 二氢 -2- 苯并呋喃 -5- 基。

13. 式 Ia 的化合物或其药学上可接受的盐,



Ia

其中 :

b 由选自 0、1、2 或 3 的整数表示 ;

每一 R^2 若存在,则由独立地选自以下的取代基表示 :氟、氯、氰基、甲基、三氟甲基、甲硫基、甲氧基和三氟甲氧基 ;

R^6 和 R^7 各自独立地选自 :氢、(C_1-C_6) 烷基、$-(CH_2)_m-(C_3-C_{10})$ 环烷基和 $-(CH_2)_m-$(5 至 10 元) 杂芳基 ;其中所述 (C_1-C_6) 烷基、(C_3-C_{10}) 环烷基和 (5 至 10 元) 杂芳基任选地被 1 至 3

个独立地选自以下的取代基取代：卤素、(C_1-C_6) 烷基、卤代 (C_1-C_6) 烷基、(C_1-C_6) 烷氧基、卤代 (C_1-C_6) 烷氧基、(C_1-C_6) 烷硫基、羟基和氰基；或者 R^6 和 R^7 与其所连接的氮一起形成（4 至 6 元）杂环烷基，其中所述杂环烷基的至多 3 个碳原子任选地被独立地选自以下的取代基取代：卤素、(C_1-C_6) 烷基、卤代 (C_1-C_6) 烷基、(C_1-C_6) 烷氧基、卤代 (C_1-C_6) 烷氧基、(C_1-C_6) 烷硫基、$-C(O)NR^4R^5$、羟基和氰基，

其中 R^4 和 R^5 各自独立地选自氢和 (C_1-C_6) 烷基；

且 m 由选自 0、1 或 2 的整数表示。

14. 权利要求 13 的化合物或其药学上可接受的盐，其中 R^6 和 R^7 与其所连接的氮一起形成任选地在 1 至 3 个碳原子处被卤素取代的（4 至 6 元）杂环烷基。

15. 权利要求 14 的化合物，其中 R^6 和 R^7 与其所连接的氮一起形成任选地被 1 至 3 个卤素取代的氮杂环丁基。

16. 权利要求 15 的化合物，其中所述氮杂环丁基选自氮杂环丁 -1- 基或 3- 氟氮杂环丁 -1- 基。

17. 权利要求 13 的化合物或其药学上可接受的盐，其中 b 由选自 0、1、2 或 3 的整数表示；每一 R^2 若存在，则由独立地选自以下的取代基表示：氟、氯、氰基、甲基、三氟甲基、甲硫基、甲氧基和三氟甲氧基；R^6 和 R^7 之一由氢表示且另一者由选自以下的取代基表示：氢、(C_1-C_6) 烷基、$-(CH_2)_m-(C_3-C_{10})$ 环烷基和 $-(CH_2)_m-$（5 至 10 元）杂芳基，其中所述 (C_1-C_6) 烷基、(C_3-C_{10}) 环烷基和（5 至 10 元）杂芳基任选地被 1 至 3 个独立地选自以下的取代基取代：卤素、(C_1-C_6) 烷基、卤代 (C_1-C_6) 烷基、(C_1-C_6) 烷氧基、卤代 (C_1-C_6) 烷氧基、(C_1-C_6) 烷硫基、羟基和氰基；其中 R^4 和 R^5 各自独立地选自氢和 (C_1-C_6) 烷基；且 m 由选自 0、1 或 2 的整数表示。

18. 权利要求 17 的化合物或其药学上可接受的盐，其中 b 由选自 0、1、2 或 3 的整数表示；且每一 R^2 若存在，则由独立地选自以下的取代基表示：氯、氟、甲基和氰基；且 R^6 和 R^7 之一由氢表示且另一者由 (C_1-C_6) 烷基表示。

19. 权利要求 18 的化合物或其药学上可接受的盐，其中 R^6 和 R^7 之一由氢表示且另一者由乙基或丙基表示。

20. 权利要求 13 的化合物或其药学上可接受的盐，其中 b 由选自 0、1、2 或 3 的整数表示；且每一 R^2 若存在，则由独立地选自以下的取代基表示：氯、氟、甲基和氰基；且 R^6 和 R^7 之一由氢表示且另一者由 $-(CH_2)_m-(C_3-C_6)$ 环烷基表示。

21. 权利要求 20 的化合物或其药学上可接受的盐，其中 R^6 和 R^7 之一由氢表示且另一者由环丙基表示。

22. 权利要求 13 的化合物或其药学上可接受的盐，其中 b 由选自 0、1、2 或 3 的整数表示；且每一 R^2 若存在，则由独立地选自以下的取代基表示：氯、氟、甲基和氰基；且 R^6 和 R^7 之一由氢表示且另一者由任选地被 (C_1-C_6) 烷基取代的 $-(CH_2)_m-$（5 至 10 元）杂芳基表示。

23. 权利要求 22 的化合物或其药学上可接受的盐，其中 R^6 由任选地被甲基取代的吡唑基表示。

24. 权利要求 23 的化合物或其药学上可接受的盐，其中 R^6 和 R^7 之一由氢表示且另一者由 N-1- 甲基 -1H- 吡唑 -3- 基表示。

25. 治疗患有由 PDE4B 亚型介导的疾病或病况的患者的方法，其包括向需要所述治疗

的患者给药治疗有效量的式 I 的化合物或其药学上可接受的盐。

26. 权利要求 25 的方法，其中所述疾病选自：精神分裂症、抑郁症、焦虑症、阿尔茨海默病、帕金森氏病、多发性硬化、慢性阻塞性肺病、炎症、中风、哮喘、脑血管疾病和变应性结膜炎。

27. 药物组合物，其包含权利要求 1 至 24 中任一项的化合物或其药学上可接受的盐和药学上可接受的赋形剂。

28. 权利要求 1 至 24 中任一项所定义的化合物或其药学上可接受的盐在制备用于治疗以下的药物中的用途：精神分裂症、抑郁症、焦虑症、阿尔茨海默病、帕金森氏病、多发性硬化、慢性阻塞性肺病、炎症、中风、哮喘、脑血管疾病和变应性结膜炎。

作为PDE4亚型抑制剂用于治疗CNS和其他病症的氮杂苯并咪唑化合物

【技术领域】

[0001] 本发明涉及式I的氮杂苯并咪唑化合物（其为PDE4同功酶抑制剂，特别对PDE4B亚型具有结合亲和性）以及此类该等化合物在用于治疗某些中枢神经系统(CNS)、代谢、自身免疫及炎性疾病或病症的方法中的用途。

【背景技术】

[0002] 磷酸二酯酶(PDE)是一类参与核苷酸环腺苷酸(cAMP)水解成5'-单磷酸腺苷(AMP)的胞内酶。环核苷酸cAMP是由腺苷酸环化酶合成，且在各种细胞途径中用作第二信使。

[0003] cAMP用作调控体内的许多细胞内过程的第二信使。实例是在中枢神经系统的神经元中，其中cAMP依赖性激酶的活化及随后蛋白质的磷酸化参与突触传递的急性调控以及神经元分化及存活。环核苷酸信号传导的复杂性是由参与cAMP的合成及降解的酶的分子多样性指示。存在至少10个腺苷酸环化酶家族及11个磷酸二酯酶家族。此外，已知不同类型的神经元表达这些类别中的每一者的多种同功酶，且给定神经元内的不同同功酶的功能的划分及特异性存在良好证据。

[0004] 调控环核苷酸信号传导的主要机制是经由磷酸二酯酶催化的环核苷酸分解代谢。11个已知PDE家族是由21个不同基因编码；每一基因通常产生多个进一步促使同功酶多样性的剪接变体。基于环核苷酸基质特异性、调控机制及对抑制剂的敏感性在功能上区分PDE家族。此外，PDE在整个有机体（包括中枢神经系统）中表达不同。由于这些的不同酶活性及定位，不同PDE的同功酶可起到不同生理功能。此外，可选择性抑制不同PDE同功酶的化合物可提供特定治疗效应、较少副作用或二者(Deninno,M.,Future Directions in Phosphodiesterase Drug Discovery.Bioorganic and Medicinal Chemistry Letters 2012,22,6794-6800)。

[0005] 本发明是涉及对4个PDE家族（即，PDE4A、PDE4B、PDE4C及PDE4D）具有结合亲和性，特别对PDE4B亚型具有结合亲和性的化合物。除对PDE4B亚型具有亲和性外，本发明的化合物亦对PDE4A及PDE4C亚型具有亲和性。

[0006] PDE4同功酶的特征在于第二信使3',5'-环腺苷酸(cAMP)的选择性高亲和性水解降解以及对由Rolipram™(Schering AG)的抑制的敏感性；已在多种疾病模型中证明由该抑制产生的有益药理效应。近年来已发现多种其它PDE4抑制剂。举例而言，由Forest Pharmaceuticals公司销售的罗氟司特(Daliresp®)经批准用于严重慢性阻塞性肺病(COPD)以减少发作次数或减轻COPD症状的恶化（加剧）。阿瑞司特(Apremilast)(Celgene公司）是处于III期研发中且临床试验已证明阿瑞司特可有效治疗银屑病(Papp,K.等人，Efficacy of apremilast in the treatment of moderate to severe psoriasis:a randomized controlled trial.Lancet 2012;380(9843):738-46)。

[0007] 尽管已证明PDE4抑制剂的有益药理活性，但这些治疗的常见副作用为诱导胃肠副作用，例如恶心、呕吐及腹泻，目前据信其与PDE4D亚型的抑制相关。试图研发与PDE4D亚型相比对PDE4B亚型具有亲和性的化合物（参见：Donnell,A.F. 等人，Identification of pyridazino[4,5-b]indolizines as selective PDE4B inhibitors. Bioorganic&Medicinal Chemistry Letters 2010;20:2163-7；及 Naganuma,K. 等人，Discovery of selective PDE4B inhibitors.Bioorganic&Medicinal Chemistry Letters 2009;19:3174-6)。然而，仍需要研发PDE4抑制剂，特别是那些对PDE4B亚型具有亲和性者。具体而言，仍需要研发如下化合物：其与PDE4D亚型相比对PDE4B亚型具有增强的结合亲和性且用于治疗各种中枢神经系统(CNS)疾病及病症。本发明的选择化合物的发现解决了此持续需要，并且提供了用于治疗各种中枢神经系统(CNS)疾病及病症以及代谢、自身免疫及炎性疾病或病症的其它疗法。此类疾病及病症包括但不限于神经变性病症或精神病病症，包括精神病、认知受损、精神分裂症、焦虑症、抑郁症（例如，重度抑郁症）、痴呆、阿尔茨海默病、亨廷顿氏病、多发性硬化、肌营养不良症、镰状细胞疾病及糖尿病。

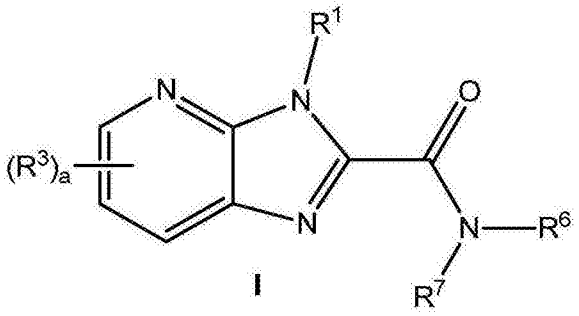
[0008] 利用本发明的PDE4B抑制剂的治疗亦可引起据信与PDE4D亚型的抑制相关的胃肠副作用（例如，恶心、呕吐及腹泻）的减少(Robichaud,A. 等人，Deletion of Phosphodiesterase 4D in Mice Shortens α 2-Adrenoreceptor-Mediated Anesthesia,A Behavioral Correlate of Emesis.Journal of Clinical Investigation 2002,第110卷，1045-1052)。

[0009] 除对PDE4B亚型具有亲和性的化合物的研发外，仍需要研发对PDE4A及PDE4C亚型具有亲和性的化合物。对PDE4A及PDE4C亚型具有亲和性的本发明的选择化合物的发现亦可用于治疗各种中枢神经系统(CNS)疾病及病症以及治疗各种代谢、自身免疫及炎性疾病或病症。

[0010] 【发明概述】

[0011] 本发明涉及式I的化合物或其药学上可接受的盐，

[0012]



I

[0013] 其中：

[0014] R^1由选自以下的取代基表示：(C_3-C_{10})环烷基、(4至10元)杂环烷基、(C_6-C_{10})芳基和(5至10元)杂芳基；其中所述(C_3-C_{10})环烷基、(C_6-C_{10})芳基和(5至10元)杂芳基任选地被$(R^2)_b$取代；并且所述(4至10元)杂环烷基任选地在1至5个碳原子处被独立地选自以下的取代基取代：卤素、(C_1-C_6)烷基、卤代(C_1-C_6)烷基、(C_1-C_6)烷氧基、卤代(C_1-C_6)烷氧基、(C_1-C_6)烷硫基、-C(O)NR^4R^5、羟基和氰基，并且任选地在每一可用的氮处被(C_1-C_6)烷基取代；

[0015] R^2由独立地选自以下的取代基表示：卤素、(C_1-C_6)烷基、卤代(C_1-C_6)烷基、(C_1-C_6)烷氧基、卤代(C_1-C_6)烷氧基、(C_1-C_6)烷硫基；$-C(O)NR^4R^5$、羟基和氰基；

[0016] R^3若存在，则在每次出现时由独立地选自以下的取代基表示：卤素、(C_1-C_6)烷基、卤代(C_1-C_6)烷基、(C_1-C_6)烷氧基、卤代(C_1-C_6)烷氧基、(C_1-C_6)烷硫基、$-C(O)NR^4R^5$、羟基和氰基；

[0017] R^4和R^5各自由独立地选自以下的取代基表示：氢、(C_1-C_6)烷基和(C_3-C_6)环烷基；

[0018] R^6和R^7各自由独立地选自以下的取代基表示：氢、(C_1-C_6)烷基、$-(CH_2)_m-(C_3-C_{10})$环烷基、$-(CH_2)_m-$(4至10元)杂环烷基、$-(CH_2)_m-(C_6-C_{10})$芳基和$-(CH_2)_m-$(5至10元)杂芳基；其中所述(C_1-C_6)烷基、(C_3-C_{10})环烷基、(C_6-C_{10})芳基和(5至10元)杂芳基任选地被1至5个独立地选自以下的取代基取代：卤素、(C_1-C_6)烷基、卤代(C_1-C_6)烷基、(C_1-C_6)烷氧基、卤代(C_1-C_6)烷氧基、(C_1-C_6)烷硫基、$-C(O)NR^4R^5$、羟基和氰基；并且所述(4至10元)杂环烷基任选地在1至5个碳原子处被独立地选自以下的取代基取代：卤素、(C_1-C_6)烷基、卤代(C_1-C_6)烷基、(C_1-C_6)烷氧基、卤代(C_1-C_6)烷氧基、(C_1-C_6)烷硫基、$-C(O)NR^4R^5$、羟基和氰基，并且任选地在每一可用的氮处被(C_1-C_6)烷基取代；或者R^6和R^7与其所连接的氮一起形成(4至10元)杂环烷基，其中所述(4至10元)杂环烷基任选地在1至5个碳原子处被独立地选自以下的取代基取代：卤素、(C_1-C_6)烷基、卤代(C_1-C_6)烷基、(C_1-C_6)烷氧基、卤代(C_1-C_6)烷氧基、(C_1-C_6)烷硫基、$-C(O)NR^4R^5$、羟基和氰基；

[0019] a由选自0、1、2或3的整数表示；

[0020] b由选自0、1、2、3、4或5的整数表示；且

[0021] m由选自0、1、2或3的整数表示。

[0022] 本发明的化合物包括如本文所述的实施例1-92或其药学上可接受的盐。

[0023] 式I的化合物是PDE4B亚型的抑制剂。

[0024] 另外，式I的化合物是PDE4A及PDE4C亚型的抑制剂。

[0025] 式I的化合物可用于治疗或预防神经变性或精神病病症，包括但不限于认知功能障碍、精神病、精神分裂症、抑郁症、痴呆、焦虑症、双相情感障碍、帕金森氏病、阿尔茨海默病(AD)、亨廷顿氏病(HD)、多发性硬化(MS)和神经炎症病症，以及哺乳动物中与PDE4B亚型活性相关的许多其它疾病或病症。其它疾病及病症包括但不限于疼痛、癌症、免疫缺陷疾病(例如，银屑病及关节炎)、炎症、哮喘、慢性阻塞性肺病(COPD)、糖尿病、肌营养不良症、镰状细胞疾病、心血管疾病、脑血管疾病、中风及变应性结膜炎。

[0026] 本发明还涉及本发明的化合物或其药学上可接受的盐的在制备用于治疗或预防适于PDE4B基因家族(亦即，PDE4B酶)的调节的病况的药物中的用途，所述基因家族由多种剪接变体(例如PDE4B1、B2、B3、PDE4B4及B5蛋白质)组成。病况的实例包括但不限于认知功能障碍、精神病、精神分裂症、抑郁症、痴呆、焦虑症、双相情感障碍、帕金森氏病、阿尔茨海默病(AD)、亨廷顿氏病(HD)、多发性硬化(MS)及神经炎症病症，以及哺乳动物中与PDE4B亚型活性相关的许多其它疾病或病症，例如但不限于疼痛、癌症、免疫缺陷疾病(例如，银屑病及关节炎)、炎症、哮喘、慢性阻塞性肺病(COPD)、糖尿病、肌营养不良症、镰状细胞疾病、心血管疾病、脑血管疾病、中风及变应性结膜炎。

[0027] 本发明还涉及包含一种或多种本发明的化合物和至少一种赋形剂的混合物的药学上可接受的制剂，其被配制成药物剂型。此类剂型的实例包括片剂、胶囊剂、注射用溶液

剂 / 混悬剂、用于吸入的气雾剂以及用于口服的溶液剂和混悬剂。

[0028] 【发明详述】

[0029] 本文中的标题仅用于促进读者的理解。其不应解释为以任何方式限制本发明或权利要求的范围。

[0030] 定义及示例

[0031] 如本申请全文（包括权利要求书）所用，除非另外明确指明，否则以下术语具有下文所定义的含义。复数及单数应处理为可互换，而非指示数字：

[0032] 如本文所用，“(C_1-C_6) 烷基”指含有 1 至 6 个碳原子的支链或直链烷基，例如但不限于甲基、乙基、正丙基、异丙基、正丁基、仲丁基、异丁基、叔丁基、正戊基、异戊基、新戊基及正己基。

[0033] 如本文所用，“卤代”或“卤素”指氯、氟、溴或碘原子。

[0034] 如本文所用，“卤代 (C_1-C_6) 烷基”指如上文所定义的 (C_1-C_6) 烷基，其中至少一个氢原子被如上文所定义的卤素替代。卤代 (C_1-C_6) 烷基的代表性实例包括但不限于氯甲基、2- 氟乙基、三氟甲基、五氟乙基及 2- 氯 -3- 氟戊基。

[0035] 如本文所用，“(C_1-C_6) 烷氧基”指经由氧原子连接到母体分子部分的如上文所定义的 (C_1-C_6) 烷基。(C_1-C_6) 烷氧基的代表性实例包括但不限于甲氧基、乙氧基、丙氧基、2- 丙氧基、丁氧基、叔丁氧基、戊氧基及己氧基。

[0036] 如本文所用，“卤代 (C_1-C_6) 烷氧基”指如上文所定义的 (C_1-C_6) 烷氧基，其中至少一个氢原子被如上文所定义的卤素替代。卤代 (C_1-C_6) 烷氧基的代表性实例包括但不限于氯甲氧基、2- 氟乙氧基、三氟甲氧基及五氟乙氧基。

[0037] 如本文所用，“硫代”意指 -S（硫）。

[0038] 如本文所用，“(C_1-C_6) 烷硫基”意指经由硫原子连接到母体分子部分的如本文中所定义的 (C_1-C_6) 烷基。(C_1-C_6) 烷硫基的代表性实例包括但不限于甲硫基、乙硫基、丙硫基及丁硫基。

[0039] 如本文所用，“(C_3-C_{10}) 环烷基”指饱和或部分饱和的单环、二环、桥接二环或三环烷基，其中环状框架具有 3 至 10 个碳。单环的实例包括环丙基、环丁基、环戊基、环己基、环庚基、环辛基、环壬基及环癸基。或者，环烷基可为二环，例如二环烷基。二环烷基可为稠合系统。例如二环 [1.1.0] 丁烷、二环 [2.1.0] 戊烷、二环 [2.2.0] 己烷、二环 [3.1.0] 己烷、二环 [3.2.0] 庚烷及二环 [3.3.0] 辛烷。术语“二环烷基”还包括桥接二环烷基系统，例如但不限于二环 [2.2.1] 庚烷及二环 [1.1.1] 戊烷。环烷基亦可为使单环稠合至芳基或杂芳基环的二环。在此情形下，具有这样的稠合环烷基作为取代基的基团与饱和或部分饱和环的碳原子键结。举例而言，环烷基部分可包括但不限于 2,3- 二氢 -1H- 茚 -2- 基。

[0040] 如本文所用，“杂环烷基”指通过从饱和或部分饱和的环结构去除氢原子获得的取代基，其中至少一个环原子为选自氧、氮或硫的杂原子。举例而言，如本文所用，术语“（4 至 6 元）杂环烷基”意指取代基含有总共 4 至 6 个环原子。“（4 至 10 元）杂环烷基”意指取代基含有总共 4 至 10 个环原子。杂环烷基可为具有多达总共 10 个成员的单环。或者，如上文所定义的杂环烷基可包含 2 或 3 个稠合在一起的环，其中至少一个此类环含有作为环原子的杂原子（亦即，氮、氧或硫）。在具有杂环烷基取代基的基团中，连接到所述基团的杂环烷基取代基的环原子可为至少一个杂原子，或其可为环碳原子，其中环碳原子可与至少

一个杂原子在同一环中，或其中环碳原子可与至少一个杂原子在不同环中。类似地，若杂环烷基取代基又被基团或取代基取代，则所述基团或取代基可与至少一个杂原子键结，或其可与环碳原子键结，其中环碳原子可与至少一个杂原子在同一环中，或其中环碳原子可与至少一个杂原子在不同环中。

[0041] 术语“杂环烷基”还包括稠合至 C_6-C_{10}芳族环或（5 至 10 元）杂芳族环的取代基，其中具有这样的稠合杂环烷基作为取代基的基团与杂环烷基的杂原子或杂环烷基的碳原子键结。当这样的稠合杂环烷基被一或多个取代基取代时，除非另有说明，否则所述一或多个取代基各自与杂环烷基的杂原子或杂环烷基的碳原子键结。稠合 C_6-C_{10}芳族环或（5 至 10 元）杂芳族环可任选地被卤素、(C_1-C_6) 烷基、(C_3-C_{10}) 环烷基、(C_1-C_6) 烷氧基或＝ 0 取代。杂环烷基取代基的实例包括但不限于四氢喹啉基、二氢苯并呋喃基等。其它杂环烷基环包括：氮杂环丁基、二氢呋喃基、四氢吡喃基、二氢噻吩基、吡咯烷基、四氢呋喃基、四氢噻吩基、哌啶基、哌嗪基、氮杂环庚烷 (azepane)、氮杂环辛烷 (azocane)、吗啉基、异铬酰基 (isochromyl)、四氢三嗪、四氢吡唑、二氢 -1H- 异吲哚、四氢噁唑基、四氢噁嗪基、硫吗啉基、四氢嘧啶基、八氢苯并呋喃基、八氢苯并咪唑基及八氢苯并噻唑基。

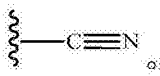
[0042] “(C_6-C_{10}) 芳基”指含有 6 至 10 个碳原子的芳族取代基，其包括一个环或两个稠合环，例如苯基或萘基。术语“芳基”还包括诸如稠合至 (C_4-C_6) 环烷基或 (C_4-C_{10}) 杂环烷基的苯基及萘基的取代基，其中具有这样的稠合芳基作为取代基的基团与芳基的芳族碳键结。当这样的芳基被一或多个取代基取代时，除非另有说明，否则所述一或多个取代基各自与稠合芳基的芳族碳键结。稠合 (C_3-C_6) 环烷基或 (C_4-C_{10}) 杂环烷基环可任选地被卤素、(C_1-C_6) 烷基、(C_3-C_{10}) 环烷基或＝ 0 取代。芳基的实例包括但不限于苯基、萘基、二氢茚基（例如，2,3- 二氢 -1H- 茚 -5- 基）、茚基及二氢苯并呋喃基（例如，1,3- 二氢 -2- 苯并呋喃 -5- 基）。

[0043] “（5 至 10 元）杂芳基”指具有 5 至 10 个环原子的芳族环，其中至少一个环原子为杂原子（亦即，氧、氮或硫），剩余的环原子独立地选自：碳、氧、氮及硫。杂芳基可为单环或 2 或 3 个稠合环。在具有杂芳基取代基的基团中，键结到所述基团的杂芳基取代基的环原子可为至少一个杂原子，或其可为环碳原子，其中环碳原子可与至少一个杂原子在同一环中，或其中环碳原子可与至少一个杂原子在不同环中。类似地，若杂芳基取代基又被基团或取代基取代，则所述基团或取代基可与至少一个杂原子键结，或其可与环碳原子键结，其中环碳原子可与至少一个杂原子在同一环中，或其中环碳原子可与至少一个杂原子在不同环中。

[0044] 术语“杂芳基”还包括诸如稠合至 (C_4-C_{10}) 环烷基或（4 至 10 元）杂环烷基的吡啶基及三唑基的取代基，其中具有这样的稠合杂芳基作为取代基的基团与杂芳基的芳族碳或杂芳基的杂原子键结。当这样的稠合杂芳基被一或多个取代基取代时，除非另有说明，否则所述一或多个取代基各自与杂芳基的芳族碳或杂芳基的杂原子键结。稠合 (C_4-C_{10}) 环烷基或（4 至 10 元）杂环烷基可任选地被卤素、(C_1-C_6) 烷基、(C_3-C_{10}) 环烷基或＝ 0 取代。杂芳基的实例包括但不限于：6 元环取代基，例如吡啶基、吡唑基、嘧啶基及哒嗪基；5 元杂芳基，例如三唑基、咪唑基、呋喃基、异噁唑基、异噻唑基、1,2,3-、1,2,4-、1,2,5- 或 1,3,4- 噁二唑基、噁唑基、噻吩基、噻唑基及吡唑基。二环杂芳基的代表性实例包括但不限于苯并咪唑基、苯并呋喃基、苯并噻吩基、苯并噁二唑基、苯并噻唑基（例如，1,3- 苯并噻唑 -6- 基及

2- 甲基 -1,3- 苯并噻唑 -6- 基）、苯并噻吩基、异苯并噻吩基、苯并异噁唑基、苯并噁唑基、1,4- 苯并噁嗪基、嘧啉基、呋喃并吡啶基、吲唑基、吲哚基、异喹啉基、萘啶基、嘌呤基、喹啉基、喹唑啉基、5,6,7,8- 四氢喹啉基、噻吩并吡啶基及三唑并吡啶基（例如，5,6,7,8- 四氢 [1,2,4] 三唑并 [1,5-a] 吡啶 -2- 基）。

[0045] 如本文所用，“羟基”意指 -OH 基团。

[0046] 如本文所用，“氰基”意指 -CN 基团，其还可绘示为：  。

[0047] 如本文所用，“任选地被取代”意指取代是任选的且因此包括未被取代的及被取代的原子及部分。“被取代的”原子或部分指示指定原子或部分上的任意氢可被选自所指示的取代基替代（至多且包括指定原子或部分上的每一氢原子被选自所指示的取代基替代），条件是不超过指定原子或部分的正常价，且取代产生稳定的化合物。举例而言，若甲基（亦即，CH_3）任选地被取代，则碳原子上的至多 3 个氢原子可被取代基替代。

[0048] 如本文所用，除非指明，否则取代基的连接点可来自取代基的任意适宜位置。举例而言，吡啶基可为 2- 吡啶基（或吡啶 -2- 基）、3- 吡啶基（或吡啶 -3- 基）或 4- 吡啶基（或吡啶 -4- 基）。

[0049] 当显示与取代基连接的键与连接环中的两个原子的键交叉时，则这样的取代基可与该环中可被取代的任意成环原子键合（亦即，与一或多个氢原子键合）。举例而言，如下式 Ia 中所示，R^2可与可被取代的任意成环原子键合（亦即，与一或多个氢原子键合）。

[0050] “治疗有效量”指将所治疗病症的一或多种症状减轻至一定程度的所给药化合物的量。

[0051] “患者”指温血动物，例如，猪、牛、鸡、马、豚鼠、小鼠、大鼠、沙鼠、猫、兔、狗、猴、猿及人类。

[0052] 除非另外指明，否则如本文所用“治疗”意指逆转、减轻、预防此术语所应用的病症或病况或此类病症或病况的一或多种症状或抑制其进展。除非另外指明，否则本文所用术语“治疗 (treatment)”指如上文刚刚定义的“治疗 (treating)”的处理动作。术语“治疗”还包括个体的辅助治疗及新辅助治疗。

[0053] “药学上可接受的”指示物质或组合物必须在化学上和 / 或毒理学上与制剂包含的其它成份和 / 或用其治疗的哺乳动物相容。

[0054] “亚型”意指同一蛋白质的若干不同形式中的任一者。

[0055] “同功酶”或“同工酶”意指氨基酸序列不同但催化相同化学反应的酶的紧密相关变体。

[0056] “异构体”意指如下文所定义的“立体异构体”及“几何异构体”。

[0057] “立体异构体”指具有一或多个可各自以 R 或 S 构型存在的手性中心的化合物。立体异构体包括所有非对映异构体、对映异构体和差向异构体形式以及外消旋体及其混合物。

[0058] “几何异构体”指可以顺式、反式、反位 (anti)、异侧 (entgegen,E) 及同侧 (zusammen,Z) 形式以及其混合物的形式存在的化合物。

[0059] 本说明书互换使用术语“取代基”和“基团 (radical 及 group)”。

[0060] 若取代基被描述为“独立地选自”某一群组，则取代基的每一实例彼此独立地选

择。因此，每一取代基可与其它取代基相同或不同。

[0061] 本文所用术语“式 I”及“式 Ia”在下文中可称作“本发明的化合物”。此类术语也被定义为包括式 I 及 Ia 化合物的所有形式，包括其水合物、溶剂合物、异构体、结晶及非结晶形式、同晶型体、多晶型物及代谢产物。举例而言，本发明的化合物或其药学上可接受盐可以非溶剂化及溶剂化形式存在。当溶剂或水紧密键结时，复合物会具有与湿度无关的定义明确的化学计量。然而，当溶剂或水键结较弱时，如在通道溶剂合物 (channel solvate) 及吸湿性化合物中，水 / 溶剂含量会取决于湿度及干燥条件。在这样的情形下，非化学计量会是标准。

[0062] 本发明的化合物可以包合物或其它复合物形式存在。本发明的范围内包括复合物，例如包合物、药物 - 宿主包合复合物（其中药物及宿主以化学计量量或非化学计量量存在）。还包括含有两种或更多种有机和 / 或无机组份的本发明的化合物的复合物，所述有机和 / 或无机组份可以化学计量量或非化学计量量存在。所得复合物可为离子化、部分离子化或未离子化的。关于此类复合物的综述，参见 J.Pharm.Sci.,64(8),1269-1288, Haleblian(1975 年 8 月）。

[0063] 本发明的化合物具有不对称碳原子。本发明的化合物的碳 - 碳键在本文中可使用实线(——)、实心楔形(▬)或虚线楔形(┈┈)绘示。使用实线绘示不对称碳原子的键意指指示包括该碳原子处的所有可能的立体异构体（例如，特定对映异构体、外消旋混合物等）。使用实心或虚线楔形绘示不对称碳原子的键意指指示存在所示立体异构体。在存在于外消旋化合物中时，实心及虚线楔形用于定义相对立体化学而非绝对立体化学。具有这样的指定相对立体化学的外消旋化合物用 (+/-) 标记。举例而言，除非另外指明，否则本发明的化合物意欲可以立体异构体形式存在，其包括顺式及反式异构体、旋光异构体（例如 R 及 S 对映异构体）、非对映异构体、几何异构体、旋转异构体、构象异构体、阻转异构体及其混合物（例如外消旋体及非对映异构体对）。本发明的化合物可呈现一种以上类型的异构现象。还包括酸加成盐或碱加成盐，其中抗衡离子具有旋光性（例如，D- 乳酸盐或 L- 赖氨酸）或外消旋性（例如，DL- 酒石酸盐或 DL- 精氨酸）。

[0064] 当任何外消旋体结晶时，可产生两种不同类型的晶体。第一类是上文提及的外消旋化合物（真实外消旋体），其中产生含有等摩尔量的两种对映异构体的一种均质形式的晶体。第二类是外消旋混合物或聚集物，其中产生等摩尔量的各自包含单一对映异构体的两种形式的晶体。

[0065] 本发明的化合物可以衍生自无机酸或有机酸的盐的形式使用。视特定化合物而定，化合物的盐由于盐的一或多种物理性质（例如在不同温度及湿度中的增强的药物稳定性或者在水或油中的期望溶解性）而有利。在一些情况下，化合物的盐也可帮助化合物的分离、纯化和 / 或再溶解。

[0066] 若意欲向患者给药盐（例如，与在体外环境下使用相反），则所述盐优选药学上可接受的。术语“药学上可接受的盐”指通过将本发明的化合物与酸或碱（酸的阴离子或碱的阳离子通常视为适于人类食用）结合而制备的盐。药学上可接受的盐由于其相对于母体化合物的较大水性溶解性而特别可用作本发明的方法的产品。

[0067] 本发明的化合物的适宜的药学上可接受酸加成盐（若可能）包括那些衍生自以下的盐：无机酸，例如但不限于盐酸、氢溴酸、氢氟酸、硼酸、氟硼酸、磷酸、偏磷酸、硝酸、碳酸、

磺酸及硫酸；及有机酸，例如乙酸、苯磺酸、苯甲酸、柠檬酸、乙磺酸、富马酸、葡糖酸、乙醇酸、羟乙磺酸 (isothionic acid)、乳酸、乳糖酸、马来酸、苹果酸、甲磺酸、三氟甲磺酸、琥珀酸、甲苯磺酸、酒石酸及三氟乙酸。适宜的有机酸通常包括但不限于脂族、环脂族、芳族、芳脂族、杂环、羧酸及磺酸类的有机酸。

[0068] 适宜的有机酸的具体实例包括但不限于乙酸、三氟乙酸、甲酸、丙酸、琥珀酸、乙醇酸、葡糖酸、二葡糖酸、乳酸、苹果酸、酒石酸、柠檬酸、抗坏血酸、葡糖醛酸、马来酸、富马酸、丙酮酸、天冬氨酸、谷氨酸、苯甲酸、邻氨基苯甲酸、硬脂酸、水杨酸、对羟基苯甲酸、苯乙酸、扁桃酸、恩波酸（双羟萘酸）、甲磺酸、乙磺酸、苯磺酸、泛酸、甲苯磺酸、2- 羟基乙磺酸、对氨基苯磺酸、环己基氨基磺酸盐、海藻酸、β - 羟基丁酸、半乳糖二酸、半乳糖醛酸、己二酸、海藻酸、丁酸、樟脑酸、樟脑磺酸、环戊烷丙酸、十二烷基硫酸、葡庚糖酸、甘油磷酸、庚酸、已酸、烟酸、2- 萘磺酸、草酸、棕榈酸、果胶酸、3- 苯基丙酸、苦味酸、新戊酸、硫氰酸及十一烷酸。

[0069] 此外，若本发明的化合物带有酸性部分，则其适宜的药学上可接受的盐因此可包括碱金属盐（例如钠盐或钾盐）；碱土金属盐（例如钙盐或镁盐）；及与适宜的有机配体形成的盐（例如季铵盐）。在另一实施例中，碱式盐是由形成无毒性盐的碱形成，包括铝盐、精氨酸盐、苄星青霉素 (benzathine) 盐、胆碱盐、二乙胺盐、二醇胺盐、甘氨酸盐、赖氨酸盐、葡甲胺盐、醇胺盐、氨丁三醇盐及锌盐。

[0070] 有机盐可由仲胺、叔胺或季胺盐（例如氨丁三醇、二乙胺、N,N'- 二苄基乙二胺、氯普罗卡因、胆碱、二乙醇胺、乙二胺、葡甲胺 (N- 甲基葡糖胺）及普罗卡因）形成。可使用诸如以下的物质使碱性含氮基团季铵化：低级烷基 (C_1-C_6) 卤化物（例如，甲基、乙基、丙基及丁基的氯化物、溴化物及碘化物）、硫酸二烷基酯（例如，硫酸二甲酯、硫酸二乙酯、硫酸二丁酯及硫酸二戊酯）、长链卤化物（例如，癸基、月桂基、肉豆蔻基及硬脂酰基的氯化物、溴化物及碘化物）、芳基烷基卤化物（例如，苄基及苯乙基的溴化物）等。

[0071] 在一个实施方案中，还可形成酸及碱的半盐，例如，半硫酸盐及半钙盐。

[0072] 本发明的某些化合物可以几何异构体形式存在。本发明的化合物可具有一或多个不对称中心，因此以两种或更多种立体异构体形式存在。本发明包括本发明的化合物的所有各立体异构体及几何异构体及其混合物。各对映异构体可通过手性分离或在合成中使用相关对映异构体获得。

[0073] 另外，本发明的化合物可以非溶剂化形式以及与药学上可接受的溶剂（例如水、乙醇等）的溶剂化形式存在。一般而言，出于本发明目的，溶剂化形式视为等同于非溶剂化形式。化合物还可以一或多种结晶态（亦即，多晶型物）存在或其可以无定型固体形式存在。权利要求书涵盖所有此类形式。

[0074] 本发明的化合物的所谓“前药”也在本发明的范围内。因此，本身可能具有较小药理活性或无药理活性的本发明的化合物的某些衍生物在给药至机体内或机体上时可通过（例如）水解裂解转化成具有期望活性的本发明的化合物。此类衍生物被称作“前药”。关于前药的使用的其它信息可参见“Pro-drugs as Novel Delivery Systems”，第 14 卷，ACS Symposium Series(T.Higuchi 及 W.Stella) 及“Bioreversible Carriers in Drug Design”，Pergamon Press,1987(E.B.Roche 编辑，American Pharmaceutical Association)。本发明的前药可（例如）通过用那些本领域技术人员已知的某些基团作为

“前基团 (pre-moieties)”来替代本发明的化合物中存在的适当的官能团来产生，例如如“Design of Prodrugs”，H.Bundgaard(Elsevier,1985) 中所述。

[0075] 本发明还涵盖含有保护基的本发明的化合物。本领域技术人员还会理解，本发明的化合物亦可利用某些保护基制备，所述保护基可用于纯化或保存且可在向患者给药之前脱除。官能团的保护及脱保护阐述于以下中：“Protective Groups in Organic Chemistry”，由 J.W.F.McOmie 编辑，Plenum Press(1973) 及“Protective Groups in Organic Synthesis”，第 3 版，T.W.Greene 及 P.G.M.Wuts,Wiley-Interscience(1999)。

[0076] 本发明还包括所有药学上可接受的同位素标记的化合物，其与那些在式 I 及 Ia 中所述的化合物相同，其中一或多个原子被具有相同原子数但原子质量或质量数不同于自然界中占主导地位的原子质量或质量数的原子替代。适合纳入本发明的化合物中的同位素的实例包括但不限于氢同位素（例如 ^{2}H、^{3}H）；碳同位素（例如 ^{11}C、^{13}C 及 ^{14}C）；氯同位素（例如 ^{36}Cl）；氟同位素（例如 ^{18}F）；碘同位素（例如 ^{123}I 及 ^{125}I）；氮同位素（例如 ^{13}N 及 ^{15}N）；氧同位素（例如 ^{15}O、^{17}O 及 ^{18}O）；磷同位素（例如 ^{32}P）；及硫同位素（例如 ^{35}S）。本发明的某些同位素标记的化合物（例如那些掺入放射性同位素的化合物）可用于药物和 / 或底物组织分布研究（例如分析）中。放射性同位素氚（亦即 ^{3}H）及碳 -14（亦即 ^{14}C）由于易于掺入且容易检测而特别用于此目的。使用较重同位素（例如氘，亦即 ^{2}H）的取代具有更强代谢稳定性，从而可提供某些治疗优势，例如，体内半衰期的增加或剂量需要量的减少，因此在一些情况下是优选的。使用正电子发射同位素（例如 ^{11}C、^{15}F、^{15}O 及 ^{13}N）进行取代可在正电子发射断层扫描 (PET) 研究中用于检验底物受体占有率。经同位素标记的本发明的化合物通常可通过那些本领域技术人员已知的常规技术来制备，或可通过与那些阐述于所附路线和 / 或实施例及制备例中的类似的方法使用适当的经同位素标记的试剂代替先前采用的非标记试剂来制备。本发明的药学上可接受的溶剂合物包括那些其中结晶溶剂可经同位素取代的，例如，D_2O、丙酮 -d_6 或 DMSO-d_6。式 I 及式 1a 的化合物以及下述实施例 1-92 中例示的化合物包括这些化合物的经同位素标记的形式，例如但不限于氘化及氚化同位素及上文论述的所有其它同位素。

[0077] 化合物

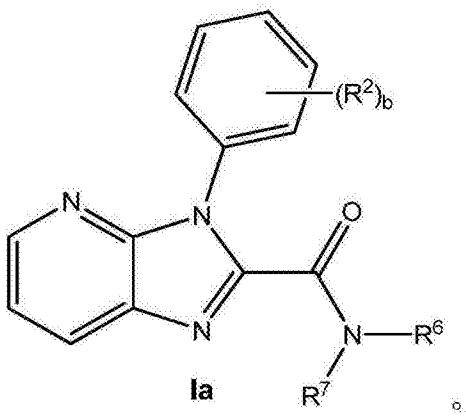
[0078] 本发明涉及如上文所述的式 I 的氮杂苯并咪唑化合物。在某些实施方案中，咪唑并吡啶核的吡啶环在环上不含任何取代。在这些情况下，$(R^3)_a$ 取代基中的“a”由整数 0 表示。

[0079] 为进一步阐明本发明的化合物，下文阐述以下子类。

[0080] 下文绘示的式 Ia 是所绘示的式 I 的亚组，其中 R^1 由任选地被 $(R^2)_b$ 取代的苯基表示；且 a 由整数 0 表示。在式 Ia 中，b 由选自 0、1、2 或 3 的整数表示；每一 R^2 若存在，则由独立地选自以下的取代基表示：氟、氯、氰基、甲基、三氟甲基、甲硫基、甲氧基和三氟甲氧基；R^6 和 R^7 各自独立地选自：氢、(C_1-C_6) 烷基、$-(CH_2)_m-(C_3-C_{10})$ 环烷基和 $-(CH_2)_m-$(5 至 10 元）杂芳基，其中所述 (C_1-C_6) 烷基、(C_3-C_{10}) 环烷基和 (5 至 10 元）杂芳基任选地被 1 至 3 个独立地选自以下的取代基取代：卤素、(C_1-C_6) 烷基、卤代 (C_1-C_6) 烷基、(C_1-C_6) 烷氧基、卤代 (C_1-C_6) 烷氧基、(C_1-C_6) 烷硫基、$-C(O)NR^4R^5$、羟基和氰基；或者 R^6 和 R^7 与其所连接的氮一起形成 (4 至 6 元）杂环烷基，其中所述杂环烷基任选地在 1 至 3 个碳原子处被独立地选自以下的取代基取代：卤素、(C_1-C_6) 烷基、卤代 (C_1-C_6) 烷基、(C_1-C_6) 烷氧基、卤代 (C_1-C_6)

烷氧基、(C_1-C_6) 烷硫基、$-C(O)NR^4R^5$、羟基和氰基；其中 R^4 和 R^5 各自独立地选自氢和 (C_1-C_6) 烷基；且 m 由整数 0、1 或 2 表示：

[0081]



Ia

[0082] 在本发明的某些实施方案中，在如上文绘示的式 Ia 中，b 由选自 0、1、2 或 3 的整数表示；每一 R^2 若存在，则由独立地选自以下的取代基表示：氯、氟、甲基和氰基；R^6 和 R^7 之一由氢表示，且另一者由选自以下的取代基表示：(C_1-C_6) 烷基、$-(CH_2)_m-(C_3-C_{10})$ 环烷基和 $-(CH_2)_m-$(5 至 10 元）杂芳基，其中所述 (C_1-C_6) 烷基、(C_3-C_{10}) 环烷基和 (5 至 10 元）杂芳基任选地被 1 至 3 个独立地选自以下的取代基取代：卤素、(C_1-C_6) 烷基、卤代 (C_1-C_6) 烷基、(C_1-C_6) 烷氧基、卤代 (C_1-C_6) 烷氧基、(C_1-C_6) 烷硫基、$-C(O)NR^4R^5$、羟基和氰基。

[0083] 在本发明的某些实施方案中，在如上文绘示的式 Ia 中，b 为选自 0、1、2 或 3 的整数；每一 R^2 若存在，则由独立地选自以下的取代基表示：氯、氟、甲基和氰基；R^6 和 R^7 之一由氢表示，且另一者由任选地被 1 至 3 个独立地选自以下的取代基取代的 (C_1-C_6) 烷基表示：卤素、(C_1-C_6) 烷基、卤代 (C_1-C_6) 烷基、(C_1-C_6) 烷氧基、卤代 (C_1-C_6) 烷氧基、(C_1-C_6) 烷硫基、羟基和氰基。在某些实施方案中，R^6 和 R^7 之一由氢表示，且另一者由选自乙基和丙基的取代基表示。在某些实施方案中，R^6 和 R^7 之一由氢表示，且另一者由丙基表示。

[0084] 在本发明的某些其它实施方案中，在如上文绘示的式 Ia 中，b 由选自 0、1、2 或 3 的整数表示；每一 R^2 若存在，则由独立地选自以下的取代基表示：氯、氟、甲基和氰基；R^6 和 R^7 之一由氢表示，且另一者由任选地被 1 至 3 个独立地选自以下的取代基取代的 $-(CH_2)_m-(C_3-C_{10})$ 环烷基表示：卤素、(C_1-C_6) 烷基、卤代 (C_1-C_6) 烷基、(C_1-C_6) 烷氧基、卤代 (C_1-C_6) 烷氧基、(C_1-C_6) 烷硫基、羟基和氰基；且 m 由选自 0、1 或 2 的整数表示。在某些实施方案中，R^6 和 R^7 之一由氢表示，且另一者由环丙基表示。

[0085] 在本发明的某些其它实施方案中，在如上文绘示的式 Ia 中，b 由选自 0、1、2 或 3 的整数表示；每一 R^2 若存在，则由独立地选自以下的取代基表示：氯、氟、甲基和氰基；R^6 和 R^7 之一由氢表示，且另一者由任选地被 1 至 3 个独立地选自以下的取代基取代的 $-(CH_2)_m-$(5 至 10 元）杂芳基表示：卤素、(C_1-C_6) 烷基、卤代 (C_1-C_6) 烷基、(C_1-C_6) 烷氧基、卤代 (C_1-C_6) 烷氧基、(C_1-C_6) 烷硫基、羟基和氰基，其中 m 由选自 0、1 或 2 的整数表示。在某些实施方案中，R^6 和 R^7 之一由氢表示，且另一者由任选地被 (C_1-C_6) 烷基取代的吡唑基表示。在某些实施方案中，R^6 和 R^7 之一由氢表示，且另一者由 N- 甲基吡唑基（例如，N- 甲基吡唑 -3- 基）表示。

[0086] 在本发明的某些实施方案中，在式 Ia 中，b 由选自 0、1、2 或 3 的整数表示；每一 R^2

若存在，则由独立地选自以下的取代基表示：氟、氯、氰基、甲基、三氟甲基、甲硫基、甲氧基和三氟甲氧基；R^6和 R^7与其所连接的氮一起形成任选地在 1 至 3 个碳原子处被独立地选自以下的取代基取代的（4 至 6 元）杂环烷基：卤素、(C_1-C_6) 烷基、卤代 (C_1-C_6) 烷基、(C_1-C_6) 烷氧基、卤代 (C_1-C_6) 烷氧基、(C_1-C_6) 烷硫基、$-C(O)NR^4R^5$、羟基和氰基，其中 R^4和 R^5各自独立地选自氢和 (C_1-C_6) 烷基。

[0087] 在本发明的某些其它实施方案中，在如上文绘示的式 Ia 中，b 由选自 0、1、2 或 3 的整数表示；每一 R^2若存在，则由独立地选自以下的取代基表示：氯、氟、甲基和氰基；且 R^6和 R^7与其所连接的氮一起形成任选地被 1 至 3 个卤素取代的氮杂环丁烷环。在某些实施方案中，R^6和 R^7与其所连接的氮一起形成 3- 氟 - 氮杂环丁 -1- 基。

[0088] 在另一实施方案中，本发明的所选化合物可用于治疗 PDE4B 介导的病症，其包括向有此需要的哺乳动物（优选人类）给药治疗有效量的有效抑制 PDE4B 活性的本发明的化合物；更优选地，给药对 PDE4B 具有改善的结合亲和性同时对 PDE4D 具有较小抑制活性的本发明的化合物的量。

[0089] 在另一实施方案中，本发明的所选化合物可用于治疗 PDE4A 介导的病症，其包括向有此需要的哺乳动物（优选人类）给药治疗有效量的有效抑制 PDE4A 活性的本发明的化合物。

[0090] 在又一实施方案中，本发明的所选化合物可用于治疗 PDE4C 介导的病症，其包括向有此需要的哺乳动物（优选人类）给药治疗有效量的有效抑制 PDE4C 活性的本发明的化合物。

[0091] 在某些其它实施方案中，本发明的所选化合物可对 PDE4A、PDE4B 及 PDE4C 亚型或其组合表现出结合亲和性。

[0092] 在某些实施方案中，本发明的化合物对 PDE4B 亚型相对于 PDE4D 亚型具有增强的结合亲和性，以使所述化合物对 PDE4B 亚型相对于 PDE4D 亚型表现出约 2 倍至约 120 倍的结合亲和性。在某些其它实施方案中，本发明的化合物对 PDE4B 亚型相对于 PDE4D 亚型表现出约 35 倍至约 75 倍的结合亲和性。在某些实施方案中，本发明的化合物对 PDE4B 亚型相对于 PDE4D 亚型表现出至少约 2 倍的结合亲和性。在某些实施方案中，本发明的化合物对 PDE4B 亚型相对于 PDE4D 亚型表现出至少约 5 倍的结合亲和性。在某些实施方案中，本发明的化合物对 PDE4B 亚型相对于 PDE4D 亚型表现出至少约 10 倍的结合亲和性。在某些实施方案中，本发明的化合物对 PDE4B 亚型相对于 PDE4D 亚型表现出至少约 20 倍的结合亲和性。在某些其它实施方案中，本发明的化合物对 PDE4B 亚型相对于 PDE4D 亚型表现出至少约 40 倍的结合亲和性。在某些其它实施方案中，本发明的化合物对 PDE4B 亚型相对于 PDE4D 亚型表现出至少约 50 倍的结合亲和性。本发明的化合物对 PDE4B 及 PDE4D 亚型的结合亲和性示于下文实验部分的表 4 中。

[0093] 在另一实施方案中，本发明提供药物组合物，其包含本发明的化合物或其药学上可接受的盐与至少一种药学上可接受的赋形剂的混合物。

[0094] 在又一实施方案中，向有此需要的患者给药本发明的化合物还可引起胃肠不适（例如呕吐、腹泻及恶心，目前据信其与对其他 PDE4 亚型特别是 PDE4D 亚型具有结合亲和性的化合物的给药相关）减少，从而引起患者顺应性以及整体治疗结果的提高。

[0095] 在另一实施方案中，本发明提供治疗中枢神经系统 (CNS)、代谢、自身免疫及炎性

疾病或病症的方法，其包括向需要此类治疗的哺乳动物特别是人类给药治疗有效量的本发明的化合物或其药学上可接受的盐。

[0096] 在另一实施方案中，本发明提供本发明的化合物或其药学上可接受的盐在制备用于治疗中枢神经系统 (CNS)、自身免疫及炎性疾病或病症的药物中的用途。

[0097] 药理学

[0098] PDE4 家族的磷酸二酯酶 (PDE) 的特征在于第二信使环核苷酸 3',5'- 环腺苷酸 (cAMP) 的选择性高亲和性水解降解。已知 PDE4A、PDE4B 及 PDE4D 亚型在整个脑中广泛表达，其中 PDE4A、PDE4B 及 PDE4D 亚型的区域分布及细胞内分布不同，而 PDE4C 亚型在整个中枢神经系统以较低水平表达（参见 :Siuciak, J.A. 等人，Antipsychotic profile of rolipram:efficacy in rats and reduced sensitivity in mice deficient in the phosphodiesterase-4B(PDE4B)enzyme, Psychopharmacology(2007)192:415-424)。PDE4 亚型的位置使得其成为探索中枢神经系统疾病及病症的新治疗的令人关注的靶标。举例而言，PDE4B 已鉴别为精神分裂症的遗传易感性因子（参见 :Millar, J.K. 等人，Disrupted in schizophrenia 1and phosphodiesterase 4B:towards an understanding of psychiatric illness, J.Physiol.584(2007) 第 401-405 页）。

[0099] 已证明 PDE4 抑制剂咯利普兰可通过神经元炎症及细胞凋亡介导的 cAMP/CREB 信号传导的衰减用于治疗或逆转 Aβ 诱导的记忆缺失，且为用于治疗与 AD 相关的认知缺陷的潜在靶标。（参见 :Wang, C. 等人，The phosphodiesterase-4 inhibitor rolipram reverses Aβ-induced cognitive impairment and neuroinflammatory and apoptotic responses in rats, International Journal of Neuropsychopharmacology(2012), 15, 749-766)。

[0100] 还已证明 PDE4 抑制剂通过减少 PDE4 在患有重度抑郁症 (MDD) 的个体中的脑水平而具有抗抑郁效应（参见 :Fujita, M. 等人，C-(R-)-Rolipram Positron Emission Tomography in Major Depressive Disorder, Biological Psychiatry, 71, 2012, 548-554)。

[0101] 此外，已证明 PDE4 抑制剂在用于治疗多发性硬化方面具有治疗活性（参见 : Sun, X. 等 人，Rolipram promotes remyelination possibly via MEK-ERK signal pathway in cuprizone-induced demyelination mouse, Experimental Neurology 2012 ; 237:304-311)。

[0102] 鉴于以上内容，在某些实施方案中，本发明的化合物具有用于治疗哺乳动物优选人类的中枢神经系统病况或疾病的多种治疗应用，所述中枢神经系统病况或疾病包括但不限于 C 型尼曼皮克病 (Niemann-Pick type C) ；巴滕病 (Batten Disease) ；神经障碍（例如头痛、偏头痛 ；癫痫 ；阿尔茨海默病 ；帕金森氏病 ；脑损伤 (TBI) ；中风 ；脑血管疾病（包括脑动脉硬化、脑淀粉样血管病变、遗传性脑出血及脑缺氧 - 局部缺血）；认知障碍（包括健忘症、老年痴呆、HIV 相关的痴呆、阿尔茨海默病、亨廷顿氏病、路易体痴呆 (Lewy body dementia)、血管性痴呆、药物有关的痴呆、迟发性运动障碍、肌阵挛、张力失常、谵妄、皮克病 (Pick's disease)、克 - 雅二氏病 (Creutzfeldt-Jacob disease)、HIV 疾病、吉累斯 • 德拉图雷特综合征 (Gilles de la Tourette's syndrome)、癫痫、肌肉痉挛及与肌肉痉挛状态或虚弱相关的病症（包括震颤）及轻度认知损伤）；心理缺陷（包括痉挛状态、唐氏综合征

(Down syndrome)及脆性X综合征(fragile X syndrome));睡眠障碍(包括睡眠过度、昼夜节律睡眠障碍、失眠、深眠状态及睡眠剥夺);精神病病症,例如焦虑症(包括急性应激病症、广泛性焦虑症、社交焦虑症、恐慌症、创伤后应激障碍、广场恐惧症及强迫症);造作性障碍(包括急性幻觉性躁狂);冲动控制障碍(包括强迫性赌博及间歇性暴躁障碍);心境障碍(包括双相性I型情感障碍、双相性II型情感障碍、躁狂症、混合型情感状态、重度抑郁症、慢性抑郁症、季节性抑郁症、精神病抑郁症、经前综合征(PMS)、经前焦虑障碍(PDD)及产后抑郁症);精神运动性障碍;精神障碍(包括精神分裂症、情感性分裂症、精神分裂症样及妄想症);药物依赖及滥用(包括麻醉品依赖、酒精中毒、安非他命及甲基安非他命依赖、类阿片依赖、可卡因成瘾、尼古丁依赖及药物戒断综合征及复发预防);进食障碍(包括厌食症、食欲亢进、暴食症、饮食过量、肥胖症、强迫性进食障碍及食冰癖);性功能障碍、尿失禁(例如,膀胱过度活动);神经元损害病症(包括眼损伤、视网膜病或眼部黄斑变性、耳鸣、听力损害及丧失、和脑水肿);及小儿精神病病症(包括注意力缺陷障碍、注意力缺乏/过动症、行为障碍及孤独症),其包括向所述哺乳动物给药治疗有效量的本发明的化合物或其药学上可接受的盐。

[0103] 在某些实施方案中,本发明涉及通过向有此需要的患者给药治疗有效量的本发明的氮杂苯并咪唑化合物来治疗精神分裂症的方法。

[0104] 在某些其它实施方案中,本发明进一步涉及通过向有此需要的患者给药治疗有效量的本发明的氮杂苯并咪唑化合物来治疗与精神分裂症相关的认识缺损的方法。

[0105] 除上文所提及的中枢神经系统病症外,本领域存在大量阐述PDE抑制剂对多种炎症细胞应答的作用的文献,所述炎症细胞应答除cAMP增加外还包括抑制超氧化物产生、脱粒、趋化性以及肿瘤坏死因子(TNF)在嗜酸细胞、中性白细胞及单核细胞中的释放。因此,本发明的氮杂苯并咪唑化合物可用于治疗自身免疫及炎性疾病。(参见:Schett,G.等人,Apremilast:A novel PDE4Inhibitor in the Treatment of Autoimmune and Inflammatory Diseases,Ther.Adv.Musculoskeletal Dis.2010;2(5):271-278)。举例而言,本发明的化合物可用于治疗与贝塞病(Behçet's disease)相关的口腔溃疡(同处)。本发明的化合物还可用于治疗与关节炎相关的疼痛(参见:Hess,A.等人,Blockade of TNF-α rapidly inhibits pain responses in the central nervous system,PNAS,第108卷,第9期,3731-3736(2011))或用于治疗银屑病或银屑病关节炎(参见:Schafer,P.,Apremilast mechanism of action and application to psoriasis and psoriatic arthritis,Biochem.Pharmacol.(2012),15;83(12):1583-90)。因此,本发明的氮杂苯并咪唑化合物还可用于治疗强直性脊柱炎[参见:Patan,E.等人,Efficacy and safety of apremilast,an oral phosphodiesterase 4inhibitor,in ankylosing spondylitis,Ann.Rheum.Dis.(2102年9月14日)]。可通过给药本发明的化合物治疗的其它病况包括但不限于多发性硬化、烧伤、败血症、哮喘、慢性或急性支气管狭窄、慢性支气管炎、支气管扩张症、小气道阻塞、肺气肿、阻塞性或炎症性气道疾病、肺尘症、季节性过敏性鼻炎或常年性过敏性鼻炎或鼻窦炎、变应性结膜炎、急性呼吸窘迫综合征(ARDS)、急性肺损伤(ALI)、关节炎(例如,类风湿性关节炎及骨关节炎)痛风及发热以及与炎症相关的疼痛、与嗜酸细胞有关的病症、皮炎或湿疹、荨麻疹、结膜炎、葡萄膜炎、银屑病、炎性肠疾病、克罗恩氏病、脓毒性休克、肝损伤、肺性高血压、骨损失疾病、神经病变及感染。

[0106] 在又一实施方案中，本发明的化合物可用于治疗癌症及肿瘤。举例而言，本发明的化合物可用于治疗脑癌（例如，髓母细胞瘤）（参见：Schmidt, A. L., BDNF and PDE4, but not GRPR, Regulate Viability of Human Medulloblastoma Cells, J. Mol. Neuroscience (2010) 40:303-310）。本发明的化合物亦可用于治疗黑色素瘤（参见：Marquette, A. 等人，ERK and PDE4 cooperate to induce RAF isoform switching in melanoma, Nature Structural&Molecular Biology，第 18 卷，第 5 期，584-91, 2011）。在某些实施方案中，本发明的化合物可用于治疗白血病，例如，慢性淋巴细胞白血病（参见：Kim, D. H. 等人，Type 4Cyclic Adenosine Monophosphate Phosphodiesterase as a Therapeutic Target in Chronic Lymphocytic Leulemia, Blood Journal of The American Society of Hematology，1998 年 10 月 1 日，第 92 卷，第 7 期，2484-2494）。

[0107] 在某些其它实施方案中，本发明的化合物可用于治疗糖尿病或与糖尿病相关的病况（参见：Vollert, S. 等人，The glucose-lowering effects of the PDE4 inhibitors roflumilast and roflumilast-N-Oxide in db/db mice, Diabetologia (2012) 55:2779-2788；Wouters, E. F. M. 等人，Effect of the Phosphodiesterase 4 Inhibitor Roflumilast on Glucose Metabolism in Patients with Treatment-*Naïve*, Newly Diagnosed Type 2 Diabetes Mellitus, Journal of Clinical Endocrinology and Metabolism 2012, 97, 1720-1725）。在某些实施方案中，本发明的化合物可用于治疗糖尿病性黄斑水肿 (DME) 及糖尿病性神经病变 (DN)。

[0108] 制剂

[0109] 本发明的化合物可口服给药。口服给药可涉及吞咽以便化合物进入胃肠道，或可采用含服或舌下给药，藉此化合物直接自口腔进入血流。

[0110] 在另一实施方案中，本发明的化合物亦可直接给药至血流、肌肉或内部器官中。适用于肠胃外给药的方式包括静脉内、动脉内、腹膜内、鞘内、心室内、尿道内、胸骨内、颅内、肌内及皮下给药。适用于肠胃外给药的装置包括针式（包括微针）注射器、无针式注射器及输注技术。

[0111] 在另一实施方案中，本发明的化合物亦可经配制以使其局部给药至皮肤或粘膜（亦即，皮肤或经皮）导致化合物的全身吸收。在另一实施方案中，本发明的化合物亦可经配制以使其鼻内或通过吸入给药导致化合物的全身吸收。在另一实施方案中，本发明的化合物可经配制以使其直肠或阴道给药导致化合物的全身吸收。

[0112] 化合物和 / 或含有化合物的组合物的剂量方案基于多种因素，包括患者的类型、年龄、体重、性别及医学病况；病况的严重程度；给药途径；以及所用特定化合物的活性。因此，剂量方案可广泛变化。约 0.01mg/ 千克体重至约 100mg/ 千克体重的剂量水平可用于治疗上文指示的病况。在一个实施方案中，本发明的化合物的总日剂量（以单次剂量或分开剂量给药）通常为约 0.01mg/kg 至约 100mg/kg。在另一实施方案中，本发明的化合物的总日剂量为约 0.1mg/kg 至约 50mg/kg，且在另一实施方案中为约 0.5mg/kg 至约 30mg/kg（亦即，若干 mg 本发明的化合物 /kg 体重）。在一个实施方案中，剂量为 0.01mg/kg/ 天至 10mg/kg/ 天。在另一实施方案中，剂量为 0.1mg/kg/ 天至 1.0mg/kg/ 天。剂量单位组合物可含有这样的量或其约数以达成日剂量。在许多情况下，化合物的给药会在一天内重复复数次（通常不多于 4 次）。若期望，每天多个剂量通常可用于增加总日剂量。

[0113] 对于口服给药而言，可以含有 0.01 毫克、0.05 毫克、0.1 毫克、0.5 毫克、1.0 毫克、2.5 毫克、5.0 毫克、10.0 毫克、15.0 毫克、25.0 毫克、50.0 毫克、75.0 毫克、100 毫克、125 毫克、150 毫克、175 毫克、200 毫克、250 毫克及 500 毫克活性成份（根据症状调节给药至患者的剂量）的片剂形式提供组合物。药物通常含有约 0.01mg 至约 500mg 活性成份，或在另一实施方案中含有约 1mg 至约 100mg 活性成份。在恒速输注期间，静脉内剂量可为约 0.1mg/kg/ 分钟至约 10mg/kg/ 分钟。

[0114] 本发明的适宜个体包括哺乳动物个体。本发明的哺乳动物包括但不限于犬类、猫科、牛、山羊、马、绵羊、猪、啮齿类动物、兔类动物、灵长类动物等，且涵盖子宫中的哺乳动物。在一个实施方案中，人类为适宜个体。人类个体可具有任一性别且处于任何发展发育阶段。

[0115] 在另一实施方案中，本发明包括一或多种本发明的化合物在制备用于治疗本文所述病况的药物中的用途。

[0116] 对于上文所提及的病况的治疗而言，本发明的化合物可以化合物本身形式给药。或者，药学上可接受的盐由于其相对于母体化合物的较大水溶性而适于医学应用。

[0117] 在另一实施方案中，本发明包括药物组合物。此类药物组合物包含与药学上可接受的载体一起提供的本发明的化合物。所述载体可为固体、液体或二者，且可与化合物一起配制为单位剂量组合物，例如片剂，其可含有 0.05 重量％至 95 重量％的活性化合物。本发明的组合物可与作为可靶向药物载体的适宜聚合物偶联。亦可存在其它药理活性物质。

[0118] 本发明的化合物可通过任何适宜途径给药，优选以适于这样的途径的药物组合物形式且以对预期治疗有效的剂量给药。活性化合物及组合物可例如口服、直肠、肠胃外或局部给药。

[0119] 固体剂型的口服给药可（例如）以离散单元（例如硬质或软质胶囊、丸剂、扁囊剂、锭剂或片剂，其各自含有预定量的至少一种本发明的化合物）提供。在另一实施方案中，口服给药可为散剂或颗粒剂形式。在另一实施方案中，口服剂型为舌下剂型，例如锭剂。在此类固体剂型中，本发明的化合物通常与一或多种辅剂组合。此类胶囊剂或片剂可包括控释制剂。在胶囊剂、片剂及丸剂的情形下，所述剂型亦可包含缓冲剂或可利用肠溶包衣制备。

[0120] 在另一实施方案中，口服给药可为液体剂型。用于口服给药的液体剂型包括（例如）含有本领域常用的惰性稀释剂（例如，水）的药学上可接受的乳剂、溶液剂、混悬剂、糖浆剂及酏剂。此类组合物亦可包含辅剂，例如润湿剂、乳化剂、助悬剂、矫味剂（例如，甜味剂）和 / 或芳香剂。

[0121] 在另一实施方案中，本发明包括肠胃外剂型。“肠胃外给药”包括（例如）皮下注射、静脉内注射、腹膜内注射、肌内注射、胸骨内注射及输注。可根据已知技术使用适宜分散剂、润湿剂和 / 或助悬剂来配制可注射制剂（亦即，无菌可注射水性或油性混悬剂）。

[0122] 在另一实施方案中，本发明包括局部剂型。“局部给药”包括例如通过例如经皮贴剂或电离子透入装置的经皮给药、眼内给药、或者鼻内或吸入给药。局部给药的组合物还包括（例如）局部凝胶剂、喷雾剂、软膏剂及乳膏剂。局部制剂可包含增强活性成份穿过皮肤或其它受感染区域的吸收或渗透的化合物。当本发明的化合物通过经皮装置给药时，会使用储库及多孔膜型的贴剂或固体基质类贴剂来实现给药。用于此目的的典型制剂包括凝胶

剂、水凝胶剂、洗剂、溶液剂、乳膏剂、软膏剂、撒粉剂、敷料、泡沫剂、膜剂、皮肤贴剂、糯米纸囊剂(wafer)、植入物、海绵、纤维、绷带及微乳剂。亦可使用脂质体。典型的载体包括醇、水、矿物油、液体矿脂、白凡士林、甘油、聚乙二醇及丙二醇。可掺入渗透促进剂,参见(例如)Finnin及Morgan,J.Pharm.Sci.,88(10),955-958(1999)。

[0123] 适于向眼部局部给药的制剂包括(例如)滴眼剂,其中本发明的化合物溶解或悬浮于适宜载体中。适于经眼部或耳部给药的典型制剂可为在等渗的pH调节的无菌盐水中的微粉化悬浮液或溶液的滴剂形式。其它适于经眼部及耳部给药的制剂包括软膏剂、可生物降解的(例如,可吸收性凝胶海绵、胶原)及不可生物降解的(例如,硅酮)植入物、糯米纸囊剂、接触镜及颗粒或泡状系统(例如脂质体(niosome或liposome))。可将诸如交联聚丙烯酸、聚乙烯醇、透明质酸、纤维素聚合物(例如,羟丙基甲基纤维素、羟乙基纤维素或甲基纤维素)或杂多糖聚合物(例如,结冷胶)的聚合物与防腐剂(例如,苯扎氯铵)一起掺入。此类制剂亦可通过离子电渗法递送。

[0124] 对于鼻内给药或通过吸入给药而言,本发明的活性化合物方便地以溶液剂或混悬剂形式从由患者挤压或泵送的泵式喷雾容器中递送,或者以气雾剂喷雾呈送形式从加压容器或喷雾器中使用适宜抛射剂递送。适于鼻内给药的制剂通常以下列形式给药:来自干粉吸入器的干粉(单独地;作为混合物(例如,与乳糖的干混物);或作为混合组份颗粒(例如,与磷脂(例如磷脂酰胆碱)混合)),或作为来自加压容器、泵、喷射器、雾化器(优选使用电流体动力学以生成细雾的雾化器)或喷雾器的气雾剂喷雾(使用或不使用适宜抛射剂,例如1,1,1,2-四氟乙烷或1,1,1,2,3,3,3-七氟丙烷)。对于鼻内使用而言,粉末可包含生物粘着剂,例如,壳聚糖或环糊精。

[0125] 在另一实施方案中,本发明包括直肠剂型。此类直肠剂型可呈(例如)栓剂形式。可可脂是传统栓剂基质,但若适当可使用多种替代物。

[0126] 亦可使用药学领域内已知的其它载体物质及给药模式。本发明的药物组合物可通过任何熟知的药物技术(例如有效配制及给药操作)制备。关于有效配制及给药操作的上述考虑因素已为本领域所熟知且阐述于标准教材中。药物的配制论述于(例如)Hoover,John E.,Remington's Pharmaceutical Sciences,Mack Publishing公司,Easton,Pennsylvania,1975;Liberman等人编辑,Pharmaceutical Dosage Forms,Marcel Decker,New York,N.Y.,1980;及Kibbe等人编辑,Handbook of Pharmaceutical Excipients(第3版),American Pharmaceutical Association,Washington,1999中。

[0127] 本发明的化合物可单独或与其它治疗剂组合用于治疗各种病况或疾病状态。一或多种本发明的化合物及一或多种其它治疗剂可同时(以同一剂型或以分开的剂型)给药或依序给药。例示性治疗剂可为(例如)代谢型谷氨酸盐受体激动剂。

[0128] 两种或更多种化合物的"组合"给药意指这两种化合物的给药时间间隔足够紧密以使一者的存在改变另一者的生物效应。两种或更多种化合物可同时(simultaneously)、并行(concurrently)或依序给药。另外,同时给药可通过以下方式实施:在给药前将化合物混合,或者在相同时间点但在不同解剖部位或使用不同给药途径来将化合物给药。

[0129] 术语"并行给药"、"共同给药(co-administration)"、"同时给药(simultaneous administration)"及"同时给药(administered simultaneously)"意指化合物组合给药。

[0130] 本发明包括使用本发明的PDE4抑制剂化合物与一或多种其它药物活性剂的组

合。若给药活性剂的组合，则其可以分开的剂型依序或同时给药或以单一剂型组合给药。因此，本发明还包括药物组合物，其包含一定量的：(a) 第一药剂，其包括本发明的化合物或该化合物的药学上可接受的盐；(b) 第二药物活性剂；及 (c) 药学上可接受的载体、载剂或稀释剂。

[0131] 根据欲治疗的疾病、病症或病况，可选择各种药物活性剂与本发明的化合物组合使用。可与本发明的组合物组合使用的药物活性剂包括但不限于：

[0132] (i) 乙酰胆碱酯酶抑制剂，例如多奈派齐盐酸盐 (ARICEPT、MEMAC)、毒扁豆碱水杨酸盐 (ANTILIRIUM)、毒扁豆碱硫酸盐 (ESERINE)、美曲膦酯、新斯的明、更斯的明、吡啶斯的明 (MESTINON)、阿伯农 (MYTELASE)、地美卡林 (demarcarium)、Debio 9902(亦称作 ZT-1；Debiopharm)、利斯的明 (EXELON)、拉多替吉、NP-0361、加兰他敏氢溴酸盐 (RAZADYNE、RIMINYL、NIVALIN)、他克林 (COGNEX)、甲基羟基丙氨酸 (tolserine)、马来酸维吖啶、美莫喹 (memoquin)、石杉碱甲 (HUP-A；NeuroHitech)、苯丝氨酸 (phenserine)、依酚氯铵 (ENLON、TENSILON) 及 INM-176；

[0133] (ii) 淀粉样蛋白-β(或其片段)，例如与泛 HLA DR 结合表位 (PADRE)、ACC-001(Elan/Wyeth)、ACI-01、ACI-24、AN-1792、Affitope AD-01、CAD106 及 V-950 偶联的 $A\beta_{1\ 15}$；

[0134] (iii) 淀粉样蛋白-β(或其片段)的抗体，例如普恩珠单抗 (ponezumab)、苏兰珠单抗、巴匹珠单抗(亦称作 AAB-001)、AAB-002(Wyeth/Elan)、ACI-01-Ab7、BAN-2401、静脉内 Ig(GAMMAGARD)、LY2062430(人类化 m266；Lilly)、R1450(Roche)、ACU-5A5、huC091 及那些以下文献所公开的：国际专利公开案第 WO04/032868 号、第 WO05/025616 号、第 WO06/036291 号、第 WO06/069081 号、第 WO06/118959 号、美国专利公开案第 US2003/0073655 号、第 US2004/0192898 号、第 US2005/0048049 号、第 US2005/0019328 号及欧洲专利公开案第 EP0994728 号及第 1257584 号及美国专利第 5,750,349 号；

[0135] (iv) 淀粉样蛋白降低或抑制剂(包括那些减少淀粉样蛋白产生、累积及纤维化的物质)，例如地美本 (dimebon)、达夫奈肽、依罗沙特、亮丙瑞林、SK-PC-B70M、塞来考昔、洛伐他汀、昂钠索 (anapsos)、奥拉西坦、普拉西坦、伐尼克兰、尼麦角林、科乐斯宁 (colostrinin)、百脑塞瑞 (bisnorcymserine)(亦称作 BNC)、NIC5-15(Humanetics)、E-2012(Eisai)、吡格列酮、氯碘羟喹(亦称作 PBT1)、PBT2(Prana Biotechnology)、氟比洛芬 (ANSAID、FROBEN) 及其 R-对映异构体他氟比尔 (FLURIZAN)、硝基氟吡洛芬、非诺洛芬 (FENOPRON、NALFON)、布洛芬 (ADVIL、MOTRIN、NUROFEN)、布洛芬赖氨酸盐、甲氯芬那酸、甲氯芬那酸钠 (MECLOMEN)、吲哚美辛 (INDOCIN)、双氯芬酸钠 (VOLTAREN)、双氯芬酸钾、舒林酸 (CLINORIL)、舒林酸硫化物、二氟尼柳 (DOLOBID)、萘普生 (NAPROSYN)、萘普生钠 (ANAPROX、ALEVE)、ARC031(Archer Pharmaceuticals)、CAD-106(Cytos)、LY450139(Lilly)、胰岛素降解酶(亦称作胰岛素溶酶)、银杏 (gingko biloba) 提取物 EGb-761(ROKAN、TEBONIN)、曲米沙特 (CEREBRIL、ALZHEMED)、伊罗地塞 (FIBRILLEX、KIACTA)、化合物 W(3,5-双 (4-硝基苯氧基)苯甲酸)、NGX-96992、肾胰岛素残基溶酶(亦称作中性内肽酶 (NEP))、鲨肌醇(亦称作 scyllitol)、阿托伐他汀 (LIPITOR)、辛伐他汀 (ZOCOR)、KLVFF-(EEX)3、SKF-74652、甲磺酸伊布莫仑、BACE 抑制剂，例如 ASP-1702、SCH-745966、JNJ-715754、AMG-0683、AZ-12304146、BMS-782450、GSK-188909、NB-533、E2609 及 TTP-854；γ 分泌酶调节剂，例

如 ELND-007；及 RAGE（高级糖基化终产物的受体）抑制剂，例如 TTP488(Transtech) 及 TTP4000(Transtech) 及那些美国专利第 7,285,293 号中所公开的（包括 PTI-777）；

[0136] (v) α-肾上腺素能受体激动剂，例如胍法辛 (INTUNIV、TENEX)、氯压定 (CATAPRES)、间羟胺 (ARAMINE)、甲基多巴 (ALDOMET、DOPAMET、NOVOMEDOPA)、替扎尼定 (ZANAFLEX)、脱羟肾上腺素（亦称作新福林）、甲氧明、西拉唑啉、胍法辛 (INTUNIV)、洛非西定、赛拉嗪、莫达非尼 (PROVIGIL)、阿屈非尼及阿莫非尼 (NUVIGIL)；

[0137] (vi) β-肾上腺素能受体阻断剂（β 阻断剂），例如卡替洛尔、艾司洛尔 (BREVIBLOC)、拉贝洛尔 (NORMODYNE、TRANDATE)、氧烯洛尔 (LARACOR、TRASACOR)、吲哚洛尔 (VISKEN)、普萘洛尔 (INDERAL)、索他洛尔 (BETAPACE、SOTALEX、SOTACOR)、噻吗洛尔 (BLOCADREN、TIMOPTIC)、醋丁洛尔 (SECTRAL、PRENT)、纳多洛尔 (CORGARD)、酒石酸美托洛尔 (LOPRESSOR)、琥珀酸美托洛尔 (TOPROL-XL)、阿替洛尔 (TENORMIN)、布托沙明及 SR 59230A(Sanofi)；

[0138] (vii) 抗胆碱能药，例如阿米替林 (ELAVIL、ENDEP)、布替林、甲磺酸苯扎托品 (COGENTIN)、苯海索 (ARTANE)、苯海拉明 (BENADRYL)、奥芬那君 (NORFLEX)、莨菪碱、阿托品 (ATROPEN)、东莨菪碱 (TRANSDERM-SCOP)、溴化甲基东莨菪碱 (PARMINE)、双环维林 (BENTYL、BYCLOMINE、DIBENT、DILOMINE)、托特罗定 (DETROL)、奥昔布宁 (DITROPAN、LYRINEL XL、OXYTROL)、喷噻溴铵、丙胺太林 (PRO-BANTHINE)、塞克力嗪、盐酸丙米嗪 (TOFRANIL)、马来酸丙米嗪 (SURMONTIL)、洛非帕明、地昔帕明 (NORPRAMIN)、多塞平 (SINEQUAN、ZONALON)、曲米帕明 (SURMONTIL) 及格隆溴铵 (ROBINUL)；

[0139] (viii) 抗惊厥药，例如卡马西平 (TEGRETOL、CARBATROL)、奥卡西平 (TRILEPTAL)、苯妥英钠 (PHENYTEK)、磷苯妥英 (CEREBYX、PRODILANTIN)、双丙戊酸钠 (divalproex sodium)(DEPAKOTE)、加巴喷丁 (NEURONTIN)、普瑞巴林 (LYRICA)、托吡酯 (topirimate) (TOPAMAX)、丙戊酸 (DEPAKENE)、丙戊酸钠 (DEPACON)、1-苄基-5-溴脲嘧啶、普罗加胺、贝克拉胺、唑尼沙胺 (TRERIEF、EXCEGRAN)、CP-465022、瑞替加滨、他仑帕奈及扑米酮 (MYSOLINE)；

[0140] (ix) 抗精神病药，例如鲁拉西酮 (LATUDA，亦称作 SM-13496；Dainippon Sumitomo)、阿立哌唑 (ABILIFY)、氯丙嗪 (THORAZINE)、氟哌啶醇 (HALDOL)、伊洛哌酮 (FANAPTA)、癸酸氟哌噻吨 (DEPIXOL、FLUANXOL)、利血平 (SERPLAN)、匹莫齐特 (ORAP)、癸酸氟奋乃静、盐酸氟奋乃静、丙氯拉嗪 (COMPRO)、阿塞奈平 (SAPHRIS)、洛沙平 (LOXITANE)、吗茚酮 (MOBAN)、奋乃静、硫利达嗪、胺砜噻吨 (thiothixine)、三氟拉嗪 (STELAZINE)、雷美尔通、氯氮平 (CLOZARIL)、去甲氯氮平 (ACP-104)、利培酮 (RISPERDAL)、帕利哌酮 (INVEGA)、美哌隆、奥氮平 (ZYPREXA)、喹硫平 (SEROQUEL)、他奈坦、氨磺必利、齐拉西酮 (GEODON)、布南色林 (LONASEN) 及 ACP-103(Acadia Pharmaceuticals)；

[0141] (x) 钙通道阻断剂，例如洛美利嗪、齐考诺肽、尼伐地平 (ESCOR、NIVADIL)、第泼地平 (diperdipine)、氨氯地平 (NORVASC、ISTIN、AMLODIN)、非洛地平 (PLENDIL)、尼卡地平 (CARDENE)、硝苯地平 (ADALAT、PROCARDIA)、MEM 1003 及其母体化合物尼莫地平 (NIMOTOP)、尼索地平 (SULAR)、尼群地平、拉西地平 (LACIPIL、MOTENS)、乐卡地平 (ZANIDIP)、利法利嗪、地尔硫卓 (CARDIZEM)、维拉帕米 (CALAN、VERELAN)、AR-R 18565(AstraZeneca) 及依奈卡定；

[0142] (xi) 儿茶酚 O- 甲基转移酶 (COMT) 抑制剂，例如硝替卡朋、托卡朋 (TASMAR)、恩他卡朋 (COMTAN) 及托酚酮；

[0143] (xii) 中枢神经系统刺激剂，例如阿托西汀、瑞波西汀、育亨宾、咖啡因、芬美曲秦、苯甲曲秦、匹莫林、芬坎法明 (GLUCOENERGAN、REACTIVAN)、苯丙胺乙茶碱 (CAPTAGON)、哌苯甲醇 (MERETRAN)、地阿诺 (亦称作二甲基氨基乙醇)、哌醋甲酯 (DAYTRANA)、盐酸哌醋甲酯 (RITALIN)、右哌甲酯 (FOCALIN)、安非他命 (单独或与其它 CNS 刺激剂 (例如，ADDERALL(天冬氨酸安非他命、硫酸安非他命盐、糖二酸右旋安非他命 (dextroamphetamine saccharate) 及硫酸右旋安非他命) 组合)、硫酸右旋安非他命 (DEXEDRINE、DEXTROSTAT)、甲基安非他命 (DESOXYN)、利右苯丙胺 (VYVANSE) 及苄非他命 (DIDREX)；

[0144] (xiii) 皮质类固醇，例如泼尼松 (STERAPRED、DELTASONE)、泼尼松龙 (PRELONE)、乙酸泼尼松龙 (OMNIPRED、PRED MILD、PRED FORTE)、泼尼松龙磷酸钠 (ORAPRED ODT)、甲泼尼龙 (MEDROL)；乙酸甲泼尼龙 (DEPO-MEDROL) 及甲泼尼龙琥珀酸钠 (A-METHAPRED、SOLU-MEDROL)；

[0145] (xiv) 多巴胺受体激动剂，例如阿扑吗啡 (APOKYN)、溴隐亭 (PARLODEL)、卡麦角林 (DOSTINEX)、地海西丁 (dihydrexidine)、双氢麦角隐亭、非诺多泮 (CORLOPAM)、利舒脲 (DOPERGIN)、特麦角脲斯培高利特 (terguride spergolide)(PERMAX)、吡贝地尔 (TRIVASTAL、TRASTAL)、普拉克索 (MIRAPEX)、喹吡罗、罗匹尼罗 (REQUIP)、罗替高汀 (NEUPRO)、SKF-82958(GlaxoSmithKline)、卡利哌嗪、帕多芦诺及沙立佐坦；

[0146] (xv) 多巴胺受体拮抗剂，例如氯丙嗪、氟奋乃静、氟哌啶醇、洛沙平 (loxzpine)、利培酮 (resperidone)、硫利达嗪、胺砜噻吨、三氟拉嗪、丁苯那嗪 (NITOMAN、XENAZINE)、7- 羟基阿莫沙平、氟哌利多 (INAPSINE、DRIDOL、DROPLETAN)、多潘立酮 (MOTILIUM)、L-741742、L-745870、雷氯必利、SB-277011A、SCH-23390、依考匹泮、SKF-83566 及甲氧氯普胺 (REGLAN)；

[0147] (xvi) 多巴胺重摄取抑制剂，例如安非他酮、沙非胺、马来酸诺米芬辛 (MERITAL)、伐诺司林 (亦称作 GBR-12909) 及其癸酸酯 DBL-583 及安咪奈丁；

[0148] (xvii) γ- 氨基丁酸 (GABA) 受体激动剂，例如巴氯芬 (LIORESAL、KEMSTRO)、西氯芬 (siclofen)、戊巴比妥 (NEMBUTAL)、普罗加胺 (GABRENE) 及氯美噻唑；

[0149] (xviii) 组胺 3(H3) 拮抗剂，例如莎芬 (ciproxifan)、替洛利生、S-38093、伊达必特 (irdabisant)、匹特利特 (pitolisant)、GSK-239512、GSK-207040、JNJ-5207852、JNJ-17216498、HPP-404、SAR-110894、反式 -3- 氟 -3-(3- 氟 -4- 吡咯烷 -1- 基甲基苯基) 环丁烷羧酸乙酰胺 (PF-3654746 及那些在以下文献中所公开的 :美国专利公开案第 US2005-0043354 号、第 US2005-0267095 号、第 US2005-0256135 号、第 US2008-0096955 号、第 US2007-1079175 号及第 US2008-0176925 号 ;国际专利公开案第 WO2006/136924 号、第 WO2007/063385 号、第 WO2007/069053 号、第 WO2007/088450 号、第 WO2007/099423 号、第 WO2007/105053 号、第 WO2007/138431 号及第 WO2007/088462 号 ;及美国专利第 7,115,600 号)；

[0150] (xix) 免疫调节剂，例如醋酸格拉默 (亦称作共聚物 -1 ;COPAXONE)、MBP-8298(合成髓磷脂碱蛋白肽)、富马酸二甲酯、芬戈莫德 (亦称作 FTY720)、罗喹美克 (LINOMIDE)、拉喹莫德 (亦称作 ABR-215062 及 SAIK-MS)、ABT-874(人类抗 -IL-12 抗体 ;Abbott)、利妥昔

单抗 (RITUXAN)、阿仑珠单抗 (CAMPATH)、达珠单抗 (ZENAPAX) 及那他珠单抗 (TYSABRI)；

[0151] (xx) 免疫抑制剂，例如氨甲蝶呤 (TREXALL、RHEUMATREX)、米托蒽醌 (NOVANTRONE)、麦考酚酸吗乙酯 (CELLCEPT)、麦考酚酸钠 (MYFORTIC)、硫唑嘌呤 (AZASAN、IMURAN)、巯嘌呤 (PURI-NETHOL)、环磷酰胺 (NEOSAR、CYTOXAN)、苯丁酸氮芥 (LEUKERAN)、克拉屈滨 (LEUSTATIN、MYLINAX)、α-胎蛋白、依那西普 (ENBREL) 及 4-苄氧基-5-((5-十一烷基-2H-吡咯-2-亚基)甲基)-2,2'-二-1H-吡咯 (亦称作 PNU-156804)；

[0152] (xxi) 干扰素，包括干扰素 β-1a(AVONEX、REBIF) 及干扰素 β-1b(BETASERON、BETAFERON)；

[0153] (xxii) 左旋多巴 (或其甲酯或乙酯)，单独或与 DOPA 脱羧酶抑制剂 (例如，卡比多巴 (SINEMET、CARBILEV、PARCOPA)、苄丝肼 (MADOPAR)、α-甲基多巴、单氟甲基多巴、二氟甲基多巴、溴克利辛或间羟基苄基肼) 组合；

[0154] (xxiii)N-甲基-D-天冬氨酸 (NMDA) 受体拮抗剂，例如美金刚 (NAMENDA、AXURA、EBIXA)、金刚烷胺 (SYMMETREL)、阿坎酸 (CAMPRAL)、百宋普洛地尔 (besonprodil)、氯胺酮 (KETALAR)、德芦西明、地塞比诺、右依法克生、右美沙芬、右啡烷、曲索罗地、CP-283097、习曼坦 (himantane)、伊旦他尔 (idantadol)、伊培沙宗、L-701252(Merck)、兰可塞明 (lancicemine)、左啡诺 (DROMORAN)、LY-233536 及 LY-235959(二者皆为 Lilly)、美沙酮、(DOLOPHINE)、奈拉美生、培净福太、苯环利定、噻奈普汀 (STABLON)、联苯西平 (亦称作 MK-801)、EAB-318(Wyeth)、伊波加因、老刺木碱、替来他明、利芦噻唑 (RILUTEK)、阿替加奈 (CERESOTAT)、加维斯替奈及瑞马米德 (remacimide)；

[0155] (xxiv) 单胺氧化酶 (MAO) 抑制剂，例如司立吉林 (EMSAM))、盐酸司立吉林 (l-地普雷尼尔、ELDEPRYL、ZELAPAR)、二甲基司立吉林、溴法罗明、苯乙肼 (NARDIL)、反苯环丙铵 (PARNATE)、吗氯贝胺 (AURORIX、MANERIX)、贝氟沙通、沙非酰胺、异卡波肼 (MARPLAN)、尼亚拉胺 (NIAMID)、雷沙吉兰 (AZILECT)、异丙异烟肼 (MARSILID、IPROZID、IPRONID)、CHF-3381(Chiesi Farmaceutici)、异丙氯肼、托洛沙酮 (HUMORYL、PERENUM)、二苯美伦、去氢骆驼蓬碱 (desoxypeganine)、哈尔明 (亦称作南美卡皮根碱或巴纳斯特 (banasterine))、哈马灵、利奈唑胺 (ZYVOX、ZYVOXID) 及帕吉林 (EUDATIN、SUPIRDYL)；

[0156] (xxv) 毒蕈碱受体 (具体而言 M1 亚型) 激动剂，例如西维美林、左乙拉西坦、氯贝胆碱 (DUVOID、URECHOLINE)、伊他美林、匹鲁卡品 (SALAGEN)、NGX267、槟榔碱、L-687306(Merck)、L-689660(Merck)、呋索碘铵 (FURAMON、FURANOL)、苯磺酸糠三甲铵、对甲苯磺酸糠三甲铵、McN-A-343、氧代震颤素、沙可美林、AC-90222(Acadia Pharmaceuticals) 及卡巴胆碱 (CARBASTAT、MIOSTAT、CARBOPTIC)；

[0157] (xxvi) 神经保护药物，例如波舒替尼、康朵莱斯 (condoliase)、阿莫氯醇 (airmoclomol)、拉莫三嗪、吡仑帕奈、茴拉西坦、苯哒吗啉 (minaprime)、韦鲁唑 (viluzole)、2,3,4,9-四氢-1H-咔唑-3-酮肟、去氨普酶、阿替班特、虾青素、神经肽 NAP(例如，AL-108 及 AL-208；二者均来自 Allon Therapeutics)、牛洛斯尔 (neurostrol)、吡仑帕奈 (perampenel)、异丙克兰、双 (4-β-D-吡喃葡萄糖基氧基苄基)-2-β-D-吡喃葡萄糖基-2-异丁基酒石酸盐 (亦称作达特罗痕 B(dactylorhin B) 或 DHB)、抚摩菌素 (formobactin)、扎利罗登 (XAPRILA)、乳胞素、盐酸地米柏林 (dimeboline hydrochloride) (DIMEBON)、地舒芬通 (disufenton) (CEROVIVE)、阿伦酸 (ONO-2506、PROGLIA、CEREACT)、胞

磷胆碱(亦称作胞苷5'-二磷酰胆碱)、依达拉奉(RADICUT)、AEOL-10113及AEOL-10150(二者均来自Aeolus Pharmaceuticals)、AGY-94806(亦称作SA-450及Msc-1)、粒细胞集落刺激因子(亦称作AX-200)、BAY-38-7271(亦称作KN-387271;Bayer AG)、安克洛酶(VIPRINEX、ARWIN)、DP-b99(D-Pharm有限公司)、HF-0220(17-β-羟基异雄酮;Newron Pharmaceuticals)、HF-0420(亦称作奥利歌平(oligotropin))、5'-磷酸吡哆醛(亦称作MC-1)、微质体、S-18986、吡氯佐坦、NP031112、他罗利姆、L-丝氨酰基-L-甲硫氨酰基-L-丙氨酰基-L-赖氨酰基-L-谷氨酰基-甘氨酰基-L-缬氨酸、AC-184897(Acadia Pharmaceuticals)、ADNF-14(National Institutes of Health)、芪甘菊蓝基硝酮(stilbazulenyl nitrone)、SUN-N8075(Daiichi Suntory Biomedical Research)及唑南帕奈;

[0158] (xxvii)烟碱受体激动剂,例如地棘蛙素、安非他酮、CP-601927、伐伦克林、ABT-089(Abbott)、ABT-594、AZD-0328(AstraZeneca)、EVP-6124、R3487(亦称作MEM3454;Roche/Memory Pharmaceuticals)、R4996(亦称作MEM63908;Roche/Memory Pharmaceuticals)、TC-4959及TC-5619(二者均来自Targacept)及RJR-2403;

[0159] (xxviii)去甲肾上腺素重摄取抑制剂,例如阿托西汀(STRATTERA)、多塞平(APONAL、ADAPIN、SINEQUAN)、去甲替林(AVENTYL、PAMELOR、NORTRILEN)、阿莫沙平(ASENDIN、DEMOLOX、MOXIDIL)、瑞波西汀(EDRONAX、VESTRA)、维洛沙秦(VIVALAN)、马普替林(DEPRILEPT、LUDIOMIL、PSYMION)、安非他酮(WELLBUTRIN)及拉达卡分(radaxafine);

[0160] (xxix)磷酸二酯酶(PDE)抑制剂,包括但不限于(a)PDE1抑制剂(例如,长春西丁(CAVINTON、CERACTIN、INTELECTOL)及那些在美国专利第6,235,742号所公开的,(b)PDE2抑制剂(例如,赤型-9-(2-羟基-3-壬基)腺嘌呤(EHNA)、BAY 60-7550及那些在美国专利第6,174,884号中所公开的,(c)PDE3抑制剂(例如,阿那格雷、西洛他唑、米力农、奥普力农、帕格雷利及匹莫苯旦),(d)PDE4抑制剂(例如,阿瑞司特、异丁司特罗氟司特(ibudilastroflumilast)、咯利普兰、Ro 20-1724、异丁司特(KETAS)、吡拉米司特(亦称作RP73401)、CDP840、西洛司特(ARIFLO)、罗氟司特、妥非司特、奥米司特(亦称作GRC 3886)、替托司特(亦称作OPC-6535)、利林司特(lirimifast)、茶碱(theophylline)(UNIPHYL、THEOLAIR)、阿罗茶碱(arofylline)(亦称作LAS-31025)、多索茶碱(doxofylline)、RPR-122818或日中花碱)及(e)PDE5抑制剂(例如,西地那非(VIAGRA、REVATIO)、他达拉非(CIALIS)、伐地那非(LEVITRA、VIVANZA)、乌地那非、阿伐那非、双嘧达莫(PERSANTINE)、E-4010、E-4021、E-8010、扎普司特、伊地那非(iodenafil)、米罗那非、DA-8159及那些在国际专利申请WO2002/020521、WO2005/049616、WO2006/120552、WO2006/126081、WO2006/126082、WO2006/126083及WO2007/122466中所公开的),(f)PDE7抑制剂;(g)PDE8抑制剂;(h)PDE9抑制剂(例如,BAY 73-6691(Bayer AG)及那些在美国专利公开第US2003/0195205号、第US2004/0220186号、第US2006/0111372号、第US2006/0106035号及第USSN 12/118,062号(于2008年5月9日提出申请)中所公开的),(i)PDE10抑制剂,例如2-[4-(1-甲基-4-吡啶-4-基-1H-吡唑-3-基)苯氧基甲基]喹啉(PF-2545920)及SCH-1518291;及(j)PDE11抑制剂;

[0161] (xxx)喹啉,例如奎宁(包括其盐酸盐、二盐酸盐、硫酸盐、硫酸氢盐及葡糖酸盐)、氯喹、甲基氯喹、羟氯喹(PLAQUENIL)、甲氟喹(LARIAM)及阿莫地喹(CAMOQUIN、

FLAVOQUINE)；

[0162] (xxxi)β-分泌酶抑制剂，例如ASP-1702、SCH-745966、JNJ-715754、AMG-0683、AZ-12304146、BMS-782450、GSK-188909、NB-533、LY-2886721、E-2609、HPP-854、(+)-苯丝氨酸酒石酸盐(POSIPHEN)、LSN-2434074(亦称作LY-2434074)、KMI-574、SCH-745966、Ac-rER(N^2-乙酰基-D-精氨酰基-L-精氨酸)、洛司他丁(loxistatin)(亦称作E64d)及CA074Me；

[0163] (xxxii)γ-分泌酶抑制剂及调节剂，例如BMS-708163(Avagacest)、WO20060430064(Merck)、DSP8658(Dainippon)、ITI-009、L-685458(Merck)、ELAN-G、ELAN-Z、4-氯-N-[2-乙基-1(S)-(羟基甲基)丁基]苯磺酰胺；

[0164] (xxxiii)5-羟色胺(5-羟基色胺)1A(5-HT_{1A})受体拮抗剂，例如螺哌隆、左旋-吲哚洛尔、BMY 7378、NAD-299、S(-)-UH-301、NAN 190、来考佐坦；

[0165] (xxxiv)5-羟色胺(5-羟基色胺)2C(5-HT2c)受体激动剂，例如戊卡色林及齐洛那平；

[0166] (xxxv)5-羟色胺(5-羟基色胺)4(5-HT_4)受体激动剂，例如PRX-03140(Epix)；

[0167] (xxxvi)5-羟色胺(5-羟基色胺)6(5-HT_6)受体拮抗剂，例如A-964324、AVI-101、AVN-211、米安色林(TORVOL、BOLVIDON、NORVAL)、甲硫替平(亦称作甲巯噻庚英)、利坦舍林、ALX-1161、ALX-1175、MS-245、LY-483518(亦称作SGS518;Lilly)、MS-245、Ro 04-6790、Ro 43-68544、Ro 63-0563、Ro 65-7199、Ro 65-7674、SB-399885、SB-214111、SB-258510、SB-271046、SB-357134、SB-699929、SB-271046、SB-742457(GlaxoSmithKline)、Lu AE58054(Lundbeck A/S)及PRX-07034(Epix)；

[0168] (xxxvii)5-羟色胺(5-HT)重摄取抑制剂，例如阿拉丙酯、西酞普兰(CELEXA、CIPRAMIL)、依他普仑(LEXAPRO、CIPRALEX)、氯米帕明(ANAFRANIL)、度洛西汀(CYMBALTA)、非莫西汀(MALEXIL)、氟苯丙胺(PONDIMIN)、去甲芬氟拉明、氟西汀(PROZAC)、氟伏沙明(LUVOX)、吲达品、米那普仑(IXEL)、帕罗西汀(PAXIL、SEROXAT)、舍曲林(ZOLOFT、LUSTRAL)、曲唑酮(DESYREL、MOLIPAXIN)、文拉法辛(EFFEXOR)、齐美定(NORMUD、ZELMID)、比西发定、去甲文拉法辛(PRISTIQ)、布索芬新、维拉佐酮、卡利哌嗪、纽络斯坦姆(neuralstem)及替索芬辛；

[0169] (xxxviii)营养因子，例如神经生长因子(NGF)、碱性成纤维细胞生长因子(bFGF;ERSOFERMIN)、神经营养蛋白-3(NT-3)、心脏营养素-1、脑源性神经营养因子(BDNF)、神经鞘胚素、美特林(meteorin)、及胶质细胞源神经营养因子(GDNF)及刺激营养因子产生的药剂，例如丙戊茶碱、艾地苯醌、PYM50028(COGANE;Phytopharm)及AIT-082(NEOTROFIN)；

[0170] (xxxix)甘氨酸转运蛋白-1抑制剂，例如帕利氟汀(paliflutine)、ORG-25935、JNJ-17305600及ORG-26041；

[0171] (xl)AMPA型谷氨酸受体调节剂，例如吡仑帕奈、米巴帕特(mibampator)、塞卤胺派(selurampanel)、GSK-729327、N-{(3S,4S)-4-[4-(5-氰基噻吩-2-基)苯氧基]四氢呋喃-3-基}丙-2-磺酰胺等。

[0172] 本发明进一步包括适用于实施上述治疗方法的药盒。在一个实施方案中，所述药盒含有包含一或多种本发明的化合物的第一剂型及用于所述剂量的容器，所述第一剂型的量足以实施本发明的方法。

[0173] 在另一实施方案中，本发明的药盒包含一或多种本发明的化合物。

[0174] 本发明的化合物或其药学上可接受的盐可通过本领域类似已知的多种方法制备。下述反应路线与有机化学领域内已知的合成方法或那些本领域技术人员熟悉的修改及衍生一起阐释制备所述化合物的六 (6) 种方法。本领域技术人员会容易地明了其它方法（包括其修改）。

[0175] 本文所用的原料可市售获得或可通过本领域已知的常规方法（例如那些标准参考书（例如 COMPENDIUM OF ORGANIC SYNTHETIC METHODS, 第 I-XII 卷（由 Wiley-Interscience) 出版）中所公开的方法）制备。优选的方法包括但不限于下文所述的那些。

[0176] 在任意下列合成顺序期间，可必需和 / 或期望保护任意所关注分子上的敏感性或反应性基团。其可借助常用保护基而实现，所述常用保护基例如阐述于以下文献中的那些 :T.W.Greene,Protective Groups in Organic Chemistry,John Wiley&Sons,1981 ; T.W.Greene 及 P.G.M.Wuts,Protective Groups in Organic Chemistry,John Wiley&Sons,1991 ; 及 T.W.Greene 及 P.G.M.Wuts,Protective Groups in Organic Chemistry,John Wiley&Sons,1999，其援引加入本文中。

[0177] 本发明的化合物或所述化合物的药学上可接受的盐或互变异构体及放射性同位素可根据下文所述的反应路线制备。除非另外指明，否则路线中的取代基如上文所定义。产物的分离及纯化通过具有普通技术的化学工作者已知的标准操作完成。

[0178] 本领域技术人员应认识到，在一些情形下，路线 1 至 6 中的化合物会作为非对映异构体和 / 或对映异构体的混合物产生 ;这些混合物可在合成路线的不同阶段使用常规技术或此类技术（例如但不限于结晶、正相色谱、反相色谱及手性色谱）的组合得以分离，以得到本发明的单一对映异构体。

[0179] 本领域技术人员应了解，路线、方法及实施例中所用的各种符号、上标及下标用于方便表示和 / 或反映将其引入路线中的次序，而并不意欲必须对应于所附权利要求书中的符号、上标或下标。这些路线代表了可用于合成本发明的化合物的方法。其并不以任何方式限制本发明的范围。

[0180] 下文路线 1 阐释用于制备式 I 的化合物的一种合成顺序。如所绘示合成中的初始步骤利用式 1 的 2- 氯 -3- 硝基吡啶作为初始原料。2- 氯 -3- 硝基吡啶 1 在作为质子清除剂的碱的存在下于室温至 200℃的温度下经历与式 2 的胺亲核剂（例如苯胺）的 S_NAr 反应，以产生式 II 的氨基硝基吡啶。在初始 S_NAr 反应步骤期间，式 2 的胺亲核剂上的 R^1 取代基应由如最终产物中期望的相同基团或其经保护变形表示。举例而言，实施例 1 的最终产物 (N- 环丙基 -3-(3- 氟 -4- 甲基苯基)-3H- 咪唑并 [4,5-b] 吡啶 -2- 甲酰胺）可利用反应路线 1 制备，其中式 2 的胺亲核剂的 R^1 由 3- 氟 -4- 甲基苯基表示。

[0181] 反应的下一步为将式 II 的硝基还原为胺，以产生式 III 的二氨基吡啶化合物。此步骤可在氢源的存在下通过钯或镍还原而实现或者在弱酸的存在下通过化学计量金属还原（例如铁及锌）而实现。

[0182] 在下一步中，可由在式 3 的草酰氯的半酯上用式 3' 的胺（亦即，HNR^6R^7）置换来产生式 IV 的半酯草酰胺。在胺置换步骤期间，式 3' 的胺上的 R^6 及 R^7 取代基应由如最终产物中期望的相同基团或其经保护变形表示。举例而言，对于上述实施例 1 的最终产物而言，式

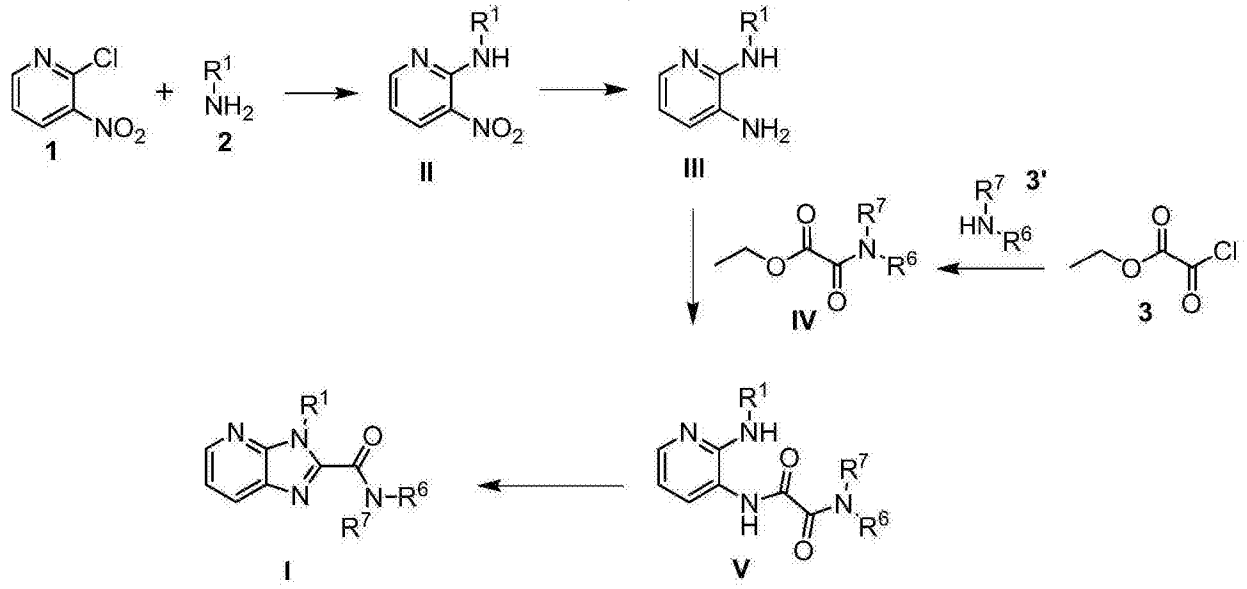
3’的胺的 R^6及 R^7之一由氢表示且另一者由环丙基表示。

[0183] 在胺置换步骤之后，可通过在热条件下缩合式 III 的二氨基吡啶与式 IV 化合物来制备式 V 化合物，反应速率在碱性条件下增加。

[0184] 在路线 1 的最终步骤中，可在脱水条件（例如热，用路易斯酸处理）或酰胺偶联条件下实现式 V 的化合物向式 I 的化合物的转化。

[0185]

路线 1

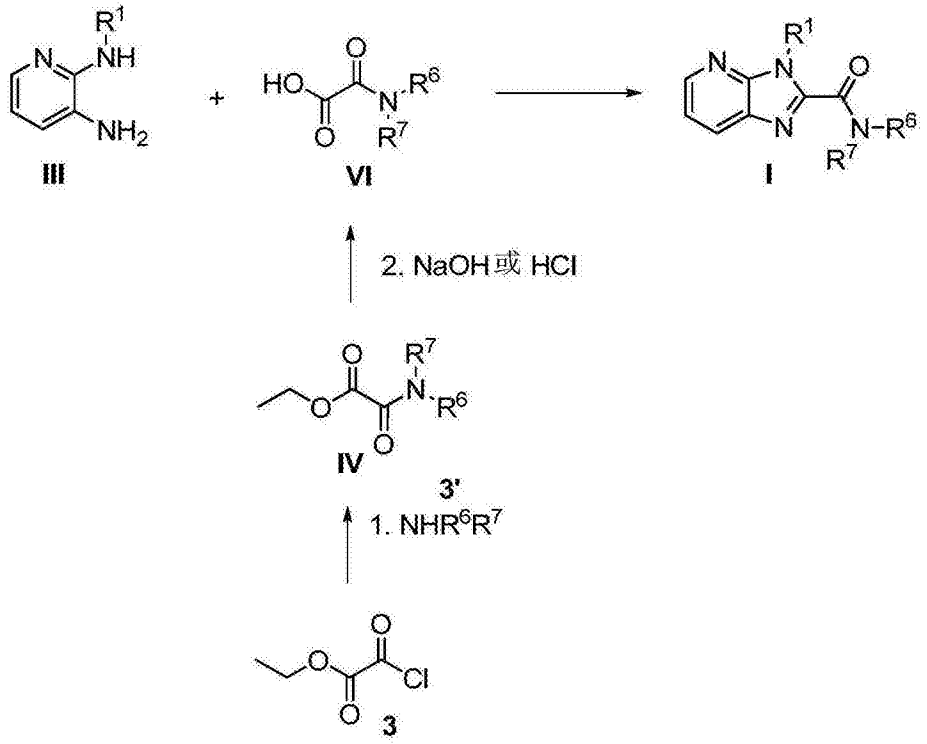


[0186] 下文路线 2 阐述式 I 的化合物的制备的替代合成顺序。可在两个步骤中由在碱的存在下通常于室温或更低温度下用式 3’的胺处理式 3 的草酰氯的半酯来产生式 VI 的草酸。可通过在酸性或碱性水性条件下于 0℃至 150℃的温度下处理将式 IV 的所得的半酯草酰胺水解成式 VI 的草酸。

[0187] 接下来，可在酰胺偶联 / 脱水试剂（例如 2,4,6- 三丙基 -1,3,5,2,4,6- 三氧杂三膦烷 2,4,6- 三氧化物 (2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane2,4,6-trioxide,T3P)、O-(7- 氮杂苯并三唑 -1- 基)-N,N,N’,N’- 四甲基脲鎓六氟磷酸盐 (HATU)、二环已基碳二亚胺 (DCC) 等）的存在下于 -20℃至 100℃的温度下将式 III 的二氨基吡啶与式 VI 的草酸混合；随后加热至 200℃，从而产生式 I 的化合物。

[0188]

路线 2



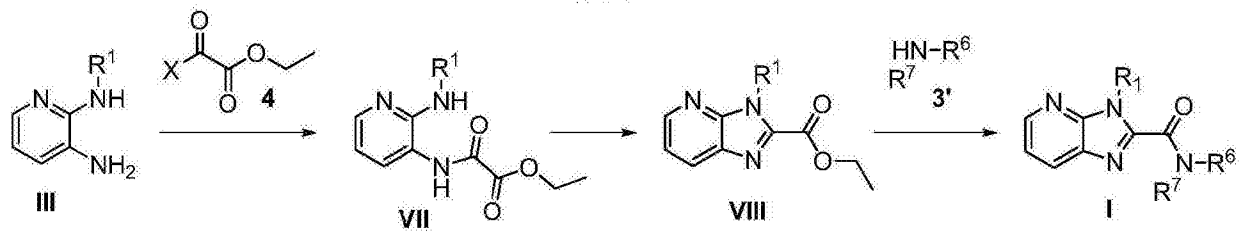
[0189] 下文路线 3 阐释式 I 的化合物的制备的替代合成顺序。可通过式 4 的酯 - 草酸酯（其中 x 由氯、烷氧基、琥珀酰亚胺等表示）上的离去基团的亲核置换酰化式 III 的二氨基吡啶，以产生式 VII 的氨基吡啶氨基氧代乙酸酯化合物。

[0190] 在下一步中，可在脱水条件（例如热，用路易斯酸处理）或酰胺偶联条件（例如 2,4,6- 三丙基 -1,3,5,2,4,6- 三氧杂三膦烷 2,4,6- 三氧化物 (T3P)、O-(7- 氮杂苯并三唑 -1- 基)-N,N,N',N'- 四甲基脲鎓六氟磷酸盐 (HATU)、二环己基碳二亚胺 (DCC) 等）下环化式 VII 的化合物，以产生式 VIII 的咪唑并吡啶酯。

[0191] 接下来，可通过于 20℃至 200℃的温度下在存在或不存在溶剂的情况下向式 VIII 的咪唑并吡啶酯中添加式 3' 的胺来实施式 VIII 的咪唑并吡啶酯向式 I 的酰胺的转化。另外，此转化可通过于 20℃至 200℃的温度下或在微波辐照及适用温度下向胺及式 VIII 的咪唑并吡啶酯的混合物中添加碱或路易斯酸来进行。

[0192]

路线 3

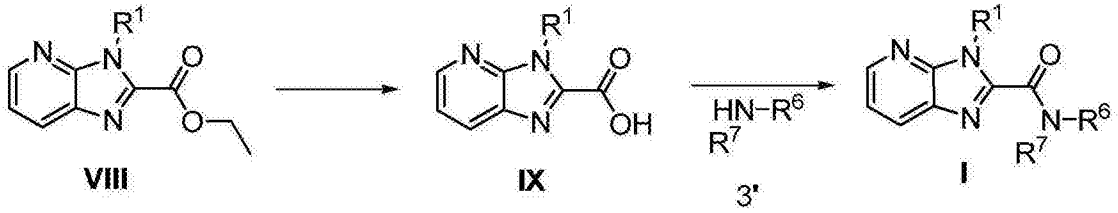


[0193] 下文路线 4 阐释由式 VIII 的酯制备式 I 的化合物的另一替代合成顺序。在初始步骤中，式 VIII 的酯可在碱性或酸性水性条件下水解成相应的式 IX 的咪唑并吡啶羧酸。在初始步骤期间，式 VIII 的酯上的 R^1 取代基应由如最终产物中期望的相同基团或其经保护变形表示。

[0194] 接下来，可使用多种酰胺偶联试剂（例如 2,4,6- 三丙基 -1,3,5,2,4,6- 三氧杂三膦烷 2,4,6- 三氧化物 (T3P)、O-(7- 氮杂苯并三唑 -1- 基)-N,N,N',N'- 四甲基脲鎓六氟磷酸盐 (HATU)、二环己基碳二亚胺 (DCC) 等）中的任一者使式 IX 的咪唑并吡啶酸与式 3' 的适当的胺反应，以提供式 I 的化合物。

[0195]

路线 4

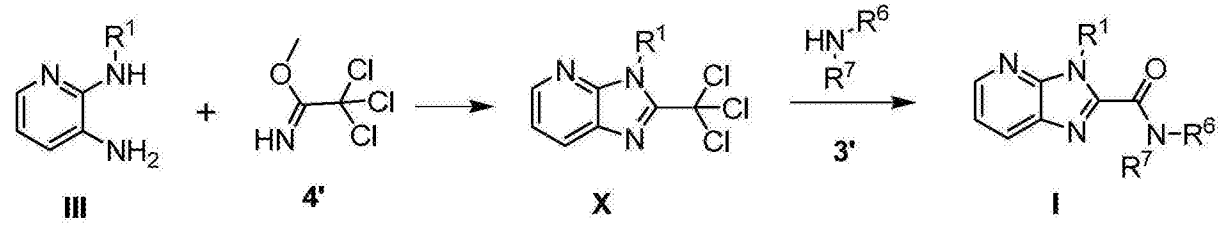


[0196] 下文路线 5 阐释由式 III 的二氨基吡啶化合物制备式 I 的化合物的另一替代合成顺序。在初始步骤中，可在弱酸的存在下用式 4' 的 2,2,2- 三氯乙酰亚氨酸甲酯 (2,2,2-trichloroacetimidate) 处理式 III 的化合物，以形成式 X 的三氯甲基取代的咪唑并 [4,5-b] 吡啶（参见 Venable,J. 等人，Journal of Medicinal Chemistry 2005,48,8289）。

[0197] 接下来，可在弱碱性水性条件下用式 3' 的胺处理式 X 化合物以提供式 I 的化合物。

[0198]

路线 5



[0199] 下文路线 6 阐释式 I 的化合物的制备的另一合成顺序，其中 R^1 为任选地被取代的芳基。

[0200] 在第一步中，在金属催化剂（钯、铜、铑等）、配体及碱的存在下于室温至约 200℃ 的温度下使 2- 氨基 -3- 硝基吡啶与式 5 的卤代芳基化合物偶联，以产生式 XI 的苯氨基吡啶结构。此一般反应有时称作 Buchwald-Hartwig 胺化。类似的偶联先前已有记载 (WO2008/4117 A1 及 Org.Lett.2009,11,5502-5505)。在此反应期间，式 5 的卤代芳基化合物上的 R^1 取代基应由如最终产物中期望的相同基团或其经保护变形表示。举例而言，实施例 7 的最终产物 [3-(4- 氰基 -3- 氟苯基)-N- 环丙基 -3H- 咪唑并 [4,5-b] 吡啶 -2- 甲酰胺] 可利用反应路线 6 制备，其中二氨基吡啶的 R^1 由 4- 氰基 -3- 氟苯基表示。

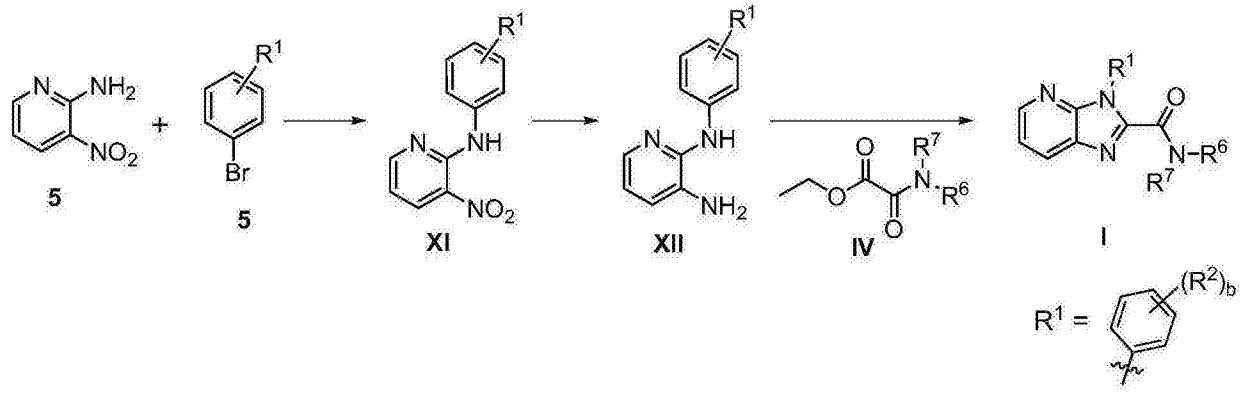
[0201] 在下一步中，可在氢源的存在下通过钯或镍还原或者在弱酸的存在下通过化学计量金属还原（例如铁及锌）来将硝基还原成胺，以产生式 XII 的化合物。

[0202] 接下来，可通过式 XII 的化合物与式 IV 的化合物（路线 2）在碱性条件下于室温至 200℃ 的温度下反应，然后室温添加脱水试剂 / 酰胺偶联试剂 2,4,6- 三丙基 -1,3,5,2,4,6- 三氧杂三膦烷 2,4,6- 三氧化物 (T3P)、O-(7- 氮杂苯并三唑 -1- 基)-N,N,N',N'- 四甲基脲鎓六氟磷酸盐 (HATU)、二环己基碳二亚胺 (DCC) 等并通

过适当加热（室温至200℃）的随后反应以产生式I的化合物，从而将式XII的化合物转化成式I的化合物，其中R^1为任选地被取代的芳基，其中任选存在的取代基由$(R^2)_b$表示。

[0203]

路线6



[0204] 实验操作及实施例

[0205] 下文阐释多种本发明的化合物的合成。本发明范围内的其它化合物可使用这些实施例中阐释的方法（单独地或与本领域公知技术组合）来制备。

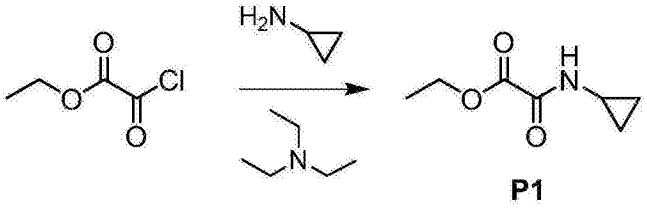
[0206] 实验通常在惰性气氛（氮或氩）下进行，特别在采用氧敏感性或水份敏感性试剂或中间体的情形下。市售溶剂及试剂通常未经进一步纯化即可使用。若适当，采用无水溶剂（通常来自Aldrich Chemical公司，Milwaukee，Wisconsin的Sure-Seal™产品，或使用那些本领域技术人员熟知的操作干燥并蒸馏的溶剂）。通常在真空下干燥产物，然后进行进一步反应或进行生物测试。质谱数据由液相色谱-质谱(LCMS)、大气压化学电离(APCI)或气相色谱-质谱(GCMS)仪器报告。核磁共振(NMR)数据的化学位移表示为百万份数(ppm，δ)，参照来自所用氘化溶剂的残余峰。

[0207] 对于其它实施例或方法中的合成参考操作而言，反应条件（反应长度及温度）可改变。一般而言，反应之后进行薄层色谱法或质谱法，且若适当进行后处理。纯化可视实验而改变：一般而言，选择用于洗脱剂/梯度的溶剂及溶剂比以提供适当的R_fs或保留时间。

[0208] 制备例P1

[0209] （环丙基氨基）（氧代）乙酸乙酯(P1)

[0210]

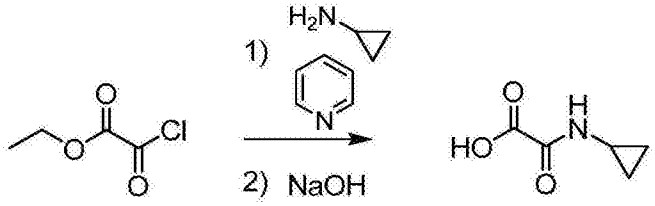


[0211] 向氯（氧代）乙酸乙酯(3.5g，26mmol)在四氢呋喃(25mL)中的0℃溶液中逐滴添加环丙胺(1.39g，24.3mmol)及三乙胺(3.5g，35mmol)的混合物。将反应混合物于0℃下搅拌10分钟并过滤；在真空中浓缩滤液以得到黄色固体状产物。收率：3.0g，19mmol，78％。^{1}H NMR(400MHz，$CDCl_3$) δ 7.14(br s，1H)，4.34(q，J = 7.2Hz，2H)，2.78-2.86(m，1H)，1.38(t，J = 7.2Hz，3H)，0.83-0.90(m，2H)，0.59-0.65(m，2H)。

[0212] 制备例P2

[0213] （环丙基氨基）（氧代）乙酸 (P2)

[0214]



P2

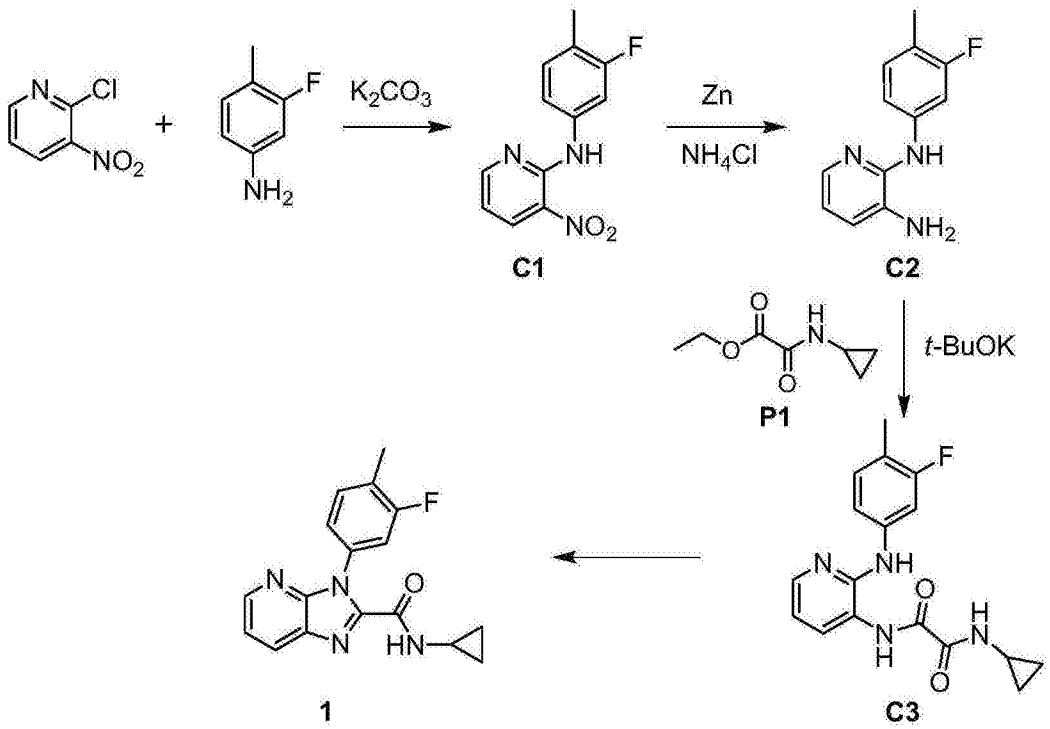
[0215] 经 10 分钟向环丙胺 (60mL, 0.86mol) 及吡啶 (70mL, 0.86mol) 在二氯甲烷 (740mL) 中的 -20℃溶液中添加氯（氧代）乙酸乙酯 (96mL, 0.86mol)，并将反应混合物于 0℃下搅拌 1 小时，随后于 20℃下搅拌 20 小时。用盐酸水溶液 (1M, 3×185mL) 洗涤反应混合物，随后将有机层与氢氧化钠水溶液 (1M, 930mL, 0.93mol) 一起搅拌 30 分钟。将所得水层用浓盐酸 (78mL) 酸化至 pH1，用氯化钠 (100g) 处理，并用二氯甲烷 (6×500mL) 及乙酸乙酯 (6×500mL) 萃取。将合并的有机层经硫酸镁干燥，过滤并在真空中浓缩；将所得固体与乙酸乙酯 (150mL) 混合并升温回流。在搅拌下经 16 小时冷却至室温后，经由过滤收集固体并用乙酸乙酯洗涤，得到闪烁白色固体状产物。收率：67.8g, 0.525mol, 61％。LCMS m/z 130.0 $[M+H]^+$。^1H NMR (400MHz, DMSO-d_6) δ 13.73 (br s, 1H), 8.83 (br d, J = 4.0Hz, 1H), 2.68-2.77 (m, 1H), 0.61-0.68 (m, 2H), 0.54-0.61 (m, 2H)。

实施例

[0216] 实施例 1

[0217] N- 环丙基 -3-(3- 氟 -4- 甲基苯基)-3H- 咪唑并 [4,5-b] 吡啶 -2- 甲酰胺 (1)

[0218]



[0219] 步骤 1. N-(3- 氟 -4- 甲基苯基)-3- 硝基吡啶 -2- 胺 (C1) 的合成

[0220] 将 2- 氯 -3- 硝基吡啶 (4.76g,30.0mmol)、3- 氟 -4- 甲基苯胺 (3.75g,30.0mmol) 及碳酸钾 (8.29g,60.0mmol) 在二甲亚砜 (30mL) 中的混合物于 140℃下搅拌 40 分钟。随后将反应混合物冷却至室温,用水稀释并用乙酸乙酯萃取。将合并的有机层用水稀释,经硫酸镁干燥,过滤并在真空中浓缩,以得到黑色固体状产物。收率:6.78g,27.4mmol,91 %。^{1}H NMR(400MHz,$CDCl_3$) δ 10.11(br s,1H),8.54(dd,J = 8.3,1.8Hz,1H),8.51(dd,J = 4.6,1.8Hz,1H),7.59-7.64(m,1H),7.15-7.21(m,2H),6.86(dd,J = 8.4,4.6Hz,1H),2.28(d,J = 2.0Hz,3H)。

[0221] 步骤 2.N^2-(3- 氟 -4- 甲基苯基)吡啶 -2,3- 二胺 (C2) 的合成 .

[0222] 向 N-(3- 氟 -4- 甲基苯基)-3- 硝基吡啶 -2- 胺 (C1)(6.78g,27.4mmol) 及氯化铵 (11.7g,219mmol) 在四氢呋喃 (55mL) 及水 (55mL) 中的搅拌混合物中添加锌粉 (14.3g,219mmol),引起混合物的温度升至 45℃。将反应混合物搅拌 10 分钟,且随后经由硅藻土垫过滤,用乙酸乙酯冲洗。将滤液的有机层用乙酸乙酯稀释,用氯化铵水溶液及饱和氯化钠水溶液洗涤,经硫酸镁干燥并过滤。在真空中浓缩滤液,以得到黑色固体状产物 (6.6g),其大部分直接进行下一步。LCMS m/z 218.1[M+H]$^+$。^{1}H NMR(400MHz,$CDCl_3$),特征产物峰:δ 7.84(dd,J = 4.9,1.6Hz,1H),7.01(dd,J = 7.6,1.6Hz,1H),6.82(br dd,J = 8,2Hz,1H),6.77(dd,J = 7.6,4.9Hz,1H),2.20(d,J = 2Hz,3H)。

[0223] 步骤 3.N- 环丙基 -N'-{2-[(3- 氟 -4- 甲基苯基)氨基]吡啶 -3- 基} 乙烷二酰胺 (C3) 的合成

[0224] 向 N^2-(3- 氟 -4- 甲基苯基)吡啶 -2,3- 二胺 (C2)(来自前述步骤,5.87g,≤ 24.4mmol) 及 (环丙基氨基)(氧代)乙酸乙酯 (P1)(6.36g,40.5mmol) 在 1- 甲基吡咯烷 -2- 酮 (27mL) 中的溶液中添加叔丁醇钾 (4.54g,40.5mmol)。将反应混合物于 120℃下加热 10 分钟,冷却至室温并用氯化铵水溶液稀释。添加四氢呋喃以帮助溶解,之后添加乙酸乙酯。将有机层用饱和氯化钠水溶液洗涤,经硫酸镁干燥,过滤并在真空中浓缩,以提供粗产物 (13.0g)。此物质的一部分直接用于下一步。LCMS m/z 329.0[M+H]$^+$。

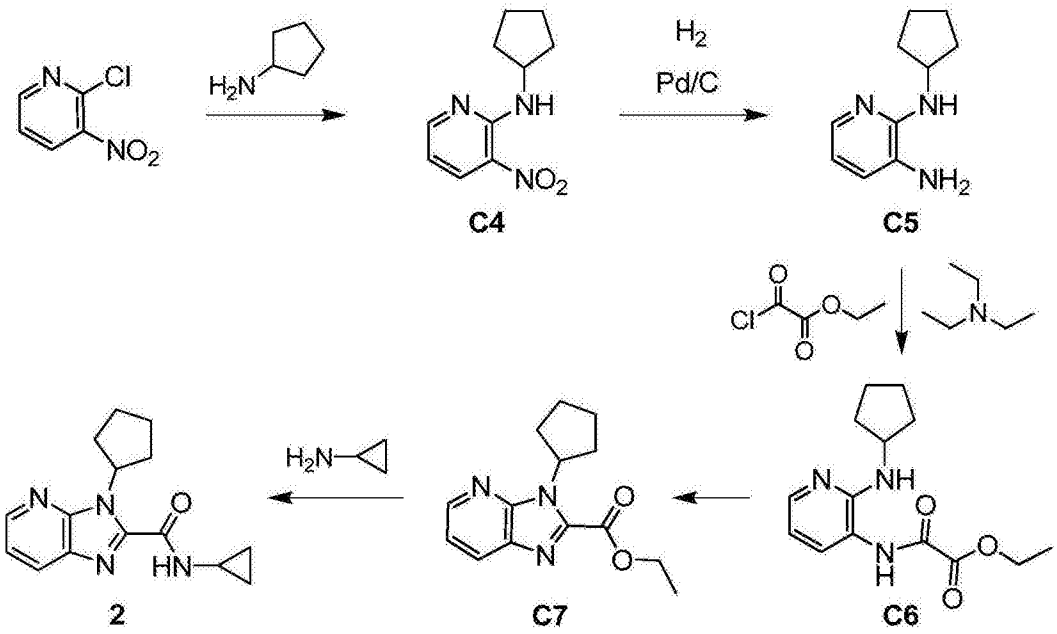
[0225] 步骤 4.N- 环丙基 -3-(3- 氟 -4- 甲基苯基)-3H- 咪唑并 [4,5-b] 吡啶 -2- 甲酰胺 (1) 的合成

[0226] 将 N- 环丙基 -N'-{2-[(3- 氟 -4- 甲基苯基)氨基]吡啶 -3- 基} 乙烷二酰胺 (C3)(来自前述步骤,8.86g,≤ 16.6mmol) 及乙烷 -1,2- 二醇 (27mL) 的混合物于 200℃下搅拌 1 小时。在冷却至室温后,将反应混合物用水 (100mL) 及氢氧化钠水溶液 (1M,100mL) 稀释,随后用乙酸乙酯萃取。将合并的有机层用饱和氯化钠水溶液洗涤,经硫酸镁干燥,过滤,并在减压下浓缩。使用硅胶色谱 (梯度:在庚烷中的 5% 至 50% 乙酸乙酯) 纯化,之后从 3:1 甲苯 / 庚烷中重结晶,以得到固体状产物。收率:2.52g,8.12mmol,经 3 个步骤 49%。LCMS m/z 311.0[M+H]$^+$。^{1}H NMR(400MHz,$CDCl_3$) δ 8.50(dd,J = 4.7,1.5Hz,1H),8.13(dd,J = 8.1,1.5Hz,1H),7.68(br s,1H),7.37(dd,J = 8.1,4.7Hz,1H),7.34-7.40(m,1H),7.10-7.15(m,2H),2.83-2.90(m,1H),2.37(br d,J = 2Hz,3H),0.83-0.89(m,2H),0.67-0.72(m,2H)。

[0227] 实施例 2

[0228] 3- 环戊基 -N- 环丙基 -3H- 咪唑并 [4,5-b] 吡啶 -2- 甲酰胺 (2)

[0229]



[0230] 步骤 1. N- 环戊基 -3- 硝基吡啶 -2- 胺 (C4) 的合成

[0231] 向 2- 氯 -3- 硝基吡啶 (5.0g, 32mmol) 在四氢呋喃 (200mL) 中的溶液中添加环戊胺 (2.7g, 32mmol), 并将反应混合物于回流温度下搅拌 18 小时。在减压下去除溶剂后, 经由硅胶色谱纯化残余物, 以产生黄色固体状产物。收率 :5.5g, 26mmol, 81 %。^{1}H NMR(400MHz, CD_3OD) δ 8.42(dd, ABX 图形的一半 , J = 8.3, 1.8Hz, 1H), 8.40(dd, ABX 图形的一半 , J = 4.5, 1.8Hz, 1H), 6.69(dd, J = 8.3, 4.5Hz, 1H), 4.51-4.59(m, 1H), 2.07-2.17(m, 2H), 1.62-1.85(m, 4H), 1.51-1.62(m, 2H)

[0232] 步骤 2. N^2- 环戊基吡啶 -2, 3- 二胺 (C5) 的合成

[0233] 向 N- 环戊基 -3- 硝基吡啶 -2- 胺 (C4)(4.7g, 23mmol) 在甲醇 (100mL) 中的溶液中添加钯 / 炭 (0.5g), 并将混合物用氢气脱气。在氢气下于室温下搅拌 4 小时后, 过滤反应混合物 ; 在真空中浓缩滤液, 以得到黑色固体状产物。收率 :3.6g, 20mmol, 87 %。^{1}H NMR(400MHz, DMSO-d_6) δ 7.35(dd, J = 5, 1Hz, 1H), 6.63(dd, J = 7.3, 1.0Hz, 1H), 6.30(dd, J = 7.3, 5.0Hz, 1H), 5.31(br d, J = 6.3Hz, 1H), 4.69(br s, 2H), 4.18-4.28(m, 1H), 1.88-2.00(m, 2H), 1.61-1.75(m, 2H), 1.36-1.60(m, 4H) 。

[0234] 步骤 3. {[2-(环戊基氨基) 吡啶 -3- 基] 氨基 }(氧代) 乙酸乙酯 (C6) 的合成

[0235] 向 N^2- 环戊基吡啶 -2, 3- 二胺 (C5)(1.78g, 10.0mmol) 及三乙胺 (1.52g, 15.0mmol) 在二氯甲烷 (100mL) 中的溶液中添加氯 (氧代) 乙酸乙酯 (1.49g, 10.9mmol), 并将反应混合物于室温下搅拌 18 小时。在真空中去除挥发物, 得到褐色固体状粗产物 (2g), 其未经进一步纯化即用于下一步。

[0236] 步骤 4. 3- 环戊基 -3H- 咪唑并 [4, 5-b] 吡啶 -2- 羧酸乙酯 (C7) 的合成

[0237] 将粗制 {[2-(环戊基氨基) 吡啶 -3- 基] 氨基 }(氧代) 乙酸乙酯 (C6)(来自前述步骤, 2g) 在甲苯 (100mL) 中的溶液于回流温度下搅拌 18 小时。在真空中浓缩反应混合物并使用硅胶色谱 (梯度 :在石油醚中的 9 % 至 50 % 乙酸乙酯) 纯化残余物, 以提供褐色固体状产物。收率 :0.70g, 2.7mmol, 经 2 个步骤 27 %。^{1}H NMR(400MHz, CD_3OD) δ 8.53(dd, J = 4.6, 1.4Hz, 1H), 8.14(dd, J = 8.2, 1.4Hz, 1H), 7.40(dd, J = 8.2, 4.7Hz, 1H), 5.79-5.89(m, 1H), 4.51(q, J = 7.1Hz, 2H), 2.48-2.61(m, 2H), 2.07-2.20(m, 4H), 1.70-1.83(m, 2H), 1.46

(t, J = 7.2Hz, 3H)。

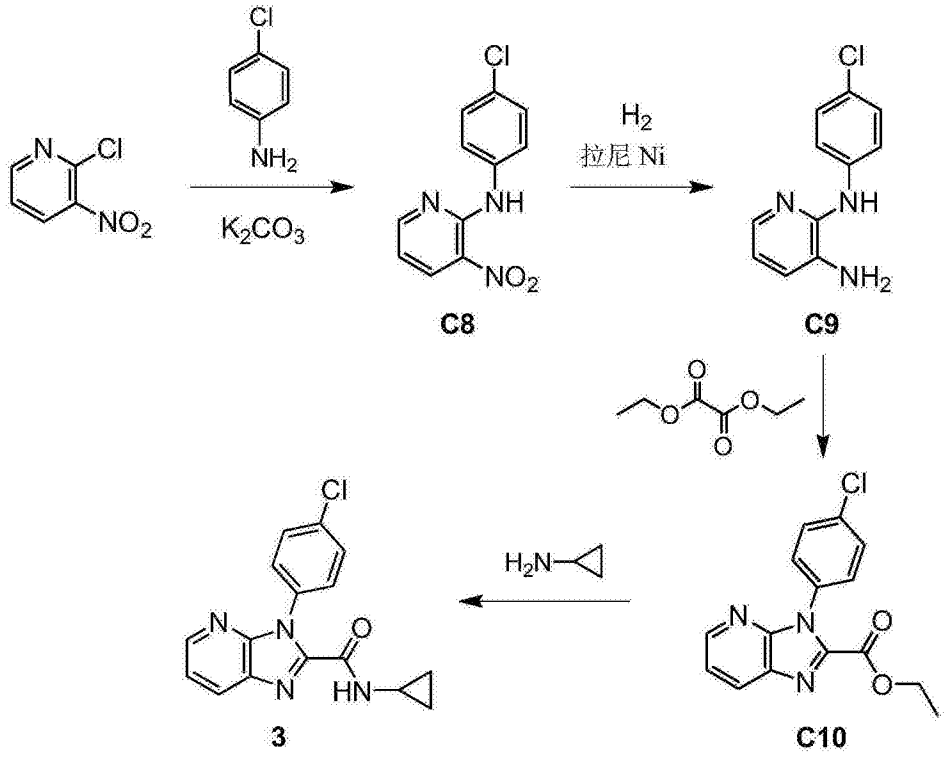
[0238] 步骤 5.3- 环戊基 -N- 环丙基 -3H- 咪唑并 [4,5-b] 吡啶 -2- 甲酰胺 (2) 的合成

[0239] 向 3- 环戊基 -3H- 咪唑并 [4,5-b] 吡啶 -2- 羧酸乙酯 (C7)(0.12g,0.46mmol) 在乙醇 (10mL) 中的溶液中添加环丙胺 (0.55g,9.6mmol),并将反应混合物于室温下搅拌 18 小时。在真空中浓缩后,经由硅胶上制备型薄层色谱 (洗脱剂 :5:1 石油醚 / 乙酸乙酯) 实现纯化,以得到黄色固体状产物。收率 :36mg,0.13mmol,28%。LCMS m/z 270.9[M+H]$^+$。^{1}H NMR(400MHz, $CDCl_3$) δ 8.47(dd, J = 4.6, 1.5Hz, 1H), 8.02(br d, J = 8Hz, 1H), 7.85(br s, 1H), 7.27(dd, J = 8.2, 4.6Hz, 1H, 假定 ;被溶剂峰部分遮蔽), 6.16-6.27(m, 1H), 2.89-2.97(m, 1H), 2.51-2.64(m, 2H), 2.06-2.19(m, 4H), 1.69-1.81(m, 2H), 0.87-0.95(m, 2H), 0.69-0.76(m, 2H)。

[0240] 实施例 3

[0241] 3-(4- 氯苯基)-N- 环丙基 -3H- 咪唑并 [4,5-b] 吡啶 -2- 甲酰胺 (3)

[0242]



[0243] 步骤 1.N-(4- 氯苯基)-3- 硝基吡啶 -2- 胺 (C8) 的合成

[0244] 向 2- 氯 -3- 硝基吡啶 (15.4g,97.1mmol) 在 N,N- 二甲基甲酰胺 (100mL) 中的溶液中添加 4- 氯苯胺 (12.4g,97.2mmol) 及碳酸钾 (20g,140mmol)。将反应混合物于 100℃ 下搅拌 18 小时,且随后倾倒至冰水 (200mL) 中。经由过滤收集沉淀并用水 (3×30mL) 稀释,以提供黑色固体状产物。收率 :15g,60mmol,62%。^{1}H NMR(400MHz, DMSO-d_6) δ 9.97(br s, 1H), 8.47-8.57(m, 2H), 7.69(d, J = 8.8Hz, 2H), 7.41(d, J = 8.8Hz, 2H), 7.01(dd, J = 8.2, 4.6Hz, 1H)。

[0245] 步骤 2.N^2-(4- 氯苯基) 吡啶 -2,3- 二胺 (C9) 的合成

[0246] 向 N-(4- 氯苯基)-3- 硝基吡啶 -2- 胺 (C8)(2.68g,10.7mmol) 在乙酸乙酯 (100mL) 中的溶液中添加拉尼镍 (1.5g),并将混合物用氢气脱气。于室温下氢化 6 小时后,

过滤反应混合物；在真空中浓缩滤液，得到黑色固体状产物。收率：1.8g，8.2mmol，77％。^{1}H NMR(400MHz，DMSO-d_6) δ 7.88(br s，1H)，7.67(d，J = 8.9Hz，2H)，7.50(br d，J = 4Hz，1H)，7.25(d，J = 8.9Hz，2H)，6.91(br d，J = 7.5Hz，1H)，6.64(dd，J = 7.3，4.8Hz，1H)，5.08(br s，2H)。

[0247] 步骤3.3-(4-氯苯基)-3H-咪唑并[4，5-b]吡啶-2-羧酸乙酯(C10)的合成

[0248] 将N^2-(4-氯苯基)吡啶-2，3-二胺(C9)(1.8g，8.2mmol)及乙二酸二乙酯(18g，123mmol)的混合物于140℃下搅拌18小时。使用硅胶色谱(梯度：在石油醚中的16％至50％乙酸乙酯)纯化，提供褐色固体状产物，通过^{1}H NMR分析得出其含有约30％的杂质。收率：250mg，0.83mmol，10％。^{1}H NMR(400MHz，CD_3OD)，仅产物峰：δ 8.49(dd，J = 4.8，1.5Hz，1H)，8.31(dd，J = 8.2，1.4Hz，1H)，7.61(br d，J = 8.9Hz，2H)，7.52(dd，J = 8.2，4.6Hz，1H)，7.49(br d，J = 8.9Hz，2H)，4.34(q，J = 7.2Hz，2H)，1.25(t，J = 7.2Hz，3H)。

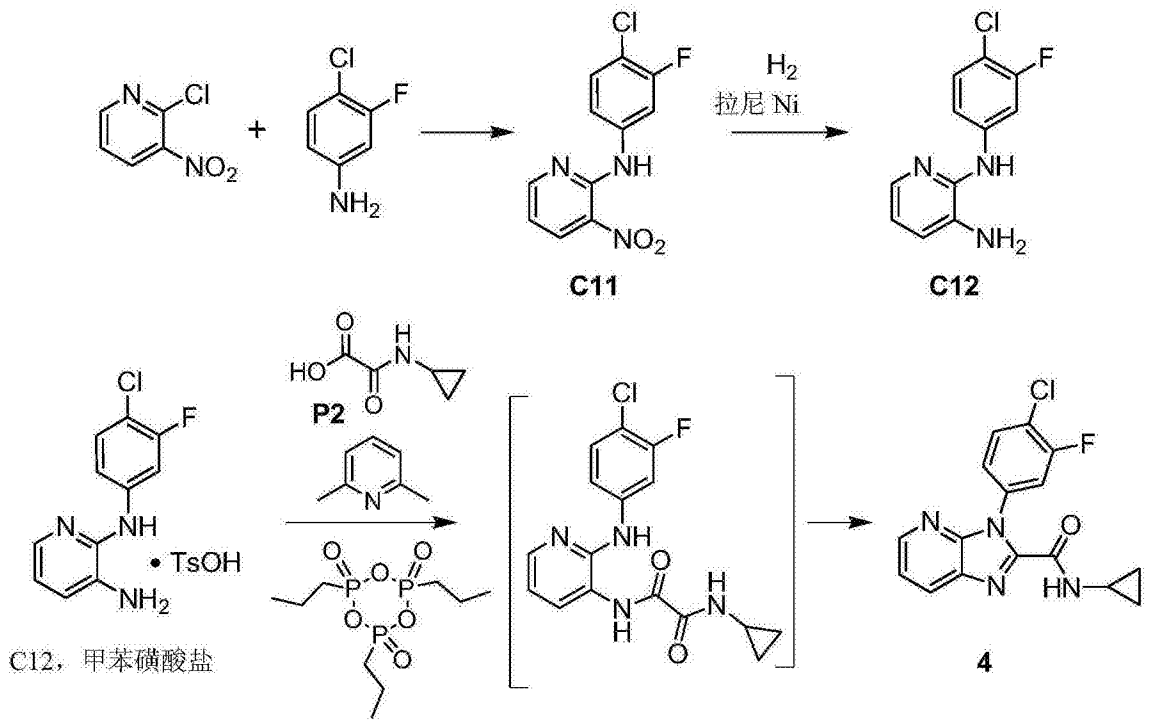
[0249] 步骤4.3-(4-氯苯基)-N-环丙基-3H-咪唑并[4，5-b]吡啶-2-甲酰胺(3)的合成

[0250] 使用对实施例2中的2的合成所述的方法将3-(4-氯苯基)-3H-咪唑并[4，5-b]吡啶-2-羧酸乙酯(C10)转化成产物。获得米白色固体状产物。收率：34.5mg，0.110mmol，28％。LCMS m/z 312.9$[M+H]^+$。^{1}H NMR(400MHz，CD_3OD) δ 8.42(dd，J = 4.8，1.5Hz，1H)，8.24(dd，J = 8.2，1.4Hz，1H)，7.58(br d，J = 8.8Hz，2H)，7.43-7.49(m，3H)，2.76-2.83(m，1H)，0.77-0.84(m，2H)，0.63-0.69(m，2H)。

[0251] 实施例4

[0252] 3-(4-氯-3-氟苯基)-N-环丙基-3H-咪唑并[4，5-b]吡啶-2-甲酰胺(4)

[0253]



[0254] 步骤1.N-(4-氯-3-氟苯基)-3-硝基吡啶-2-胺(C11)的合成

[0255] 在油浴中将4-氯-3-氟苯胺(10.0g，68.7mmol)加热至180℃。添加

2- 氯 -3- 硝基吡啶 (11.0g,69.4mmol)，并将所得混合物于 180℃下搅拌 10 分钟。随后将反应混合物冷却至 15℃并用石油醚洗涤，从而提供橙红色固体状产物。收率 :15g,56mmol,82 %。^{1}H NMR(400MHz,$CDCl_3$) δ 10.20(br s,1H),8.57(dd,J = 8.3,1.6Hz,1H),8.54(dd,J = 4.6,1.7Hz,1H),7.90(dd,J = 11.3,2.4Hz,1H),7.38(dd,J = 8.5,8.3Hz,1H),7.23-7.28(m,1H, 假定；被溶剂峰部分遮蔽),6.94(dd,J = 8.3,4.5Hz,1H)。

[0256] 步骤 2.N^2-(4- 氯 -3- 氟苯基) 吡啶 -2,3- 二胺 (C12) 的合成

[0257] 将 N-(4- 氯 -3- 氟苯基)-3- 硝基吡啶 -2- 胺 (C11)(5.0g,19mmol) 及拉尼镍 (3g) 在乙酸乙酯 (400mL) 中的混合物用氢气脱气三次。随后将反应混合物于室温下氢化 20 小时。经由过滤去除催化剂之后，在真空中浓缩滤液。经由硅胶色谱纯化，得到灰色固体状产物。收率 :3.1g,13mmol,68 %。^{1}H NMR(400MHz,$CDCl_3$) δ 7.87(dd,J = 4.9,1.6Hz,1H),7.38(dd,J = 11.5,2.5Hz,1H),7.24(dd,J = 8.5,8.4Hz,1H),7.06(dd,J = 7.6,1.6Hz,1H),6.92(ddd,J = 8.7,2.5,1.0Hz,1H),6.82(dd,J = 7.6,4.9Hz,1H),6.37(br s,1H),3.38(br s,2H)。

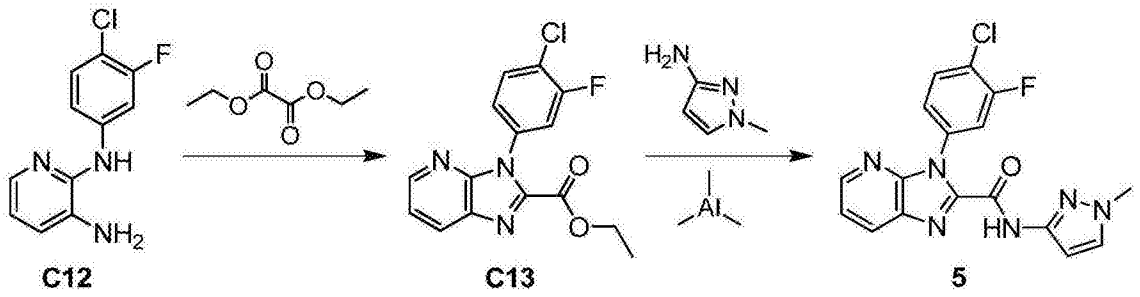
[0258] 步骤 3.3-(4- 氯 -3- 氟苯基)-N- 环丙基 -3H- 咪唑并 [4,5-b] 吡啶 -2- 甲酰胺 (4) 的合成

[0259] 将 N^2-(4- 氯 -3- 氟苯基) 吡啶 -2,3- 二胺 (C12) 的单甲苯磺酸盐 [通过于 80℃下用乙醇中的对甲苯磺酸单水合物 (1.5 当量) 处理 C12，之后冷却至室温并经由过滤分离来制备](1.003g,2.447mmol)、(环丙基氨基)(氧代) 乙酸 (P2)(0.304g,2.35mmol)、2,6- 二甲基吡啶 (0.91mL,0.84g,7.8mmol) 及 2- 甲基四氢呋喃 (10mL) 的混合物冷却至 -10℃，并用 2,4,6- 三丙基 -1,3,5,2,4,6- 三氧杂三膦烷 2,4,6- 三氧化物 (在乙酸乙酯中的 50 重量％溶液，4.3mL，4.6g，7.2mmol) 处理。将反应混合物升温至 0℃并保持 1 小时，于回流温度下加热 20 小时，且随后冷却至 0℃并过滤，用 2- 甲基四氢呋喃冲洗。依序用水 (10mL,5mL)、氢氧化铵水溶液 (15％ ,3×5mL)、盐酸水溶液 (0.1M,10mL,5mL) 及水 (10mL) 洗涤滤液。将有机层蒸馏至约 4mL 之体积，用 2- 甲基四氢呋喃 (13mL) 稀释，并再次蒸馏至约 4mL，其后将其冷却至 50℃并用庚烷 (3mL) 处理。将所得浆液于 50℃下搅拌 2 小时，冷却至 20℃并搅拌 12 小时。经由过滤收集固体并用庚烷及 2- 甲基四氢呋喃 (2:1,5mL) 的混合物洗涤。将所得物质 (0.488g) 于 2- 丙醇及乙酸乙酯的混合物 (9:1,4.9mL) 中再浆化，升温至 40℃，冷却至 20℃并搅拌 16 小时。过滤并用 2- 丙醇 (3mL) 洗涤，得到米白色固体状产物。收率 :410mg,1.24mmol,53％。LCMS m/z 330.9,332.9$[M+H]^+$。^{1}H NMR(400MHz,DMSO-d_6) δ 9.17(d,J = 4.8Hz,1H),8.45(d,J = 4.5Hz,1H),8.27(d,J = 8.0Hz,1H),7.71-7.80(m,2H),7.47(dd,J = 8.0,4.8Hz,1H),7.40(br d,J = 8.5Hz,1H),2.77-2.86(m,1H),0.65-0.69(m,4H)。

[0260] 实施例 5

[0261] 3-(4- 氯 -3- 氟苯基)-N-(1- 甲基 -1H- 吡唑 -3- 基)-3H- 咪唑并 [4,5-b] 吡啶 -2- 甲酰胺 (5)

[0262]



[0263] 步骤 1.3-(4- 氯 -3- 氟苯基)-3H- 咪唑并 [4,5-b] 吡啶 -2- 羧酸乙酯 (C13) 的合成

[0264] 使用对实施例 3 中的 C10 的合成所述的方法实现 N^2-(4- 氯 -3- 氟苯基) 吡啶 -2,3- 二胺 (C12) 向产物的转化。获得褐色固体状产物。收率 :700mg,2.2mmol,17 %。^{1}H NMR(400MHz,$CDCl_3$) δ 8.55(dd,J = 4.6,1.4Hz,1H),8.29(dd,J = 8.2,1.4Hz,1H),7.61(dd,J = 8.3,8.0Hz,1H),7.42(dd,J = 8.2,4.8Hz,1H),7.29(dd,J = 8.9,2.3Hz,1H, 假定 ; 被溶剂峰部分遮蔽),7.18-7.22(m,1H),4.44(q,J = 7.2Hz,2H),1.41(t,J = 7.1Hz,3H)。

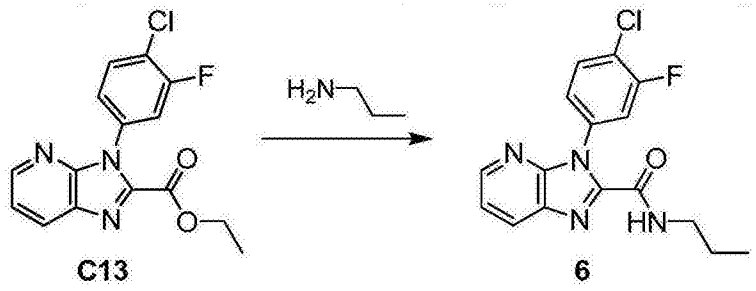
[0265] 步骤 2.3-(4- 氯 -3- 氟苯基)-N-(1- 甲基 -1H- 吡唑 -3- 基)-3H- 咪唑并 [4,5-b] 吡啶 -2- 甲酰胺 (5) 的合成

[0266] 于室温下向 3-(4- 氯 -3- 氟苯基)-3H- 咪唑并 [4,5-b] 吡啶 -2- 羧酸乙酯 (C13) (32mg,0.10mmol) 及 1- 甲基 -1H- 吡唑 -3- 胺 (29mg,0.30mol) 在甲苯 (3mL) 中的溶液中添加三甲基铝 (在甲苯中的 2M 溶液,0.3mL,0.6mmol)。于 150℃下将反应混合物在微波反应器中辐照 1 小时,其后将其在水 (20mL) 与乙酸乙酯 (50mL) 之间分配。将有机层用饱和氯化钠水溶液 (20mL) 洗涤,经硫酸钠干燥,过滤并在真空中浓缩。经由反相 HPLC(柱 :Agella Venusil ASB-C18,5 μm ;流动相 A :在水中的 0.225% 甲酸 ;流动相 B :在乙腈中的 0.225% 甲酸 ;梯度 :33% 至 63% B) 纯化,得到黄色固体状产物。收率 :2.0mg,5.4 μmol,5%。LCMS m/z 371.1[M+H]$^+$。^{1}H NMR(400MHz,CD_3OD) δ 8.47(br d,J = 4.6Hz,1H),8.32(br d,J = 8Hz,1H),7.69(dd,J = 8,8Hz,1H),7.48-7.56(m,3H),7.35(br d,J = 8Hz,1H),6.52-6.55(m,1H),3.83(s,3H)。

[0267] 实施例 6

[0268] 3-(4- 氯 -3- 氟苯基)-N- 丙基 -3H- 咪唑并 [4,5-b] 吡啶 -2- 甲酰胺 (6)

[0269]



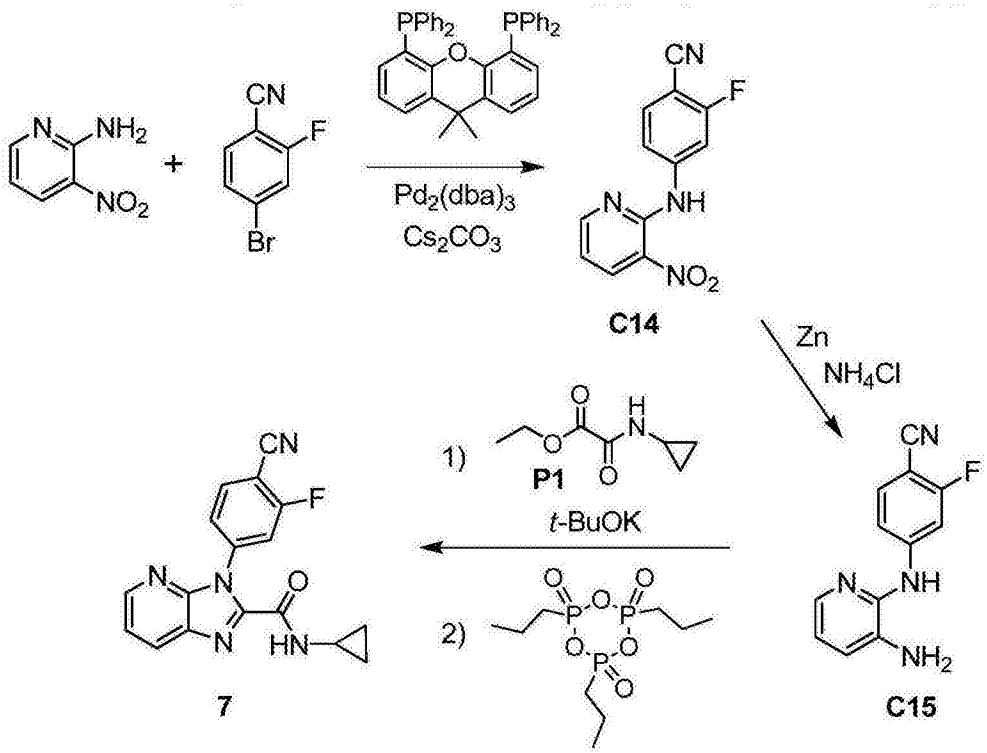
[0270] 向 3-(4- 氯 -3- 氟苯基)-3H- 咪唑并 [4,5-b] 吡啶 -2- 羧酸乙酯 (C13) (80mg,0.25mmol) 在乙醇 (5mL) 中的溶液中添加正丙基胺 (148mg,2.5mol),并将反应混合物于室温下搅拌 18 小时。在减压下浓缩后,通过硅胶上制备型薄层色谱法

(洗脱剂:1:1 石油醚 / 乙酸乙酯)纯化残余物,以提供浅黄色固体状产物。收率:28mg,84 μmol,34 %。LCMS m/z 332.9[M+H]$^+$。^{1}H NMR(400MHz,CD_3OD) δ 8.43(dd,J = 4.8,1.4Hz,1H),8.26(dd,J = 8.2,1.5Hz,1H),7.67(dd,J = 8.4,8.2Hz,1H),7.45-7.50(m,2H),7.30(ddd,J = 8.5,2.3,1.2Hz,1H),3.28-3.34(m,2H,假定;被溶剂峰部分遮蔽),1.58-1.68(m,2H),0.96(t,J = 7.4Hz,3H)。

[0271] 实施例 7

[0272] 3-(4- 氰基 -3- 氟苯基)-N- 环丙基 -3H- 咪唑并 [4,5-b] 吡啶 -2- 甲酰胺 (7)

[0273]



[0274] 步骤 1.2- 氟 -4-[(3- 硝基吡啶 -2- 基)氨基]苄腈 (C14) 的合成

[0275] 将 3- 硝基吡啶 -2- 胺 (3.44g,24.7mmol)、4- 溴 -2- 氟苄腈 (4.95g,24.7mmol)、三(二亚苄基丙酮)二钯 (0)(226mg,0.247mmol)、4,5- 双(二苯基膦基)-9,9- 二甲基呫吨 (XantPhos,286mg,0.494mmol) 及碳酸铯 (32.3g,99.0mmol) 在 1,4- 二氧杂环己烷 (124mL) 中的混合物脱气,放置于氮气下并于 100℃下搅拌 30 分钟。经由硅藻土垫使用四氢呋喃过滤反应混合物,并在真空中浓缩滤液。向残余物中添加庚烷及乙酸乙酯的 1:1 混合物,并在冰 / 水浴中冷却混合物。经由过滤收集固体并用冷的 1:1 庚烷 / 乙酸乙酯洗涤,以得到灰色固体状产物。收率:6.2g,24mmol,97%。LCMS m/z 259.1[M+H]$^+$。^{1}H NMR(400MHz,$CDCl_3$) δ 10.46(br s,1H),8.60-8.63(m,2H),8.16(dd,J = 11.8,2.1Hz,1H),7.59(dd,J = 8.5,7.2Hz,1H),7.40(br dd,J = 8.6,2Hz,1H),7.05-7.09(m,1H)。

[0276] 步骤 2.4-[(3- 氨基吡啶 -2- 基)氨基]-2- 氟苄腈 (C15) 的合成

[0277] 向 2- 氟 -4-[(3- 硝基吡啶 -2- 基)氨基]苄腈 (C14)(5.4g,21mmol) 在四氢呋喃及水的 1:1 混合物 (40mL) 中的溶液中添加氯化铵 (8.9g,170mmol),之后添加锌 (10.8g,165mmol)。将混合物于 60℃下搅拌 30 分钟,其后经由硅藻土垫对其进行过滤。将滤液的有机层用乙酸乙酯稀释,用饱和氯化铵水溶液洗涤,经硫酸钠干燥,过滤并

在真空中浓缩；将残余物用庚烷洗涤，以得到褐色固体状产物。收率：4.2g，18mmol，86％。LCMS m/z 229.1[M+H]$^+$。^{1}H NMR(400MHz，DMSO-d_6) δ 8.68(br s，1H)，7.82(dd，J = 13.6，2.0Hz，1H)，7.66(dd，J = 8.4，8.3Hz，1H)，7.61(dd，J = 4.8，1.6Hz，1H)，7.37(dd，J = 8.8，2.0Hz，1H)，7.03(dd，J = 7.8，1.6Hz，1H)，6.82(dd，J = 7.8，4.8Hz，1H)，5.24(br s，2H)。

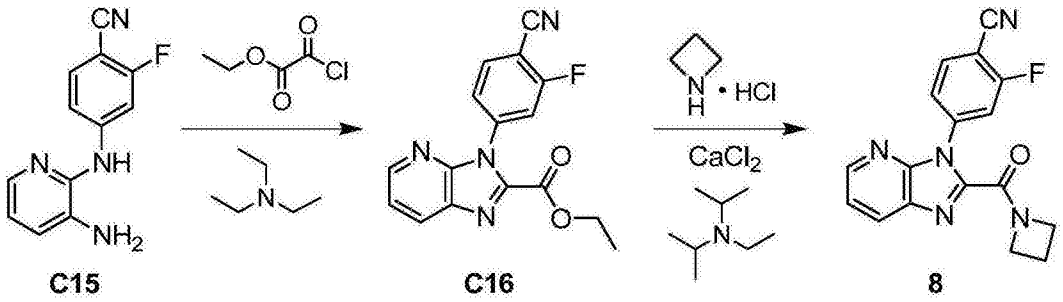
[0278] 步骤3.3-(4-氰基-3-氟苯基)-N-环丙基-3H-咪唑并[4，5-b]吡啶-2-甲酰胺(7)的合成

[0279] 向4-[(3-氨基吡啶-2-基)氨基]-2-氟苄腈(C15)(3.9g，17mmol)及(环丙基氨基)(氧代)乙酸乙酯(P1)(4.03g，25.6mmol)在1-甲基吡咯烷-2-酮(17mL)中的混合物中添加叔丁醇钾(2.88g，25.7mmol)。将反应混合物于120℃下搅拌30分钟，冷却至室温，并用2，4，6-三丙基-1，3，5，2，4，6-三氧杂三膦烷2，4，6-三氧化物(T3P)(约50重量％溶液，20.3mL，32mmol)处理。在将反应混合物于120℃下搅拌18小时后，使其冷却。添加水(10mL)并继续搅拌10分钟。引入饱和硫酸氢钠水溶液(20mL)，并将混合物用乙酸乙酯(3×50mL)萃取。将合并的有机层用饱和氯化钠水溶液洗涤，过滤并在真空下浓缩。硅胶色谱(梯度：在石油醚中的10％至50％乙酸乙酯)，得到白色固体状产物。收率：2.29g，7.13mmol，42％。LCMS m/z 322.2[M+H]$^+$。^{1}H NMR(400MHz，$CDCl_3$) δ 8.50(dd，J = 4.7，1.4Hz，1H)，8.17(dd，J = 8.2，1.5Hz，1H)，7.79-7.85(m，1H)，7.69(br s，1H)，7.38-7.45(m，3H)，2.83-2.90(m，1H)，0.87-0.93(m，2H)，0.68-0.73(m，2H)。

[0280] 实施例8

[0281] 4-[2-(氮杂环丁-1-基羰基)-3H-咪唑并[4，5-b]吡啶-3-基]-2-氟苄腈(8)

[0282]



[0283] 步骤1.3-(4-氰基-3-氟苯基)-3H-咪唑并[4，5-b]吡啶-2-羧酸乙酯(C16)的合成

[0284] 向4-[(3-氨基吡啶-2-基)氨基]-2-氟苄腈(C15)(300mg，1.31mmol)及三乙胺(270mg，2.67mmol)在二氯甲烷(20mL)中的0℃溶液中添加氯(氧代)乙酸乙酯(220mg，1.61mmol)，并将溶液于0℃下搅拌2小时。在添加水(20mL)后，用二氯甲烷(3×20mL)萃取混合物；将合并的有机层用饱和氯化钠水溶液(20mL)洗涤，经硫酸钠干燥，过滤，在减压下浓缩并通过硅胶上制备型薄层色谱(洗脱剂：10:1二氯甲烷/甲醇)纯化，以得到黄色固体状产物。收率：40mg，0.13mmol，10％。^{1}H NMR(400MHz，$CDCl_3$)，特征峰：δ 8.55(d，J = 5Hz，1H)，4.46(q，J = 7Hz，2H)，1.43(t，J = 7Hz，3H)。

[0285] 步骤2.4-[2-(氮杂环丁-1-基羰基)-3H-咪唑并[4，5-b]吡啶-3-基]-2-氟苄腈(8)的合成

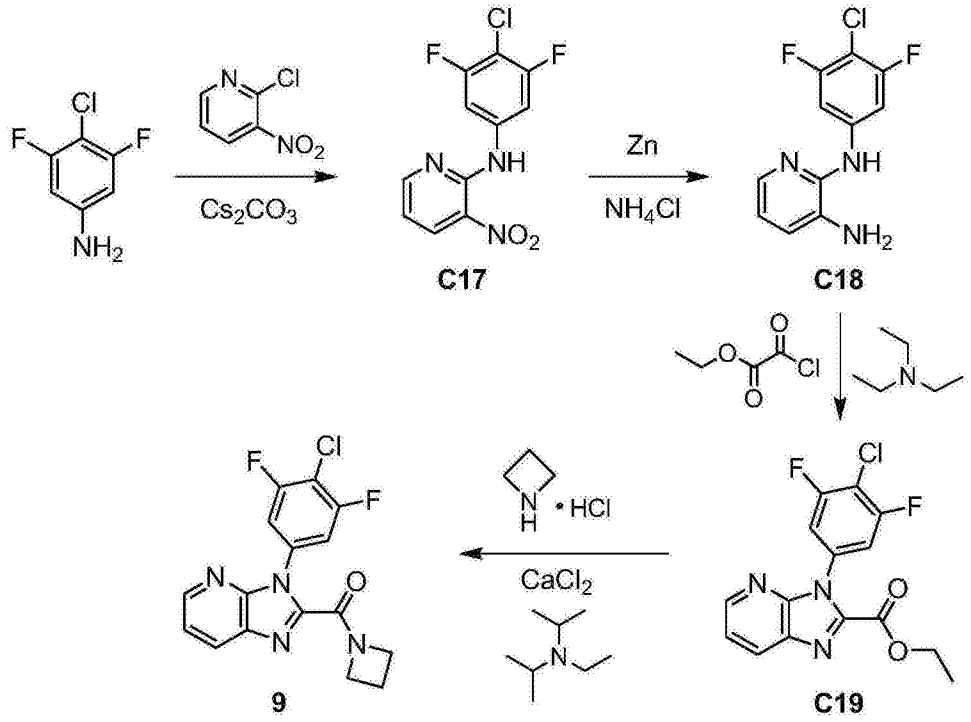
[0286] 将氮杂环丁烷盐酸盐(120mg，1.3mmol)及N，N-二异丙基乙胺(168mg，1.30mmol)

在甲醇 (2mL) 中的混合物于室温下搅拌 1 小时。此时，添加 3-(4- 氰基 -3- 氟苯基)-3H- 咪唑并 [4,5-b] 吡啶 -2- 羧酸乙酯 (C16)(40mg,0.13mmol) 及氯化钙 (15mg,0.13mmol)，并将反应混合物于室温下再搅拌 2 小时。在真空中去除溶剂后，通过反相 HPLC(柱：DIKMA Diamonsil C18(2),5μm；流动相 A：在水中的 0.225％甲酸；流动相 B：在乙腈中的 0.225％甲酸；梯度：15％至 45％ B) 纯化残余物，以提供黄色固体状产物。收率：4.0mg,12μmol,9 ％。LCMS m/z 322.1[M+H]$^+$。^{1}H NMR(400MHz,$CDCl_3$) δ 8.49(dd,J = 4.8,1.3Hz,1H),8.20(dd,J = 8.2,1.4Hz,1H),7.77-7.82(m,1H),7.36-7.43(m,3H),4.80-4.89(m,2H),4.18-4.26(m,2H),2.39-2.50(m,2H)。

[0287] 实施例 9

[0288] 氮杂环丁 -1- 基 [3-(4- 氯 -3,5- 二氟苯基)-3H- 咪唑并 [4,5-b] 吡啶 -2- 基] 甲酮 (9)

[0289]



[0290] 步骤 1.N-(4- 氯 -3,5- 二氟苯基)-3- 硝基吡啶 -2- 胺 (C17) 的合成

[0291] 将 4- 氯 -3,5- 二氟苯胺 (1.64g,10.0mmol)、2- 氯 -3- 硝基吡啶 (1.56g,9.84mmol) 及碳酸铯 (6.56g,20.1mmol) 在 N,N- 二甲基甲酰胺 (30mL) 中的混合物于 80℃下搅拌 36 小时。将反应混合物冷却至室温，用水 (200mL) 稀释并用乙酸乙酯 (3×200mL) 萃取。将合并的有机层用饱和氯化钠水溶液 (5×50mL) 洗涤，经硫酸钠干燥，过滤，在真空中浓缩并通过硅胶色谱 (梯度：在石油醚中的 0％至 5％乙酸乙酯) 纯化，以提供黄色固体状产物。收率：200mg,0.70mmol,7％。^{1}H NMR(400MHz,$CDCl_3$) δ 10.23(br s,1H),8.55-8.61(m,2H),7.52(br d,J = 9Hz,2H),6.96-7.01(m,1H)。

[0292] 步骤 2.N^2-(4- 氯 -3,5- 二氟苯基) 吡啶 -2,3- 二胺 (C18) 的合成

[0293] 向 N-(4- 氯 -3,5- 二氟苯基)-3- 硝基吡啶 -2- 胺 (C17)(100mg,0.35mmol) 在四氢呋喃与水的 1:1 混合物 (20mL) 中的溶液中添加氯化铵 (148mg,2.77mmol)，之后添加锌 (182mg,2.78mmol)，并将反应混合物于室温下搅拌 2 小时。随后将其用水 (10mL) 稀释

并用乙酸乙酯 (3×20mL) 萃取；将合并的有机层用饱和氯化钠水溶液 (20mL) 洗涤，经硫酸钠干燥，过滤并在真空中浓缩，以得到黄色固体状产物。此物质直接用于下一步。收率：80mg, 0.31mmol, 89%。

[0294] 步骤 3. 3-(4- 氯 -3,5- 二氟苯基)-3H- 咪唑并 [4,5-b] 吡啶 -2- 羧酸乙酯 (C19) 的合成

[0295] 使用对实施例 8 中的 C16 的合成所述的方法将 N^2-(4- 氯 -3,5- 二氟苯基) 吡啶 -2,3- 二胺 (C18) 转化成产物。获得黄色固体状产物。收率：40mg, 0.12mmol, 41 %。^{1}H NMR(400MHz, $CDCl_3$) δ 8.56(dd, J = 4.7, 1.3Hz, 1H), 8.30(dd, J = 8.1, 1.5Hz, 1H), 7.44(dd, J = 8.2, 4.7Hz, 1H), 7.11-7.15(m, 2H), 4.46(q, J = 7.2Hz, 2H), 1.43(t, J = 7.2Hz, 3H)。

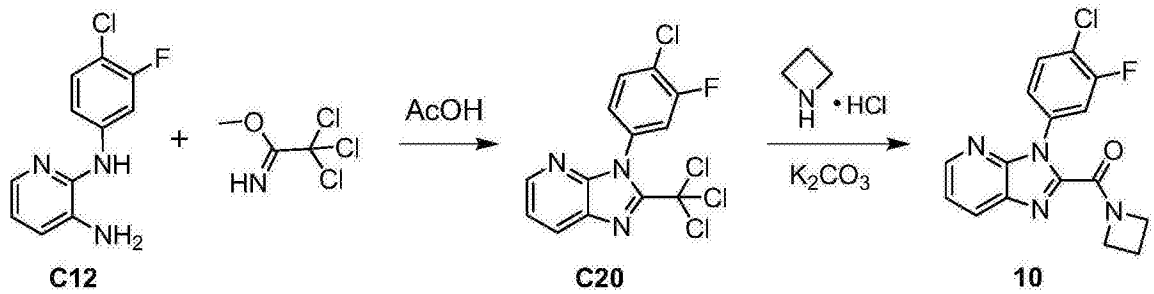
[0296] 步骤 4. 氮杂环丁 -1- 基 [3-(4- 氯 -3,5- 二氟苯基)-3H- 咪唑并 [4,5-b] 吡啶 -2- 基] 甲酮 (9) 的合成

[0297] 使用对实施例 8 中的 8 的合成所述的方法将 3-(4- 氯 -3,5- 二氟苯基)-3H- 咪唑并 [4,5-b] 吡啶 -2- 羧酸乙酯 (C19) 转化成产物。获得黄色固体状产物。收率：7.9mg, 23 μmol, 39 %。LCMS m/z 349.1 $[M+H]^+$。^{1}H NMR(400MHz, $CDCl_3$) δ 8.50(dd, J = 4.7, 1.4Hz, 1H), 8.19(dd, J = 8.1, 1.4Hz, 1H), 7.39(dd, J = 8.1, 4.7Hz, 1H), 7.10-7.15(m, 2H), 4.80-4.85(m, 2H), 4.19-4.25(m, 2H), 2.40-2.49(m, 2H)。

[0298] 实施例 10

[0299] 氮杂环丁 -1- 基 [3-(4- 氯 -3- 氟苯基)-3H- 咪唑并 [4,5-b] 吡啶 -2- 基] 甲酮 (10)

[0300]



C12 C20 10

[0301] 步骤 1. 3-(4- 氯 -3- 氟苯基)-2-(三氯甲基)-3H- 咪唑并 [4,5-b] 吡啶 (C20) 的合成

[0302] 向 N^2-(4- 氯 -3- 氟苯基) 吡啶 -2,3- 二胺 (C12)(951mg, 4.00mmol) 在乙酸 (4mL) 中的溶液中添加 2,2,2- 三氯乙酰亚氨酸甲酯 (0.743mL, 6.00mmol)，并将反应混合物于室温下搅拌 5 小时。在真空中浓缩后，经由硅胶色谱 (梯度：在庚烷中的 5% 至 100% 乙酸乙酯) 纯化残余物，以得到白色固体状产物。收率：1.04g, 2.85mmol, 71 %。LCMS m/z 366.0 $[M+H]^+$。^{1}H NMR(400MHz, $CDCl_3$) δ 8.49(dd, J = 4.7, 1.5Hz, 1H), 8.27(dd, J = 8.1, 1.5Hz, 1H), 7.64(ddd, J = 8.5, 7.8, 0.3Hz, 1H), 7.42(dd, J = 8.1, 4.7Hz, 1H), 7.39(ddd, J = 8.8, 2.4, 0.2Hz, 1H), 7.32(ddd, J = 8.5, 2.4, 1.3Hz, 1H)。

[0303] 步骤 2. 氮杂环丁 -1- 基 [3-(4- 氯 -3- 氟苯基)-3H- 咪唑并 [4,5-b] 吡啶 -2- 基] 甲酮 (10) 的合成

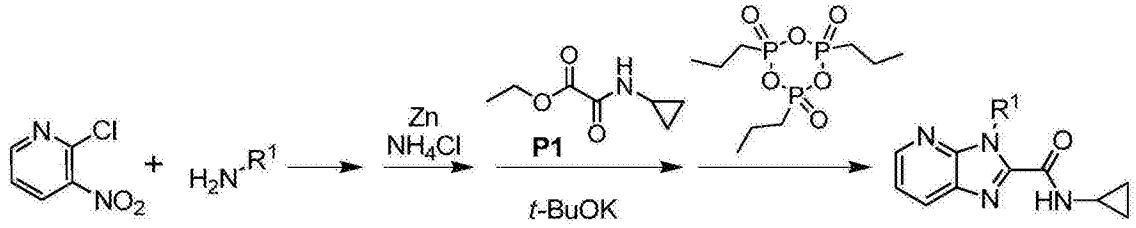
[0304] 将 3-(4- 氯 -3- 氟苯基)-2-(三氯甲基)-3H- 咪唑并 [4,5-b] 吡啶 (C20)

(50mg,0.14mmol) 溶解于乙腈与水的 3:1 混合物 (1.4mL) 中。添加氮杂环丁烷盐酸盐 (25.6mg,0.274mmol),之后添加碳酸钾水溶液 (4M,0.15mL,0.60mmol),并将反应混合物于 50℃下加热 22 小时,随后于 80℃下加热 3 小时,且最后于 100℃下加热 18 小时。分离各层,并在真空中浓缩有机层;经由反相 HPLC(柱:Waters Sunfire C18,5μm;流动相 A:在水中的 0.05%三氟乙酸 (v/v);流动相 B:在乙腈中的 0.05%三氟乙酸 (v/v);梯度:30%至 50% B) 纯化,得到产物。收率:17mg,51μmol,36%。LCMS m/z 331.1,333.1[M+H]$^+$。^{1}H NMR(600MHz,DMSO-d_6) δ 8.45(dd,J = 4.6,1.5Hz,1H),8.30(dd,J = 7.9,1.3Hz,1H),7.76(dd,J = 8.3,8.3Hz,1H),7.73(dd,J = 10.1,2.2Hz,1H),7.46(dd,J = 8.1,4.6Hz,1H),7.40-7.43(m,1H),4.64-4.68(m,2H),4.02-4.07(m,2H),2.29-2.35(m,2H)。

[0305] 方法 A

[0306] 以 2-氯 -3-硝基吡啶和胺为原料的实施例的合成

[0307]

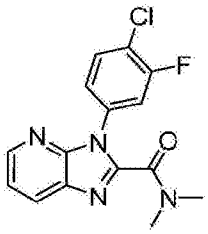
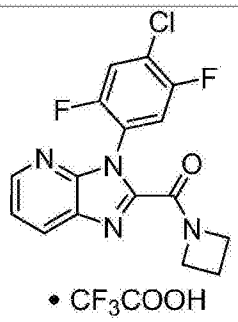


[0308] 将需要的胺 (0.20mmol) 与 2-氯 -3-硝基吡啶 (31.7mg,0.200mmol) 在四氢呋喃 (0.1mL) 和聚乙二醇 400(PEG 400,0.1mL) 中的溶液合并;若使用胺盐,则亦添加三乙胺 (28μL,0.20mmol)。将反应混合物于 150℃下振荡 1 至 1.5 小时,随后冷却至室温。向其中添加四氢呋喃 (0.4mL) 及氯化铵 (85.6mg,1.60mmol) 在水 (0.4mL) 中的溶液,之后添加锌 (约 105mg,1.6mmol)。将反应混合物于 65℃下振荡 1.5 小时,随后在水 (1mL) 与乙酸乙酯 (2.5mL) 之间分配。经由填充有硫酸钠 (约 1g) 的 6mL 固相萃取柱洗脱有机层。将此萃取重复两次,并在真空中浓缩来自柱的合并洗脱物。向粗制残余物中添加 (环丙基氨基)(氧代) 乙酸乙酯 (P1)(47mg,0.30mmol) 在 1-甲基吡咯烷 -2-酮 (0.2mL) 中的溶液及叔丁醇钾在四氢呋喃 (1M,0.3mL,0.3mmol) 中的溶液;将此反应混合物于 120℃下振荡 30 分钟,随后冷却至室温并用乙酸 (18μL,0.31mmol) 处理。添加 2,4,6-三丙基 -1,3,5,2,4,6-三氧杂三膦烷 2,4,6-三氧化物 (T3P,在乙酸乙酯中的 50 重量%溶液,254mg,0.40mmol),并将反应混合物于 120℃下振荡 24 小时。随后将反应混合物在乙酸乙酯 (2.5mL) 与氢氧化钠水溶液 (1M,1.5mL) 之间分配;经由填充有硫酸钠 (约 1g) 的 6mL 固相萃取柱洗脱有机层。将此萃取重复两次,并将来自柱的合并洗脱物在真空中浓缩并经由反相 HPLC 使用下列系统之一纯化:1) 柱:Waters XBridge C18,5μm;流动相 A:在水中的 0.03%氢氧化铵 (v/v);流动相 B:在乙腈中的 0.03%氢氧化铵 (v/v);梯度:20%至 60% B 或 10%至 100% B;2) 柱:Waters Sunfire C18,5μm;流动相 A:在水中的 0.05%三氟乙酸 (v/v);流动相 B:在乙腈中的 0.05%三氟乙酸 (v/v);梯度:10%至 100% B。

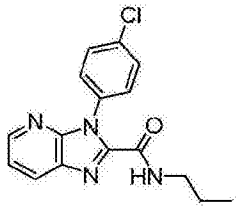
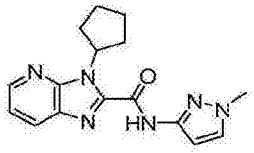
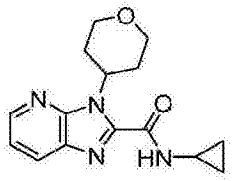
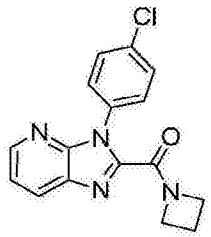
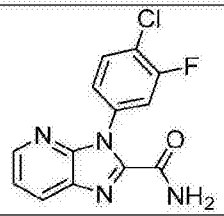
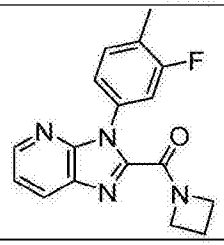
[0309] 使用上文对实施例 1-10 所述的方法,亦制备表 1 及表 2 中的化合物 (关于表征数据,参见表 1 及 2)。

[0310] 表 1

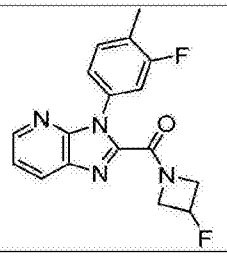
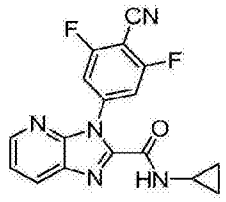
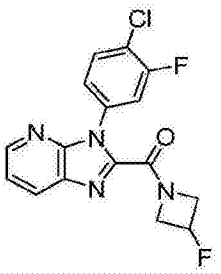
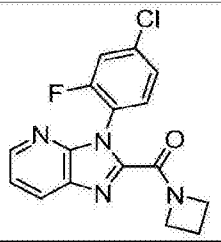
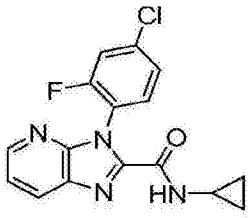
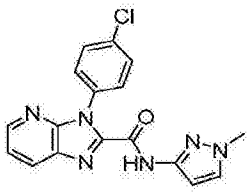
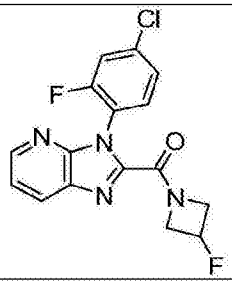
[0311]

实施例编号	结构	制备方法；非市售原料	^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm)；质谱，观察离子 *m/z* $[M+H]^+$或 HPLC 保留时间 [1] (分钟)；质谱 *m/z* $[M+H]^+$ (除非另外指明)
11		实施例 1[2]；**C12**	^{1}H NMR (600 MHz, DMSO-d_6), δ 8.46 (dd, *J*=4.6, 1.5 Hz, 1H), 8.28 (dd, *J*=8.1, 1.5 Hz, 1H), 7.81 (dd, *J*=8.3, 8.3 Hz, 1H), 7.74 (dd, *J*=10.1, 2.2 Hz, 1H), 7.47 (dd, *J*=8.1, 4.6 Hz, 1H), 7.41-7.44 (m, 1H), 3.15 (s, 3H), 2.98 (s, 3H)；319.0, 321.0
12	 • CF_3COOH	实施例 10	^{1}H NMR (600 MHz, DMSO-d_6), δ 8.46-8.49 (m, 1H), 8.32-8.36 (m, 1H), 7.90-7.96 (m, 2H), 7.47-7.51 (m, 1H), 4.71 (dd, *J*=7.7, 7.7 Hz, 2H), 4.06 (dd, *J*=7.7, 7.4 Hz, 2H), 2.30-2.37 (m, 2H)；349.1, 351.1

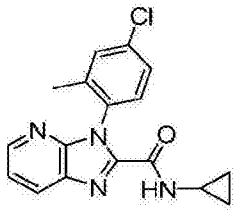
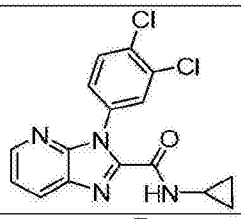
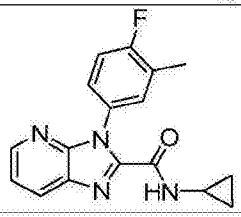
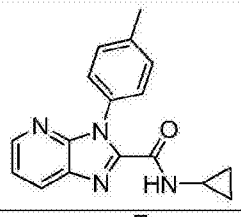
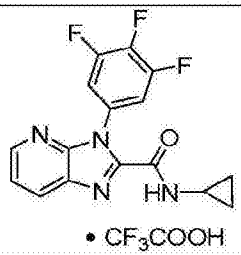
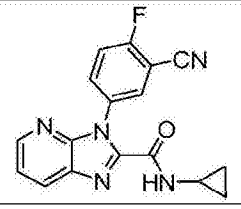
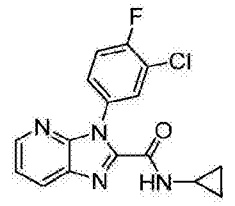
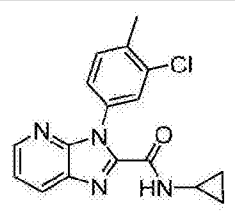
[0312]

13		实施例 6；**C10**	特征峰：8.46-8.53 (m, 1H), 8.15 (br d, *J*=8 Hz, 1H), 7.63-7.73 (br m, 1H), 7.53 (br d, *J*=8 Hz, 2H), 7.39 (br d, *J*=8 Hz, 2H), 3.33-3.43 (m, 2H), 0.99 (t, *J*=7.3 Hz, 3H)；314.8
14		**C7**[3]	10.09 (br s, 1H), 8.49 (dd, *J*=4.6, 1.5 Hz, 1H), 8.07 (dd, *J*=8.2, 1.5 Hz, 1H), 7.32 (d, *J*=2.3 Hz, 1H), 7.29 (dd, *J*=8.2, 4.6 Hz, 1H), 6.78 (d, *J*=2.3 Hz, 1H), 6.22-6.33 (m, 1H), 3.87 (s, 3H), 2.55-2.67 (m, 2H), 2.08-2.21 (m, 4H), 1.70-1.83 (m, 2H)；311.0
15		实施例 2	^{1}H NMR (400 MHz, CD_3OD), δ 8.47 (dd, *J*=4.7, 1.4 Hz, 1H), 8.09 (dd, *J*=8.2, 1.4 Hz, 1H), 7.36 (dd, *J*=8.2, 4.6 Hz, 1H), 5.68 (tt, *J*=12, 4 Hz, 1H), 4.13 (dd, *J*=11.5, 4.5 Hz, 2H), 3.60 (ddd, *J*=12.4, 11.8, 1.5 Hz, 2H), 3.03-3.15 (m, 2H), 2.89-2.96 (m, 1H), 1.81-1.89 (m, 2H), 0.83-0.90 (m, 2H), 0.69-0.76 (m, 2H)；286.9
16		实施例 10；**C9**	^{1}H NMR (600 MHz, DMSO-d_6), δ 8.44 (dd, *J*=4.7, 1.3 Hz, 1H), 8.28 (dd, *J*=8.1, 1.3 Hz, 1H), 7.56 (br AB 四重峰, J_{AB}=8.7 Hz, $\Delta\nu_{AB}$=39.2 Hz, 4H), 7.45 (dd, *J*=8.1, 4.7 Hz, 1H), 4.63 (dd, *J*=7.8, 7.7 Hz, 2H), 4.04 (dd, *J*=7.8, 7.7 Hz, 2H), 2.28-2.35 (m, 2H)；313.1, 315.1
17		实施例 7；**C12**	8.52 (dd, *J*=4.7, 1.3 Hz, 1H), 8.19 (dd, *J*=8.2, 1.3 Hz, 1H), 7.59 (dd, *J*=8.2, 8.2 Hz, 1H), 7.41 (dd, *J*=8.1, 4.7 Hz, 1H), 7.28-7.32 (m, 1H), 7.20-7.24 (m, 1H)；290.8
18		实施例 3[4]	8.49 (d, *J*=4.4 Hz, 1H), 8.15 (d, *J*=7.6 Hz, 1H), 7.31-7.38 (m, 2H), 7.10-7.16 (m, 2H), 4.73-4.80 (m, 2H), 4.16-4.24 (m, 2H), 2.36 (s, 3H), 2.36-2.45 (m, 2H)；311.0

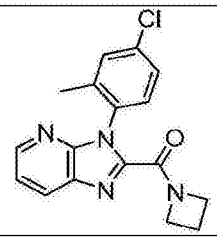
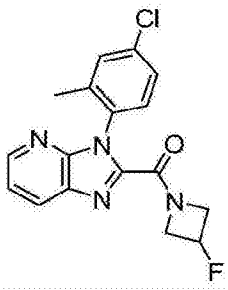
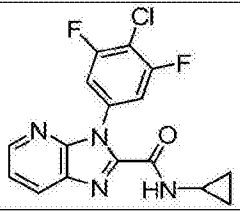
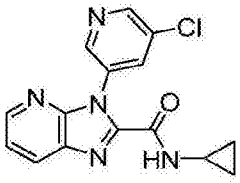
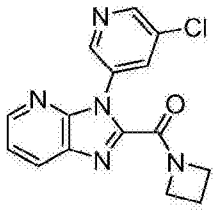
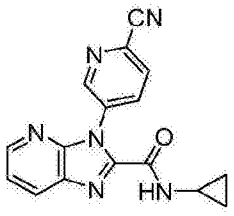
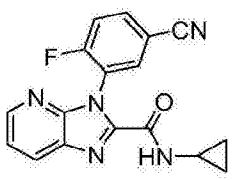
[0313]

19		实施例 3[4]	8.45 (dd, *J*=4.8, 1.3 Hz, 1H), 8.30 (dd, *J*=8.2, 1.1 Hz, 1H), 7.38-7.49 (m, 3H), 7.23-7.27 (m, 1H), 5.49 (br d, J_{HF}=57 Hz, 1H), 4.93-5.05 (m, 1H), 4.63-4.76 (m, 1H), 4.32-4.44 (m, 1H), 4.04-4.16 (m, 1H), 2.33 (s, 3H)；329.0
20		实施例 7	8.50 (dd, *J*=4.7, 1.5 Hz, 1H), 8.17 (dd, *J*=8.2, 1.5 Hz, 1H), 7.67 (br d, 1H), 7.44 (dd, *J*=8.1, 4.7 Hz, 1H), 7.21-7.25 (m, 2H), 2.83-2.90 (m, 1H), 0.88-0.94 (m, 2H), 0.69-0.74 (m, 2H)；340.1
21		实施例 3[4]	8.51 (dd, *J*=4.6, 1.2 Hz, 1H), 8.19 (dd, *J*=8.2, 1.1 Hz, 1H), 7.57 (dd, *J*=8.3, 8.0 Hz, 1H), 7.39 (dd, *J*=8.2, 4.6 Hz, 1H), 7.27 (dd, *J*=8.8, 2.3 Hz, 1H), 7.16-7.22 (m, 1H), 5.33-5.54 (m, J_{HF}=57 Hz, 1H), 5.08-5.20 (m, 1H), 4.85-4.98 (m, 1H), 4.40-4.52 (m, 1H), 4.23-4.36 (m, 1H)；348.9
22		实施例 3[4]	8.49 (dd, *J*=4.7, 1.4 Hz, 1H), 8.18 (dd, *J*=8.2, 1.4 Hz, 1H), 7.47 (dd, *J*=8.4, 7.4 Hz, 1H), 7.37 (dd, *J*=8.1, 4.8 Hz, 1H), 7.28-7.35 (m, 2H), 4.69-4.96 (br m, 2H), 4.16-4.26 (m, 2H), 2.37-2.47 (m, 2H)；331.0
23		实施例 3[4]	8.50 (dd, *J*=4.8, 1.5 Hz, 1H), 8.15 (dd, *J*=8.1, 1.4 Hz, 1H), 7.66 (br s, 1H), 7.45 (dd, *J*=9.0, 7.4 Hz, 1H), 7.40 (dd, *J*=8.1, 4.7 Hz, 1H), 7.31-7.37 (m, 2H), 2.83-2.89 (m, 1H), 0.84-0.91 (m, 2H), 0.68-0.73 (m, 2H)；330.9
24		实施例 5；**C10**	特征峰：9.94 (br s, 1H), 8.52 (dd, *J*=4.8, 1.5 Hz, 1H), 8.20 (dd, *J*=8.2, 1.4 Hz, 1H), 7.56 (br d, *J*=8.8 Hz, 2H), 7.43 (br d, *J*=8.7 Hz, 2H), 7.40 (dd, *J*=8.2, 4.6 Hz, 1H), 6.68 (d, *J*=2.1 Hz, 1H), 3.85 (s, 3H)；352.9
25		实施例 3[4]	8.51 (dd, *J*=4.8, 1.4 Hz, 1H), 8.20 (dd, *J*=8.2, 1.4 Hz, 1H), 7.46 (dd, *J*=8.4, 7.9 Hz, 1H), 7.39 (dd, *J*=8.2, 4.8 Hz, 1H), 7.29-7.37 (m, 2H), 5.33-5.54 (m, J_{HF}=57 Hz, 1H), 4.8-5.3 (v br m, 2H), 4.40-4.54 (m, 1H), 4.23-4.37 (m, 1H)；348.9

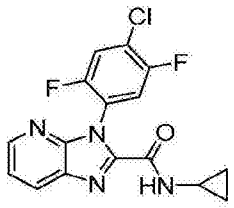
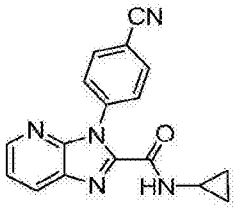
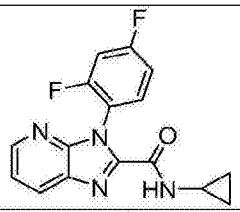
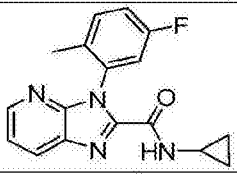
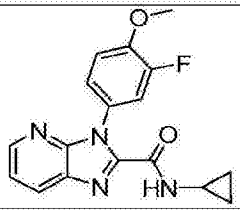
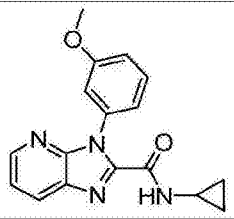
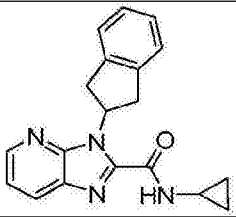
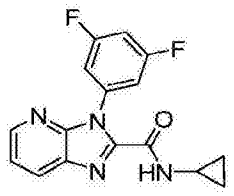
[0314]

26		实施例 3[4]	8.49 (dd, *J*=4.8, 1.1 Hz, 1H), 8.15 (dd, *J*=7.9, 1.1 Hz, 1H), 7.66 (br s, 1H), 7.32-7.43 (m, 3H), 7.19 (d, *J*=8.2 Hz, 1H), 2.81-2.89 (m, 1H), 1.98 (s, 3H), 0.83-0.89 (m, 2H), 0.66-0.71 (m, 2H)；327.0
27		方法 A	2.97 分钟；347.0, 349.0
28		方法 A	2.59 分钟；311.1
29		方法 A	2.51 分钟；293.1
30		方法 A	2.70 分钟；333.0
31		方法 A	2.46 分钟；322.1
32		方法 A	2.53 分钟；331.0, 333.0
33		方法 A	2.90 分钟；327.0, 329.0

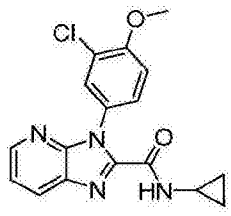
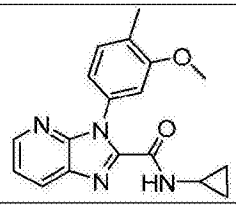
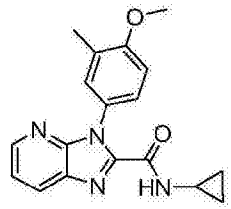
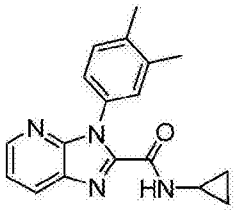
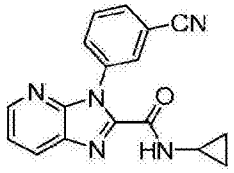
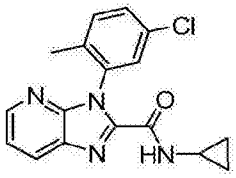
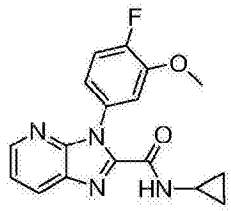
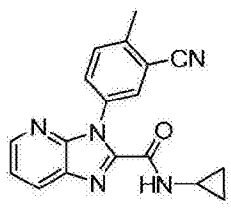
[0315]

34		实施例 3[4]	8.48 (dd, *J*=4.8, 1.5 Hz, 1H), 8.18 (dd, *J*=8.2, 1.4 Hz, 1H), 7.30-7.40 (m, 3H), 7.17 (d, *J*=8.3 Hz, 1H), 4.75-4.92 (m, 2H), 4.15-4.22 (m, 2H), 2.36-2.46 (m, 2H), 1.99 (s, 3H)；327.0
35		实施例 3[4]	假定为旋转异构体的混合物；8.50 (dd, *J*=4.6, 1.4 Hz, 1H), 8.20 (br d, *J*=8.0 Hz, 1H), 7.31-7.42 (m, 3H), 7.14-7.19 (m, 1H), 5.32-5.52 (m, J_{HF}=57 Hz, 1H), 5.04-5.26 (m, 1H), 4.82-5.03 (m, 1H), 4.38-4.50 (m, 1H), 4.21-4.34 (m, 1H), 1.99 及 1.97 (2 s，总 3H)；345.0
36		实施例 9	8.51 (dd, *J*=4.6, 1.5 Hz, 1H), 8.15 (dd, *J*=8.2, 1.5 Hz, 1H), 7.68 (br s, 1H), 7.41 (dd, *J*=8.2, 4.8 Hz, 1H), 7.11-7.16 (m, 2H), 2.82-2.90 (m, 1H), 0.86-0.92 (m, 2H), 0.68-0.73 (m, 2H)；349.1
37		实施例 2[5]	8.72 (d, *J*=2.0 Hz, 1H), 8.60 (d, *J*=2.1 Hz, 1H), 8.51 (dd, *J*=4.6, 1.4 Hz, 1H), 8.16 (dd, *J*=8.2, 1.4 Hz, 1H), 7.86 (dd, *J*=2.1, 2.0 Hz, 1H), 7.69 (br s, 1H), 7.42 (dd, *J*=8.3, 4.6 Hz, 1H), 2.83-2.91 (m, 1H), 0.86-0.92 (m, 2H), 0.68-0.73 (m, 2H)；314.1, 316.0
38		实施例 37	8.69 (d, *J*=2.3 Hz, 1H), 8.56 (d, *J*=1.9 Hz, 1H), 8.50 (dd, *J*=4.6, 1.3 Hz, 1H), 8.20 (dd, *J*=8.1, 1.3 Hz, 1H), 7.85-7.88 (m, 1H), 7.40 (dd, *J*=8.2, 4.6 Hz, 1H), 4.82-4.87 (m, 2H), 4.19-4.25 (m, 2H), 2.39-2.49 (m, 2H)；313.9, 315.9
39		实施例 7[6]	8.84 (br d, *J*=2.4 Hz, 1H), 8.50 (dd, *J*=4.7, 1.4 Hz, 1H), 8.18 (dd, *J*=8.2, 1.4 Hz, 1H), 8.03 (dd, ABX 图形的一半, *J*=8.3, 2.4 Hz, 1H), 7.91 (dd, ABX 图形的一半, *J*=8.3, 0.5 Hz, 1H), 7.72 (br s, 1H), 7.44 (dd, *J*=8.2, 4.8 Hz, 1H), 2.82-2.90 (m, 1H), 0.87-0.93 (m, 2H), 0.68-0.73 (m, 2H)；305.1
40		实施例 7	8.50 (dd, *J*=4.9, 1.4 Hz, 1H), 8.17 (dd, *J*=8.3, 1.3 Hz, 1H), 7.81-7.87 (m, 2H), 7.68 (br s, 1H), 7.39-7.45 (m, 2H), 2.82-2.89 (m, 1H), 0.86-0.92 (m, 2H), 0.68-0.74 (m, 2H)；322.2

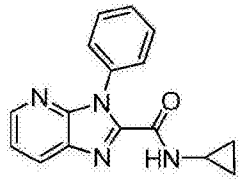
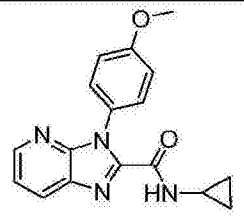
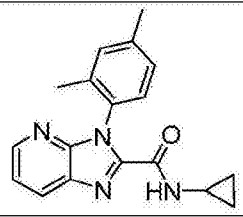
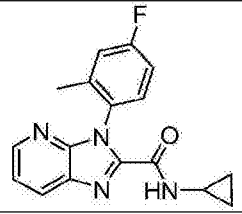
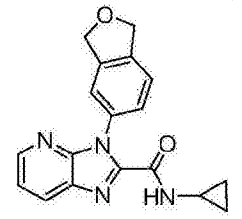
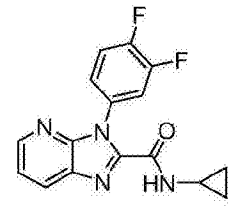
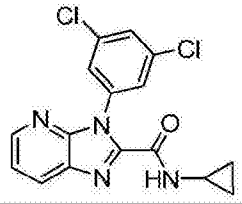
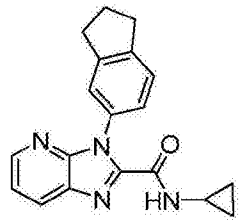
[0316]

41		实施例 7[7]	8.51 (dd, *J*=4.6, 1.5 Hz, 1H), 8.16 (dd, *J*=8.0, 1.3 Hz, 1H), 7.64 (br s, 1H), 7.32-7.43 (m, 3H), 2.83-2.90 (m, 1H), 0.85-0.92 (m, 2H), 0.68-0.74 (m, 2H); 349.1
42		方法 A	2.32 分钟；304.1
43		方法 A	2.47 分钟；315.1
44		方法 A	2.54 分钟；311.1
45		方法 A	2.44 分钟；327.1
46		方法 A	2.34 分钟；309.1
47		方法 A	3.25 分钟；319.1
48		方法 A	2.55 分钟；315.0

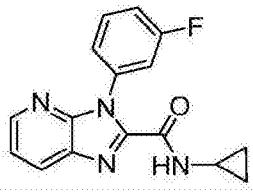
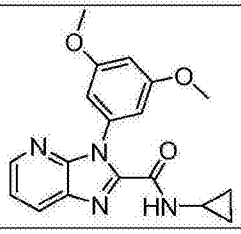
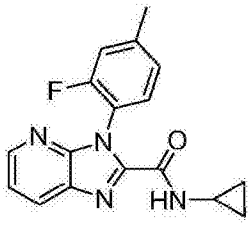
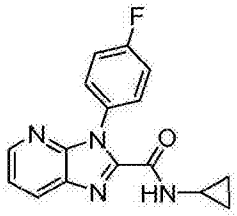
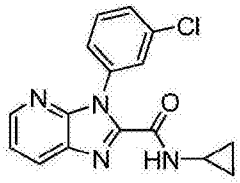
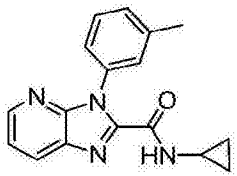
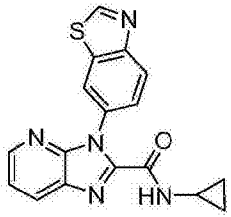
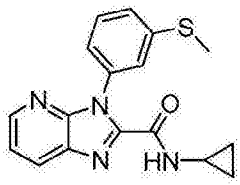
[0317]

49		方法 A	2.66 分钟；343.0, 345.0
50		方法 A	2.60 分钟；323.1
51		方法 A	2.60 分钟；323.1
52		方法 A	2.71 分钟；307.1
53		方法 A	2.30 分钟；304.1
54		方法 A	2.85 分钟；327.1, 329.1
55		方法 A	2.40 分钟；327.1
56		方法 A	2.52 分钟；318.1

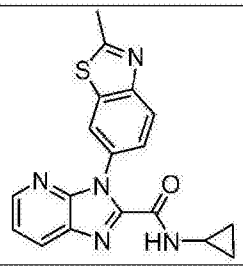
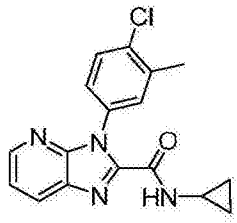
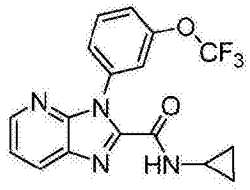
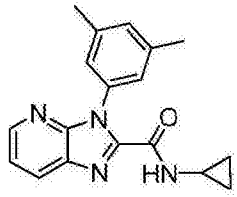
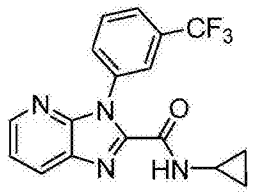
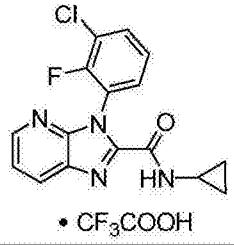
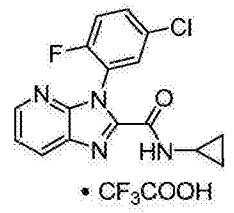
[0318]

57		方法 A	2.13 分钟；279.1
58		方法 A	2.33 分钟；309.1
59		方法 A	2.74 分钟；307.1
60		方法 A	2.55 分钟；311.1
61		方法 A	2.10 分钟；321.1
62		方法 A	2.52 分钟；315.0
63		方法 A	3.06 分钟；347.0, 349.0
64		方法 A	2.83 分钟；319.1

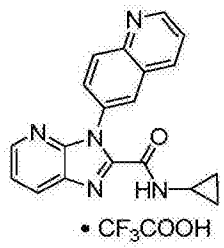
[0319]

65		方法 A	2.39 分钟；297.1
66		方法 A	2.46 分钟；339.1
67		方法 A	2.69 分钟；311.1
68		方法 A	2.35 分钟；297.1
69		实施例 7[8]	8.50 (dd, *J*=4.8, 1.3 Hz, 1H), 8.14 (dd, *J*=8.2, 1.1 Hz, 1H), 7.69 (br s, 1H), 7.47-7.53 (m, 2H), 7.45 (br s, 1H), 7.33-7.41 (m, 2H), 2.83-2.90 (m, 1H), 0.83-0.90 (m, 2H), 0.67-0.73 (m, 2H)；312.9
70		方法 A	2.48 分钟；293.1
71		方法 A	2.13 分钟；336.0
72		方法 A	2.65 分钟；325.0

[0320]

73		方法 A	2.27 分钟；350.0
74		方法 A	2.85 分钟；327.1, 329.0
75		方法 A	2.95 分钟；363.0
76		方法 A	2.71 分钟；307.1
77		方法 A	2.88 分钟；347.0
78		方法 A	2.79 分钟；331.0, 333.0
79		方法 A	2.76 分钟；331.0, 333.0

[0321]

80		方法 A	1.59 分钟；330.1

[0322] 1. 分析型 HPLC 的条件 . 柱 :Waters Atlantis dC18,4.6×50mm,5μm ;流动相 A :在水中的 0.05％三氟乙酸 (v/v) ;流动相 B :在乙腈中的 0.05％三氟乙酸 (v/v) ;梯度 :5.0％至 95％ B,经 4.0 分钟线性 ;流速 :2mL/ 分钟。

[0323] 2. 采用 (二甲基氨基)(氧代) 乙酸乙酯替代 (环丙基氨基)(氧代) 乙酸乙酯 (P1)。

[0324] 3. 利用氢氧化锂水解 C7,得到相应羧酸 ;使用 1-[3-(二甲基氨基) 丙基]-3- 乙基碳二亚胺盐酸盐及 1H- 苯并三唑 -1- 醇将此物质与 1- 甲基 -1H- 吡唑 -3- 胺缩合。

[0325] 4. 最终步骤中利用 N,N- 二异丙基乙胺。

[0326] 5. 使用乙酸钯 (II) 及 4,5- 双 (二苯基膦基)-9,9- 二甲基呫吨,通过使 2- 氯 -3- 硝基吡啶与 5- 氯吡啶 -3- 胺反应,之后用拉尼镍处理来制备需要的 N^2-(5- 氯吡啶 -3- 基) 吡啶 -2,3- 二胺。

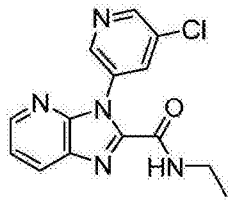
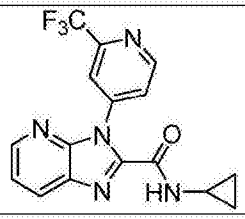
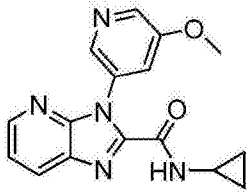
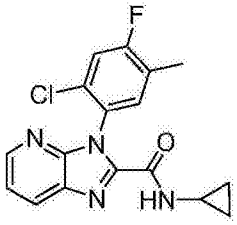
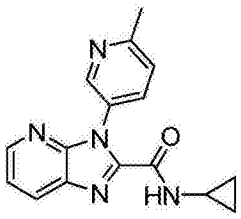
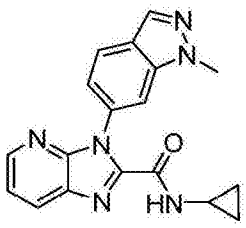
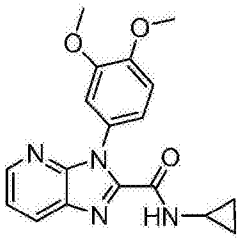
[0327] 6. 通过用于实施例 9 中的 C17 的合成的方法制备 5-[(3- 硝基吡啶 -2- 基) 氨基] 吡啶 -2- 腈。

[0328] 7. 通过用于实施例 9 中的 C17 的合成的方法制备 N-(4- 氯 -2,5- 二氟苯基)-3- 硝基吡啶 -2- 胺。

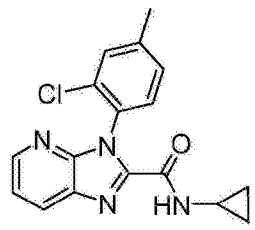
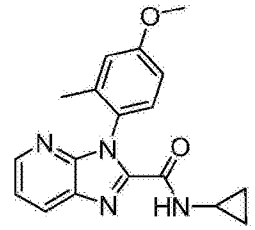
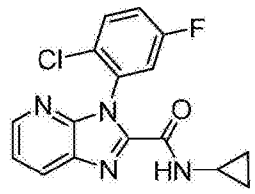
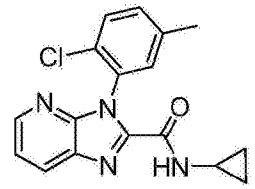
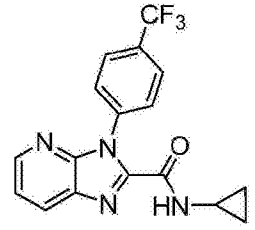
[0329] 8. 通过于 150℃下加热 2- 氯 -3- 硝基吡啶与 3- 氯苯胺制备 N-(3- 氯苯基)-3- 硝基吡啶 -2- 胺。

[0330] 表 2

[0331]

实施例编号	结构	制备方法；非市售原料	质谱，观察离子 *m/z* $[M+H]^+$
81		实施例 2[1]	302.0
82		实施例 7[2]	348.2
83		实施例 7	309.9
84		方法 A	345.0, 347.0
85		方法 A	294.1
86		方法 A	333.1
87		方法 A	339.1

[0332]

88		方法 A	327.1, 329.0
89		方法 A	323.1
90		方法 A	331.0, 333.0
91		方法 A	327.1, 329.0
92		方法 A	347.1

[0333] 1. 参见表 1 中的脚注 5。

[0334] 2. 使用实施例 9 中的 C17 的合成的方法由 2- 氯 -3- 硝基吡啶和 2-(三氟甲基) 吡啶 -4- 胺制备 3- 硝基 -N-[2-(三氟甲基) 吡啶 -4- 基] 吡啶 -2- 胺。

[0335] 实施例 1-92 中的化合物对 PDE4B 亚型的结合亲和性示于下表 3 的第 2 栏中，且这些化合物对 PDE4D 亚型的亲和性示于第 3 栏中。数据显示所选化合物相对于 PDE4D 亚型对 PDE4B 亚型具有增强的结合亲和性。举例而言，实施例 2、15、17、81、82、83、85、90 及 91 的数据显示这些化合物表现出相对于 PDE4D 亚型至少约 2 倍的选择性。实施例 13、14、21、25、35、40、47、77、88、89 及 92 的数据显示这些化合物表现出相对于 PDE4D 亚型至少约 5 倍的选择性。实施例 19、20、33、38、41、44、49、57、61、72、75、79 及 87 的数据显示这些化合物表现出相对于 PDE4D 亚型至少约 10 倍的选择性。实施例 6、9、10、11、12、22、27、31、34、37、39、43、56、59、60、63、66、69、70、73、74、78 及 80 的数据显示这些化合物表现出相对于 PDE4D 亚型至少约 20 倍的选择性。实施例 4、7、18、36、46、62、67 及 71 的数据显示这些化合物表现出相对于 PDE4D 亚型至少约 40 倍的选择性。实施例 1、3、8、16、23、26、28、30、32、33、42、45、48、50、51、52、54、55、58、64、65、68 及 76 的数据显示这些化合物表现出相对于 PDE4D 亚

型至少约 50 倍的选择性。

[0336] 利用下列生物分析测定本发明的化合物的 PDE4B 及 PDE4D 结合亲和性：

[0337] 生物分析

[0338] 将一部分人类 PDE4D3 编码序列（来自具有登录号 Q08499-2 的序列的氨基酸 50 至 672）克隆至经改造以包括 C 端 His6 亲和性标签以帮助纯化的杆状病毒表达载体 pFastBac(Invitrogen) 中，如 Seeger, T.F. 等人，Brain Research 985(2003)113-126 中所述。分离重组杆粒并用于转染昆虫细胞以产生病毒原液。为了产生供纯化的细胞糊，将昆虫细胞感染并在感染后 72 小时收获细胞。将昆虫细胞糊裂解，并在离心后在 Ni-NTA 琼脂糖 (Qiagen) 上对上清液进行层析，如 Seeger, T.F. 等人，Brain Research 985(2003)113-126 中所述。汇集含有 PDE4 的 Ni-NTA 琼脂糖洗脱流分，用 Q 缓冲液 A(50mM Tris HCl pH 8，4％甘油，100mM NaCl，1mM TCEP，不含蛋白酶抑制剂 EDTA(Roche)) 稀释以将 NaCl 减少至约 200mM，并装载于 Q Sepharose(GE Healthcare) 柱上。在用 Q 缓冲液 A 洗涤至基线后，将 PDE4D 用 10％至 60％的缓冲液 B(50mM Tris HCl pH 8，1M NaCl，4％甘油，1mM TCEP) 的梯度洗脱。通过 SDS-PAGE 考马斯蓝染色来分析 PDE4D 流分，基于纯度汇集，冷冻并保存在 -80℃下。

[0339] 将具有因氨基酸取代 S134E、S654A、S659A 及 S661A 产生的突变的人类 PDE4B1 编码序列（来自具有登录号 Q07343 的序列的氨基酸 122 至 736）克隆至经改造以包括用以帮助纯化的 N 端 His6 亲和性标签，之后凝血酶裂解位点的杆状病毒表现载体 pFastBac(Invitrogen) 中。分离重组杆粒并用于转染昆虫细胞以产生病毒原液。为产生供纯化的细胞糊，用病毒原液感染昆虫细胞并在感染后 72 小时收获细胞，如 Seeger, T.F. 等人，Brain Research985(2003)113-126 中所述。将昆虫细胞糊裂解，并在离心后在 Ni-NTA 琼脂糖 (Qiagen) 上对上清液进行层析，如 Seeger, T.F. 等人，Brain Research 985(2003)113-126 中所述。汇集含有 PDE4 的 Ni-NTA 琼脂糖洗脱流分，用 Q 缓冲液 A(20mM Tris HCl pH 8，5％甘油，1mM TCEP) 稀释以将 NaCl 减少至约 100mM 并装载于 Source 15Q(GE Healthcare) 柱上。在用 Q 缓冲液 A/10％缓冲液 B 洗涤至基线后，将 PDE4D 用 10％至 60％缓冲液 B(20mM Tris HCl pH 8，1M NaCl，5％甘油，1mM TCEP) 的梯度洗脱。通过 SDS-PAGE 考马斯蓝染色分析 PDE4D 流分，基于纯度汇集，冷冻并保存在 -80℃下。

[0340] PDE4B 及 4D 分析使用闪烁迫近分析 (SPA) 技术以测量化合物在体外对人类重组 PDE4B 及 PDE4D 酶活性的抑制。PDE4B 及 4D 分析使用相同参数平行运行，酶的浓度除外（约 32pM PDE4B 及约 16pM PDE4D）。该分析在具有 50μL 分析缓冲液 (50mM Tris pH 7.5；1.3mM $MgCl_2$；0.01％ Brij) 及多种抑制剂的 384 孔模式中进行，所述分析缓冲液含有足够的 PDE4B 及 PDE4D 以转化约 20％的底物（1μM cAMP，由 20nM ^{3}H-cAMP+980μM 冷 cAMP 组成）。将反应物于 25℃下孵育 30min。添加 20μL 8mg/mL 硅酸钇 SPA 珠粒 (PerkinElmer) 停止反应。将板密封 (TopSeal, PerkinElmer) 并使珠粒沉降 8hr，然后在 Trilux Microbeta 上对其读数过夜。

[0341] 表 3

[0342]

实施例编号	人类 PDE4B FL；IC_{50} (nM)[a]	人类 PDE4D FL；IC_{50} (μM)[a]	IUPAC 名称
1	31.8[b]	2.21[b]	*N*-环丙基-3-(3-氟-4-甲基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
2	426	1.27[b]	3-环戊基-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
3	131[b]	7.95[b]	3-(4-氯苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
4	18.4[b]	0.908[b]	3-(4-氯-3-氟苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
5	54.1	5.64	3-(4-氯-3-氟苯基)-*N*-(1-甲基-1*H*-吡唑-3-基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
6	38.1[b]	0.778[b]	3-(4-氯-3-氟苯基)-*N*-丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
7	40.8[b]	1.88[b]	3-(4-氰基-3-氟苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
8	16.0	0.910	4-[2-(氮杂环丁-1-基羰基)-3*H*-咪唑并[4,5-*b*]吡啶-3-基]-2-氟苄腈
9	14.2[b]	0.420[b]	氮杂环丁-1-基[3-(4-氯-3,5-二氟苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-基]甲酮
10	15.2[b]	0.567[b]	氮杂环丁-1-基[3-(4-氯-3-氟苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-基]甲酮
11	405	9.64	3-(4-氯-3-氟苯基)-*N*,*N*-二甲基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
12	99.4	1.52	氮杂环丁-1-基[3-(4-氯-2,5-二氟苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-基]甲酮三氟乙酸盐
13	944	6.64[b]	3-(4-氯苯基)-*N*-丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
14	822	4.38	3-环戊基-*N*-(1-甲基-1*H*-吡唑-3-基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
15	1730	6.90	*N*-环丙基-3-(四氢-2*H*-吡喃-4-基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
16	196	5.50	氮杂环丁-1-基[3-(4-氯苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-基]甲酮
17	8510	>30.0	3-(4-氯-3-氟苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
18	48.7	2.14	氮杂环丁-1-基[3-(3-氟-4-甲基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-基]甲酮
19	281	5.28	(3-氟氮杂环丁-1-基)[3-(3-氟-4-甲基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-基]甲酮
20	13.8	0.262[b]	3-(4-氰基-3,5-二氟苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺

[0343]

21	42.6	0.316	[3-(4-氯-3-氟苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-基](3-氟氮杂环丁-1-基)甲酮
22	273	5.59	氮杂环丁-1-基[3-(4-氯-2-氟苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-基]甲酮
23	632	>30.0	3-(4-氯-2-氟苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
24	211	>24.1	3-(4-氯苯基)-*N*-(1-甲基-1*H*-吡唑-3-基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
25	910	5.84	[3-(4-氯-2-氟苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-基](3-氟氮杂环丁-1-基)甲酮
26	319	>17.9	3-(4-氯-2-甲基苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
27	12.2[b]	0.511[b]	*N*-环丙基-3-(3,4-二氯苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
28	114	8.23	*N*-环丙基-3-(4-氟-3-甲基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
29	225	>28.0[b]	*N*-环丙基-3-(4-甲基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
30	5.77	0.333	*N*-环丙基-3-(3,4,5-三氟苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺三氟乙酸盐
31	87.5	2.55	3-(3-氰基-4-氟苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
32	15.7	0.886	3-(3-氯-4-氟苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
33	15.9	1.23[b]	3-(3-氯-4-甲基苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
34	399	10.2	氮杂环丁-1-基[3-(4-氯-2-甲基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-基]甲酮
35	1130	8.28	[3-(4-氯-2-甲基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-基](3-氟氮杂环丁-1-基)甲酮
36	5.65	0.255	3-(4-氯-3,5-二氟苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
37	409	10.7	3-(5-氯吡啶-3-基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
38	466	6.67	氮杂环丁-1-基[3-(5-氯吡啶-3-基)-3*H*-咪唑并[4,5-*b*]吡啶-2-基]甲酮
39	363	10.2	3-(6-氰基吡啶-3-基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
40	1710	15.2	3-(5-氰基-2-氟苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
41	100	1.17	3-(4-氯-2,5-二氟苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
42	276[b]	>22.4[b]	3-(4-氰基苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺

[0344]

43	927	>26.6	*N*-环丙基-3-(2,4-二氟苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
44	1660	>29.0	*N*-环丙基-3-(5-氟-2-甲基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
45	205	14.8	*N*-环丙基-3-(3-氟-4-甲氧基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
46	329	13.8	*N*-环丙基-3-(3-甲氧基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
47	1260	6.39	*N*-环丙基-3-(2,3-二氢-1*H*-茚-2-基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
48	88.9	4.82	*N*-环丙基-3-(3,5-二氟苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
49	629	12.3	3-(3-氯-4-甲氧基苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
50	339	>30.0	*N*-环丙基-3-(3-甲氧基-4-甲基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
51	207	13.2	*N*-环丙基-3-(4-甲氧基-3-甲基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
52	271	25.8	*N*-环丙基-3-(3,4-二甲基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
53	287	3.40	3-(3-氰基苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
54	329	19.2	3-(5-氯-2-甲基苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
55	304	>23.7	*N*-环丙基-3-(4-氟-3-甲氧基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
56	167	4.85	3-(3-氰基-4-甲基苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
57	1160	>19.7	*N*-环丙基-3-苯基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
58	506	>30.0	*N*-环丙基-3-(4-甲氧基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
59	1020	>30.0	*N*-环丙基-3-(2,4-二甲基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
60	1200	>30.0	*N*-环丙基-3-(4-氟-2-甲基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
61	1580	>30.0	*N*-环丙基-3-(1,3-二氢-2-苯并呋喃-5-基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
62	34.9	1.49[b]	*N*-环丙基-3-(3,4-二氟苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
63	68.0	2.55	*N*-环丙基-3-(3,5-二氯苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
64	206	15.7	*N*-环丙基-3-(2,3-二氢-1*H*-茚-5-基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺

[0345]

65	188	10.9	*N*-环丙基-3-(3-氟苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
66	759	19.4	*N*-环丙基-3-(3,5-二甲氧基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
67	619	>30.0	*N*-环丙基-3-(2-氟-4-甲基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
68	219	11.9	*N*-环丙基-3-(4-氟苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
69	70.9[b]	1.91[b]	3-(3-氯苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
70	421	14.9	*N*-环丙基-3-(3-甲基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
71	155	6.34	3-(1,3-苯并噻唑-6-基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
72	40.9	0.753	*N*-环丙基-3-[3-(甲硫基)苯基]-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
73	516	12.6	*N*-环丙基-3-(2-甲基-1,3-苯并噻唑-6-基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
74	58.8	1.99	3-(4-氯-3-甲基苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
75	389	3.98	*N*-环丙基-3-[3-(三氟甲氧基)苯基]-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
76	374	>18.8	*N*-环丙基-3-(3,5-二甲基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
77	1150	8.64	*N*-环丙基-3-[3-(三氟甲基)苯基]-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
78	387	11.4	3-(3-氯-2-氟苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺三氟乙酸盐
79	106	1.76	3-(5-氯-2-氟苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺三氟乙酸盐
80	1470	>30.0	*N*-环丙基-3-(喹啉-6-基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺三氟乙酸盐
81	8270	>30.0	3-(5-氯吡啶-3-基)-*N*-乙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
82	6070	17.5	*N*-环丙基-3-[2-(三氟甲基)吡啶-4-基]-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
83	13600	>29.3	*N*-环丙基-3-(5-甲氧基吡啶-3-基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
84	16600	>30.0	3-(2-氯-4-氟-5-甲基苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
85	7730	>30.0	*N*-环丙基-3-(6-甲基吡啶-3-基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
86	24500	>30.0	*N*-环丙基-3-(1-甲基-1*H*-吲唑-6-基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺

[0346]

87	2720	>30.0	*N*-环丙基-3-(3,4-二甲氧基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
88	3700	>30.0	3-(2-氯-4-甲基苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
89	3520	>30.0	*N*-环丙基-3-(4-甲氧基-2-甲基苯基)-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
90	9230	>30.0	3-(2-氯-5-氟苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
91	9420	>30.0	3-(2-氯-5-甲基苯基)-*N*-环丙基-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺
92	3110	>30.0	*N*-环丙基-3-[4-(三氟甲基)苯基]-3*H*-咪唑并[4,5-*b*]吡啶-2-甲酰胺

[0347] a. 值表示 2 至 6 次测定的几何平均值。

[0348] b. 值表示≥ 7 次测定的几何平均值。