

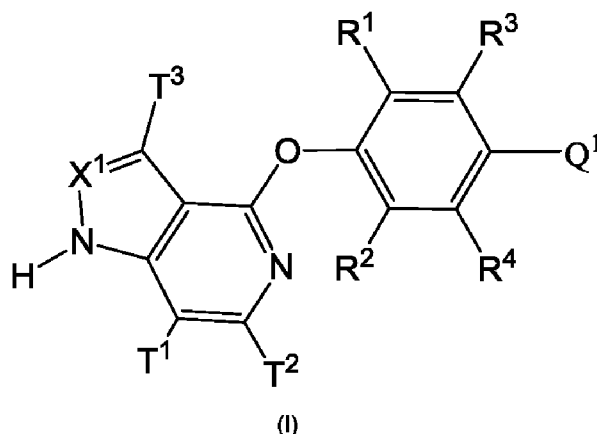


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Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i))
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(54) **Title:** HETEROAROMATIC COMPOUNDS AS DOPAMINE D1 LIGANDS

(57) **Abstract:** The present invention provides, in part, compounds of Formula I and pharmaceutically acceptable salts thereof and *N*-oxides of the foregoing; processes for the preparation of; intermediates used in the preparation of; and compositions containing such compounds, salts or *N*-oxides, and their uses for treating D1-mediated (or D1-associated) disorders including, e.g., schizophrenia (e.g., its cognitive and negative symptoms), cognitive impairment (e.g., cognitive impairment associated with schizophrenia, AD, PD, or pharmacotherapy therapy), ADHD, impulsivity, compulsive gambling, overeating, autism spectrum disorder, MCI, age-related cognitive decline, dementia, RLS, Parkinson's disease, Huntington's chorea, anxiety, depression, MDD, TRD, and bipolar disorder.



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FIELD OF THE INVENTION

The present invention generally relates to heteroaromatic compounds, which are dopamine D1 ligands, for example dopamine D1 agonists or partial agonists.

BACKGROUND OF THE INVENTION

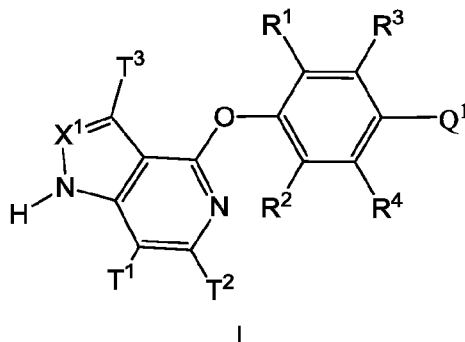
Dopamine acts upon neurons through two families of dopamine receptors, D1-like receptors (D1Rs) and D2-like receptors (D2Rs). The D1-like receptor family consists of D1 and D5 receptors which are expressed in many regions of the brain. D1 mRNA has been found, for example, in the striatum and nucleus accumbens. See e.g., Missale C, Nash SR, Robinson SW, Jaber M, Caron MG "Dopamine receptors: from structure to function", *Physiological Reviews* 78:189–225 (1998). Pharmacological studies have reported that D1 and D5 receptors (D1/D5), namely D1-like receptors, are linked to stimulation of adenylyl cyclase, whereas D2, D3, and D4 receptors, namely D2-like receptors, are linked to inhibition of cAMP production.

Dopamine D1 receptors are implicated in numerous neuropharmacological and neurobiological functions. For example, D1 receptors are involved in different types of memory function and synaptic plasticity. See e.g., Goldman-Rakic PS et al., "Targeting the dopamine D1 receptor in schizophrenia: insights for cognitive dysfunction", *Psychopharmacology* 174(1):3-16 (2004). Moreover, D1 receptors have been implicated in a variety of psychiatric, neurological, neurodevelopmental, neurodegenerative, mood, motivational, metabolic, cardiovascular, renal, ophthalmic, endocrine, and/or other disorders described herein including schizophrenia (e.g., cognitive and negative symptoms in schizophrenia), cognitive impairment associated with D2 antagonist therapy, ADHD, impulsivity, autism spectrum disorder, mild cognitive impairment (MCI), age-related cognitive decline, Alzheimer's dementia, Parkinson's disease (PD), Huntington's chorea, depression, anxiety, treatment-resistant depression (TRD), bipolar disorder, chronic apathy, anhedonia, chronic fatigue, post-traumatic stress disorder, seasonal affective disorder, social anxiety disorder, post-partum depression, serotonin syndrome, substance abuse and drug dependence, Tourette's syndrome, tardive dyskinesia, drowsiness, sexual dysfunction, migraine, systemic lupus erythematosus (SLE), hyperglycemia, dislipidemia, obesity, diabetes, sepsis, post-ischemic tubular necrosis, renal failure, resistant edema, narcolepsy, hypertension, congestive heart failure, postoperative ocular hypotonia, sleep disorders, pain, and other disorders in a mammal. See e.g., Goulet M, Madras BK "D(1) dopamine receptor agonists are more effective in alleviating advanced than mild parkinsonism in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated monkeys", *Journal of Pharmacology and Experimental Therapy* 292(2):714-24 (2000); Surmeier DJ et al., "The role of dopamine in modulating the structure and function of striatal circuits", *Prog. Brain Res.* 183:149-67 (2010).

New or improved agents that modulate (such as agonize or partially agonize) D1 are needed for developing new and more effective pharmaceuticals to treat diseases or conditions associated with dysregulated activation of D1, such as those described herein.

SUMMARY OF THE INVENTION

The present invention provides, in part, a compound of Formula I:



5 or a pharmaceutically acceptable salt thereof, wherein:

X^1 is N or CT^4 ;

Q^1 is an N-containing 5- to 6-membered heteroaryl or an N-containing 5- to 6-membered heterocycloalkyl, each optionally substituted with one R^9 and further optionally substituted with 1, 2, 3, or 4 R^{10} ;

10 each of T^1 , T^2 , T^3 , and T^4 is independently selected from the group consisting of H, halogen, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, cyclopropyl, fluorocyclopropyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, and -C(=O)-O-(C_{1-4} alkyl);

each of R^1 and R^2 is independently selected from the group consisting of H, halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, -C(=O)OH, and
 15 -C(=O)-O-(C_{1-4} alkyl), wherein each of said C_{1-6} alkyl and C_{3-6} cycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents each independently selected from halo, -OH, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy;

each of R^3 and R^4 is independently selected from the group consisting of H, halogen, -OH, -NO₂, -CN, -SF₅, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7}
 20 cycloalkyl, a 4- to 10-membered heterocycloalkyl, -N(R^5)(R^6), -N(R^7)(C(=O) R^8), -C(=O)-N(R^5)(R^6), -C(=O)- R^8 , -C(=O)-OR⁸, -N(R^7)(S(=O)₂ R^8), -S(=O)₂-N(R^5)(R^6), -SR⁸, and -OR⁸,
 wherein each of said C_{1-6} alkyl, C_{3-7} cycloalkyl, and heterocycloalkyl is optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of halogen, -CN, -OH, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, -N(R^5)(R^6),
 25 -N(R^7)(C(=O) R^8), -C(=O)-OR⁸, -C(=O)H, -C(=O) R^8 , -C(=O)N(R^5)(R^6), -N(R^7)(S(=O)₂ R^8), -S(=O)₂-N(R^5)(R^6), -SR⁸, and -OR⁸;

R^5 is H, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{3-7} cycloalkyl;

R^6 is H or selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} cycloalkyl, a 4- to 10-membered heterocycloalkyl, C_{6-10} aryl, a 5- to 10-membered heteroaryl, C_{3-7}
 30 cycloalkyl)- C_{1-4} alkyl-, (4- to 10-membered heterocycloalkyl)- C_{1-4} alkyl-, (C_{6-10} aryl)- C_{1-4} alkyl-, and (5- to 10-membered heteroaryl)- C_{1-4} alkyl-, wherein each of the selections from the group is optionally substituted with 1, 2, 3, or 4 substituents each independently selected from the group consisting of -OH, -CN, C_{1-4} alkyl, C_{3-7} cycloalkyl, C_{1-4} hydroxylalkyl, -S- C_{1-4} alkyl, -C(=O)H,

-C(=O)-C₁₋₄ alkyl, -C(=O)-O-C₁₋₄ alkyl, -C(=O)-NH₂, -C(=O)-N(C₁₋₄ alkyl)₂, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy;

or R⁵ and R⁶ together with the N atom to which they are attached form a 4- to 10-membered heterocycloalkyl or a 5- to 10-membered heteroaryl, each optionally substituted with 1, 2, 3, 4, or 5 substituents each independently selected from the group consisting of halogen, -OH, oxo, -C(=O)H, -C(=O)OH, -C(=O)-C₁₋₄ alkyl, -C(=O)-NH₂, -C(=O)-N(C₁₋₄ alkyl)₂, -CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ hydroxylalkyl, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy;

R⁷ is selected from the group consisting of H, C₁₋₄ alkyl, and C₃₋₇ cycloalkyl;

R⁸ is selected from the group consisting of C₁₋₆ alkyl, C₃₋₇ cycloalkyl, a 4- to 14-membered heterocycloalkyl, C₆₋₁₀ aryl, a 5- to 10-membered heteroaryl, (C₃₋₇ cycloalkyl)-C₁₋₄ alkyl-, (4- to 10-membered heterocycloalkyl)-C₁₋₄ alkyl-, (C₆₋₁₀ aryl)-C₁₋₄ alkyl-, and (5- to 10-membered heteroaryl)-C₁₋₄ alkyl-, wherein each of the selections from the group is optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of halogen, -CF₃, -CN, -OH, oxo, -S-C₁₋₄ alkyl, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy;

R⁹ is C₁₋₄ alkyl, C₁₋₄ haloalkyl, -CN, -SF₅, -N(R⁵)(R⁶), C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₇ cycloalkoxy, or C₃₋₇ cycloalkyl, wherein each of the C₁₋₄ alkyl and C₃₋₇ cycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents each independently selected from the group consisting of halogen, -N(R⁵)(R⁶), C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₃₋₇ cycloalkyl, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy;

each R¹⁰ is independently selected from the group consisting of halogen, -OH, -CN, -SF₅, -NO₂, oxo, thiono ("=S"), C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxylalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₇ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, a 4- to 10-membered heterocycloalkyl, a 5- to 10-membered heteroaryl, (C₃₋₇ cycloalkyl)-C₁₋₄ alkyl-, (4- to 10-membered heterocycloalkyl)-C₁₋₄ alkyl-, (C₆₋₁₀ aryl)-C₁₋₄ alkyl-, (5- to 10-membered heteroaryl)-C₁₋₄ alkyl-, -N(R⁵)(R⁶), -N(R⁷)(C(=O)R⁸), -S(=O)₂N(R⁵)(R⁶), -C(=O)-N(R⁵)(R⁶), -C(=O)-R⁸, -C(=O)-OR⁸, -SR⁸, and -OR⁸, wherein each of said C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₆₋₁₀ aryl, 4- to 10-membered heterocycloalkyl, 5- to 10-membered heteroaryl, (C₃₋₇ cycloalkyl)-C₁₋₄ alkyl-, (4- to 10-membered heterocycloalkyl)-C₁₋₄ alkyl-, (C₆₋₁₀ aryl)-C₁₋₄ alkyl-, and (5- to 10-membered heteroaryl)-C₁₋₄ alkyl- is optionally substituted with 1, 2, 3, or 4 substituents each independently selected from the group consisting of halogen, OH, -CN, -NO₂, C₁₋₄ alkyl, C₁₋₄ hydroxylalkyl, C₁₋₄ alkoxy, -N(R⁵)(R⁶), -S-(C₁₋₄ alkyl), -S(=O)₂-(C₁₋₄ alkyl), C₆₋₁₀ aryloxy, [(C₆₋₁₀ aryl)-C₁₋₄ alkyloxy- optionally substituted with 1 or 2 C₁₋₄ alkyl], oxo, -C(=O)H, -C(=O)-C₁₋₄ alkyl, -C(=O)O-C₁₋₄ alkyl, -C(=O)NH₂, -NHC(=O)H, -NHC(=O)-(C₁₋₄ alkyl), C₃₋₇ cycloalkyl, a 5- or 6-membered heteroaryl, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy;

or R⁹ and an adjacent R¹⁰ together with the two ring atoms on Q¹ to which they are attached form a fused benzene ring or a fused 5- or 6-membered heteroaryl, each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^{10a}; and

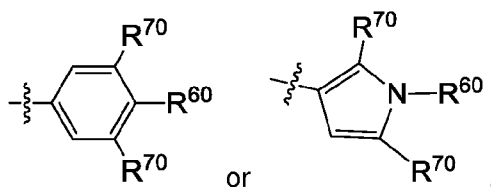
each R^{10a} is independently from the group consisting of halogen, -OH, -N(R^5)(R^6), -C(=O)OH, -C(=O)-C₁₋₄ alkyl, -C(=O)-NH₂, -C(=O)-N(C₁₋₄ alkyl)₂, -CN, -SF₅, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ hydroxylalkyl, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy;

provided that the compound of Formula I is not 4-(4-imidazol-1-yl-phenoxy)-3-methyl-1*H*-pyrazolo[4,3-*c*]pyridine.

The present invention also provides a composition (e.g., a pharmaceutical composition) comprising a compound of Formula I (including an *N*-oxide thereof or a pharmaceutically acceptable salt of the compound or the *N*-oxide).

Compounds of Formula I (including *N*-oxides thereof and pharmaceutically acceptable salts of the compounds or the *N*-oxides) are D1 modulators (e.g., D1 agonists or partial agonists). According, the present invention further provides a method for treating a D1-mediated (or D1-associated) disorder (e.g., cognitive impairment such as cognitive impairment associated with schizophrenia or cognitive impairment associated with Alzheimer's disease; schizophrenia; Alzheimer's disease; or Parkinson's disease), comprising administering to a mammal (e.g., a human) in need thereof an amount of a compound of Formula I (including a pharmaceutically acceptable salt thereof or an *N*-oxide of the compound or salt) effective in modulating (e.g., agonizing or partially agonizing) D1.

As used herein, the term "adjacent" in describing the relative positions of two substituent groups on a ring structure refers to two substituent groups that are respectively attached to two ring-forming atoms of the same ring, wherein the two ring-forming atoms are directly connected through a chemical bond. For example, in each of the following structures:



either of the two R^{70} groups is an adjacent group of R^{60} .

As used herein, the term "n-membered" where n is an integer typically describes the number of ring-forming atoms in a moiety where the number of ring-forming atoms is n. For example, pyridine is an example of a 6-membered heteroaryl ring and thiophene is an example of a 5-membered heteroaryl group.

At various places in the present specification, substituents of compounds of the invention are disclosed in groups or in ranges. It is specifically intended that the invention include each and every individual subcombination of the members of such groups and ranges. For example, the term "C₁₋₆ alkyl" is specifically intended to include C₁ alkyl (methyl), C₂ alkyl (ethyl), C₃ alkyl, C₄ alkyl, C₅ alkyl, and C₆ alkyl. For another example, the term "a 5- to 10-membered heteroaryl group" is specifically intended to include any 5-, 6-, 7-, 8-, 9- or 10-membered heteroaryl group.

As used herein, the term "alkyl" is defined to include saturated aliphatic hydrocarbons including straight chains and branched chains. In some embodiments, the alkyl group has 1 to

6, e.g., 1 to 4, carbon atoms. For example, as used herein, the term "C₁₋₆ alkyl," as well as the alkyl moieties of other groups referred to herein (e.g., C₁₋₆ alkoxy) refers to linear or branched radicals of 1 to 6 carbon atoms (e.g., methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, or *n*-hexyl), optionally substituted by 1 or more (such as 1 to 5) suitable substituents. The term "C₁₋₄ alkyl" refers to linear or branched aliphatic hydrocarbon chains of 1 to 4 carbon atoms (i.e., methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl). The term "C₁₋₃ alkyl" refers to linear or branched aliphatic hydrocarbon chains of 1 to 3 carbon atoms

As used herein, the term "alkenyl" refers to aliphatic hydrocarbons having at least one carbon-carbon double bond, including straight chains and branched chains having at least one carbon-carbon double bond. In some embodiments, the alkenyl group has 2 to 6 carbon atoms. In some embodiments, the alkenyl group has 2 to 4 carbon atoms. For example, as used herein, the term "C₂₋₆ alkenyl" means straight or branched chain unsaturated radicals of 2 to 6 carbon atoms, including, but not limited to, ethenyl, 1-propenyl, 2-propenyl (allyl), isopropenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like, optionally substituted by 1 to 5 suitable substituents. When the compounds of Formula I contain an alkenyl group, the alkenyl group may exist as the pure E form, the pure Z form, or any mixture thereof.

As used herein, the term "alkynyl" refers to aliphatic hydrocarbons having at least one carbon-carbon triple bond, including straight chains and branched chains having at least one carbon-carbon triple bond. In some embodiments, the alkynyl group has 2 to 6 carbon atoms. For example, as used herein, the term "C₂₋₆ alkynyl" is used herein to mean straight or branched hydrocarbon chain alkynyl radicals as defined above, having 2 to 6 carbon atoms and one triple bond, optionally substituted by 1 or more (such as 1 to 5) suitable substituents.

As used herein, the term "cycloalkyl" refers to saturated or unsaturated, non-aromatic, monocyclic or polycyclic (such as bicyclic) hydrocarbon rings (e.g., monocyclics such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, or bicyclics including spiro, fused, or bridged systems (such as bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[3.2.1]octanyl or bicyclo[5.2.0]nonanyl, decahydronaphthalenyl, etc.), optionally substituted by 1 or more (such as 1 to 5) suitable substituents. The cycloalkyl group has 3 to 15 carbon atoms. In some embodiments the cycloalkyl may optionally contain one, two or more non-cumulative non-aromatic double or triple bonds and/or one to three oxo groups. In some embodiments, the bicycloalkyl group has 6 to 15 carbon atoms. For example, the term "C₃₋₇ cycloalkyl" refers to saturated or unsaturated, non-aromatic, monocyclic or polycyclic (such as bicyclic) hydrocarbon rings of 3 to 7 ring-forming carbon atoms (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or bicyclo[1.1.1]pentanyl). For another example, the term "C₃₋₆ cycloalkyl" refers to saturated or unsaturated, non-aromatic, monocyclic or polycyclic (such as bicyclic) hydrocarbon rings of 3 to 6 ring-forming carbon atoms. For yet another example, the term "C₃₋₄ cycloalkyl" refers to cyclopropyl or cyclobutyl. Also included in the definition of

cycloalkyl are moieties that have one or more aromatic rings (including aryl and heteroaryl) fused to the cycloalkyl ring, for example, benzo or thienyl derivatives of cyclopentane, cyclopentene, cyclohexane, and the like (e.g., 2,3-dihydro-1*H*-indene-1-yl, or 1*H*-inden-2(3*H*)-one-1-yl). The cycloalkyl group is optionally substituted by 1 or more (such as 1 to 5) suitable substituents.

As used herein, the term "aryl" refers to all-carbon monocyclic or fused-ring polycyclic aromatic groups having a conjugated pi-electron system. The aryl group has 6 or 10 carbon atoms in the ring(s). Most commonly, the aryl group has 6 carbon atoms in the ring. For example, as used herein, the term "C₆₋₁₀ aryl" means aromatic radicals containing from 6 to 10 carbon atoms such as phenyl or naphthyl. The aryl group is optionally substituted by 1 or more (such as 1 to 5) suitable substituents.

As used herein, the term "heteroaryl" refers to monocyclic or fused-ring polycyclic aromatic heterocyclic groups with one or more heteroatom ring members (ring-forming atoms) each independently selected from O, S and N in at least one ring. The heteroaryl group has 5 to 14 ring-forming atoms, including 1 to 13 carbon atoms, and 1 to 8 heteroatoms selected from O, S, and N. In some embodiments, the heteroaryl group has 5 to 10 ring-forming atoms including one to four heteroatoms. The heteroaryl group can also contain one to three oxo or thiono groups. In some embodiments, the heteroaryl group has 5 to 8 ring-forming atoms including one, two or three heteroatoms. Examples of monocyclic heteroaryls include those with 5 ring-forming atoms including one to three heteroatoms or those with 6 ring-forming atoms including one, two or three nitrogen heteroatoms. Examples of fused bicyclic heteroaryls include two fused 5- and/or 6-membered monocyclic rings including one to four heteroatoms.

Examples of heteroaryl groups include pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl, furyl, imidazolyl, pyrrolyl, oxazolyl (e.g., 1,3-oxazolyl, 1,2-oxazolyl), thiazolyl (e.g., 1,2-thiazolyl, 1,3-thiazolyl), pyrazolyl, tetrazolyl, triazolyl (e.g., 1,2,3-triazolyl, 1,2,4-triazolyl), oxadiazolyl (e.g., 1,2,3-oxadiazolyl), thiadiazolyl (e.g., 1,3,4-thiadiazolyl), quinolyl, isoquinolyl, benzothienyl, benzofuryl, indolyl, 1*H*-imidazo[4,5-*c*]pyridinyl, imidazo[1,2-*a*]pyridinyl, 1*H*-pyrrolo[3,2-*c*]pyridinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[2,1-*c*][1,2,4]triazinyl, imidazo[1,5-*a*]pyrazinyl, imidazo[1,2-*a*]pyrimidinyl, 1*H*-indazolyl, 9*H*-purinyl, imidazo[1,2-*a*]pyrimidinyl, [1,2,4]triazolo[1,5-*a*]pyrimidinyl, [1,2,4]triazolo[4,3-*b*]pyridazinyl, isoxazolo[5,4-*c*]pyridazinyl, isoxazolo[3,4-*c*]pyridazinyl, pyridone, pyrimidone, pyrazinone, pyrimidinone, 1*H*-imidazol-2(3*H*)-one, 1*H*-pyrrole-2,5-dione, 3-oxo-2*H*-pyridazinyl, 1*H*-2-oxo-pyrimidinyl, 1*H*-2-oxo-pyridinyl, 2,4(1*H*,3*H*)-dioxo-pyrimidinyl, 1*H*-2-oxo-pyrazinyl, and the like. The heteroaryl group is optionally substituted by 1 or more (such as 1 to 5) suitable substituents.

As used herein, the term "N-containing" when used in connection with a heteroaryl or heterocycloalkyl means that the heteroaryl or heterocycloalkyl comprises at least one ring-forming nitrogen (N) atom and optionally one or more (e.g., 1, 2, 3, or 4) ring-forming heteroatoms each independently selected from O, S and N. The term "N-containing 5- to 10-

membered heteroaryl" refers to a 5- to 10-membered heteroaryl group (including monocyclic or bicyclic systems) comprising at least one ring-forming nitrogen (N) atom and optionally one or more (e.g., 1, 2, 3, or 4) ring-forming heteroatoms each independently selected from O, S and N. The term "N-containing 5- or 6-membered heteroaryl" refers to a 5- or 6-membered

heteroaryl group comprising at least one ring-forming nitrogen (N) atom and optionally one or more (e.g., 1, 2, 3, or 4) ring-forming heteroatoms each independently selected from O, S and N. Examples of N-containing 5- to 10-membered heteroaryl groups include pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, imidazolyl, pyrrolyl, oxazolyl (e.g., 1,3-oxazolyl, 1,2-oxazolyl), thiazolyl (e.g., 1,2-thiazolyl, 1,3-thiazolyl), pyrazolyl, tetrazolyl, triazolyl (e.g., 1,2,3-triazolyl, 1,2,4-triazolyl), oxadiazolyl (e.g., 1,2,3-oxadiazolyl), thiadiazolyl (e.g., 1,3,4-thiadiazolyl), quinolyl, isoquinolyl, 1*H*-imidazo[4,5-*c*]pyridinyl, imidazo[1,2-*a*]pyridinyl, 1*H*-pyrrolo[3,2-*c*]pyridinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[2,1-*c*][1,2,4]triazinyl, imidazo[1,5-*a*]pyrazinyl, imidazo[1,2-*a*]pyrimidinyl, 1*H*-indazolyl, 9*H*-purinyl, imidazo[1,2-*a*]pyrimidinyl, [1,2,4]triazolo[1,5-*a*]pyrimidinyl, [1,2,4]triazolo[4,3-*b*]pyridazinyl, isoxazolo[5,4-*c*]pyridazinyl, isoxazolo[3,4-*c*]pyridazinyl, pyridone, pyrimidone, pyrazinone, pyrimidinone, 1*H*-imidazol-2(3*H*)-one, 1*H*-pyrrole-2,5-dione, 3-oxo-2*H*-pyridazinyl, 1*H*-2-oxo-pyrimidinyl (e.g., 1*H*-2-oxo-pyrimidin-6-yl), 1*H*-2-oxo-pyridinyl, 2,4(1*H*,3*H*)-dioxo-pyrimidinyl, 1*H*-2-oxo-pyrazinyl, and the like. Examples of N-containing 5- or 6-membered heteroaryl groups include pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, imidazolyl, pyrrolyl, oxazolyl (e.g., 1,3-oxazolyl, 1,2-oxazolyl), thiazolyl (e.g., 1,2-thiazolyl, 1,3-thiazolyl), pyrazolyl, tetrazolyl, triazolyl (e.g., 1,2,3-triazolyl, 1,2,4-triazolyl), oxadiazolyl (e.g., 1,2,3-oxadiazolyl), thiadiazolyl (e.g., 1,3,4-thiadiazolyl), 3-oxo-2*H*-pyridazinyl, 1*H*-2-oxo-pyrimidinyl (e.g., 1*H*-2-oxo-pyrimidin-6-yl), 1*H*-2-oxo-pyridinyl, 2,4(1*H*,3*H*)-dioxo-pyrimidinyl, and 1*H*-2-oxo-pyrazinyl. The N-containing 5- to 10-membered heteroaryl group or the N-containing 5- or 6-membered heteroaryl is optionally substituted by 1 or more (such as 1 to 5) suitable substituents.

As used herein, the term "heterocycloalkyl" refers to a monocyclic or polycyclic [including 2 or more rings that are fused together, including spiro, fused, or bridged systems, for example, a bicyclic ring system], saturated or unsaturated, non-aromatic 4- to 15-membered ring system (such as a 4- to 14-membered ring system, 4- to 10-membered ring system, 5- to 10-membered ring system, 4- to 7-membered ring system, or 5- to 6-membered ring system), including 1 to 14 ring-forming carbon atoms and 1 to 10 ring-forming heteroatoms each independently selected from O, S and N. For example, the term "4- to 10-membered heterocycloalkyl" refers to a monocyclic or polycyclic, saturated or unsaturated, non-aromatic 4- to 10-membered ring system that comprises one or more ring-forming heteroatoms each independently selected from O, S and N. For another example, the term "4- to 7-membered heterocycloalkyl" refers to a monocyclic or polycyclic, saturated or unsaturated, non-aromatic 4- to 7-membered ring system that comprises one or more ring-forming heteroatoms each independently selected from O, S and N. For yet another example, the term "5- to 6-membered heterocycloalkyl" refers to a

monocyclic, saturated or unsaturated, non-aromatic 5- to 6-membered ring system that comprises one or more ring-forming heteroatoms each independently selected from O, S and N. The heterocycloalkyl group is optionally substituted by 1 or more (such as 1 to 5) suitable substituents. The heterocycloalkyl group can also include one to three oxo or thiono groups.

5 Examples of such heterocycloalkyl rings include azetidiny, tetrahydrofuranyl, imidazolidiny, pyrrolidiny, piperidiny, piperaziny, oxazolidiny, thiazolidiny, pyrazolidiny, thiomorpholiny, tetrahydrothiaziny, tetrahydrothiadiaziny, morpholiny, oxetany, tetrahydrodiaziny, oxaziny, oxathiaziny, quinuclidiny, chromany, isochromany, benzoxaziny, 2-azabicyclo[2.2.1]heptanony, 3-azabicyclo[3.1.0]hexany, 3-azabicyclo[4.1.0]heptany and the
10 like. Further examples of heterocycloalkyl rings include tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, imidazolidin-1-yl, imidazolidin-2-yl, imidazolidin-4-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazin-1-yl, piperazin-2-yl, 1,3-oxazolidin-3-yl, 1,4-oxazepan-1-yl, isothiazolidiny, 1,3-thiazolidin-3-yl, 1,2-pyrazolidin-2-yl, 1,2-tetrahydrothiazin-2-yl, 1,3-thiazinan-3-yl, 1,2-tetrahydrodiazin-2-yl, 1,3-tetrahydrodiazin-1-yl, 1,4-oxazin-4-yl, oxazolidinony, 2-oxo-piperidiny (e.g., 2-oxo-piperidin-1-yl), and the like. Also
15 included in the definition of heterocycloalkyl are moieties that have one or more aromatic rings (including aryl and heteroaryl) fused to the nonaromatic heterocycloalkyl ring, for example pyridiny, pyrimidiny, thiopheny, pyrazoly, phthalimidyl, naphthalimidyl, and benzo derivatives of the nonaromatic heterocycloalkyl rings. Examples of such aromatic-fused heterocycloalkyl
20 groups include indoliny, isoindoliny, isoindolin-1-one-3-yl, 5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl, 6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-6-yl, 4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-5-yl, 5,6-dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one-5-yl, 1,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazol-5-yl, and 3,4-dihydroisoquinolin-1(2*H*)-one-3-yl groups. The heterocycloalkyl group is optionally substituted by 1 or more (such as 1 to 5) suitable substituents. Examples of heterocycloalkyl
25 groups include 5- or 6-membered monocyclic rings and 9- or 10-membered fused bicyclic rings.

As used herein, the term "N-containing 4- to 10-membered heterocycloalkyl" refers to a 4- to 10-membered heterocycloalkyl group comprising at least one ring-forming nitrogen (N) atom and optionally one or more ring-forming heteroatoms each independently selected from O, S and N. The term "N-containing 5- or 6-membered heterocycloalkyl" refers to a 5- or 6-
30 membered heterocycloalkyl group comprising at least one ring-forming nitrogen (N) atom and optionally one or more ring-forming heteroatoms each independently selected from O, S and N. Examples of N-containing 4- to 10-membered heterocycloalkyl groups include azetidiny, piperidin-1-yl, piperidin-4-yl, piperazin-1-yl, 1,3-thiazinan-3-yl, 1,4,5,6-tetrahydropyrrolo[3,4-*c*]pyrazol-5-yl, and 3,4-dihydroisoquinolin-1(2*H*)-one-3-yl. Examples of N-containing 5- or 6-
35 membered heterocycloalkyl groups include piperidin-1-yl, piperidin-4-yl, piperazin-1-yl, 1,3-thiazinan-3-yl, and morpholino. The N-containing 4- to 10-membered heterocycloalkyl or the N-containing 5- or 6-membered heterocycloalkyl is optionally substituted by 1 or more (such as 1 to 5) suitable substituents.

As used herein, the term "halo" or "halogen" group is defined to include fluorine, chlorine, bromine or iodine.

As used herein, the term "haloalkyl" refers to an alkyl group having one or more halogen substituents (up to perhaloalkyl, i.e., every hydrogen atom of the alkyl group has been replaced by a halogen atom). For example, the term "C₁₋₆ haloalkyl" refers to a C₁₋₆ alkyl group having one or more halogen substituents (up to perhaloalkyl, i.e., every hydrogen atom of the alkyl group has been replaced by a halogen atom). The term "C₁₋₄ haloalkyl" refers to a C₁₋₄ alkyl group having one or more halogen substituents (up to perhaloalkyl, i.e., every hydrogen atom of the alkyl group has been replaced by a halogen atom). The term "C₁₋₃ haloalkyl" refers to a C₁₋₃ alkyl group having one or more halogen substituents (up to perhaloalkyl, i.e., every hydrogen atom of the alkyl group has been replaced by a halogen atom). The term "C₁ haloalkyl" refers to a methyl group having one, two, or three halogen substituents. Examples of haloalkyl groups include CF₃, C₂F₅, CHF₂, CH₂F, CH₂CF₃, CH₂Cl and the like.

As used herein, the term "alkoxy" or "alkyloxy" refers to an -O-alkyl group. The term "C₁₋₆ alkoxy" or "C₁₋₆ alkyloxy" refers to an -O-(C₁₋₆ alkyl) group. The term "C₁₋₄ alkoxy" or "C₁₋₄ alkyloxy" refers to an -O-(C₁₋₄ alkyl) group. The term "C₁₋₃ alkoxy" or "C₁₋₃ alkyloxy" refers to an -O-(C₁₋₃ alkyl) group. Examples of alkoxy include methoxy, ethoxy, propoxy (e.g., *n*-propoxy and isopropoxy), *tert*-butoxy, and the like.

As used here, the term "haloalkoxy" refers to an -O-haloalkyl group. The term "C₁₋₆ haloalkoxy" refers to an -O-(C₁₋₆ haloalkyl) group. The term "C₁₋₄ haloalkoxy" refers to an -O-(C₁₋₄ haloalkyl) group. The term "C₁₋₃ haloalkoxy" refers to an -O-(C₁₋₃ haloalkyl) group. The term "C₁ haloalkoxy" refers to a methoxy group having one, two, or three halogen substituents. An example of a haloalkoxy group is -OCF₃ or -OCHF₂.

As used herein, the term "cycloalkoxy" or "cycloalkyloxy" refers to an -O-cycloalkyl group. The term "C₃₋₇ cycloalkoxy" or "C₃₋₇ cycloalkyloxy" refers to an -O-(C₃₋₇ cycloalkyl) group. Examples of cycloalkoxy include C₃₋₇ cycloalkoxy (e.g., cyclopropoxy, cyclobutoxy, cyclopentoxo, and the like).

As used here, the term "C₆₋₁₀ aryloxy" refers to an -O-(C₆₋₁₀ aryl) group. An example of a C₆₋₁₀ aryloxy group is -O-phenyl [i.e., phenoxy].

As used herein, the term "fluoroalkyl" refers to an alkyl group having one or more fluorine substituents (up to perfluoroalkyl, i.e., every hydrogen atom of the alkyl group has been replaced by fluorine). For example, the term "C₁₋₆ fluoroalkyl" refers to a C₁₋₆ alkyl group having one or more fluorine substituents (up to perfluoroalkyl, i.e., every hydrogen atom of the C₁₋₆ alkyl group has been replaced by fluorine). The term "C₁ fluoroalkyl" refers to a C₁ alkyl group (i.e., methyl) having 1, 2, or 3 fluorine substituents). Examples of fluoroalkyl groups include CF₃, C₂F₅, CH₂CF₃, CHF₂, CH₂F, and the like.

As used here, the term “fluoroalkoxy” refers to an -O-fluoroalkyl group. The term “C₁ fluoroalkoxy” refers to a methoxy group having one, two, or three fluorine substituents. An example of a C₁ fluoroalkoxy group is -OCF₃ or -OCHF₂.

As used herein, the term “fluorocyclopropyl” refers to a cyclopropyl group having one or more fluorine substituents (up to perfluorocyclopropyl, i.e., every hydrogen atom of the cyclopropyl group has been replaced by fluorine). Examples of fluorocyclopropyl include 2-fluoro-cyclopropan-1-yl or 2,3-difluorocyclopropan-1-yl.

As used herein, the term “hydroxylalkyl” or “hydroxyalkyl” refers to an alkyl group having one or more (e.g., 1, 2, or 3) OH substituents. The term “C₁₋₆ hydroxylalkyl” or “C₁₋₆ hydroxyalkyl” refers to a C₁₋₆ alkyl group having one or more (e.g., 1, 2, or 3) OH substituents. The term “C₁₋₄ hydroxylalkyl” or “C₁₋₄ hydroxyalkyl” refers to a C₁₋₄ alkyl group having one or more (e.g., 1, 2, or 3) OH substituents. Examples of hydroxylalkyl groups include -CH₂OH and -CH₂CH₂OH.

As used herein, the term “oxo” refers to =O. When an oxo is substituted on a carbon atom, they together form a carbonyl moiety [-C(=O)-]. When an oxo is substituted on a sulfur atom, they together form a sulfinyl moiety [-S(=O)-]; when two oxo groups are substituted on a sulfur atom, they together form a sulfonyl moiety [-S(=O)₂-].

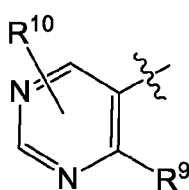
As used herein, the term “thiono” refers to =S. When an thiono is substituted on a carbon atom, they together form a moiety having the structure of -C(=S)-.

As used herein, the term “optionally substituted” 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 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., CH₃) is optionally substituted, then up to 3 hydrogen atoms on the carbon atom can be replaced with substituent groups.

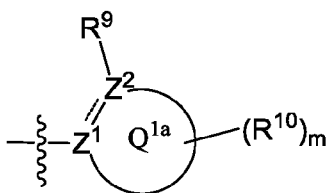
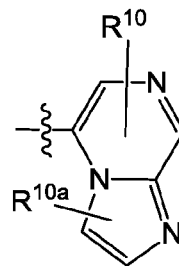
As used herein, unless specified, the point of attachment of a substituent can be from any suitable position of the substituent. For example, piperidinyl can be piperidin-1-yl (attached through the N atom of the piperidinyl), piperidin-2-yl (attached through the C atom at the 2-position of the piperidinyl), piperidin-3-yl (attached through the C atom at the 3-position of the piperidinyl), or piperidin-4-yl (attached through the C atom at the 4-position of the piperidinyl). For another 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

a-101 below, R^{10} may be bonded to either of the two ring carbon atoms, each of which bears a hydrogen atom. For another example, as shown in Moiety M^1 below, an R^{10} may be bonded to any ring-forming atom that is substitutable (i.e., bonded to one or more hydrogen atoms; for example, a C or N ring-forming atom). For yet another example, as shown in Formula a-102 below (a substituted imidazo[1,2-*a*]pyrazine ring), R^{10} may be bonded to either of the two ring carbon atoms in the pyrazine ring (each of which bears a hydrogen atom), and R^{10a} may be bonded to either of the two ring carbon atoms in the imidazo ring (each of which bears a hydrogen atom).



a-101

 M^1 

a-102

When a substituted or optionally substituted moiety is described without indicating the atom via which such moiety is bonded to a substituent, then a substituent may be bonded via any appropriate atom in such moiety. For example in a substituted arylalkyl, a substituent on the arylalkyl [e.g., (C_{6-10} aryl)- C_{1-4} alkyl-] can be bonded to any carbon atom on the alkyl part or on the aryl part of the arylalkyl. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As noted above, the compounds of Formula I may exist in the form of pharmaceutically acceptable salts such as acid addition salts and/or base addition salts of the compounds of Formula I. The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes acid addition or base salts which may be present in the compounds of Formula I.

Pharmaceutically acceptable salts of the compounds of Formula I include the acid addition and base salts thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulfate/sulfate, borate, camphorsulfonate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulfate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts.

Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

Hemisalts of acids and bases may also be formed, for example, hemisulfate and hemicalcium salts.

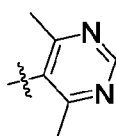
For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, 2002). Methods for making pharmaceutically acceptable salts of compounds of Formula I are known to one of skill in the art.

As used herein the terms "Formula I", "Formula I or pharmaceutically acceptable salts thereof", "pharmaceutically acceptable salts of the compound or the salt [of Formula I]" are defined to include all forms of the compound of Formula I, including hydrates, solvates, isomers (including for example rotational stereoisomers), crystalline and non-crystalline forms, isomorphs, polymorphs, metabolites, and prodrugs thereof.

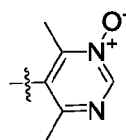
As it is known to the person skilled in the art, amine compounds (i.e., those comprising one or more nitrogen atoms), for example tertiary amines, can form *N*-oxides (also known as amine oxides or amine *N*-oxides). An *N*-oxide has the formula of $(R^{100}R^{200}R^{300})N^+-O^-$ wherein the parent amine $(R^{100}R^{200}R^{300})N$ can be for example, a tertiary amine (for example, each of R^{100} , R^{200} , R^{300} is independently alkyl, arylalkyl, aryl, heteroaryl, or the like), a heterocyclic or heteroaromatic amine [for example, $(R^{100}R^{200}R^{300})N$ together forms 1-alkylpiperidine, 1-alkylpyrrolidine, 1-benzylpyrrolidine, or pyridine]. For instance, an imine nitrogen, especially heterocyclic or heteroaromatic imine nitrogen, or pyridine-type nitrogen ($\text{--}\overset{\text{Z}}{\text{N}}\text{--}\overset{\text{Z}}{\text{Z}}$) atom [such as a nitrogen atom in pyridine, pyridazine, or pyrazine], can be *N*-oxidized to form the *N*-oxide

comprising the group $(\text{--}\overset{\text{O}^-}{\underset{+}{\text{N}}}\text{--}\overset{\text{Z}}{\text{Z}})$. Thus, a compound according to the present invention

comprising one or more nitrogen atoms (e.g., an imine nitrogen atom), for example, as a part of Q^1 of Formula I, may be capable of forming an *N*-oxide thereof (e.g., mono-*N*-oxides, bis-*N*-oxides or multi-*N*-oxides, or mixtures thereof depending on the number of nitrogen atoms suitable to form stable *N*-oxides). For example, a compound of Formula I wherein Q^1 is an optionally substituted pyrimidinyl, pyrazinyl, pyridinyl, or pyridazinyl can be oxidized (e.g., in the presence of a suitable oxidizing reagent such as *m*-chloroperoxybenzoic acid or in the presence of a suitable enzyme) to form its corresponding *N*-oxide wherein Q^1 is converted to its corresponding *N*-oxide form. For another example, a compound of Formula I wherein Q^1 is Q^1 -101 can be oxidized to form its corresponding *N*-oxide wherein Q^1 -101 is converted to Q^1 -102.



Q^1 -101



Q^1 -102

As used herein, the term "*N*-oxide(s)" refer to all possible, and in particular all stable, *N*-oxide forms of the amine compounds (e.g., compounds comprising one or more imine nitrogen atoms) described herein, such as mono-*N*-oxides (including different isomers when more than one nitrogen atom of an amine compound can form a mono-*N*-oxide) or multi-*N*-oxides (e.g., bis-*N*-oxides), or mixtures thereof in any ratio.

The compounds of Formula I can be converted, optionally, into *N*-oxides thereof, for example, in the presence of a suitable oxidizing reagent in a suitable solvent (e.g., in the presence of hydrogen peroxide in methanol or in the presence of *m*-chloroperoxybenzoic acid in dichloromethane) or in the presence of an enzyme (e.g. forming an *N*-oxide thereof as a metabolite). One skilled in the art would readily recognize the reaction conditions suitable for carrying out the *N*-oxidation reactions.

Compounds of Formula I described herein (compounds of the invention) include *N*-oxides thereof and pharmaceutically acceptable salts of the compounds or the *N*-oxides. Examples of *N*-oxides of compounds of Formula I include those wherein Q¹ of Formula I (e.g., an optionally substituted pyrimidinyl such as Q¹-101) may be capable of forming an *N*-oxide thereof.

Compounds of Formula I may exist in a continuum of solid states ranging from fully amorphous to fully crystalline. The term 'amorphous' refers to a state in which the material lacks long-range order at the molecular level and, depending upon temperature, may exhibit the physical properties of a solid or a liquid. Typically such materials do not give distinctive X-ray diffraction patterns and, while exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from apparent solid to a material with liquid properties occurs, which is characterised by a change of state, typically second order ('glass transition'). The term 'crystalline' refers to a solid phase in which the material has a regular ordered internal structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but the change from solid to liquid is characterized by a phase change, typically first order ('melting point').

Compounds of Formula I 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 Formula I may exist as clathrates or other complexes (e.g., co-crystals). 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 Formula I 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. Co-crystals are typically defined as crystalline complexes of neutral molecular constituents that are bound together through non-covalent interactions, but could also be a complex of a neutral molecule with a salt. Co-crystals may be prepared by melt crystallization, by recrystallization from solvents, or by physically grinding the components together; see O.

- 5 Almarsson and M. J. Zaworotko, *Chem. Commun.* **2004**, 17, 1889-1896. For a general review of multi-component complexes, see J. K. Halebian, *J. Pharm. Sci.* **1975**, 64, 1269-1288.

The compounds of the invention may also exist in a mesomorphic state (mesophase or liquid crystal) when subjected to suitable conditions. The mesomorphic state is intermediate between the true crystalline state and the true liquid state (either melt or solution).

- 10 Mesomorphism arising as the result of a change in temperature is described as 'thermotropic' and that resulting from the addition of a second component, such as water or another solvent, is described as 'lyotropic'. Compounds that have the potential to form lyotropic mesophases are described as 'amphiphilic' and consist of molecules which possess an ionic (such as $-\text{COO}^-\text{Na}^+$, $-\text{COO}^-\text{K}^+$, or $-\text{SO}_3^-\text{Na}^+$) or non-ionic (such as $-\text{N}^+(\text{CH}_3)_3$) polar head group. For more
15 information, see *Crystals and the Polarizing Microscope* by N. H. Hartshorne and A. Stuart, 4th Edition (Edward Arnold, 1970).

The invention also relates to prodrugs of the compounds of Formula I. Thus certain derivatives of compounds of Formula I which may have little or no pharmacological activity themselves can, when administered into or onto the body, be converted into compounds of
20 Formula I 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).

- 25 Prodrugs in accordance with the invention can, for example, be produced by replacing appropriate functionalities present in the compounds of Formula I 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).

- 30 Moreover, certain compounds of Formula I may themselves act as prodrugs of other compounds of Formula I.

- Also included within the scope of the invention are metabolites of compounds of Formula I, that is, compounds formed *in vivo* upon administration of the drug. Examples of metabolites of compounds of Formula I include *N*-oxides of compounds of Formula I wherein Q^1 of Formula I may be capable of forming an *N*-oxide thereof (e.g., wherein Q^1 is an optionally substituted
35 pyrimidinyl such as 4,6-dimethylpyrimidin-5-yl).

In some embodiments, the compounds of Formula I include *N*-oxides thereof and pharmaceutically acceptable salts of the compounds or the *N*-oxides.

The compounds of Formula I include all stereoisomers and tautomers. Stereoisomers of Formula I include *cis* and *trans* isomers, optical isomers such as *R* and *S* enantiomers, diastereomers, geometric isomers, rotational isomers, atropisomers, and conformational isomers of the compounds of Formula I, including compounds exhibiting more than one type of isomerism; and mixtures thereof (such as racemates and diastereomeric pairs). 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.

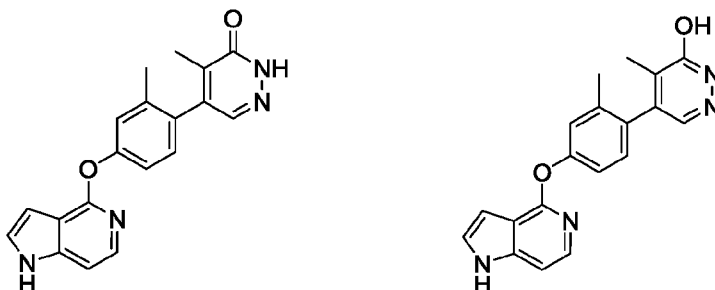
In some embodiments, the compounds of Formula I may have asymmetric carbon atoms. The carbon-carbon bonds of the compounds of Formula I may be depicted herein using a solid line (—), a solid wedge (), or a dotted wedge (). The use of a solid line to depict bonds to asymmetric carbon atoms is meant to 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 only the stereoisomer shown is meant to be included. It is possible that compounds of Formula I may contain more than one asymmetric carbon atom. In those compounds, the use of a solid line to depict bonds to asymmetric carbon atoms is meant to indicate that all possible stereoisomers are meant to be included. For example, unless stated otherwise, it is intended that the compounds of Formula I can exist as enantiomers and diastereomers or as racemates and mixtures thereof. The use of a solid line to depict bonds to one or more asymmetric carbon atoms in a compound of Formula I and the use of a solid or dotted wedge to depict bonds to other asymmetric carbon atoms in the same compound is meant to indicate that a mixture of diastereomers is present.

In some embodiments, the compounds of Formula I may exist in and/or be isolated as atropisomers (e.g., one or more atropenantiomers). Those skilled in the art would recognize that atropisomerism may exist in a compound that has two or more aromatic rings (for example, two aromatic rings linked through a single bond). See e.g., Freedman, T. B. et al., Absolute Configuration Determination of Chiral Molecules in the Solution State Using Vibrational Circular Dichroism. *Chirality* **2003**, 15, 743–758; and Bringmann, G. et al., Atroposelective Synthesis of Axially Chiral Biaryl Compounds. *Angew. Chem., Int. Ed.* **2005**, 44, 5384–5427.

When any racemate crystallizes, crystals of different types are possible. One type is the racemic compound (true racemate) wherein one homogeneous form of crystal is produced containing both enantiomers in equimolar amounts. Another type is a racemic mixture or conglomerate wherein two forms of crystal are produced in equal or different molar amounts each comprising a single enantiomer.

The compounds of Formula I may exhibit the phenomena of tautomerism and structural isomerism. For example, the compounds of Formula I may exist in several tautomeric forms, including the enol and imine form, and the keto and enamine form and geometric isomers and mixtures thereof. All such tautomeric forms are included within the scope of the compounds of

Formula I. Tautomers may exist as mixtures of a tautomeric set in solution. In solid form, usually one tautomer predominates. Even though one tautomer may be described, the present invention includes all tautomers of the compounds of Formula I. For example, when one of the following two tautomers of the invention is disclosed in the experimental section herein, those skilled in the art would readily recognize that the invention also includes the other.



The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of Formula I wherein one or more atoms are replaced by atoms 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 invention include isotopes of hydrogen, such as ^2H and ^3H , 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 sulphur, such as ^{35}S .

Certain isotopically-labelled compounds of Formula I, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e., ^3H , 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., ^2H , 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 , ^{18}F , ^{15}O and ^{13}N , can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of Formula I (or pharmaceutically acceptable salts thereof or *N*-oxides of the compounds or salts) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

An embodiment of the present invention is a compound of Formula I wherein X^1 is N.

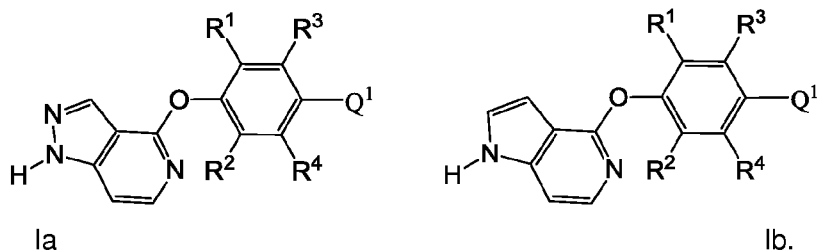
An embodiment of the present invention is a compound of Formula I wherein X^1 is CT^4 .

An embodiment of the present invention is a compound of Formula I wherein each of T^1 , T^2 , T^3 , and T^4 is independently selected from the group consisting of H, F, -CN, methoxy, C_1 fluoroalkoxy, methyl, and C_1 fluoroalkyl. In a further embodiment, T^1 is H. In a yet further

embodiment, T^2 is H. In a still further embodiment, T^3 is H, methyl or $-CN$. In a still further embodiment, T^3 is H. In a still further embodiment, T^4 is H.

An embodiment of the present invention is a compound of Formula I wherein T^3 is H. In a further embodiment, T^2 is H and T^3 is H.

- 5 An embodiment of the present invention is a compound of Formula I wherein the compound is a compound of Formula Ia or Ib:



- 10 An embodiment of the present invention is a compound of Formula I wherein the compound is a compound of Formula Ia.

An embodiment of the present invention is a compound of Formula I wherein the compound is a compound of Formula Ib.

An embodiment of the present invention is a compound of Formula I (including a compound of Formula Ia or Ib) wherein:

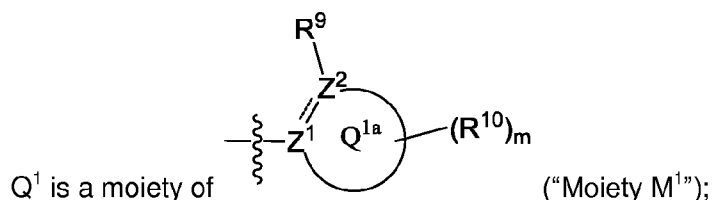
- 15 each of R^1 and R^2 is independently selected from the group consisting of H, halogen, $-CN$, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, and C_{3-4} cycloalkyl;
 each of R^3 and R^4 is independently selected from the group consisting of H, halogen, $-OH$, $-CN$, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{3-4} cycloalkyl, a 4- to 7-membered heterocycloalkyl, $-N(R^5)(R^6)$, and $-OR^8$,
 20 each of R^5 and R^6 independently is H or selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{3-7} cycloalkyl;
 or R^5 and R^6 together with the N atom to which they are attached form a 4- to 7-membered heterocycloalkyl or a 5-membered heteroaryl, each optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of halogen, $-CN$, C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy; and
 25 R^8 is selected from the group consisting of C_{1-4} alkyl, C_{3-6} cycloalkyl, a 4- to 7-membered heterocycloalkyl, phenyl, and a 5- to 6-membered heteroaryl, each optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of halogen, $-CN$, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy;
 30 An embodiment of the present invention is a compound of Formula I (including a compound of Formula Ia or Ib) wherein each of R^1 and R^2 is independently H or halogen. In a further embodiment, each of R^1 and R^2 is independently H or F. In a yet further embodiment, R^1 is H and R^2 is H or F. In a still further embodiment, each of R^1 and R^2 is H
 An embodiment of the present invention is a compound of Formula I (including a
 35 compound of Formula Ia or Ib) wherein each of R^3 and R^4 is independently H, halogen, $-CN$,

methyl, C₁ haloalkyl, methoxy, or C₁ haloalkoxy. In a further embodiment, each of R³ and R⁴ is independently H, halogen, -CN, methyl, or C₁ haloalkyl. In a yet further embodiment, R³ is H and R⁴ is H, F, Cl, -CN, methyl, or C₁ haloalkyl. In a still further embodiment, R³ is H and R⁴ is H, F, or methyl. In a yet still further embodiment, R³ is H and R⁴ is methyl.

- 5 An embodiment of the present invention is a compound of Formula I (including a compound of Formula Ia or Ib) wherein R¹ is H; R² is H or F; R³ is H and R⁴ is H, F, Cl, -CN, methyl, or C₁ haloalkyl. In a further embodiment, each of R¹, R², and R³ is H and R⁴ is H, or methyl. In a still further embodiment, R⁴ is methyl.

- 10 An embodiment of the present invention is a compound of Formula I (including a compound of Formula Ia or Ib) wherein each of R² and R⁴ is H.

An embodiment of the present invention is a compound of Formula I (including a compound of Formula Ia or Ib) wherein:



- 15 ring Q^{1a} is an N-containing 5- to 6-membered heteroaryl or an N-containing 5- to 6-membered heterocycloalkyl;

----- represents a single bond or double bond;

each of Z¹ and Z² is independently C or N;

- 20 R⁹ is C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₃₋₇ cycloalkyl, -CN, -N(R⁵)(R⁶), C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, or C₃₋₇ cycloalkoxy, wherein each of the C₁₋₄ alkyl and C₃₋₇ cycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents each independently selected from the group consisting of halogen, -N(R⁵)(R⁶), C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₃₋₇ cycloalkyl, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy;

- 25 each R¹⁰ is independently selected from the group consisting of halogen, -OH, -CN, -NO₂, oxo, thiono, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxylalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₇ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, a 4- to 10-membered heterocycloalkyl, a 5- to 10-membered heteroaryl, (C₃₋₇ cycloalkyl)-C₁₋₄ alkyl-, (4- to 10-membered heterocycloalkyl)-C₁₋₄ alkyl-, (C₆₋₁₀ aryl)-C₁₋₄ alkyl-, (5- to 10-membered heteroaryl)-C₁₋₄ alkyl-, (5- to 10-membered heteroaryl)-C₂₋₄ alkenyl-, -N(R⁵)(R⁶), -N(R⁷)(C(=O)R⁸), -S(=O)₂N(R⁵)(R⁶), -C(=O)-N(R⁵)(R⁶), -C(=O)-R⁸, -C(=O)-OR⁸, and -OR⁸, wherein each of said C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₆₋₁₀ aryl, 4- to 30 10-membered heterocycloalkyl, 5- to 10-membered heteroaryl, (C₃₋₇ cycloalkyl)-C₁₋₄ alkyl-, (4- to 10-membered heterocycloalkyl)-C₁₋₄ alkyl-, (C₆₋₁₀ aryl)-C₁₋₄ alkyl-, (5- to 10-membered heteroaryl)-C₁₋₄ alkyl-, and (5- to 10-membered heteroaryl)-C₂₋₄ alkenyl- is optionally substituted with 1, 2, 3, or 4 substituents each independently selected from the group consisting of halogen, OH, -CN, -NO₂, C₁₋₄ alkyl, C₁₋₄ hydroxylalkyl, C₁₋₄ alkoxy, -N(R⁵)(R⁶), -S-(C₁₋₄ alkyl), -S(=O)₂-(C₁₋₄ alkyl), C₆₋₁₀ aryloxy, (C₆₋₁₀ aryl)-C₁₋₄ alkyloxy- optionally substituted with 1 or 2 C₁₋₄ alkyl, oxo, -
- 35

C(=O)H, -C(=O)-C₁₋₄ alkyl, -C(=O)O-C₁₋₄ alkyl, -C(=O)NH₂, -NHC(=O)H, -NHC(=O)-(C₁₋₄ alkyl), C₃₋₇ cycloalkyl, a 5- or 6-membered heteroaryl, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy;

or R⁹ and the adjacent R¹⁰ together with the two ring atoms on ring Q^{1a} to which they are attached form a fused benzene ring or a fused 5- or 6-membered heteroaryl, each optionally

5 substituted with 1, 2, 3, 4, or 5 independently selected R^{10a};

each R^{10a} is independently selected from the group consisting of halogen, -OH, -C(=O)OH, -C(=O)-C₁₋₄ alkyl, -C(=O)-NH₂, -C(=O)-N(C₁₋₄ alkyl)₂, -CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ hydroxylalkyl, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy; and

m is 0, 1, 2, 3, or 4.

10 An embodiment of the present invention is a compound of Formula I (including a compound of Formula Ia or Ib) wherein Q¹ is Moiety M¹ and Z¹ is C.

An embodiment of the present invention is a compound of Formula I (including a compound of Formula Ia or Ib) wherein Q¹ is Moiety M¹ and Z¹ is N.

15 An embodiment of the present invention is a compound of Formula I (including a compound of Formula Ia or Ib) wherein Q¹ or ring Q^{1a} (when Q¹ is Moiety M¹) is an optionally substituted N-containing 6-membered heteroaryl. In a further embodiment, each of the ring-forming atoms of the 6-membered heteroaryl is independently selected from N and C.

20 An embodiment of the present invention is a compound of Formula I (including a compound of Formula Ia or Ib) wherein Q¹ or ring Q^{1a} (when Q¹ is Moiety M¹) is an optionally substituted pyridinyl, pyrimidinyl, pyridazinyl, or pyrazinyl. In a further embodiment, Q¹ or ring Q^{1a} is optionally substituted pyrimidinyl. In a further embodiment, Q¹ or ring Q^{1a} is pyrimidinyl substituted with 1 or 2 C₁₋₄ alkyl (e.g., CH₃).

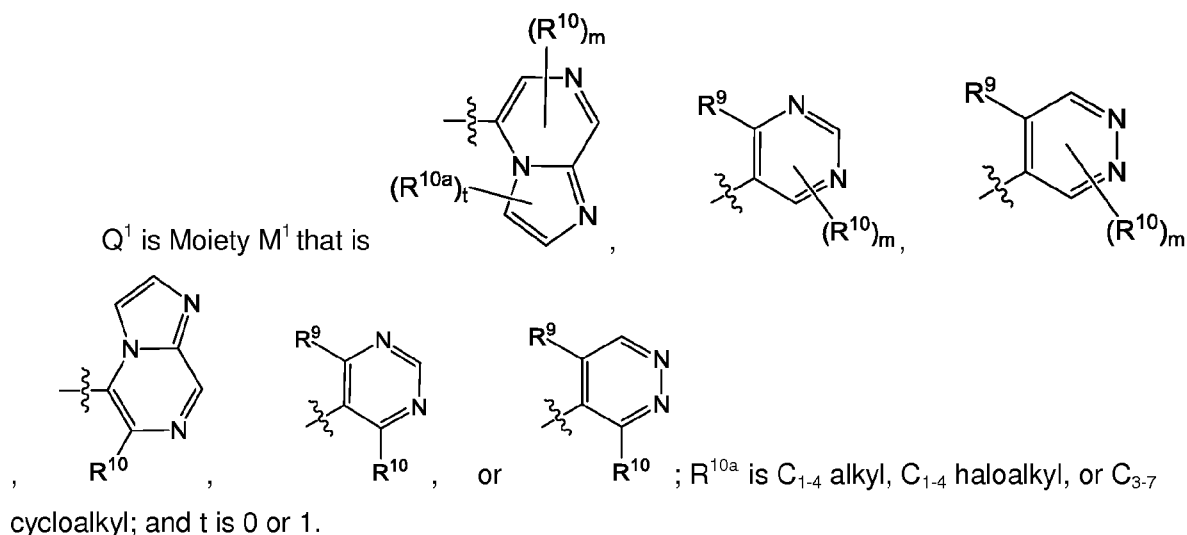
25 An embodiment of the present invention is a compound of Formula I (including a compound of Formula Ia or Ib) wherein Q¹ is Moiety M¹ that is selected from the group consisting of quinolinyl, isoquinolinyl, 1*H*-imidazo[4,5-*c*]pyridinyl, imidazo[1,2-*a*]pyridinyl, 1*H*-pyrrolo[3,2-*c*]pyridinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[2,1-*c*][1,2,4]triazinyl, imidazo[1,5-*a*]pyrazinyl, imidazo[1,2-*a*]pyrimidinyl, 1*H*-indazolyl, 9*H*-purinyl, [1,2,4]triazolo[1,5-*a*]pyrimidinyl, isoxazolo[5,4-*c*]pyridazinyl, isoxazolo[3,4-*c*]pyridazinyl, and [1,2,4]triazolo[4,3-*b*]pyridazinyl, each optionally substituted with 1, 2, or 3 R¹⁰ and further optionally substituted with 1 or 2 R^{10a};

30 or wherein Moiety M¹ is selected from the group consisting of pyrimidinyl, pyrazinyl, pyridinyl, pyridazinyl, 1*H*-pyrazolyl, 1*H*-pyrrolyl, 4*H*-pyrazolyl, 1*H*-imidazolyl, 3-oxo-2*H*-pyridazinyl, 1*H*-2-oxo-pyrimidinyl, 1*H*-2-oxo-pyridinyl, 2,4(1*H*,3*H*)-dioxo-pyrimidinyl, and 1*H*-2-oxo-pyrazinyl, each substituted with R⁹ and further optionally substituted with 1, 2, or 3 R¹⁰.

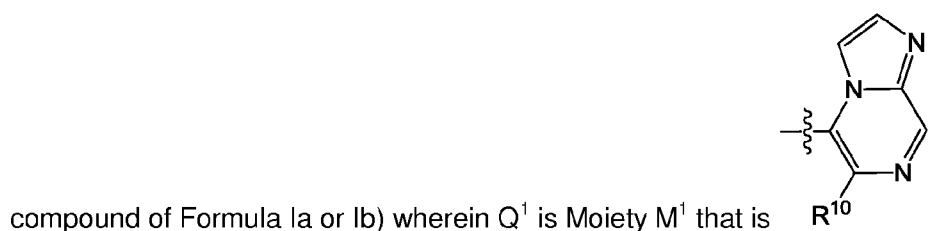
35 In a further embodiment, Moiety M¹ is selected from the group consisting of pyrimidinyl, pyrazinyl, pyridinyl, and pyridazinyl, each substituted with R⁹ and further optionally substituted with 1, 2, or 3 R¹⁰. In a yet further embodiment, Moiety M¹ is pyrimidinyl substituted with R⁹ and further optionally substituted with 1, 2, or 3 R¹⁰.

An embodiment of the present invention is a compound of Formula I (including a compound of Formula Ia or Ib) wherein Q^1 is Moiety M^1 that is selected from the group consisting of 3-oxo-2*H*-pyridazinyl, 2,4(1*H*,3*H*)-dioxo-pyrimidinyl, and 1*H*-2-oxo-pyrazinyl, each substituted with R^9 and further optionally substituted with 1, 2, or 3 R^{10} .

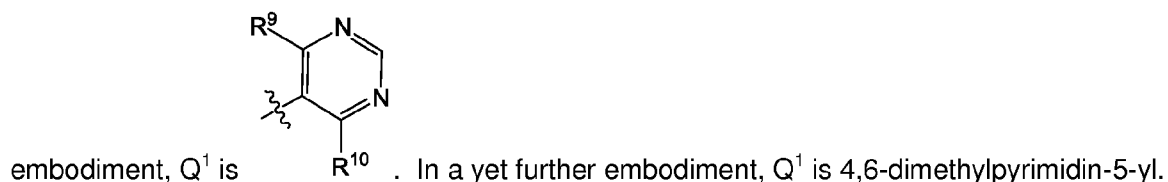
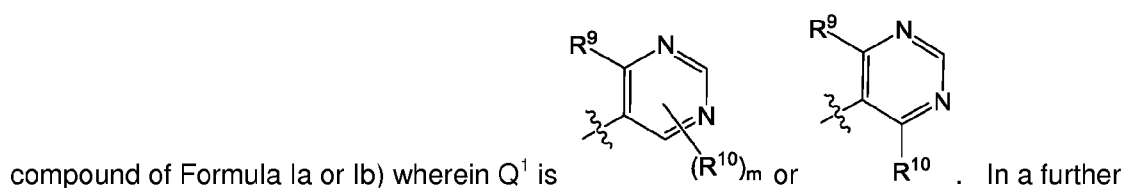
- 5 An embodiment of the present invention is a compound of Formula I (including a compound of Formula Ia or Ib) wherein:



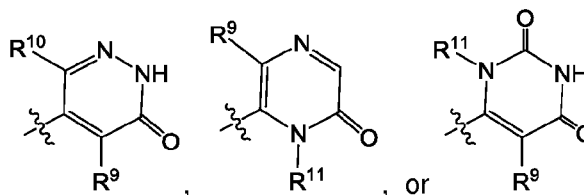
- 10 An embodiment of the present invention is a compound of Formula I (including a



An embodiment of the present invention is a compound of Formula I (including a



- 15 An embodiment of the present invention is a compound of Formula I (including a compound of Formula Ia or Ib) wherein:



Q¹ is Moiety M¹ that is , or ; and

R¹¹ is H, C₁₋₄ alkyl, C₁₋₄ haloalkyl, or C₃₋₇ cycloalkyl. In a further embodiment, each of R⁹ and R¹⁰ (or R¹¹) is independently C₁₋₄ alkyl (e.g., CH₃).

An embodiment of the present invention is a compound of Formula I (including a compound of Formula Ia or Ib) wherein Q¹ is 3-oxo-4,6-dimethyl-(2*H*)pyridazin-5-yl.

An embodiment of the present invention is a compound of Formula I (including a compound of Formula Ia or Ib) wherein Q¹ is 2-oxo-1,5-dimethyl-(1*H*)pyrazin-6-yl.

An embodiment of the present invention is a compound of Formula I (including a compound of Formula Ia or Ib) wherein Q¹ is 2,4-dioxo-1,5-dimethyl-(1*H*,3*H*)pyrimidin-6-yl.

An embodiment of the present invention is a compound of Formula I (including a compound of Formula Ia or Ib) wherein R⁹ is C₁₋₄ alkyl or -CN. In a further embodiment, R⁹ is methyl, ethyl, or -CN. In a yet further embodiment, R⁹ is methyl or -CN. In a still further embodiment, R⁹ is methyl.

An embodiment of the present invention is a compound of Formula I (including a compound of Formula Ia or Ib) wherein each R¹⁰ is independently selected from the group consisting of C₁₋₄ alkyl, C₁₋₄ haloalkyl, -CN, and -N(R⁵)(R⁶), wherein each of R⁵ and R⁶ is independently H or is selected from the group consisting of C₁₋₄ alkyl, C₁₋₄ haloalkyl, and C₃₋₇ cycloalkyl; or R⁵ and R⁶ together with the N atom to which they are attached form a 4- to 7-membered heterocycloalkyl or a 5-membered heteroaryl, each optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of halogen, -CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy. In a further embodiment, each R¹⁰ is independently selected from the group consisting of methyl, ethyl, and -N(R⁵)(R⁶), wherein R⁵ and R⁶ together with the N atom to which they are attached form azetidinyl, pyrrolidinyl, or piperidinyl, each optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of halogen, -CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₃₋₆ cycloalkyl, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy. In a yet further embodiment, each R¹⁰ is independently selected from the group consisting of methyl, ethyl, and azetidin-1-yl, wherein the azetidin-1-yl is optionally substituted with 1, 2, or 3, halogen (e.g., F).

An embodiment of the present invention is a compound of Formula I (including a compound of Formula Ia or Ib) wherein each R¹⁰ is independently C₁₋₄ alkyl. In a further embodiment, each R¹⁰ is methyl.

In one embodiment, the invention also provides one or more of the compounds described as Examples 1-47 in the Examples section of the subject application, *N*-oxides thereof, and pharmaceutically acceptable salts of the compounds or the *N*-oxides.

Another embodiment of the invention relates to a compound selected from the group consisting of:

4-[4-(4,6-dimethylpyrimidin-5-yl)-3-fluorophenoxy]-1*H*-pyrrolo[3,2-*c*]pyridine;
(+)-4,6-dimethyl-5-[2-methyl-4-(1*H*-pyrazolo[4,3-*c*]pyridin-4-yloxy)phenyl]pyridazin-3(2*H*)-

5 one;

(-)-4,6-dimethyl-5-[2-methyl-4-(1*H*-pyrazolo[4,3-*c*]pyridin-4-yloxy)phenyl]pyridazin-3(2*H*)-
one;

4-[4-(4,6-dimethylpyrimidin-5-yl)-3-methylphenoxy]-1*H*-pyrrolo[3,2-*c*]pyridine;

4-[4-(4,6-dimethylpyrimidin-5-yl)-3-methylphenoxy]-1*H*-pyrazolo[4,3-*c*]pyridine;

10 4,6-dimethyl-5-[4-(1*H*-pyrrolo[3,2-*c*]pyridin-4-yloxy)phenyl]pyridazin-3(2*H*)-one;

(-)-1,5-dimethyl-6-[2-methyl-4-(1*H*-pyrazolo[4,3-*c*]pyridin-4-yloxy)phenyl]pyrimidine-
2,4(1*H*,3*H*)-dione;

4,6-dimethyl-5-[2-methyl-4-(1*H*-pyrrolo[3,2-*c*]pyridin-4-yloxy)phenyl]pyridazin-3(2*H*)-one,
ENT-1;

15 4,6-dimethyl-5-[2-methyl-4-(1*H*-pyrrolo[3,2-*c*]pyridin-4-yloxy)phenyl]pyridazin-3(2*H*)-one,
ENT-2

4-[4-(4,6-dimethyl-1-oxidopyrimidin-5-yl)-3-methylphenoxy]-1*H*-pyrazolo[4,3-*c*]pyridine;

6-methyl-5-[2-methyl-4-(1*H*-pyrrolo[3,2-*c*]pyridin-4-yloxy)phenyl]imidazo[1,2-*a*]pyrazine;

4-[4-(4,6-dimethylpyrimidin-5-yl)phenoxy]-1*H*-pyrrolo[3,2-*c*]pyridine;

20 2-(4,6-dimethylpyrimidin-5-yl)-5-(1*H*-pyrrolo[3,2-*c*]pyridin-4-yloxy)benzonitrile;

4-[3-chloro-4-(4,6-dimethylpyrimidin-5-yl)phenoxy]-1*H*-pyrrolo[3,2-*c*]pyridine;

(-)-1,5-dimethyl-6-[2-methyl-4-(1*H*-pyrrolo[3,2-*c*]pyridin-4-yloxy)phenyl]pyrazin-2(1*H*)-
one;

4-[4-(4,6-dimethylpyrimidin-5-yl)-3-fluorophenoxy]-1*H*-pyrazolo[4,3-*c*]pyridine;

25 4-[4-(4,6-dimethylpyrimidin-5-yl)-3-methoxyphenoxy]-1*H*-pyrazolo[4,3-*c*]pyridine;

4-[3-chloro-4-(4,6-dimethylpyrimidin-5-yl)phenoxy]-1*H*-pyrazolo[4,3-*c*]pyridine;

(+)-1,5-dimethyl-6-[2-methyl-4-(1*H*-pyrazolo[4,3-*c*]pyridin-4-yloxy)phenyl]pyrazin-2(1*H*)-
one;

4,6-dimethyl-5-[4-(1*H*-pyrazolo[4,3-*c*]pyridin-4-yloxy)phenyl]pyridazin-3(2*H*)-one; and

30 1,5-dimethyl-6-[4-(1*H*-pyrazolo[4,3-*c*]pyridin-4-yloxy)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione,
or a pharmaceutically acceptable salt thereof.

The present invention also provides compositions (e.g., pharmaceutical compositions) comprising a compound of Formula I (including an *N*-oxide thereof or a pharmaceutically acceptable salt of the compound or the *N*-oxide). Accordingly, in one embodiment, the
35 invention provides a pharmaceutical composition comprising (a therapeutically effective amount of) a compound of Formula I (an *N*-oxide thereof or a pharmaceutically acceptable salt of the compound or the *N*-oxide) and optionally comprising a pharmaceutically acceptable carrier. In one further embodiment, the invention provides a pharmaceutical composition comprising (a

therapeutically effective amount of) a compound of Formula I (an *N*-oxide thereof or a pharmaceutically acceptable salt of the compound or the *N*-oxide), optionally comprising a pharmaceutically acceptable carrier and, optionally, at least one additional medicinal or pharmaceutical agent (such as an antipsychotic agent or anti-schizophrenia agent described below). In one embodiment, the additional medicinal or pharmaceutical agent is an anti-schizophrenia agent as described below.

The pharmaceutically acceptable carrier may comprise any conventional pharmaceutical carrier or excipient. Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents (such as hydrates and solvates). The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid, may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Non-limiting examples of materials, therefore, include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

The pharmaceutical composition may, for example, be in a form suitable for oral administration as a tablet, capsule, pill, powder, sustained release formulation, solution or suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

Exemplary parenteral administration forms include solutions or suspensions of active compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms may be suitably buffered, if desired.

The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. One of ordinary skill in the art would appreciate that the composition may be formulated in sub-therapeutic dosage such that multiple doses are envisioned.

In one embodiment the composition comprises a therapeutically effective amount of a compound of Formula I (or an *N*-oxide thereof or a pharmaceutically acceptable salt of the compound or the *N*-oxide) and a pharmaceutically acceptable carrier.

Compounds of Formula I (including *N*-oxides thereof and pharmaceutically acceptable salts of the compounds or the *N*-oxides) are D1 modulators. In some embodiments, a compound of Formula I is a D1 agonist [i.e., binding (having affinity for) and activating D1

receptors]. In some embodiments, using dopamine as a reference full D1 agonist, a compound of Formula I is a superagonist (i.e., a compound that is capable of producing a greater maximal response than the endogenous D1 agonist, dopamine, for a D1 receptor, and thus exhibiting an efficacy of more than about 100%, for example 120%). In some embodiments, using dopamine as a reference full agonist, a compound of Formula I is a full D1 agonist (i.e., having an efficacy of about 100%, for example, 90%-100%, compared to that of dopamine). In some embodiments, using dopamine as a reference full D1 agonist, a compound of Formula I is a partial agonist [i.e., a compound having only partial efficacy (i.e., less than 100%, for example 10%-80% or 50%-70%) at a D1 receptor relative to the full agonist, dopamine, although it binds and activates a D1 receptor]. A D1 agonist (including superagonist, full agonist, and partial agonist) can agonize or partially agonize an activity of D1. In some embodiments, the EC₅₀ of a compound of Formula I with respect to D1 is less than about 10 μ M, 5 μ M, 2 μ M, 1 μ M, 500 nM, 200 nM, 100 nM, 50, 40, 30, 20, 10, 5, 2, or 1 nM.

The present invention further provides a method for modulating (such as agonizing or partially agonizing) an activity of D1 receptor (either *in vitro* or *in vivo*), comprising contacting (including incubating) the D1 receptor with a compound of Formula I (such as one selected from Examples 1-47), or an *N*-oxide thereof or a pharmaceutically acceptable salt of the compound or the *N*-oxide.

Another embodiment of the invention includes a method for treating a D1-mediated (or D1-associated) disorder, comprising administering to a mammal (e.g., a human) in need thereof an amount of a compound of Formula I (including a pharmaceutically acceptable salt thereof or an *N*-oxide of the compound or salt) effective in modulating (e.g., agonizing or partially agonizing) D1.

The compounds of Formula I used for treatment of a D1-mediated disorder also include *N*-oxides thereof or pharmaceutically acceptable salts of the compounds or the *N*-oxides.

D1-mediated (or D1-associated) disorders include *neurological disorders* [such as Tourette's syndrome; tardive dyskinesia; Parkinson's disease (including e.g., cognitive impairment associated with PD); cognitive disorders {including amnesia, age-related cognitive decline, dementia [e.g., senile dementia, Alzheimer's-associated dementia, HIV-associated dementia, Huntington's-associated dementia, Lewy body dementia, vascular dementia, frontotemporal dementia, drug-related dementia (for example, dementia associated with pharmacotherapy therapy such as D2 antagonist therapy)], delirium, and cognitive impairment (e.g., cognitive impairment associated with AD or cognitive impairment associated with PD,) and mild cognitive impairment}; Huntington's chorea/ disease; and restless leg syndrome (RLS)]; *psychiatric disorders* [such as cognitive impairment (e.g., cognitive impairment associated with schizophrenia or cognitive impairment associated with pharmacotherapy therapy (e.g., D2 antagonist therapy)); anxiety (including acute stress disorder, generalized anxiety disorder, social anxiety disorder, panic disorder, post-traumatic stress disorder, and

obsessive-compulsive disorder); factitious disorder (including acute hallucinatory mania); impulse control disorders/impulsivity (including compulsive gambling and intermittent explosive disorder); mood disorders (including bipolar I disorder, bipolar II disorder, mania, mixed affective state, depression {e.g., age-related depression, major depression, chronic depression, seasonal depression, psychotic depression, postpartum depression, and treatment resistant depression (TRD)}; psychomotor disorders; psychotic disorders [including schizophrenia (including, for example, cognitive and negative symptoms in schizophrenia), schizoaffective disorder, schizophreniform, and delusional disorder]; substance abuse and drug dependence (including narcotic dependence, alcoholism, amphetamine dependence, cocaine addiction, nicotine dependence, and drug withdrawal syndrome); drug abuse relapse, eating disorders (including anorexia, bulimia, binge eating disorder, overeating, hyperphagia, and pagophagia); autism spectrum disorder (e.g., autism); chronic apathy, anhedonia, chronic fatigue, seasonal affective disorder, and pediatric psychiatric disorders (including attention deficit disorder, attention deficit hyperactive disorder (ADHD), conduct disorder, and autism)], *endocrine disorders* (such as hyperprolactinemia), or other disorders including drowsiness, excessive daytime sleepiness, cachexia, inattention, sexual dysfunction (e.g., erectile dysfunction, post-SSRI sexual dysfunction), pain, migraine, systemic lupus erythematosus (SLE), hyperglycemia, atherosclerosis, dislipidemia, obesity, diabetes, sepsis, post-ischemic tubular necrosis, renal failure, hyponatremia, resistant edema, narcolepsy, cardiovascular disease (e.g., hypertension), congestive heart failure, postoperative ocular hypotonia, sleep disorders, and serotonin syndrome.

Another embodiment of the invention provides a method for treating *neurological disorders* [such as Tourette's syndrome; tardive dyskinesia; Parkinson's disease; cognitive disorders {including amnesia, senile dementia, HIV-associated dementia, Alzheimer's-associated dementia, Huntington's-associated dementia, Lewy body dementia, vascular dementia, drug-related dementia (for example, cognitive impairment associated with D2 antagonist therapy), delirium, and mild cognitive impairment}]; RLS; and Huntington's chorea/disease], *psychiatric disorders* [such as anxiety (including acute stress disorder, generalized anxiety disorder, social anxiety disorder, panic disorder, post-traumatic stress disorder and obsessive-compulsive disorder); factitious disorder (including acute hallucinatory mania); impulse control disorders/impulsivity (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, and postpartum depression); psychomotor disorders; psychotic disorders (including schizophrenia, schizoaffective disorder, schizophreniform, and delusional disorder); drug dependence (including narcotic dependence, alcoholism, amphetamine dependence, cocaine addiction, nicotine dependence, and drug withdrawal syndrome); eating disorders (including anorexia, bulimia, binge eating disorder, hyperphagia, and pagophagia); and pediatric psychiatric

disorders (including attention deficit disorder, attention deficit/hyperactive disorder, conduct disorder, and autism)], or *endocrine disorders* (such as hyperprolactinemia) in a mammal, for example a human, comprising administering to said mammal a therapeutically effective amount of a compound of Formula I.

5 Another embodiment of the invention includes a method for treating a disorder in a mammal (e.g., a human), which method comprises administering to said mammal a therapeutically effective amount of a compound of Formula I, wherein the disorder is selected from schizophrenia (e.g., cognitive and negative symptoms in schizophrenia), cognitive impairment [e.g., cognitive impairment associated with schizophrenia, cognitive impairment
10 associated with AD, cognitive impairment associated with PD, cognitive impairment associated with pharmacotherapy therapy (e.g., D2 antagonist therapy), and mild cognitive impairment], attention deficit hyperactivity disorder (ADHD), impulsivity, compulsive gambling, an eating disorder (e.g., anorexia, bulimia, binge eating disorder, overeating, hyperphagia, and
15 pagophagia), autism spectrum disorder, mild cognitive impairment (MCI), age-related cognitive decline, dementia (e.g., senile dementia, HIV-associated dementia, Alzheimer's dementia, Lewy body dementia, vascular dementia, or frontotemporal dementia), restless leg syndrome (RLS), Parkinson's disease, Huntington's chorea, anxiety, depression (e.g., age-related depression), major depressive disorder (MDD), treatment resistant depression (TRD), bipolar disorder, chronic apathy, anhedonia, chronic fatigue, post-traumatic stress disorder, seasonal affective
20 disorder, social anxiety disorder, post-partum depression, serotonin syndrome, substance abuse and drug dependence, drug abuse relapse, Tourette's syndrome, tardive dyskinesia, drowsiness, excessive daytime sleepiness, cachexia, inattention, sexual dysfunction (e.g., erectile dysfunction or post-SSRI sexual dysfunction), migraine, systemic lupus erythematosus (SLE), hyperglycemia, atherosclerosis, dislipidemia, obesity, diabetes, sepsis, post-ischemic
25 tubular necrosis, renal failure, hyponatremia, resistant edema, narcolepsy, hypertension, congestive heart failure, postoperative ocular hypotonia, sleep disorders, and pain.

Another embodiment of the invention includes a method for treating schizophrenia (e.g., cognitive and negative symptoms in schizophrenia or cognitive impairment associated with schizophrenia) or psychosis in a mammal, for example a human, comprising administering to
30 said mammal (e.g., a human) a therapeutically effective amount of a compound of Formula I.

Another embodiment of the invention includes a method for treating schizophrenia (e.g., cognitive and negative symptoms in schizophrenia or cognitive impairment associated with schizophrenia) in a mammal, for example a human, comprising administering to said mammal a therapeutically effective amount of a compound of Formula I.

35 Another embodiment of the invention includes a method for the treatment of cognitive impairment [e.g., cognitive impairment associated with schizophrenia, cognitive impairment associated with AD, or cognitive impairment associated with PD] in a mammal, for example a human, comprising administering to said mammal a therapeutically effective amount of a

compound of Formula I.

Another embodiment of the invention includes a method for treating AD (e.g., treating cognitive impairment associated with AD), PD (e.g., treating cognitive impairment associated with PD), RLS, depression, or MDD in a mammal, for example a human, comprising

- 5 administering to said mammal a therapeutically effective amount of a compound of Formula I.

The term "therapeutically effective amount" as used herein refers to that amount of the compound (including a pharmaceutically acceptable salt thereof or an *N*-oxide of the compound or salt) being administered which will relieve to some extent one or more of the symptoms of the disorder being treated. In reference to the treatment of a D1-mediated disorder (e.g.,

10 schizophrenia), a therapeutically effective amount refers to that amount which has the effect of relieving to some extent (or, for example, eliminating) one or more symptoms associated with a D1-mediated disorder (e.g., schizophrenia, or cognitive and negative symptoms in schizophrenia, or cognitive impairment associated with schizophrenia).

The term "treating", as used herein, unless otherwise indicated, means reversing,

15 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 herein. The term "treating" also includes adjuvant and neo-adjuvant treatment of a subject.

Administration of the compounds of Formula I may be effected by any method that

20 enables delivery of the compounds to the site of action. These methods include oral routes, intranasal routes, inhaled routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), topical, and rectal administration.

In one embodiment of the present invention, the compounds of Formula I may be

25 administered/effected by oral routes.

Dosage regimens may be adjusted to provide the optimum desired response. For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It may be advantageous to formulate parenteral compositions in

30 dosage unit form for ease of administration and uniformity of dosage. Dosage unit form, as used herein, refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specifications for the dosage unit forms of the invention are dictated

35 by a variety of factors such as the unique characteristics of the therapeutic agent and the particular therapeutic or prophylactic effect to be achieved. In one embodiment of the present invention, the compounds of Formula I may be used to treat humans.

It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated, and may include single or multiple doses. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. For example, doses may be adjusted based on pharmacokinetic or pharmacodynamic parameters, which may include clinical effects such as toxic effects and/or laboratory values. Thus, the present invention encompasses intra-patient dose-escalation as determined by the skilled artisan.

Determining appropriate dosages and regimens for administration of the chemotherapeutic agent is well-known in the relevant art and would be understood to be encompassed by the skilled artisan once provided the teachings disclosed herein.

The amount of the compound of Formula I administered will be dependent on the subject being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compound and the discretion of the prescribing physician. Generally, an effective dosage is in the range of about 0.0001 to about 50 mg per kg body weight per day, for example about 0.01 to about 10 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.007 mg to about 3500 mg/day, for example about 0.7 mg to about 700 mg/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

As used herein, the term "combination therapy" refers to the administration of a compound of Formula I together with an at least one additional pharmaceutical or medicinal agent (e.g., an anti-schizophrenia agent), either sequentially or simultaneously.

The present invention includes the use of a combination of a compound of Formula I 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 Formula I (including an *N*-oxide thereof or a pharmaceutically acceptable salt of the compound or the *N*-oxide); (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 Formula I, 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); or Adenosine A_{2A} receptor antagonists such as Preladenant (SCH 420814) or SCH 412348;
- (ii) amyloid- β (or fragments thereof), such as A β ₁₋₁₅ conjugated to pan HLA DR-binding epitope (PADRE) and ACC-001 (Elan/Wyeth);
- 5 (iii) antibodies to amyloid- β (or fragments thereof), such as bapineuzumab (also known as AAB-001) and AAB-002 (Wyeth/Elan);
- (iv) amyloid-lowering or -inhibiting agents (including those that reduce amyloid production, accumulation and fibrillization) such as colostrinin and bisnorcymserine (also known as BNC);
- 10 (v) alpha-adrenergic receptor agonists such as clonidine (CATAPRES);
- (vi) beta-adrenergic receptor blocking agents (beta blockers) such as carteolol;
- (vii) anticholinergics such as amitriptyline (ELAVIL, ENDEP);
- (viii) anticonvulsants such as carbamazepine (TEGRETOL, CARBATROL);
- (ix) antipsychotics, such as lurasidone (also known as SM-13496; Daiippon Sumitomo);
- 15 (x) calcium channel blockers such as nilvadipine (ESCOR, NIVADIL);
- (xi) catechol *O*-methyltransferase (COMT) inhibitors such as tolcapone (TASMAR);
- (xii) central nervous system stimulants such as caffeine;
- (xiii) corticosteroids such as prednisone (STERAPRED, DELTASONE);
- (xiv) dopamine receptor agonists such as apomorphine (APOKYN);
- 20 (xv) dopamine receptor antagonists such as tetrabenazine (NITOMAN, XENAZINE, dopamine D2 antagonist such as Quetiapine);
- (xvi) dopamine reuptake inhibitors such as nomifensine maleate (MERITAL);
- (xvii) gamma-aminobutyric acid (GABA) receptor agonists such as baclofen (LIORESAL, KEMSTRO);
- 25 (xviii) histamine 3 (H₃) antagonists such as ciproxifan;
- (xix) immunomodulators such as glatiramer acetate (also known as copolymer-1; COPAXONE);
- (xx) immunosuppressants such as methotrexate (TREXALL, RHEUMATREX);
- (xxi) interferons, including interferon beta-1a (AVONEX, REBIF) and interferon beta-1b
- 30 (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));
- (xxiii) *N*-methyl-D-aspartate (NMDA) receptor antagonists such as memantine (NAMENDA, AXURA, EBIXA);
- 35 (xxiv) monoamine oxidase (MAO) inhibitors such as selegiline (EMSAM);
- (xxv) muscarinic receptor (particularly M1 subtype) agonists such as bethanechol chloride (DUVOID, URECHOLINE);
- (xxvi) neuroprotective drugs such as 2,3,4,9-tetrahydro-1*H*-carbazol-3-one oxime;

(xxvii) nicotinic receptor agonists such as epibatidine;
 (xxviii) norepinephrine (noradrenaline) reuptake inhibitors such as atomoxetine (STRATTERA);
 (xxix) phosphodiesterase (PDE) inhibitors, for example, PDE9 inhibitors such as BAY 73-
 5 6691 (Bayer AG) and PDE 10 (e.g. PDE10A) inhibitors such as papaverine;
 (xxx) other PDE inhibitors including (a) PDE1 inhibitors (e.g., vinpocetine), (b) PDE2 inhibitors (e.g., erythro-9-(2-hydroxy-3-nonyl)adenine (EHNA)), (c) PDE4 inhibitors (e.g., rolipram), and (d) PDE5 inhibitors (e.g., sildenafil (VIAGRA, REVATIO));
 (xxxi) quinolines such as quinine (including its hydrochloride, dihydrochloride, sulfate,
 10 bisulfate and gluconate salts);
 (xxxii) β -secretase inhibitors such as WY-25105;
 (xxxiii) γ -secretase inhibitors such as LY-411575 (Lilly);
 (xxxiv) serotonin (5-hydroxytryptamine) 1A (5-HT_{1A}) receptor antagonists such as spiperone;
 15 (xxxv) serotonin (5-hydroxytryptamine) 4 (5-HT₄) receptor agonists such as PRX-03140 (Epix);
 (xxxvi) serotonin (5-hydroxytryptamine) 6 (5-HT₆) receptor antagonists such as mianserin (TORVOL, BOLVIDON, NORVAL);
 (xxxvii) serotonin (5-HT) reuptake inhibitors such as alaproclate, citalopram (CELEXA,
 20 CIPRAMIL);
 (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;
 25 and the like.

The compound of Formula I is optionally used in combination with another active agent. Such an active agent may be, for example, an atypical antipsychotic or an anti-Parkinson's disease agent or an anti-Alzheimer's agent. Accordingly, another embodiment of the invention provides methods of treating a D1-mediated disorder (e.g., a neurological and psychiatric
 30 disorder associated with D1), comprising administering to a mammal an effective amount of a compound of Formula I (including an *N*-oxide thereof or a pharmaceutically acceptable salt of the compound or the *N*-oxide) and further comprising administering another active agent.

As used herein, the term "another active agent" refers to any therapeutic agent, other than the compound of Formula I (including an *N*-oxide thereof or a pharmaceutically acceptable
 35 salt of the compound or the *N*-oxide) that is useful for the treatment of a subject disorder. Examples of additional therapeutic agents include antidepressants, antipsychotics (such as anti-schizophrenia), anti-pain, anti-Parkinson's disease agents, anti-LID (levodopa-induced dyskinesia), anti-Alzheimer's and anti-anxiety agents. Examples of particular classes of

antidepressants that can be used in combination with the compounds of the invention include norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), NK-1 receptor antagonists, monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs),

5 corticotropin releasing factor (CRF) antagonists, α -adrenoreceptor antagonists, and atypical antidepressants. Suitable norepinephrine reuptake inhibitors include tertiary amine tricyclics and secondary amine tricyclics. Examples of suitable tertiary amine tricyclics and secondary amine tricyclics include amitriptyline, clomipramine, doxepin, imipramine, trimipramine, dothiepin, butriptyline, iprindole, lofepramine, nortriptyline, protriptyline, amoxapine, desipramine

10 and maprotiline. Examples of suitable selective serotonin reuptake inhibitors include fluoxetine, fluvoxamine, paroxetine, and sertraline. Examples of monoamine oxidase inhibitors include isocarboxazid, phenelzine, and tranylcyclopramine. Examples of suitable reversible inhibitors of monoamine oxidase include moclobemide. Examples of suitable serotonin and noradrenaline reuptake inhibitors of use in the present invention include venlafaxine. Examples of suitable

15 atypical anti-depressants include bupropion, lithium, nefazodone, trazodone and viloxazine. Examples of anti-Alzheimer's agents include Dimebon, NMDA receptor antagonists such as memantine; and cholinesterase inhibitors such as donepezil and galantamine. Examples of suitable classes of anti-anxiety agents that can be used in combination with the compounds of the invention include benzodiazepines and serotonin 1A (5-HT_{1A}) agonists or antagonists,

20 especially 5-HT_{1A} partial agonists, and corticotropin releasing factor (CRF) antagonists. Suitable benzodiazepines include alprazolam, chlordiazepoxide, clonazepam, chlorazepate, diazepam, halazepam, lorazepam, oxazepam, and prazepam. Suitable 5-HT_{1A} receptor agonists or antagonists include buspirone, flesinoxan, gepirone, and ipsapirone. Suitable atypical antipsychotics include paliperidone, bifeprunox, ziprasidone, risperidone, aripiprazole,

25 olanzapine, and quetiapine. Suitable nicotine acetylcholine agonists include ispronicline, varenicline and MEM 3454. Anti-pain agents include pregabalin, gabapentin, clonidine, neostigmine, baclofen, midazolam, ketamine and ziconotide. Examples of suitable anti-Parkinson's disease agents include L-DOPA (or its methyl or ethyl ester), a DOPA decarboxylase inhibitor (e.g., carbidopa (SINEMET, CARBILEV, PARCOPA), an Adenosine A_{2A}

30 receptor antagonist [e.g., Preladenant (SCH 420814) or SCH 412348], benserazide (MADOPAR), α -methyldopa, monofluoromethyldopa, difluoromethyldopa, brocresine, or *m*-hydroxybenzylhydrazine), a dopamine agonist [such as apomorphine (APOKYN), bromocriptine (PARLODEL), cabergoline (DOSTINEX), dihydrexidine, dihydroergocryptine, fenoldopam (CORLOPAM), lisuride (DOPERGIN), pergolide (PERMAX), piribedil (TRIVASTAL, TRASTAL),

35 pramipexole (MIRAPEX), quinpirole, ropinirole (REQUIP), rotigotine (NEUPRO), SKF-82958 (GlaxoSmithKline), and sarizotan], a monoamine oxidase (MAO) inhibitor [such as selegiline (EMSAM), selegiline hydrochloride (L-deprenyl, ELDEPRYL, ZELAPAR), dimethylselegiline, brofaromine, phenelzine (NARDIL), tranylcypromine (PARNATE), moclobemide (AURORIX,

MANERIX), befloxacitane, safinamide, isocarboxazid (MARPLAN), nialamide (NIAMID), rasagiline (AZILECT), iproniazide (MARSILID, IPROZID, IPRONID), CHF-3381 (Chiesi Farmaceutici), iproclozide, tolloxatone (HUMORYL, PERENUM), bifemelane, desoxypeganine, harmine (also known as telepathine or banasterine), harmaline, linezolid (ZYVOX, ZYVOXID), and pargyline (EUDATIN, SUPIRDYL)], a catechol *O*-methyltransferase (COMT) inhibitor [such as tolcapone (TASMAR), entacapone (COMTAN), and tropolone], an *N*-methyl-D-aspartate (NMDA) receptor antagonist [such as amantadine (SYMMETREL)], anticholinergics [such as amitriptyline (ELAVIL, ENDEP), butriptyline, benzotropine 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)], or a combination thereof. Examples of anti-schizophrenia agents include ziprasidone, risperidone, olanzapine, quetiapine, aripiprazole, asenapine, blonanserin, or iloperidone.

As noted above, the compounds of Formula I (including *N*-oxides thereof and pharmaceutically acceptable salts of the compounds or salts) may be used in combination with one or more additional anti-schizophrenia agents which are described herein. When a combination therapy is used, the one or more additional anti-schizophrenia agents may be administered sequentially or simultaneously with the compound of the invention. In one embodiment, the additional anti-schizophrenia agent is administered to a mammal (e.g., a human) prior to administration of the compound of the invention. In another embodiment, the additional anti-schizophrenia agent is administered to the mammal after administration of the compound of the invention. In another embodiment, the additional anti-schizophrenia agent is administered to the mammal (e.g., a human) simultaneously with the administration of the compound of the invention (or an *N*-oxide thereof or a pharmaceutically acceptable salt of the foregoing).

The invention also provides a pharmaceutical composition for the treatment of schizophrenia in a mammal, including a human, which comprises an amount of a compound of Formula I (or an *N*-oxide thereof or a pharmaceutically acceptable salt of the foregoing), as defined above (including hydrates, solvates and polymorphs of said compound or pharmaceutically acceptable salts thereof), in combination with one or more (for example one to three) anti-schizophrenia agents such as ziprasidone, risperidone, olanzapine, quetiapine, aripiprazole, asenapine, blonanserin, or iloperidone, wherein the amounts of the active agent and the combination when taken as a whole are therapeutically effective for treating schizophrenia.

The invention also provides a pharmaceutical composition for the treatment of Parkinson's disease in a mammal (including cognition impairment associated with PD), including a human, which comprises an amount of a compound of Formula I (or an *N*-oxide thereof or a pharmaceutically acceptable salt of the foregoing), as defined above (including
5 hydrates, solvates and polymorphs of said compound or pharmaceutically acceptable salts thereof), in combination with one or more (for example one to three) anti-Parkinson's disease agents such as L-DOPA, wherein the amounts of the active agent and the combination when taken as a whole are therapeutically effective for treating Parkinson's disease.

It will be understood that the compounds of Formula I depicted above are not limited to
10 the particular enantiomer shown, but also include all stereoisomers and mixtures thereof.

DETAILED DESCRIPTION OF THE INVENTION

Compounds of the invention, including *N*-oxides and salts of the compounds or *N*-oxides, can be prepared using known organic synthesis techniques and can be synthesized according to any of numerous possible synthetic routes.

15 The reactions for preparing compounds of the invention can be carried out in suitable solvents, which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, i.e., temperatures that can range from the solvent's freezing temperature to the solvent's boiling
20 temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step can be selected by the skilled artisan.

Preparation of compounds of the invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of
25 appropriate protecting groups, can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., Wiley & Sons, Inc., New York (1999), which is incorporated herein by reference in its entirety.

Reactions can be monitored according to any suitable method known in the art. For
30 example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ¹H or ¹³C), infrared spectroscopy, spectrophotometry (e.g., UV-visible), mass spectrometry, or by chromatographic methods such as high performance liquid chromatography (HPLC) or thin layer chromatography (TLC).

Compounds of Formula I and intermediates thereof may be prepared according to the
35 following reaction schemes and accompanying discussion. Unless otherwise indicated, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, R¹¹, T¹, T², T³, Q¹, and X¹, and structural Formula I in the reaction schemes and discussion that follow are as defined above. In general the compounds of this invention may be made by processes which include processes analogous to those known in the

chemical arts, particularly in light of the description contained herein. Certain processes for the manufacture of the compounds of this invention and intermediates thereof are provided as further features of the invention and are illustrated by the following reaction schemes. Other processes are described in the experimental section. The schemes and examples provided
5 herein (including the corresponding description) are for illustration only, and not intended to limit the scope of the present invention.

Scheme 1 refers to preparation of compounds of Formula I. Referring to Scheme 1, compounds of Formula **1-1** [where Lg^1 is a suitable leaving group such as halo (e.g., Cl or Br) and Pg^1 is a suitable protecting group, such as *tert*-butoxycarbonyl (Boc), [2-(trimethylsilyl)ethoxy]methyl (SEM), or 2-tetrahydropyranyl (THP)] and **1-2** [wherein Z^1 is a
10 halogen (Cl, Br, or I)] are commercially available or can be made by methods described herein or other methods well known to those skilled in the art. A compound of Formula **1-3** can be prepared by coupling a compound of Formula **1-1** with a compound of Formula **1-2** under suitable conditions. The coupling can be accomplished, for example, by heating a mixture of a
15 compound of Formula **1-1** with a compound of Formula **1-2** in the presence of a base, such as Cs_2CO_3 , in an appropriate solvent, such as DMSO. Alternatively, a metal-catalyzed (such as using a palladium or copper catalyst) coupling may be employed to accomplish the aforesaid coupling. In this variant of the coupling, a mixture of a compound of Formula **1-1** and a
20 compound of Formula **1-2** can be heated in the presence of a base (such as Cs_2CO_3), a metal catalyst [such as a palladium catalyst, e.g., $[Pd(OAc)_2]$, and a ligand (such as BINAP) in an appropriate solvent, such as 1,4-dioxane. A compound of Formula **1-3** can subsequently be reacted with a compound of Formula Q^1-Z^2 [wherein Z^2 can be Br; $B(OH)_2$; $B(OR)_2$ wherein each
R is independently H or C_{1-6} alkyl, or wherein the two (OR) groups, together with the B atom to which they are attached, form a 5- to 10-membered heterocycloalkyl or heteroaryl optionally
25 substituted with one or more C_{1-6} alkyl; a trialkyltin moiety; or the like] by a metal-catalyzed (such as using a palladium catalyst) coupling reaction to obtain a compound of Formula I. Compounds of Formula Q^1-Z^2 are commercially available or can be made by methods described herein or by methods analogous to those described in the chemical art. Alternatively, a
30 compound of Formula **1-3** can be converted to a compound of Formula **1-4** (wherein Z^2 is defined as above). For example, a compound of Formula **1-3** (wherein Z^1 is halogen such as Br) can be converted to a compound of Formula **1-4** [wherein Z^2 is $B(OH)_2$; $B(OR)_2$ wherein each R is independently H or C_{1-6} alkyl, or wherein the two (OR) groups, together with the B
atom to which they are attached, form a 5- to 10-membered heterocycloalkyl or heteroaryl optionally substituted with one or more C_{1-6} alkyl] by methods described herein or other methods
35 well known to those skilled in the art. In this example, this reaction can be accomplished, for example, by reacting a compound of Formula **1-3** (wherein Z^1 is halogen such as Br) with 4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane, a suitable base (such as potassium acetate), and a palladium catalyst {such as [1,1'-

bis(diphenylphosphino)ferrocene]dichloropalladium(II)} in a suitable solvent such as 1,4-dioxane. In another example, a compound of Formula **1-3** (wherein Z^1 is halogen such as Br) can be converted to a compound of Formula **1-4** (wherein Z^2 is a trialkyltin moiety) by alternate methods described herein or other methods well known to those skilled in the art. In this

5 example, this reaction can be accomplished, for example, by reacting a compound of Formula **1-3** (wherein Z^1 is halogen such as Br) with a hexaalkyldistannane (such as hexamethyldistannane) in the presence of a palladium catalyst [such as tetrakis(triphenylphosphine)palladium(0)] in a suitable solvent such as 1,4-dioxane. A compound of Formula **1-4** can then be reacted with a compound of Formula Q^1-Z^1 (wherein Z^1 is

10 defined as above) by a metal-catalyzed (such as using a palladium catalyst) coupling reaction to obtain a compound of Formula I. Compounds of Formula Q^1-Z^1 are commercially available or can be made by methods described herein or by methods analogous to those described in the chemical art. The type of reaction employed depends on the selection of Z^1 and Z^2 . For example, when Z^1 is halogen or triflate and the Q^1-Z^2 reagent is a boronic acid or boronic ester,

15 a Suzuki reaction may be used [A. Suzuki, *J. Organomet. Chem.* **1999**, 576, 147-168; N. Miyaura and A. Suzuki, *Chem. Rev.* **1995**, 95, 2457-2483; A. F. Littke et al., *J. Am. Chem. Soc.* **2000**, 122, 4020-4028]. In some specific embodiments, an aromatic iodide, bromide, or triflate of Formula **1-3** is combined with an aryl or heteroaryl boronic acid or boronic ester of Formula Q^1-Z^2 and a suitable base, such as potassium phosphate, in a suitable organic solvent such as tetrahydrofuran (THF). A palladium catalyst is added, such as S-Phos precatalyst {also known

20 as chloro(2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl)[2-(2-aminoethylphenyl)]palladium(II) – *tert*-butyl methyl ether adduct}, and the reaction mixture is heated. Alternatively, when Z^1 is halogen or triflate and Z^2 is trialkyltin, a Stille coupling may be employed [V. Farina et al., *Organic Reactions* **1997**, 50, 1-652]. More specifically, a compound

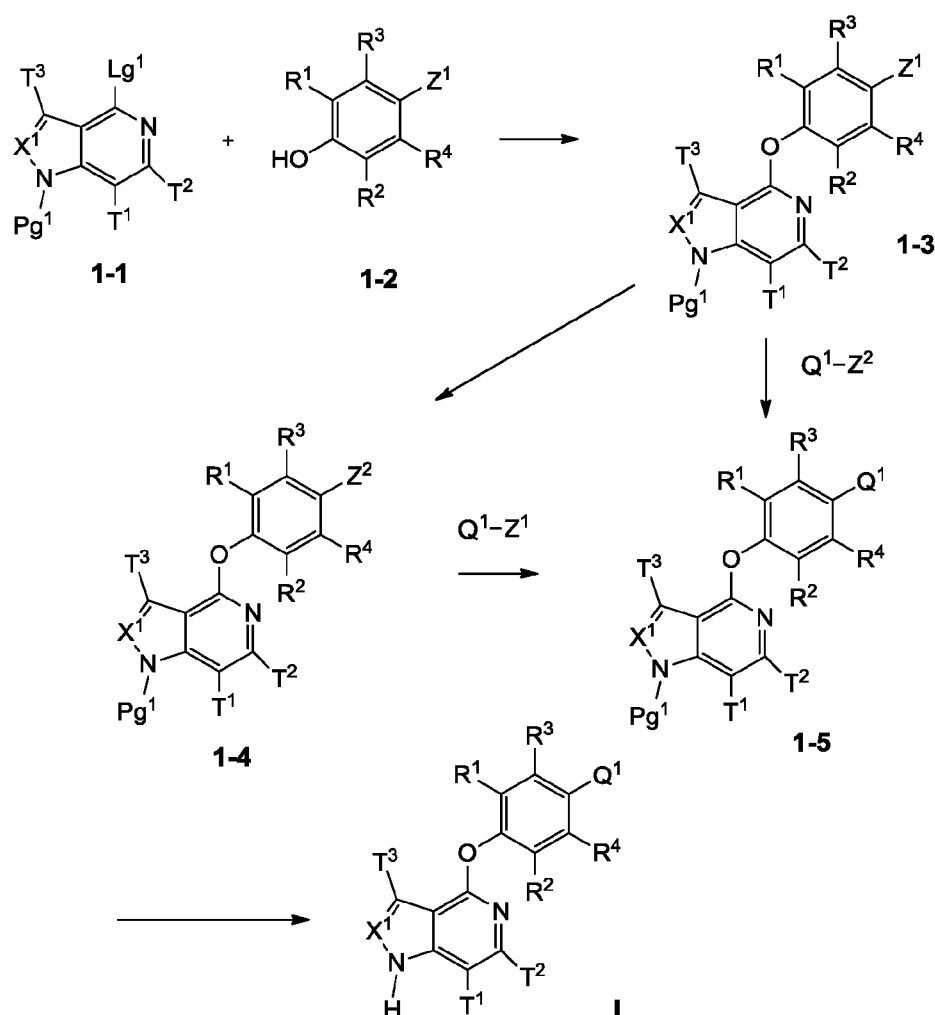
25 of Formula **1-3** (wherein Z^1 is bromide, iodide, or triflate) may be combined with a compound of Formula Q^1-Z^2 (wherein the Q^1-Z^2 compound is a Q^1 stannane compound) in the presence of a palladium catalyst, such as dichlorobis(triphenylphosphine)palladium(II), in a suitable organic solvent such as toluene, and the reaction may be heated. Where Z^1 is Br, I, or triflate and Z^2 is Br or I, a Negishi coupling may be used [E. Erdik, *Tetrahedron* **1992**, 48, 9577-9648]. More

30 specifically, a compound of Formula **1-3** (wherein Z^1 is bromide, iodide, or triflate) may be transmetalated by treatment with 1 to 1.1 equivalents of an alkyllithium reagent followed by a solution of 1.2 to 1.4 equivalents of zinc chloride in an appropriate solvent such as THF at a temperature ranging from -80 °C to -65 °C. After warming to a temperature between 10 °C and 30 °C, the reaction mixture may be treated with a compound of Formula Q^1-Z^2 (wherein Z^2 is Br

35 or I), and heated at 50 °C to 70 °C with addition of a catalyst such as tetrakis(triphenylphosphine)palladium(0). The reaction may be carried out for times ranging from 1 to 24 hours. The compound of Formula **1-5** may then be deprotected, using appropriate conditions depending on the selection of the Pg^1 group, to obtain a compound of Formula I.

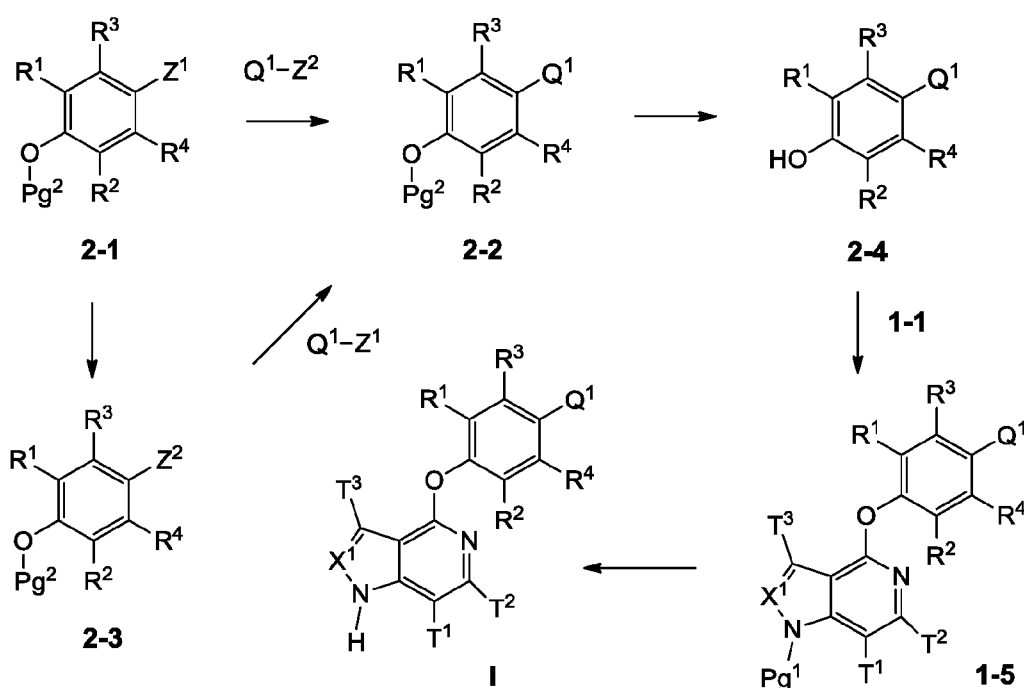
None of these reactions are limited to the employment of the solvent, base, catalyst, or ligand described above, as many other conditions may be used.

Scheme 1



- 5 Scheme 2 also refers to preparation of compounds of Formula I. Referring to Scheme 2, compounds of Formula I may be prepared utilizing analogous chemical transformations to those described in Scheme 1, but with a different ordering of steps. Compounds of Formula **2-1** [wherein Pg^2 is a suitable protecting group such as methyl, benzyl, THP, or triisopropylsilyl (TIPS)] are commercially available or can be made by methods described herein or other
- 10 methods well known to those skilled in the art. A compound of Formula **2-1** can be converted to a compound of Formula **2-2** either directly or after conversion to a compound of Formula **2-3** using methods analogous to those described in Scheme 1. A compound of Formula **2-2** may then be deprotected, using appropriate conditions depending on the selection of the Pg^2 group, to obtain a compound of Formula **2-4**, which in turn can be coupled with a compound of Formula
- 15 **1-1** in Scheme 1 to afford a compound of Formula **1-5**. The coupling conditions employed may be analogous to those described for the preparation of a compound of Formula **1-3** in Scheme 1. A compound of Formula **1-5** may then be deprotected, using appropriate conditions depending on the selection of the Pg^1 group, to obtain a compound of Formula I.

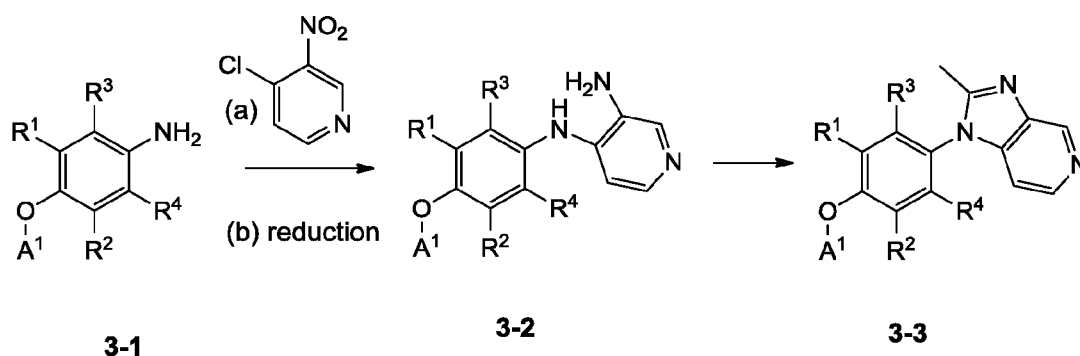
Scheme 2



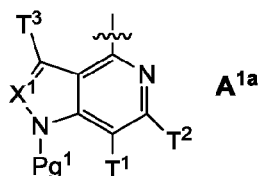
Scheme 3 refers to a preparation of a compound of Formula **3-3** (wherein A^1 is either Pg^2 as defined above or a moiety of Formula A^{1a}), which can be used in Scheme 2 as

- 5 intermediate/starting material for the preparation of compounds of Formula I. Referring to Scheme 3, compounds of Formula **3-1** are commercially available or can be made by methods described herein or other methods well known to those skilled in the art. A compound of Formula **3-1** can be reacted with 4-chloro-3-nitropyridine and the initial product can be subsequently reduced to obtain a compound of Formula **3-2**. Examples of suitable reaction
- 10 conditions for the coupling of a compound of Formula **3-1** with 4-chloro-3-nitropyridine include mixing the two reactants with a suitable base, such as triethylamine, in a suitable reaction solvent such as ethanol. The subsequent reduction of the nitro group to afford a compound of Formula **3-2** can be achieved by, for example, hydrogenation in the presence of a catalyst such as palladium on carbon in a suitable solvent such as methanol. Suitable hydrogen pressures for
- 15 the aforesaid reaction are typically between 1 atm and 4 atm. A compound of Formula **3-2** can then be heated with acetic anhydride and triethyl orthoformate to obtain a compound of Formula **3-3**.

Scheme 3

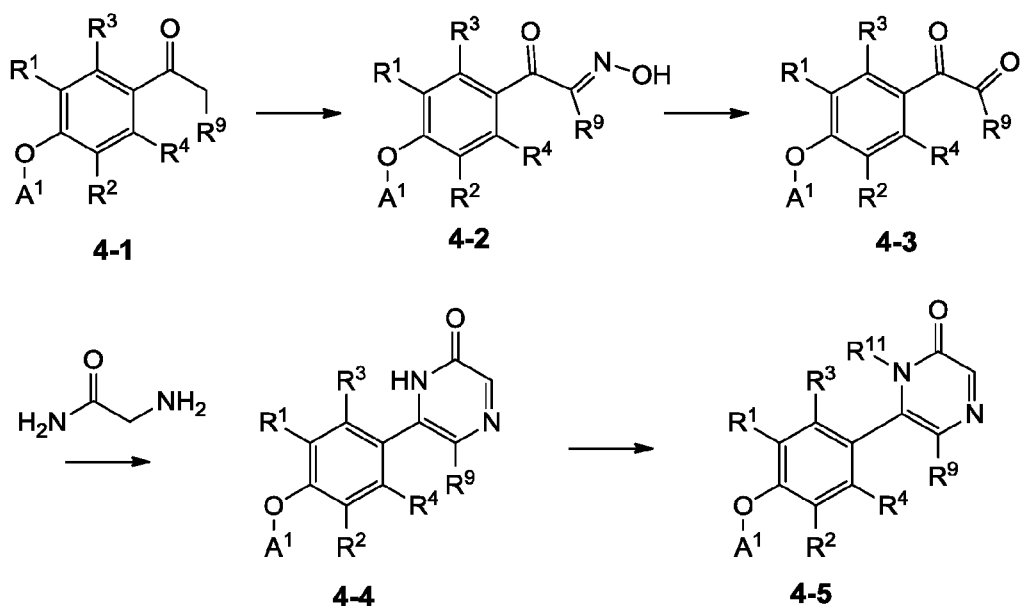


A^1 is Pg^2 or a moiety of A^{1a} :



Scheme 4 refers to a preparation of a compound of Formula **4-4** or **4-5** (wherein R^9 is such as C_{1-3} alkyl, for example methyl), which can be used in Scheme 2 as intermediate/starting material for the preparation of compounds of Formula I. Referring to Scheme 4, compounds of Formula **4-1** are commercially available or can be made by methods described herein or other methods well known to those skilled in the art. A compound of Formula **4-2** can be prepared by reacting an arylketone of Formula **4-1** with an alkyl nitrite (e.g., isoamyl nitrite) in the presence of an acid (such as hydrochloric acid). The resulting oxime of Formula **4-2** can be converted to the diketone of Formula **4-3** upon treatment with formaldehyde (or its equivalent such as metaformaldehyde or polyformaldehyde) in the presence of an acid (such as an aqueous hydrochloric acid solution). Diketones of Formula **4-3** can be reacted with glycineamide or a salt thereof (such as an acetic acid salt) in the presence of a base such as sodium hydroxide to obtain pyrazinones of Formula **4-4**. Alkylation of the pyrazinone nitrogen to obtain a compound of Formula **4-5** can be achieved by treatment of a compound of Formula **4-4** with a base [such as LDA, LHMDs, and the like] and a compound of the formula $R^{11}-Z^3$ [wherein Z^3 is an acceptable leaving group such as Cl, Br, I, methanesulfonate, and the like and wherein R^{11} is for example C_{1-3} alkyl (e.g., methyl)]. Suitable reaction solvents typically can be selected from polar aprotic solvents such as *N,N*-dimethylformamide (DMF), 1,4-dioxane, or THF.

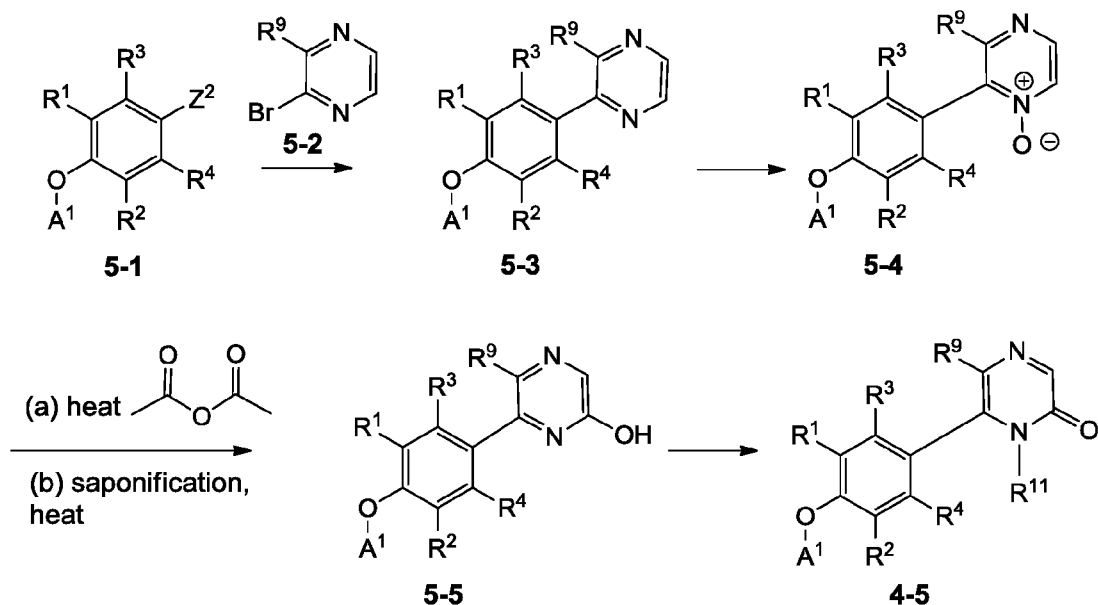
Scheme 4



Alternatively, a compound of Formula 4-5 may be prepared as in Scheme 5 [wherein R¹¹ is, for example, H or C₁₋₃ alkyl (e.g., methyl)], which can be used in Scheme 2 as

- 5 intermediate/starting material for the preparation of compounds of Formula I. Referring to Scheme 5, compounds of Formula 5-1 and 5-2 are commercially available or can be made by methods described herein or other methods well known to those skilled in the art. A compound of Formula 5-3 can be prepared by coupling a compound of Formula 5-1 with a compound of Formula 5-2. The aforesaid coupling may be accomplished by reacting a compound of Formula
- 10 5-1 with a compound of Formula 5-2 in the presence of a suitable base (such as potassium carbonate), a suitable catalyst [such as tetrakis(triphenylphosphine)palladium(0)], and a suitable solvent (such as ethanol). A compound of Formula 5-3 can be reacted with maleic anhydride and hydrogen peroxide in a solvent (such as dichloromethane) to provide a compound of Formula 5-4, which may contain a mixture of *N*-oxide regioisomers. A compound of Formula 5-5
- 15 can be prepared from a compound of Formula 5-4 by heating with acetic anhydride; the initial product can be saponified using a base (such as NaOH) in a suitable polar solvent (such as water or methanol). A compound of Formula 4-5 can be prepared from a compound of Formula 5-5 by reaction with a suitable base (such as LDA, LHMDs and the like), lithium bromide, and a compound of the formula R¹¹-Z³ (wherein Z³ is an acceptable leaving group such as Cl, Br, I, methanesulfonate, and the like). Suitable reaction solvents typically can be selected from polar
- 20 aprotic solvents (such as DMF, 1,4-dioxane, or THF).

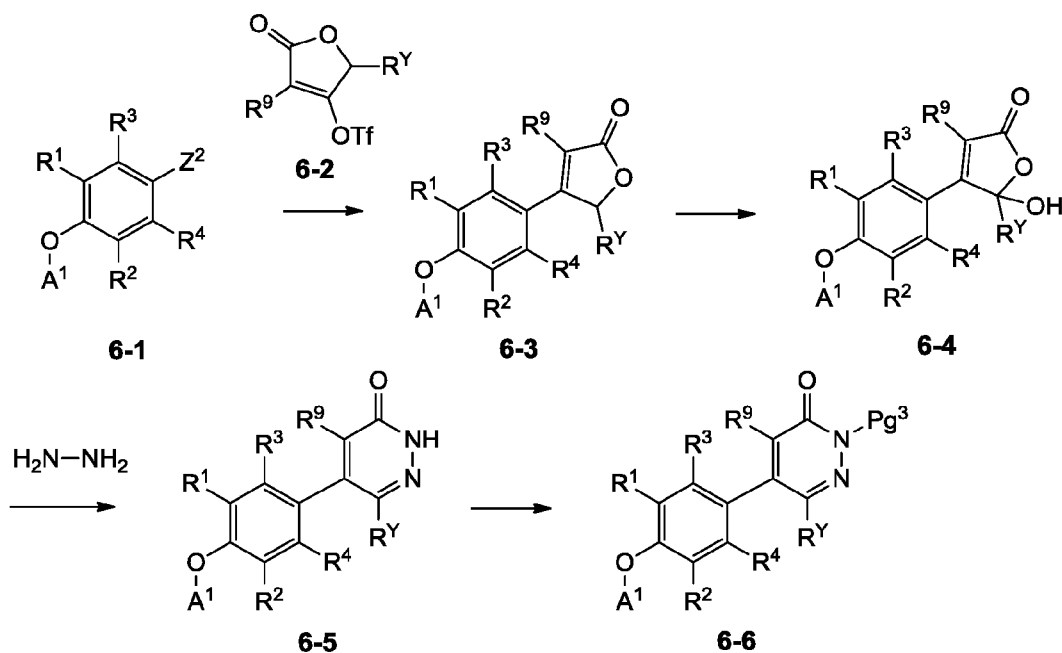
Scheme 5



Scheme 6 refers to a preparation of a compound of Formula 6-6 [wherein R^Y is H or R^{10} (such as C_{1-3} alkyl, for example methyl) and Pg^3 is a suitable protecting group, such as THP],

which can be used in Scheme 2 as intermediate/starting material for the preparation of compounds of Formula I. Referring to Scheme 6, compounds of Formula 6-1 and 6-2 are commercially available or can be made by methods described herein or other methods well known to those skilled in the art. A compound of Formula 6-3 can be prepared by coupling a compound of Formula 6-1 with an enol triflate of Formula 6-2. The aforesaid coupling may be accomplished by reacting a compound of Formula 6-1 with a triflate of Formula 6-2 in the presence of a suitable base (such as potassium carbonate), a suitable catalyst [such as palladium(II) acetate], a suitable ligand (such as tricyclohexylphosphine), and optionally a suitable phase transfer catalyst such as tetrabutylammonium chloride. Suitable reaction solvents typically can be selected from polar aprotic solvents such as 1,4-dioxane or THF. A compound of Formula 6-3 can be reacted with 1 to 5 equivalents of a suitable base (such as DBU) under an oxygen atmosphere to obtain a compound of Formula 6-4. Suitable reaction solvents typically can be selected from polar aprotic solvents such as DMF, 1,4-dioxane, or THF. A compound of Formula 6-5 can be obtained by reacting a compound of Formula 6-4 with hydrazine in a suitable solvent such as 1-butanol. A compound of Formula 6-5 can be converted to a suitably protected compound of Formula 6-6 using methods described herein or other methods well known to those skilled in the art.

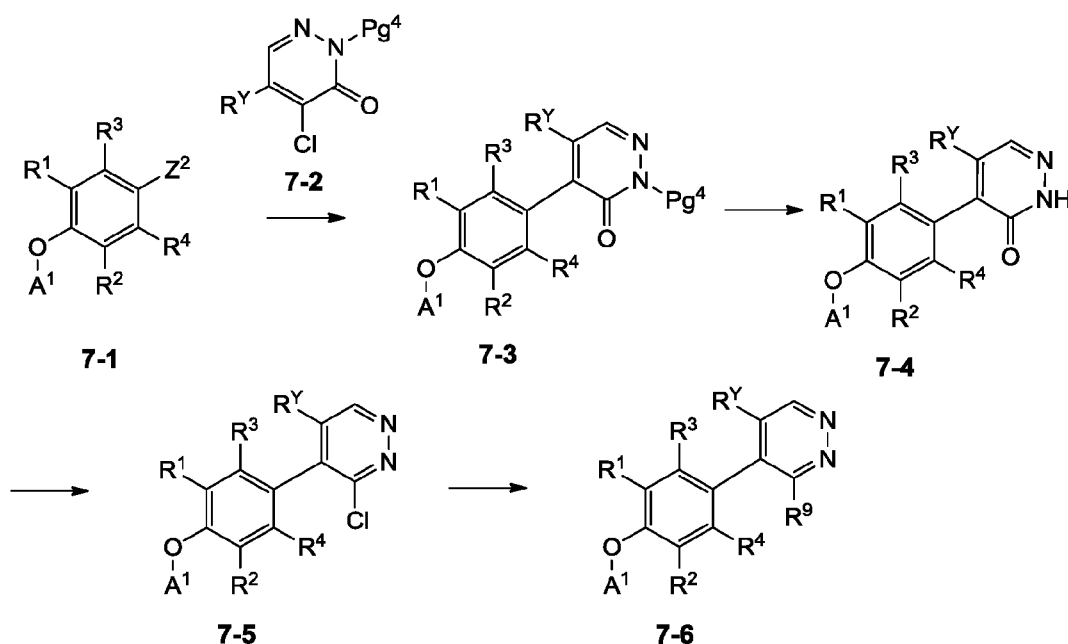
Scheme 6



Scheme 7 refers to a preparation of a compound of Formula 7-6 [wherein R^Y is H or R^{10} (such as C_{1-3} alkyl, for example methyl)], which can be used in Scheme 2 as

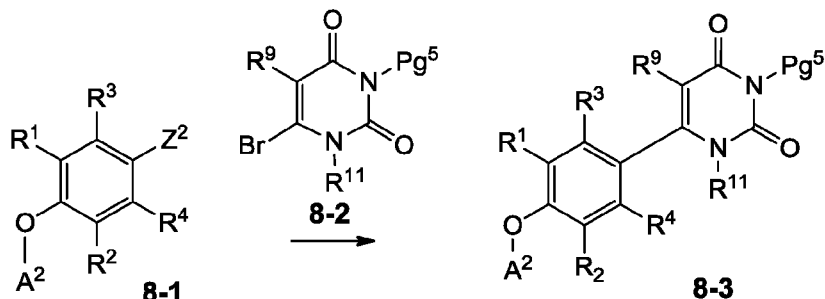
- 5 intermediate/starting material for the preparation of compounds of Formula I. Referring to Scheme 7, compounds of Formula 7-1 and 7-2 are commercially available or can be made by methods described herein or other methods well known to those skilled in the art. A compound of Formula 7-3 can be prepared by coupling a compound of Formula 7-1 with a compound of Formula 7-2 [wherein Pg^4 is a suitable protecting group such as THP]. The aforesaid coupling
- 10 may be accomplished by heating a compound of Formula 7-1 with a compound of Formula 7-2 in the presence of a suitable base (such as cesium carbonate) and a suitable catalyst {such as [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)}. Suitable reaction solvents typically can be selected from polar aprotic solvents such as 1,4-dioxane or THF. A compound of Formula 7-4 can be obtained by removing the protecting group Pg^4 , for example, by treating a
- 15 compound of Formula 7-3 (wherein Pg^4 is, for example, THP) with HCl in an alcoholic solvent (such as 2-propanol). Treatment of a compound of Formula 7-4 with phosphorous oxychloride at elevated temperature can provide a compound of Formula 7-5. A compound of Formula 7-5 can be a reactive intermediate in numerous chemical transformations to obtain a compound of Formula 7-6. For example, a compound of Formula 7-5 can be reacted with trimethylaluminum
- 20 and a suitable palladium catalyst [such as tetrakis(triphenylphosphine)palladium(0)] in 1,4-dioxane to afford a compound of Formula 7-6 (wherein the newly introduced R^9 is methyl).

Scheme 7



Scheme 8 refers to a preparation of a compound of Formula 8-3 [wherein R⁹ is for example C₁₋₃ alkyl (e.g., methyl); R¹¹ is for example H or C₁₋₃ alkyl (e.g., methyl); and Pg⁵ is a suitable protecting group [e.g., SEM, Boc, or benzyloxymethyl acetal (BOM)]; A² is H or Pg²; and Pg² is a suitable protecting group (e.g., methoxymethyl (MOM) or benzyl)], which can be used in Scheme 2 as intermediate/starting material for the preparation of compounds of Formula I. Referring to Scheme 8, compounds of Formula 8-1 and 8-2 are commercially available or can be prepared by methods described herein or other methods well known to those skilled in the art. A compound of Formula 8-3 can be prepared by coupling a compound of Formula 8-1 with a compound of Formula 8-2. The aforesaid coupling may be accomplished by heating a compound of Formula 8-1 with a compound of Formula 8-2 in the presence of a suitable base (such as potassium carbonate) and a suitable catalyst [such as [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)].

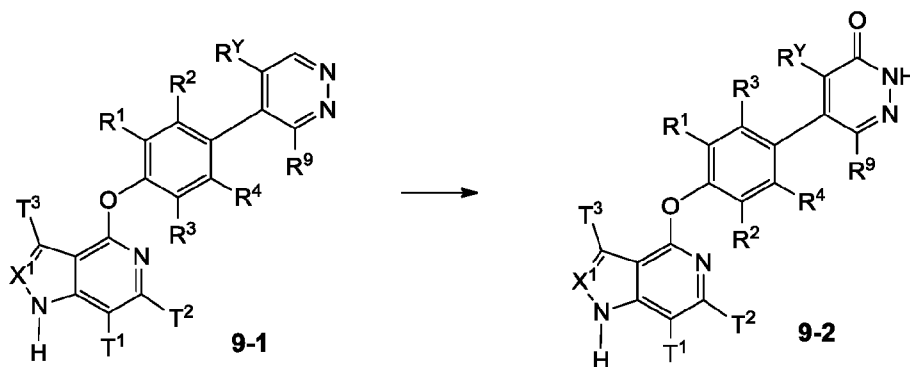
Scheme 8



Alternatively, a compound of Formula I may also be prepared by enzymatic modification (such as a microbial oxidation) of a related compound of Formula I. For example, as shown in Scheme 9, incubation of a compound of Formula I [for example, wherein Q¹ is a moiety that can

be oxidized, such as an optionally substituted pyridazinyl in a compound of Formula **9-1** [wherein R^Y is H or R^{10} (such as C_{1-3} alkyl, for example methyl)] with *Pseudomonas putida* for a reaction time between 24 and 96 hours in a suitable buffer can provide an alternate compound of Formula I (for example, wherein Q^1 is an optionally substituted pyridazinonyl in a compound of Formula **9-2**).

Scheme 9



Additional starting materials and intermediates useful for making the compounds of the present invention can be obtained from chemical vendors such as Sigma-Aldrich or can be made according to methods described in the chemical art.

Those skilled in the art can recognize that in all of the Schemes described herein, if there are functional (reactive) groups present on a part of the compound structure such as a substituent group, for example R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , R^9 , R^{10} , Q^1 , etc., further modification can be made if appropriate and/or desired, using methods well known to those skilled in the art. For example, a -CN group can be hydrolyzed to afford an amide group; a carboxylic acid can be converted to an amide; a carboxylic acid can be converted to an ester, which in turn can be reduced to an alcohol, which in turn can be further modified. For another example, an OH group can be converted into a better leaving group such as a mesylate, which in turn is suitable for nucleophilic substitution, such as by a cyanide ion (CN^-). For another example, an -S- can be oxidized to $-S(=O)-$ and/or $-S(=O)_2-$. For yet another example, an unsaturated bond such as $C=C$ or $C\equiv C$ can be reduced to a saturated bond by hydrogenation. In some embodiments, a primary amine or a secondary amine moiety (present on a substituent group such as R^3 , R^4 , R^9 , R^{10} , etc.) can be converted to an amide, sulfonamide, urea, or thiourea moiety by reacting it with an appropriate reagent such as an acid chloride, a sulfonyl chloride, an isocyanate, or a thioisocyanate compound. One skilled in the art will recognize further such modifications. Thus, a compound of Formula I having a substituent that contains a functional group can be converted to another compound of Formula I having a different substituent group.

Similarly, those skilled in the art can also recognize that in all of the schemes described herein, if there are functional (reactive) groups present on a substituent group such as R^3 , R^4 , R^9 , R^{10} , etc., these functional groups can be protected/deprotected in the course of the synthetic

scheme described here, if appropriate and/or desired. For example, an OH group can be protected by a benzyl, methyl, or acetyl group, which can be deprotected and converted back to the OH group in a later stage of the synthetic process. For another example, an NH₂ group can be protected by a benzyloxycarbonyl (Cbz) or Boc group; conversion back to the NH₂ group can be carried out at a later stage of the synthetic process via deprotection.

As used herein, the term "reacting" (or "reaction" or "reacted") refers to the bringing together of designated chemical reactants such that a chemical transformation takes place generating a compound different from any initially introduced into the system. Reactions can take place in the presence or absence of solvent.

Compounds of Formula I may exist as stereoisomers, such as atropisomers, racemates, enantiomers, or diastereomers. Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate using, for example, chiral high pressure liquid chromatography (HPLC). Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to one skilled in the art. Chiral compounds of Formula I (and chiral precursors thereof) may be obtained in enantiomerically enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0% to 50% 2-propanol, typically from 2% to 20%, and from 0% to 5% of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture. Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art. *See, e.g., Stereochemistry of Organic Compounds* by E. L. Eliel and S. H. Wilen (Wiley, New York, 1994), the disclosure of which is incorporated herein by reference in its entirety. Suitable stereoselective techniques are well-known to those of ordinary skill in the art.

Where a compound of Formula I contains an alkenyl or alkenylene (alkylidene) group, geometric *cis/trans* (or *Z/E*) isomers are possible. *Cis/trans* isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallization. Salts of the present invention can be prepared according to methods known to those of skill in the art.

The compounds of Formula I that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. Although such salts must be pharmaceutically acceptable for administration to animals, it is often desirable in practice to initially isolate the compound of the present invention from the reaction mixture as a pharmaceutically unacceptable salt and then simply convert the latter back to the free base

compound by treatment with an alkaline reagent and subsequently convert the latter free base to a pharmaceutically acceptable acid addition salt. The acid addition salts of the basic compounds of this invention can be prepared by treating the basic compound with a substantially equivalent amount of the selected mineral or organic acid in an aqueous solvent medium or in a suitable organic solvent, such as methanol or ethanol. Upon evaporation of the solvent, the desired solid salt is obtained. The desired acid salt can also be precipitated from a solution of the free base in an organic solvent by adding an appropriate mineral or organic acid to the solution.

If the inventive compound is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, maleic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, isonicotinic acid, lactic acid, pantothenic acid, bitartric acid, ascorbic acid, 2,5-dihydroxybenzoic acid, gluconic acid, saccharic acid, formic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, and pamoic [i.e., 4,4'-methanediylbis(3-hydroxynaphthalene-2-carboxylic acid)] acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid or cinnamic acid, a sulfonic acid, such as ethanesulfonic acid, or the like.

Those compounds of Formula I that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline earth metal salts, and particularly the sodium and potassium salts. These salts are all prepared by conventional techniques. The chemical bases which are used as reagents to prepare the pharmaceutically acceptable base salts of this invention are those which form non-toxic base salts with the acidic compounds of Formula I. These salts may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. These salts can also be prepared by treating the corresponding acidic compounds with an aqueous solution containing the desired pharmacologically acceptable cations, and then evaporating the resulting solution to dryness, for example under reduced pressure. Alternatively, they may also be prepared by mixing lower alkanolic solutions of the acidic compounds and the desired alkali metal alkoxide together, and then evaporating the resulting solution to dryness in the same manner as before. In either case, stoichiometric quantities of reagents are, for example, employed in order to ensure completeness of reaction and maximum yields of the desired final product.

Pharmaceutically acceptable salts of compounds of Formula I (including compounds of Formula Ia or Ib) may be prepared by one or more of three methods:

(i) by reacting the compound of Formula I with the desired acid or base;
(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of Formula I or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

5 (iii) by converting one salt of the compound of Formula I to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the resulting salt may vary from completely ionized to almost non-ionized.

10 Polymorphs can be prepared according to techniques well-known to those skilled in the art, for example, by crystallization.

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
15 is the racemic mixture or conglomerate wherein two forms of crystal are produced in equimolar amounts each comprising a single enantiomer.

While both of the crystal forms present in a racemic mixture may have almost identical physical properties, they may have different physical properties compared to the true racemate. Racemic mixtures may be separated by conventional techniques known to those skilled in the
20 art - see, for example, *Stereochemistry of Organic Compounds* by E. L. Eliel and S. H. Wilen (Wiley, New York, 1994).

The invention also includes isotopically labeled compounds of Formula I wherein one or more atoms is replaced by an atom having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.
25 Isotopically labeled compounds of Formula I (or pharmaceutically acceptable salts thereof or *N*-oxides thereof) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically labeled reagent in place of the non-labeled reagent otherwise employed.

Prodrugs in accordance with the invention can, for example, be produced by replacing
30 appropriate functionalities present in the compounds of Formula I 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).

The compounds of Formula I should be assessed for their biopharmaceutical properties, such as solubility and solution stability (across pH), permeability, etc., in order to select the most
35 appropriate dosage form and route of administration for treatment of the proposed indication.

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders,

or films by methods such as precipitation, crystallization, freeze drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof).

5 Generally, they will be administered as a formulation in association with one or more pharmaceutically acceptable excipients. The term "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

10 Pharmaceutical compositions suitable for the delivery of compounds of the present invention (or pharmaceutically acceptable salts thereof) and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in *Remington's Pharmaceutical Sciences*, 19th Edition (Mack Publishing Company, 1995).

15 The compounds of the invention (including pharmaceutically acceptable salts thereof and *N*-oxides thereof) may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, and/or buccal, lingual, or sublingual administration by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid, semi-solid and liquid systems
20 such as tablets; soft or hard capsules containing multi- or nano-particulates, liquids, or powders; lozenges (including liquid-filled); chews; gels; fast dispersing dosage forms; films; ovules; sprays; and buccal/mucoadhesive patches.

Liquid formulations include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules (made, for example, from gelatin or
25 hydroxypropyl methyl cellulose) and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methyl cellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating
30 dosage forms such as those described by Liang and Chen, *Expert Opinion in Therapeutic Patents* **2001**, *11*, 981-986.

For tablet dosage forms, depending on dose, the drug may make up from 1 weight % to 80 weight % of the dosage form, more typically from 5 weight % to 60 weight % of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants
35 include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinized

starch and sodium alginate. Generally, the disintegrant will comprise from 1 weight % to 25 weight %, for example, from 5 weight % to 20 weight % of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinized starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from 0.2 weight % to 5 weight % of the tablet, and glidants may comprise from 0.2 weight % to 1 weight % of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulfate. Lubricants generally comprise from 0.25 weight % to 10 weight %, for example, from 0.5 weight % to 3 weight % of the tablet.

Other possible ingredients include anti-oxidants, colorants, flavoring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 weight % to about 90 weight % binder, from about 0 weight % to about 85 weight % diluent, from about 2 weight % to about 10 weight % disintegrant, and from about 0.25 weight % to about 10 weight % lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt-congealed, or extruded before tableting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

The formulation of tablets is discussed in *Pharmaceutical Dosage Forms: Tablets*, Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

Consumable oral films for human or veterinary use are typically pliable water-soluble or water-swellaible thin film dosage forms which may be rapidly dissolving or mucoadhesive and typically comprise a compound of Formula I, a film-forming polymer, a binder, a solvent, a humectant, a plasticizer, a stabilizer or emulsifier, a viscosity-modifying agent and a solvent. Some components of the formulation may perform more than one function.

The compound of Formula I (or pharmaceutically acceptable salts thereof or *N*-oxides thereof) may be water-soluble or insoluble. A water-soluble compound typically comprises from 1 weight % to 80 weight %, more typically from 20 weight % to 50 weight %, of the solutes. Less soluble compounds may comprise a smaller proportion of the composition, typically up to 30 weight % of the solutes. Alternatively, the compound of Formula I may be in the form of multiparticulate beads.

The film-forming polymer may be selected from natural polysaccharides, proteins, or synthetic hydrocolloids and is typically present in the range 0.01 to 99 weight %, more typically in the range 30 to 80 weight %.

Other possible ingredients include anti-oxidants, colorants, flavorings and flavor enhancers, preservatives, salivary stimulating agents, cooling agents, co-solvents (including oils), emollients, bulking agents, anti-foaming agents, surfactants and taste-masking agents.

Films in accordance with the invention are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper. This may be done in a drying oven or tunnel, typically a combined coater dryer, or by freeze-drying or vacuuming.

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Verma et al., *Pharmaceutical Technology On-line*, 25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

The compounds of the invention (including pharmaceutically acceptable salts thereof and *N*-oxides thereof) 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, intrasynovial and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (for example to a pH of from 3 to 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilization, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of Formula I used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a suspension or as a solid, semi-solid, or thixotropic liquid for administration as an

implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and semi-solids and suspensions comprising drug-loaded poly(DL-lactic-co-glycolic acid) (PLGA) microspheres.

The compounds of the invention (including pharmaceutically acceptable salts thereof and *N*-oxides thereof) may also be administered topically, (intra)dermally, or transdermally to the skin or mucosa. 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 e.g., Finnin and Morgan, *J. Pharm. Sci.* **1999**, *88*, 955-958.

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free (e.g., Powderject™, Bioject™, etc.) injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention (including pharmaceutically acceptable salts thereof and *N*-oxides thereof) can also be administered intranasally or by inhalation, typically 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, as an aerosol spray from a pressurized container, pump, spray, atomizer (for example 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, or as nasal drops. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurized container, pump, spray, atomizer, or nebulizer contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronized to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization, or spray drying.

Capsules (made, for example, from gelatin or hydroxypropyl methyl cellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a

performance modifier such as L-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomizer using electrohydrodynamics to produce a fine mist may contain from 1 μg to 20 mg of the compound of the invention per actuation and the actuation volume may vary from 1 μL to 100 μL . A typical formulation may comprise a compound of Formula I or a pharmaceutically acceptable salt thereof, propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavors, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration.

Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, PGLA. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff" containing from 0.01 to 100 mg of the compound of Formula I. The overall daily dose will typically be in the range 1 μg to 200 mg, which may be administered in a single dose or, more usually, as divided doses throughout the day.

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

The compounds of the invention may also be administered directly to the eye or ear, typically 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, gels, 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, polyvinylalcohol, hyaluronic acid, a cellulosic polymer, for example, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, or methyl cellulose, or a heteropolysaccharide polymer, for example, gelatin gum, may be incorporated together with a preservative, such as benzalkonium chloride. Such formulations may also be delivered by iontophoresis.

Formulations for ocular/aural administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted, or programmed release.

5 The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be
10 used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, i.e., as a carrier, diluent, or solubilizer. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in International Patent Applications Nos. WO 91/11172, WO 94/02518 and WO 98/55148.

Since the present invention has an aspect that relates to the treatment of the
15 disease/conditions described herein with a combination of active ingredients which may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. The kit comprises two separate pharmaceutical compositions: a compound of Formula I a prodrug thereof or a salt of such compound or prodrug and a second compound as described above. The kit comprises means for containing the separate
20 compositions such as a container, a divided bottle or a divided foil packet. Typically the kit comprises directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are for example administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the
25 prescribing physician.

An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a transparent plastic material. During the packaging process
30 recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. In some embodiments, the
35 strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It may be desirable to provide a memory aid on the kit, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, e.g., as follows "First Week, Monday, Tuesday, etc.... Second Week, Monday, Tuesday,..." etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of Formula I compound can consist of one tablet or capsule while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

In another specific embodiment of the invention, a dispenser designed to dispense the daily doses one at a time in the order of their intended use is provided. For example, the dispenser is equipped with a memory aid, so as to further facilitate compliance with the regimen. An example of such a memory aid is a mechanical counter which indicates the number of daily doses that has been dispensed. Another example of such a memory aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters that can be changed or modified to yield essentially the same results. In the following Examples and Preparations, "DMSO" means dimethyl sulfoxide, "N" where referring to concentration means Normal, "M" means molar, "mL" means milliliter, "mmol" means millimoles, "μmol" means micromoles, "eq." means equivalent, "°C" means degrees Celsius, "MHz" means megahertz, "HPLC" means high-performance liquid chromatography.

EXAMPLES

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, including anhydrous solvents where appropriate (generally Sure-Seal™ products from the Aldrich Chemical Company, Milwaukee, Wisconsin). 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. In some examples, chiral separations were carried out to separate atropisomers (or atropenantiomers) of certain compounds of the invention (in some examples,

the separated atropisomers are designated as ENT-1 and ENT-2, according to their order of elution). In some examples, the optical rotation of an atropisomer was measured using a polarimeter. According to its observed rotation data (or its specific rotation data), an atropisomer (or atropenantiomer) with a clockwise rotation was designated as the (+)-atropisomer [or the (+) atropenantiomer] and an atropisomer (or atropenantiomer) with a counter-clockwise rotation was designated as the (-)-atropisomer [or the (-) atropenantiomer].

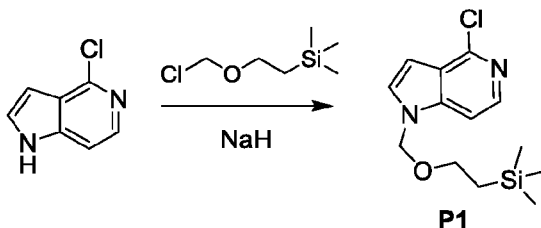
For syntheses referencing procedures in other Examples or Methods, reaction conditions (length of reaction and temperature) may vary. In general, reactions were followed by thin layer chromatography or mass spectrometry, and subjected to work-up when appropriate. Purifications may vary between experiments: in general, solvents and the solvent ratios used for eluents/gradients were chosen to provide appropriate R_fs or retention times.

PREPARATIONS

Preparations P1-P8 describe preparations of some starting materials or intermediates used for preparation of certain compounds of the invention.

Preparation P1

4-Chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrrolo[3,2-c]pyridine (**P1**)

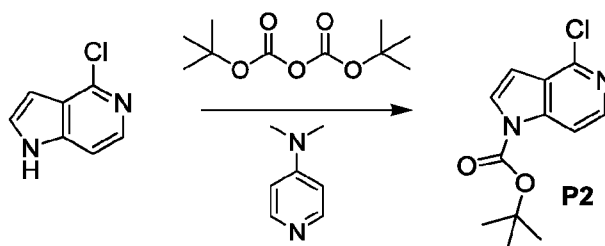


A mixture of 4-chloro-1H-pyrrolo[3,2-c]pyridine (98%, 2.0 g, 13 mmol) and tetrahydrofuran (20 mL) was cooled to 0 °C. Sodium hydride (60% in oil, 1.03 g, 25.8 mmol) was added portion-wise over 5 minutes, and the reaction mixture was allowed to stir at 0 °C for 10 minutes. 2-(Trimethylsilyl)ethoxymethyl chloride (3.40 mL, 19.3 mmol) was then added drop-wise over 5 minutes, and stirring was continued at 0 °C for 15 minutes. The reaction mixture was quenched with saturated aqueous ammonium chloride solution; the aqueous layer was extracted twice with ethyl acetate, and the combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Silica gel chromatography (Gradient: 10% to 20% ethyl acetate in heptane) afforded the product as a colorless oil. Yield: 2.64 g, 9.33 mmol, 72%. LCMS *m/z* 283.0 [M+H⁺]. ¹H NMR (400 MHz, CDCl₃) δ 8.13 (d, *J*=5.8 Hz, 1H), 7.34 (dd, *J*=5.8, 0.7 Hz, 1H), 7.25 (d, *J*=3.3 Hz, 1H), 6.69 (dd, *J*=3.3, 0.7 Hz, 1H), 5.48 (s, 2H), 3.46 (dd, *J*=8.2, 8.1 Hz, 2H), 0.89 (dd, *J*=8.2, 8.1 Hz, 2H), -0.05 (s, 9H).

Preparation P2

tert-Butyl 4-chloro-1H-pyrrolo[3,2-c]pyridine-1-carboxylate (**P2**).

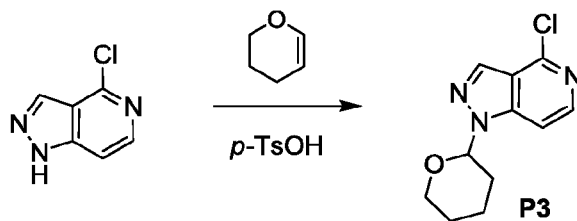
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Di-*tert*-butyl dicarbonate (99%, 650 mg, 2.95 mmol) was added to a solution of 4-chloro-1*H*-pyrrolo[3,2-*c*]pyridine (300 mg, 1.97 mmol) and 4-(dimethylamino)pyridine (97%, 124 mg, 0.984 mmol) in acetonitrile (3 mL), and the reaction mixture was stirred at room temperature for 18 hours. Volatiles were removed *in vacuo*, and the residue was purified via chromatography on silica gel (Gradient: 0% to 50% ethyl acetate in heptane) to afford the product as a white solid. Yield: 410 mg, 1.62 mmol, 82%. LCMS *m/z* 253.0 [*M*+*H*⁺]. ¹H NMR (400 MHz, CDCl₃) δ 8.24 (d, *J*=5.7 Hz, 1H), 7.95 (br d, *J*=5.7 Hz, 1H), 7.65 (d, *J*=3.7 Hz, 1H), 6.72 (dd, *J*=3.7, 0.8 Hz, 1H), 1.70 (s, 9H).

Preparation P3

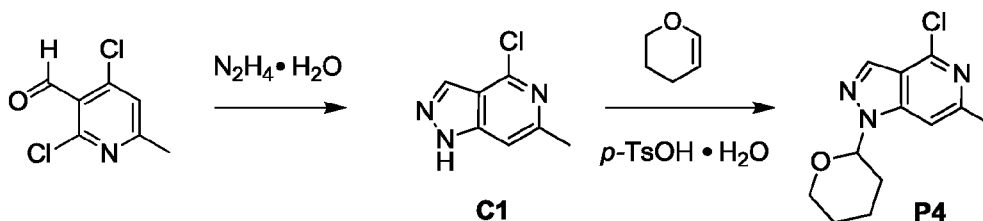
4-Chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[4,3-*c*]pyridine (**P3**)



p-Toluenesulfonic acid monohydrate (2.4 g, 13 mmol) and 3,4-dihydro-2*H*-pyran (99%, 45 mL, 520 mmol) were sequentially added to a suspension of 4-chloro-1*H*-pyrazolo[4,3-*c*]pyridine (20.0 g, 130 mmol) in dichloromethane (400 mL). The reaction mixture was allowed to stir at room temperature for 24 hours, at which time it was washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via silica gel chromatography (Eluents: 10%, then 30%, then 50% ethyl acetate in heptane) afforded the product as a white solid. Yield: 27.51 g, 115.7 mmol, 89%. LCMS *m/z* 238.1 [*M*+*H*⁺]. ¹H NMR (400 MHz, CDCl₃) δ 8.19 (d, *J*=6.0 Hz, 1H), 8.16 (d, *J*=0.9 Hz, 1H), 7.47 (dd, *J*=6.0, 0.9 Hz, 1H), 5.73 (br dd, *J*=9.0, 2.7 Hz, 1H), 3.97-4.04 (m, 1H), 3.72-3.80 (m, 1H), 2.43-2.53 (m, 1H), 2.07-2.20 (m, 2H), 1.65-1.85 (m, 3H).

Preparation P4

4-Chloro-6-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[4,3-*c*]pyridine (**P4**)



Step 1. Synthesis of 4-chloro-6-methyl-1*H*-pyrazolo[4,3-*c*]pyridine (**C1**).

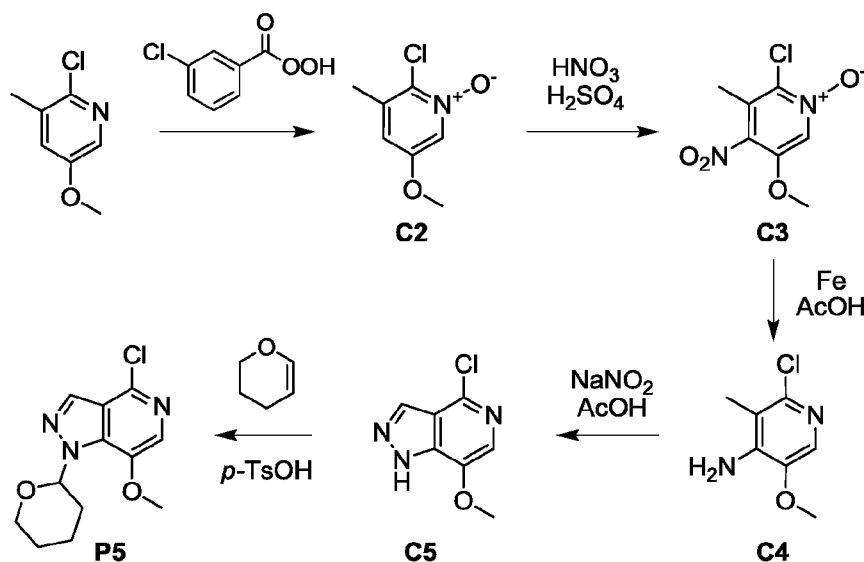
To a solution of 2,4-dichloro-6-methylpyridine-3-carbaldehyde (12 g, 63 mmol) in 1,2-dichloroethane (200 mL) was added hydrazine monohydrate (9.52 g, 0.190 mol), and the reaction mixture was heated at 80 °C for 18 hours. After removal of solvents *in vacuo*, the residue was suspended in water (150 mL) and stirred for 30 minutes. The resulting precipitate was collected by filtration and washed with petroleum ether (2 x 250 mL), then was suspended in chloroform (150 mL), stirred for 30 minutes and filtered. The chloroform suspension was repeated twice to afford the product as a white solid. Yield: 6.7 g, 40 mmol, 63%. LCMS *m/z* 168.1 [M+H⁺]. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.70 (br s, 1H), 8.21 (s, 1H), 7.38 (s, 1H), 2.52 (s, 3H).

Step 2. Synthesis of **P4**.

p-Toluenesulfonic acid monohydrate (29 mg, 0.15 mmol) and 3,4-dihydro-2*H*-pyran (99%, 205 μL, 2.39 mmol) were sequentially added to a suspension of **C1** (250 mg, 1.49 mmol) and 4Å molecular sieves in dichloromethane (10 mL). The reaction mixture was allowed to stir at room temperature for 4 hours, at which time it was filtered, concentrated *in vacuo*, and washed three times with heptane. Purification via silica gel chromatography (Gradient: 20% to 50% ethyl acetate in heptane) afforded the product as a colorless oil. Yield: 65 mg, 0.26 mmol, 17%. LCMS *m/z* 252.1 [M+H⁺]. ¹H NMR (400 MHz, CDCl₃), characteristic peaks: δ 8.08 (d, *J*=0.9 Hz, 1H), 7.26-7.27 (m, 1H), 5.67 (dd, *J*=9.1, 2.8 Hz, 1H), 3.99-4.05 (m, 1H), 3.71-3.79 (m, 1H), 2.65 (d, *J*=0.8 Hz, 3H), 2.06-2.2 (m, 2H).

Preparation P5

4-Chloro-7-methoxy-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[4,3-*c*]pyridine (**P5**)



Step 1. Synthesis of 2-chloro-5-methoxy-3-methylpyridine 1-oxide (**C2**).

3-Chloroperoxybenzoic acid (70%, 695 mg, 2.82 mmol) was added to a solution of 2-chloro-5-methoxy-3-methylpyridine (370 mg, 2.35 mmol) in dichloromethane (10 mL). After stirring for 18 hours at room temperature, the reaction mixture was concentrated *in vacuo* and purified via silica gel chromatography (Gradient: 0% to 10% methanol in ethyl acetate) to afford

the product as a white solid. Yield: 370 mg, 2.13 mmol, 91%. ^1H NMR (400 MHz, CD_3OD) δ 8.14 (d, $J=2.5$ Hz, 1H), 7.23 (d, $J=2.3$ Hz, 1H), 3.88 (s, 3H), 2.44 (s, 3H).

Step 2. Synthesis of 2-chloro-5-methoxy-3-methyl-4-nitropyridine 1-oxide (C3).

Concentrated nitric acid (2.5 mL) was added drop-wise to a 0 °C solution of **C2** (350 mg, 2.02 mmol) in concentrated sulfuric acid (2.5 mL). The reaction mixture was heated at 90 °C for 1 hour, then cooled to room temperature and poured onto crushed ice. The resulting mixture was neutralized to pH 6 – 7 with saturated aqueous sodium carbonate solution, and extracted with ethyl acetate. The combined organic layers were washed with water, washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to provide the product as a light yellow solid. Yield: 370 mg, 1.69 mmol, 84%. LCMS m/z 219.0, 221.1 $[\text{M}+\text{H}^+]$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.65 (s, 1H), 3.94 (s, 3H), 2.31 (s, 3H).

Step 3. Synthesis of 2-chloro-5-methoxy-3-methylpyridin-4-amine (C4).

Iron powder (700 mg, 12 mmol) was added to a solution of **C3** (350 mg, 1.60 mmol) in acetic acid (8 mL), and the reaction mixture was heated at 100 °C for 1 hour, then cooled to room temperature. After filtration through Celite and thorough washing of the filter pad with ethyl acetate and methanol, the combined filtrates were concentrated *in vacuo*. The residue was diluted with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate. The combined organic layers were washed with water, washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Silica gel chromatography (Gradient: 50% to 75% ethyl acetate in heptane) afforded the product as a white solid. Yield: 240 mg, 1.39 mmol, 87%. LCMS m/z 173.0 $[\text{M}+\text{H}^+]$. ^1H NMR (400 MHz, CDCl_3) δ 7.65 (s, 1H), 4.38 (br s, 2H), 3.91 (s, 3H), 2.20 (s, 3H).

Step 4. Synthesis of 4-chloro-7-methoxy-1H-pyrazolo[4,3-c]pyridine (C5).

A solution of sodium nitrite (98%, 326 mg, 4.63 mmol) in water (0.6 mL) was added to a solution of **C4** (200 mg, 1.16 mmol) in acetic acid (8 mL), and the reaction mixture was heated at 75 °C for 1 hour. After the reaction mixture had cooled to room temperature, it was concentrated *in vacuo*, diluted with saturated aqueous sodium bicarbonate solution, and 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. Silica gel chromatography (Gradient: 25% to 50% ethyl acetate in heptane) provided the product as a yellow solid. Yield: 140 mg, 0.763 mmol, 66%. LCMS m/z 184.0 $[\text{M}+\text{H}^+]$. ^1H NMR (400 MHz, CDCl_3) δ 8.17 (s, 1H), 7.74 (s, 1H), 4.06 (s, 3H).

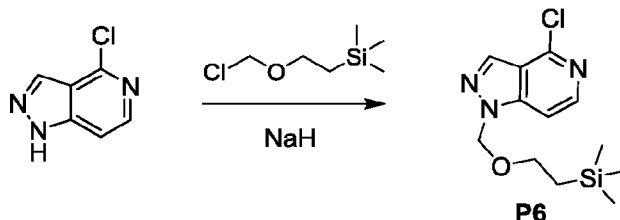
Step 5. Synthesis of P5.

C5 was converted to the product using the method described for synthesis of 4-chloro-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[4,3-c]pyridine **P3** in Preparation P3. The product was obtained as a light yellow oil, which solidified upon standing. Yield: 120 mg, 0.448 mmol, 41%. LCMS m/z 268.1 $[\text{M}+\text{H}^+]$. ^1H NMR (400 MHz, CDCl_3) δ 8.11-8.12 (m, 1H), 7.72 (s, 1H), 6.12 (dd,

$J=10.0$, 2.6 Hz, 1H), 4.06 (s, 3H), 4.04-4.10 (m, 1H), 3.69-3.77 (m, 1H), 2.51-2.62 (m, 1H), 2.12-2.21 (m, 1H), 2.00-2.08 (m, 1H), 1.5-1.8 (m, 3H).

Preparation P6

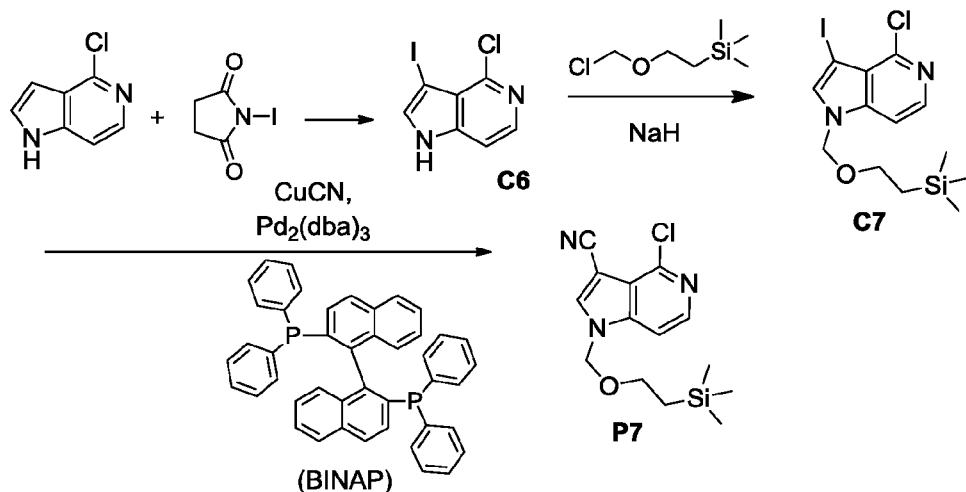
4-Chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrazolo[4,3-c]pyridine (**P6**)



4-Chloro-1H-pyrazolo[4,3-c]pyridine was converted to the product using the method described for synthesis of **P1** in Preparation P1. The product was isolated as a white solid. Yield: 686 mg, 2.42 mmol, 50%. ^1H NMR (400 MHz, CDCl_3) δ 8.24 (d, $J=5.8$ Hz, 1H), 8.17 (s, 1H), 7.43 (d, $J=5.8$ Hz, 1H), 5.74 (s, 2H), 3.54-3.60 (m, 2H), 0.86-0.92 (m, 2H), -0.05 (s, 9H).

Preparation P7

4-Chloro-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrrolo[3,2-c]pyridine-3-carbonitrile (**P7**)



Step 1. Synthesis of 4-chloro-3-iodo-1H-pyrrolo[3,2-c]pyridine (**C6**).

N-Iodosuccinimide (1.3 g, 5.8 mmol) was added to a 0 °C solution of 4-chloro-1H-pyrrolo[3,2-c]pyridine (0.60 g, 3.9 mmol) in *N,N*-dimethylformamide (10 mL). The reaction mixture was stirred at room temperature for 18 hours, whereupon it was concentrated *in vacuo*. Purification via silica gel chromatography (0% to 50% ethyl acetate in petroleum ether) afforded the product as a yellow solid. Yield: 900 mg, 3.2 mmol, 82%. ^1H NMR (400 MHz, CDCl_3) δ 8.10 (d, $J=5.5$ Hz, 1H), 7.42 (d, $J=2.5$ Hz, 1H), 7.34 (d, $J=5.8$ Hz, 1H).

Step 2. Synthesis of 4-chloro-3-iodo-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrrolo[3,2-c]pyridine (**C7**).

To a 0 °C solution of **C6** (900 mg, 3.2 mmol) in *N,N*-dimethylformamide (3 mL) and tetrahydrofuran (70 mL) was added sodium hydride (60% in mineral oil, 168 mg, 4.2 mmol).

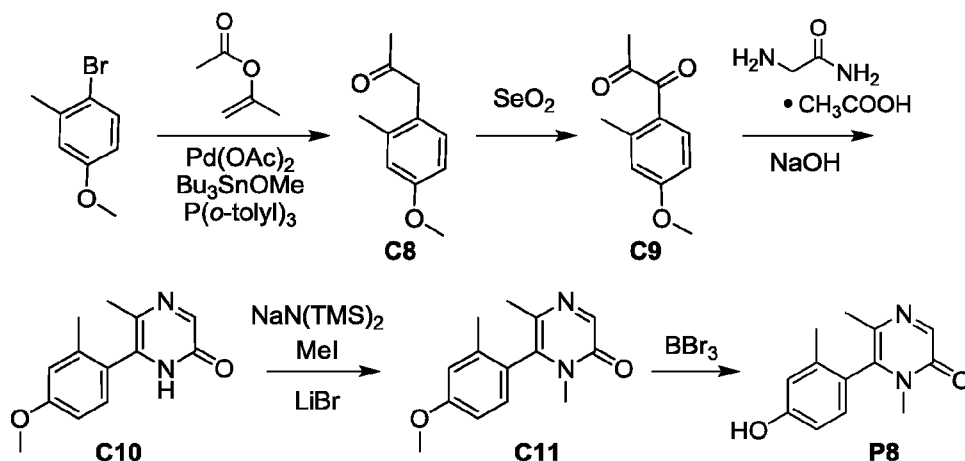
After 5 minutes, 2-(trimethylsilyl)ethoxymethyl chloride (592 mg, 3.55 mmol) was added to the cold mixture. The reaction mixture was stirred at room temperature for 3 hours, then cooled to 0 °C and treated with additional sodium hydride (56 mg, 1.4 mmol) and 2-(trimethylsilyl)ethoxymethyl chloride (197 mg, 1.18 mmol). After stirring at room temperature for 18 hours, the reaction mixture was diluted with saturated aqueous sodium chloride solution (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried, filtered, and concentrated *in vacuo*. Silica gel chromatography (Gradient: 0% to 30% ethyl acetate in petroleum ether) provided the product as a yellow oil. Yield: 650 mg, 1.59 mmol, 50%. ¹H NMR (400 MHz, CDCl₃) δ 8.14 (d, *J*=6.0 Hz, 1H), 7.39 (d, *J*=6.0 Hz, 1H), 7.38 (s, 1H), 5.44 (s, 2H), 3.44-3.50 (m, 2H), 0.86-0.92 (m, 2H), -0.03 (s, 9H).

Step 3. Synthesis of **P7**.

To a mixture of **C7** (1.2 g, 2.9 mmol) and copper(I) cyanide (540 mg, 6.0 mmol) in 1,4-dioxane (40 mL) were added tris(dibenzylideneacetone)dipalladium(0) (275 mg, 0.300 mmol) and 1,1'-binaphthalene-2,2'-diylbis(diphenylphosphane) (BINAP, 540 mg, 0.87 mmol). After the reaction mixture had been stirred at 110 °C for 18 hours, it was filtered and concentrated under reduced pressure. Purification via silica gel chromatography (Gradient: 5% to 20% ethyl acetate in petroleum ether) afforded the product as a yellow solid. Yield: 380 mg, 1.2 mmol, 41%. ¹H NMR (400 MHz, CDCl₃) δ 8.27 (d, *J*=5.8 Hz, 1H), 7.80 (s, 1H), 7.43 (d, *J*=5.8 Hz, 1H), 5.52 (s, 2H), 3.47-3.54 (m, 2H), 0.88-0.95 (m, 2H), -0.02 (s, 9H).

Preparation P8

6-(4-Hydroxy-2-methylphenyl)-1,5-dimethylpyrazin-2(1H)-one (**P8**)



Step 1. Synthesis of 1-(4-methoxy-2-methylphenyl)propan-2-one (**C8**).

Four batches of this experiment were carried out (4 x 250 g substrate).

Tributyl(methoxy)stannane (400 g, 1.24 mol), 1-bromo-4-methoxy-2-methylbenzene (250 g, 1.24 mol), prop-1-en-2-yl acetate (187 g, 1.87 mol), palladium(II) acetate (7.5 g, 33 mmol) and tris(2-methylphenyl)phosphane (10 g, 33 mmol) were stirred together in toluene (2 L) at 100 °C for 18 hours. After cooling to room temperature, the reaction mixture was treated with aqueous potassium fluoride solution (4 M, 400 mL) and stirred for 2 hours at 40 °C. The resulting mixture

was diluted with toluene (500 mL) and filtered through Celite; the filter pad was thoroughly washed with ethyl acetate (2 x 1.5 L). The organic phase from the combined filtrates was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via silica gel chromatography (Gradient: 0% to 5% ethyl acetate in petroleum ether) provided the product as a yellow oil. Combined yield: 602 g, 3.38 mol, 68%. LCMS m/z 179.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, $J=8.3$ Hz, 1H), 6.70-6.77 (m, 2H), 3.79 (s, 3H), 3.65 (s, 2H), 2.22 (s, 3H), 2.14 (s, 3H).

Step 2. Synthesis of 1-(4-methoxy-2-methylphenyl)propane-1,2-dione (C9).

C8 (6.00 g, 33.7 mmol) and selenium dioxide (7.47 g, 67.3 mmol) were suspended in 1,4-dioxane (50 mL) and heated at 100 °C for 18 hours. The reaction mixture was cooled to room temperature and filtered through Celite; the filtrate was concentrated *in vacuo*. Silica gel chromatography (Eluent: 10% ethyl acetate in heptane) afforded the product as a bright yellow oil. Yield: 2.55 g, 13.3 mmol, 39%. LCMS m/z 193.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, $J=8.6$ Hz, 1H), 6.81 (br d, half of AB quartet, $J=2.5$ Hz, 1H), 6.78 (br dd, half of ABX pattern, $J=8.7$, 2.6 Hz, 1H), 3.87 (s, 3H), 2.60 (br s, 3H), 2.51 (s, 3H).

Step 3. Synthesis of 6-(4-methoxy-2-methylphenyl)-5-methylpyrazin-2(1H)-one (C10).

C9 (4.0 g, 21 mmol) and glycineamide acetate (2.79 g, 20.8 mmol) were dissolved in methanol (40 mL) and cooled to -10 °C. Aqueous sodium hydroxide solution (12 N, 3.5 mL, 42 mmol) was added, and the resulting mixture was slowly warmed to room temperature. After stirring for 3 days, the reaction mixture was concentrated *in vacuo*. The residue was diluted with water, and 1 N aqueous hydrochloric acid was added until the pH was approximately 7. The aqueous phase was extracted with ethyl acetate, and the combined organic extracts were washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting residue was slurried with 3:1 ethyl acetate / heptane, stirred for 5 minutes, filtered, and concentrated *in vacuo*. Silica gel chromatography (Eluent: ethyl acetate) provided the product as a tan solid that contained 15% of an undesired regioisomer; this material was used without further purification. Yield: 2.0 g. LCMS m/z 231.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.14 (d, $J=8.2$ Hz, 1H), 6.82-6.87 (m, 2H), 3.86 (s, 3H), 2.20 (s, 3H), 2.11 (s, 3H).

Step 4. Synthesis of 6-(4-methoxy-2-methylphenyl)-1,5-dimethylpyrazin-2(1H)-one (C11)

C10 (from the previous step, 1.9 g) was dissolved in *N,N*-dimethylformamide (40 mL). Lithium bromide (0.86 g, 9.9 mmol) and sodium bis(trimethylsilyl)amide (95%, 1.91 g, 9.89 mmol) were added, and the resulting solution was stirred for 30 minutes. Methyl iodide (0.635 mL, 10.2 mmol) was added and stirring was continued at room temperature for 18 hours. The reaction mixture was then diluted with water and brought to a pH of approximately 7 by slow portion-wise addition of 1 N aqueous hydrochloric acid. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed several times with water, dried over magnesium sulfate, filtered, and concentrated. Silica gel chromatography (Gradient: 75% to

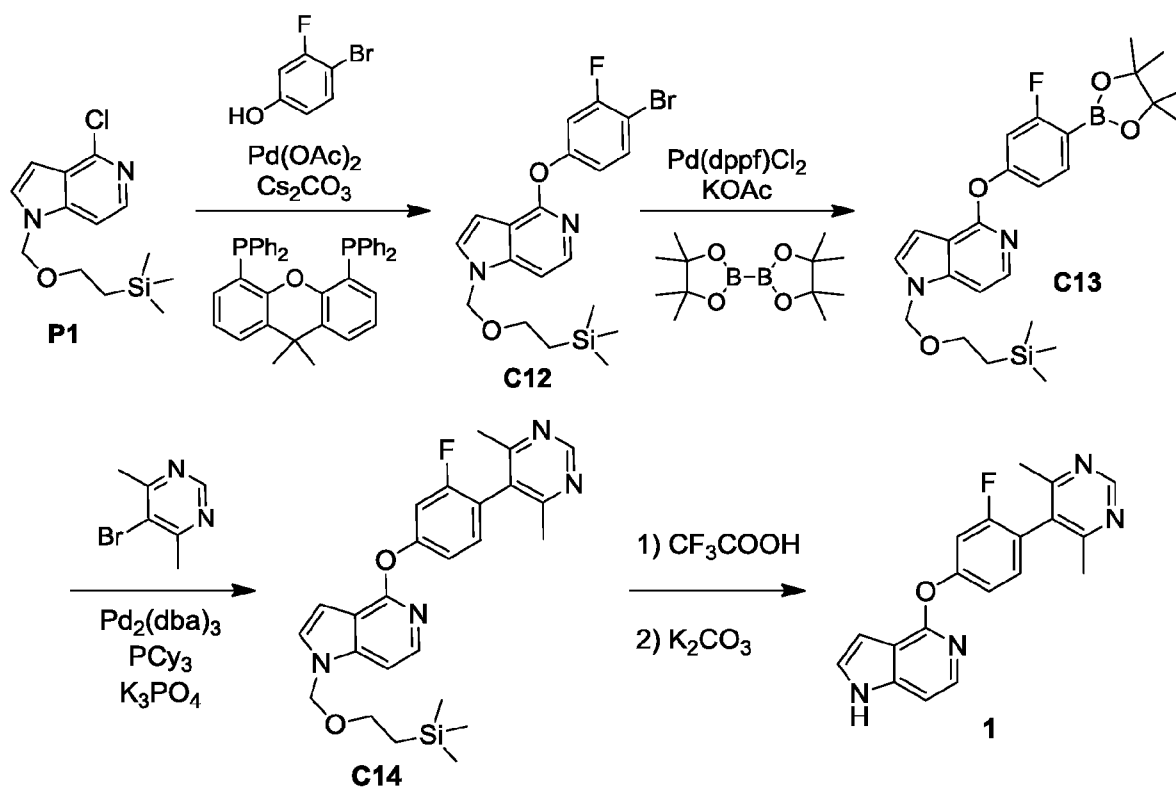
100% ethyl acetate in heptane) afforded the product as a viscous orange oil. Yield: 1.67 g, 6.84 mmol, 33% over two steps. LCMS m/z 245.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.03 (br d, $J=8$ Hz, 1H), 6.85-6.90 (m, 2H), 3.86 (s, 3H), 3.18 (s, 3H), 2.08 (br s, 3H), 2.00 (s, 3H).

5 Step 5. Synthesis of **P8**.

To a -78 °C solution of **C11** (1.8 g, 7.37 mmol) in dichloromethane (40 mL) was added a solution of boron tribromide in dichloromethane (1 M, 22 mL, 22 mmol). The cooling bath was removed after 30 minutes, and the reaction mixture was allowed to warm to room temperature and stir for 18 hours. The reaction was cooled to -78 °C, and methanol (10 mL) was slowly added; the resulting mixture was slowly warmed to room temperature. The reaction mixture was concentrated *in vacuo*, methanol (20 mL) was added, and the mixture was again concentrated under reduced pressure. The residue was diluted with ethyl acetate (300 mL) and water (200 mL) and the aqueous layer was brought to pH 7 via portion-wise addition of saturated aqueous sodium carbonate solution. The mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with water and with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford the product as a light tan solid. Yield: 1.4 g, 6.0 mmol, 81%. LCMS m/z 231.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 6.98 (d, $J=8.2$ Hz, 1H), 6.87-6.89 (m, 1H), 6.85 (br dd, $J=8.2, 2.5$ Hz, 1H), 3.22 (s, 3H), 2.06 (br s, 3H), 2.03 (s, 3H).

Example 1

4-[4-(4,6-Dimethylpyrimidin-5-yl)-3-fluorophenoxy]-1H-pyrrolo[3,2-c]pyridine (**1**)



Step 1. Synthesis of 4-(4-bromo-3-fluorophenoxy)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrrolo[3,2-c]pyridine (C12).

A mixture of **P1** (2.9 g, 10 mmol), 4-bromo-3-fluorophenol (3.4 g, 18 mmol), palladium(II) acetate (168 mg, 0.748 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos, 0.87 g, 1.5 mmol) and cesium carbonate (9.8 g, 30 mmol) in 1,4-dioxane (60 mL) was stirred at 120 °C for 4 hours. The mixture was filtered, the filtrate was concentrated *in vacuo*, and the residue was purified by silica gel chromatography (Eluent: 10:1 petroleum ether / ethyl acetate) to provide the product as a colorless oil. Yield: 1.6 g, 3.7 mmol, 37%. ¹H NMR (400 MHz, CDCl₃) δ 7.90 (d, *J*=5.8 Hz, 1H), 7.55 (dd, *J*=8.5, 8.0 Hz, 1H), 7.17-7.21 (m, 2H), 7.08 (dd, *J*=9.4, 2.6 Hz, 1H), 6.94-6.99 (m, 1H), 6.68 (d, *J*=3.3 Hz, 1H), 5.49 (s, 2H), 3.50 (t, *J*=8.0 Hz, 2H), 0.91 (t, *J*=8.1 Hz, 2H), -0.04 (s, 9H).

Step 2. Synthesis of 4-[3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrrolo[3,2-c]pyridine (C13).

A mixture of **C12** (1.2 g, 2.7 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (1.38 g, 5.43 mmol), potassium acetate (0.8 g, 8 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (150 mg, 0.20 mmol) in 1,4-dioxane (20 mL) was stirred at 120 °C for 5 hours. After completion of the reaction, the mixture was filtered and the filtrate was concentrated under reduced pressure. Purification using silica gel chromatography (Eluent: 15:1 petroleum ether / ethyl acetate) afforded the product as an orange oil. Yield: 0.94 g, 1.9 mmol, 70%. ¹H NMR (400 MHz, CDCl₃) δ 7.92 (d, *J*=5.8 Hz, 1H), 7.77 (dd, *J*=7.9, 7.2 Hz, 1H), 7.19 (d, *J*=5.9 Hz, 1H), 7.17 (d, *J*=3.3 Hz, 1H), 6.99-7.03 (m, 1H), 6.90-6.94 (m, 1H), 6.62 (d, *J*=3.3 Hz, 1H), 5.49 (s, 2H), 3.49 (t, *J*=8.1 Hz, 2H), 1.36 (s, 12H), 0.90 (t, *J*=8.2 Hz, 2H), -0.04 (s, 9H).

Step 3. Synthesis of 4-[4-(4,6-dimethylpyrimidin-5-yl)-3-fluorophenoxy]-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrrolo[3,2-c]pyridine (C14).

A mixture of **C13** (427 mg, 0.881 mmol), 5-bromo-4,6-dimethylpyrimidine (150 mg, 0.802 mmol), tris(dibenzylideneacetone)dipalladium(0) (147 mg, 0.160 mmol), tricyclohexylphosphine (90 mg, 0.32 mmol) and potassium phosphate (341 mg, 1.61 mmol) in 1,4-dioxane (4 mL) containing 5 drops of water was heated at 120 °C for 2 hours under microwave irradiation. The mixture was filtered, the filtrate was concentrated under reduced pressure, and the residue was purified by preparative thin layer chromatography on silica gel (Eluent: ethyl acetate) to give the product, which was used without further purification. Yield: 180 mg, 0.387 mmol, 48%. LCMS *m/z* 465.3 [M+H⁺].

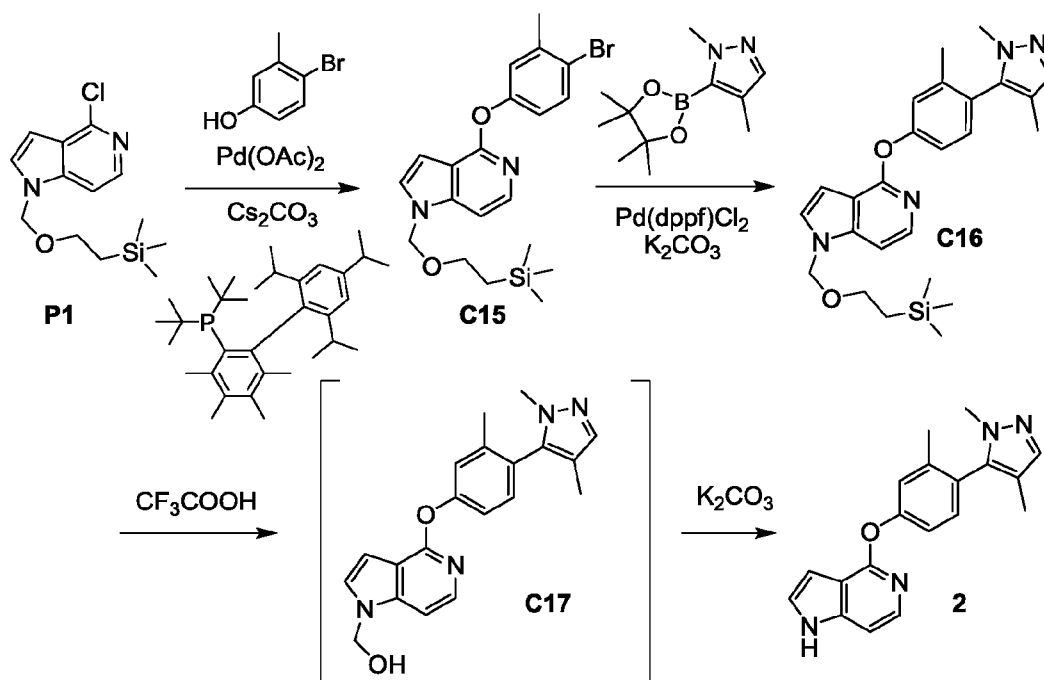
Step 4. Synthesis of 4-[4-(4,6-dimethylpyrimidin-5-yl)-3-fluorophenoxy]-1H-pyrrolo[3,2-c]pyridine (1).

A solution of **C14** (180 mg, 0.387 mmol) in trifluoroacetic acid (6 mL) was heated to 90 °C for 2 hours. The mixture was concentrated under reduced pressure and the residue was

dissolved in acetonitrile (5 mL) and water (1 mL). Solid potassium carbonate (1 g) was added, and the mixture was refluxed for 2 hours. The suspension was filtered and the filtrate was concentrated *in vacuo*. Purification via preparative reversed phase high-performance liquid chromatography (Column: Phenomenex Synergi C18, 4 μ m; Mobile phase A: 0.1% formic acid in water; Mobile phase B: 0.1% formic acid in acetonitrile; Gradient: 18% to 28% B) afforded the product as a white solid. Yield: 114 mg, 0.341 mmol, 88%. LCMS m/z 334.9 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.96 (s, 1H), 8.01 (d, $J=6.5$ Hz, 1H), 7.67 (d, $J=6.5$ Hz, 1H), 7.61 (d, $J=3.0$ Hz, 1H), 7.47-7.58 (m, 2H), 7.41 (br d, $J=8.5$ Hz, 1H), 6.17 (d, $J=3.0$ Hz, 1H), 2.39 (s, 6H).

Example 2

4-[4-(1,4-Dimethyl-1H-pyrazol-5-yl)-3-methylphenoxy]-1H-pyrrolo[3,2-c]pyridine (2)



Step 1. Synthesis of 4-(4-bromo-3-methylphenoxy)-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrrolo[3,2-c]pyridine (C15).

P1 (326 mg, 1.15 mmol), 4-bromo-3-methylphenol (216 mg, 1.15 mmol), di-*tert*-butyl[3,4,5,6-tetramethyl-2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane (97%, 114 mg, 0.230 mmol), palladium(II) acetate (95%, 19.1 mg, 80.8 μ mol) and cesium carbonate (1.13 g, 3.47 mmol) were combined in 1,4-dioxane (7 mL) in a sealable tube, and the reaction mixture was heated at 130 $^{\circ}C$ for 18 hours. Ethyl acetate was added, and the mixture was filtered through Celite, concentrated *in vacuo* and purified twice via silica gel chromatography (Gradient: 0% to 50% ethyl acetate in heptane). The product was obtained as an oil that still contained some of the phenol starting material. Yield: 395 mg, <0.91 mmol, <79%. LCMS m/z 434.9 $[M+H]^+$. ^1H NMR (500 MHz, $CDCl_3$), product peaks only: δ 7.91 (d, $J=5.9$ Hz, 1H), 7.52 (d, $J=8.5$ Hz, 1H), 7.19-7.22 (m, 2H), 7.12 (br d, $J=2.7$ Hz, 1H), 6.94 (br dd, $J=8.7$, 2.8 Hz, 1H), 6.69 (br d, $J=3.2$ Hz, 1H), 5.51 (s, 2H), 3.51-3.56 (m, 2H), 2.36 (s, 3H), 0.92-0.97 (m, 2H), 0.01 (s, 9H).

Step 2. Synthesis of 4-[4-(1,4-dimethyl-1H-pyrazol-5-yl)-3-methylphenoxy]-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrrolo[3,2-c]pyridine (**C16**).

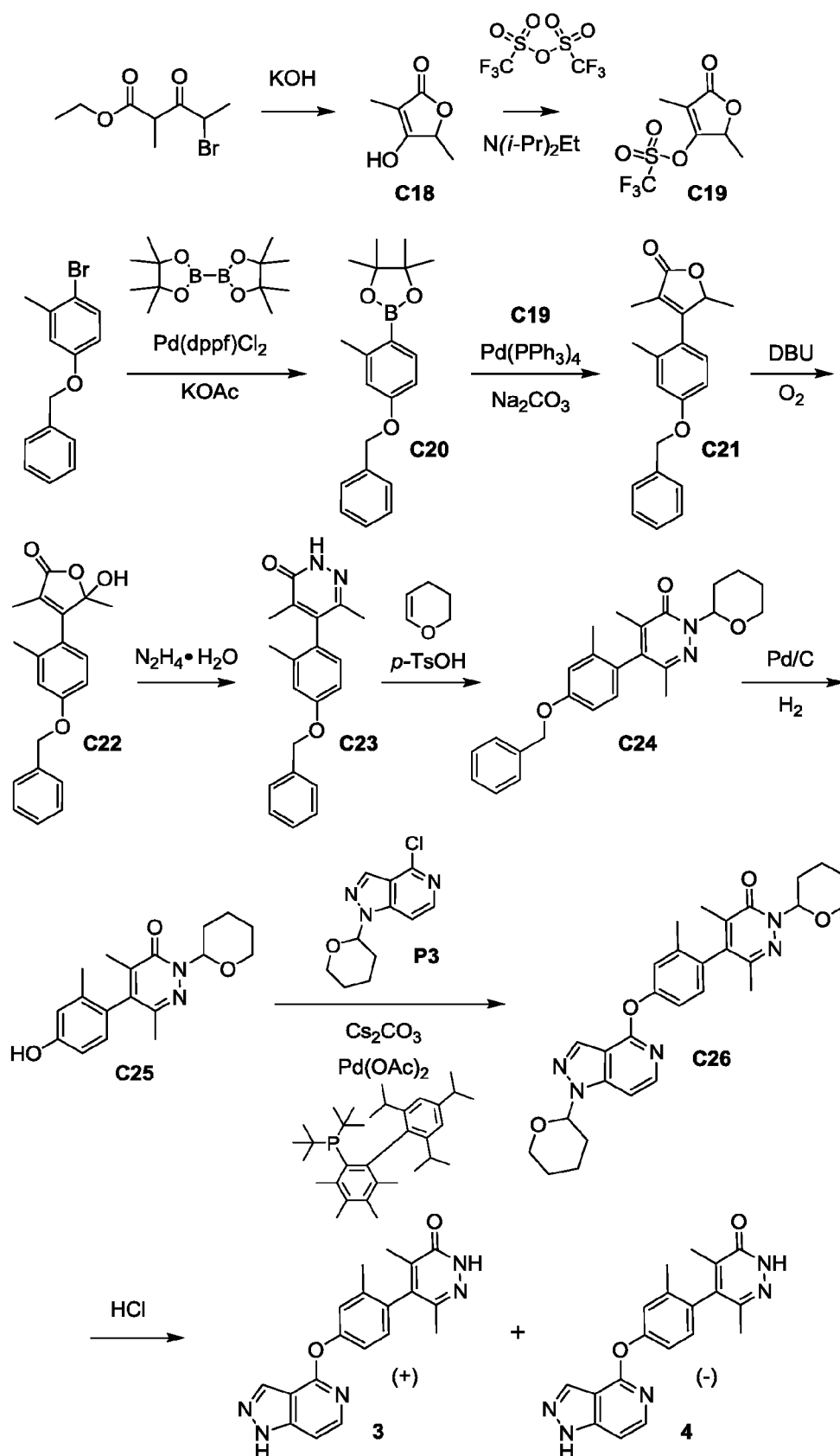
To a mixture of **C15** (100 mg, 0.231 mmol), 1,4-dioxane (2 mL) and water (0.5 mL) was added 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (56 mg, 0.25 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (25.6 mg, 0.0350 mmol) and potassium carbonate (97 mg, 0.70 mmol) at room temperature. The reaction mixture was stirred at 120 °C for 1 hour; after cooling to room temperature, the mixture was filtered and the filtrate was concentrated *in vacuo*. Purification via preparative thin layer chromatography on silica gel (Eluent: 1:1 petroleum ether/ ethyl acetate) provided the product as a red oil. Yield: 51 mg, 0.11 mmol, 48%. ¹H NMR (400 MHz, CD₃OD) δ 7.80 (d, *J*=6.0 Hz, 1H), 7.43 (d, *J*=3.3 Hz, 1H), 7.37-7.40 (m, 2H), 7.21 (d, *J*=8.3 Hz, 1H), 7.16 (br d, *J*=2.0 Hz, 1H), 7.08 (br dd, *J*=8.3, 2.5 Hz, 1H), 6.61 (d, *J*=3.3 Hz, 1H), 5.60 (s, 2H), 3.61 (s, 3H), 3.51-3.57 (m, 2H), 2.09 (s, 3H), 1.91 (s, 3H), 0.85-0.91 (m, 2H), -0.06 (s, 9H).

Step 3. Synthesis of 4-[4-(1,4-dimethyl-1H-pyrazol-5-yl)-3-methylphenoxy]-1H-pyrrolo[3,2-c]pyridine (**2**).

A solution of **C16** (51 mg, 0.11 mmol) in trifluoroacetic acid (2 mL) was stirred at 80 °C for 1 hour. After cooling to room temperature, the mixture was concentrated *in vacuo* to afford {4-[4-(1,4-dimethyl-1H-pyrazol-5-yl)-3-methylphenoxy]-1H-pyrrolo[3,2-c]pyridin-1-yl}methanol (**C17**) (38 mg, 100%), which was combined with potassium carbonate (100 mg), acetonitrile (2 mL) and water (0.3 mL). This reaction mixture was stirred at 80 – 85 °C for 24 hours. The reaction mixture was cooled to room temperature and concentrated under reduced pressure; purification by preparative thin layer chromatography on silica gel (Eluent: 1:3 petroleum ether / ethyl acetate) provided the product as a white solid. Yield: 16 mg, 50 μmol, 45%. LCMS *m/z* 318.9 [M+H⁺]. ¹H NMR (400 MHz, CD₃OD) δ 7.71 (d, *J*=5.5 Hz, 1H), 7.38 (s, 1H), 7.32 (d, *J*=3.5 Hz, 1H), 7.23 (d, *J*=6.0 Hz, 1H), 7.20 (d, *J*=8.5 Hz, 1H), 7.14 (d, *J*=2.5 Hz, 1H), 7.06 (dd, *J*=8.3, 2.3 Hz, 1H), 6.53 (d, *J*=3.0 Hz, 1H), 3.60 (s, 3H), 2.09 (s, 3H), 1.91 (s, 3H).

Examples 3 and 4

(+)-4,6-Dimethyl-5-[2-methyl-4-(1H-pyrazolo[4,3-c]pyridin-4-yloxy)phenyl]pyridazin-3(2H)-one (**3**) and (-)-4,6-Dimethyl-5-[2-methyl-4-(1H-pyrazolo[4,3-c]pyridin-4-yloxy)phenyl]pyridazin-3(2H)-one (**4**)



Step 1. Synthesis of 4-hydroxy-3,5-dimethylfuran-2(5H)-one (**C18**).

- 5 Methylation of ethyl 3-oxopentanoate according to the method of D. Kalaitzakis et al., *Tetrahedron: Asymmetry* **2007**, 18, 2418-2426, afforded ethyl 2-methyl-3-oxopentanoate;

subsequent treatment with 1 equivalent of bromine in chloroform provided ethyl 4-bromo-2-methyl-3-oxopentanoate. This crude material (139 g, 586 mmol) was slowly added to a 0 °C solution of potassium hydroxide (98.7 g, 1.76 mol) in water (700 mL). The internal reaction temperature rose to 30 °C during the addition. The reaction mixture was subjected to vigorous stirring for 4 hours in an ice bath, at which point it was acidified via slow addition of concentrated hydrochloric acid. After extraction with ethyl acetate, the aqueous layer was saturated with solid sodium chloride and extracted three additional times 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 to afford a mixture of oil and solid (81.3 g). This material was suspended in chloroform (200 mL); the solids were removed via filtration and washed with chloroform (2 x 50 mL). The combined filtrates were concentrated *in vacuo* and treated with a 3:1 mixture of heptane and diethyl ether (300 mL). The mixture was vigorously swirled until some of the oil began to solidify. It was then concentrated under reduced pressure to afford an oily solid (60.2 g). After addition of a 3:1 mixture of heptane and diethyl ether (300 mL) and vigorous stirring for 10 minutes, the solid was collected by filtration to afford the product as an off-white solid. Yield: 28.0 g, 219 mmol, 37%. ¹H NMR (400 MHz, CDCl₃) δ 4.84 (br q, *J*=6.8 Hz, 1H), 1.74 (br s, 3H), 1.50 (d, *J*=6.8 Hz, 3H).

Step 2. Synthesis of 2,4-dimethyl-5-oxo-2,5-dihydrofuran-3-yl trifluoromethanesulfonate (C19)

Trifluoromethanesulfonic anhydride (23.7 mL, 140 mmol) was added portion-wise to a solution of **C18** (15.0 g, 117 mmol) and *N,N*-diisopropylethylamine (99%, 24.8 mL, 140 mmol) in dichloromethane (500 mL) at -20 °C, at a rate sufficient to maintain the internal reaction temperature below -10 °C. The reaction mixture was stirred at -20 °C, and allowed to warm gradually to 0 °C over 5 hours. The reaction mixture was then passed through a plug of silica gel, dried over magnesium sulfate, and concentrated *in vacuo*. The residue was suspended in diethyl ether and filtered; the filtrate was concentrated under reduced pressure. Purification using silica gel chromatography (Gradient: 0% to 17% ethyl acetate in heptane) afforded the product as a pale yellow oil. Yield: 21.06 g, 80.94 mmol, 69%. ¹H NMR (400 MHz, CDCl₃) δ 5.09-5.16 (m, 1H), 1.94-1.96 (m, 3H), 1.56 (d, *J*=6.6 Hz, 3H).

Step 3. Synthesis of 2-[4-(benzyloxy)-2-methylphenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (C20).

Benzyl 4-bromo-3-methylphenyl ether (19 g, 69 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (7.5 g, 10.2 mmol), potassium acetate (26.9 g, 274 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (20 g, 79 mmol) were combined in 1,4-dioxane (500 mL) and heated at reflux for 2 hours. The reaction mixture was filtered through Celite; the filtrate was concentrated *in vacuo* and purified by silica gel chromatography (Gradient: 0% to 1% ethyl acetate in petroleum ether) to afford the product as a yellow gel. Yield: 15 g, 46 mmol, 67%. ¹H NMR (400 MHz, CDCl₃) δ 7.73 (d, *J*=8.0 Hz, 1H), 7.30-7.46 (m, 5H), 6.76-6.82 (m, 2H), 5.08 (s, 2H), 2.53 (s, 3H), 1.34 (s, 12H).

Step 4. Synthesis of 4-[4-(benzyloxy)-2-methylphenyl]-3,5-dimethylfuran-2(5H)-one (C21).

C19 (5.0 g, 19 mmol), **C20** (7.48 g, 23.1 mmol), tetrakis(triphenylphosphine)palladium(0) (2.22 g, 1.92 mmol) and sodium carbonate (4.07 g, 38.4 mmol) were combined in 1,4-dioxane (100 mL) and water (5 mL), and heated at reflux for 2 hours. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. Purification using silica gel chromatography (Eluents: 10:1, then 5:1 petroleum ether / ethyl acetate) provided the product as a white solid. Yield: 5.8 g, 19 mmol, 100%. NMR (400 MHz, CDCl₃) δ 7.33-7.49 (m, 5H), 6.98 (d, *J*=8.5 Hz, 1H), 6.94 (br d, *J*=2.5 Hz, 1H), 6.88 (br dd, *J*=8.3, 2.5 Hz, 1H), 5.20 (qq, *J*=6.7, 1.8 Hz, 1H), 5.09 (s, 2H), 2.21 (s, 3H), 1.78 (d, *J*=1.8 Hz, 3H), 1.31 (d, *J*=6.8 Hz, 3H).

Step 5. Synthesis of 4-[4-(benzyloxy)-2-methylphenyl]-5-hydroxy-3,5-dimethylfuran-2(5H)-one (C22).

A solution of **C21** (5.4 g, 18 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 13.3 g, 87.4 mmol) in acetonitrile (100 mL) was cooled to -60 °C. Oxygen was bubbled into the reaction mixture for 20 minutes at -60 °C; the solution was then stirred at 50 °C for 18 hours. The reaction mixture was concentrated *in vacuo* and purified via silica gel chromatography (Eluent: 5:1 petroleum ether / ethyl acetate) to provide the product as a colorless oil. Yield: 3.5 g, 11 mmol, 61%. ¹H NMR (400 MHz, CDCl₃), characteristic peaks: δ 7.33-7.49 (m, 5H), 6.92-6.96 (m, 1H), 6.88 (dd, *J*=8.5, 2.5 Hz, 1H), 5.09 (s, 2H), 2.20 (s, 3H), 1.73 (s, 3H).

Step 6. Synthesis of 5-[4-(benzyloxy)-2-methylphenyl]-4,6-dimethylpyridazin-3(2H)-one (C23).

A mixture of **C22** (3.5 g, 11 mmol) and hydrazine hydrate (85% in water, 1.9 g, 32 mmol) in *n*-butanol (60 mL) was heated at reflux for 18 hours. After removal of volatiles under reduced pressure, the residue was stirred with ethyl acetate (20 mL) for 30 minutes, whereupon filtration provided the product as a white solid. Yield: 2.0 g, 6.2 mmol, 56%. ¹H NMR (400 MHz, CDCl₃) δ 10.93 (br s, 1H), 7.33-7.51 (m, 5H), 6.96 (s, 1H), 6.88-6.94 (m, 2H), 5.10 (s, 2H), 2.04 (s, 3H), 1.95 (s, 3H), 1.91 (s, 3H).

Step 7. Synthesis of 5-[4-(benzyloxy)-2-methylphenyl]-4,6-dimethyl-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (C24).

A mixture of **C23** (1.04 g, 3.25 mmol), 3,4-dihydro-2H-pyran (12.3 g, 1.46 mmol) and *p*-toluenesulfonic acid (59.4 mg, 0.652 mmol) in tetrahydrofuran (100 mL) was heated at reflux for 24 hours. The reaction mixture was then concentrated *in vacuo* and partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. Silica gel chromatography (Gradient: 0% to 40% ethyl acetate in heptane) afforded the product as a gum, presumed to be a mixture of diastereomeric atropisomers from the ¹H NMR spectrum. Yield: 560 mg, 1.38 mmol, 42%. LCMS *m/z* 405.3 [M+H⁺]. ¹H NMR (400 MHz, CDCl₃), characteristic peaks: δ 7.33-7.49 (m, 5H), 6.83-6.95 (m, 3H), 6.12-6.17 (m, 1H), 5.09 (s, 2H), 4.15-4.24 (m, 1H), 3.76-3.85 (m, 1H), 2.29-2.41 (m, 1H), 2.02 and 2.04 (2 s, total 3H), 1.98 and 1.98 (2 s, total 3H), 1.89 and 1.89 (2 s, total 3H).

Step 8. Synthesis of 5-(4-hydroxy-2-methylphenyl)-4,6-dimethyl-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (C25).

Palladium (10% on carbon, 1.16 g, 1.09 mmol) was added to a solution of **C24** (1.47 g, 3.63 mmol) in methanol (30 mL) and ethyl acetate (10 mL), and the mixture was hydrogenated (50 psi) on a Parr shaker for 18 hours at room temperature. The reaction mixture was filtered through Celite, and the filter pad was rinsed with ethyl acetate; the combined filtrates were concentrated *in vacuo* and triturated with heptane, affording the product as a white solid, judged to be a mixture of diastereomeric atropisomers from the ¹H NMR spectrum. Yield: 1.01 g, 3.21 mmol, 88%. ¹H NMR (400 MHz, CDCl₃), characteristic peaks: δ 6.74-6.85 (m, 3H), 6.12-6.17 (m, 1H), 4.15-4.23 (m, 1H), 3.76-3.84 (m, 1H), 2.28-2.41 (m, 1H), 1.99 and 2.01 (2 s, total 3H), 1.97 and 1.98 (2 s, total 3H), 1.89 and 1.89 (2 s, total 3H).

Step 9. Synthesis of 4,6-dimethyl-5-(2-methyl-4-[[1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[4,3-c]pyridin-4-yl]oxy]phenyl)-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (C26).

Cesium carbonate (2.06 g, 6.32 mmol) was added to a solution of **P3** (550 mg, 2.31 mmol) and **C25** (662 mg, 2.10 mmol) in 1,4-dioxane (40 mL). After addition of palladium(II) acetate (48 mg, 0.21 mmol), the reaction mixture was purged with nitrogen for 10 minutes. Di-*tert*-butyl[3,4,5,6-tetramethyl-2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane (97%, 210 mg, 0.42 mmol) was introduced, and the reaction mixture was briefly purged with nitrogen, then heated at 100 °C for 3.5 hours. After the reaction mixture had been cooled and filtered through Celite, the filter pad was thoroughly rinsed with ethyl acetate, and the combined filtrates were concentrated *in vacuo*. Silica gel chromatography (Eluents: 10%, then 30%, then 50%, then 90% ethyl acetate in heptane) afforded the product as a tan solid, judged to be a mixture of diastereomeric atropisomers from its ¹H NMR spectrum. Yield: 690 mg, 1.34 mmol, 58%. LCMS *m/z* 516.3 [M+H⁺]. ¹H NMR (400 MHz, CDCl₃), characteristic peaks: δ 8.09 (s, 1H), 7.97 (d, *J*=6.0 Hz, 1H), 7.25 (d, *J*=6.0 Hz, 1H), 7.17-7.24 (m, 2H), [7.04 (d, *J*=8.2 Hz) and 7.00 (d, *J*=8.2 Hz), total 1H], 6.16 (br d, *J*=10.7 Hz, 1H), 5.72 (dd, *J*=9.4, 2.5 Hz, 1H), 4.16-4.24 (m, 1H), 4.03-4.10 (m, 2H), 3.73-3.85 (m, 2H), 2.48-2.59 (m, 1H), 2.29-2.43 (m, 1H), 2.04 (br s, 3H), 1.95 (2 s, total 3H).

Step 10. Synthesis of (+)-4,6-dimethyl-5-[2-methyl-4-(1H-pyrazolo[4,3-c]pyridin-4-yloxy)phenyl]pyridazin-3(2H)-one (3) and (-)-4,6-dimethyl-5-[2-methyl-4-(1H-pyrazolo[4,3-c]pyridin-4-yloxy)phenyl]pyridazin-3(2H)-one (4).

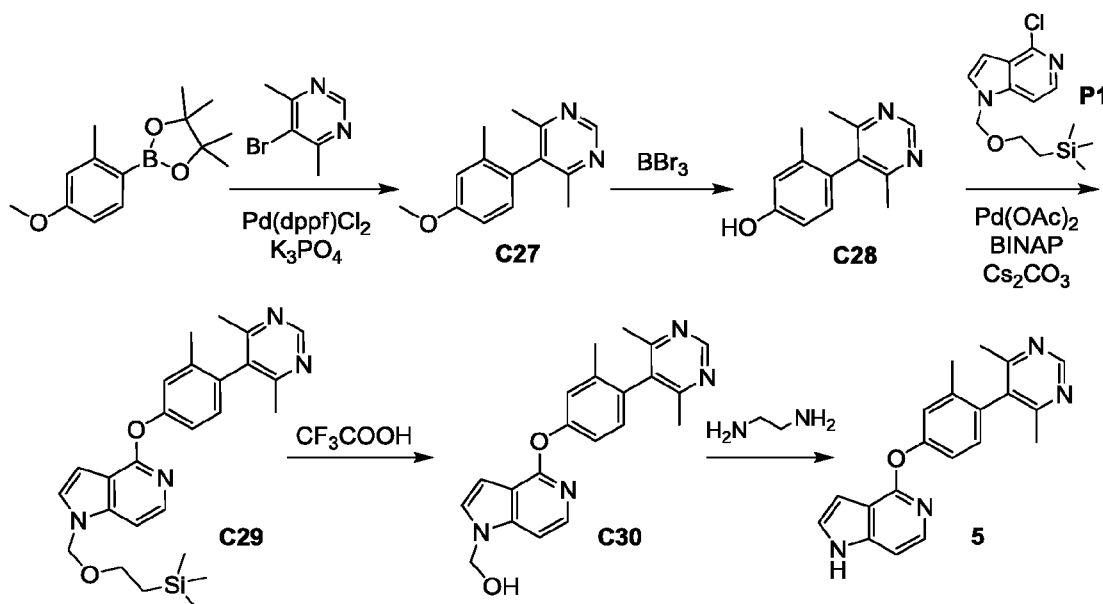
C26 (807 mg, 1.56 mmol) was dissolved in 1,4-dioxane (80 mL) and dichloromethane (80 mL). A solution of hydrogen chloride in 1,4-dioxane (4 M, 39.0 mL, 156 mmol) was added, and the reaction mixture was allowed to stir at room temperature for 18 hours. After removal of solvent *in vacuo*, the residue was partitioned between saturated aqueous sodium bicarbonate solution and ethyl acetate. The aqueous layer was extracted twice with ethyl acetate, and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. Trituration with diethyl ether afforded racemic 4,6-dimethyl-5-[2-methyl-4-(1H-pyrazolo[4,3-c]pyridin-4-yloxy)phenyl]pyridazin-3(2H)-one as a white solid. Yield: 396 mg,

1.14 mmol, 73%. LCMS m/z 348.1 $[M+H]^+$. Separation into atropenantiomers was carried out using supercritical fluid chromatography (Column: Chiral Technologies, Chiralcel OJ-H, 5 μ m; Eluent: 1:3 methanol / carbon dioxide). The first-eluting product, obtained as an off-white solid, which exhibited a positive (+) rotation, was designated as compound Example 3. Yield: 155 mg,

0.446 mmol, 28%. LCMS m/z 348.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 7.86 (d, $J=6.2$ Hz, 1H), 7.26-7.30 (m, 2H), 7.22 (br dd, half of ABX pattern, $J=8.2$, 2.3 Hz, 1H), 7.17 (d, half of AB quartet, $J=8.2$ Hz, 1H), 2.11 (s, 3H), 2.03 (s, 3H), 1.93 (s, 3H). Retention time: 5.47 minutes (Column: Chiral Technologies, Chiralcel OJ-H, 250 x 4.6 mm, 5 μ m; Eluent: 1:3 methanol / carbon dioxide; Flow rate: 2.5 mL/minute). The second-eluting product, also an off-white solid, which exhibited a negative (-) rotation, was designated as compound Example 4. Yield: 159 mg, 0.458 mmol, 29%. LCMS m/z 348.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1H), 7.86 (d, $J=6.0$ Hz, 1H), 7.26-7.30 (m, 2H), 7.22 (br dd, half of ABX pattern, $J=8.2$, 2.3 Hz, 1H), 7.17 (d, half of AB quartet, $J=8.2$ Hz, 1H), 2.11 (s, 3H), 2.03 (s, 3H), 1.93 (s, 3H). Retention time: 5.86 minutes (HPLC conditions identical to those used for Example 3 above).

Example 5

4-[4-(4,6-Dimethylpyrimidin-5-yl)-3-methylphenoxy]-1H-pyrrolo[3,2-c]pyridine (5)



Step 1. Synthesis of 5-(4-methoxy-2-methylphenyl)-4,6-dimethylpyrimidine (C27).

1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)-dichloromethane complex (5 g, 6 mmol) was added to a degassed mixture of 2-(4-methoxy-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30 g, 120 mmol), 5-bromo-4,6-dimethylpyrimidine (22.5 g, 120 mmol), and potassium phosphate (76.3 g, 359 mmol) in 1,4-dioxane (300 mL) and water (150 mL). The reaction mixture was heated at reflux for 4 hours, whereupon it was filtered and concentrated *in vacuo*. Purification via silica gel chromatography (Gradient: ethyl acetate in petroleum ether) provided the product as a brown solid. Yield: 25 g, 110 mmol, 92%. LCMS m/z

229.3 [M+H⁺]. ¹H NMR (300 MHz, CDCl₃) δ 8.95 (s, 1H), 6.94 (d, *J*=8.2 Hz, 1H), 6.87-6.89 (m, 1H), 6.84 (dd, *J*=8.3, 2.5 Hz, 1H), 3.86 (s, 3H), 2.21 (s, 6H), 1.99 (s, 3H).

Step 2. Synthesis of 4-(4,6-dimethylpyrimidin-5-yl)-3-methylphenol (C28).

Boron tribromide (3.8 mL, 40 mmol) was added drop-wise to a solution of **C27** (3.0 g, 13 mmol) in dichloromethane (150 mL) at -70 °C. The reaction mixture was stirred at room temperature for 16 hours, then adjusted to pH 8 with saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane (3 x 200 mL), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Silica gel chromatography (Gradient: 60% to 90% ethyl acetate in petroleum ether) afforded the product as a yellow solid. Yield: 1.2 g, 5.6 mmol, 43%. LCMS *m/z* 215.0 [M+H⁺]. ¹H NMR (400 MHz, CDCl₃) δ 8.98 (s, 1H), 6.89 (d, *J*=8.0 Hz, 1H), 6.86 (d, *J*=2.3 Hz, 1H), 6.80 (dd, *J*=8.3, 2.5 Hz, 1H), 2.24 (s, 6H), 1.96 (s, 3H).

Step 3. Synthesis of 4-[4-(4,6-dimethylpyrimidin-5-yl)-3-methylphenoxy]-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrrolo[3,2-c]pyridine (C29).

To a mixture of **C28** (390 mg, 1.82 mmol) and 1,4-dioxane (10 mL) was added **P1** (566 mg, 2.0 mmol), palladium(II) acetate (40 mg, 0.18 mmol), 1,1'-binaphthalene-2,2'-diylbis(diphenylphosphane) (224 mg, 0.360 mmol) and cesium carbonate (1.76 g, 5.40 mmol). The reaction mixture was stirred at 120 °C for 2 hours, whereupon it was cooled to room temperature, filtered, and concentrated *in vacuo*. Silica gel chromatography (Eluent: 70:1 dichloromethane / methanol) provided the product as a red oil. Yield: 620 mg, 1.35 mmol, 74%. ¹H NMR (400 MHz, CD₃OD) δ 8.89 (s, 1H), 7.81 (d, *J*=6.0 Hz, 1H), 7.43 (d, *J*=3.3 Hz, 1H), 7.39 (br d, *J*=6 Hz, 1H), 7.18-7.20 (m, 1H), 7.15 (d, half of AB quartet, *J*=8.3 Hz, 1H), 7.11 (dd, half of ABX pattern, *J*=8.3, 2.3 Hz, 1H), 6.60 (d, *J*=3.3 Hz, 1H), 5.60 (s, 2H), 3.52-3.58 (m, 2H), 2.28 (s, 6H), 2.02 (s, 3H), 0.85-0.91 (m, 2H), -0.06 (s, 9H).

Step 4. Synthesis of 4-[4-(4,6-dimethylpyrimidin-5-yl)-3-methylphenoxy]-1H-pyrrolo[3,2-c]pyridin-1-yl}methanol (C30).

A solution of **C29** (430 mg, 0.93 mmol) in trifluoroacetic acid (3 mL) was stirred at 80 °C for 1 hour. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated *in vacuo*. Chromatography on silica gel (Gradient: 3% to 9% methanol in dichloromethane) provided the product as a yellow solid. Yield: 330 mg, 0.92 mmol, 99%.

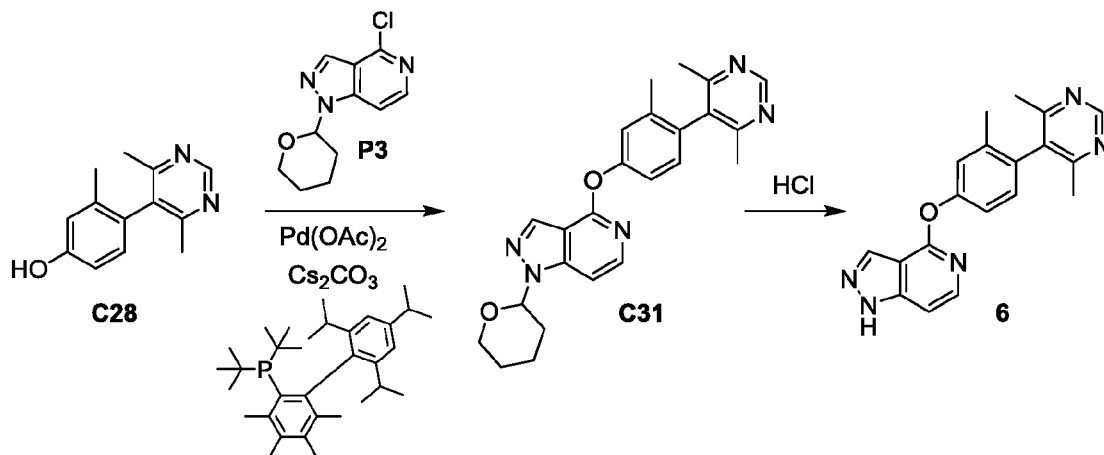
Step 5. Synthesis of 4-[4-(4,6-dimethylpyrimidin-5-yl)-3-methylphenoxy]-1H-pyrrolo[3,2-c]pyridine (5)

To a solution of **C30** (330 mg, 0.92 mmol) in methanol (8 mL) was added ethane-1,2-diamine (300 mg, 5.0 mmol), and the reaction mixture was stirred at 45 °C for 1 hour. After cooling to room temperature, the mixture was concentrated *in vacuo* and purified using silica gel chromatography (Eluent: 20:1 dichloromethane / methanol) to afford the product as a white solid. Yield: 256 mg, 0.775 mmol, 84%. LCMS *m/z* 331.1 [M+H⁺]. ¹H NMR (400 MHz, CD₃OD) δ 8.89 (s, 1H), 7.73 (d, *J*=5.8 Hz, 1H), 7.32 (d, *J*=3.0 Hz, 1H), 7.23 (dd, *J*=5.9, 0.9 Hz, 1H), 7.17

(br d, $J=2$ Hz, 1H), 7.13 (d, half of AB quartet, $J=8.3$ Hz, 1H), 7.09 (br dd, half of ABX pattern, $J=8.2, 2.4$ Hz, 1H), 6.52 (dd, $J=3.3, 0.8$ Hz, 1H), 2.28 (s, 6H), 2.02 (br s, 3H).

Example 6

4-[4-(4,6-Dimethylpyrimidin-5-yl)-3-methylphenoxy]-1H-pyrazolo[4,3-c]pyridine (**6**)



Step 1. Synthesis of 4-[4-(4,6-dimethylpyrimidin-5-yl)-3-methylphenoxy]-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[4,3-c]pyridine (**C31**).

Cesium carbonate (1.03 g, 3.16 mmol) and palladium(II) acetate (24 mg, 0.11 mmol) were added to a solution of **C28** (225 mg, 1.05 mmol) and **P3** (250 mg, 1.05 mmol) in 1,4-dioxane (10 mL) in a sealable reaction vessel, and the solution was purged with nitrogen for 10 minutes. Di-*tert*-butyl[3,4,5,6-tetramethyl-2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane (97%, 104 mg, 0.210 mmol) was added, and the reaction mixture was briefly purged with nitrogen. The vessel was sealed and the reaction mixture was stirred at 100 °C for 3 hours. After cooling to room temperature, the mixture was filtered through Celite and the filter pad was washed with ethyl acetate; the combined filtrates were concentrated *in vacuo* and purified via silica gel chromatography (Eluents: 20%, then 50%, then 100% ethyl acetate in heptane). The product was obtained as an off-white solid. Yield: 272 mg, 0.655 mmol, 62%. LCMS m/z 416.5 [$M+H^+$]. ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.11 (d, $J=0.6$ Hz, 1H), 7.99 (d, $J=6.0$ Hz, 1H), 7.25-7.27 (m, 2H, assumed; partially obscured by solvent peak), 7.20-7.24 (m, 1H), 7.10 (d, $J=8.4$ Hz, 1H), 5.73 (dd, $J=9.4, 2.5$ Hz, 1H), 4.04-4.10 (m, 1H), 3.74-3.82 (m, 1H), 2.49-2.59 (m, 1H), 2.28 (s, 6H), 2.08-2.21 (m, 2H), 2.04 (s, 3H), 1.66-1.84 (s, 3H).

Step 2. Synthesis of 4-[4-(4,6-dimethylpyrimidin-5-yl)-3-methylphenoxy]-1H-pyrazolo[4,3-c]pyridine (**6**).

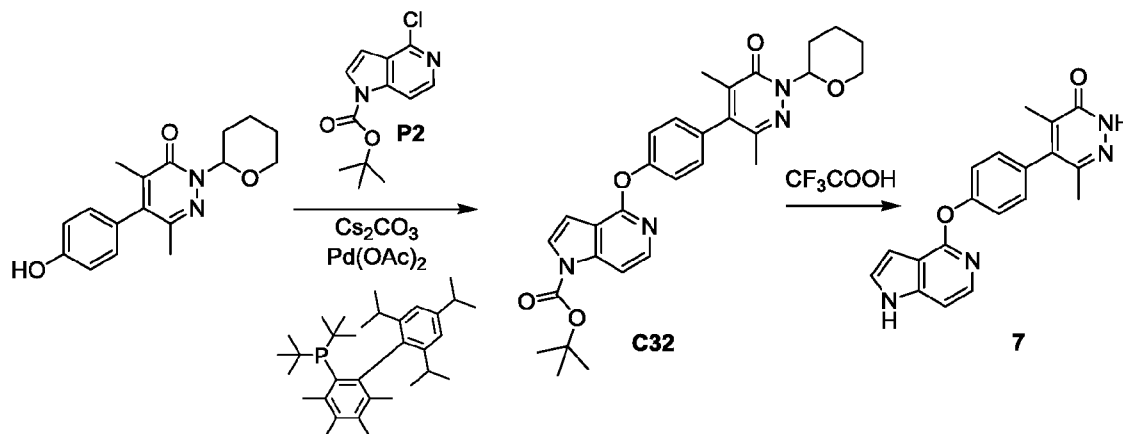
C31 (172 mg, 0.414 mmol) was dissolved in 1,4-dioxane (5 mL) and dichloromethane (5 mL), and cooled to 0 °C. A solution of hydrogen chloride in 1,4-dioxane (4 M, 1.04 mL, 4.16 mmol) was added, and the reaction mixture was allowed to stir at room temperature for 45 hours. After removal of solvent *in vacuo*, the residue was partitioned between saturated aqueous sodium bicarbonate solution and dichloromethane. The aqueous layer was extracted twice with dichloromethane, and the combined organic layers were dried over sodium sulfate,

filtered, and concentrated under reduced pressure, affording the product as an off-white solid. Yield: 130 mg, 0.392 mmol, 95%. LCMS m/z 332.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.20 (br s, 1H), 7.99 (d, $J=6.0$ Hz, 1H), 7.28-7.30 (m, 1H), 7.23-7.27 (m, 1H), 7.16 (dd, $J=6.0, 1.0$ Hz, 1H), 7.11 (d, $J=8.2$ Hz, 1H), 2.28 (s, 6H), 2.05 (s, 3H).

5

Example 7

4,6-Dimethyl-5-[4-(1H-pyrrolo[3,2-c]pyridin-4-yloxy)phenyl]pyridazin-3(2H)-one (7)



Step 1. Synthesis of tert-butyl 4-[4-[3,5-dimethyl-6-oxo-1-(tetrahydro-2H-pyran-2-yl)-1,6-dihydropyridazin-4-yl]phenoxy]-1H-pyrrolo[3,2-c]pyridine-1-carboxylate (C32).

10 A mixture of 5-(4-hydroxyphenyl)-4,6-dimethyl-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (prepared in a manner analogous to **C25** in Examples 3 and 4) (600 mg, 2.00 mmol), **P2** (757 mg, 3.00 mmol), cesium carbonate (1.95 g, 5.99 mmol), palladium(II) acetate (44 mg, 0.20 mmol) and di-*tert*-butyl[3,4,5,6-tetramethyl-2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane (97%, 200 mg, 0.40 mmol) in 1,4-dioxane (15 mL) was purged with nitrogen for 10 minutes, and
15 then heated at 80 °C for 18 hours. After filtration, the filtrate was diluted with water and extracted several times with ethyl acetate. The combined organic layers were washed with water, washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification via silica gel chromatography (Gradient: 25% to 50% ethyl acetate in heptane) provided the product as a white solid. Yield: 860 mg, 1.66 mmol,
20 83%. LCMS m/z 517.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$), characteristic peaks: δ 8.04 (d, $J=5.8$ Hz, 1H), 7.80 (br d, $J=5.8$ Hz, 1H), 7.62 (d, $J=3.7$ Hz, 1H), 7.31-7.36 (m, 2H), 7.11-7.19 (m, 2H), 6.75 (dd, $J=3.7, 0.6$ Hz, 1H), 6.15 (dd, $J=10.7, 2.0$ Hz, 1H), 4.15-4.21 (m, 1H), 3.76-3.84 (m, 1H), 2.29-2.41 (m, 1H), 2.12 (s, 3H), 2.01 (s, 3H), 1.71 (s, 9H).

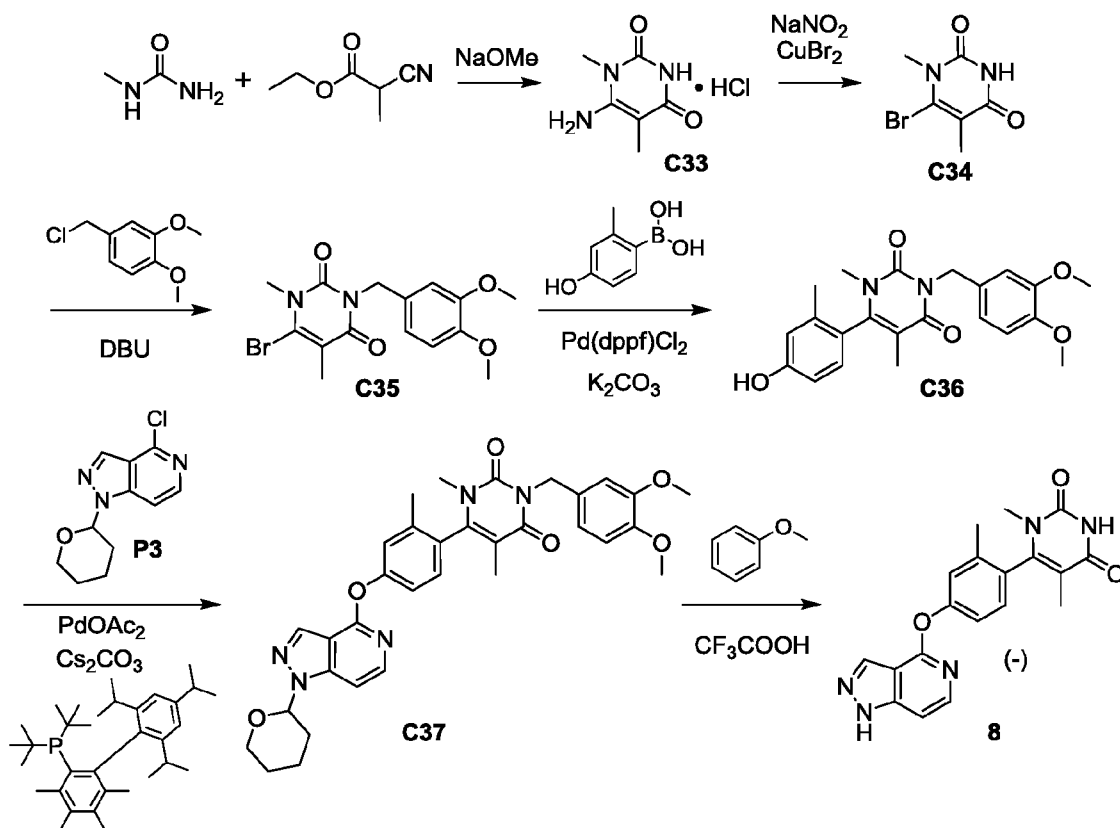
Step 2. Synthesis of 4,6-dimethyl-5-[4-(1H-pyrrolo[3,2-c]pyridin-4-yloxy)phenyl]pyridazin-3(2H)-one (7).

25 Trifluoroacetic acid (5 mL) was added to a solution of **C32** (850 mg, 1.64 mmol) in dichloromethane (15 mL), and the reaction mixture was allowed to stir at room temperature for 18 hours. After removal of volatiles under reduced pressure, the residue was dissolved in saturated aqueous sodium bicarbonate solution and extracted several times with ethyl acetate.
30 The combined organic layers were washed with water, washed with saturated aqueous sodium

chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting material was suspended in ethyl acetate, stirred for 10 minutes and filtered, affording the product as a white solid. Yield: 280 mg, 0.842 mmol, 51%. LCMS m/z 333.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 12.77 (br s, 1H), 11.69 (br s, 1H), 7.72 (d, $J=5.8$ Hz, 1H), 7.43 (dd, $J=3.2, 2.3$ Hz, 1H), 7.29 (s, 4H), 7.20 (dd, $J=5.8, 0.9$ Hz, 1H), 6.55 (ddd, $J=3.2, 2.0, 0.9$ Hz, 1H), 1.97 (s, 3H), 1.83 (s, 3H).

Example 8

(-)-1,5-Dimethyl-6-[2-methyl-4-(1H-pyrazolo[4,3-c]pyridin-4-yloxy)phenyl]pyrimidine-2,4(1H,3H)-dione (**8**)



Step 1. Synthesis of 6-amino-1,5-dimethylpyrimidine-2,4(1H,3H)-dione, hydrochloride salt (**C33**).

A solution of sodium methoxide in methanol (4.4 M, 27 mL, 119 mmol) was added to a solution of ethyl 2-cyanopropanoate (95%, 13.2 mL, 99.6 mmol) and 1-methylurea (98%, 8.26 g, 109 mmol) in methanol (75 mL), and the reaction mixture was heated at reflux for 18 hours, then cooled to room temperature. After removal of solvent *in vacuo*, the residue was repeatedly evaporated under reduced pressure with acetonitrile (3 x 50 mL), then partitioned between acetonitrile (100 mL) and water (100 mL). Aqueous 6 M hydrochloric acid was slowly added until the pH had reached approximately 2; the resulting mixture was stirred for one hour. The precipitate was collected via filtration and washed with *tert*-butyl methyl ether, affording the

product as a white solid. Yield: 15.2 g, 79.3 mmol, 80%. LCMS m/z 156.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 10.38 (br s, 1H), 6.39 (s, 2H), 3.22 (s, 3H), 1.67 (s, 3H).

Step 2. Synthesis of 6-bromo-1,5-dimethylpyrimidine-2,4(1H,3H)-dione (C34).

A 1:1 mixture of acetonitrile and water (120 mL) was added to a mixture of **C33** (9.50 g, 49.6 mmol), sodium nitrite (5.24 g, 76 mmol), and copper(II) bromide (22.4 g, 100 mmol), and the reaction mixture was allowed to stir at room temperature for 66 hours. Addition of aqueous sulfuric acid (1 N, 200 mL) and ethyl acetate (100 mL) provided a precipitate, which was collected via filtration and washed with water and ethyl acetate to afford the product as a light yellow solid (7.70 g). The organic layer of the filtrate was concentrated to a smaller volume, during which additional precipitate formed; this was isolated via filtration and washed with 1:1 ethyl acetate / heptane to provide additional product (0.4 g). Total yield: 8.1 g, 37 mmol, 75%. LCMS m/z 217.9 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 11.58 (br s, 1H), 3.45 (s, 3H), 1.93 (s, 3H).

Step 3. Synthesis of 6-bromo-3-(3,4-dimethoxybenzyl)-1,5-dimethylpyrimidine-2,4(1H,3H)-dione (C35).

1,8-Diazabicyclo[5.4.0]undec-7-ene (98%, 5.57 mL, 36.5 mmol) was added to a suspension of **C34** (4.00 g, 18.3 mmol) and 4-(chloromethyl)-1,2-dimethoxybenzene (5.16 g, 27.6 mmol) in acetonitrile (80 mL), and the reaction mixture was heated at 60 °C for 18 hours. After removal of solvent *in vacuo*, the residue was purified via silica gel chromatography (Gradient: 25% to 50% ethyl acetate in heptane) to afford the product as a white solid. Yield: 5.70 g, 15.4 mmol, 84%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.08-7.12 (m, 2H), 6.80 (d, $J=8.0$ Hz, 1H), 5.07 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.65 (s, 3H), 2.14 (s, 3H).

Other suitable protecting groups can also be used to protect the "NH" group of **C34**. For example, SEM, BOM, or Boc can be used instead of the dimethoxybenzyl in **C35**.

Step 4. Synthesis of 3-(3,4-dimethoxybenzyl)-6-(4-hydroxy-2-methylphenyl)-1,5-dimethylpyrimidine-2,4(1H,3H)-dione (C36).

An aqueous solution of potassium carbonate (3.0 M, 3.3 mL, 9.9 mmol) was added to a mixture of **C35** (1.20 g, 3.25 mmol), (4-hydroxy-2-methylphenyl)boronic acid (988 mg, 6.50 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), dichloromethane complex (98%, 271 mg, 0.325 mmol) and 1,4-dioxane (30 mL). After the reaction mixture had been heated at 100 °C for 66 hours, it was cooled to room temperature, diluted with ethyl acetate and water, and filtered through Celite. The organic layer from the filtrate was washed with saturated aqueous sodium bicarbonate solution, washed with saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification using silica gel chromatography (Gradient: 25% to 50% ethyl acetate in heptane) afforded the product as a white foam. Yield: 650 mg, 1.64 mmol, 50%. LCMS m/z 397.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, $J=2.0$ Hz, 1H), 7.19 (dd, $J=8.2, 2.0$ Hz, 1H), 6.92 (d, $J=8.1$ Hz, 1H), 6.81-6.84

(m, 2H), 6.79 (br dd, $J=8.2, 2.5$ Hz, 1H), 5.53 (br s, 1H), 5.17 (AB quartet, $J_{AB}=13.4$ Hz, $\Delta\nu_{AB}=18.8$ Hz, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.03 (s, 3H), 2.10 (br s, 3H), 1.66 (s, 3H).

Alternatively, the free OH group of (4-hydroxy-2-methylphenyl)boronic acid can be protected by a suitable protecting group (e.g., MOM or benzyl) before (4-hydroxy-2-

methylphenyl)boronic acid is coupled to **C35**. In such a case, the product of the coupling reaction can be deprotected to afford **C36**.

Step 5. Synthesis of 3-(3,4-dimethoxybenzyl)-1,5-dimethyl-6-(2-methyl-4-[[1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[4,3-c]pyridin-4-yl]oxy]phenyl)pyrimidine-2,4(1H,3H)-dione (C37).

C36 was converted to the product using the method employed for synthesis of **C26** in Examples 3 and 4. In this case, after filtration through Celite and rinsing of the filter pad with ethyl acetate, the organic layer of the combined filtrates was washed with water, washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification via silica gel chromatography (Gradient: 50% to 100% ethyl acetate in heptanes) provided the product as a tan solid. Yield: 490 mg, 0.820 mmol, 63%.

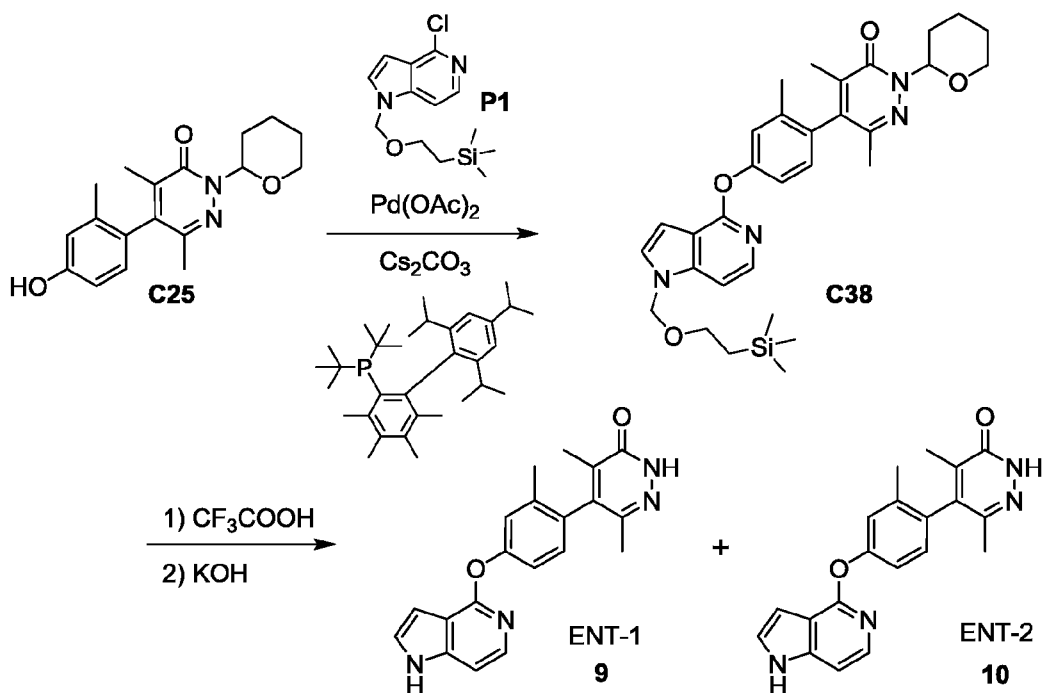
LCMS m/z 598.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$), characteristic peaks: δ 8.06-8.08 (m, 1H), 7.99 (d, $J=6.2$ Hz, 1H), 7.32 (dd, $J=6.2, 0.9$ Hz, 1H), 7.24 (br d, $J=2.0$ Hz, 1H), 7.21 (br dd, $J=8.1, 2.0$ Hz, 1H), 7.15 (d, $J=8.2$ Hz, 1H), 6.84 (d, $J=8.2$ Hz, 1H), 5.74 (dd, $J=9.2, 2.5$ Hz, 1H), 5.18 (AB quartet, $J_{AB}=13.4$ Hz, $\Delta\nu_{AB}=19.1$ Hz, 2H), 4.03-4.09 (m, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.74-3.82 (m, 1H), 3.11 (s, 3H), 2.21 (br s, 3H), 1.71 (s, 3H).

Step 6. Synthesis of (-)-1,5-dimethyl-6-[2-methyl-4-(1H-pyrazolo[4,3-c]pyridin-4-yloxy)phenyl]pyrimidine-2,4(1H,3H)-dione (8).

C37 (490 mg, 0.820 mmol), trifluoroacetic acid (8 mL) and methoxybenzene (0.446 mL, 4.10 mmol) were combined in a pressure tube; the tube was sealed and the reaction mixture was heated at 120 °C for 42 hours. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and partitioned between ethyl acetate (100 mL) and saturated aqueous sodium bicarbonate solution (20 mL). The organic layer was washed sequentially with water (10 mL) and with saturated aqueous sodium chloride solution (10 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. After chromatography on silica gel (Gradient: 65% to 100% ethyl acetate in heptane), the product was subjected to supercritical fluid chromatography on a chiral column. One atropenantiomer was collected, providing the product as a solid; this material exhibited a negative (-) rotation. Yield: 95 mg, 0.26 mmol, 32%. LCMS m/z 364.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (br s, 1H), 8.24 (br s, 1H), 7.98 (d, $J=6.1$ Hz, 1H), 7.27-7.32 (m, 2H, assumed; partially obscured by solvent peak), 7.19 (dd, $J=6.1, 1.0$ Hz, 1H), 7.18 (br d, $J=8$ Hz, 1H), 3.08 (s, 3H), 2.23 (br s, 3H), 1.70 (s, 3H)

Examples 9 and 10

4,6-Dimethyl-5-[2-methyl-4-(1H-pyrrolo[3,2-c]pyridin-4-yloxy)phenyl]pyridazin-3(2H)-one, ENT-1 (**9**) and 4,6-Dimethyl-5-[2-methyl-4-(1H-pyrrolo[3,2-c]pyridin-4-yloxy)phenyl]pyridazin-3(2H)-one, ENT-2 (**10**)



Step 1. Synthesis of 4,6-dimethyl-5-[2-methyl-4-[(1-[[2-(trimethylsilyl)ethoxy]methyl])-1H-pyrrolo[3,2-c]pyridin-4-yl]oxy]phenyl]-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (C38).

C25 was reacted with P1 using the method described for synthesis of C31 in Example 6.

- 5 The product, assigned as a mixture of diastereomeric atropisomers on the basis of its ¹H NMR spectrum, was obtained as a solid. Yield: 53 mg, 94 μmol, 27%. LCMS *m/z* 561.4 [M+H⁺]. ¹H NMR (400 MHz, CDCl₃), characteristic peaks: δ 7.98 (br d, *J*=6 Hz, 1H), 6.96-7.04 (m, 1H), 6.13-6.18 (m, 1H), 5.51 (s, 2H), 4.16-4.24 (m, 1H), 3.77-3.85 (m, 1H), 3.48-3.54 (m, 2H), 2.04 (2 s, total 3H), 1.95 (2 s, total 3H), 0.89-0.94 (m, 2H), -0.03 (s, 9H).
- 10 Step 2. Synthesis of 4,6-dimethyl-5-[2-methyl-4-(1H-pyrrolo[3,2-c]pyridin-4-yloxy)phenyl]pyridazin-3(2H)-one, ENT-1 (9) and 4,6-dimethyl-5-[2-methyl-4-(1H-pyrrolo[3,2-c]pyridin-4-yloxy)phenyl]pyridazin-3(2H)-one, ENT-2 (10).

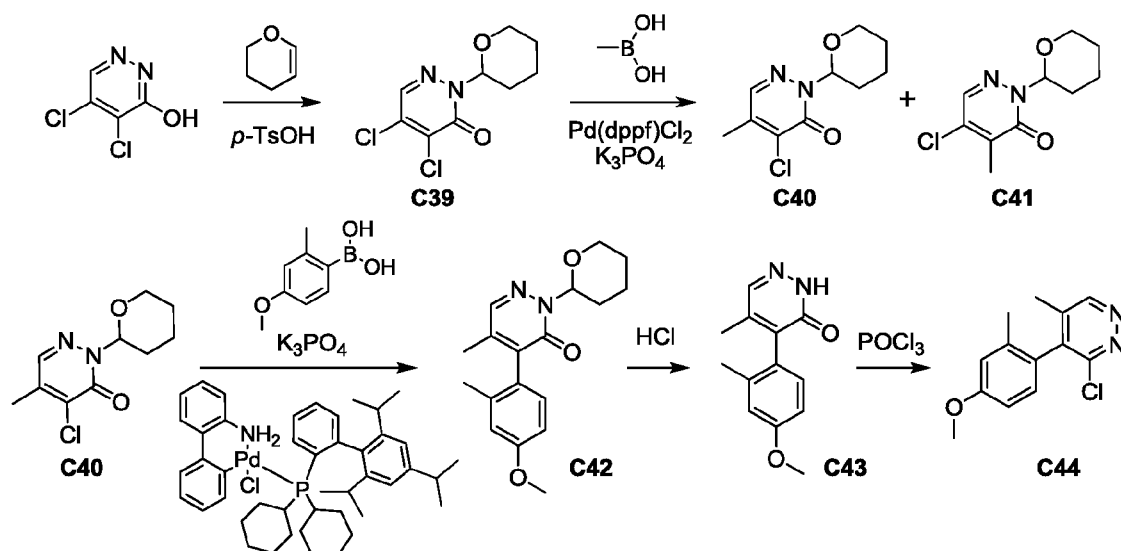
Trifluoroacetic acid (1 mL) was added to a solution of C38 (53 mg, 94 μmol) in dichloromethane (3 mL) and the reaction mixture was stirred at room temperature for 18 hours.

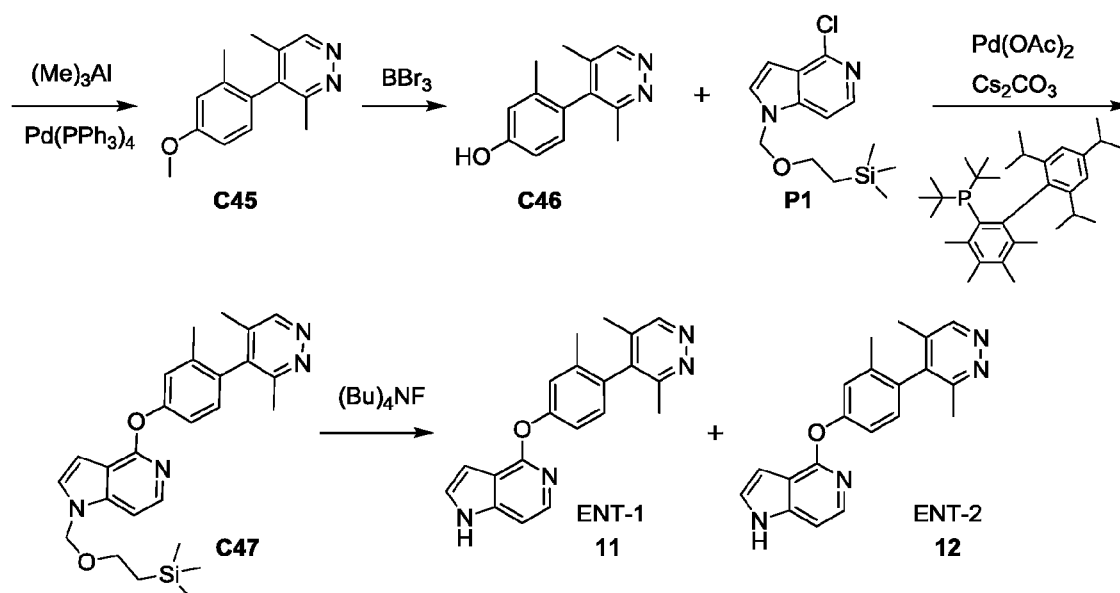
- 15 The solution was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution; the aqueous layer was extracted three times with ethyl acetate, and the combined organic layers were combined, dried, filtered, and concentrated *in vacuo*. The residue was taken up in tetrahydrofuran (5 mL) and water (1 mL), treated with potassium hydroxide (300 mg, 5.3 mmol), and stirred at room temperature for 18 hours. The reaction mixture was then partitioned
- 20 between ethyl acetate and saturated aqueous ammonium chloride solution; the aqueous layer was extracted three times with ethyl acetate, and the combined organic layers were dried, filtered, and concentrated under reduced pressure. The resulting solid (40 mg) was subjected to supercritical fluid chromatography (Column: Chiral Technologies, Chiralpak AS-H, 5 μm, Eluent: 7:3 carbon dioxide / methanol). The first-eluting atropenantiomer, isolated as a solid, was

designated as compound **9**. Yield: 8 mg, 20 μ mol, 20%. LCMS m/z 347.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.78 (br d, $J=5.8$ Hz, 1H), 7.36 (d, $J=3.1$ Hz, 1H), 7.31 (d, $J=6.0$ Hz, 1H), 7.20-7.22 (m, 1H), 7.10-7.16 (m, 2H), 6.39 (d, $J=3.1$ Hz, 1H), 2.08 (s, 3H), 2.02 (s, 3H), 1.92 (s, 3H). Retention time: 4.07 minutes (Column: Chiral Technologies, Chiralpak AS-H, 4.6 x 250 mm, 5 μ m; Eluent: 5% methanol in carbon dioxide for 1.0 minute, followed by a gradient of 5% to 50% methanol in carbon dioxide over 6.0 minutes; Flow rate: 4.0 mL/minute). The second-eluting atropenantiomer, designated as compound **10**, was also obtained as a solid. Yield: 8 mg, 20 μ mol, 20%. LCMS m/z 347.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.88 (br d, $J=6.4$ Hz, 1H), 7.47 (br d, $J=6$ Hz, 1H), 7.45 (d, $J=3.3$ Hz, 1H), 7.34 (br d, $J=2$ Hz, 1H), 7.27 (br dd, half of ABX pattern, $J=8.3, 2.2$ Hz, 1H), 7.21 (d, half of AB quartet, $J=8.4$ Hz, 1H), 6.16 (dd, $J=3.3, 0.6$ Hz, 1H), 2.11 (s, 3H), 2.02 (s, 3H), 1.92 (s, 3H). Retention time: 5.47 minutes (HPLC conditions identical to those described for compound **9**).

Examples 11 and 12

4-[4-(3,5-Dimethylpyridazin-4-yl)-3-methylphenoxy]-1H-pyrrolo[3,2-c]pyridine, ENT-1 (**11**) and 4-[4-(3,5-Dimethylpyridazin-4-yl)-3-methylphenoxy]-1H-pyrrolo[3,2-c]pyridine, ENT-2 (**12**)





Step 1. Synthesis of 4,5-dichloro-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (C39).

A mixture of 4,5-dichloropyridazin-3-ol (42 g, 250 mmol), 3,4-dihydro-2H-pyran (168 g, 2.00 mol) and *p*-toluenesulfonic acid (8.8 g, 51 mmol) in tetrahydrofuran (2 L) was heated at reflux for 2 days. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* and purified by silica gel chromatography (Gradient: 3% to 5% ethyl acetate in petroleum ether). The product was obtained as a white solid. Yield: 42 g, 170 mmol, 68%. ^1H NMR (400 MHz, CDCl_3) δ 7.84 (s, 1H), 6.01 (br d, $J=11$ Hz, 1H), 4.10-4.16 (m, 1H), 3.70-3.79 (m, 1H), 1.99-2.19 (m, 2H), 1.50-1.80 (m, 4H).

Step 2. Synthesis of 4-chloro-5-methyl-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (C40) and 5-chloro-4-methyl-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (C41).

To a mixture of **C39** (40 g, 0.16 mol), methylboronic acid (9.6 g, 0.16 mol) and cesium carbonate (156 g, 479 mmol) in 1,4-dioxane (500 mL) and water (50 mL) was added [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (5 g, 7 mmol). The reaction mixture was stirred at 110 °C for 2 hours, whereupon it was cooled to room temperature and concentrated *in vacuo*. Purification via silica gel chromatography (Gradient: 3% to 6% ethyl acetate in petroleum ether) afforded compound **C40** as a pale yellow solid. Yield: 9.0 g, 39 mmol, 24%. LCMS m/z 250.8 $[\text{M}+\text{Na}^+]$. ^1H NMR (400 MHz, CDCl_3) δ 7.71 (s, 1H), 6.07 (dd, $J=10.7$, 2.1 Hz, 1H), 4.10-4.18 (m, 1H), 3.71-3.81 (m, 1H), 2.30 (s, 3H), 1.98-2.19 (m, 2H), 1.53-1.81 (m, 4H). Also obtained was **C41**, as a pale yellow solid. Yield: 9.3 g, 41 mmol, 26%. LCMS m/z 250.7 $[\text{M}+\text{Na}^+]$. ^1H NMR (400 MHz, CDCl_3) δ 7.77 (s, 1H), 6.02 (dd, $J=10.7$, 2.1 Hz, 1H), 4.10-4.17 (m, 1H), 3.71-3.79 (m, 1H), 2.27 (s, 3H), 1.99-2.22 (m, 2H), 1.51-1.79 (m, 4H).

Step 3. Synthesis of 4-(4-methoxy-2-methylphenyl)-5-methyl-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one (C42).

A degassed aqueous potassium phosphate solution (0.5 M, 4.37 mL, 2.18 mmol) was added to a degassed solution of (4-methoxy-2-methylphenyl)boronic acid (200 mg, 1.20 mmol),

C40 (250 mg, 1.09 mmol), and [2'-(azanidyl-κN)biphenyl-2-yl-κC₂](chloro){dicyclohexyl[2',4',6'-tri(propan-2-yl)biphenyl-2-yl]-λ⁵-phosphanyl}palladium (22 mg, 28 μmol) in tetrahydrofuran (4 mL). After 4 hours at room temperature, the reaction mixture was diluted with ethyl acetate; the organic layer was washed twice with saturated aqueous sodium chloride solution, then dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Silica gel chromatography (Eluent: 3:7 ethyl acetate / heptane) afforded the product as a gum. Yield: 290 mg, 0.922 mmol, 85%. LCMS *m/z* 315.1 [M+H⁺]. ¹H NMR (400 MHz, CDCl₃), presumed to be a mixture of diastereomeric atropisomers; δ 7.76 and 7.77 (2 s, total 1H), [6.92 (d, *J*=8.4 Hz) and 6.93 (d, *J*=8.4 Hz), total 1H], 6.79-6.82 (m, 1H), 6.76 (dd, *J*=8.4, 2.5 Hz, 1H), 6.06 (dd, *J*=10.7, 2.1 Hz, 1H), 4.09-4.17 (m, 1H), 3.78 (s, 3H), 3.66-3.76 (m, 1H), 2.09-2.26 (m, 1H), 2.08 and 2.08 (2 s, total 3H), 1.96-2.05 (m, 1H), 1.93 and 1.94 (2 s, total 3H), 1.63-1.80 (m, 3H), 1.48-1.60 (m, 1H).
Step 4. Synthesis of 4-(4-methoxy-2-methylphenyl)-5-methylpyridazin-3(2H)-one (C43).

C42 (184 mg, 0.585 mmol) was mixed with a solution of hydrogen chloride in 1,4-dioxane (4 M, 8 mL) and allowed to stir for 1 hour. Concentration *in vacuo* provided the product as a solid (140 mg), which was taken directly to the next step. LCMS *m/z* 231.1 [M+H⁺]. ¹H NMR (400 MHz, CD₃OD) δ 7.98 (br s, 1H), 6.98 (d, *J*=8.4 Hz, 1H), 6.89 (br d, *J*=2.5 Hz, 1H), 6.84 (br dd, *J*=8.4, 2.7 Hz, 1H), 3.82 (s, 3H), 2.09 (br s, 3H), 2.01 (s, 3H).

Step 5. Synthesis of 3-chloro-4-(4-methoxy-2-methylphenyl)-5-methylpyridazine (C44).

A mixture of **C43** (from the previous step, 140 mg) and phosphorus oxychloride (1.5 mL, 16 mmol) was stirred at 90 °C for 1.5 hours. After removal of the phosphorus oxychloride *in vacuo*, the residue was partitioned between dichloromethane (120 mL) and water (20 mL) and neutralized with sodium bicarbonate. The organic layer was washed sequentially with aqueous sodium bicarbonate solution (2 x 50 mL) and water (2 x 50 mL), then dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The product was obtained as a gum. Yield: 133 mg, 0.535 mmol, 91% over two steps. LCMS *m/z* 249.1 [M+H⁺]. ¹H NMR (400 MHz, CDCl₃) δ 9.03 (s, 1H), 6.94 (d, half of AB quartet, *J*=8.2 Hz, 1H), 6.84-6.91 (m, 2H), 3.87 (s, 3H), 2.11 (s, 3H), 2.03 (s, 3H).

Step 6. Synthesis of 4-(4-methoxy-2-methylphenyl)-3,5-dimethylpyridazine (C45).

Nitrogen was bubbled for 10 minutes into a stirring mixture of tetrakis(triphenylphosphine)palladium(0) (32 mg, 28 μmol) and **C44** (133 mg, 0.535 mmol) in 1,4-dioxane (5 mL). Trimethylaluminum (2 M in toluene, 0.5 mL, 1.0 mmol) was then added, and the reaction mixture was heated at 95 °C for 1.5 hours. After cooling, the reaction mixture was quenched via drop-wise addition of methanol, then diluted with methanol. The mixture was filtered through Celite, and the filtrate was concentrated *in vacuo*. Silica gel chromatography (Eluent: 5% methanol in ethyl acetate) afforded the product as an oil. Yield: 94 mg, 0.41 mmol, 77%. LCMS *m/z* 229.1 [M+H⁺]. ¹H NMR (400 MHz, CDCl₃) δ 8.91 (s, 1H), 6.78-6.86 (m, 3H), 3.80 (s, 3H), 2.32 (s, 3H), 1.97 (s, 3H), 1.91 (s, 3H).

Step 7. Synthesis of 4-(3,5-dimethylpyridazin-4-yl)-3-methylphenol (C46).

Boron tribromide (1 M solution in dichloromethane, 13.0 mL, 13.0 mmol) was added drop-wise to a -78°C solution of **C45** (740 mg, 3.24 mmol) in dichloromethane (10 mL). After stirring at -78°C for 15 minutes, the reaction mixture was gradually warmed to room temperature over 1 hour, and stirred at room temperature for 2 hours. It was then cooled to -78°C , quenched with anhydrous methanol (15 mL), and allowed to warm to room temperature. Solvents were removed *in vacuo*, and the residue was treated with methanol (20 mL) and heated at reflux for 30 minutes. The reaction mixture was cooled and concentrated under reduced pressure; the residue was partitioned between dichloromethane and water. The aqueous layer was adjusted to a pH of 14 with 1 N aqueous sodium hydroxide solution, then extracted with additional dichloromethane. The aqueous layer was brought to pH 6 – 7 by addition of 1 N aqueous hydrochloric acid and stirred for 10 minutes; the resulting precipitate was isolated via filtration, affording the product as an off-white solid. Yield: 599 mg, 2.80 mmol, 86%. LCMS m/z 215.1 $[\text{M}+\text{H}^+]$. ^1H NMR (400 MHz, CD_3OD) δ 8.97 (s, 1H), 6.74-6.89 (m, 3H), 2.33 (s, 3H), 2.07 (s, 3H), 1.91 (s, 3H).

Step 8. Synthesis of 4-[4-(3,5-dimethylpyridazin-4-yl)-3-methylphenoxy]-1-[[2-(trimethylsilyl)ethoxy]methyl]-1H-pyrrolo[3,2-c]pyridine (C47).

C46 was converted to the product using the method described for synthesis of **C15** in Example 2. In this case, purification was carried out via silica gel chromatography (Mobile phase A: dichloromethane; Mobile phase B: 80:20:1 dichloromethane / methanol / concentrated ammonium hydroxide solution; Gradient: 0% to 25% B). The product was obtained as a yellow gum. Yield: 67 mg, 0.15 mmol, 65%. LCMS m/z 461.3 $[\text{M}+\text{H}^+]$. ^1H NMR (400 MHz, CDCl_3) δ 8.98 (s, 1H), 7.94 (d, $J=5.7$ Hz, 1H), 7.16-7.26 (m, 4H), 7.00 (d, $J=8.2$ Hz, 1H), 6.68-6.72 (m, 1H), 5.50 (s, 2H), 3.47-3.55 (m, 2H), 2.42 (s, 3H), 2.07 (s, 3H), 1.98 (s, 3H), 0.87-0.95 (m, 2H), -0.04 (s, 9H).

Step 9. Synthesis of 4-[4-(3,5-dimethylpyridazin-4-yl)-3-methylphenoxy]-1H-pyrrolo[3,2-c]pyridine, ENT-1 (11) and 4-[4-(3,5-dimethylpyridazin-4-yl)-3-methylphenoxy]-1H-pyrrolo[3,2-c]pyridine, ENT-2 (12).

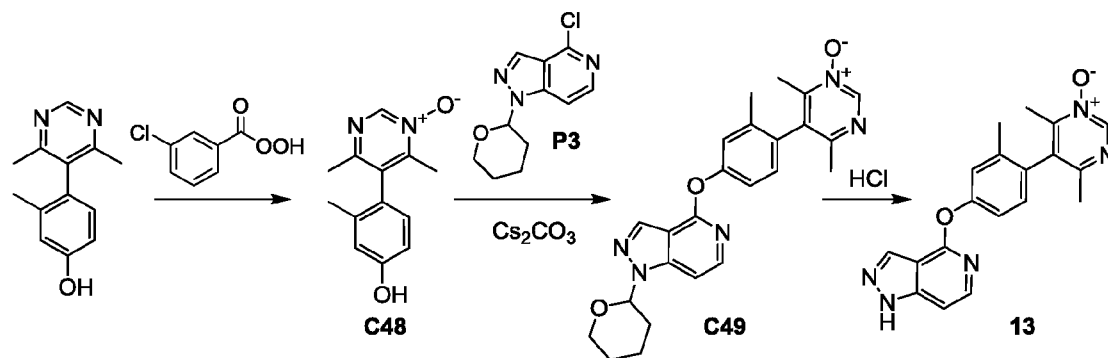
Tetrabutylammonium fluoride (1 M solution in tetrahydrofuran, 1 mL, 1 mmol) was added to a solution of **C47** (44.9 mg, 97.5 μmol) in tetrahydrofuran (1 mL), and the reaction mixture was heated at 80°C for 2 hours. The reaction mixture was cooled and extracted with ethyl acetate. The combined organic layers were washed with water and with saturated aqueous sodium chloride solution, then dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification using high-performance liquid chromatography (Column: Princeton Silica, 5 μm ; Gradient: 5% to 100% ethanol in heptane) was followed by atropenantomer separation via supercritical fluid chromatography (Column: Chiral Technologies, Chiralpak AS-H, 5 μm ; Eluent: 3:1 carbon dioxide / methanol). The first-eluting atropenantomer was designated as compound **11**, obtained as a solid. Yield: 4.1 mg, 12 μmol , 12%. LCMS m/z 331.2 $[\text{M}+\text{H}^+]$. ^1H NMR (400 MHz, CDCl_3) δ 8.99 (s, 1H), 8.72 (br s, 1H), 7.91 (d, $J=5.9$ Hz, 1H), 7.23-7.27 (m, 2H), 7.21 (br

dd, $J=8.2$, 2.3 Hz, 1H), 7.14 (dd, $J=5.8$, 0.9 Hz, 1H), 7.01 (d, $J=8.2$ Hz, 1H), 6.72-6.74 (m, 1H), 2.43 (s, 3H), 2.07 (s, 3H), 1.99 (s, 3H). Retention time: 4.43 minutes (Column: Chiral Technologies, Chiralpak AS-H, 250 x 4.6 mm, 5 μ m; Eluent: 3:1 carbon dioxide / methanol; Flow rate: 2.5 mL/minute).

- 5 The second-eluting atropenantiomer, designated as compound **12**, was also obtained as a solid. Yield: 4.5 mg, 14 μ mol, 14%. LCMS m/z 331.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.73 (br s, 1H), 7.91 (d, $J=5.9$ Hz, 1H), 7.23-7.27 (m, 2H), 7.21 (br dd, $J=8.3$, 2.4 Hz, 1H), 7.14 (dd, $J=5.9$, 1.0 Hz, 1H), 7.01 (d, $J=8.2$ Hz, 1H), 6.71-6.74 (m, 1H), 2.43 (s, 3H), 2.07 (s, 3H), 1.99 (s, 3H). Retention time: 6.74 minutes (HPLC conditions identical to those
- 10 described for compound **11**).

Example 13

4-[4-(4,6-Dimethyl-1-oxypyrimidin-5-yl)-3-methylphenoxy]-1H-pyrazolo[4,3-c]pyridine (**13**)



Step 1. Synthesis of 4-(4,6-dimethyl-1-oxypyrimidin-5-yl)-3-methylphenol (**C48**).

- 15 To a solution of 4-(4,6-dimethylpyrimidin-5-yl)-3-methylphenol (1.0 g, 4.7 mmol) in dichloromethane (25 mL) was added 3-chloroperoxybenzoic acid (887 mg, 5.14 mmol) at 0 $^{\circ}C$. The reaction was stirred at 0 $^{\circ}C$ for 2 hours, then at room temperature for 14 hours. After removal of solvent *in vacuo*, purification by chromatography on silica gel (Gradient: 0% to 100% ethyl acetate in petroleum ether) provided the product. Yield: 742 mg, 3.22 mmol, 69%. ^1H NMR
- 20 (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 6.82-6.91 (m, 3H), 2.30 (s, 3H), 2.22 (s, 3H), 1.97 (s, 3H).

Step 2. Synthesis of 4-[4-(4,6-dimethyl-1-oxypyrimidin-5-yl)-3-methylphenoxy]-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazolo[4,3-c]pyridine (**C49**).

- To a solution of **C48** (230 mg, 1.0 mmol) in acetonitrile (25 mL) were added **P3** (238 mg, 1.00 mmol) and cesium carbonate (650 mg, 2.0 mmol), and the reaction mixture was stirred at
- 25 110 $^{\circ}C$ for 60 hours. The reaction mixture was filtered and concentrated *in vacuo*; silica gel chromatography (Gradient: 0% to 5% methanol in dichloromethane) afforded the product as a yellow solid. Yield: 290 mg, 0.67 mmol, 67%.

Step 3. Synthesis of 4-[4-(4,6-dimethyl-1-oxypyrimidin-5-yl)-3-methylphenoxy]-1H-pyrazolo[4,3-c]pyridine (**13**).

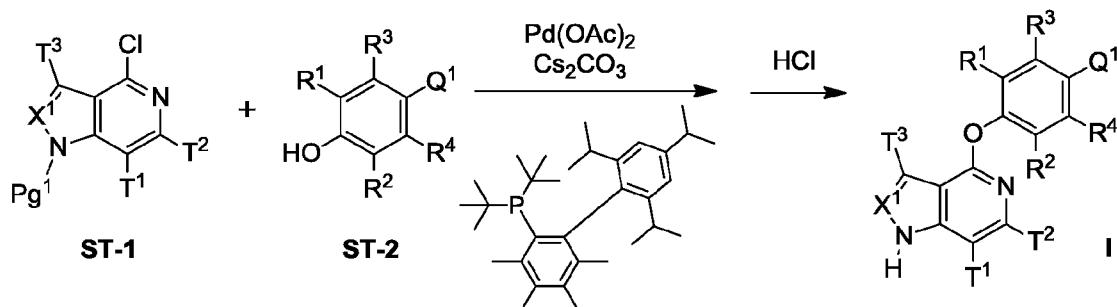
- 30 A solution of hydrogen chloride in 1,4-dioxane (10 mL) was added to **C49** (290 mg, 0.67 mmol) at 0 $^{\circ}C$. The reaction mixture was stirred for 2 hours at room temperature, and then

concentrated *in vacuo*. The residue was neutralized with aqueous ammonium hydroxide solution until the pH reached 9. After removal of solvent under reduced pressure, purification was carried out via preparative thin layer chromatography on silica gel (Eluent: 10:1 dichloromethane / methanol) to provide the product as a white solid. Yield: 70 mg, 0.20 mmol, 30%. LCMS m/z 347.9 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 9.05 (s, 1H), 8.15 (s, 1H), 7.85 (d, $J=6.0$ Hz, 1H), 7.33 (br s, 1H), 7.29 (d, $J=5.5$ Hz, 1H), 7.24-7.26 (m, 2H), 2.33 (s, 3H), 2.30 (s, 3H), 2.09 (s, 3H).

Method A

Coupling of N-protected 4-chloro-1H-pyrrolo[3,2-c]pyridines or 4-chloro-1H-pyrazolo[4,3-c]pyridines with phenols

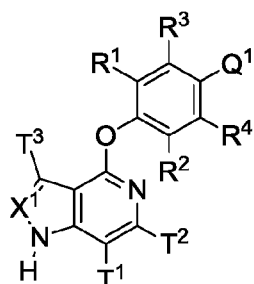
Method A describes a specific method for preparations of certain compounds of the invention.



An N-protected compound of Formula **ST-1** wherein Pg^1 is a protecting group (e.g., **P2** or **P3**) (0.11 mmol) in degassed 1,4-dioxane (1 mL) was added to a phenol of Formula **ST-2** (0.1 mmol) in a 2-dram vial. Cesium carbonate (~98 mg, 0.3 mmol), palladium(II) acetate (~2.5 mg, 10 μ mol) and di-*tert*-butyl[3,4,5,6-tetramethyl-2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane (~10 mg, 20 μ mol) were added, and the reaction mixture was degassed twice using sequential vacuum and nitrogen fill. The vial was shaken and heated at 80 $^{\circ}C$ for 20 hours, then cooled to room temperature. The reaction mixture was partitioned between water (1.5 mL) and ethyl acetate (2.5 mL) and filtered through Celite; the organic layer was passed through a 6 mL solid-phase extraction cartridge filled with sodium sulfate. The aqueous layer was extracted twice via the same procedure, and the combined filtrates from the sodium sulfate cartridges were concentrated *in vacuo*. The residue was dissolved in dichloromethane (0.5 mL) and treated with hydrogen chloride in 1,4-dioxane (4 M, 0.5 mL, 2 mmol). This reaction mixture was shaken at room temperature for 66 hours, then diluted with ethyl acetate (2.5 mL) and quenched with aqueous sodium hydroxide solution (6 N, 0.35 mL) and water (1 mL). The organic layer was passed through a 6 mL solid-phase extraction cartridge filled with sodium sulfate. The aqueous layer was extracted twice via the same procedure, and the combined filtrates from the sodium sulfate cartridges were concentrated *in vacuo*. Purification was carried out using reversed phase high-performance liquid chromatography (Column: Waters XBridge C18, 5 μ m; Mobile phase A:

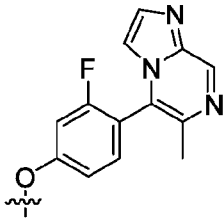
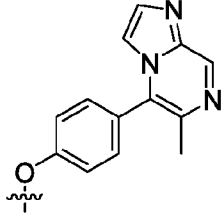
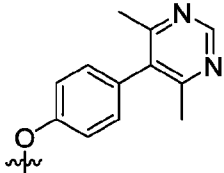
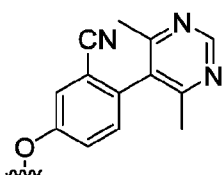
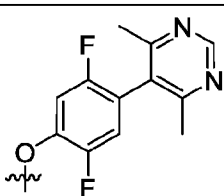
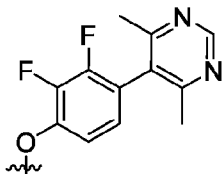
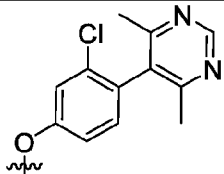
0.03% ammonium hydroxide in water (v/v); Mobile phase B: 0.03% ammonium hydroxide in acetonitrile (v/v); Gradient: 10% to 100% B) to provide the product.

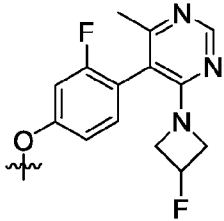
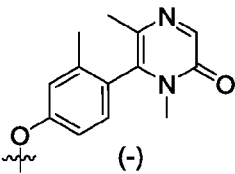
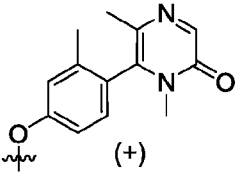
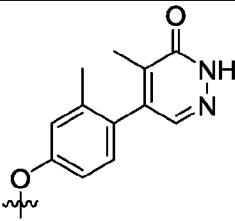
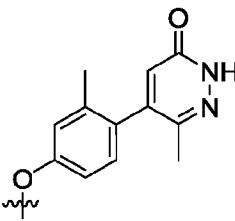
Table 1. Examples 14 – 29



$X^1 = CT^4$;
each of T^1 , T^2 , T^3 , and T^4 is H

Example Number		Method of Preparation; Non-commercial Starting Materials	^1H NMR (400 MHz, $CDCl_3$), δ (ppm); Mass spectrum, observed ion m/z [$M+H^+$] or HPLC retention time (minutes); Mass spectrum m/z [$M+H^+$] (unless otherwise indicated)
14		Example 1 ^{1,2,3}	9.72 (br s, 1H), 9.07 (s, 1H), 7.88 (d, $J=5.8$ Hz, 1H), 7.71 (d, $J=1.0$ Hz, 1H), 7.32-7.34 (m, 1H), 7.27-7.29 (m, 2H), 7.26 (dd, $J=3.1, 2.3$ Hz, 1H), 7.15 (dd, $J=5.8, 0.8$ Hz, 1H), 7.07-7.09 (m, 1H), 6.73-6.76 (m, 1H), 2.34 (s, 3H), 2.03 (s, 3H); 356.0
15		Example 1 ⁴	9.62 (br s, 1H), 9.16 (s, 1H), 7.89 (d, $J=6.0$ Hz, 1H), 7.81-7.84 (m, 2H), 7.41 (d, $J=8.3$ Hz, 1H), 7.25-7.34 (m, 4H), 7.14 (d, $J=6.0$ Hz, 1H), 6.77-6.81 (m, 1H), 2.14 (s, 3H); 342.2
16		Example 2; C13	^1H NMR (400 MHz, CD_3OD) δ 9.19 (s, 1H), 7.79 (d, $J=5.8$ Hz, 1H), 7.51 (dd, $J=9.3, 8.0$ Hz, 1H), 7.36 (d, $J=3.0$ Hz, 1H), 7.30 (d, $J=6.0$ Hz, 1H), 7.14-7.20 (m, 2H), 6.57 (d, $J=3.3$ Hz, 1H), 2.53 (s, 3H); 345.9
17		Example 16	^1H NMR (400 MHz, CD_3OD) δ 9.18 (s, 1H), 7.76 (d, $J=5.8$ Hz, 1H), 7.31 (d, $J=3.3$ Hz, 1H), 7.25-7.28 (m, 2H), 7.20 (br d, $J=2.5$ Hz, 1H), 7.12 (br dd, $J=8.3, 2.3$ Hz, 1H), 6.47 (dd, $J=3.3, 0.8$ Hz, 1H), 2.44 (s, 3H), 2.10 (br s, 3H); 342.0

18		Example 1 ^{1,2}	9.10 (s, 1H), 8.68 (br s, 1H), 7.95 (d, $J=5.8$ Hz, 1H), 7.75 (d, $J=1.0$ Hz, 1H), 7.46 (dd, $J=8.8, 7.8$ Hz, 1H), 7.36-7.38 (m, 1H), 7.25-7.32 (m, 3H, assumed; partially obscured by solvent peak), 7.21 (dd, $J=5.8, 1.0$ Hz, 1H), 6.77-6.79 (m, 1H), 2.46 (s, 3H); 360.1
19		Example 5 ^{1,5}	9.11 (br s, 1H), 9.10 (s, 1H), 7.91 (d, $J=5.8$ Hz, 1H), 7.74 (br s, 1H), 7.49 (s, 4H), 7.40 (br s, 1H), 7.26-7.29 (m, 1H, assumed; partially obscured by solvent peak), 7.18 (br d, $J=5.8$ Hz, 1H), 6.74-6.78 (m, 1H), 2.46 (s, 3H); 342.0
20		Examples 9 and 10 ^{6,3}	9.64-9.80 (br m, 1H), 8.94 (s, 1H), 7.85 (br d, $J=5.8$ Hz, 1H), 7.36 (br d, $J=8.6$ Hz, 2H), 7.17-7.22 (m, 3H), 7.12 (br d, $J=5.7$ Hz, 1H), 6.65-6.68 (m, 1H), 2.29 (s, 6H); 317.1
21		Example 5 ⁷ ; P2 ⁸	9.04 (s, 1H), 8.72 (br s, 1H), 7.91 (d, $J=5.9$ Hz, 1H), 7.76 (dd, $J=2.5, 0.4$ Hz, 1H), 7.66 (dd, $J=8.5, 2.5$ Hz, 1H), 7.33 (dd, $J=8.5, 0.3$ Hz, 1H), 7.29 (dd, $J=3.3, 2.3$ Hz, 1H), 7.20 (dd, $J=5.9, 1.0$ Hz, 1H), 6.76 (ddd, $J=3.3, 2.0, 1.0$ Hz, 1H), 2.36 (s, 6H); 342.2
22		Example 5 ^{9,3}	¹ H NMR (600 MHz, DMSO- d_6) δ 8.96 (s, 1H), 7.69 (d, $J=5.7$ Hz, 1H), 7.55-7.60 (m, 2H), 7.48 (dd, $J=3.1, 2.6$ Hz, 1H), 7.23 (br d, $J=6$ Hz, 1H), 6.64-6.66 (m, 1H), 2.30 (s, 6H); 353.1
23		Example 6; P2 ¹⁰	¹ H NMR (600 MHz, DMSO- d_6) δ 8.98 (s, 1H), 7.69 (d, $J=5.7$ Hz, 1H), 7.48-7.50 (m, 1H), 7.36-7.40 (m, 1H), 7.27-7.31 (m, 1H), 7.24 (br d, $J=5.7$ Hz, 1H), 6.65-6.68 (m, 1H), 2.29 (s, 6H); 353.2
24		Method A	2.02 minutes ¹¹ ; 351.1, 353.1

25		Method A	2.33 minutes ¹² ; 394.2
26		Example 6; P2, P8 ¹³	¹ H NMR (400 MHz, CD ₃ OD) δ 8.09 (s, 1H), 7.73 (d, <i>J</i> =5.9 Hz, 1H), 7.33 (d, <i>J</i> =3.2 Hz, 1H), 7.23-7.28 (m, 2H), 7.19-7.21 (m, 1H), 7.13 (br dd, <i>J</i> =8.2, 2.3 Hz, 1H), 6.54-6.56 (m, 1H), 3.28 (s, 3H), 2.12 (s, 3H), 2.06 (s, 3H); 347.1
27		Example 6; P2, P8 ¹⁴	¹ H NMR (400 MHz, CD ₃ OD) δ 8.09 (s, 1H), 7.73 (d, <i>J</i> =5.8 Hz, 1H), 7.33 (d, <i>J</i> =3.1 Hz, 1H), 7.23-7.28 (m, 2H), 7.19-7.21 (m, 1H), 7.13 (br dd, <i>J</i> =8.5, 2.4 Hz, 1H), 6.54-6.56 (m, 1H), 3.28 (s, 3H), 2.13 (s, 3H), 2.06 (s, 3H); 347.1
28		Example 6; P2, C41 ¹⁵	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ 7.70 (d, <i>J</i> =5.7 Hz, 1H), 7.68 (s, 1H), 7.42 (dd, <i>J</i> =2.8, 2.6 Hz, 1H), 7.18-7.20 (m, 2H), 7.17 (br d, <i>J</i> =2.2 Hz, 1H), 7.09 (dd, <i>J</i> =8.3, 2.4 Hz, 1H), 6.54-6.56 (m, 1H), 2.11 (s, 3H), 1.86 (s, 3H); 333.0
29		Examples 3 and 4 ¹⁶	¹ H NMR (400 MHz, CD ₃ OD) δ 7.72 (d, <i>J</i> =6.1 Hz, 1H), 7.32 (d, <i>J</i> =3.1 Hz, 1H), 7.23 (dd, <i>J</i> =6.0, 0.9 Hz, 1H), 7.18 (d, <i>J</i> =8.2 Hz, 1H), 7.10-7.12 (m, 1H), 7.05 (br dd, <i>J</i> =8.3, 2.4 Hz, 1H), 6.76 (d, <i>J</i> =0.4 Hz, 1H), 6.51 (dd, <i>J</i> =3.1, 1.0 Hz, 1H), 2.16 (br s, 3H), 2.11 (d, <i>J</i> =0.4 Hz, 3H); 333.2

1. The requisite 5-bromo-6-methylimidazo[1,2-*a*]pyrazine was prepared via the method of A. R. Harris et al., *Tetrahedron* **2011**, 67, 9063-9066.

2. In the penultimate step, the coupling was carried out using tetrakis(triphenylphosphine)palladium(0) and sodium carbonate.

5 3. The final deprotection was effected with tetrabutylammonium fluoride.

4. The requisite 4-(imidazo[1,2-*a*]pyrazin-5-yl)-3-methylphenol was prepared by the general method used for synthesis of **C28** in Example 5.

5. The final deprotection was carried out using trifluoroacetic acid, followed by treatment with potassium carbonate.

6. 4-(4,6-Dimethylpyrimidin-5-yl)phenol was prepared using the method described in Example 5.

7. The final deprotection was carried out with trifluoroacetic acid.

8. 5-Bromo-4,6-dimethylpyrimidine was converted to 4,6-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine using the general method described for preparation of **C20** in Examples 3 and 4. This compound was converted to the requisite 2-(4,6-dimethylpyrimidin-5-yl)-5-hydroxybenzonitrile via Suzuki reaction with 2-bromo-5-methoxybenzonitrile and deprotection according to the general method given in Example 5 for synthesis of **C28**.

9. The requisite 4-(4,6-dimethylpyrimidin-5-yl)-2,5-difluorophenol was prepared via Suzuki reaction between (2,5-difluoro-4-methoxyphenyl)boronic acid and 5-bromo-4,6-dimethylpyrimidine, mediated by tetrakis(triphenylphosphine)palladium(0), followed by demethylation using boron tribromide.

10. Suzuki reaction between 5-bromo-4,6-dimethylpyrimidine and (2,3-difluoro-4-methoxyphenyl)boronic acid was mediated via tris(dibenzylideneacetone)dipalladium(0) and tricyclohexylphosphine; deprotection with boron tribromide afforded the requisite 4-(4,6-dimethylpyrimidin-5-yl)-2,3-difluorophenol.

11. Conditions for analytical HPLC. Column: Waters Atlantis dC18, 4.6 x 50 mm, 5 μ m; 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.

12. Conditions for analytical HPLC. Column: Waters XBridge C18, 4.6 x 50 mm, 5 μ m; Mobile phase A: 0.03% ammonium hydroxide in water (v/v); Mobile phase B: 0.03% ammonium hydroxide in acetonitrile (v/v); Gradient: 5.0% to 95% B, linear over 4.0 minutes; Flow rate: 2 mL/minute).

13. The racemic product was separated using supercritical fluid chromatography (Column: Chiral Technologies Chiralcel OJ-H, 5 μ m; Eluent: 1:4 methanol / carbon dioxide).

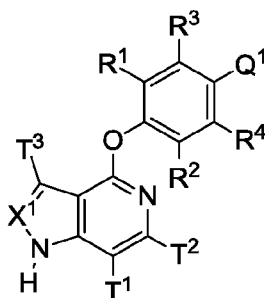
Atropenantiomer Example 26 was the first-eluting isomer, exhibiting a negative (-) rotation, and a retention time of 4.28 minutes (Column: Chiral Technologies Chiralcel OJ-H, 4.6 x 250 mm, 5 μ m; Eluent: 1:4 methanol / carbon dioxide; Flow rate 2.5 mL/min).

14. The racemic product was separated as described in footnote 13. Atropenantiomer Example 27 was the second-eluting isomer, exhibiting a positive (+) rotation and a retention time of 4.97 minutes (analytical conditions identical to those in footnote 13).

15. Compound **C41** was reacted with **C20**, using conditions similar to those employed for preparation of **C27** in Example 5. The resulting 5-[4-(benzyloxy)-2-methylphenyl]-4-methyl-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one was hydrogenated to provide 5-(4-hydroxy-2-methylphenyl)-4-methyl-2-(tetrahydro-2H-pyran-2-yl)pyridazin-3(2H)-one.

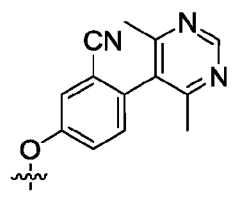
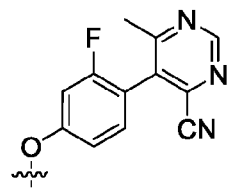
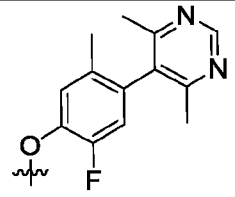
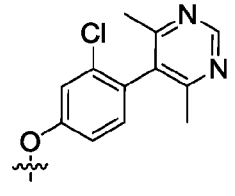
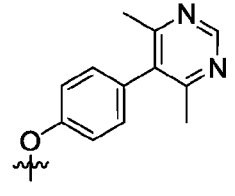
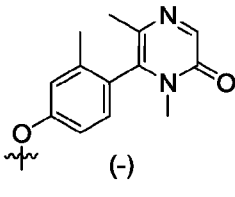
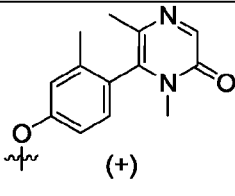
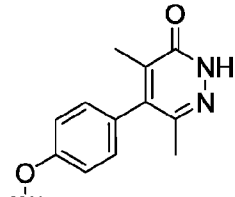
16. 2-Methyl-5-oxo-2,5-dihydrofuran-3-yl trifluoromethanesulfonate was prepared from ethyl 4-bromo-3-oxopentanoate using the general methods outlined for preparation of **C19** in Examples 3 and 4.

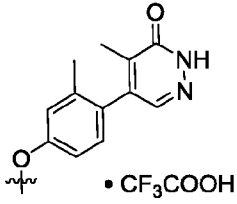
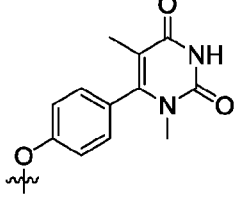
Table 2. Examples 30 – 43



$X^1 = N$;
each of T^1 , T^2 , and T^3 is H

Example Number		Method of Preparation; Non-commercial Starting Materials	^1H NMR (400 MHz, CD_3OD), δ (ppm); Mass spectrum, observed ion m/z $[M+H]^+$ or HPLC retention time (minutes); Mass spectrum m/z $[M+H]^+$ (unless otherwise indicated)
30		Examples 11 and 12 ¹ ; P6²	^1H NMR (400 MHz, $CDCl_3$), δ 9.10 (s, 1H), 8.41 (d, $J=5.5$ Hz, 1H), 8.26 (s, 1H), 7.94 (d, $J=6.0$ Hz, 1H), 7.40 (br d, $J=2.5$ Hz, 1H), 7.35 (br dd, half of ABX pattern, $J=8.5$, 2.4 Hz, 1H), 7.30 (d, half of AB quartet, $J=8.6$ Hz, 1H), 7.25-7.29 (m, 1H, assumed; partially obscured by solvent peak), 7.01 (dd, $J=5.5$, 0.8 Hz, 1H), 2.49 (s, 3H), 2.00 (s, 3H); 357.2
31		Examples 3 and 4 ³	8.11 (br s, 1H), 7.83 (d, $J=6.3$ Hz, 1H), 7.23-7.28 (m, 3H), 7.17-7.21 (m, 1H), 6.79-6.80 (m, 1H), 2.20 (br s, 3H), 2.13 (d, $J=0.4$ Hz, 3H); 334.2
32		Example 5; P6⁴	^1H NMR (400 MHz, $CDCl_3$), δ 9.00 (s, 1H), 8.27 (s, 1H), 8.00 (d, $J=6.0$ Hz, 1H), 7.19-7.28 (m, 4H, assumed; partially obscured by solvent peak), 2.38 (s, 6H); 336.1
33		Example 5; P6⁵	9.27 (s, 1H), 8.08 (d, $J=6.5$ Hz, 1H), 7.62-7.69 (m, 1H), 7.58 (s, 1H), 7.45-7.55 (m, 2H), 7.27-7.33 (m, 1H), 3.84 (s, 3H), 2.55 (s, 6H); 348.1

34		Example 5 ⁶ ; P6 ⁷	¹ H NMR (400 MHz, CDCl ₃), δ 9.05 (s, 1H), 8.30 (d, <i>J</i> =0.8 Hz, 1H), 7.97 (d, <i>J</i> =6.0 Hz, 1H), 7.84 (d, <i>J</i> =2.5 Hz, 1H), 7.70 (dd, <i>J</i> =8.5, 2.5 Hz, 1H), 7.39 (d, <i>J</i> =8.5 Hz, 1H), 7.24 (dd, <i>J</i> =6.0, 1.0 Hz, 1H), 2.37 (s, 6H); 343.1
35		Example 5 ⁸ ; P3 ⁹	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆), δ 9.33 (s, 1H), 8.31 (br s, 1H), 7.91 (dd, <i>J</i> =5.9, 0.4 Hz, 1H), 7.73 (dd, <i>J</i> =8.6, 8.6 Hz, 1H), 7.56 (dd, <i>J</i> =10.8, 2.2 Hz, 1H), 7.39 (dd, <i>J</i> =8.4, 2.2 Hz, 1H), 7.36 (br d, <i>J</i> =5.9 Hz, 1H), 2.48 (s, 3H); 347.2
36		Method A	2.33 minutes; 350.1 ¹⁰
37		Method A	2.40 minutes; 352.1 ¹⁰
38		Example 5; P6	¹ H NMR (400 MHz, CDCl ₃), δ 8.97 (s, 1H), 8.23 (s, 1H), 7.98 (d, <i>J</i> =6.0 Hz, 1H), 7.42 (br d, <i>J</i> =8.5 Hz, 2H), 7.24-7.29 (m, 2H, assumed; partially obscured by solvent peak), 7.17 (d, <i>J</i> =6.0 Hz, 1H), 2.35 (s, 6H); 318.1
39		Example 6; P8 ¹¹	8.18 (s, 1H), 8.10 (s, 1H), 7.85 (d, <i>J</i> =6.2 Hz, 1H), 7.32-7.36 (m, 2H), 7.25-7.30 (m, 2H), 3.29 (s, 3H), 2.16 (s, 3H), 2.07 (s, 3H); 348.4
40		Example 6; P8 ¹²	8.17-8.18 (m, 1H), 8.10 (s, 1H), 7.85 (d, <i>J</i> =6.1 Hz, 1H), 7.32-7.36 (m, 2H), 7.25-7.30 (m, 2H), 3.29 (s, 3H), 2.16 (s, 3H), 2.07 (s, 3H); 348.4
41		Examples 3 and 4	8.12 (s, 1H), 7.86 (d, <i>J</i> =6.2 Hz, 1H), 7.37 (br AB quartet, <i>J</i> _{AB} =8.6 Hz, Δ <i>v</i> _{AB} =28 Hz, 4H), 7.28 (d, <i>J</i> =5.8 Hz, 1H), 2.11 (s, 3H), 1.99 (s, 3H); 334.2

42	 $\bullet$ CF ₃ COOH	Examples 3 and 4 ^{13,14}	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆), δ 8.23 (br s, 1H), 7.84 (d, <i>J</i> =6.2 Hz, 1H), 7.72 (s, 1H), 7.26-7.30 (m, 2H), 7.25 (d, half of AB quartet, <i>J</i> =7.9 Hz, 1H), 7.19 (dd, half of ABX pattern, <i>J</i> =7.9, 2.2 Hz, 1H), 2.13 (s, 3H), 1.86 (s, 3H); 334.0
43		Example 8	8.18 (d, <i>J</i> =1.0 Hz, 1H), 7.85 (d, <i>J</i> =6.1 Hz, 1H), 7.42-7.47 (m, 4H), 7.29 (dd, <i>J</i> =6.1, 1.0 Hz, 1H), 3.11 (s, 3H), 1.71 (s, 3H); 350.2

1. In the penultimate step, the coupling was carried out using 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene rather than di-*tert*-butyl[3,4,5,6-tetramethyl-2',4',6'-tri(propan-2-yl)biphenyl-2-yl]phosphane.

2. The requisite 3-methyl-4-(2-methyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)phenol was prepared in the following manner: reaction of 4-methoxy-2-methylaniline with 4-chloro-3-nitropyridine provided *N*-(4-methoxy-2-methylphenyl)-3-nitropyridin-4-amine. After hydrogenation of the nitro group, the resulting amine was cyclized with ethyl orthoacetate and acetic anhydride to afford 1-(4-methoxy-2-methylphenyl)-2-methyl-1*H*-imidazo[4,5-*c*]pyridine, which was demethylated with boron tribromide.

3. 2-Methyl-5-oxo-2,5-dihydrofuran-3-yl trifluoromethanesulfonate was prepared from ethyl 4-bromo-3-oxopentanoate using the general methods outlined for preparation of **C19** in Examples 3 and 4.

4. 1-Bromo-2-fluoro-4-methoxybenzene was converted to intermediate 5-(2-fluoro-4-methoxyphenyl)-4,6-dimethylpyrimidine using the procedure described for synthesis of **C14** in Example 1.

5. 4-Bromo-3-methoxyphenol was protected as its [tri(propan-2-yl)]silane ether, and subsequently converted to [3-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy][tri(propan-2-yl)]silane with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) catalyst. This was reacted with 5-bromo-4,6-dimethylpyrimidine using the conditions described for synthesis of **C27** in Example 5 to afford 5-(2-methoxy-4-[[tri(propan-2-yl)silyl]oxy]phenyl)-4,6-dimethylpyrimidine; deprotection with tetraethylammonium fluoride provided the requisite 4-(4,6-dimethylpyrimidin-5-yl)-3-methoxyphenol.

6. The final deprotection was carried out with trifluoroacetic acid, followed by treatment with sodium acetate in methanol.

7. 2-Bromo-5-hydroxybenzonitrile was protected as its [tri(propan-2-yl)]silane ether. Reaction with 4,6-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrimidine (prepared from 5-bromo-4,6-dimethylpyrimidine using the conditions described for synthesis of **C13** in Example 1)

according to the method used for preparation of **C14** in Example 1 provided the requisite 2-(4,6-dimethylpyrimidin-5-yl)-5-hydroxybenzonitrile.

8. The final deprotection was carried out with hydrochloric acid.

9. 5-Bromo-6-methylpyrimidine-4-carbonitrile was prepared from 5-bromo-4-chloro-6-

- 5 methylpyrimidine via reaction with potassium cyanide and 1,4,7,10,13,16-hexaoxacyclooctadecane. 4-Bromo-3-fluorophenol was converted to [3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy][tri(propan-2-yl)]silane using the conditions outlined in footnote 5. These two reagents were subjected to Suzuki reaction and desilylation as described in footnote 5, affording 5-(2-fluoro-4-hydroxyphenyl)-6-methylpyrimidine-4-
- 10 carbonitrile.

10. Conditions for analytical HPLC. Column: Waters Atlantis dC18, 4.6 x 50 mm, 5 μ m; 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.

11. The racemic product was separated using supercritical fluid chromatography (Column: 15 Chiral Technologies Chiralcel OJ-H, 5 μ m; Eluent: 1:4 methanol / carbon dioxide). Atropenantiomer Example 39 was the first-eluting isomer, exhibiting a negative (-) rotation, and a retention time of 2.91 minutes (Column: Chiral Technologies Chiralcel OJ-H, 4.6 x 250 mm, 5 μ m; Eluent: 1:4 methanol / carbon dioxide; Flow rate 2.5 mL/min).

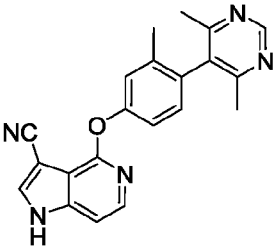
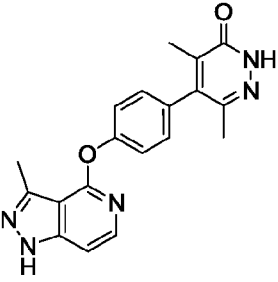
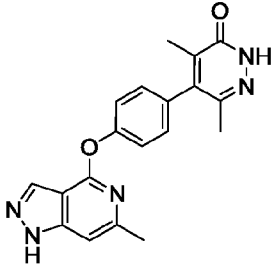
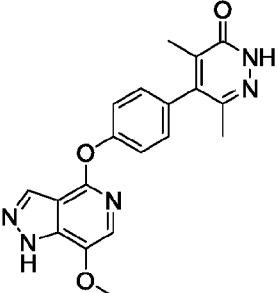
12. The racemic product was separated as described in footnote 11. Atropenantiomer Example 20 40 was the second-eluting isomer, exhibiting a positive (+) rotation and a retention time of 3.28 minutes (analytical conditions identical to those in footnote 11).

13. In the penultimate step, the coupling was carried out using copper(I) iodide and cesium carbonate in pyridine at 100 °C.

14. Compound **C41** was reacted with **C20**, using conditions similar to those employed for 25 preparation of **C27** in Example 5. The resulting 5-[4-(benzyloxy)-2-methylphenyl]-4-methyl-2-(tetrahydro-2*H*-pyran-2-yl)pyridazin-3(2*H*)-one was hydrogenated to provide 5-(4-hydroxy-2-methylphenyl)-4-methyl-2-(tetrahydro-2*H*-pyran-2-yl)pyridazin-3(2*H*)-one.

Table 3. Examples 44 – 47

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 ⁺]
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44		Example 5; P7 ¹	9.44 (br s, 1H), 8.98 (s, 1H), 8.00 (d, $J=5.5$ Hz, 1H), 7.79 (br d, $J=2$ Hz, 1H), 7.32-7.35 (m, 1H), 7.27-7.31 (m, 1H, assumed; partially obscured by solvent peak), 7.16 (d, $J=5.5$ Hz, 1H), 7.09 (d, $J=8.0$ Hz, 1H), 2.27 (s, 6H), 2.04 (s, 3H); 355.9
45		Examples 3 and 4 ²	7.78 (d, $J=6.2$ Hz, 1H), 7.35 (br AB quartet, $J_{AB}=8.7$ Hz, $\Delta\nu_{AB}=25.9$ Hz, 4H), 7.18 (d, $J=6.2$ Hz, 1H), 2.73 (s, 3H), 2.10 (s, 3H), 1.99 (s, 3H); 348.3
46		Examples 3 and 4; P4	7.79 (d, $J=0.6$ Hz, 1H), 7.37 (br AB quartet, $J_{AB}=8.8$ Hz, $\Delta\nu_{AB}=34.9$ Hz, 4H), 7.09-7.11 (m, 1H), 2.47 (d, $J=0.8$ Hz, 3H), 2.10 (s, 3H), 1.99 (s, 3H); 348.1
47		Examples 3 and 4; P5	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆), δ 8.16 (br s, 1H), 7.50 (s, 1H), 7.32 (br AB quartet, $J_{AB}=8.3$ Hz, $\Delta\nu_{AB}=19.3$ Hz, 4H), 3.97 (s, 3H), 1.97 (s, 3H), 1.83 (s, 3H); 364.0

1. The final deprotection was carried out with trifluoroacetic acid, followed by treatment with sodium acetate in methanol.

2. 4-Chloro-3-methyl-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazolo[4,3-*c*]pyridine was prepared using the method described in Preparation P3.

5

Example AA: Human D1 Receptor Binding Assay and Data

The affinity of the compounds described herein was determined by competition binding assays similar to those described in Ryman-Rasmussen et al., "Differential activation of adenylate cyclase and receptor internalization by novel dopamine D1 receptor agonists",

10 *Molecular Pharmacology* 68(4):1039-1048 (2005). This radioligand binding assay used [³H]-SCH23390, a radiolabeled D1 ligand, to evaluate the ability of a test compound to compete with the radioligand when binding to a D1 receptor.

D1 binding assays were performed using over-expressing LTK human cell lines. To determine basic assay parameters, ligand concentrations were determined from saturation binding studies where the K_d for [^{3} H]-SCH23390 was found to be 1.3 nM. From tissue concentration curve studies, the optimal amount of tissue was determined to be 1.75 mg/mL per 96 well plate using 0.5 nM of [^{3} H]-SCH23390. These ligand and tissue concentrations were used in time course studies to determine linearity and equilibrium conditions for binding. Binding was at equilibrium with the specified amount of tissue in 30 minutes at 37 °C. From these parameters, K_i values were determined by homogenizing the specified amount of tissue for each species in 50 mM Tris (pH 7.4 at 4 °C) containing 2.0 mM $MgCl_2$ using a Polytron and spun in a centrifuge at 40,000 x g for 10 minutes. The pellet was resuspended in assay buffer [50 mM Tris (pH 7.4@ RT) containing 4 mM $MgSO_4$ and 0.5 mM EDTA]. Incubations were initiated by the addition of 200 μ L of tissue to 96-well plates containing test drugs (2.5 μ L) and 0.5 nM [^{3} H]-SCH23390 (50 μ L) in a final volume of 250 μ L. Non-specific binding was determined by radioligand binding in the presence of a saturating concentration of (+)-Butaclamol (10 μ M), a D1 antagonist. After a 30 minute incubation period at 37 °C, assay samples were rapidly filtered through Unifilter-96 GF/B PEI-coated filter plates and rinsed with 50 mM Tris buffer (pH 7.4 at 4 °C). Membrane bound [^{3} H]-SCH23390 levels were determined by liquid scintillation counting of the filterplates in Ecolume. The IC_{50} value (concentration at which 50% inhibition of specific binding occurs) was calculated by linear regression of the concentration-response data in Microsoft Excel. K_i values were calculated according to the Cheng-Prusoff equation:

$$K_i = \frac{IC_{50}}{1 + ([L]/K_d)}$$

where [L] = concentration of free radioligand and K_d = dissociation constant of radioligand for D1 receptor (1.3 nM for [^{3} H]-SCH23390).

Example BB: D1 cAMP HTRF Assay and Data

The D1 cAMP (Cyclic Adenosine Monophosphate) HTRF (Homogeneous Time-Resolved Fluorescence) Assay used and described herein is a competitive immunoassay between native cAMP produced by cells and cAMP labeled with XL-665. This assay was used to determine the ability of a test compound to agonize (including partially agonize) D1. A Mab anti-cAMP labeled Cryptate visualizes the tracer. The maximum signal is achieved if the samples do not contain free cAMP due to the proximity of donor (Eu-cryptate) and acceptor (XL665) entities. The signal, therefore, is inversely proportional to the concentration of cAMP in the sample. A time-resolved and ratiometric measurement (em 665 nm/em 620 nm) minimizes the interference with medium. cAMP HTRF assays are commercially available, for example, from Cisbio Bioassays, IBA group.

Materials and Methods

Materials: The cAMP Dynamic kit was obtained from Cisbio International (Cisbio 62AM4PEJ). Multidrop Combi (Thermo Scientific) was used for assay additions. An EnVision (PerkinElmer) reader was used to read HTRF.

Cell Culture: A HEK293T/hD1#1 stable cell line was constructed internally (Pfizer Ann Arbor). The cells were grown as adherent cells in NuncT₅₀₀ flasks in high glucose DMEM (Invitrogen 11995-065), 10% fetal bovine serum dialyzed (Invitrogen 26400-044), 1x MEM NEAA (Invitrogen 1140, 25 mM HEPES (Invitrogen 15630), 1x Pen/Strep (Invitrogen 15070-063) and 500 µg/mL Genenticin (Invitrogen 10131-035) at 37 °C and 5% CO₂. At 72 or 96 hours post-growth, cells were rinsed with DPBS, and 0.25% Trypsin-EDTA was added to dislodge the cells. Media was then added and cells were centrifuged and media removed. The cell pellets were re-suspended in Cell Culture Freezing Medium (Invitrogen 12648-056) at a density of 4e7 cells/mL. One mL aliquots of the cells were made in Cryo-vials and frozen at -80 °C for future use in the D1 HTRF assay.

D1 cAMP HTRF assay procedure: Frozen cells were quickly thawed, re-suspended in 50 mL warm media and allowed to sit for 5 min prior to centrifugation (1000 rpm) at room temperature. Media was removed and cell pellet was re-suspended in PBS/0.5 µM IBMX generating 2e5 cells/mL. Using a Multidrop Combi, 5 µL cells/well was added to the assay plate (Greiner 784085), which already contained 5 µL of a test compound. Compound controls [5 µM dopamine (final) and 0.5% DMSO (final)] were also included on every plate for data analysis. Cells and compounds were incubated at room temperature for 30 min. Working solutions of cAMP-D2 and anti-cAMP-cryptate were prepared according to Cisbio instructions. Using Multidrop, 5 µL cAMP-D2 working solution was added to the assay plate containing the test compound and cells. Using Multidrop, 5 µL anti-cAMP-cryptate working solutions was added to assay plate containing test compound, cells and cAMP-D2. The assay plate was incubated for 1 hour at room temperature. The assay plate was read on an EnVision plate reader using Cisbio recommended settings. A cAMP standard curve was generated using cAMP stock solution provided in the Cisbio kit.

Data Analysis: Data analysis was done using computer software. Percent effects were calculated from the compound controls. Ratio EC₅₀ was determined using the raw ratio data from the EnVision reader. The cAMP standard curve was used in an analysis program to determine cAMP concentrations from raw ratio data. cAMP EC₅₀ was determined using the calculated cAMP data.

Table 4. Biological Data for Examples 1-47

Example Number	Compound IUPAC Name	Human D1 Receptor Binding, K _i (µM); Geometric	Human D1 cAMP HTRF, EC ₅₀ (µM); Geometric
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		mean of 2 - 3 determina- tions	mean of 2 - 6 determina- tions
1	4-[4-(4,6-dimethylpyrimidin-5-yl)-3-fluorophenoxy]-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridine	0.0303 ^c	0.176 ^a
2	4-[4-(1,4-dimethyl-1 <i>H</i> -pyrazol-5-yl)-3-methylphenoxy]-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridine	0.0348 ^b	0.355
3	(+)-4,6-dimethyl-5-[2-methyl-4-(1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-yloxy)phenyl]pyridazin-3(2 <i>H</i>)-one	0.00976	0.0151
4	(-)-4,6-dimethyl-5-[2-methyl-4-(1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-yloxy)phenyl]pyridazin-3(2 <i>H</i>)-one	0.0104	0.0105
5	4-[4-(4,6-dimethylpyrimidin-5-yl)-3-methylphenoxy]-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridine	0.0130 ^c	0.146 ^a
6	4-[4-(4,6-dimethylpyrimidin-5-yl)-3-methylphenoxy]-1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridine	0.113 ^c	0.568 ^a
7	4,6-dimethyl-5-[4-(1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridin-4-yloxy)phenyl]pyridazin-3(2 <i>H</i>)-one	0.00412	0.0192 ^a
8	(-)-1,5-dimethyl-6-[2-methyl-4-(1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-yloxy)phenyl]pyrimidine-2,4(1 <i>H</i> ,3 <i>H</i>)-dione	0.00183	<0.00222 ^a
9	4,6-dimethyl-5-[2-methyl-4-(1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridin-4-yloxy)phenyl]pyridazin-3(2 <i>H</i>)-one, ENT-1	0.00487	0.00733 ^a
10	4,6-dimethyl-5-[2-methyl-4-(1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridin-4-yloxy)phenyl]pyridazin-3(2 <i>H</i>)-one, ENT-2	0.00504	0.00431
11	4-[4-(3,5-dimethylpyridazin-4-yl)-3-methylphenoxy]-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridine, ENT-1	0.0141 ^b	0.117
12	4-[4-(3,5-dimethylpyridazin-4-yl)-3-methylphenoxy]-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridine, ENT-2	0.0883 ^b	0.520
13	4-[4-(4,6-dimethyl-1-oxidopyrimidin-5-yl)-3-methylphenoxy]-1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridine	0.0931 ^b	0.260
14	6-methyl-5-[2-methyl-4-(1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridin-4-yloxy)phenyl]imidazo[1,2- <i>a</i>]pyrazine	0.00798 ^c	0.137
15	5-[2-methyl-4-(1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridin-4-yloxy)phenyl]imidazo[1,2- <i>a</i>]pyrazine	0.0975	0.417
16	5-[2-fluoro-4-(1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridin-4-yloxy)phenyl]-6-methylpyrimidine-4-carbonitrile	0.0283	0.396
17	6-methyl-5-[2-methyl-4-(1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridin-4-	0.0392	0.374

	yloxy)phenyl]pyrimidine-4-carbonitrile		
18	5-[2-fluoro-4-(1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridin-4-yloxy)phenyl]-6-methylimidazo[1,2- <i>a</i>]pyrazine	0.0294 ^c	0.141
19	6-methyl-5-[4-(1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridin-4-yloxy)phenyl]imidazo[1,2- <i>a</i>]pyrazine	0.0159	0.464 ^a
20	4-[4-(4,6-dimethylpyrimidin-5-yl)phenoxy]-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridine	0.0443	0.238
21	2-(4,6-dimethylpyrimidin-5-yl)-5-(1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridin-4-yloxy)benzonitrile	0.102	0.247
22	4-[4-(4,6-dimethylpyrimidin-5-yl)-2,5-difluorophenoxy]-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridine	0.0548	0.538
23	4-[4-(4,6-dimethylpyrimidin-5-yl)-2,3-difluorophenoxy]-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridine	0.0538 ^c	0.590 ^a
24	4-[3-chloro-4-(4,6-dimethylpyrimidin-5-yl)phenoxy]-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridine	0.00984	0.102
25	4-{3-fluoro-4-[4-(3-fluoroazetidin-1-yl)-6-methylpyrimidin-5-yl]phenoxy}-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridine	0.00509	0.156
26	(-)-1,5-dimethyl-6-[2-methyl-4-(1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridin-4-yloxy)phenyl]pyrazin-2(1 <i>H</i>)-one	0.00456	0.0730
27	(+)-1,5-dimethyl-6-[2-methyl-4-(1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridin-4-yloxy)phenyl]pyrazin-2(1 <i>H</i>)-one	0.0106	0.0646
28	4-methyl-5-[2-methyl-4-(1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridin-4-yloxy)phenyl]pyridazin-3(2 <i>H</i>)-one	0.0357	0.0549
29	6-methyl-5-[2-methyl-4-(1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridin-4-yloxy)phenyl]pyridazin-3(2 <i>H</i>)-one	0.0679 ^b	0.119
30	4-[3-methyl-4-(2-methyl-1 <i>H</i> -imidazo[4,5- <i>c</i>]pyridin-1-yl)phenoxy]-1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridine	0.268 ^b	2.76
31	6-methyl-5-[2-methyl-4-(1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-yloxy)phenyl]pyridazin-3(2 <i>H</i>)-one	0.287 ^b	0.548
32	4-[4-(4,6-dimethylpyrimidin-5-yl)-3-fluorophenoxy]-1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridine	0.0723 ^b	0.903 ^a
33	4-[4-(4,6-dimethylpyrimidin-5-yl)-3-methoxyphenoxy]-1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridine	0.124 ^b	2.08 ^a
34	2-(4,6-dimethylpyrimidin-5-yl)-5-(1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-yloxy)benzonitrile	0.391 ^b	2.38
35	5-[2-fluoro-4-(1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-yloxy)phenyl]-6-methylpyrimidine-4-carbonitrile	0.0696 ^b	1.34

36	4-[4-(4,6-dimethylpyrimidin-5-yl)-2-fluoro-5-methylphenoxy]-1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridine	0.118 ^b	0.733
37	4-[3-chloro-4-(4,6-dimethylpyrimidin-5-yl)phenoxy]-1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridine	0.0523	0.248 ^a
38	4-[4-(4,6-dimethylpyrimidin-5-yl)phenoxy]-1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridine	0.129 ^b	2.52 ^a
39	(-)-1,5-dimethyl-6-[2-methyl-4-(1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-yloxy)phenyl]pyrazin-2(1 <i>H</i>)-one	0.0418 ^c	0.168 ^a
40	(+)-1,5-dimethyl-6-[2-methyl-4-(1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-yloxy)phenyl]pyrazin-2(1 <i>H</i>)-one	0.0281 ^b	0.674
41	4,6-dimethyl-5-[4-(1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-yloxy)phenyl]pyridazin-3(2 <i>H</i>)-one	0.0409 ^c	0.127 ^a
42	4-methyl-5-[2-methyl-4-(1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-yloxy)phenyl]pyridazin-3(2 <i>H</i>)-one, trifluoroacetate salt	0.123	0.340
43	1,5-dimethyl-6-[4-(1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-yloxy)phenyl]pyrimidine-2,4(1 <i>H</i> ,3 <i>H</i>)-dione	0.0175	0.0282
44	4-[4-(4,6-dimethylpyrimidin-5-yl)-3-methylphenoxy]-1 <i>H</i> -pyrrolo[3,2- <i>c</i>]pyridine-3-carbonitrile	0.00460	0.0553 ^a
45	4,6-dimethyl-5-{4-[(3-methyl-1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-yl)oxy]phenyl}pyridazin-3(2 <i>H</i>)-one	0.0103	0.0663 ^a
46	4,6-dimethyl-5-{4-[(6-methyl-1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-yl)oxy]phenyl}pyridazin-3(2 <i>H</i>)-one	0.0247	0.0891
47	5-{4-[(7-methoxy-1 <i>H</i> -pyrazolo[4,3- <i>c</i>]pyridin-4-yl)oxy]phenyl}-4,6-dimethylpyridazin-3(2 <i>H</i>)-one	0.695 ^b	1.30

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

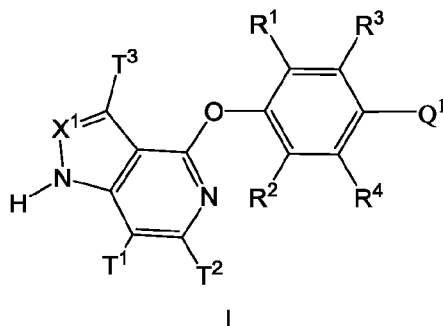
b. Value represents a single determination.

c. Value represents the geometric mean of ≥ 4 determinations.

- 5 Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appendant claims. Each reference (including all patents, patent applications, journal articles, books, and any other publications) cited in the present application is hereby incorporated by reference in its entirety.

WHAT IS CLAIMED IS:

1. A compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

X^1 is N or CT^4 ;

Q^1 is an N-containing 5- to 6-membered heteroaryl or an N-containing 5- to 6-membered heterocycloalkyl, each optionally substituted with one R^9 and further optionally substituted with 1, 2, 3, or 4 R^{10} ;

each of T^1 , T^2 , T^3 , and T^4 is independently selected from the group consisting of H, halogen, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, cyclopropyl, fluorocyclopropyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, and -C(=O)-O-(C_{1-4} alkyl);

each of R^1 and R^2 is independently selected from the group consisting of H, halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-6} cycloalkyl, -C(=O)OH, and C(=O)-O-(C_{1-4} alkyl), wherein each of said C_{1-6} alkyl and C_{3-6} cycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents each independently selected from halo, -OH, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy;

each of R^3 and R^4 is independently selected from the group consisting of H, halogen, -OH, -NO₂, -CN, -SF₅, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, a 4- to 10-membered heterocycloalkyl, -N(R^5)(R^6), -N(R^7)(C(=O) R^8), -C(=O)-N(R^5)(R^6), -C(=O)- R^8 , -C(=O)-OR⁸, -N(R^7)(S(=O)₂ R^8), -S(=O)₂-N(R^5)(R^6), -SR⁸, and -OR⁸, wherein each of said C_{1-6} alkyl, C_{3-7} cycloalkyl, and heterocycloalkyl is optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of halogen, -CN, -OH, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{3-6} cycloalkyl, -N(R^5)(R^6), -N(R^7)(C(=O) R^8), -C(=O)-OR⁸, -C(=O)H, -C(=O) R^8 , -C(=O)N(R^5)(R^6), -N(R^7)(S(=O)₂ R^8), -S(=O)₂-N(R^5)(R^6), -SR⁸, and -OR⁸;

R^5 is H, C_{1-4} alkyl, C_{1-4} haloalkyl, or C_{3-7} cycloalkyl;

R^6 is H or selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-7} cycloalkyl, a 4- to 10-membered heterocycloalkyl, C_{6-10} aryl, a 5- to 10-membered heteroaryl, (C_{3-7} cycloalkyl)- C_{1-4} alkyl-, (4- to 10-membered heterocycloalkyl)- C_{1-4} alkyl-, (C_{6-10} aryl)- C_{1-4} alkyl-,

and (5- to 10-membered heteroaryl)-C₁₋₄ alkyl-, wherein each of the selections from the group is optionally substituted with 1, 2, 3, or 4 substituents each independently selected from the group consisting of -OH, -CN, C₁₋₄ alkyl, C₃₋₇ cycloalkyl, C₁₋₄ hydroxylalkyl, -S-C₁₋₄ alkyl, -C(=O)H, -C(=O)-C₁₋₄ alkyl, -C(=O)-O-C₁₋₄ alkyl, -C(=O)-NH₂, -C(=O)-N(C₁₋₄ alkyl)₂, C₁₋₄ haloalkyl, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy;

or R⁵ and R⁶ together with the N atom to which they are attached form a 4- to 10-membered heterocycloalkyl or a 5- to 10-membered heteroaryl, each optionally substituted with 1, 2, 3, 4, or 5 substituents each independently selected from the group consisting of halogen, -OH, oxo, -C(=O)H, -C(=O)OH, -C(=O)-C₁₋₄ alkyl, -C(=O)-NH₂, -C(=O)-N(C₁₋₄ alkyl)₂, -CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ hydroxylalkyl, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy;

R⁷ is selected from the group consisting of H, C₁₋₄ alkyl, and C₃₋₇ cycloalkyl;

R⁸ is selected from the group consisting of C₁₋₆ alkyl, C₃₋₇ cycloalkyl, a 4- to 14-membered heterocycloalkyl, C₆₋₁₀ aryl, a 5- to 10-membered heteroaryl, (C₃₋₇ cycloalkyl)-C₁₋₄ alkyl-, (4- to 10-membered heterocycloalkyl)-C₁₋₄ alkyl-, (C₆₋₁₀ aryl)-C₁₋₄ alkyl-, and (5- to 10-membered heteroaryl)-C₁₋₄ alkyl-, wherein each of the selections from the group is optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of halogen, -CF₃, -CN, -OH, oxo, -S-C₁₋₄ alkyl, C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₇ cycloalkyl, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy;

R⁹ is C₁₋₄ alkyl, C₁₋₄ haloalkyl, -CN, -SF₅, -N(R⁵)(R⁶), C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₇ cycloalkoxy, or C₃₋₇ cycloalkyl, wherein each of the C₁₋₄ alkyl and C₃₋₇ cycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents each independently selected from the group consisting of halogen, -N(R⁵)(R⁶), C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₃₋₇ cycloalkyl, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy;

each R¹⁰ is independently selected from the group consisting of halogen, -OH, -CN, -SF₅, -NO₂, oxo, thiono, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxylalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₇ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, a 4- to 10-membered heterocycloalkyl, a 5- to 10-membered heteroaryl, (C₃₋₇ cycloalkyl)-C₁₋₄ alkyl-, (4- to 10-membered heterocycloalkyl)-C₁₋₄ alkyl-, (C₆₋₁₀ aryl)-C₁₋₄ alkyl-, (5- to 10-membered heteroaryl)-C₁₋₄ alkyl-, -N(R⁵)(R⁶), -N(R⁷)(C(=O)R⁸), -S(=O)₂N(R⁵)(R⁶), -C(=O)-N(R⁵)(R⁶), -C(=O)-R⁸, -C(=O)-OR⁸, -SR⁸, and -OR⁸, wherein each of said C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₆₋₁₀ aryl, 4- to 10-membered heterocycloalkyl, 5- to 10-membered heteroaryl, (C₃₋₇ cycloalkyl)-C₁₋₄ alkyl-, (4- to 10-membered heterocycloalkyl)-C₁₋₄ alkyl-, (C₆₋₁₀ aryl)-C₁₋₄ alkyl-, and (5- to 10-membered heteroaryl)-C₁₋₄ alkyl- is optionally substituted with 1, 2, 3, or 4 substituents each independently selected from the group consisting of halogen, OH, -CN, -NO₂, C₁₋₄ alkyl, C₁₋₄ hydroxylalkyl, C₁₋₄ alkoxy, -N(R⁵)(R⁶), -S-(C₁₋₄ alkyl), -S(=O)₂-(C₁₋₄ alkyl), C₆₋₁₀ aryloxy, [(C₆₋₁₀ aryl)-C₁₋₄ alkoxy- optionally substituted with 1 or 2 C₁₋₄

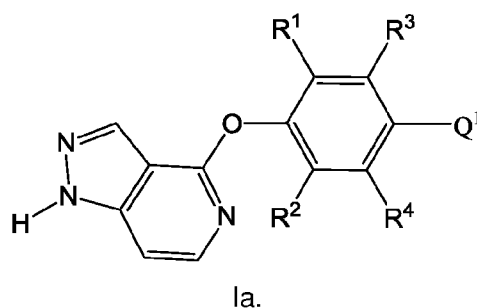
alkyl], oxo, -C(=O)H, -C(=O)-C₁₋₄ alkyl, -C(=O)O-C₁₋₄ alkyl, -C(=O)NH₂, -NHC(=O)H, -NHC(=O)-(C₁₋₄ alkyl), C₃₋₇ cycloalkyl, a 5- or 6-membered heteroaryl, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy;

or R⁹ and an adjacent R¹⁰ together with the two ring atoms on Q¹ to which they are attached form a fused benzene ring or a fused 5- or 6-membered heteroaryl, each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^{10a}; and

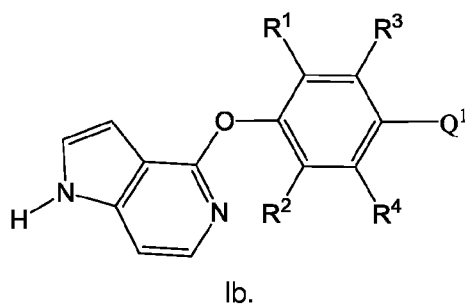
each R^{10a} is independently selected from the group consisting of halogen, -OH, -N(R⁵)(R⁶), -C(=O)OH, -C(=O)-C₁₋₄ alkyl, -C(=O)-NH₂, -C(=O)-N(C₁₋₄ alkyl)₂, -CN, -SF₅, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ hydroxylalkyl, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy;

provided that the compound of Formula I is not 4-(4-imidazol-1-yl-phenoxy)-3-methyl-1*H*-pyrazolo[4,3-*c*]pyridine.

2. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein X¹ is N.
3. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein X¹ is CT⁴.
4. The compound of any one of Claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein each of T¹, T², T³, and T⁴ is independently selected from the group consisting of H, F, -CN, methoxy, C₁ fluoroalkoxy, methyl, and C₁ fluoroalkyl,
5. The compound of any one of Claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein T² is H and T³ is H.
6. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of Formula Ia:



7. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein the compound is a compound of Formula Ib:



8. The compound of any one of Claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein:

each of R^1 and R^2 is independently selected from the group consisting of H, halogen, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, and C_{3-4} cycloalkyl;

each of R^3 and R^4 is independently selected from the group consisting of H, halogen, -OH, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{3-4} cycloalkyl, a 4- to 7-membered heterocycloalkyl, $-N(R^5)(R^6)$, and $-OR^8$,

each of R^5 and R^6 independently is H or selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, and C_{3-7} cycloalkyl;

or R^5 and R^6 together with the N atom to which they are attached form a 4- to 7-membered heterocycloalkyl or a 5-membered heteroaryl, each optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of halogen, -CN, C_{1-4} alkyl, C_{1-4} alkoxy, C_{3-6} cycloalkyl, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy; and

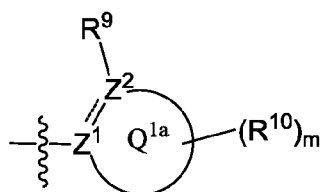
R^8 is selected from the group consisting of C_{1-4} alkyl, C_{3-6} cycloalkyl, a 4- to 7-membered heterocycloalkyl, phenyl, and a 5- to 6-membered heteroaryl, each optionally substituted with 1, 2, or 3 substituents each independently selected from the group consisting of halogen, -CN, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-6} cycloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy.

9. The compound of any one of Claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein each of R^1 and R^2 is independently H or halogen.

10. The compound of any one of Claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^3 is H and R^4 is H, halogen, -CN, methyl, or C_1 haloalkyl.

11. The compound of any one of Claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein Q^1 is an N-containing 5- to 6-membered heteroaryl or an N-containing 5- to 6-membered heterocycloalkyl, each substituted with one R^9 and further optionally substituted with 1, 2, 3, or 4 R^{10} .

12. The compound of any one of Claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein:



Q¹ is a moiety of ("Moiety M¹");

ring Q^{1a} is an N-containing 5- to 6-membered heteroaryl or an N-containing 5- to 6-membered heterocycloalkyl;

----- represents a single bond or double bond;

Z¹ is C;

Z² is C or N;

R⁹ is C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₃₋₇ cycloalkyl, -CN, -N(R⁵)(R⁶), C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, or C₃₋₇ cycloalkoxy, wherein each of the C₁₋₄ alkyl and C₃₋₇ cycloalkyl is optionally substituted with 1, 2, 3, 4, or 5 substituents each independently selected from the group consisting of halogen, -N(R⁵)(R⁶), C₁₋₄ alkyl, C₁₋₄ haloalkyl, C₃₋₇ cycloalkyl, C₁₋₄ alkoxy, and C₁₋₄ haloalkoxy;

each R¹⁰ is independently selected from the group consisting of halogen, -OH, -CN, -NO₂, oxo, thiono, C₁₋₆ alkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxylalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₇ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, a 4- to 10-membered heterocycloalkyl, a 5- to 10-membered heteroaryl, (C₃₋₇ cycloalkyl)-C₁₋₄ alkyl-, (4- to 10-membered heterocycloalkyl)-C₁₋₄ alkyl-, (C₆₋₁₀ aryl)-C₁₋₄ alkyl-, (5- to 10-membered heteroaryl)-C₁₋₄ alkyl-, (5- to 10-membered heteroaryl)-C₂₋₄ alkenyl-, -N(R⁵)(R⁶), -N(R⁷)(C(=O)R⁸), -S(=O)₂N(R⁵)(R⁶), -C(=O)-N(R⁵)(R⁶), -C(=O)-R⁸, -C(=O)-OR⁸, and -OR⁸, wherein each of said C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₆₋₁₀ aryl, 4- to 10-membered heterocycloalkyl, 5- to 10-membered heteroaryl, (C₃₋₇ cycloalkyl)-C₁₋₄ alkyl-, (4- to 10-membered heterocycloalkyl)-C₁₋₄ alkyl-, (C₆₋₁₀ aryl)-C₁₋₄ alkyl-, (5- to 10-membered heteroaryl)-C₁₋₄ alkyl-, and (5- to 10-membered heteroaryl)-C₂₋₄ alkenyl- is optionally substituted with 1, 2, 3, or 4 substituents each independently selected from the group consisting of halogen, OH, -CN, -NO₂, C₁₋₄ alkyl, C₁₋₄ hydroxylalkyl, C₁₋₄ alkoxy, -N(R⁵)(R⁶), -S-(C₁₋₄ alkyl), -S(=O)₂-(C₁₋₄ alkyl), C₆₋₁₀ aryloxy, (C₆₋₁₀ aryl)-C₁₋₄ alkyloxy- optionally substituted with 1 or 2 C₁₋₄ alkyl, oxo, -C(=O)H, -C(=O)-C₁₋₄ alkyl, -C(=O)O-C₁₋₄ alkyl, -C(=O)NH₂, -NHC(=O)H, -NHC(=O)-(C₁₋₄ alkyl), C₃₋₇ cycloalkyl, a 5- or 6-membered heteroaryl, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy;

or R⁹ and the adjacent R¹⁰ together with the two ring atoms on ring Q^{1a} to which they are attached form a fused benzene ring or a fused 5- or 6-membered heteroaryl, each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^{10a};

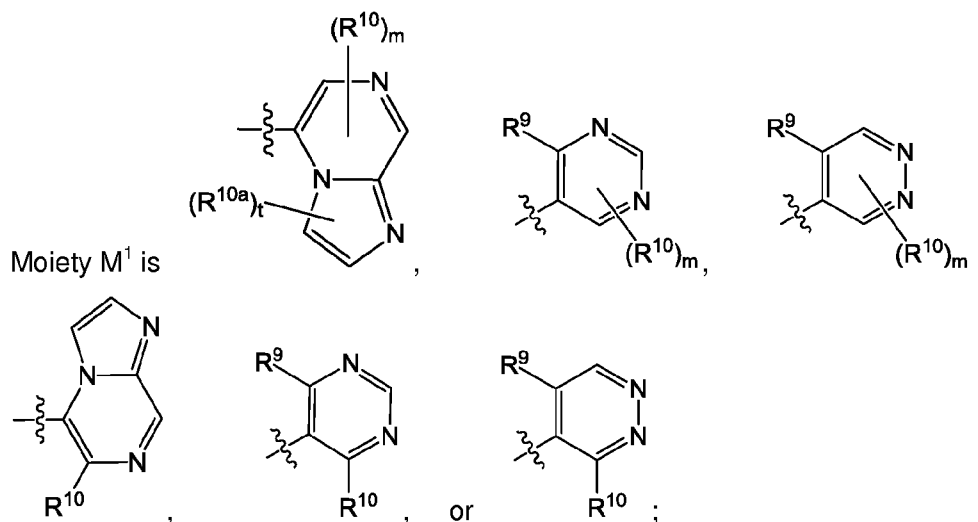
each R^{10a} is independently selected from the group consisting of halogen, -OH, -C(=O)OH, -C(=O)-C₁₋₄ alkyl, -C(=O)-NH₂, -C(=O)-N(C₁₋₄ alkyl)₂, -CN, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ hydroxylalkyl, C₁₋₄ haloalkyl, and C₁₋₄ haloalkoxy; and

m is 0, 1, 2, 3, or 4.

13. The compound of any one of Claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein Q¹ or ring Q^{1a} is an optionally substituted pyridinyl, pyrimidinyl, pyridazinyl, or pyrazinyl.

14. The compound of Claim 12, or a pharmaceutically acceptable salt thereof, wherein Moiety M¹ is selected from the group consisting of quinolinyl, isoquinolinyl, 1*H*-imidazo[4,5-*c*]pyridinyl, imidazo[1,2-*a*]pyridinyl, 1*H*-pyrrolo[3,2-*c*]pyridinyl, imidazo[1,2-*a*]pyrazinyl, imidazo[2,1-*c*][1,2,4]triazinyl, imidazo[1,5-*a*]pyrazinyl, imidazo[1,2-*a*]pyrimidinyl, 1*H*-indazolyl, 9*H*-purinyl, imidazo[1,2-*a*]pyrimidinyl, [1,2,4]triazolo[1,5-*a*]pyrimidinyl, isoxazolo[5,4-*c*]pyridazinyl, isoxazolo[3,4-*c*]pyridazinyl, and [1,2,4]triazolo[4,3-*b*]pyridazinyl, each optionally substituted with 1, 2, or 3 R¹⁰ and further optionally substituted with 1 or 2 R^{10a}; or wherein Moiety M¹ is selected from the group consisting of pyrimidinyl, pyrazinyl, pyridinyl, pyridazinyl, 1*H*-pyrazolyl, 1*H*-pyrrolyl, 4*H*-pyrazolyl, 1*H*-imidazolyl, 1*H*-imidazolyl, 3-oxo-2*H*-pyridazinyl, 1*H*-2-oxo-pyrimidinyl, 1*H*-2-oxo-pyridinyl, 2,4(1*H*,3*H*)-dioxo-pyrimidinyl, and 1*H*-2-oxo-pyrazinyl, each substituted with R⁹ and further optionally substituted with 1, 2, or 3 R¹⁰.

15. The compound of Claim 12, or a pharmaceutically acceptable salt thereof, wherein:



R^{10a} is C₁₋₄ alkyl, C₁₋₄ haloalkyl, or C₃₋₇ cycloalkyl; and

t is 0 or 1.

16. The compound of any one of Claims 1 to 15, or a pharmaceutically acceptable salt thereof, wherein R⁹ is C₁₋₄ alkyl or –CN; and each R¹⁰ is independently C₁₋₄ alkyl.
17. A compound of Claim 1 selected from:
- 4-[4-(4,6-dimethylpyrimidin-5-yl)-3-fluorophenoxy]-1*H*-pyrrolo[3,2-*c*]pyridine;
(+)-4,6-dimethyl-5-[2-methyl-4-(1*H*-pyrazolo[4,3-*c*]pyridin-4-yloxy)phenyl]pyridazin-3(2*H*)-one;
(-)-4,6-dimethyl-5-[2-methyl-4-(1*H*-pyrazolo[4,3-*c*]pyridin-4-yloxy)phenyl]pyridazin-3(2*H*)-one;
4-[4-(4,6-dimethylpyrimidin-5-yl)-3-methylphenoxy]-1*H*-pyrrolo[3,2-*c*]pyridine;
4-[4-(4,6-dimethylpyrimidin-5-yl)-3-methylphenoxy]-1*H*-pyrazolo[4,3-*c*]pyridine;
4,6-dimethyl-5-[4-(1*H*-pyrrolo[3,2-*c*]pyridin-4-yloxy)phenyl]pyridazin-3(2*H*)-one;
(-)-1,5-dimethyl-6-[2-methyl-4-(1*H*-pyrazolo[4,3-*c*]pyridin-4-yloxy)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione;
4,6-dimethyl-5-[2-methyl-4-(1*H*-pyrrolo[3,2-*c*]pyridin-4-yloxy)phenyl]pyridazin-3(2*H*)-one, ENT-1;
4,6-dimethyl-5-[2-methyl-4-(1*H*-pyrrolo[3,2-*c*]pyridin-4-yloxy)phenyl]pyridazin-3(2*H*)-one, ENT-2
4-[4-(4,6-dimethyl-1-oxidopyrimidin-5-yl)-3-methylphenoxy]-1*H*-pyrazolo[4,3-*c*]pyridine;
6-methyl-5-[2-methyl-4-(1*H*-pyrrolo[3,2-*c*]pyridin-4-yloxy)phenyl]imidazo[1,2-*a*]pyrazine;
4-[4-(4,6-dimethylpyrimidin-5-yl)phenoxy]-1*H*-pyrrolo[3,2-*c*]pyridine;
2-(4,6-dimethylpyrimidin-5-yl)-5-(1*H*-pyrrolo[3,2-*c*]pyridin-4-yloxy)benzonitrile;
4-[3-chloro-4-(4,6-dimethylpyrimidin-5-yl)phenoxy]-1*H*-pyrrolo[3,2-*c*]pyridine;
(-)-1,5-dimethyl-6-[2-methyl-4-(1*H*-pyrrolo[3,2-*c*]pyridin-4-yloxy)phenyl]pyrazin-2(1*H*)-one;
4-[4-(4,6-dimethylpyrimidin-5-yl)-3-fluorophenoxy]-1*H*-pyrazolo[4,3-*c*]pyridine;
4-[4-(4,6-dimethylpyrimidin-5-yl)-3-methoxyphenoxy]-1*H*-pyrazolo[4,3-*c*]pyridine;
4-[3-chloro-4-(4,6-dimethylpyrimidin-5-yl)phenoxy]-1*H*-pyrazolo[4,3-*c*]pyridine;
(+)-1,5-dimethyl-6-[2-methyl-4-(1*H*-pyrazolo[4,3-*c*]pyridin-4-yloxy)phenyl]pyrazin-2(1*H*)-one;
4,6-dimethyl-5-[4-(1*H*-pyrazolo[4,3-*c*]pyridin-4-yloxy)phenyl]pyridazin-3(2*H*)-one; and
1,5-dimethyl-6-[4-(1*H*-pyrazolo[4,3-*c*]pyridin-4-yloxy)phenyl]pyrimidine-2,4(1*H*,3*H*)-dione, or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising a compound according to any one of Claims 1-17 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
19. A method for treating a D1-mediated (or D1-associated) disorder in a mammal, which method comprises administering to said mammal a therapeutically effective amount of a compound according to any one of Claims 1-17 or a pharmaceutically acceptable salt thereof.
20. A method for treating a disorder in a human, which method comprises administering to said human a therapeutically effective amount of a compound according to any one of Claims 1-17 or a pharmaceutically acceptable salt thereof, wherein the disorder is selected from schizophrenia (e.g., cognitive and negative symptoms in schizophrenia), cognitive impairment [e.g., cognitive impairment associated with schizophrenia, cognitive impairment associated with AD, cognitive impairment associated with PD, cognitive impairment associated with pharmacotherapy therapy (e.g., D2 antagonist therapy)], attention deficit hyperactivity disorder (ADHD), impulsivity, compulsive gambling, overeating, autism spectrum disorder, mild cognitive impairment (MCI), age-related cognitive decline, dementia (e.g., senile dementia, HIV-associated dementia, Alzheimer's dementia, Lewy body dementia, vascular dementia, or frontotemporal dementia), restless leg syndrome (RLS), Parkinson's disease, Huntington's chorea, anxiety, depression (e.g., age-related depression), major depressive disorder (MDD), treatment resistant depression (TRD), bipolar disorder, chronic apathy, anhedonia, chronic fatigue, post-traumatic stress disorder, seasonal affective disorder, social anxiety disorder, post-partum depression, serotonin syndrome, substance abuse and drug dependence, drug abuse relapse, Tourette's syndrome, tardive dyskinesia, drowsiness, excessive daytime sleepiness, cachexia, inattention, sexual dysfunction (e.g., erectile dysfunction or post-SSRI sexual dysfunction), migraine, systemic lupus erythematosus (SLE), hyperglycemia, atherosclerosis, dislipidemia, obesity, diabetes, sepsis, post-ischemic tubular necrosis, renal failure, hyponatremia, resistant edema, narcolepsy, hypertension, congestive heart failure, postoperative ocular hypotonia, sleep disorders, and pain.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2013/059768

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 A61K31/437
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

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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/106333 A1 (MEDICAL RES COUNCIL TECHNOLOGY [GB]; MCIVER EDWARD GILES [GB]; SMILJAN) 23 September 2010 (2010-09-23) claims 1-25; example 120 -----	1-16
A	WO 2004/113303 A1 (ASTRAZENECA AB [SE]; FORD RHONAN [GB]; LEROUX FREDERIC [FR]; STOCKS MI) 29 December 2004 (2004-12-29) claims 1-39 -----	1-20
A	WO 2006/077401 A1 (BIOLIPOX AB [SE]; PELCMAN BENJAMIN [SE]; OLOFSSON KRISTOFER [SE]; ARSE) 27 July 2006 (2006-07-27) claims 1-43 -----	1-20

☐

Further documents are listed in the continuation of Box C.

☒

See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

7 March 2014

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Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2013/059768

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		JP 2008527031 A	24-07-2008
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		WO 2006077401 A1	27-07-2006



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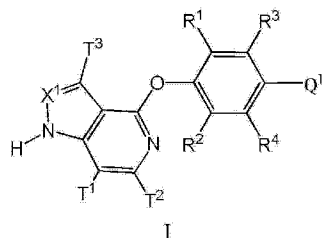
A61K 31/437(2006. 01)

权利要求书6页 说明书82页

(54) 发明名称

作为多巴胺 D1 配体的杂芳族化合物

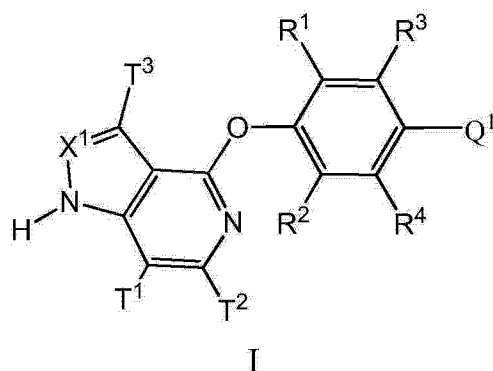
(57) 摘要



本发明一部分提

供式 I 的化合物及其药学上可接受的盐及前述的 N- 氧化物 ; 用于制备所述化合物、盐或 N- 氧化物的方法 ; 用于制备所述化合物、盐或 N- 氧化物的中间体 ; 及含有所述化合物、盐或 N- 氧化物的组合物, 及其用于治疗 D1 介导 (或 D1 相关) 的病症的用途, 所述病症包括例如精神分裂症 (例如其认知症状及负性症状)、认知损害 (例如与精神分裂症、AD、PD 或药物疗法相关的认知损害)、ADHD、冲动、强迫性赌博、进食过量、自闭症谱系障碍、MCI、年龄相关的认知下降、痴呆、RLS、帕金森氏病、亨廷顿舞蹈症、焦虑、抑郁症、MDD、TRD 及双相型障碍。

1. 式 I 的化合物或其药学上可接受的盐：



其中：

X^1 为 N 或 CT^4 ；

Q^1 为含 N 的 5 元至 6 元杂芳基或含 N 的 5 元至 6 元杂环烷基，其各自任选地被一个 R^9 取代，且进一步任选地被 1、2、3 或 4 个 R^{10} 取代；

T^1 、 T^2 、 T^3 及 T^4 各自独立地选自：H、卤素、 $-CN$ 、 C_{1-4} 烷基、 C_{1-4} 卤代烷基、环丙基、氟环丙基、 C_{1-4} 烷氧基、 C_{1-4} 卤代烷氧基及 $-C(=O)-O-(C_{1-4} \text{ 烷基})$ ；

R^1 及 R^2 各自独立地选自：H、卤素、 $-CN$ 、 C_{1-6} 烷基、 C_{1-6} 卤代烷基、 C_{1-6} 烷氧基、 C_{1-6} 卤代烷氧基、 C_{3-6} 环烷基、 $-C(=O)OH$ 及 $-C(=O)-O-(C_{1-4} \text{ 烷基})$ ，其中所述 C_{1-6} 烷基及 C_{3-6} 环烷基各自任选地被 1、2、3、4 或 5 个各自独立地选自以下的取代基取代：卤代、 $-OH$ 、 $-CN$ 、 C_{1-4} 烷基、 C_{1-4} 卤代烷基、 C_{1-4} 烷氧基及 C_{1-4} 卤代烷氧基；

R^3 及 R^4 各自独立地选自：H、卤素、 $-OH$ 、 $-NO_2$ 、 $-CN$ 、 $-SF_5$ 、 C_{1-6} 烷基、 C_{1-6} 卤代烷基、 C_{1-6} 卤代烷氧基、 C_{2-6} 烯基、 C_{2-6} 炔基、 C_{3-7} 环烷基、4 元至 10 元杂环烷基、 $-N(R^5)(R^6)$ 、 $-N(R^7)(C(=O)R^8)$ 、 $-C(=O)-N(R^5)(R^6)$ 、 $-C(=O)R^8$ 、 $-C(=O)-OR^8$ 、 $-N(R^7)(S(=O)_2R^8)$ 、 $-S(=O)_2-N(R^5)(R^6)$ 、 $-SR^8$ 及 $-OR^8$ ，其中所述 C_{1-6} 烷基、 C_{3-7} 环烷基及杂环烷基各自任选地被 1、2 或 3 个各自独立地选自下列的取代基取代：卤素、 $-CN$ 、 $-OH$ 、 C_{1-4} 烷基、 C_{1-4} 烷氧基、 C_{1-4} 卤代烷基、 C_{1-4} 卤代烷氧基、 C_{3-6} 环烷基、 $-N(R^5)(R^6)$ 、 $-N(R^7)(C(=O)R^8)$ 、 $-C(=O)-OR^8$ 、 $-C(=O)H$ 、 $-C(=O)R^8$ 、 $-C(=O)N(R^5)(R^6)$ 、 $-N(R^7)(S(=O)_2R^8)$ 、 $-S(=O)_2-N(R^5)(R^6)$ 、 $-SR^8$ 及 $-OR^8$ ；

R^5 为 H、 C_{1-4} 烷基、 C_{1-4} 卤代烷基或 C_{3-7} 环烷基；

R^6 为 H 或选自： C_{1-4} 烷基、 C_{1-4} 卤代烷基、 C_{3-7} 环烷基、4 元至 10 元杂环烷基、 C_{6-10} 芳基、5 元至 10 元杂芳基、 $(C_{3-7} \text{ 环烷基})-C_{1-4} \text{ 烷基}-$ 、 $(4 \text{ 元至 } 10 \text{ 元杂环烷基})-C_{1-4} \text{ 烷基}-$ 、 $(C_{6-10} \text{ 芳基})-C_{1-4} \text{ 烷基}-$ 及 $(5 \text{ 元至 } 10 \text{ 元杂芳基})-C_{1-4} \text{ 烷基}-$ ，其中上述各个选项任选地被 1、2、3 或 4 个各自独立地选自下列的取代基取代： $-OH$ 、 $-CN$ 、 C_{1-4} 烷基、 C_{3-7} 环烷基、 C_{1-4} 羟基烷基、 $-S-C_{1-4} \text{ 烷基}$ 、 $-C(=O)H$ 、 $-C(=O)-C_{1-4} \text{ 烷基}$ 、 $-C(=O)-O-C_{1-4} \text{ 烷基}$ 、 $-C(=O)-NH_2$ 、 $-C(=O)-N(C_{1-4} \text{ 烷基})_2$ 、 C_{1-4} 卤代烷基、 C_{1-4} 烷氧基及 C_{1-4} 卤代烷氧基；

或 R^5 及 R^6 与它们所连接的 N 原子一起形成 4 元至 10 元杂环烷基或 5 元至 10 元杂芳基，其各自任选地被 1、2、3、4 或 5 个各自独立地选自下列的取代基取代：卤素、 $-OH$ 、氧代、 $-C(=O)H$ 、 $-C(=O)OH$ 、 $-C(=O)-C_{1-4} \text{ 烷基}$ 、 $-C(=O)-NH_2$ 、 $-C(=O)-N(C_{1-4} \text{ 烷基})_2$ 、 $-CN$ 、 C_{1-4} 烷基、 C_{1-4} 烷氧基、 C_{1-4} 羟基烷基、 C_{1-4} 卤代烷基及 C_{1-4} 卤代烷氧基；

R^7 选自 H、 C_{1-4} 烷基及 C_{3-7} 环烷基；

R^8 选自 C_{1-6} 烷基、 C_{3-7} 环烷基、4 元至 14 元杂环烷基、 C_{6-10} 芳基、5 元至 10 元杂芳基、 $(C_{3-7}$

环烷基)-C₁₋₄烷基-, (4元至10元杂环烷基)-C₁₋₄烷基-, (C₆₋₁₀芳基)-C₁₋₄烷基-及(5元至10元杂芳基)-C₁₋₄烷基-, 其中上述各个选项任选地被1、2或3个各自独立地选自下列的取代基取代: 卤素、-CF₃、-CN、-OH、氧代、-S-C₁₋₄烷基、C₁₋₄烷基、C₁₋₄卤代烷基、C₂₋₆烯基、C₂₋₆炔基、C₃₋₇环烷基、C₁₋₄烷氧基及C₁₋₄卤代烷氧基;

R⁹为C₁₋₄烷基、C₁₋₄卤代烷基、-CN、-SF₅、-N(R⁵)(R⁶)、C₁₋₆烷氧基、C₁₋₆卤代烷氧基、C₃₋₇环烷氧基或C₃₋₇环烷基, 其中所述C₁₋₄烷基及C₃₋₇环烷基各自任选地被1、2、3、4或5个各自独立地选自下列的取代基取代: 卤素、-N(R⁵)(R⁶)、C₁₋₄烷基、C₁₋₄卤代烷基、C₃₋₇环烷基、C₁₋₄烷氧基及C₁₋₄卤代烷氧基;

各R¹⁰独立地选自: 卤素、-OH、-CN、-SF₅、-NO₂、氧代、硫羰基、C₁₋₆烷基、C₁₋₆卤代烷基、C₁₋₆羟基烷基、C₁₋₆烷氧基、C₁₋₆卤代烷氧基、C₃₋₇环烷基、C₂₋₆烯基、C₂₋₆炔基、C₆₋₁₀芳基、4元至10元杂环烷基、5元至10元杂芳基、(C₃₋₇环烷基)-C₁₋₄烷基-, (4元至10元杂环烷基)-C₁₋₄烷基-, (C₆₋₁₀芳基)-C₁₋₄烷基-, (5元至10元杂芳基)-C₁₋₄烷基-, -N(R⁵)(R⁶)、-N(R⁷)(C(=O)R⁸)、-S(=O)₂N(R⁵)(R⁶)、-C(=O)-N(R⁵)(R⁶)、-C(=O)-R⁸、-C(=O)-OR⁸、-SR⁸及-OR⁸, 其中所述C₁₋₆烷基、C₃₋₇环烷基、C₆₋₁₀芳基、4元至10元杂环烷基、5元至10元杂芳基、(C₃₋₇环烷基)-C₁₋₄烷基-, (4元至10元杂环烷基)-C₁₋₄烷基-, (C₆₋₁₀芳基)-C₁₋₄烷基-及(5元至10元杂芳基)-C₁₋₄烷基-各自任选地被1、2、3或4个各自独立地选自下列的取代基取代: 卤素、OH、-CN、-NO₂、C₁₋₄烷基、C₁₋₄羟基烷基、C₁₋₄烷氧基、-N(R⁵)(R⁶)、-S-(C₁₋₄烷基)、-S(=O)₂-(C₁₋₄烷基)、C₆₋₁₀芳基氧基、[任选地被1或2个C₁₋₄烷基取代的(C₆₋₁₀芳基)-C₁₋₄烷基氧基-]、氧代、-C(=O)H、-C(=O)-C₁₋₄烷基、-C(=O)O-C₁₋₄烷基、-C(=O)NH₂、-NHC(=O)H、-NHC(=O)-(C₁₋₄烷基)、C₃₋₇环烷基、5元或6元杂芳基、C₁₋₄卤代烷基及C₁₋₄卤代烷氧基;

或R⁹及邻近的R¹⁰与它们所连接的Q¹上的两个环原子一起形成稠合苯环或稠合5元或6元杂芳基, 其各自任选地被1、2、3、4或5个独立地选择的R^{10a}取代; 且

各R^{10a}独立地选自卤素、-OH、-N(R⁵)(R⁶)、-C(=O)OH、-C(=O)-C₁₋₄烷基、-C(=O)-NH₂、-C(=O)-N(C₁₋₄烷基)₂、-CN、-SF₅、C₁₋₄烷基、C₁₋₄烷氧基、C₁₋₄羟基烷基、C₁₋₄卤代烷基及C₁₋₄卤代烷氧基;

条件是所述式I的化合物不为4-(4-咪唑-1-基-苯氧基)-3-甲基-1H-吡唑并[4,3-c]吡啶。

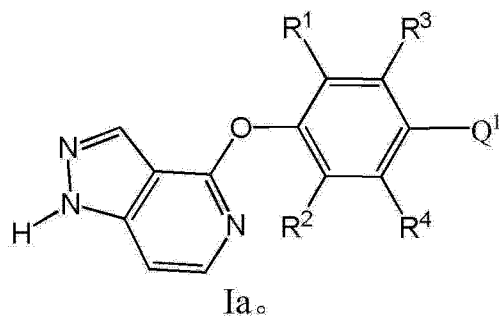
2. 权利要求1的化合物或其药学上可接受的盐, 其中X¹为N。

3. 权利要求1的化合物或其药学上可接受的盐, 其中X¹为CT⁴。

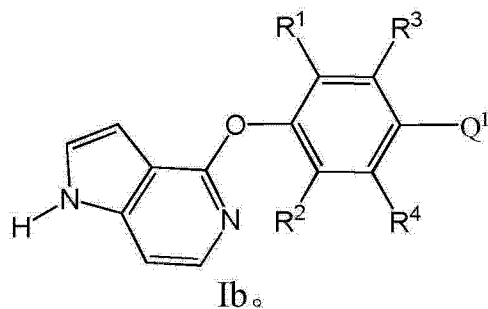
4. 权利要求1-3中任一项的化合物或其药学上可接受的盐, 其中T¹、T²、T³及T⁴各自独立地选自H、F、-CN、甲氧基、C₁氟烷氧基、甲基和C₁氟烷基。

5. 权利要求1-4中任一项的化合物或其药学上可接受的盐, 其中T²为H并且T³为H。

6. 权利要求1的化合物或其药学上可接受的盐, 其中所述化合物为式Ia的化合物:



7. 权利要求 1 的化合物或其药学上可接受的盐,其中所述化合物为式 Ib 的化合物:



8. 权利要求 1-7 中任一项的化合物或其药学上可接受的盐,其中:

R^1 及 R^2 各自独立地选自: H、卤素、 $-\text{CN}$ 、 C_{1-4} 烷基、 C_{1-4} 卤代烷基、 C_{1-4} 烷氧基、 C_{1-4} 卤代烷氧基及 C_{3-4} 环烷基;

R^3 及 R^4 各自独立地选自: H、卤素、 $-\text{OH}$ 、 $-\text{CN}$ 、 C_{1-4} 烷基、 C_{1-4} 卤代烷基、 C_{1-4} 卤代烷氧基、 C_{3-4} 环烷基、4 元至 7 元杂环烷基、 $-\text{N}(\text{R}^5)(\text{R}^6)$ 及 $-\text{OR}^8$;

R^5 及 R^6 各自独立地为 H 或选自 C_{1-4} 烷基、 C_{1-4} 卤代烷基及 C_{3-7} 环烷基;

或 R^5 及 R^6 与它们所连接的 N 原子一起形成 4 元至 7 元杂环烷基或 5 元杂芳基,其各自任选地被 1、2 或 3 个各自独立地选自下列的取代基取代: 卤素、 $-\text{CN}$ 、 C_{1-4} 烷基、 C_{1-4} 烷氧基、 C_{3-6} 环烷基、 C_{1-4} 卤代烷基及 C_{1-4} 卤代烷氧基;并且

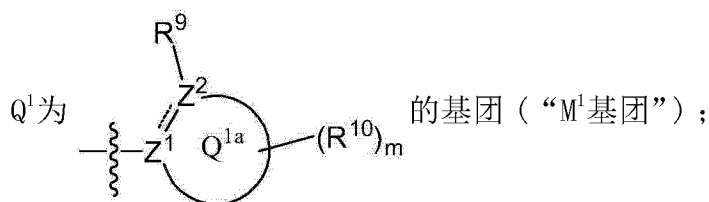
R^8 选自 C_{1-4} 烷基、 C_{3-6} 环烷基、4 元至 7 元杂环烷基、苯基及 5 元至 6 元杂芳基,其各自任选地被 1、2 或 3 个各自独立地选自下列的取代基取代: 卤素、 $-\text{CN}$ 、 C_{1-4} 烷基、 C_{1-4} 卤代烷基、 C_{3-6} 环烷基、 C_{1-4} 烷氧基及 C_{1-4} 卤代烷氧基。

9. 权利要求 1-8 中任一项的化合物或其药学上可接受的盐,其中 R^1 及 R^2 各自独立地为 H 或卤素。

10. 权利要求 1-9 中任一项的化合物或其药学上可接受的盐,其中 R^3 为 H 并且 R^4 为 H、卤素、 $-\text{CN}$ 、甲基或 C_1 卤代烷基。

11. 权利要求 1-10 中任一项的化合物或其药学上可接受的盐,其中 Q^1 为含 N 的 5 元至 6 元杂芳基或含 N 的 5 元至 6 元杂环烷基,其各自被一个 R^9 取代,且进一步任选地被 1、2、3 或 4 个 R^{10} 取代。

12. 权利要求 1-11 中任一项的化合物或其药学上可接受的盐,其中:



环 Q^{1a} 为含 N 的 5 元至 6 元杂芳基或含 N 的 5 元至 6 元杂环烷基；

===== 表示单键或双键；

Z^1 为 C；

Z^2 为 C 或 N；

R^9 为 C_{1-4} 烷基、 C_{1-4} 卤代烷基、 C_{3-7} 环烷基、-CN、-N(R^5) (R^6)、 C_{1-6} 烷氧基、 C_{1-6} 卤代烷氧基或 C_{3-7} 环烷氧基，其中所述 C_{1-4} 烷基及 C_{3-7} 环烷基各自任选地被 1、2、3、4 或 5 个各自独立地选自下列的取代基取代：卤素、-N(R^5) (R^6)、 C_{1-4} 烷基、 C_{1-4} 卤代烷基、 C_{3-7} 环烷基、 C_{1-4} 烷氧基及 C_{1-4} 卤代烷氧基；

各 R^{10} 独立地选自：卤素、-OH、-CN、-NO₂、氧代、硫羰基、 C_{1-6} 烷基、 C_{1-6} 卤代烷基、 C_{1-6} 羟基烷基、 C_{1-6} 烷氧基、 C_{1-6} 卤代烷氧基、 C_{3-7} 环烷基、 C_{2-6} 烯基、 C_{2-6} 炔基、 C_{6-10} 芳基、4 元至 10 元杂环烷基、5 元至 10 元杂芳基、(C_{3-7} 环烷基)- C_{1-4} 烷基-、(4 元至 10 元杂环烷基)- C_{1-4} 烷基-、(C_{6-10} 芳基)- C_{1-4} 烷基-、(5 元至 10 元杂芳基)- C_{1-4} 烷基-、(5 元至 10 元杂芳基)- C_{2-4} 烯基-、-N(R^5) (R^6)、-N(R^7) (C(=O) R^8)、-S(=O)₂N(R^5) (R^6)、-C(=O)-N(R^5) (R^6)、-C(=O)- R^8 、-C(=O)-OR⁸ 及 -OR⁸，其中所述 C_{1-6} 烷基、 C_{3-7} 环烷基、 C_{6-10} 芳基、4 元至 10 元杂环烷基、5 元至 10 元杂芳基、(C_{3-7} 环烷基)- C_{1-4} 烷基-、(4 元至 10 元杂环烷基)- C_{1-4} 烷基-、(C_{6-10} 芳基)- C_{1-4} 烷基-、(5 元至 10 元杂芳基)- C_{1-4} 烷基- 及 (5 元至 10 元杂芳基)- C_{2-4} 烯基- 各自任选地被 1、2、3 或 4 个各自独立地选自下列的取代基取代：卤素、OH、-CN、-NO₂、 C_{1-4} 烷基、 C_{1-4} 羟基烷基、 C_{1-4} 烷氧基、-N(R^5) (R^6)、-S-(C_{1-4} 烷基)、-S(=O)₂-(C_{1-4} 烷基)、 C_{6-10} 芳基氧基、任选地被 1 或 2 个 C_{1-4} 烷基取代的 (C_{6-10} 芳基)- C_{1-4} 烷基氧基-、氧代、-C(=O)H、-C(=O)- C_{1-4} 烷基、-C(=O)O- C_{1-4} 烷基、-C(=O)NH₂、-NHC(=O)H、-NHC(=O)-(C₁₋₄ 烷基)、 C_{3-7} 环烷基、5 元或 6 元杂芳基、 C_{1-4} 卤代烷基及 C_{1-4} 卤代烷氧基；

或 R^9 及邻近的 R^{10} 与它们所连接的环 Q^{1a} 上的两个环原子一起形成稠合苯环或稠合 5 元或 6 元杂芳基，其各自任选地被 1、2、3、4 或 5 个独立地选择的 R^{10a} 取代；

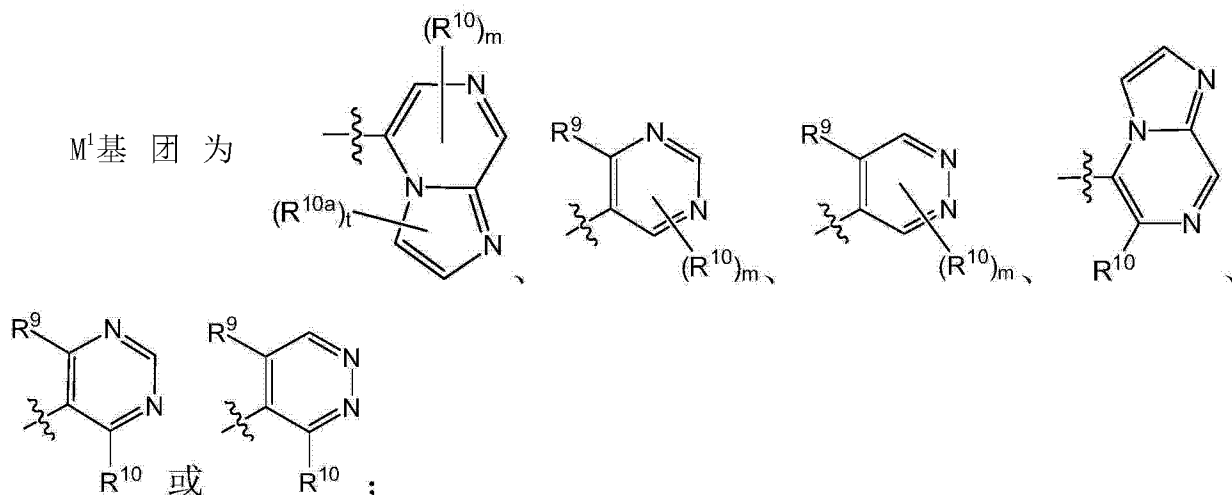
各 R^{10a} 独立地选自：卤素、-OH、-C(=O)OH、-C(=O)- C_{1-4} 烷基、-C(=O)-NH₂、-C(=O)-N(C_{1-4} 烷基)₂、-CN、 C_{1-4} 烷基、 C_{1-4} 烷氧基、 C_{1-4} 羟基烷基、 C_{1-4} 卤代烷基及 C_{1-4} 卤代烷氧基；且

m 为 0、1、2、3 或 4。

13. 权利要求 1-12 中任一项的化合物或其药学上可接受的盐，其中 Q^1 或环 Q^{1a} 为任选地被取代的吡啶基、嘧啶基、哒嗪基或吡嗪基。

14. 权利要求 12 的化合物或其药学上可接受的盐，其中 M^1 基团选自：喹啉基、异喹啉基、1H-咪唑并[4,5-c]吡啶基、咪唑并[1,2-a]吡啶基、1H-吡咯并[3,2-c]吡啶基、咪唑并[1,2-a]吡嗪基、咪唑并[2,1-c][1,2,4]三嗪基、咪唑并[1,5-a]吡嗪基、咪唑并[1,2-a]嘧啶基、1H-吡啶基、9H-嘌呤基、咪唑并[1,2-a]嘧啶基、[1,2,4]三唑并[1,5-a]嘧啶基、异噁唑并[5,4-c]哒嗪基、异噁唑并[3,4-c]哒嗪基及[1,2,4]三唑并[4,3-b]哒嗪基，其各自任选地被 1、2 或 3 个 R^{10} 取代，且进一步任选地被 1 或 2 个 R^{10a} 取代；或其中 M^1 基团选自：嘧啶基、吡嗪基、吡啶基、哒嗪基、1H-吡啶基、1H-吡咯基、4H-吡啶基、1H-咪唑基、1H-咪唑基、3-氧代-2H-哒嗪基、1H-2-氧代-嘧啶基、1H-2-氧代-吡啶基、2,4(1H,3H)-二氧代-嘧啶基及 1H-2-氧代-吡嗪基，其各自被 R^9 取代，且进一步任选地被 1、2 或 3 个 R^{10} 取代。

15. 权利要求 12 的化合物或其药学上可接受的盐, 其中:



R^{10a} 为 C_{1-4} 烷基、 C_{1-4} 卤代烷基或 C_{3-7} 环烷基; 且

t 为 0 或 1。

16. 权利要求 1 至 15 中任一项的化合物或其药学上可接受的盐, 其中 R^9 为 C_{1-4} 烷基或 $-CN$; 且各 R^{10} 独立地为 C_{1-4} 烷基。

17. 权利要求 1 的化合物或其药学上可接受的盐, 所述化合物选自:

4-[4-(4,6-二甲基嘧啶-5-基)-3-氟苯氧基]-1H-吡咯并[3,2-c]吡啶;

(+)-4,6-二甲基-5-[2-甲基-4-(1H-吡唑并[4,3-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮;

(-)-4,6-二甲基-5-[2-甲基-4-(1H-吡唑并[4,3-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮;

4-[4-(4,6-二甲基嘧啶-5-基)-3-甲基苯氧基]-1H-吡咯并[3,2-c]吡啶;

4-[4-(4,6-二甲基嘧啶-5-基)-3-甲基苯氧基]-1H-吡唑并[4,3-c]吡啶;

4,6-二甲基-5-[4-(1H-吡咯并[3,2-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮;

(-)-1,5-二甲基-6-[2-甲基-4-(1H-吡唑并[4,3-c]吡啶-4-基氧基)苯基]嘧啶-2,4(1H,3H)-二酮;

4,6-二甲基-5-[2-甲基-4-(1H-吡咯并[3,2-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮, ENT-1;

4,6-二甲基-5-[2-甲基-4-(1H-吡咯并[3,2-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮, ENT-2;

4-[4-(4,6-二甲基-1-氧化嘧啶-5-基)-3-甲基苯氧基]-1H-吡唑并[4,3-c]吡啶;

6-甲基-5-[2-甲基-4-(1H-吡咯并[3,2-c]吡啶-4-基氧基)苯基]咪唑并[1,2-a]吡啶;

4-[4-(4,6-二甲基嘧啶-5-基)苯氧基]-1H-吡咯并[3,2-c]吡啶;

2-(4,6-二甲基嘧啶-5-基)-5-(1H-吡咯并[3,2-c]吡啶-4-基氧基)苯甲腈;

4-[3-氯-4-(4,6-二甲基嘧啶-5-基)苯氧基]-1H-吡咯并[3,2-c]吡啶;

(-)-1,5-二甲基-6-[2-甲基-4-(1H-吡咯并[3,2-c]吡啶-4-基氧基)苯基]吡嗪-2(1H)-酮;

4-[4-(4,6-二甲基嘧啶-5-基)-3-氟苯氧基]-1H-吡唑并[4,3-c]吡啶；
4-[4-(4,6-二甲基嘧啶-5-基)-3-甲氧基苯氧基]-1H-吡唑并[4,3-c]吡啶；
4-[3-氯-4-(4,6-二甲基嘧啶-5-基)苯氧基]-1H-吡唑并[4,3-c]吡啶；
(+)-1,5-二甲基-6-[2-甲基-4-(1H-吡唑并[4,3-c]吡啶-4-基氧基)苯基]吡
嗪-2(1H)-酮；
4,6-二甲基-5-[4-(1H-吡唑并[4,3-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮；
及
1,5-二甲基-6-[4-(1H-吡唑并[4,3-c]吡啶-4-基氧基)苯基]嘧啶-2,4(1H,3H)-二
酮。

18. 药物组合物，其包含权利要求 1-17 中任一项的化合物或其药学上可接受的盐，及药学上可接受的载体。

19. 治疗哺乳动物中 D1 介导（或 D1 相关）的病症的方法，所述方法包括向所述哺乳动物给药治疗有效量的权利要求 1-17 中任一项的化合物或其药学上可接受的盐。

20. 治疗人的病症的方法，所述方法包括向所述人给药治疗有效量的权利要求 1-17 中任一项的化合物或其药学上可接受的盐，其中所述病症选自精神分裂症（例如精神分裂症中的认知症状及负性症状）、认知损害〔例如与精神分裂症相关的认知损害、与 AD 相关的认知损害、与 PD 相关的认知损害、与药物疗法（例如 D2 拮抗剂疗法）相关的认知损害〕、注意缺陷多动障碍（ADHD）、冲动、强迫性赌博、进食过量、自闭症谱系障碍、轻度认知损害（MCI）、年龄相关的认知下降、痴呆（例如老年痴呆、HIV 相关的痴呆、阿尔茨海默痴呆、Lewy 体性痴呆、血管性痴呆或额颞叶型痴呆）、下肢不宁综合征（RLS）、帕金森氏病、亨廷顿舞蹈症、焦虑、抑郁症（例如年龄相关的抑郁症）、重度抑郁症（MDD）、难治性抑郁症（TRD）、双相型障碍、慢性情感淡漠、兴趣缺失、慢性疲劳、创伤后应激障碍、季节性情感障碍、社交焦虑障碍、产后抑郁症、血清素综合征、物质滥用及药物依赖、药物滥用复发、图雷特综合征、迟发性运动障碍、嗜睡、过度日间嗜睡、恶病质、注意力不集中、性功能障碍（例如勃起功能障碍或 SSRI 后性功能障碍）、偏头痛、系统性红斑狼疮（SLE）、高血糖症、动脉粥样硬化、血脂异常、肥胖症、糖尿病、败血症、缺血后肾小管坏死、肾衰竭、低钠血症、顽固性水肿、发作性睡病、高血压、充血性心力衰竭、手术后眼部张力过低、睡眠障碍及疼痛。

作为多巴胺 D1 配体的杂芳族化合物

发明领域

[0001] 本发明大体上涉及杂芳族化合物,其为多巴胺 D1 配体,例如多巴胺 D1 激动剂或部分激动剂。

[0002] 发明背景

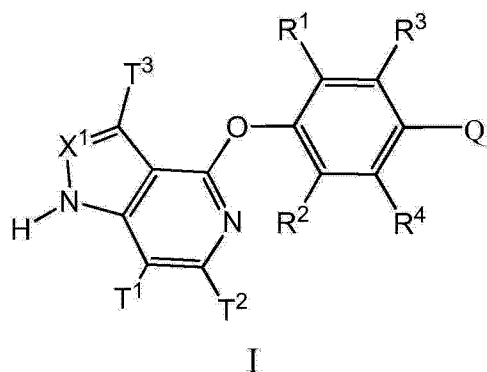
[0003] 多巴胺通过两种多巴胺受体家族 (D1 样受体 (D1R) 及 D2 样受体 (D2R)) 而对神经元起作用。D1 样受体家族由在大脑的许多区域中表达的 D1 及 D5 受体组成。已在例如纹状体及伏隔核 (nucleus accumbens) 中发现 D1mRNA。参见例如 Missale C, Nash SR, Robinson SW, Jaber M, Caron MG “Dopamine receptors: from structure to function”, *Physiological Reviews* 78:189-225(1998)。药理学研究已报道 D1 及 D5 受体 (D1/D5) (即 D1 样受体) 与腺苷酸环化酶的刺激有关,而 D2、D3 及 D4 受体 (即 D2 样受体) 与 cAMP 产生的抑制有关。

[0004] 多巴胺 D1 受体牵涉大量神经药理学及神经生物学功能。例如, D1 受体涉及不同类型的记忆功能及突触可塑性。参见例如 Goldman-Rakic PS 等人, “Targeting the dopamine D1 receptor in schizophrenia: insights for cognitive dysfunction”, *Psychopharmacology* 174(1):3-16(2004)。此外, D1 受体已牵涉多种精神、神经、神经发育、神经变性、情绪、动机性、代谢、心血管、肾、眼、内分泌和 / 或本文中描述的其它病症,包括精神分裂症 (例如精神分裂症中的认知症状及负性症状)、与 D2 拮抗剂疗法相关的认知损害、ADHD、冲动、自闭症谱系障碍 (autism spectrum disorder)、轻度认知损害 (MCI)、年龄相关的认知下降、阿尔茨海默痴呆、帕金森氏病 (PD)、亨廷顿舞蹈症、抑郁症、焦虑、难治性抑郁症 (TRD)、双相型障碍、慢性情感淡漠、兴趣缺失、慢性疲劳、创伤后应激障碍、季节性情感障碍、社交焦虑障碍、产后抑郁症、血清素综合征、物质滥用及药物依赖、图雷特综合征 (Tourette's syndrome)、迟发性运动障碍、嗜睡、性功能障碍、偏头痛、系统性红斑狼疮 (SLE)、高血糖症、血脂异常、肥胖症、糖尿病、败血症、缺血后肾小管坏死、肾衰竭、顽固性水肿 (resistant edema)、发作性睡病、高血压、充血性心力衰竭、手术后眼部张力过低、睡眠障碍、疼痛及哺乳动物中的其它病症。参见例如 Goulet M, Madras BK “D(1) dopamine receptor agonists are more effective in alleviating advanced than mild parkinsonism in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-treated monkeys”, *Journal of Pharmacology and Experimental Therapy* 292(2):714-24(2000); Surmeier DJ 等人, “The role of dopamine in modulating the structure and function of striatal circuits”, *Prog. Brain Res.* 183:149-67(2010)。

[0005] 为了研发新颖且更有效的药物以治疗与 D1 活化失调相关的疾病或病况 (诸如本文中描述的那些), 需要调节 (诸如激动或部分激动) D1 的新颖或改良的药剂。

[0006] 发明概述

[0007] 本发明一部分提供式 I 的化合物：



[0008] 或其药学上可接受的盐，其中：

[0009] X^1 为 N 或 CT^4 ；

[0010] Q^1 为含 N 的 5 元至 6 元杂芳基或含 N 的 5 元至 6 元杂环烷基，其各自任选地被一个 R^9 取代，且进一步任选地被 1、2、3 或 4 个 R^{10} 取代；

[0011] T^1 、 T^2 、 T^3 及 T^4 各自独立地选自：H、卤素、 $-CN$ 、 C_{1-4} 烷基、 C_{1-4} 卤代烷基、环丙基、氟环丙基、 C_{1-4} 烷氧基、 C_{1-4} 卤代烷氧基及 $-C(=O)-O-(C_{1-4}$ 烷基)；

[0012] R^1 及 R^2 各自独立地选自：H、卤素、 $-CN$ 、 C_{1-6} 烷基、 C_{1-6} 卤代烷基、 C_{1-6} 烷氧基、 C_{1-6} 卤代烷氧基、 C_{3-6} 环烷基、 $-C(=O)OH$ 及 $-C(=O)-O-(C_{1-4}$ 烷基)，其中所述 C_{1-6} 烷基及 C_{3-6} 环烷基各自任选地被 1、2、3、4 或 5 个各自独立地选自以下的取代基取代：卤代、 $-OH$ 、 $-CN$ 、 C_{1-4} 烷基、 C_{1-4} 卤代烷基、 C_{1-4} 烷氧基及 C_{1-4} 卤代烷氧基；

[0013] R^3 及 R^4 各自独立地选自：H、卤素、 $-OH$ 、 $-NO_2$ 、 $-CN$ 、 $-SF_5$ 、 C_{1-6} 烷基、 C_{1-6} 卤代烷基、 C_{1-6} 卤代烷氧基、 C_{2-6} 烯基、 C_{2-6} 炔基、 C_{3-7} 环烷基、4 元至 10 元杂环烷基、 $-N(R^5)(R^6)$ 、 $-N(R^7)(C(=O)R^8)$ 、 $-C(=O)-N(R^5)(R^6)$ 、 $-C(=O)R^8$ 、 $-C(=O)-OR^8$ 、 $-N(R^7)(S(=O)_2R^8)$ 、 $-S(=O)_2-N(R^5)(R^6)$ 、 $-SR^8$ 及 $-OR^8$ ，其中所述 C_{1-6} 烷基、 C_{3-7} 环烷基及杂环烷基各自任选地被 1、2 或 3 个各自独立地选自下列的取代基取代：卤素、 $-CN$ 、 $-OH$ 、 C_{1-4} 烷基、 C_{1-4} 烷氧基、 C_{1-4} 卤代烷基、 C_{1-4} 卤代烷氧基、 C_{3-6} 环烷基、 $-N(R^5)(R^6)$ 、 $-N(R^7)(C(=O)R^8)$ 、 $-C(=O)-OR^8$ 、 $-C(=O)H$ 、 $-C(=O)N(R^5)(R^6)$ 、 $-N(R^7)(S(=O)_2R^8)$ 、 $-S(=O)_2-N(R^5)(R^6)$ 、 $-SR^8$ 及 $-OR^8$ ；

[0014] R^5 为 H、 C_{1-4} 烷基、 C_{1-4} 卤代烷基或 C_{3-7} 环烷基；

[0015] R^6 为 H 或选自： C_{1-4} 烷基、 C_{1-4} 卤代烷基、 C_{3-7} 环烷基、4 元至 10 元杂环烷基、 C_{6-10} 芳基、5 元至 10 元杂芳基、 $(C_{3-7}$ 环烷基)- C_{1-4} 烷基-、(4 元至 10 元杂环烷基)- C_{1-4} 烷基-、 $(C_{6-10}$ 芳基)- C_{1-4} 烷基- 及 (5 元至 10 元杂芳基)- C_{1-4} 烷基-，其中上述各个选项任选地被 1、2、3 或 4 个各自独立地选自下列的取代基取代： $-OH$ 、 $-CN$ 、 C_{1-4} 烷基、 C_{3-7} 环烷基、 C_{1-4} 羟基烷基、 $-S-C_{1-4}$ 烷基、 $-C(=O)H$ 、 $-C(=O)-C_{1-4}$ 烷基、 $-C(=O)-O-C_{1-4}$ 烷基、 $-C(=O)-NH_2$ 、 $-C(=O)-N(C_{1-4}$ 烷基) $_2$ 、 C_{1-4} 卤代烷基、 C_{1-4} 烷氧基及 C_{1-4} 卤代烷氧基；

[0016] 或 R^5 及 R^6 与它们所连接的 N 原子一起形成 4 元至 10 元杂环烷基或 5 元至 10 元杂芳基，其各自任选地被 1、2、3、4 或 5 个各自独立地选自下列的取代基取代：卤素、 $-OH$ 、氧代、 $-C(=O)H$ 、 $-C(=O)OH$ 、 $-C(=O)-C_{1-4}$ 烷基、 $-C(=O)-NH_2$ 、 $-C(=O)-N(C_{1-4}$ 烷基) $_2$ 、 $-CN$ 、 C_{1-4} 烷基、 C_{1-4} 烷氧基、 C_{1-4} 羟基烷基、 C_{1-4} 卤代烷基及 C_{1-4} 卤代烷氧基；

[0017] R^7 选自：H、 C_{1-4} 烷基及 C_{3-7} 环烷基；

[0018] R^8 选自： C_{1-6} 烷基、 C_{3-7} 环烷基、4 元至 14 元杂环烷基、 C_{6-10} 芳基、5 元至 10 元杂芳基、 $(C_{3-7}$ 环烷基)- C_{1-4} 烷基-、(4 元至 10 元杂环烷基)- C_{1-4} 烷基-、 $(C_{6-10}$ 芳基)- C_{1-4} 烷基- 及

(5 元至 10 元杂芳基)-C₁₋₄烷基-, 其中上述各个选项任选地被 1、2 或 3 个各自独立地选自下列的取代基取代: 卤素、-CF₃、-CN、-OH、氧代、-S-C₁₋₄烷基、C₁₋₄烷基、C₁₋₄卤代烷基、C₂₋₆烯基、C₂₋₆炔基、C₃₋₇环烷基、C₁₋₄烷氧基及 C₁₋₄卤代烷氧基;

[0019] R⁹为 C₁₋₄烷基、C₁₋₄卤代烷基、-CN、-SF₅、-N(R⁵)(R⁶)、C₁₋₆烷氧基、C₁₋₆卤代烷氧基、C₃₋₇环烷氧基或 C₃₋₇环烷基, 其中所述 C₁₋₄烷基及 C₃₋₇环烷基各自任选地被 1、2、3、4 或 5 个各自独立地选自下列的取代基取代: 卤素、-N(R⁵)(R⁶)、C₁₋₄烷基、C₁₋₄卤代烷基、C₃₋₇环烷基、C₁₋₄烷氧基及 C₁₋₄卤代烷氧基;

[0020] 各 R¹⁰独立地选自: 卤素、-OH、-CN、-SF₅、-NO₂、氧代、硫羰基(“=S”)、C₁₋₆烷基、C₁₋₆卤代烷基、C₁₋₆羟基烷基、C₁₋₆烷氧基、C₁₋₆卤代烷氧基、C₃₋₇环烷基、C₂₋₆烯基、C₂₋₆炔基、C₆₋₁₀芳基、4 元至 10 元杂环烷基、5 元至 10 元杂芳基、(C₃₋₇环烷基)-C₁₋₄烷基-、(4 元至 10 元杂环烷基)-C₁₋₄烷基-、(C₆₋₁₀芳基)-C₁₋₄烷基-、(5 元至 10 元杂芳基)-C₁₋₄烷基-、-N(R⁵)(R⁶)、-N(R⁷)(C(=O)R⁸)、-S(=O)₂N(R⁵)(R⁶)、-C(=O)-N(R⁵)(R⁶)、-C(=O)-R⁸、-C(=O)-OR⁸、-SR⁸及 -OR⁸, 其中所述 C₁₋₆烷基、C₃₋₇环烷基、C₆₋₁₀芳基、4 元至 10 元杂环烷基、5 元至 10 元杂芳基、(C₃₋₇环烷基)-C₁₋₄烷基-、(4 元至 10 元杂环烷基)-C₁₋₄烷基-、(C₆₋₁₀芳基)-C₁₋₄烷基-及 (5 元至 10 元杂芳基)-C₁₋₄烷基-各自任选地被 1、2、3 或 4 个各自独立地选自下列的取代基取代: 卤素、OH、-CN、-NO₂、C₁₋₄烷基、C₁₋₄羟基烷基、C₁₋₄烷氧基、-N(R⁵)(R⁶)、-S-(C₁₋₄烷基)、-S(=O)₂-(C₁₋₄烷基)、C₆₋₁₀芳基氧基、[任选地被 1 或 2 个 C₁₋₄烷基取代的 (C₆₋₁₀芳基)-C₁₋₄烷基氧基-]、氧代、-C(=O)H、-C(=O)-C₁₋₄烷基、-C(=O)O-C₁₋₄烷基、-C(=O)NH₂、-NHC(=O)H、-NHC(=O)-(C₁₋₄烷基)、C₃₋₇环烷基、5 元或 6 元杂芳基、C₁₋₄卤代烷基及 C₁₋₄卤代烷氧基;

[0021] 或 R⁹及邻近的 R¹⁰与它们所连接的 Q¹上的两个环原子一起形成稠合苯环或稠合 5 元或 6 元杂芳基, 其各自任选地被 1、2、3、4 或 5 个独立地选择的 R^{10a}取代; 且

[0022] 各 R^{10a}独立地选自: 卤素、-OH、-N(R⁵)(R⁶)、-C(=O)OH、-C(=O)-C₁₋₄烷基、-C(=O)-NH₂、-C(=O)-N(C₁₋₄烷基)₂、-CN、-SF₅、C₁₋₄烷基、C₁₋₄烷氧基、C₁₋₄羟基烷基、C₁₋₄卤代烷基及 C₁₋₄卤代烷氧基;

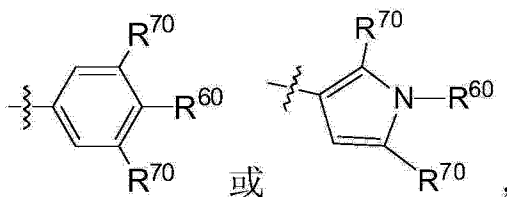
[0023] 条件是式 I 的化合物不为 4-(4-咪唑-1-基-苯氧基)-3-甲基-1H-吡唑并[4,3-c]吡啶。

[0024] 本发明还提供组合物(例如药物组合物), 其包含式 I 的化合物(包括其 N-氧化物或所述化合物或所述 N-氧化物的药学上可接受的盐)。

[0025] 式 I 的化合物(包括其 N-氧化物, 及所述化合物或所述 N-氧化物的药学上可接受的盐)为 D1 调节剂(例如 D1 激动剂或部分激动剂)。相应地, 本发明进一步提供用于治疗 D1 介导(或 D1 相关)的病症(例如认知损害, 诸如与精神分裂症相关的认知损害或与阿尔茨海默病相关的认知损害; 精神分裂症; 阿尔茨海默病或帕金森氏病)的方法, 其包括向需要其的哺乳动物(例如人)给药有效调节(例如激动或部分激动)D1 的量的式 I 的化合物(包括其药学上可接受的盐, 或所述化合物或盐的 N-氧化物)。

[0026] 如本文中所使用, 描述环结构上两个取代基的相对位置的术语“邻近的”指分别连接至相同环的两个成环原子上的两个取代基, 其中所述两个成环原子通过化学键直接连接。例如, 在各个以下结构中:

[0027]



[0028] 两个 R^{70} 基团中的每一个均为 R^{60} 的邻近基团。

[0029] 如本文中所使用,其中 n 为整数的术语“ n 元”通常描述基团中成环原子的数目,其中成环原子的数目为 n 。例如,吡啶为 6 元杂芳基环的实例,并且噻吩为 5 元杂芳基的实例。

[0030] 在本说明书中多个位置处,本发明的化合物的取代基以组或范围的形式公开。具体地,意图使本发明包括这样的组及范围的成员的各个及每一个单独的子组合(subcombination)。例如,术语“ C_{1-6} 烷基”具体意图包括 C_1 烷基(甲基)、 C_2 烷基(乙基)、 C_3 烷基、 C_4 烷基、 C_5 烷基及 C_6 烷基。另外例如,术语“5 元至 10 元杂芳基”具体意图包括任何 5 元、6 元、7 元、8 元、9 元或 10 元杂芳基。

[0031] 如本文中所使用,术语“烷基”定义为包括饱和脂肪族烃,所述饱和脂肪族烃包括直链及支链。在一些实施方案中,烷基具有 1 至 6 个,例如 1 至 4 个碳原子。例如,如本文中所使用,术语“ C_{1-6} 烷基”以及本文中所提及的其它基团(例如 C_{1-6} 烷氧基)的烷基部分指 1 至 6 个碳原子的线性或支化的基团(例如甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基、叔丁基、正戊基或正己基),其任选地被 1 或多个(诸如 1 至 5 个)适合的取代基取代。术语“ C_{1-4} 烷基”指 1 至 4 个碳原子的线性或支化的脂肪族烃链(即甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基、叔丁基)。术语“ C_{1-3} 烷基”指 1 至 3 个碳原子的线性或支化的脂肪族烃链。

[0032] 如本文中所使用,术语“烯基”指具有至少一个碳碳双键的脂肪族烃,其包括具有至少一个碳碳双键的直链及支链。在一些实施方案中,所述烯基具有 2 至 6 个碳原子。在一些实施方案中,所述烯基具有 2 至 4 个碳原子。例如,如本文中所使用,术语“ C_{2-6} 烯基”意指 2 至 6 个碳原子的直链或支链的不饱和基团,其包括(但不限于)乙烯基、1-丙烯基、2-丙烯基(烯丙基)、异丙烯基、2-甲基-1-丙烯基、1-丁烯基、2-丁烯基等,其任选地被 1 至 5 个适合的取代基取代。当式 I 的化合物含有一个烯基时,该烯基可以纯 E 形式、纯 Z 形式或其任意混合物的形式存在。

[0033] 如本文中所使用,术语“炔基”指具有至少一个碳碳三键的脂肪族烃,其包括具有至少一个碳碳三键的直链及支链。在一些实施方案中,所述炔基具有 2 至 6 个碳原子。例如,如本文中所使用,本文中所使用的术语“ C_{2-6} 炔基”意指具有 2 至 6 个碳原子及一个三键的如上文所定义的线性或支化的烃链炔基,其任选地被 1 或多个(诸如 1 至 5 个)适合的取代基取代。

[0034] 如本文中所使用,术语“环烷基”指饱和或不饱和的非芳族单环或多环(诸如双环)烃环(例如单环,诸如环丙基、环丁基、环戊基、环己基、环庚基、环辛基、环壬基,或双环,包括螺环、稠合或桥连系统(诸如双环[1.1.1]戊基、双环[2.2.1]庚基、双环[3.2.1]辛基或双环[5.2.0]壬基、十氢化萘基等),其任选地被 1 或多个(诸如 1 至 5 个)适合的取代基取代。所述环烷基具有 3 至 15 个碳原子。在一些实施方案中,所述环烷基可任选地包含一个、两个或更多个非累积性(non-cumulative)非芳族双键或三键和/或一至三个

氧代基团。在一些实施方案中,双环烷基具有 6 至 15 个碳原子。例如,术语“ C_{3-7} 环烷基”指 3 至 7 个成环碳原子的饱和或不饱和的非芳族单环或多环(诸如双环)烃环(例如环丙基、环丁基、环戊基、环己基或双环[1.1.1]戊基)。另外例如,术语“ C_{3-6} 环烷基”指 3 至 6 个成环碳原子的饱和或不饱和的非芳族单环或多环(诸如双环)烃环。又另外例如,术语“ C_{3-4} 环烷基”指环丙基或环丁基。在环烷基的定义中还包括具有一或多个稠合至环烷基环的芳环(包括芳基及杂芳基)的基团,例如环戊烷、环戊烯、环己烷等的苯并或噻吩基衍生物(例如 2,3-二氢-1H-茚-1-基或 1H-茚-2(3H)-酮-1-基)。环烷基任选地被 1 或多个(诸如 1 至 5 个)适合的取代基取代。

[0035] 如本文中所使用,术语“芳基”指具有共轭 π 电子系统的全碳单环或稠合环多环芳族基团。芳基在一个或多个环中具有 6 或 10 个碳原子。芳基最常在环中具有 6 个碳原子。例如,如本文中所使用,术语“ C_{6-10} 芳基”意指含有 6 至 10 个碳原子的芳族基团,诸如苯基或萘基。芳基任选地被 1 或多个(诸如 1 至 5 个)适合的取代基取代。

[0036] 如本文中所使用,术语“杂芳基”指在至少一个环中具有一或多个各自独立地选自 O、S 及 N 的杂原子环成员(成环原子)的单环或稠合环多环芳族杂环基团。杂芳基具有 5 至 14 个成环原子,其包括 1 至 13 个碳原子及 1 至 8 个选自 O、S 及 N 的杂原子。在一些实施方案中,所述杂芳基具有 5 至 10 个成环原子(包括一至四个杂原子)。所述杂芳基还可含有一至三个氧代或硫羰基。在一些实施方案中,所述杂芳基具有 5 至 8 个成环原子(包括一、二或三个杂原子)。单环杂芳基的实例包括具有 5 个成环原子(包括一至三个杂原子)的那些,或具有 6 个成环原子(包括一、二或三个氮杂原子)的那些。稠合双环杂芳基的实例包括两个稠合的 5 元和/或 6 元单环(包括一至四个杂原子)。

[0037] 杂芳基的实例包括吡啶基、吡嗪基、嘧啶基、哒嗪基、噻吩基、呋喃基、咪唑基、吡咯基、噁唑基(例如 1,3-噁唑基、1,2-噁唑基)、噻唑基(例如 1,2-噻唑基、1,3-噻唑基)、吡唑基、四唑基、三唑基(例如 1,2,3-三唑基、1,2,4-三唑基)、噁二唑基(例如 1,2,3-噁二唑基)、噻二唑基(例如 1,3,4-噻二唑基)、喹啉基、异喹啉基、苯并噻吩基、苯并呋喃基、吲哚基、1H-咪唑并[4,5-c]吡啶基、咪唑并[1,2-a]吡啶基、1H-吡咯并[3,2-c]吡啶基、咪唑并[1,2-a]吡嗪基、咪唑并[2,1-c][1,2,4]三嗪基、咪唑并[1,5-a]吡嗪基、咪唑并[1,2-a]嘧啶基、1H-吲唑基、9H-嘌呤基、咪唑并[1,2-a]嘧啶基、[1,2,4]三唑并[1,5-a]嘧啶基、[1,2,4]三唑并[4,3-b]哒嗪基、异噁唑并[5,4-c]哒嗪基、异噁唑并[3,4-c]哒嗪基、吡啶酮、嘧啶酮(pyrimidone)、吡嗪酮、嘧啶酮(pyrimidinone)、1H-咪唑-2(3H)-酮、1H-吡咯-2,5-二酮、3-氧代-2H-哒嗪基、1H-2-氧代-嘧啶基、1H-2-氧代-吡啶基、2,4(1H,3H)-二氧化-嘧啶基、1H-2-氧代-吡嗪基等。杂芳基任选地被 1 或多个(诸如 1 至 5 个)适合的取代基取代。

[0038] 如本文中所使用,术语“含 N 的”在与杂芳基或杂环烷基结合使用时意指所述杂芳基或杂环烷基包含至少一个成环氮(N)原子及任选的一或多个(例如 1、2、3 或 4 个)各自独立地选自 O、S 及 N 的成环杂原子。术语“含 N 的 5 元至 10 元杂芳基”指包含至少一个成环氮(N)原子及任选的一或多个(例如 1、2、3 或 4 个)各自独立地选自 O、S 及 N 的成环杂原子的 5 元至 10 元杂芳基(包括单环或双环系统)。术语“含 N 的 5 元或 6 元杂芳基”指包含至少一个成环氮(N)原子及任选的一或多个(例如 1、2、3 或 4 个)各自独立地选自 O、S 及 N 的成环杂原子的 5 元或 6 元杂芳基。含 N 的 5 元至 10 元杂芳基的实例包括吡啶基、

吡嗪基、嘧啶基、哒嗪基、咪唑基、吡咯基、噁唑基（例如 1, 3-噁唑基、1, 2-噁唑基）、噻唑基（例如 1, 2-噻唑基、1, 3-噻唑基）、吡唑基、四唑基、三唑基（例如 1, 2, 3-三唑基、1, 2, 4-三唑基）、噁二唑基（例如 1, 2, 3-噁二唑基）、噻二唑基（例如 1, 3, 4-噻二唑基）、喹啉基、异喹啉基、1H-咪唑并[4, 5-c]吡啶基、咪唑并[1, 2-a]吡啶基、1H-吡咯并[3, 2-c]吡啶基、咪唑并[1, 2-a]吡嗪基、咪唑并[2, 1-c][1, 2, 4]三嗪基、咪唑并[1, 5-a]吡嗪基、咪唑并[1, 2-a]嘧啶基、1H-吡啶基、9H-嘌呤基、咪唑并[1, 2-a]嘧啶基、[1, 2, 4]三唑并[1, 5-a]嘧啶基、[1, 2, 4]三唑并[4, 3-b]哒嗪基、异噁唑并[5, 4-c]哒嗪基、异噁唑并[3, 4-c]哒嗪基、吡啶酮、嘧啶酮(pyrimidone)、吡嗪酮、嘧啶酮(pyrimidinone)、1H-咪唑-2(3H)-酮、1H-吡咯-2, 5-二酮、3-氧代-2H-哒嗪基、1H-2-氧代-嘧啶基（例如 1H-2-氧代-嘧啶-6-基）、1H-2-氧代-吡啶基、2, 4(1H, 3H)-二氧代-嘧啶基、1H-2-氧代-吡嗪基等。含 N 的 5 元或 6 元杂芳基的实例包括吡啶基、吡嗪基、嘧啶基、哒嗪基、咪唑基、吡咯基、噁唑基（例如 1, 3-噁唑基、1, 2-噁唑基）、噻唑基（例如 1, 2-噻唑基、1, 3-噻唑基）、吡唑基、四唑基、三唑基（例如 1, 2, 3-三唑基、1, 2, 4-三唑基）、噁二唑基（例如 1, 2, 3-噁二唑基）、噻二唑基（例如 1, 3, 4-噻二唑基）、3-氧代-2H-哒嗪基、1H-2-氧代-嘧啶基（例如 1H-2-氧代-嘧啶-6-基）、1H-2-氧代-吡啶基、2, 4(1H, 3H)-二氧代-嘧啶基及 1H-2-氧代-吡嗪基。含 N 的 5 元至 10 元杂芳基或含 N 的 5 元或 6 元杂芳基任选地被 1 或多个（诸如 1 至 5 个）适合的取代基取代。

[0039] 如本文中所使用，术语“杂环烷基”指包含 1 至 14 个成环碳原子及 1 至 10 个各自独立地选自 O、S 及 N 的成环杂原子的单环或多环 [包含稠合在一起的 2 个或多个环，包括螺环、稠合或桥连系统，例如双环环系]、饱和或不饱和非芳族 4 元至 15 元环系（诸如 4 元至 14 元环系、4 元至 10 元环系、5 元至 10 元环系、4 元至 7 元环系或 5 元至 6 元环系）。例如，术语“4 元至 10 元杂环烷基”指包含一或多个各自独立地选自 O、S 及 N 的成环杂原子的单环或多环的饱和或不饱和非芳族 4 元至 10 元环系。另外例如，术语“4 元至 7 元杂环烷基”指包含一或多个各自独立地选自 O、S 及 N 的成环杂原子的单环或多环的饱和或不饱和非芳族 4 元至 7 元环系。又另外例如，术语“5 元至 6 元杂环烷基”指包含一或多个各自独立地选自 O、S 及 N 的成环杂原子的单环饱和或不饱和非芳族 5 元至 6 元环系。所述杂环烷基任选地被 1 或多个（诸如 1 至 5 个）适合的取代基取代。所述杂环烷基还可包含一至三个氧代或硫羰基。

[0040] 这样的杂环烷基环的实例包括氮杂环丁烷基、四氢呋喃基、咪唑烷基、吡咯烷基、哌啶基、哌嗪基、噁唑烷基、噻唑烷基、吡唑烷基、硫吗啉基(thiomorpholinyl)、四氢噻嗪基、四氢噻二嗪基、吗啉基、氧杂环丁烷基、四氢二嗪基、噁嗪基、噁噻嗪基、奎宁环基(quinuclidinyl)、色满基、异色满基、苯并噁嗪基、2-氮杂双环[2.2.1]庚酮基、3-氮杂双环[3.1.0]己基、3-氮杂双环[4.1.0]庚基等。杂环烷基环的其它实例包括四氢呋喃-2-基、四氢呋喃-3-基、咪唑烷-1-基、咪唑烷-2-基、咪唑烷-4-基、吡咯烷-1-基、吡咯烷-2-基、吡咯烷-3-基、哌啶-1-基、哌啶-2-基、哌啶-3-基、哌啶-4-基、哌嗪-1-基、哌嗪-2-基、1, 3-噁唑烷-3-基、1, 4-氧杂氮杂环庚烷-1-基、异噻唑烷基、1, 3-噻唑啉-3-基、1, 2-吡唑烷-2-基、1, 2-四氢噻嗪-2-基、1, 3-噻嗪烷-3-基、1, 2-四氢二嗪-2-基、1, 3-四氢二嗪-1-基、1, 4-噁嗪-4-基、噁唑烷酮基、2-氧代-哌啶基（例如 2-氧代-哌啶-1-基）等。在杂环烷基的定义中还包括具有一或多个稠合至非芳族杂环

烷基环上的芳环（包括芳基及杂芳基）的基团，例如吡啶基、嘧啶基、噻吩基、吡唑基、邻苯二甲酰亚胺基、萘二甲酰亚胺基及非芳族杂环烷基环的苯并衍生物。这样的芳族稠合杂环烷基的实例包括二氢吡啶基、异二氢吡啶基、异二氢吡啶-1-酮-3-基、5,7-二氢-6H-吡咯并[3,4-b]吡啶-6-基、6,7-二氢-5H-吡咯并[3,4-d]嘧啶-6-基、4,5,6,7-四氢噻吩并[2,3-c]吡啶-5-基、5,6-二氢噻吩并[2,3-c]吡啶-7(4H)-酮-5-基、1,4,5,6-四氢吡咯并[3,4-c]吡唑-5-基及3,4-二氢异喹啉-1(2H)-酮-3-基。所述杂环烷基任选地被1或多个（诸如1至5个）适合的取代基取代。所述杂环烷基的实例包括5元或6元单环及9元或10元稠合双环。

[0041] 如本文中所使用，术语“含N的4元至10元杂环烷基”指包含至少一个成环氮(N)原子及任选的一或多个各自独立地选自O、S及N的成环杂原子的4元至10元杂环烷基。术语“含N的5元或6元杂环烷基”指包含至少一个成环氮(N)原子及任选的一或多个各自独立地选自O、S及N的成环杂原子的5元或6元杂环烷基。含N的4元至10元杂环烷基的实例包括氮杂环丁烷基、哌啶-1-基、哌啶-4-基、哌嗪-1-基、1,3-噻嗪烷-3-基、1,4,5,6-四氢吡咯并[3,4-c]吡唑-5-基及3,4-二氢异喹啉-1(2H)-酮-3-基。含N的5元或6元杂环烷基的实例包括哌啶-1-基、哌啶-4-基、哌嗪-1-基、1,3-噻嗪烷-3-基及吗啉代基。含N的4元至10元杂环烷基或含N的5元或6元杂环烷基任选地被1或多个（诸如1至5个）适合的取代基取代。

[0042] 如本文中所使用，术语“卤代”或“卤素”基团定义为包括氟、氯、溴或碘。

[0043] 如本文中所使用，术语“卤代烷基”指具有一或多个卤素取代基的烷基（至多全卤代烷基，即烷基的每个氢原子均被卤素原子替换）。例如，术语“C₁₋₆卤代烷基”指具有一或多个卤素取代基的C₁₋₆烷基（至多全卤代烷基，即烷基的每个氢原子均被卤素原子替换）。术语“C₁₋₄卤代烷基”指具有一或多个卤素取代基的C₁₋₄烷基（至多全卤代烷基，即烷基的每个氢原子均被卤素原子替换）。术语“C₁₋₃卤代烷基”指具有一或多个卤素取代基的C₁₋₃烷基（至多全卤代烷基，即烷基的每个氢原子均被卤素原子替换）。术语“C₁卤代烷基”指具有一、二或三个卤素取代基的甲基。卤代烷基的实例包括CF₃、C₂F₅、CHF₂、CH₂F、CH₂CF₃、CH₂Cl等。

[0044] 如本文中所使用，术语“烷氧基”或“烷基氧基”指-O-烷基。术语“C₁₋₆烷氧基”或“C₁₋₆烷基氧基”指-O-(C₁₋₆烷基)。术语“C₁₋₄烷氧基”或“C₁₋₄烷基氧基”指-O-(C₁₋₄烷基)。术语“C₁₋₃烷氧基”或“C₁₋₃烷基氧基”指-O-(C₁₋₃烷基)。烷氧基的实例包括甲氧基、乙氧基、丙氧基（例如正丙氧基及异丙氧基）、叔丁氧基等。

[0045] 如此处所使用，术语“卤代烷氧基”指-O-卤代烷基。术语“C₁₋₆卤代烷氧基”指-O-(C₁₋₆卤代烷基)。术语“C₁₋₄卤代烷氧基”指-O-(C₁₋₄卤代烷基)。术语“C₁₋₃卤代烷氧基”指-O-(C₁₋₃卤代烷基)。术语“C₁卤代烷氧基”指具有一、二或三个卤素取代基的甲氧基。卤代烷氧基的实例为-OCF₃或-OCHF₂。

[0046] 如本文中所使用，术语“环烷氧基”或“环烷基氧基”指-O-环烷基。术语“C₃₋₇环烷氧基”或“C₃₋₇环烷基氧基”指-O-(C₃₋₇环烷基)。环烷氧基的实例包括C₃₋₇环烷氧基（例如环丙氧基、环丁氧基、环戊氧基等）。

[0047] 如此处所使用，术语“C₆₋₁₀芳基氧基”指-O-(C₆₋₁₀芳基)。C₆₋₁₀芳基氧基的实例为-O-苯基[即苯氧基]。

[0048] 如本文中所使用,术语“氟烷基”指具有一或多个氟取代基的烷基(至多全氟烷基,即烷基的每个氢原子均被氟替换)。例如,术语“C₁₋₆氟烷基”指具有一或多个氟取代基的 C₁₋₆烷基(至多全氟烷基,即 C₁₋₆烷基的每个氢原子均被氟替换。术语“C₁氟烷基”指具有 1、2 或 3 个氟取代基的 C₁烷基(即甲基)。氟烷基的实例包括 CF₃、C₂F₅、CH₂CF₃、CHF₂、CH₂F 等。

[0049] 如此处所使用,术语“氟烷氧基”指 -O- 氟烷基。术语“C₁氟烷氧基”指具有一、二或三个氟取代基的甲氧基。C₁氟烷氧基的实例为 -OCF₃或 -OCHF₂。

[0050] 如本文中所使用,术语“氟环丙基”指具有一或多个氟取代基的环丙基(至多全氟环丙基,即环丙基的每个氢原子均被氟替换)。氟环丙基的实例包括 2- 氟 - 环丙 -1- 基或 2,3- 二氟环丙 -1- 基。

[0051] 如本文中所使用,术语“羟基烷基”或“羟烷基”指具有一或多个(例如 1、2 或 3 个)OH 取代基的烷基。术语“C₁₋₆羟基烷基”或“C₁₋₆羟烷基”指具有一或多个(例如 1、2 或 3 个)OH 取代基的 C₁₋₆烷基。术语“C₁₋₄羟基烷基”或“C₁₋₄羟烷基”指具有一或多个(例如 1、2 或 3 个)OH 取代基的 C₁₋₄烷基。羟基烷基的实例包括 -CH₂OH 及 -CH₂CH₂OH。

[0052] 如本文中所使用,术语“氧代”指 = O。当氧代在碳原子上取代时,其一起形成羰基基团 [-C(=O)-]。当一个氧代在硫原子上取代时,其一起形成亚磺酰基基团 [-S(=O)-] ; 当两个氧代在硫原子上取代时,其一起形成磺酰基基团 [-S(=O)₂-]。

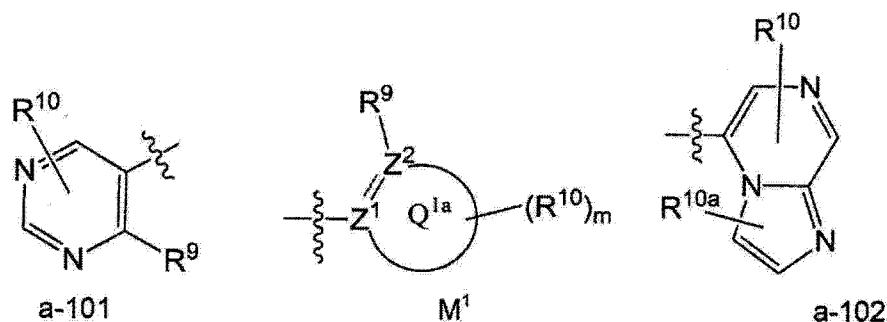
[0053] 如本文中所使用,术语“硫羰基”指 = S。当硫羰基在碳原子上取代时,其一起形成具有 -C(=S)- 结构的基团。

[0054] 如本文中所使用,术语“任选地被取代”意指取代为任选的,且因此包括未被取代与被取代的原子及基团。“被取代”的原子或基团表明在所指定的原子或基团上的任何氢可被来自指定的取代基群的选择替换(至多所指定的原子或基团上的每个氢原子均被来自指定的取代基群的选择替换),条件是不超过所指定的原子或基团的正常化合价,且取代产生稳定的化合物。例如,如果甲基(即 CH₃) 任选地被取代,则碳原子上至多 3 个氢原子可被取代基替换。

[0055] 如本文中所使用,除非指定,否则取代基的连接点可为取代基的任何适合的位置。例如,哌啶基可为哌啶 -1- 基(通过哌啶基的 N 原子连接)、哌啶 -2- 基(通过哌啶基 2- 位的 C 原子连接)、哌啶 -3- 基(通过哌啶基 3- 位的 C 原子连接)或哌啶 -4- 基(通过哌啶基 4- 位的 C 原子连接)。另外例如,吡啶基(pyridinyl)(或吡啶基(pyridyl))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)。

[0056] 当取代基的键显示为穿过环中连接两个原子的键时,则这样的取代基可键连至该可取代的环中的任一成环原子(即键连至一或多个氢原子)。例如,如以下式 a-101 中所示, R¹⁰可键连至两个环碳原子中的每一个,其中的每一个均携有氢原子。另外例如,如以下基团 M¹中所示, R¹⁰可键连至可取代的任何成环原子(即键连至一或多个氢原子;例如 C 或 N 成环原子)。又另外例如,如以下式 a-102(被取代的咪唑并 [1,2-a] 吡嗪环)中所示, R¹⁰可键连至吡嗪环中两个环碳原子中的每一个(其中的每一个均携有氢原子),且 R^{10a}可键连至咪唑并环中两个环碳原子中的每一个(其中的每一个均携有氢原子)。

[0057]



[0058] 当被取代或任选地被取代的基团在未表明所述基团键连至取代基所通过的原子的情況下加以描述时,则取代基可通过这样的基团中任何适当的原子进行键连。例如,在被取代的芳基烷基中,芳基烷基[例如(C₆₋₁₀芳基)-C₁₋₄烷基-]上的取代基可键连至芳基烷基的烷基部分或芳基部分上的任意碳原子。取代基和/或变量的组合为可容许的,只要这样的组合产生稳定化合物。

[0059] 如上所述,式I的化合物可以药学上可接受的盐的形式存在,诸如式I的化合物的酸加成盐和/或碱加成盐。除非另外说明,否则如本文中所使用的短语“药学上可接受的盐”包括可在式I的化合物中存在的酸加成盐或碱盐。

[0060] 式I的化合物的药学上可接受的盐包括其酸加成盐及碱盐。

[0061] 适合的酸加成盐由形成无毒盐的酸来形成。实例包括乙酸盐、己二酸盐、天冬氨酸盐、苯甲酸盐、苯磺酸盐、碳酸氢盐/碳酸盐、硫酸氢盐/硫酸盐、硼酸盐、樟脑磺酸盐、柠檬酸盐、环己氨磺酸盐、乙二磺酸盐、乙磺酸盐、甲酸盐、延胡索酸盐、葡庚糖酸盐、葡萄糖酸盐、葡萄糖醛酸盐、六氟磷酸盐、海苯酸盐、盐酸盐/氯化物、氢溴酸盐/溴化物、氢碘酸盐/碘化物、羟乙基磺酸盐、乳酸盐、苹果酸盐、顺丁烯二酸盐、丙二酸盐、甲磺酸盐、甲基硫酸盐、萘甲酸盐(naphthylate)、2-萘磺酸盐、烟酸盐、硝酸盐、乳清酸盐、草酸盐、棕榈酸盐、双羟萘酸盐、磷酸盐/磷酸氢盐/磷酸二氢盐、焦谷氨酸盐、糖二酸盐、硬脂酸盐、丁二酸盐、单宁酸盐、酒石酸盐、甲苯磺酸盐、三氟乙酸盐及昔萘酸盐(xinofoate)。

[0062] 适合的碱盐由形成无毒盐的碱来形成。实例包括铝盐、精氨酸盐、苜星青霉素盐、钙盐、胆碱盐、二乙胺盐、二乙醇胺盐、甘氨酸盐、赖氨酸盐、镁盐、葡甲胺盐、乙醇胺盐、钾盐、钠盐、氨丁三醇盐及锌盐。

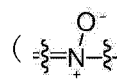
[0063] 还可形成酸与碱的半盐(hemisalt),例如半硫酸盐及半钙盐。

[0064] 适合的盐的综述参见Stahl及Wermuth的“Handbook of Pharmaceutical Salts: Properties, Selection, and Use”(Wiley-VCH, 2002)。用于制备式I的化合物的药学上可接受的盐的方法为本领域技术人员已知的。

[0065] 如本文中所使用,术语“式I”、“式I或其药学上可接受的盐”、“化合物的药学上可接受的盐或[式I]的盐”定义为包括式I的化合物的所有形式,包括其水合物、溶剂合物、异构体(包括例如旋转立体异构体)、结晶及非结晶形式、同晶型体、多晶型物、代谢物及前药。

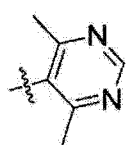
[0066] 如本领域技术人员已知,胺化合物(即包含一或多个氮原子的那些)(例如叔胺)可形成N-氧化物(还称为氧化胺或胺N-氧化物)。N-氧化物具有式(R¹⁰⁰R²⁰⁰R³⁰⁰)N⁺-O⁻,其中母体胺(R¹⁰⁰R²⁰⁰R³⁰⁰)N可为例如叔胺(例如R¹⁰⁰、R²⁰⁰、R³⁰⁰各自独立地为烷基、芳基烷基、芳基、杂芳基等)、杂环或杂芳族胺[例如(R¹⁰⁰R²⁰⁰R³⁰⁰)N共同形成1-烷基哌啶、1-烷基吡咯

烷、1-苯甲基吡咯烷或吡啶]。例如,亚胺氮原子(特别是杂环或杂芳族亚胺氮原子)或吡啶型氮(>N-)原子[诸如吡啶、哒嗪或吡嗪中的氮原子]可被N-氧化以形成包含基团

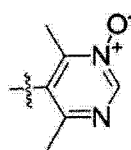


的N-氧化物。因此,包含一或多个氮原子(例如亚胺氮原子)作为例如式I的 Q^1 一部分的本发明的化合物能够形成其N-氧化物(例如单N-氧化物、双N-氧化物或多N-氧化物或其混合物,取决于适于形成稳定N-氧化物的氮原子数目)。例如,其中 Q^1 为任选地被取代的嘧啶基、吡嗪基、吡啶基或哒嗪基的式I的化合物可被氧化(例如在适合的氧化试剂(诸如间氯过氧苯甲酸)的存在下或在适合的酶的存在下)以形成其相应的N-氧化物,其中 Q^1 转化为其相应的N-氧化物形式。另外例如,其中 Q^1 为 Q^1 -101的式I的化合物可被氧化以形成其相应的N-氧化物,其中 Q^1 -101转化为 Q^1 -102。

[0067]



Q^1 -101



Q^1 -102

[0068] 如本文中所使用,术语“N-氧化物”指本文中描述的胺化合物(例如包含一或多个亚胺氮原子的化合物)的所有可能且特别是所有稳定的N-氧化物形式,诸如单N-氧化物(包括当在胺化合物的一个以上的氮原子可形成单N-氧化物时的不同的异构体)或多N-氧化物(例如双N-氧化物)或其任何比率的混合物。

[0069] 式I的化合物可被任选地转化为其N-氧化物,例如在适合的氧化试剂存在下于适合的溶剂中(例如在过氧化氢存在下于甲醇中,或在间氯过氧苯甲酸存在下于二氯甲烷中),或在酶(例如以代谢物形式形成其N-氧化物)存在下。本领域技术人员会容易地认识到适合于进行N-氧化反应的反应条件。

[0070] 本文中描述的式I的化合物(本发明的化合物)包括其N-氧化物及所述化合物或所述N-氧化物的药学上可接受的盐。式I的化合物的N-氧化物的实例包括其中式I的 Q^1 (例如任选地被取代的嘧啶基,诸如 Q^1 -101)能够形成其N-氧化物的那些。

[0071] 式I的化合物可以自完全无定形至完全结晶的范围内的连续固态形式存在。术语“无定形”指其中物质在分子水平上缺乏长程有序性,且取决于温度,可展现固体或液体的物理特性的状态。这样的物质通常不产生独特的X射线衍射图样,且尽管展现固体特性,但更正式地描述为液体。在加热时,自外观上固体变为具有液体特性的物质,其特征于状态的变化,通常为二级变化(“玻璃化转变”)。术语“结晶”指其中物质在分子水平上具有规则有序的内部结构且产生具有确定的峰的独特X射线衍射图样的固相。这样的物质在充分加热时还会展现液体的特性,但自固体变为液体的特征在于相变,通常为一级相变(“熔点”)。

[0072] 式I的化合物可以非溶剂化及溶剂化形式存在。当溶剂或水紧密结合时,络合物会具有与湿度无关的明确化学计量。然而当溶剂或水弱结合时(如在通道溶剂合物(channel solvate)及吸湿化合物中),水/溶剂含量会取决于湿度及干燥条件。在这样的情况下,非化学计量会是平均数(norm)。

[0073] 式 I 的化合物可以包含物或其它络合物（例如共晶）的形式存在。在本发明的范围内包括络合物，诸如包含物、药物-宿主包含络合物 (drug-host inclusion complexe)，其中药物及宿主以化学计量或非化学计量呈现。还包括含有两种或更多种有机和 / 或无机组分的式 I 的化合物的络合物，其可为化学计量的或非化学计量的。所得络合物可为离子化、部分离子化或非离子化的。共晶通常定义为通过非共价相互作用结合在一起的中性分子成分的结晶络合物，但还可为中性分子与盐的络合物。共晶可通过熔体结晶、通过自溶剂重结晶或通过将组分在一起物理研磨来制备；参见 O. Almarsson 及 M. J. Zaworotko, Chem. Commun. 2004, 17, 1889-1896。多组分络合物的一般性综述参见 J. K. Haleblan, J. Pharm. Sci. 1975, 64, 1269-1288。

[0074] 本发明的化合物在经受适合的条件时还可以介晶态（中间相或液晶）形式存在。介晶态为真正结晶状态与真正液态（熔体或溶液）之间的中间态。因温度变化而出现的介晶性描述为“热致性”的，因添加另一组分（诸如水或另一种溶剂）而产生的介晶性描述为“溶致性”的。具有形成溶致性中间相的潜力的化合物被描述为“两亲的”，并且由具有离子极性头基（诸如 $\text{-COO}^-\text{Na}^+$ 、 $\text{-COO}^-\text{K}^+$ 或 $\text{-SO}_3^-\text{Na}^+$ ）或非离子极性头基（诸如 $\text{-NN}^+(\text{CH}_3)_3$ ）的分子组成。更多信息参见 N. H. Hartshorne 及 A. Stuart 的 Crystals and the Polarizing Microscope, 第 4 版 (Edward Arnold, 1970)。

[0075] 本发明还涉及式 I 的化合物的前药。因此，本身可具有极少或不具有药理学活性的式 I 的化合物的某些衍生物在被向体内或体表给药时可例如通过水解分裂而转化为具有所需活性的式 I 的化合物。这样的衍生物称为“前药”。使用前药的其它信息可见于 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, American Pharmaceutical Association) 中。

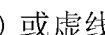
[0076] 本发明的前药可例如通过用本领域技术人员已知的某些基团（例如在 H. Bundgaard 的 Design of Prodrugs (Elsevier, 1985) 中所描述的“前-基团”）来替换式 I 的化合物中存在的适当官能团来产生。

[0077] 此外，某些式 I 的化合物本身可用作其它式 I 的化合物的前药。

[0078] 在本发明的范围内还包括式 I 的化合物的代谢物，即在给药药物时体内形成的化合物。式 I 的化合物的代谢物的实例包括式 I 的化合物的 N-氧化物，其中式 I 的 Q^1 能够形成其 N-氧化物（例如其中 Q^1 为任选地被取代的嘧啶基，诸如 4, 6-二甲基嘧啶-5-基）。

[0079] 在一些实施方案中，式 I 的化合物包括其 N-氧化物及所述化合物或所述 N-氧化物的药学上可接受的盐。

[0080] 式 I 的化合物包括所有立体异构体及互变异构体。式 I 的立体异构体包括式 I 的化合物的顺式及反式异构体、光学异构体（诸如 R 及 S 对映异构体、非对映异构体）、几何异构体、旋转异构体、阻转异构体及构象异构体，包括展现一种以上类型的异构现象的化合物；及其混合物（诸如外消旋体与非对映异构对）。还包括酸加成盐或碱加成盐，其中平衡离子为光学活性的（例如 D-乳酸盐或 L-赖氨酸）或外消旋的（例如 DL-酒石酸盐或 DL-精氨酸）。

[0081] 在一些实施方案中，式 I 的化合物可具有不对称碳原子。式 I 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（）来描绘。使用

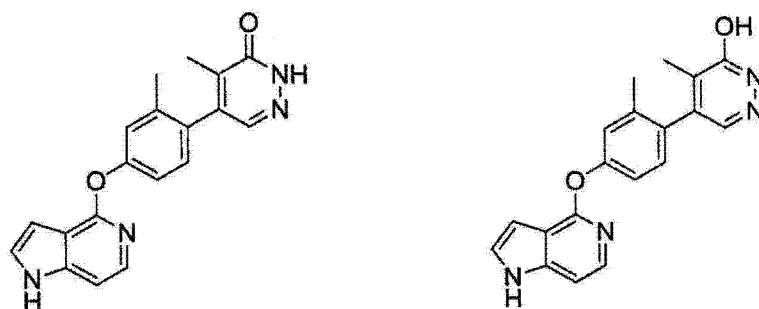
实线描绘连接至不对称碳原子的键意指包括该碳原子处的所有可能的立体异构体（例如具体对映异构体、外消旋混合物等）。使用实心或虚线楔形描绘连接至不对称碳原子的键意指仅意图包括所示的立体异构体。式 I 的化合物可能含有一个以上不对称碳原子。在那些化合物中，使用实线描绘连接至不对称碳原子的键意指意图包括所有可能的立体异构体。例如，除非另外说明，否则希望式 I 的化合物可以对映异构体及非对映异构体形式或以外消旋体及其混合物形式存在。使用实线描绘连接至式 I 的化合物中一或多个不对称碳原子的键并使用实心楔形或虚线楔形描绘连接至同一化合物中其它不对称碳原子的键意指存在非对映异构体的混合物。

[0082] 在一些实施方案中，式 I 的化合物可以阻转异构体形式存在和 / 或分离为阻转异构体（例如一或多种阻转对映异构体。本领域技术人员会认识到阻转异构性可在具有两个或更多个芳环（例如通过单键连接的两个芳环）的化合物中存在。参见例如 Freedman, T. B. 等人, Absolute Configuration Determination of Chiral Molecules in the Solution State Using Vibrational Circular Dichroism. *Chirality* 2003, 15, 743-758; 及 Bringmann, G. 等人, Atroposelective Synthesis of Axially Chiral Biaryl Compounds. *Angew. Chem., Int. Ed.* 2005, 44, 5384-5427。

[0083] 当任何外消旋体结晶时，可能有不同类型的晶体。一种类型为外消旋化合物（真正外消旋体），其中产生含有两种等摩尔量的对映异构体的一种均质形式晶体。另一种类型为外消旋混合物或聚集物，其中产生等摩尔量或不等摩尔量的各自包含单一对映异构体的两种形式的晶体。

[0084] 式 I 的化合物可展现互变异构及结构异构现象。例如，式 I 的化合物可以数种互变异构形式存在，包括烯醇与亚胺形式及酮与烯胺形式、以及几何异构体及其混合物。所有这样的互变异构形式均包括在式 I 的化合物的范围内。互变异构体可以溶液中互变异构集合的混合物形式存在。在固体形式中，通常一种互变异构体占大多数。即使可能描述一种互变异构体，本发明包括式 I 的化合物的所有互变异构体。例如，当在本文中的实验部分中揭示本发明的以下两种互变异构体之一时，本领域技术人员会容易认识到本发明还包括另一个。

[0085]



[0086] 本发明包括所有药学上可接受的同位素标记的式 I 的化合物，其中一或多个原子被具有相同原子序数但原子质量或质量数不同于在自然界中占大多数的原子质量或质量数的原子替换。

[0087] 适合于包含在本发明的化合物中的同位素的实例包括氢的同位素，诸如 ^2H 及 ^3H ；碳的同位素，诸如 ^{11}C 、 ^{13}C 及 ^{14}C ；氯的同位素，诸如 ^{36}Cl ；氟的同位素，诸如 ^{18}F ；碘的同位素，

诸如 ^{123}I 及 ^{125}I ; 氮的同位素, 诸如 ^{13}N 及 ^{15}N ; 氧的同位素, 诸如 ^{15}O 、 ^{17}O 及 ^{18}O ; 磷的同位素, 诸如 ^{32}P ; 及硫的同位素, 诸如 ^{35}S 。

[0088] 某些同位素标记的式 I 的化合物 (例如掺入放射性同位素的那些) 可用于药物和 / 或底物组织分布研究。由于放射性同位素氚 (即 ^3H) 及碳 -14 (即 ^{14}C) 易于掺入并有现成的检测手段, 所以其特别可用于此目的。

[0089] 用诸如氘 (即 ^2H) 的较重同位素取代可得到由较高代谢稳定性产生的某些治疗优势, 例如体内半衰期增加或剂量需求减少, 且因此在某些情况下可为优选的。

[0090] 用正电子发射同位素 (诸如 ^{11}C 、 ^{18}F 、 ^{15}O 及 ^{13}N) 取代可用于正电子发射断层造影术 (PET) 研究, 以检查底物受体占有率。

[0091] 同位素标记的式 I 的化合物 (或其药学上可接受的盐, 或者所述化合物或盐的 N-氧化物) 通常可通过本领域技术人员已知的常规技术或通过在本所附实施例及制备中所述的类似的方法, 使用适当的同位素标记的试剂代替先前采用的未标记试剂来制备。

[0092] 本发明的一实施方案为其中 X^1 为 N 的式 I 的化合物。

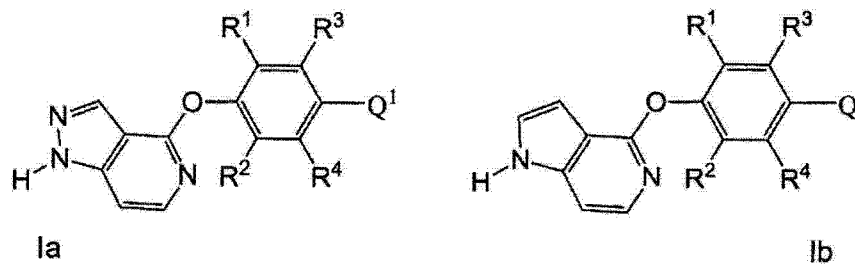
[0093] 本发明的一实施方案为其中 X^1 为 CT^4 的式 I 的化合物。

[0094] 本发明的一实施方案为其中 T^1 、 T^2 、 T^3 及 T^4 各自独立地选自 :H、F、-CN、甲氧基、 C_{1-4} 氟烷氧基、甲基及 C_{1-4} 氟烷基的式 I 的化合物。在另一个实施方案中, T^1 为 H。在另一个实施方案中, T^2 为 H。在另一个实施方案中, T^3 为 H、甲基或 -CN。在另一个实施方案中, T^3 为 H。在另一个实施方案中, T^4 为 H。

[0095] 本发明的一实施方案为其中 T^3 为 H 的式 I 的化合物。在另一个实施方案中, T^2 为 H 且 T^3 为 H。

[0096] 本发明的一实施方案为其中所述化合物为式 Ia 或 Ib 的化合物的式 I 的化合物 :

[0097]



[0098] 本发明的一实施方案为其中所述化合物为式 Ia 的化合物的式 I 的化合物。

[0099] 本发明的一实施方案为其中所述化合物为式 Ib 的化合物的式 I 的化合物。

[0100] 本发明的一实施方案为式 I 的化合物 (包括式 Ia 或 Ib 的化合物), 其中 :

[0101] R^1 及 R^2 各自独立地选自 :H、卤素、-CN、 C_{1-4} 烷基、 C_{1-4} 卤代烷基、 C_{1-4} 烷氧基、 C_{1-4} 卤代烷氧基及 C_{3-4} 环烷基 ;

[0102] R^3 及 R^4 各自独立地选自 :H、卤素、-OH、-CN、 C_{1-4} 烷基、 C_{1-4} 卤代烷基、 C_{1-4} 卤代烷氧基、 C_{3-4} 环烷基、4 元至 7 元杂环烷基、 $-\text{N}(\text{R}^5)(\text{R}^6)$ 及 $-\text{OR}^8$;

[0103] R^5 及 R^6 各自独立地为 H 或选自 : C_{1-4} 烷基、 C_{1-4} 卤代烷基及 C_{3-7} 环烷基 ;

[0104] 或 R^5 及 R^6 与它们所连接的 N 原子一起形成 4 元至 7 元杂环烷基或 5 元杂芳基, 其各自任选地被 1、2 或 3 个各自独立地选自下列的取代基取代 : 卤素、-CN、 C_{1-4} 烷基、 C_{1-4} 烷氧基、 C_{3-6} 环烷基、 C_{1-4} 卤代烷基及 C_{1-4} 卤代烷氧基 ; 且

[0105] R^8 选自： C_{1-4} 烷基、 C_{3-6} 环烷基、4元至7元杂环烷基、苯基及5元至6元杂芳基，其各自任选地被1、2或3个各自独立地选自下列的取代基取代：卤素、 $-\text{CN}$ 、 C_{1-4} 烷基、 C_{1-4} 卤代烷基、 C_{3-6} 环烷基、 C_{1-4} 烷氧基及 C_{1-4} 卤代烷氧基；

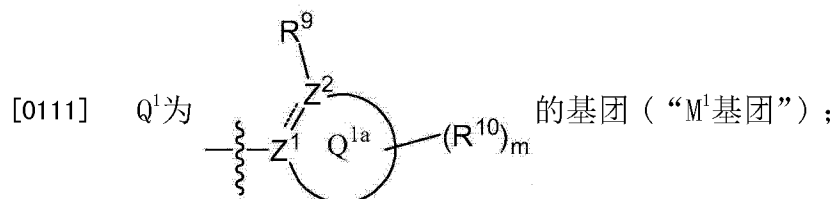
[0106] 本发明的一实施方案为其中 R^1 及 R^2 各自独立地为H或卤素的式I的化合物（包括式Ia或Ib的化合物）。在另一个实施方案中， R^1 及 R^2 各自独立地为H或F。在另一个实施方案中， R^1 为H，且 R^2 为H或F。在另一个实施方案中， R^1 及 R^2 各自为H。

[0107] 本发明的一实施方案为其中 R^3 及 R^4 各自独立地为H、卤素、 $-\text{CN}$ 、甲基、 C_1 卤代烷基、甲氧基或 C_1 卤代烷氧基的式I的化合物（包括式Ia或Ib的化合物）。在另一个实施方案中， R^3 及 R^4 各自独立地为H、卤素、 $-\text{CN}$ 、甲基或 C_1 卤代烷基。在另一个实施方案中， R^3 为H，且 R^4 为H、F、Cl、 $-\text{CN}$ 、甲基或 C_1 卤代烷基。在另一个实施方案中， R^3 为H，且 R^4 为H、F或甲基。在另一个实施方案中， R^3 为H，且 R^4 为甲基。

[0108] 本发明的一实施方案为其中 R^1 为H； R^2 为H或F； R^3 为H；且 R^4 为H、F、Cl、 $-\text{CN}$ 、甲基或 C_1 卤代烷基的式I的化合物（包括式Ia或Ib的化合物）。在另一个实施方案中， R^1 、 R^2 及 R^3 各自为H，且 R^4 为H或甲基。在另一个实施方案中， R^4 为甲基。

[0109] 本发明的一实施方案为其中 R^2 及 R^4 各自为H的式I的化合物（包括式Ia或Ib的化合物）。

[0110] 本发明的一实施方案为式I的化合物（包括式Ia或Ib的化合物），其中：



[0112] 环 Q^{1a} 为含N的5元至6元杂芳基或含N的5元至6元杂环烷基；

[0113] --- 表示单键或双键；

[0114] Z^1 及 Z^2 各自独立地为C或N；

[0115] R^9 为 C_{1-4} 烷基、 C_{1-4} 卤代烷基、 C_{3-7} 环烷基、 $-\text{CN}$ 、 $-\text{N}(R^5)(R^6)$ 、 C_{1-6} 烷氧基、 C_{1-6} 卤代烷氧基或 C_{3-7} 环烷氧基，其中所述 C_{1-4} 烷基及 C_{3-7} 环烷基各自任选地被1、2、3、4或5个各自独立地选自下列的取代基取代：卤素、 $-\text{N}(R^5)(R^6)$ 、 C_{1-4} 烷基、 C_{1-4} 卤代烷基、 C_{3-7} 环烷基、 C_{1-4} 烷氧基及 C_{1-4} 卤代烷氧基；

[0116] 各 R^{10} 独立地选自：卤素、 $-\text{OH}$ 、 $-\text{CN}$ 、 $-\text{NO}_2$ 、氧代、硫羰基、 C_{1-6} 烷基、 C_{1-6} 卤代烷基、 C_{1-6} 羟基烷基、 C_{1-6} 烷氧基、 C_{1-6} 卤代烷氧基、 C_{3-7} 环烷基、 C_{2-6} 烯基、 C_{2-6} 炔基、 C_{6-10} 芳基、4元至10元杂环烷基、5元至10元杂芳基、 $(C_{3-7}$ 环烷基)- C_{1-4} 烷基-、(4元至10元杂环烷基)- C_{1-4} 烷基-、 $(C_{6-10}$ 芳基)- C_{1-4} 烷基-、(5元至10元杂芳基)- C_{1-4} 烷基-、(5元至10元杂芳基)- C_{2-4} 烯基-、 $-\text{N}(R^5)(R^6)$ 、 $-\text{N}(R^7)(\text{C}(=\text{O})R^8)$ 、 $-\text{S}(=\text{O})\text{N}(R^5)(R^6)$ 、 $-\text{C}(=\text{O})-\text{N}(R^5)(R^6)$ 、 $-\text{C}(=\text{O})-R^8$ 、 $-\text{C}(=\text{O})-\text{OR}^8$ 及 $-\text{OR}^8$ ，其中所述 C_{1-6} 烷基、 C_{3-7} 环烷基、 C_{6-10} 芳基、4元至10元杂环烷基、5元至10元杂芳基、 $(C_{3-7}$ 环烷基)- C_{1-4} 烷基-、(4元至10元杂环烷基)- C_{1-4} 烷基-、 $(C_{6-10}$ 芳基)- C_{1-4} 烷基-、(5元至10元杂芳基)- C_{1-4} 烷基-及(5元至10元杂芳基)- C_{2-4} 烯基-各自任选地被1、2、3或4个各自独立地选自下列的取代基取代：卤素、 OH 、 $-\text{CN}$ 、 $-\text{NO}_2$ 、 C_{1-4} 烷基、 C_{1-4} 羟基烷基、 C_{1-4} 烷氧基、 $-\text{N}(R^5)(R^6)$ 、 $-\text{S}(C_{1-4}\text{烷基})$ 、 $-\text{S}(=\text{O})_2(C_{1-4}\text{烷基})$ 、 C_{6-10}

芳基氧基、任选地被 1 或 2 个 C_{1-4} 烷基取代的 (C_{6-10} 芳基) $-C_{1-4}$ 烷基氧基、-、氧代、 $-C(=O)$ H、 $-C(=O)-C_{1-4}$ 烷基、 $-C(=O)O-C_{1-4}$ 烷基、 $-C(=O)NH_2$ 、 $-NHC(=O)H$ 、 $-NHC(=O)-(C_{1-4}$ 烷基)、 C_{3-7} 环烷基、5 元或 6 元杂芳基、 C_{1-4} 卤代烷基及 C_{1-4} 卤代烷氧基；

[0117] 或 R^9 及邻近的 R^{10} 与它们所连接的环 Q^{1a} 上的两个环原子一起形成稠合苯环或稠合 5 元或 6 元杂芳基，其各自任选地被 1、2、3、4 或 5 个独立地选择的 R^{10a} 取代；

[0118] 各 R^{10a} 独立地选自：卤素、-OH、 $-C(=O)OH$ 、 $-C(=O)-C_{1-4}$ 烷基、 $-C(=O)-NH_2$ 、 $-C(=O)-N(C_{1-4} \text{ 烷基})_2$ 、-CN、 C_{1-4} 烷基、 C_{1-4} 烷氧基、 C_{1-4} 羟基烷基、 C_{1-4} 卤代烷基及 C_{1-4} 卤代烷氧基；且

[0119] m 为 0、1、2、3 或 4。

[0120] 本发明的一实施方案为其中 Q^1 为 M^1 基团且 Z^1 为 C 的式 I 的化合物（包括式 Ia 或 Ib 的化合物）。

[0121] 本发明的一实施方案为其中 Q^1 为 M^1 基团且 Z^1 为 N 的式 I 的化合物（包括式 Ia 或 Ib 的化合物）。

[0122] 本发明的一实施方案为其中 Q^1 或环 Q^{1a} （当 Q^1 为 M^1 基团时）为任选地被取代的含 N 的 6 元杂芳基的式 I 的化合物（包括式 Ia 或 Ib 的化合物）。在另一个实施方案中，6 元杂芳基的成环原子各自独立地选自 N 及 C。

[0123] 本发明的一实施方案为其中 Q^1 或环 Q^{1a} （当 Q^1 为 M^1 基团时）为任选地被取代的吡啶基、嘧啶基、哒嗪基或吡嗪基的式 I 的化合物（包括式 Ia 或 Ib 的化合物）。在另一个实施方案中， Q^1 或环 Q^{1a} 为任选地被取代的嘧啶基。在另一个实施方案中， Q^1 或环 Q^{1a} 为被 1 或 2 个 C_{1-4} 烷基（例如 CH_3 ）取代的嘧啶基。

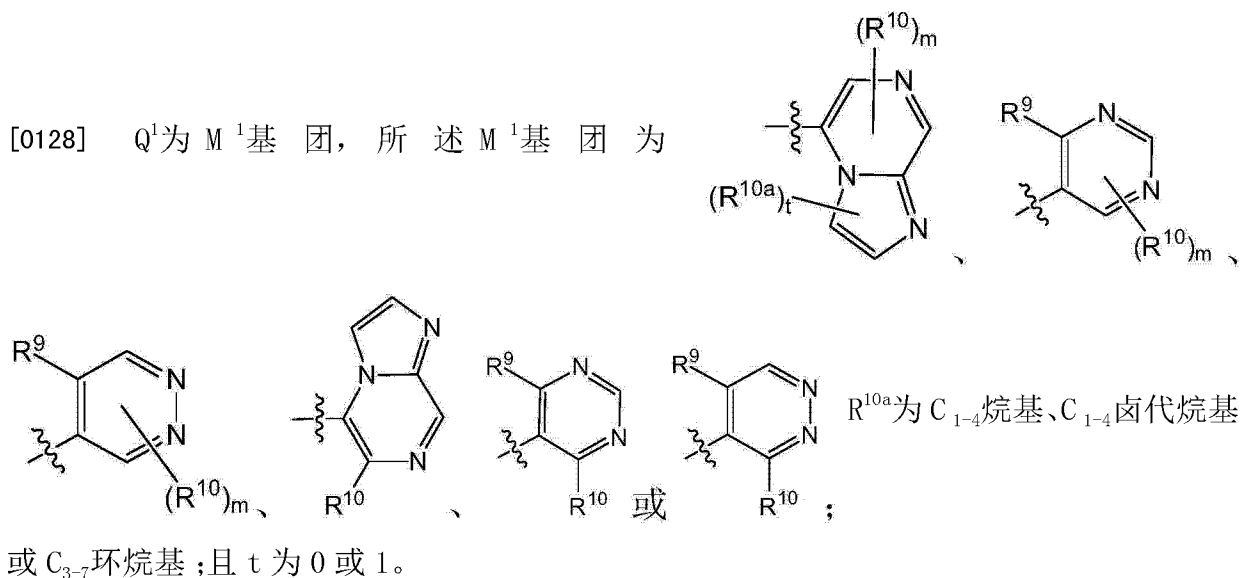
[0124] 本发明的一实施方案为其中 Q^1 为 M^1 基团的式 I 的化合物（包括式 Ia 或 Ib 的化合物），所述 M^1 基团选自：喹啉基、异喹啉基、1H-咪唑并 [4, 5-c] 吡啶基、咪唑并 [1, 2-a] 吡啶基、1H-吡咯并 [3, 2-c] 吡啶基、咪唑并 [1, 2-a] 吡嗪基、咪唑并 [2, 1-c] [1, 2, 4] 三嗪基、咪唑并 [1, 5-a] 吡嗪基、咪唑并 [1, 2-a] 嘧啶基、1H-吡啶基、9H-嘌呤基、[1, 2, 4] 三唑并 [1, 5-a] 嘧啶基、异噁唑并 [5, 4-c] 哒嗪基、异噁唑并 [3, 4-c] 哒嗪基及 [1, 2, 4] 三唑并 [4, 3-b] 哒嗪基，其各自任选地被 1、2 或 3 个 R^{10} 取代，且进一步任选地被 1 或 2 个 R^{10a} 取代；或其中 M^1 基团选自：嘧啶基、吡嗪基、吡啶基、哒嗪基、1H-吡啶基、1H-吡咯基、4H-吡嗪基、1H-咪唑基、3-氧代-2H-哒嗪基、1H-2-氧代-嘧啶基、1H-2-氧代-吡啶基、2, 4(1H, 3H)-二氧代-嘧啶基及 1H-2-氧代-吡嗪基，其各自被 R^9 取代且进一步任选地被 1、2 或 3 个 R^{10} 取代。

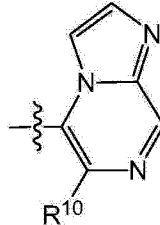
[0125] 在另一个实施方案中， M^1 基团选自：嘧啶基、吡嗪基、吡啶基及哒嗪基，其各自被 R^9 取代且进一步任选地被 1、2 或 3 个 R^{10} 取代。在另一个实施方案中， M^1 基团为被 R^9 取代及进一步任选地被 1、2 或 3 个 R^{10} 取代的嘧啶基。

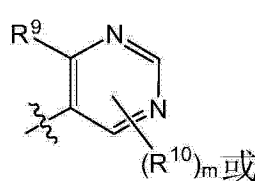
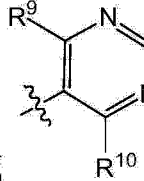
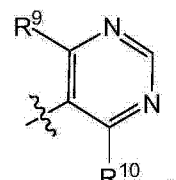
[0126] 本发明的一实施方案为其中 Q^1 为 M^1 基团的式 I 的化合物（包括式 Ia 或 Ib 的化合物），所述 M^1 基团选自：3-氧代-2H-哒嗪基、2, 4(1H, 3H)-二氧代-嘧啶基及 1H-2-氧代-吡嗪基，其各自被 R^9 取代且进一步任选地被 1、2 或 3 个 R^{10} 取代。

[0127] 本发明的一实施方案为式 I 的化合物（包括式 Ia 或 Ib 的化合物），其中：

[0128] Q^1 为 M^1 基团, 所述 M^1 基团为

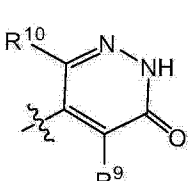
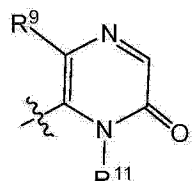
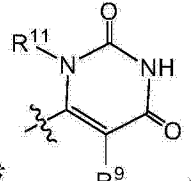


[0129] 本发明的一实施方案为其中 Q^1 为 M^1 基团 (其为 ) 的式 I 的化合物 (包括式 Ia 或 Ib 的化合物)。

[0130] 本发明的一实施方案为其中 Q^1 为  或  的式 I 的化合物 (包括式 Ia 或 Ib 的化合物)。在另一个实施方案中, Q^1 为  在另一个实施方案

中, Q^1 为 4,6-二甲基嘧啶-5-基。

[0131] 本发明的一实施方案为式 I 的化合物 (包括式 Ia 或 Ib 的化合物), 其中:

[0132] Q^1 为 M^1 基团, 所述 M^1 基团为 、 或 ;

[0133] 且

[0134] R^{11} 为 H、 C_{1-4} 烷基、 C_{1-4} 卤代烷基或 C_{3-7} 环烷基。在另一个实施方案中, R^9 及 R^{10} (或 R^{11}) 各自独立地为 C_{1-4} 烷基 (例如 CH_3)。

[0135] 本发明的一实施方案为其中 Q^1 为 3-氧代-4,6-二甲基-(2H) 哒嗪-5-基的式 I 的化合物 (包括式 Ia 或 Ib 的化合物)。

[0136] 本发明的一实施方案为其中 Q^1 为 2-氧代-1,5-二甲基-(1H)吡嗪-6-基的式 I 的化合物(包括式 Ia 或 Ib 的化合物)。

[0137] 本发明的一实施方案为其中 Q^1 为 2,4-二氧化-1,5-二甲基-(1H,3H)嘧啶-6-基的式 I 的化合物(包括式 Ia 或 Ib 的化合物)。

[0138] 本发明的一实施方案为其中 R^9 为 C_{1-4} 烷基或 -CN 的式 I 的化合物(包括式 Ia 或 Ib 的化合物)。在另一个实施方案中, R^9 为甲基、乙基或 -CN。在另一个实施方案中, R^9 为甲基或 -CN。在另一个实施方案中, R^9 为甲基。

[0139] 本发明的一实施方案为式 I 的化合物(包括式 Ia 或 Ib 的化合物), 其中各 R^{10} 独立地选自: C_{1-4} 烷基、 C_{1-4} 卤代烷基、-CN 及 $-N(R^5)(R^6)$, 其中 R^5 及 R^6 各自独立地为 H 或选自: C_{1-4} 烷基、 C_{1-4} 卤代烷基及 C_{3-7} 环烷基; 或 R^5 及 R^6 与它们所连接的 N 原子一起形成 4 元至 7 元杂环烷基或 5 元杂芳基, 其各自任选地被 1、2 或 3 个各自独立地选自下列的取代基取代: 卤素、-CN、 C_{1-4} 烷基、 C_{1-4} 烷氧基、 C_{3-6} 环烷基、 C_{1-4} 卤代烷基及 C_{1-4} 卤代烷氧基。在另一个实施方案中, 各 R^{10} 独立地选自: 甲基、乙基及 $-N(R^5)(R^6)$, 其中 R^5 及 R^6 与它们所连接的 N 原子一起形成氮杂环丁烷基、吡咯烷基或哌啶基, 其各自任选地被 1、2 或 3 个各自独立地选自下列的取代基取代: 卤素、-CN、 C_{1-4} 烷基、 C_{1-4} 烷氧基、 C_{3-6} 环烷基、 C_{1-4} 卤代烷基及 C_{1-4} 卤代烷氧基。在另一个实施方案中, 各 R^{10} 独立地选自: 甲基、乙基及氮杂环丁烷-1-基, 其中所述氮杂环丁烷-1-基任选地被 1、2 或 3 个卤素(例如 F)取代。

[0140] 本发明的一实施方案为其中各 R^{10} 独立地为 C_{1-4} 烷基的式 I 的化合物(包括式 Ia 或 Ib 的化合物)。在另一个实施方案中, 各 R^{10} 为甲基。

[0141] 在一个实施方案中, 本发明还提供如本申请实例部分中的实施例 1-47 所描述的一或多个化合物、其 N-氧化物, 及所述化合物或所述 N-氧化物的药学上可接受的盐。

[0142] 本发明的另一实施方案涉及选自下列的化合物:

[0143] 4-[4-(4,6-二甲基嘧啶-5-基)-3-氟苯氧基]-1H-吡咯并[3,2-c]吡啶;

[0144] (+)-4,6-二甲基-5-[2-甲基-4-(1H-吡啶并[4,3-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮;

[0145] (-)-4,6-二甲基-5-[2-甲基-4-(1H-吡啶并[4,3-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮;

[0146] 4-[4-(4,6-二甲基嘧啶-5-基)-3-甲基苯氧基]-1H-吡咯并[3,2-c]吡啶;

[0147] 4-[4-(4,6-二甲基嘧啶-5-基)-3-甲基苯氧基]-1H-吡啶并[4,3-c]吡啶;

[0148] 4,6-二甲基-5-[4-(1H-吡咯并[3,2-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮;

[0149] (-)-1,5-二甲基-6-[2-甲基-4-(1H-吡啶并[4,3-c]吡啶-4-基氧基)苯基]嘧啶-2,4(1H,3H)-二酮;

[0150] 4,6-二甲基-5-[2-甲基-4-(1H-吡咯并[3,2-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮, ENT-1;

[0151] 4,6-二甲基-5-[2-甲基-4-(1H-吡咯并[3,2-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮, ENT-2;

[0152] 4-[4-(4,6-二甲基-1-氧化嘧啶-5-基)-3-甲基苯氧基]-1H-吡啶并[4,3-c]吡啶;

[0153] 6-甲基-5-[2-甲基-4-(1H-吡咯并[3,2-c]吡啶-4-基氧基)苯基]咪唑并[1,2-a]吡嗪;

[0154] 4-[4-(4,6-二甲基嘧啶-5-基)苯氧基]-1H-吡咯并[3,2-c]吡啶;

[0155] 2-(4,6-二甲基嘧啶-5-基)-5-(1H-吡咯并[3,2-c]吡啶-4-基氧基)苯甲腈;

[0156] 4-[3-氯-4-(4,6-二甲基嘧啶-5-基)苯氧基]-1H-吡咯并[3,2-c]吡啶;

[0157] (-)-1,5-二甲基-6-[2-甲基-4-(1H-吡咯并[3,2-c]吡啶-4-基氧基)苯基]吡嗪-2(1H)-酮;

[0158] 4-[4-(4,6-二甲基嘧啶-5-基)-3-氟苯氧基]-1H-吡唑并[4,3-c]吡啶;

[0159] 4-[4-(4,6-二甲基嘧啶-5-基)-3-甲氧基苯氧基]-1H-吡唑并[4,3-c]吡啶;

[0160] 4-[3-氯-4-(4,6-二甲基嘧啶-5-基)苯氧基]-1H-吡唑并[4,3-c]吡啶;

[0161] (+)-1,5-二甲基-6-[2-甲基-4-(1H-吡唑并[4,3-c]吡啶-4-基氧基)苯基]吡嗪-2(1H)-酮;

[0162] 4,6-二甲基-5-[4-(1H-吡唑并[4,3-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮;
及

[0163] 1,5-二甲基-6-[4-(1H-吡唑并[4,3-c]吡啶-4-基氧基)苯基]嘧啶-2,4(1H,3H)-二酮,

[0164] 或其药学上可接受的盐。

[0165] 本发明还提供组合物(例如药物组合物),其包含式 I 的化合物(包括其 N-氧化物或者所述化合物或所述 N-氧化物的药学上可接受的盐)。相应地,在一个实施方案中,本发明提供药物组合物,其包含(治疗有效量的)式 I 的化合物(其 N-氧化物或者所述化合物或所述 N-氧化物的药学上可接受的盐),且任选地包含药学上可接受的载体。在另一个实施方案中,本发明提供药物组合物,其包含(治疗有效量的)式 I 的化合物(其 N-氧化物或者所述化合物或所述 N-氧化物的药学上可接受的盐),任选地包含药学上可接受的载体及任选的至少一种额外的药物或药剂(诸如下文描述的抗精神病药或抗精神分裂症药)。在一个实施方案中,所述额外的药物或药剂为如下所描述的抗精神分裂症药。

[0166] 所述药学上可接受的载体可包含任何常规药物载体或赋形剂。适合的药物载体包括惰性稀释剂或填充剂、水及多种有机溶剂(诸如水合物及溶剂合物)。若需要,所述药物组合物可包含额外的成分,诸如调味剂、粘合剂、赋形剂等。因此,对于口服给药,可将含有多种赋形剂(诸如柠檬酸)的片剂与多种崩解剂(诸如淀粉、海藻酸及某些复合硅酸盐)以及粘合剂(诸如蔗糖、明胶及阿拉伯胶)一起使用。另外,润滑剂(诸如硬脂酸镁、月桂基硫酸钠及滑石)常可用于压片的目的。相似类型的固体组合物还可以软填充及硬填充的明胶胶囊剂形式使用。因此,材料的非限制性实例包括乳糖(lactose)或乳糖(milk sugar)及高分子量聚乙二醇。当需要将水性混悬剂或酏剂用于口服给药时,可将其中活性化合物与多种甜味剂或调味剂、着色物或染料、及(若需要)乳化剂或助悬剂,以及与稀释剂(诸如水、乙醇、丙二醇、甘油或其组合)一起组合。

[0167] 所述药物组合物可例如呈适合于口服给药的形式(如片剂、胶囊剂、丸剂、散剂、持续释放制剂、溶液剂或混悬剂),适合于肠胃外注射的形式(如无菌溶液剂、混悬剂或乳剂);适合于局部给药的形式(如软膏剂或乳膏剂),或适合于直肠给药的形式(如栓剂)。

[0168] 示例性肠胃外给药形式包括活性化合物于无菌水溶液(例如丙二醇或葡萄糖水

溶液)中的溶液剂或混悬剂。若需要,这样的剂型可适当地加以缓冲。

[0169] 所述药物组合物可呈适合于单次给药精确剂量的单位剂型。本领域普通技术人员会理解,可将所述组合物配制为低于治疗剂量,以用于预想的多次给药。

[0170] 在一个实施方案中,所述组合物包含治疗有效量的式 I 的化合物(或其 N-氧化物或者所述化合物或所述 N-氧化物的药学上可接受的盐)及药学上可接受的载体。

[0171] 式 I 的化合物(包括其 N-氧化物,及所述化合物或所述 N-氧化物的药学上可接受的盐)为 D1 调节剂。在一些实施方案中,式 I 的化合物为 D1 激动剂[即结合 D1 受体(具有与 D1 受体的亲和性)且活化 D1 受体]。在一些实施方案中,在使用多巴胺作为参考完全 D1 激动剂的情况下,式 I 的化合物为超激动剂(即对 D1 受体所能够产生的最大响应比内源性 D1 激动剂(多巴胺)更大,且因此展现超过约 100%(例如 120%)的功的化合物)。在一些实施方案中,在使用多巴胺作为参考完全激动剂的情况下,式 I 的化合物为完全 D1 激动剂(即与多巴胺的功相比,其功为约 100%,例如 90%-100%)。在一些实施方案中,在使用多巴胺作为参考完全 D1 激动剂的情况下,式 I 的化合物为部分激动剂[即尽管化合物结合 D1 受体且活化 D1 受体,相对于完全激动剂(多巴胺),其对 D1 受体仅具有部分功(即小于 100%,例如 10%-80%或 50%-70%)]。D1 激动剂(包括超激动剂、完全激动剂及部分激动剂)可激动或部分激动 D1 的活性。在一些实施方案中,式 I 的化合物对 D1 的 EC_{50} 为小于约 10 μ M、5 μ M、2 μ M、1 μ M、500nM、200nM、100nM、50nM、40nM、30nM、20nM、10nM、5nM、2nM 或 1nM。

[0172] 本发明还提供用于调节(诸如激动或部分激动)D1 受体(体外或体内)的活性的方法,其包括使 D1 受体与式 I 的化合物(诸如选自实施例 1-47 的一种)或其 N-氧化物或者所述化合物或所述 N-氧化物的药学上可接受的盐接触。

[0173] 本发明的另一实施方案包括用于治疗 D1 介导(或 D1 相关)的病症的方法,其包括向需要其的哺乳动物(例如人)给药有效调节(例如激动或部分激动)D1 的量的式 I 的化合物(包括其药学上可接受的盐,或所述化合物或盐的 N-氧化物)。

[0174] 用于治疗 D1 介导的病症的式 I 的化合物还包括其 N-氧化物或者所述化合物或所述 N-氧化物的药学上可接受的盐。

[0175] D1 介导(或 D1 相关)的病症包括神经病症[诸如图雷特综合征;迟发性运动障碍;帕金森氏病(包括例如与 PD 相关的认知损害);认知障碍{包括遗忘症、年龄相关的认知下降、痴呆[例如老年痴呆、阿尔茨海默病相关的痴呆、HIV 相关的痴呆、亨廷顿症相关的痴呆、Lewy 体性痴呆、血管性痴呆、额颞叶型痴呆、药物相关的痴呆(例如与药物疗法(诸如 D2 拮抗剂疗法)相关的痴呆)]、谵妄及认知损害(例如与 AD 相关的认知损害或与 PD 相关的认知损害)及轻度认知损害};亨廷顿舞蹈症/疾病;及下肢不宁综合征(RLS)];精神病[诸如认知损害(例如与精神分裂症相关的认知损害或与药物疗法(例如 D2 拮抗剂疗法)相关的认知损害);焦虑(包括急性应激障碍、广泛性焦虑症、社交焦虑障碍、惊恐病、创伤后应激障碍及强迫症);造作性障碍(包括急性幻觉性躁狂症);冲动控制障碍/冲动(包括强迫性赌博及间歇性暴躁障碍);心境障碍(包括 I 型双相性精神障碍、II 型双相性精神障碍、躁狂症、混合情感状态(mixed affective state)、抑郁症{例如年龄相关的抑郁症、重性抑郁症、慢性抑郁症、季节性抑郁症、精神病性抑郁症、产后抑郁症及难治性抑郁症(TRD)};精神运动性(psychomotor)病症;精神障碍[包括精神分裂症(包括例如精神分裂

症中的认知症状及负性症状)、情感性分裂症、精神分裂症样及妄想症];物质滥用及药物依赖(包括麻醉品依赖、酒精中毒、安非他明依赖、可卡因成瘾、尼古丁依赖及药物戒断综合征);药物滥用复发、进食障碍(包括食欲缺乏、贪食症、暴食症、进食过量、饮食过多及食冰癖);自闭症谱系障碍(例如自闭症);慢性情感淡漠、兴趣缺失、慢性疲劳、季节性情感障碍及儿科精神病症(包括注意障碍、注意缺陷多动障碍(ADHD)、品行障碍及自闭症)]、内分泌病症(诸如高催乳素血症)或其它病症,包括嗜睡、过度日间嗜睡、恶病质、注意力不集中、性功能障碍(例如勃起功能障碍、SSRI 后性功能障碍)、疼痛、偏头痛、系统性红斑狼疮(SLE)、高血糖症、动脉粥样硬化、血脂异常、肥胖症、糖尿病、败血症、缺血后肾小管坏死、肾衰竭、低钠血症、顽固性水肿、发作性睡病、心血管疾病(例如高血压)、充血性心力衰竭、手术后眼部张力过低、睡眠障碍及血清素综合征。

[0176] 本发明的另一实施方案提供用于治疗哺乳动物(例如人)的下列病症的方法,所述病症为神经病症[诸如图雷特综合征;迟发性运动障碍;帕金森氏病;认知障碍{包括遗忘症、老年痴呆、HIV 相关的痴呆、阿尔茨海默病相关的痴呆、亨廷顿症相关的痴呆、Lewy 体性痴呆、血管性痴呆、药物相关的痴呆(例如与 D2 拮抗剂疗法相关的认知损害)、谵妄及轻度认知损害}];RLS 及亨廷顿舞蹈症/疾病];精神病症[诸如焦虑(包括急性应激障碍、广泛性焦虑症、社交焦虑障碍、惊恐病、创伤后应激障碍及强迫症);造作性障碍(包括急性幻觉性躁狂症);冲动控制障碍/冲动(包括强迫性赌博及间歇性暴躁障碍);心境障碍(包括 I 型双相性精神障碍、II 型双相性精神障碍、躁狂症、混合情感状态、重性抑郁症、慢性抑郁症、季节性抑郁症、精神病性抑郁症及产后抑郁症);精神运动性病症;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(包括麻醉品依赖、酒精中毒、安非他明依赖、可卡因成瘾、尼古丁依赖及药物戒断综合征);进食障碍(包括食欲缺乏、贪食症、暴食症、饮食过多及食冰癖);及儿科精神病症(包括注意障碍、注意缺陷/多动障碍、品行障碍及自闭症)]、或内分泌病症(诸如高催乳素血症),所述方法包括向所述哺乳动物给药治疗有效量的式 I 的化合物。

[0177] 本发明的另一实施方案包括用于治疗哺乳动物(例如人)的病症的方法,所述方法包括向所述哺乳动物给药治疗有效量的式 I 的化合物,其中所述病症选自精神分裂症(例如精神分裂症中的认知症状及负性症状)、认知损害[例如与精神分裂症相关的认知损害、与 AD 相关的认知损害、与 PD 相关的认知损害、与药物疗法(例如 D2 拮抗剂疗法)相关的认知损害及轻度认知损害]、注意缺陷多动障碍(ADHD)、冲动、强迫性赌博、进食障碍(例如食欲缺乏、贪食症、暴食症、进食过量、饮食过多及食冰癖)、自闭症谱系障碍、轻度认知损害(MCI)、年龄相关的认知下降、痴呆(例如老年痴呆、HIV 相关的痴呆、阿尔茨海默痴呆、Lewy 体性痴呆、血管性痴呆或额颞叶型痴呆)、下肢不宁综合征(RLS)、帕金森氏病、亨廷顿舞蹈症、焦虑、抑郁症(例如年龄相关的抑郁症)、重度抑郁症(MDD)、难治性抑郁症(TRD)、双相型障碍、慢性情感淡漠、兴趣缺失、慢性疲劳、创伤后应激障碍、季节性情感障碍、社交焦虑障碍、产后抑郁症、血清素综合征、物质滥用及药物依赖、药物滥用复发、图雷特综合征、迟发性运动障碍、嗜睡、过度日间嗜睡、恶病质、注意力不集中、性功能障碍(例如勃起功能障碍或 SSRI 后性功能障碍)、偏头痛、系统性红斑狼疮(SLE)、高血糖症、动脉粥样硬化、血脂异常、肥胖症、糖尿病、败血症、缺血后肾小管坏死、肾衰竭、低钠血症、顽固性水肿、发作性睡病、高血压、充血性心力衰竭、手术后眼部张力过低、睡眠障碍及疼痛。

[0178] 本发明的另一实施方案包括用于治疗哺乳动物（例如人）的精神分裂症（例如精神分裂症中的认知症状及负性症状或与精神分裂症相关的认知损害）或精神病的方法，所述方法包括向所述哺乳动物（例如人）给药治疗有效量的式 I 的化合物。

[0179] 本发明的另一实施方案包括用于治疗哺乳动物（例如人）的精神分裂症（例如精神分裂症中的认知症状及负性症状或与精神分裂症相关的认知损害）的方法，所述方法包括向所述哺乳动物给药治疗有效量的式 I 的化合物。

[0180] 本发明的另一实施方案包括用于治疗哺乳动物（例如人）的认知损害 [例如与精神分裂症相关的认知损害、与 AD 相关的认知损害或与 PD 相关的认知损害] 的方法，所述方法包括向所述哺乳动物给药治疗有效量的式 I 的化合物。

[0181] 本发明的另一实施方案包括用于治疗哺乳动物（例如人）的 AD（例如治疗与 AD 相关的认知损害）、PD（例如治疗与 PD 相关的认知损害）、RLS、抑郁症或 MDD 的方法，所述方法包括向所述哺乳动物给药治疗有效量的式 I 的化合物。

[0182] 如本文中所使用的术语“治疗有效量”指被给药后会在一定程度上缓解所治疗病症的一或多种症状的化合物（包括其药学上可接受的盐，或所述化合物或盐的 N-氧化物）的量。对于 D1 介导的病症（例如精神分裂症）的治疗，治疗有效量指在一定程度上有效缓解（或例如消除）与 D1 介导的病症（例如精神分裂症或精神分裂症中的认知症状及负性症状或与精神分裂症相关的认知损害）相关的一或多种症状的量。

[0183] 除非另外说明，否则如本文中所使用，术语“治疗 (treating)”意指逆转、减轻、抑制这样的术语所应用的病症或病况或者这样的病症或病况的一或多种症状的进展，或预防这样的病症或病况或者这样的病症或病况的一或多种症状。除非另外说明，否则如本文中所使用，术语“治疗 (treatment)”指如本文所定义的“治疗 (treating)”的治疗行为。术语“治疗”还包括对个体的辅助及新辅助治疗。

[0184] 式 I 的化合物的给药可通过使得能够将化合物递送至作用部位的任何方法来实现。这些方法包括口服途径、鼻内途径、吸入途径、十二指肠内途径、肠胃外注射（包括静脉内、皮下、肌肉内、血管内或输注）、局部及直肠给药。

[0185] 在本发明的一个实施方案中，式 I 的化合物可由口服途径来给药 / 实现。

[0186] 可调整给药方案以提供最佳所需响应。例如，可给药单次推注，可随时间给药数个分剂量，或可如治疗情况的急需所表明而按比例减少或增加剂量。将肠胃外组合物配制为单位剂量形式以易于给药且使剂量均一是有利的。如本文中所使用，单位剂量形式指适合以整体剂量用于待治疗的哺乳动物个体的物理离散单元；各单元均含有与所需药物载体联合后经计算以产生所需治疗效果的预定量的活性化合物。本发明的单位剂量形式的规格由多种因素支配，诸如治疗剂的独特特征及要取得的特定治疗或预防效果。在本发明的一个实施方案中，式 I 的化合物可用于治疗人。

[0187] 要注意，剂量值可随要减轻的病况的类型及严重性而变化，且可包括单次或多次剂量。要进一步理解，对于任何特定个体，具体的给药方案应根据个体需要及给药组合物或监督组合物的给药的人员的专业判断来随时间调整，且本文中所阐述的剂量范围仅为示例性的，并不意图限制所请求保护的组合物的范围或实践。例如，可基于药物代谢动力学或药效学参数来调整剂量，所述参数可包括临床效果，诸如毒性效果和 / 或实验值。因此，本发明涵盖如本领域技术人员所确定的患者内剂量递增。确定给药化学治疗剂的适当剂量及方

案为相关领域中所熟知的,且一旦提供本文中所公开的教导,则本领域技术人员会理解所述适当剂量及方案涵盖于其中。

[0188] 所给药的式 I 的化合物的量会取决于所治疗的个体、病症或病况的严重性、给药的速率、化合物的处置及处方医师的判断。一般而言,有效剂量在每日每 kg 体重约 0.0001 至约 50mg,例如约 0.01 至约 10mg/kg/日(单次或分次给药)。对 70kg 的人而言,这会合计为约 0.007mg/日至约 3500mg/日,例如约 0.7mg/日至约 700mg/日。在一些情况下,低于前述范围的下限的剂量水平可以是足够的,而在其它情况下,仍可在不引起任何有害副作用的情况下采用较大剂量,条件是首先将所述较大剂量分成数个较小剂量以在一整天中给药。

[0189] 如本文中所使用,术语“组合疗法”指将式 I 的化合物与至少一种额外的药物或药剂(例如抗精神分裂症药剂)顺序或同时给药。

[0190] 本发明包括式 I 的化合物与一或多种额外的药物活性剂的组合的用途。若给药活性剂的组合,则所述活性剂可以分开的剂型或以在单个剂型中组合的形式顺序或同时给药。相应地,本发明还包括药物组合物,其包含一定量的:(a) 第一药剂,其包含式 I 的化合物(包括其 N-氧化物或者所述化合物或所述 N-氧化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、媒介物或稀释剂。

[0191] 根据要治疗的疾病、病症或病况,可选择多种药物活性剂以与式 I 的化合物结合使用。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):

[0192] (i) 乙酰胆碱酯酶抑制剂,诸如盐酸多奈哌齐 (ARICEPT、MEMAC);或腺苷 A_{2A}受体拮抗剂,诸如普瑞丁奈 (SCH 420814) 或 SCH 412348;

[0193] (ii) 淀粉样蛋白- β (或其片段),诸如与结合 pan HLA DR 的表位 (PADRE) 缀合的 A β ₁₋₁₅,以及 ACC-001 (Elan/Wyeth);

[0194] (iii) 淀粉样蛋白- β (或其片段)的抗体,诸如巴匹珠单抗(还称为 AAB-001)及 AAB-002 (Wyeth/Elan);

[0195] (iv) 淀粉样蛋白减少或抑制剂(包括减少淀粉样蛋白产生、蓄积及纤维化的那些),诸如 colostrinin 及 bisnorcymserine(还称为 BNC);

[0196] (v) α -肾上腺素能受体激动剂,诸如可乐定 (CATAPRES);

[0197] (vi) β -肾上腺素能受体阻断剂(β -阻滞剂),诸如卡替洛尔;

[0198] (vii) 抗胆碱能药,诸如阿米替林 (ELAVIL、ENDEP);

[0199] (viii) 抗惊厥药,诸如卡马西平 (TEGRETOL、CARBATROL);

[0200] (ix) 抗精神病药,诸如鲁拉西酮(还称为 SM-13496;Dainippon Sumitomo);

[0201] (x) 钙通道阻滞药,诸如尼伐地平 (ESCOR、NIVADIL);

[0202] (xi) 儿茶酚 O-甲基转移酶 (COMT) 抑制剂,诸如托卡朋 (TASMAR);

[0203] (xii) 中枢神经系统兴奋剂,诸如咖啡因;

[0204] (xiii) 皮质类固醇,诸如泼尼松 (STERAPRED、DELTASONE);

[0205] (xiv) 多巴胺受体激动剂,诸如阿扑吗啡 (APOKYN);

[0206] (xv) 多巴胺受体拮抗剂,诸如丁苯那嗪 (NITOMAN、XENAZINE、诸如喹硫平的多巴胺 D2 拮抗剂);

[0207] (xvi) 多巴胺重摄取抑制剂,诸如顺丁烯二酸诺米芬辛 (MERITAL);

- [0208] (xvii) γ -氨基丁酸 (GABA) 受体激动剂, 诸如巴氯芬 (LIORESAL、KEMSTRO) ;
- [0209] (xviii) 组胺 $3(H_3)$ 拮抗剂, 诸如 ciproxifan ;
- [0210] (xix) 免疫调节剂, 诸如格拉默醋酸盐 (还称为共聚物 -1 ; COPAXONE) ;
- [0211] (xx) 免疫抑制剂, 诸如甲氨蝶呤 (TREXALL、RHEUMATREX) ;
- [0212] (xxi) 干扰素, 包括干扰素 β -1a (AVONEX、REBIF) 及干扰素 β -1b (BETASERON、BETAFERON) ;
- [0213] (xxii) 左旋多巴 (或其甲酯或乙酯), 单独或与 DOPA 脱羧酶抑制剂组合 (例如卡比多巴 (SINEMET、CARBILEV、PARCOPA)) ;
- [0214] (xxiii) N-甲基-D-天冬氨酸 (NMDA) 受体拮抗剂, 诸如美金刚 (NAMENDA、AXURA、EBIXA) ;
- [0215] (xxiv) 单胺氧化酶 (MAO) 抑制剂, 诸如司来吉兰 (EMSAM) ;
- [0216] (xxv) 毒蕈碱性受体 (尤其 $M1$ 亚型) 激动剂, 诸如氯贝胆碱 (DUVOID、URECHOLINE) ;
- [0217] (xxvi) 神经保护性药物, 诸如 2, 3, 4, 9-四氢-1H-吡唑-3-酮肟 ;
- [0218] (xxvii) 烟碱性受体激动剂, 诸如地棘蛙素 ;
- [0219] (xxviii) 去甲肾上腺素 (norepinephrine/noradrenaline) 重摄取抑制剂, 诸如托莫西汀 (STRATTERA) ;
- [0220] (xxix) 磷酸二酯酶 (PDE) 抑制剂, 例如 PDE9 抑制剂, 诸如 BAY 73-6691 (Bayer AG) 及 PDE 10 (例如 PDE10A) 抑制剂, 诸如罂粟碱 ;
- [0221] (xxx) 其它 PDE 抑制剂, 其包括 (a) PDE1 抑制剂 (例如长春西汀), (b) PDE2 抑制剂 (例如赤-9-(2-羟基-3-壬基) 腺嘌呤 (EHNA)), (c) PDE4 抑制剂 (例如咯利普兰), 及 (d) PDE5 抑制剂 (例如西地那非 (VIAGRA、REVATIO)) ;
- [0222] (xxxix) 喹啉, 诸如奎宁 (包括其盐酸盐、二盐酸盐、硫酸盐、硫酸氢盐及葡萄糖酸盐) ;
- [0223] (xxxixii) β -分泌酶抑制剂, 诸如 WY-25105 ;
- [0224] (xxxixiii) γ -分泌酶抑制剂, 诸如 LY-411575 (Lilly) ;
- [0225] (xxxixiv) 血清素 (5-羟色胺) $1A(5-HT_{1A})$ 受体拮抗剂, 诸如螺哌隆 ;
- [0226] (xxxixv) 血清素 (5-羟色胺) $4(5-HT_4)$ 受体激动剂, 诸如 PRX-03140 (Epix) ;
- [0227] (xxxixvi) 血清素 (5-羟色胺) $6(5-HT_6)$ 受体拮抗剂, 诸如米安色林 (TORVOL、BOLVIDON、NORVAL) ;
- [0228] (xxxixvii) 血清素 (5-HT) 重摄取抑制剂, 诸如阿拉丙酯、西酞普兰 (CELEXA、CIPRAMIL) ;
- [0229] (xxxixviii) 营养因子, 诸如神经生长因子 (NGF)、碱性成纤维细胞生长因子 (bFGF ; ERSOFERMIN)、神经营养因子-3 (NT-3)、心脏营养因子-1、脑源性神经营养因子 (BDNF)、神经鞘脂素、镍纹蛋白及胶质细胞衍生的神经营养因子 (GDNF), 及刺激营养因子产生的药剂, 诸如丙戊茶碱 ;
- [0230] 等。
- [0231] 式 I 的化合物任选地与另一种活性剂组合使用。这样的活性剂可为例如非典型抗精神病药剂或抗帕金森氏病药剂或抗阿尔茨海默病药剂。相应地, 本发明的另一实施方案

提供治疗 D1 介导的病症（例如与 D1 相关的神经及精神病症）的方法，其包括向哺乳动物给药有效量的式 I 的化合物（包括其 N-氧化物或者所述化合物或所述 N-氧化物的药学上可接受的盐），且还包括给药另一种活性剂。

[0232] 如本文中所使用，术语“另一种活性剂”指可用于治疗个体病症的除式 I 的化合物（包括其 N-氧化物或者所述化合物或所述 N-氧化物的药学上可接受的盐）以外的任何治疗剂。额外治疗剂的实例包括抗抑郁药、抗精神病（诸如抗精神分裂症）药、抗疼痛剂、抗帕金森氏病药剂、抗 LID（左旋多巴诱导的运动障碍）剂、抗阿尔茨海默病药剂及抗焦虑剂。可与本发明的化合物组合使用的特定类别的抗抑郁药的实例包括去甲肾上腺素重摄取抑制剂、选择性血清素重摄取抑制剂（SSRI）、NK-1 受体拮抗剂、单胺氧化酶抑制剂（MAOI）、单胺氧化酶的可逆性抑制剂（RIMA）、血清素及去甲肾上腺素重摄取抑制剂（SNRI）、促皮质素释放因子（CRF）拮抗剂、 α -肾上腺素能受体拮抗剂及非典型抗抑郁药。适合的去甲肾上腺素重摄取抑制剂包括叔胺三环药及仲胺三环药。适合的叔胺三环药及仲胺三环药的实例包括阿米替林、氯米帕明、多塞平、丙米嗪、曲米帕明、度硫平、布替林、伊普吲哚、洛非帕明、去甲替林、普罗替林、阿莫沙平、地昔帕明及马普替林。适合的选择性血清素重摄取抑制剂的实例包括氟西汀、氟伏沙明、帕罗西汀及舍曲林。单胺氧化酶抑制剂的实例包括异卡波肼、苯乙肼及 tranlycyclopramine。适合的单胺氧化酶的可逆性抑制剂的实例包括吗氯贝胺。适合用于本发明中的血清素及去甲肾上腺素重摄取抑制剂的实例包括文拉法辛。适合的非典型抗抑郁药的实例包括安非他酮、锂、奈法唑酮、曲唑酮及维洛沙秦。抗阿尔茨海默病药剂的实例包括 Dimebon、NMDA 受体拮抗剂（诸如美金刚）及胆碱酯酶抑制剂（诸如多奈哌齐及加兰他敏）。可与本发明的化合物组合使用的适合类别的抗焦虑剂的实例包括苯并二氮䓬及血清素 1A (5-HT_{1A}) 激动剂或拮抗剂（特别是 5-HT_{1A} 部分激动剂），及促皮质素释放因子（CRF）拮抗剂。适合的苯并二氮䓬包括阿普唑仑、氯氮䓬、氯硝西泮、氯胺丁酯、安定、哈拉西泮、劳拉西泮、奥沙西泮及普拉西泮。适合的 5-HT_{1A} 受体激动剂或拮抗剂包括丁螺酮、氟辛克生、吉哌隆及伊茨匹隆。适合的非典型抗精神病药包括帕利哌酮、联苯芦诺、齐拉西酮、利培酮、阿立哌唑、奥氮平及喹硫平。适合的烟碱乙酰胆碱激动剂包括异丙克兰、伐尼克兰及 MEM3454。抗疼痛剂包括普瑞巴林、加巴喷丁、可乐定、新斯的明、巴氯芬、咪达唑仑、氯胺酮及齐考诺肽。适合的抗帕金森氏病药剂的实例包括 L-DOPA（或其甲酯或乙酯）、DOPA 脱羧酶抑制剂（例如卡比多巴（SINEMET、CARBILEV、PARCOPA）、腺苷 A_{2A} 受体拮抗剂 [例如普瑞丁奈（SCH 420814）或 SCH 412348]、苄丝肼（MADOPAR）、 α -甲基多巴、单氟甲基多巴、二氟甲基多巴、溴克立新或间羟基苄肼）、多巴胺激动剂 [诸如阿扑吗啡（APOKYN）、溴隐亭（PARLODEL）、卡麦角林（DOSTINEX）、D₁ 受体激动剂（dihydrexidine）、双氢麦角隐亭、非诺多泮（CORLOPAM）、利舒脲（DOPERGIN）、培高莱（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）及沙立佐坦]、单胺氧化酶（MAO）抑制剂 [诸如司来吉兰（EMSAM）、盐酸司来吉兰（L-司来吉兰（L-deprenyl）、ELDEPRYL、ZELAPAR）、二甲基司来吉兰（dimethylselegiline）、溴法罗明、苯乙肼（NARDIL）、反苯环丙胺（PARNATE）、吗氯贝胺（AURORIX、MANERIX）、贝氟沙通、沙非胺、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、脱氧鸭嘴花碱

(desoxypeganine)、哈尔明（还称为骆驼蓬碱或 banasterine）、哈马灵、利奈唑胺 (ZYVOX、ZYVOXID) 及帕吉林 (EUDATIN、SUPIRDYL)、儿茶酚 O- 甲基转移酶 (COMT) 抑制剂 [诸如托卡朋 (TASMAR)、恩他卡朋 (COMTAN) 及托酚酮]、N- 甲基 -D- 天冬氨酸 (NMDA) 受体拮抗剂 [诸如金刚烷胺 (SYMMETREL)]、抗胆碱能药 [诸如阿米替林 (ELAVIL、ENDEP)、布替林、甲磺酸苄托品 (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)、赛克力嗪、盐酸丙米嗪 (TOFRANIL)、顺丁烯二酸丙米嗪 (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)] 或其组合。抗精神分裂症药剂的实例包括齐拉西酮、利培酮、奥氮平、喹硫平、阿立哌唑、阿塞那平、布南色林或伊洛哌酮。

[0233] 如上所述, 式 I 的化合物 (包括其 N- 氧化物及所述化合物或盐的药学上可接受的盐) 可与本文中描述的一或多种额外的抗精神分裂症药剂组合使用。当使用组合疗法时, 一或多种额外抗精神分裂症药剂可与本发明的化合物顺序或同时给药。在一个实施方案中, 在给药本发明的化合物之前, 向哺乳动物 (例如人) 给药额外抗精神分裂症药剂。在另一个实施方案中, 在给药本发明的化合物之后, 向哺乳动物给药额外抗精神分裂症药剂。在另一个实施方案中, 在给药本发明的化合物 (或其 N- 氧化物或前述的药学上可接受的盐) 的同时向哺乳动物 (例如人) 给药额外抗精神分裂症药剂。

[0234] 本发明还提供药物组合物, 其用于治疗哺乳动物 (包括人) 的精神分裂症, 所述药物组合物包含一定量的如上文所定义的式 I 的化合物 (或其 N- 氧化物或前述的药学上可接受的盐) (包括所述化合物或其药学上可接受的盐的水合物、溶剂合物及多晶型物) 与一或多种 (例如一至三种) 抗精神分裂症药剂 (诸如齐拉西酮、利培酮、奥氮平、喹硫平、阿立哌唑、阿塞那平、布南色林或伊洛哌酮) 组合, 其中所述活性剂与所述组合的量在作为整体服用时在治疗学上对治疗精神分裂症有效。

[0235] 本发明还提供药物组合物, 其用于治疗哺乳动物 (包括人) 的帕金森氏病 (包括与 PD 相关的认知损害), 所述药物组合物包含一定量的如上文所定义的式 I 的化合物 (或其 N- 氧化物或前述的药学上可接受的盐) (包括所述化合物或其药学上可接受的盐的水合物、溶剂合物及多晶型物) 与一或多种 (例如一至三种) 抗帕金森氏病药剂 (诸如 L-DOPA) 组合, 其中所述活性剂与所述组合的量在作为整体服用时在治疗学上对治疗帕金森氏病有效。

[0236] 应理解以上描绘的式 I 的化合物不限于所示的特定对映异构体, 而还包括其所有立体异构体及混合物。

[0237] 发明详述

[0238] 本发明的化合物 (包括 N- 氧化物及所述化合物或 N- 氧化物的盐) 可使用已知的有机合成技术来制备, 且可根据大量可能合成路线中的任何一种来合成。

[0239] 用于制备本发明的化合物的反应可在适合的溶剂中进行, 所述溶剂可由有机合成领域的技术人员容易地选择。适合的溶剂可在反应所进行的温度 (即可在溶剂的凝固温度至溶剂的沸腾温度的范围内的温度) 下基本上不与原料 (反应物)、中间体或产物反应。指定的反应可在一种溶剂或一种以上溶剂的混合物中进行。根据特定的反应步骤, 对于特定

反应步骤适合的溶剂可由本领域技术人员选择。

[0240] 本发明的化合物的制备可涉及多种化学基团的保护及脱保护。对于保护及脱保护的需求,以及选择适当的保护基可由本领域技术人员容易地确定。保护基化学可见于例如 T.W. Greene 及 P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 第 3 版, Wiley&Sons, Inc., New York (1999) 中, 将其以其整体援引加入本文中。

[0241] 反应可根据本领域中已知的任何适合的方法来监测。例如, 产物形成可通过光谱手段 (诸如核磁共振光谱法 (例如 ^1H 或 ^{13}C)、红外光谱法、分光光度法 (例如 UV- 可见)、质谱) 或通过色谱方法 (诸如高效液相色谱法 (HPLC) 或薄层色谱法 (TLC)) 来监测。

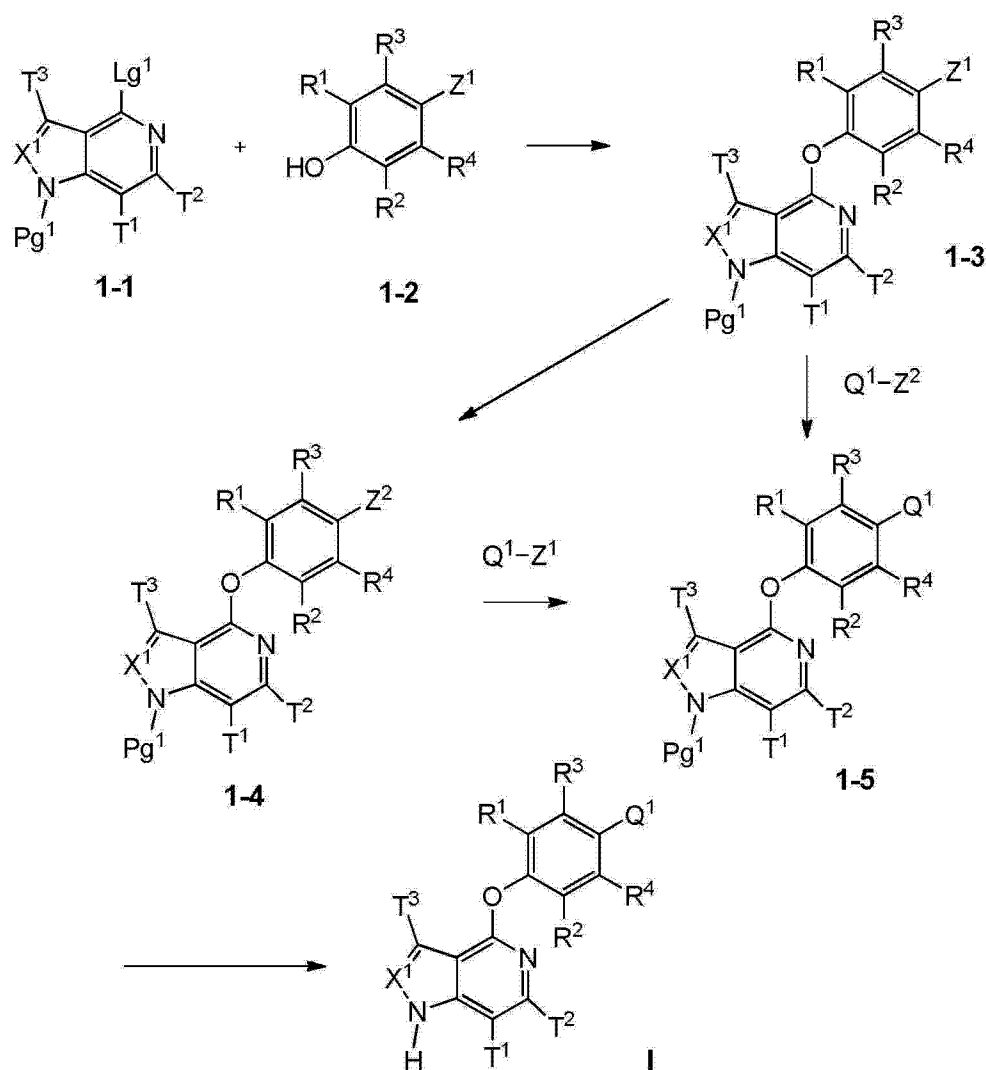
[0242] 式 I 的化合物及其中间体可根据以下反应路线及随附论述来进行制备。除非另外说明, 否则反应路线及随后论述中的 R^1 、 R^2 、 R^3 、 R^4 、 R^5 、 R^6 、 R^7 、 R^8 、 R^9 、 R^{10} 、 R^{11} 、 T^1 、 T^2 、 T^3 、 Q^1 及 X^1 、以及结构式 I 均如上文所定义。一般而言, 本发明的化合物可通过包括与化学领域中已知的那些类似的方法的方法, 特别是根据本文中所包含的描述来制得。用于制备本发明的化合物及其中间体的某些方法作为本发明的其它特征来提供, 且通过以下反应路线来加以说明。其它方法描述于实验部分中。本文中提供的路线及实施例 (包括相应描述) 仅用于说明, 并不意图限制本发明的范围。

[0243] 路线 1 指式 I 的化合物的制备。参照路线 1, 式 1-1 的化合物 [其中 Lg^1 为适合的离去基团, 诸如卤代 (例如 Cl 或 Br); 而 Pg^1 为适合的保护基, 诸如叔丁氧羰基 (Boc)、[2-(三甲基硅烷基) 乙氧基] 甲基 (SEM) 或 2-四氢吡喃基 (THP)] 及式 1-2 的化合物 [其中 Z^1 为卤素 (Cl、Br 或 I)] 为可商购的, 或可通过本文中描述的方法或本领域技术人员熟知的其它方法来制得。式 1-3 的化合物可通过将式 1-1 的化合物与式 1-2 的化合物在适合的条件下来偶联来制备。所述偶联可例如通过在碱 (诸如 Cs_2CO_3) 存在下于适当的溶剂 (诸如 DMSO) 中加热式 1-1 的化合物与式 1-2 的化合物的混合物来实现。或者, 可采用金属催化 (诸如使用钯或铜催化剂) 的偶联来实现前述偶联。在该偶联的变化形式中, 可在碱 (诸如 Cs_2CO_3)、金属催化剂 [诸如钯催化剂, 例如 $[\text{Pd}(\text{OAc})_2]$] 及配体 (诸如 BINAP) 存在下, 于适当的溶剂 (诸如 1,4-二氧杂环己烷) 中加热式 1-1 的化合物与式 1-2 的化合物的混合物。可随后将式 1-3 的化合物通过金属催化 (诸如使用钯催化剂) 的偶联反应与式 $\text{Q}^1\text{-Z}^2$ 的化合物 [其中 Z^2 可为 Br; $\text{B}(\text{OH})_2$; $\text{B}(\text{OR})_2$, 其中各 R 均独立地为 H 或 C_{1-6} 烷基, 或其中两个 (OR) 基团与它们所连接的 B 原子一起形成任选地被一或多个 C_{1-6} 烷基取代的 5 元至 10 元杂环烷基或杂芳基; 三烷基锡基团; 等] 反应以获得式 I 的化合物。式 $\text{Q}^1\text{-Z}^2$ 的化合物为可商购的, 或可通过本文中描述的方法或通过类似于化学领域中所描述的那些的方法来制备。或者, 可将式 1-3 的化合物转化为式 1-4 的化合物 (其中 Z^2 如以上所定义)。例如, 可将式 1-3 的化合物 (其中 Z^1 为卤素, 诸如 Br) 通过本文中描述的方法或本领域技术人员熟知的其它方法转化为式 1-4 的化合物 [其中 Z^2 为 $\text{B}(\text{OH})_2$; $\text{B}(\text{OR})_2$, 其中各 R 均独立地为 H 或 C_{1-6} 烷基, 或其中两个 (OR) 基团与它们所连接的 B 原子一起形成任选地被一或多个 C_{1-6} 烷基取代的 5 元至 10 元杂环烷基或杂芳基]。在该实施例中, 该反应可例如通过在适合的溶剂 (诸如 1,4-二氧杂环己烷) 中将式 1-3 的化合物 (其中 Z^1 为卤素, 诸如 Br) 与 4,4',4'',5,5,5'',5'-八甲基-2,2'-双-1,3,2-二氧杂硼戊环、适合的碱 (诸如乙酸钾) 及钯催化剂 { 诸如 [1,1'-双(二苯基膦基)二茂铁] 二氯化钯 (II) } 反应来实现。在另一实施例中, 可将式 1-3 的化合物 (其中 Z^1 为卤素, 诸如 Br) 通过本文中描述的其它供选

择方法或本领域技术人员熟知的其它方法转化为式 1-4 的化合物（其中 Z^2 为三烷基锡基团）。在该实施例中，该反应可例如通过在钯催化剂 [诸如四（三苯基膦）钯 (0)] 存在下于适合的溶剂（诸如 1,4- 二氧杂环己烷）中将式 1-3 的化合物（其中 Z^1 为卤素，诸如 Br）与六烷基二锡烷（诸如六甲基二锡烷）反应来实现。然后可将式 1-4 的化合物通过金属催化（诸如使用钯催化剂）的偶联反应来与式 Q^1-Z^1 的化合物（其中 Z^1 如以上所定义）反应以获得式 I 的化合物。式 Q^1-Z^1 的化合物为可商购的，或可通过本文中描述的方法或通过类似于化学领域中所描述的那些的方法来制备。所采用的反应类型取决于所选择的 Z^1 及 Z^2 。例如，当 Z^1 为卤素或三氟甲磺酸酯且 Q^1-Z^2 试剂为硼酸或硼酸酯时，可使用 Suzuki 反应 [A. Suzuki, J. Organomet. Chem. 1999, 576, 147-168 ;N. Miyaura 及 A. Suzuki, Chem. Rev. 1995, 95, 2457-2483 ;A. F. Littke 等人, J. Am. Chem. Soc. 2000, 122, 4020-4028]。在一些具体实施方案中，将式 1-3 的芳族碘化物、溴化物或三氟甲磺酸酯在适合的有机溶剂（诸如四氢呋喃 (THF)）中与式 Q^1-Z^2 的芳基或杂芳基硼酸或硼酸酯及适合的碱（诸如磷酸钾）合并。添加钯催化剂，诸如 S-Phos 前催化剂 (precatalyst) { 还称为氯 (2- 二环己基膦基 -2',6'- 二甲氧基 -1,1'- 联苯) [2-(2- 氨基乙基苯基)] 钯 (II)- 叔丁基甲基醚加合物 }，且加热反应混合物。或者，当 Z^1 为卤素或三氟甲磺酸酯且 Z^2 为三烷基锡时，可采用 Stille 偶联 [V. Farina 等人, Organic Reactions 1997, 50, 1-652]。更具体地，可将式 1-3 的化合物（其中 Z^1 为溴化物、碘化物或三氟甲磺酸酯）在钯催化剂（诸如二氯双（三苯基膦）钯 (II)）存在下于适合的有机溶剂（诸如甲苯）中与式 Q^1-Z^2 的化合物（其中 Q^1-Z^2 的化合物为 Q^1 锡烷化合物）合并，且可加热反应。当 Z^1 为 Br、I 或三氟甲磺酸酯且 Z^2 为 Br 或 I 时，可使用 Negishi 偶联 [E. Erdik, Tetrahedron 1992, 48, 9577-9648]。更具体地，可将式 1-3 的化合物（其中 Z^1 为溴化物、碘化物或三氟甲磺酸酯）通过在适当的溶剂（诸如 THF）中，于 -80°C 至 -65°C 的温度下，用 1 至 1.1 当量的烷基锂试剂，随后用 1.2 至 1.4 当量氯化锌的溶液处理来进行金属转移 (transmetallate)。在温热至 10°C 与 30°C 的温度之后，可用式 Q^1-Z^2 的化合物（其中 Z^2 为 Br 或 I）处理反应混合物，且在添加催化剂（诸如四（三苯基膦）钯 (0)）的情况下在 50°C 至 70°C 下加热。反应可在 1 至 24 小时的时间内进行。然后可将式 1-5 的化合物使用取决于 Pg^1 基团的选择的适当条件来脱保护，以获得式 I 的化合物。这些反应均不限于使用上述溶剂、碱、催化剂或配体，而是可使用许多其它条件。

[0244] 路线 1

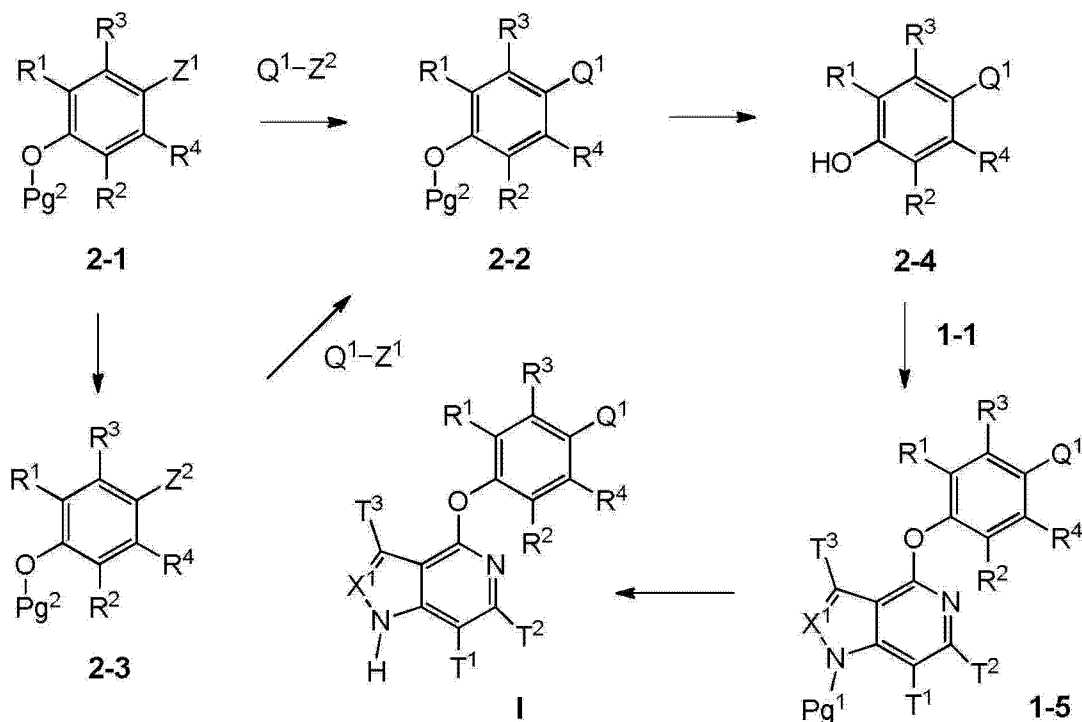
[0245]



[0246] 路线 2 也指式 I 的化合物的制备。参照路线 2, 式 I 的化合物可利用类似于路线 1 中所描述的那些的化学转化来制备, 但步骤排序不同。式 2-1 的化合物 [其中 Pg^2 为适合的保护基, 诸如甲基、苯甲基、THP 或三异丙基硅烷基 (TIPS)] 为可商购的, 或可通过本文中描述的方法或本领域技术人员熟知的其它方法来制备。可将式 2-1 的化合物使用类似于路线 1 中所描述的那些的方法直接转化为式 2-2 的化合物, 或在转化为式 2-3 的化合物之后再转化为式 2-2 的化合物。随后可使用取决于所选择的 Pg^2 基团的适当条件来将式 2-2 的化合物脱保护, 以获得式 2-4 的化合物, 又可将其与路线 1 中的式 1-1 的化合物偶联, 得到式 1-5 的化合物。所采用的偶联条件可类似于路线 1 中的制备式 1-3 的化合物时所描述的那些。然后可使用取决于所选择的 Pg^1 基团的适当条件来将式 1-5 的化合物脱保护, 获得式 I 的化合物。

[0247] 路线 2

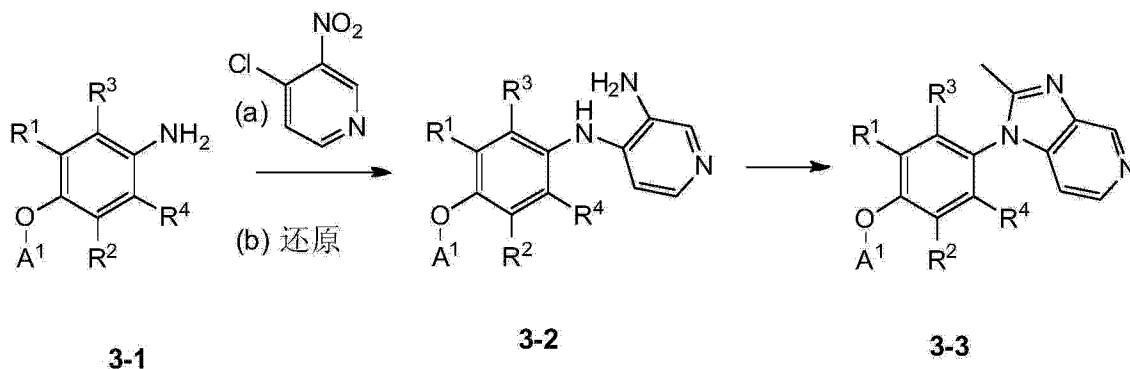
[0248]



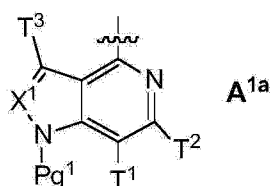
[0249] 路线3指式3-3的化合物(其中 A^1 为如上文所定义的 Pg^2 或式 A^{1a} 的基团)的制备,所述化合物可在路线2中用作制备式I的化合物的中间体/原料。参照路线3,式3-1的化合物为可商购的,或可通过本文中描述的方法或本领域技术人员熟知的其它方法来制得。可将式3-1的化合物与4-氯-3-硝基吡啶反应,且随后可将初始产物还原以获得式3-2的化合物。对于式3-1的化合物与4-氯-3-硝基吡啶的偶联适合的反应条件的实例包括在适合的反应溶剂(诸如乙醇)中将两种反应物与适合的碱(诸如三乙胺)混合。随后可通过例如在催化剂(诸如钯/碳)存在下于适合的溶剂(诸如甲醇)中氢化来还原硝基得到式3-2的化合物。适用于前述反应的氢气压力通常为1atm至4atm。然后可将式3-2的化合物与乙酸酐及原甲酸三乙酯一起加热,获得式3-3的化合物。

[0250] 路线3

[0251]



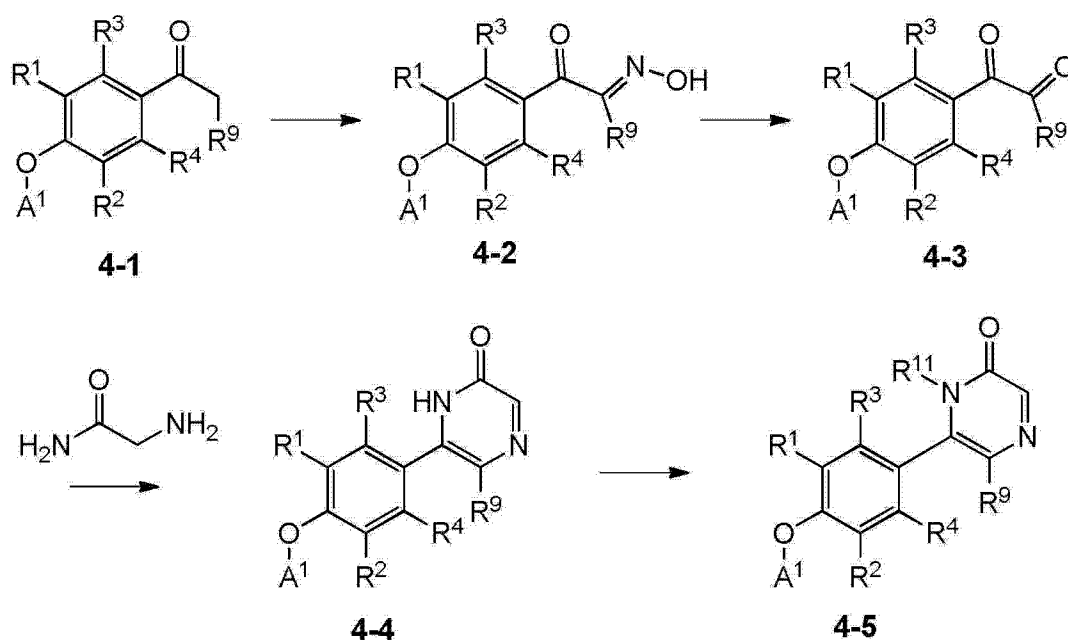
A¹为Pg²或A^{1a}的基团:



[0252] 路线4指式4-4或4-5的化合物(其中R⁹为诸如C₁₋₃烷基,例如甲基)的制备,该化合物可在路线2中用作制备式I的化合物的中间体/原料。参照路线4,式4-1的化合物为可商购的,或可通过本文中描述的方法或本领域技术人员熟知的其它方法来制得。式4-2的化合物可通过在酸(诸如盐酸)存在下将式4-1的芳基酮与亚硝酸烷基酯(例如亚硝酸异戊酯)反应来制备。所得的式4-2的肟可在酸(诸如盐酸水溶液)存在下用甲醛(或其等效物,诸如变甲醛或聚甲醛)处理后转化为式4-3的二酮。式4-3的二酮可在碱(诸如氢氧化钠)存在下与甘氨酸或其盐(诸如乙酸盐)反应,获得式4-4的吡嗪酮。可通过用碱[诸如LDA、LHMDS等]及式R¹¹-Z³的化合物[其中Z³为可接受的离去基团,诸如Cl、Br、I、甲磺酸酯等,且其中R¹¹为例如C₁₋₃烷基(例如甲基)]处理式4-4的化合物来使吡嗪酮氮烷基化以获得式4-5的化合物。适合的反应溶剂通常可选自极性非质子性溶剂,诸如N,N-二甲基甲酰胺(DMF)、1,4-二氧杂环己烷或THF。

[0253] 路线4

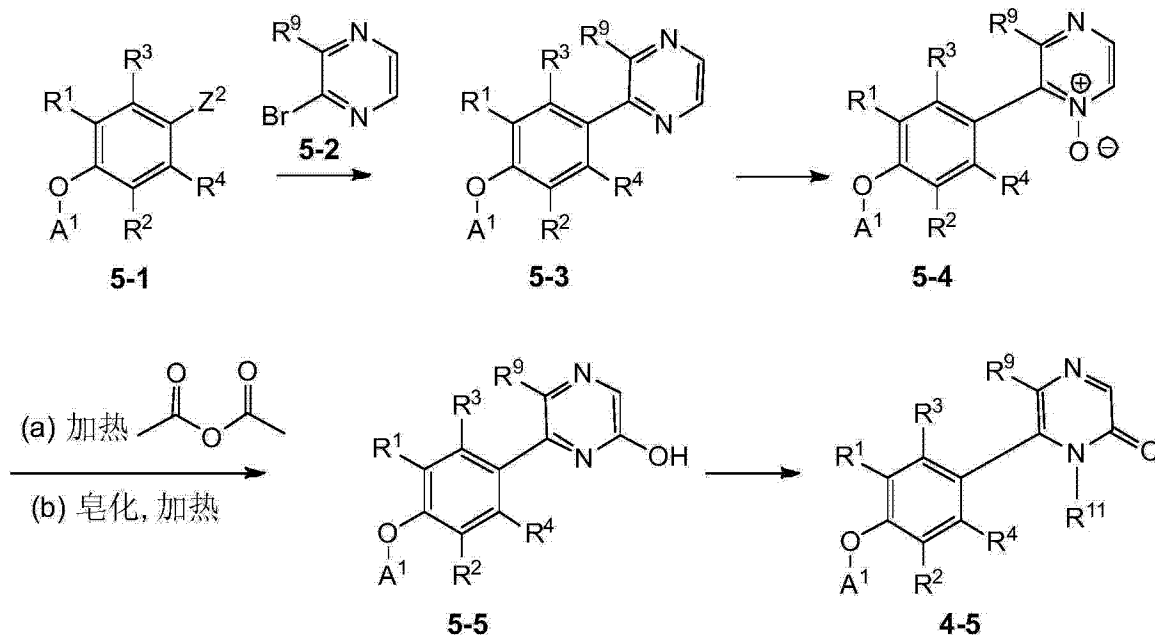
[0254]



[0255] 或者,式 4-5 的化合物可如路线 5 中 [其中 R^{11} 为例如 H 或 C_{1-3} 烷基 (例如甲基)] 进行制备,该化合物可在路线 2 中用作制备式 I 的化合物的中间体 / 原料。参照路线 5,式 5-1 及 5-2 的化合物为可商购的,或可通过本文中描述的方法或本领域技术人员熟知的其它方法来制得。式 5-3 的化合物可通过将式 5-1 的化合物与式 5-2 的化合物偶联来制备。前述偶联可通过在适合的碱 (诸如碳酸钾)、适合的催化剂 [诸如四 (三苯基膦) 钯 (0)] 及适合的溶剂 (诸如乙醇) 存在下将式 5-1 的化合物与式 5-2 的化合物反应来实现。式 5-3 的化合物可在溶剂 (诸如二氯甲烷) 中与顺丁烯二酸酐及过氧化氢反应以提供式 5-4 的化合物,该化合物可包含 N-氧化物区域异构体的混合物。式 5-5 的化合物可自式 5-4 的化合物通过与乙酸酐一起加热来制备;该初始产物可在适合的极性溶剂 (诸如水或甲醇) 中使用碱 (诸如 NaOH) 来皂化。式 4-5 的化合物可自式 5-5 的化合物通过与适合的碱 (诸如 LDA、LHMDS 等)、溴化锂及式 $R^{11}-Z^3$ 的化合物 (其中 Z^3 为可接受的离去基团,诸如 Cl、Br、I、甲磺酸酯等) 反应来制备。适合的反应溶剂通常可选自极性非质子性溶剂 (诸如 DMF、1,4-二氧杂环己烷或 THF)。

[0256] 路线 5

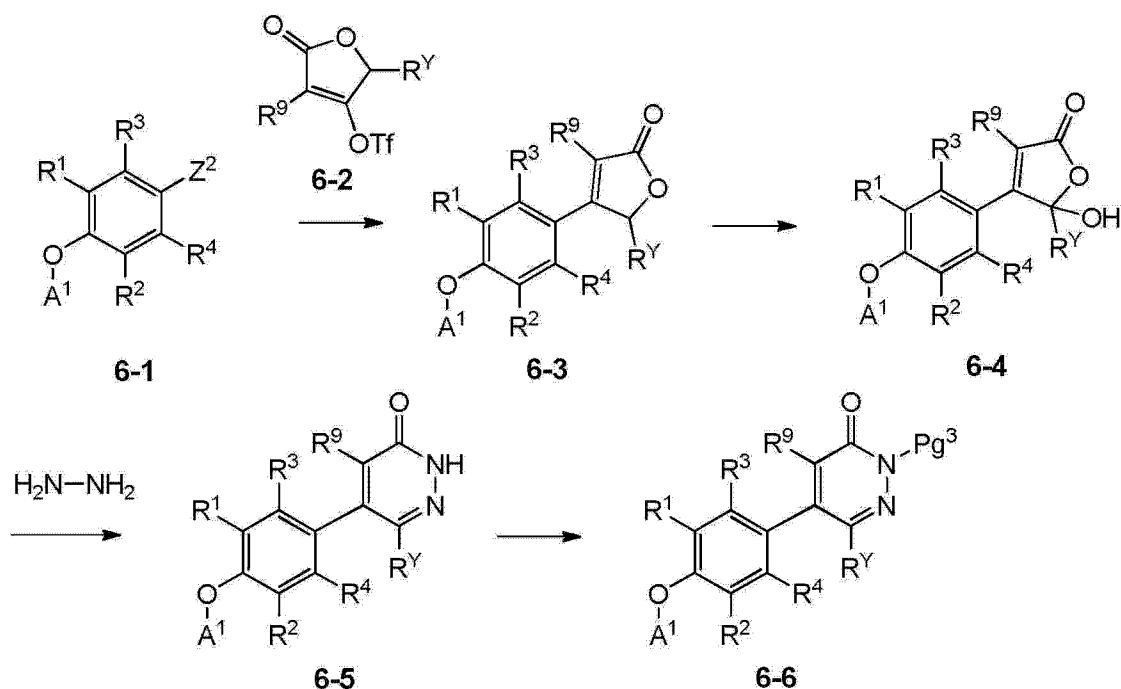
[0257]



[0258] 路线 6 指式 6-6 的化合物 [其中 R^Y 为 H 或 R^{10} (诸如 C_{1-3} 烷基, 例如甲基), 且 Pg^3 为适合的保护基, 诸如 THP] 的制备, 该化合物可在路线 2 中用作制备式 I 的化合物的中间体 / 原料。参照路线 6, 式 6-1 及 6-2 的化合物为可商购的, 或可通过本文中描述的方法或本领域技术人员熟知的其它方法来制得。式 6-3 的化合物可通过将式 6-1 的化合物与式 6-2 的烯醇三氟甲磺酸酯偶联来制备。前述偶联可通过在适合的碱 (诸如碳酸钾)、适合的催化剂 [诸如乙酸钯 (II)]、适合的配体 (诸如三环己基膦) 及任选的适合的相转移催化剂 (诸如四丁基氯化铵) 存在下将式 6-1 的化合物与式 6-2 的三氟甲磺酸酯反应来实现。适合的反应溶剂通常可选自极性非质子性溶剂, 诸如 1, 4- 二氧杂环己烷或 THF。式 6-3 的化合物可在氧气氛围下与 1 至 5 当量的适合的碱 (诸如 DBU) 反应, 获得式 6-4 的化合物。适合的反应溶剂通常可选自极性非质子性溶剂, 诸如 DMF、1, 4- 二氧杂环己烷或 THF。式 6-5 的化合物可通过在适合的溶剂 (诸如 1- 丁醇) 中将式 6-4 的化合物与肼反应来获得。式 6-5 的化合物可使用本文中描述的方法或本领域技术人员熟知的其它方法来转化为被适当保护的式 6-6 化合物。

[0259] 路线 6

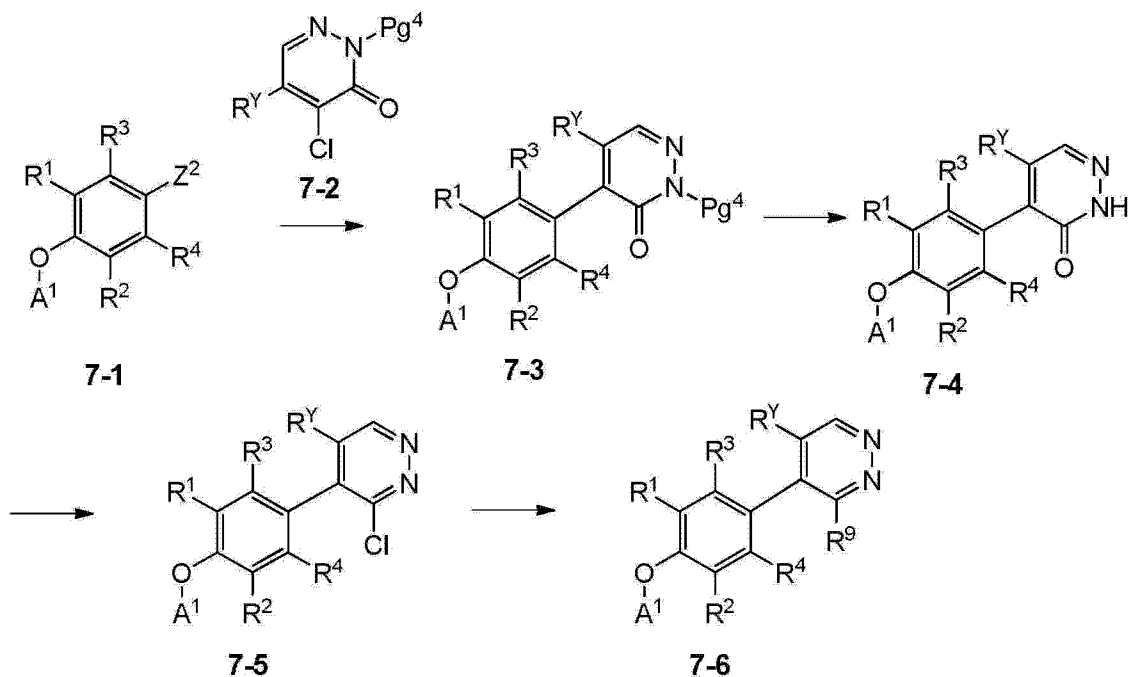
[0260]



[0261] 路线 7 指式 7-6 的化合物 [其中 R^Y 为 H 或 R^{10} (诸如 C_{1-3} 烷基, 例如甲基)] 的制备, 该化合物可在路线 2 中用作制备式 I 的化合物的中间体 / 原料。参照路线 7, 式 7-1 及式 7-2 的化合物为可商购的, 或可通过本文中描述的方法或本领域技术人员熟知的其它方法来制得。式 7-3 的化合物可通过将式 7-1 的化合物与式 7-2 的化合物 [其中 Pg^4 为适合的保护基, 诸如 THP] 偶联来制备。前述偶联可通过在适合的碱 (诸如碳酸铯) 及适合的催化剂 { 诸如 [1, 1'- 双 (二苯基膦基) 二茂铁] 二氯化钯 (II) } 存在下加热式 7-1 的化合物与式 7-2 的化合物来实现。适合的反应溶剂通常可选自极性非质子性溶剂, 诸如 1, 4- 二氧杂环己烷或 THF。式 7-4 的化合物可通过移除保护基 Pg^4 来获得, 例如通过在醇性溶剂 (诸如 2- 丙醇) 中用 HCl 来处理式 7-3 的化合物 (其中 Pg^4 为例如 THP)。在升高的温度下用氯化磷处理式 7-4 的化合物可提供式 7-5 的化合物。式 7-5 的化合物可为获得式 7-6 化合物的多种化学转换中的反应性中间体。例如, 式 7-5 的化合物可在 1, 4- 二氧杂环己烷中与三甲基铝及适合的钯催化剂 [诸如四 (三苯基膦) 钯 (0)] 反应, 得到式 7-6 的化合物 (其中新引入的 R^9 为甲基)。

[0262] 路线 7

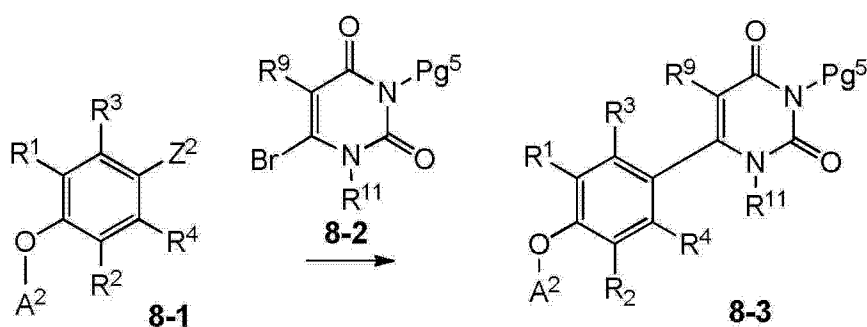
[0263]



[0264] 路线 8 指式 8-3 的化合物 [其中 R^9 为例如 C_{1-3} 烷基 (例如甲基); R^{11} 为例如 H 或 C_{1-3} 烷基 (例如甲基); 且 Pg^5 为适合的保护基 [例如 SEM、Boc 或苯甲氧基甲基缩醛 (BOM)]; A^2 为 H 或 Pg^2 ; 且 Pg^2 为适合的保护基 (例如甲氧基甲基 (MOM) 或苯甲基)] 的制备, 该化合物可在路线 2 中用作制备式 I 的化合物的中间体 / 原料。参照路线 8, 式 8-1 及式 8-2 的化合物为可商购的, 或可通过本文中描述的方法或本领域技术人员熟知的其它方法来制得。式 8-3 的化合物可通过将式 8-1 的化合物与式 8-2 的化合物偶联来制备。前述偶联可通过在适合的碱 (诸如碳酸钾) 及适合的催化剂 { 诸如 [1, 1'-双 (二苯基膦基) 二茂铁] 二氯化钯 (II) } 存在下加热式 8-1 的化合物与式 8-2 的化合物来实现。

[0265] 路线 8

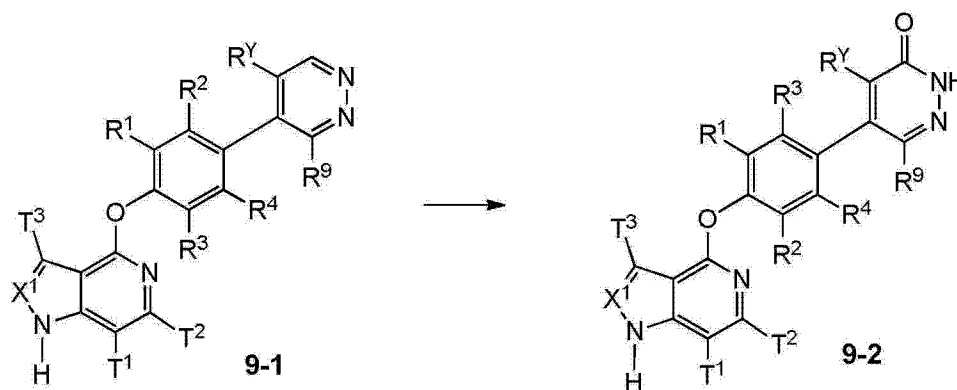
[0266]



[0267] 或者, 式 I 的化合物还可通过相关式 I 的化合物的酶修饰 (诸如微生物氧化) 来制备。例如, 如路线 9 中所示, 在适合的缓冲剂中用恶臭假单胞菌 (*Pseudomonas putida*) 孵育式 I 的化合物 { 例如, 其中 Q^1 为可氧化的基团, 诸如式 9-1 的化合物中的任选地被取代的吡嗪基 [其中 R^y 为 H 或 R^{10} (诸如 C_{1-3} 烷基, 例如甲基)] } 持续 24-96 小时的反应时间可提供其它供选择的式 I 的化合物 (例如其中 Q^1 为式 9-2 的化合物中任选地被取代的吡嗪酮基)。

[0268] 路线 9

[0269]



[0270] 可用于制备本发明的化合物的其它原料及中间体可自化学品销售商（诸如 Sigma-Aldrich）获得，或可根据化学领域中所描述的方法来制得。

[0271] 本领域技术人员可认识到，在本文中描述的所有路线中，若在化合物结构的一部分上存在官能性（反应性）基团（诸如取代基，例如 R^1 、 R^2 、 R^3 、 R^4 、 R^5 、 R^6 、 R^7 、 R^8 、 R^9 、 R^{10} 、 Q^1 等），则适宜和 / 或需要时可使用本领域技术人员熟知的方法来进行进一步修饰。例如，-CN 基团可经水解以得到酰胺基团；羧酸可转化为酰胺；羧酸可转化为酯，其又可经还原为醇，该醇又可经进一步修饰。另外例如，OH 基团可转化为更好的离去基团（诸如甲磺酸酯基），其又适合于（诸如由氰离子 CN^- ）亲核取代。另外例如，-S- 可氧化为 $-S(=O)-$ 和 / 或 $-S(=O)_2-$ 。又另外例如，不饱和键（诸如 $C=C$ 或 $C\equiv C$ ）可通过氢化还原为饱和键。在一些实施方案中，伯胺或仲胺基团（存在于取代基（诸如 R^3 、 R^4 、 R^9 、 R^{10} 等）上）可通过使其与适当的试剂（诸如酰氯、磺酰氯、异氰酸酯或异硫氰酸酯化合物）反应来转化为酰胺、磺酰胺、脲或硫脲基团。本领域技术人员会认识到其它这样的修饰。因此，具有包含官能基的取代基的式 I 的化合物可转化为具有不同取代基的另外的式 I 的化合物。

[0272] 类似地，本领域技术人员还可认识到，在本文中描述的所有路线中，若在取代基上存在官能性（反应性）基团（诸如 R^3 、 R^4 、 R^9 、 R^{10} 等），则适宜和 / 或需要时，在本文中描述的合成路线过程中，这些官能基可被保护 / 脱保护。例如，OH 基团可由苯甲基、甲基或乙酰基保护，其可在合成过程后期脱保护并转化回 OH 基团。另外例如， NH_2 基团可由苯甲氧羰基（Cbz）或 Boc 基团保护；其可在合成过程的后期通过脱保护来转化回 NH_2 基团。

[0273] 如本文中所使用，术语“反应 (reacting/reaction/reacted)”指使所指定的化学反应物混合在一起，以进行化学转换来产生与最初引入系统中的任何化合物不同的化合物。反应可在溶剂存在或不存在下进行。

[0274] 式 I 的化合物可以立体异构体（诸如阻转异构体、外消旋体、对映异构体或非对映异构体）的形式存在。制备 / 分离单个对映异构体的常规技术包括由适合的光学纯前体进行手性合成，或使用例如手性高压液相色谱法（HPLC）来拆分外消旋体。或者，外消旋体（或外消旋前体）可与适合的光学活性化合物（例如醇）反应，或在化合物含有酸性或碱性基团的情况下与酸或碱（诸如酒石酸或 1- 苯乙胺）反应。所得非对映异构混合物可通过色谱法和 / 或分步结晶来分离，且通过本领域技术人员熟知的手段将非对映异构体中之一或二者转化为相应的纯对映异构体。式 I 的手性化合物（及其手性前体）可使用色谱法（通常为 HPLC）在不对称树脂上以对映异构性富集形式获得，其中流动相由烃（通常为庚烷或己烷）组成且含有 0% 至 50%（通常 2% 至 20%）2- 丙醇及 0% 至 5% 烷基胺（通常 0.1% 二乙胺）。浓缩洗脱物得到富集的混合物。立体异构聚结物可通过本领域技术人员已

知的常规技术来分离。参见例如 E. L. Eliel 及 S. H. Wilen 的 *Stereochemistry of Organic Compounds* (Wiley, New York, 1994), 其内容以其整体援引加入本文。适合的立体选择技术为本领域普通技术人员所熟知的。

[0275] 当式 I 的化合物含有烯基或亚烯基 (亚烷基 (alkylidene)) 时, 可能有几何顺 / 反 (或 Z/E) 异构体。顺 / 反异构体可通过本领域技术人员熟知的常规技术 (例如色谱法及分步结晶) 来分离。本发明的盐可根据本领域技术人员已知的方法来制备。

[0276] 本质上为碱性的式 I 的化合物能够与多种无机酸及有机酸形成多种盐。尽管这样的盐在向动物给药时必须为药学上可接受的, 在实践中常常需要首先由反应混合物分离呈药学上不可接受的盐的形式本发明的化合物, 然后通过用碱性试剂处理来简单地将后者 (所述药学上不可接受的盐) 转化回为游离碱化合物, 且随后将后者游离碱转化为药学上可接受的酸加成盐。本发明的碱性化合物的酸加成盐可通过在水性溶剂介质中或在适合的有机溶剂 (诸如甲醇或乙醇) 中用疾病上等量的所选择的无机或有机酸处理该碱性化合物来制备。在蒸发溶剂之后, 获得所需固体盐。所需酸式盐还可通过向游离碱于有机溶剂中的溶液中添加适当的无机或有机酸来由所述溶液中沉淀。

[0277] 若本发明的化合物为碱, 则所需药学上可接受的盐可通过本领域中可获得的任何适合的方法来制备, 例如用无机酸或有机酸来处理游离碱, 所述无机酸诸如盐酸、氢溴酸、硫酸、硝酸、磷酸等, 所述有机酸诸如乙酸、顺丁烯二酸、丁二酸、苦杏仁酸、反丁烯二酸、丙二酸、丙酮酸、草酸、乙醇酸、水杨酸、异烟酸、乳酸、泛酸、双酒石酸 (bitartric acid)、抗坏血酸、2, 5-二羟基苯甲酸、葡萄糖酸、葡萄糖二酸、甲酸、甲磺酸、乙磺酸、苯磺酸、对甲苯磺酸及双羟萘酸 [即 4, 4'-甲烷二基双 (3-羟基萘-2-甲酸)], pyranosidyl 酸 (诸如葡萄糖醛酸或半乳糖醛酸)、 α -羟基酸 (诸如柠檬酸或酒石酸)、氨基酸 (诸如天冬氨酸或谷氨酸)、芳族酸 (诸如苯甲酸或肉桂酸)、磺酸 (诸如乙磺酸) 等。

[0278] 本质上为酸性的那些式 I 的化合物能够与多种药理学上可接受的阳离子形成碱式盐。这样的盐的实例包括碱金属盐或碱土金属盐, 并特别是钠及钾盐。这些盐全部通过常规技术来制备。用作制备本发明的药学上可接受的碱式盐的试剂的化学碱为与酸性式 I 的化合物形成无毒碱式盐的那些。这些盐可通过任何适合的方法来制备, 例如用无机或有机碱来处理游离酸, 所述碱诸如胺 (伯胺、仲胺或叔胺)、碱金属氢氧化物或碱土金属氢氧化物等。这些盐还可通过用含有所需药理学上可接受的阳离子的水溶液处理相应酸性化合物, 且然后 (例如在减压下) 将所得溶液蒸发至干燥来制备。或者, 其还可通过将酸性化合物的低级烷醇溶液与所需碱金属醇盐混合在一起, 且然后以与之前相同的方式将所得溶液蒸发至干燥来制备。在任一情况下, 使用化学计量的试剂以确保反应完全且所需最终产物的收率最高。

[0279] 式 I 的化合物 (包括式 Ia 或式 Ib 的化合物) 的药学上可接受的盐可通过三种方法中的一或多种来制备:

[0280] (i) 通过将式 I 的化合物与所需的酸或碱反应;

[0281] (ii) 通过使用所需的酸或碱将式 I 的化合物的适合前体的酸不稳定或碱不稳定保护基移除, 或通过使用所需的酸或碱将适合的环状前体 (例如内酯或内酰胺) 开环; 或

[0282] (iii) 通过与适当的酸或碱反应或通过适合的离子交换柱来将式 I 的化合物的一种盐转化为另一种盐。

[0283] 所有三种反应均通常在溶液中进行。所得盐可沉淀出且通过过滤来收集,或可通过蒸发溶剂来回收。所得盐的离子化程度可在完全离子化至几乎非离子化的范围内变化。

[0284] 多晶型物可根据本领域技术人员熟知的技术(例如通过结晶)来制备。

[0285] 当任意外消旋体结晶时,可能有两种不同类型的晶体。第一种类型为上文所提及的外消旋化合物(真正的外消旋体),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。第二种类型为外消旋混合物或聚结物,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。

[0286] 存在于外消旋混合物中的两种晶体形式可具有几乎相同的物理特性,但其可具有与真正外消旋体相比不同的物理特性。外消旋混合物可通过本领域技术人员已知的常规技术来分离-参见例如 E. L. Eliel 及 S. H. Wilen 的 *Stereochemistry of Organic Compounds* (Wiley, New York, 1994)。

[0287] 本发明还包括同位素标记的式 I 的化合物,其中一或多个原子由具有相同原子序数但原子质量或质量数与自然界中常见的原子质量或质量数不同的原子替换。同位素标记的式 I 的化合物(或其药学上可接受的盐或其 N-氧化物)通常可通过本领域技术人员已知的常规技术或通过类似于本文中描述的那些的方法,使用经适当同位素标记的试剂代替在其它情况下使用的未标记的试剂来制备。

[0288] 本发明的前药可例如通过用本领域技术人员已知的某些基团(例如在 H. Bundgaard 的 *Design of Prodrugs* (Elsevier, 1985) 中所描述的“前部分”)来替换式 I 的化合物中存在的适当官能团来产生。

[0289] 应评估式 I 的化合物的生物医药特性(诸如溶解度及溶液稳定性(跨 pH)、渗透率等),以为治疗所建议的适应症来选择最适当的剂型及给药途径。

[0290] 意图用于制药用途的本发明的化合物可以结晶或无定形产物的形式给药。其可通过诸如沉淀、结晶、冷冻干燥、喷雾干燥或蒸发干燥的方法以例如固体塞、散剂或薄膜形式获得。微波或射频干燥可用于此目的。

[0291] 可将其单独给药,或与本发明的一或多种其它化合物组合给药,或与一或多种其它药物(或以其任何组合形式)组合给药。一般而言,会将其以制剂形式与一或多种药学上可接受的赋形剂联合给药。术语“赋形剂”在本文中用于描述除本发明的化合物以外的任何成分。赋形剂的选择在很大程度上会视诸如特定给药模式、赋形剂对溶解性及稳定性的作用及剂型性质的因素而定。

[0292] 适合于递送本发明的化合物(或其药学上可接受的盐)的药物组合物及其制备方法对本领域技术人员而言为显而易见的。所述组合物及其制备方法可见于例如 Remington's Pharmaceutical Sciences, 第 19 版 (Mack Publishing Company, 1995) 中。

[0293] 本发明的化合物(包括其药学上可接受的盐及其 N-氧化物)可经口给药。口服给药可涉及吞咽,以使化合物进入胃肠道;和/或含服、经舌或舌下给药,由此使化合物直接自口进入血流。

[0294] 适合于口服给药的制剂包括固体、半固体及液体系统,诸如片剂;含有多颗粒或纳米颗粒、液体或散剂的软胶囊剂或硬胶囊剂;锭剂(包括液体填充的);咀嚼剂(chew);凝胶剂;快速分散剂型;薄膜剂;卵形剂(ovule);喷雾剂;及含服贴剂/粘膜粘着贴剂。

[0295] 液体制剂包括混悬剂、溶液剂、糖浆剂及酞剂。这样的制剂可以软胶囊剂或硬胶囊

剂（例如由明胶或羟丙基甲基纤维素制得）中的填充剂形式使用，且通常包含载体（例如水、乙醇、聚乙二醇、丙二醇、甲基纤维素或适合的油）及一或多种乳化剂和 / 或助悬剂。液体制剂还可通过使（例如来自药囊的）固体复原来制备。

[0296] 本发明的化合物还可以快速溶解、快速崩解剂型使用，诸如由 Liang 及 Chen 于 Expert Opinion in Therapeutic Patents 2001, 11, 981-986 中所描述的那些。

[0297] 对片剂剂型而言，根据剂量，药物可占剂型的 1 重量%至 80 重量%，更通常占剂型的 5 重量%至 60 重量%。除药物外，片剂通常含有崩解剂。崩解剂的实例包括羟基乙酸淀粉钠、羧甲基纤维素钠、羧甲基纤维素钙、交联羧甲基纤维素钠、交聚维酮、聚乙烯吡咯烷酮、甲基纤维素、微晶纤维素、低级烷基取代的羟丙基纤维素、淀粉、预胶化淀粉及海藻酸钠。一般而言，崩解剂会占剂型的 1 重量%至 25 重量%，例如 5 重量%至 20 重量%。

[0298] 粘合剂通常用于向片剂制剂赋予粘合性质。适合的粘合剂包括微晶纤维素、明胶、糖、聚乙二醇、天然及合成树胶、聚乙烯吡咯烷酮、预胶化淀粉、羟丙基纤维素及羟丙基甲基纤维素。片剂还可含有稀释剂，诸如乳糖（一水合物、喷雾干燥的一水合物、无水物等）、甘露醇、木糖醇、葡萄糖、蔗糖、山梨糖醇、微晶纤维素、淀粉及二水合磷酸氢钙。

[0299] 片剂还可任选地包含表面活性剂（诸如月桂基硫酸钠及聚山梨醇酯 80）及助流剂（诸如二氧化硅及滑石）。当存在时，表面活性剂可占片剂的 0.2 重量%至 5 重量%，助流剂可占片剂的 0.2 重量%至 1 重量%。

[0300] 片剂通常还含有润滑剂，诸如硬脂酸镁、硬脂酸钙、硬脂酸锌、硬脂酰醇富马酸钠及硬脂酸镁与月桂基硫酸钠的混合物。润滑剂通常占片剂的 0.25 重量%至 10 重量%，例如 0.5 重量%至 3 重量%。

[0301] 其它可能的成分包括抗氧化剂、着色剂、调味剂、防腐剂及味道掩蔽剂。

[0302] 示例性片剂含有至多约 80% 的药物、约 10 重量%至约 90 重量%的粘合剂、约 0 重量%至约 85 重量%的稀释剂、约 2 重量%至约 10 重量%的崩解剂、及约 0.25 重量%至约 10 重量%的润滑剂。

[0303] 片剂掺合物可直接或通过滚筒压缩以形成片剂。或者，在压片之前，可将片剂掺合物或掺合物的部分湿法造粒、干法造粒或熔融造粒、熔融聚结或挤出。最终制剂可包含一或多个层，且可被包衣或未被包衣；甚至可将其装入胶囊。

[0304] 片剂的制剂在 H. Lieberman 及 L. Lachman 的 Pharmaceutical Dosage Forms: Tablets, 第 1 卷 (Marcel Dekker, New York, 1980) 中讨论。

[0305] 人用或兽用的可服用经口薄膜剂通常为柔韧的水溶性或水可膨胀性薄膜剂型，其可快速溶解或具有粘膜粘着性，且通常包含式 I 的化合物、成膜聚合物、粘合剂、溶剂、保湿剂、增塑剂、稳定剂或乳化剂、粘度调节剂及溶剂。制剂的一些组分可发挥多于一种功能。

[0306] 式 I 的化合物（或其药学上可接受的盐或其 N-氧化物）可溶于水或不溶于水。水溶性化合物通常占溶质的 1 重量%至 80 重量%，更通常 20 重量%至 50 重量%。较低溶解性的化合物可占组合物较小的比例，通常至多溶质的 30 重量%。或者，式 I 的化合物可呈多颗粒珠的形式。

[0307] 成膜聚合物可选自天然多醣、蛋白质或合成水胶体，且通常以 0.01 至 99 重量%，更通常以 30 至 80 重量%存在。

[0308] 其它可能的成分包括抗氧化剂、着色剂、调味剂及增味剂、防腐剂、唾液刺激剂、冷

却剂、共溶剂（包括油）、软化剂、膨胀剂、消泡剂、表面活性剂及味道掩蔽剂。

[0309] 本发明的薄膜剂通常通过使涂布在可剥离的背托或纸上的水性薄膜蒸发干燥来制备。此可在干燥烘箱或干燥隧道（通常为组合涂布干燥器）中或通过冷冻干燥或抽真空来进行。

[0310] 用于口服给药的固体制剂可配制为立即释放和 / 或修饰释放制剂。修饰释放制剂包括延迟释放、持续释放、脉冲释放、控制释放、靶向释放及程控释放制剂。

[0311] 为达成本发明的目的适合的修饰释放制剂描述于第 6, 106, 864 号美国专利中。其它适合的释放技术（诸如高能分散体及渗透且包衣的颗粒）的细节可见于 Verma 等人, *Pharmaceutical Technology On-line*, 25(2), 1-14(2001) 中。使用口嚼锭 (chewing gum) 以达到控制释放描述于 WO 00/35298 中。

[0312] 本发明的化合物（包括其药学上可接受的盐及其 N- 氧化物）还可直接向血流中、向肌肉中或向内脏器官中给药。适用于肠胃外给药的手段包括静脉内、动脉内、腹膜内、鞘内、心室内、尿道内、胸骨内、颅内、肌肉内、滑膜内及皮下给药。适用于肠胃外给药的装置包括针（包括微针）注射器、无针注射器及输注技术。

[0313] 肠胃外制剂通常为水溶液，其可含有赋形剂，诸如盐、碳水化合物及缓冲剂（例如缓冲至 pH 为 3 至 9），但对一些应用而言，肠胃外制剂可更适合配制为与适合的媒介物（诸如无菌无热原的水）结合使用的无菌非水性溶液或干燥形式。

[0314] 在无菌条件下例如通过冻干来制备肠胃外制剂可使用本领域技术人员熟知的标准医药技术来容易地实现。

[0315] 用于制备肠胃外溶液的式 I 的化合物的溶解度可通过使用适当的制剂技术（诸如掺入溶解性增强剂）来增加。

[0316] 用于肠胃外给药的制剂可配制为立即释放和 / 或修饰释放制剂。修饰释放制剂包括延迟释放、持续释放、脉冲释放、控制释放、靶向释放及程控释放制剂。因此，本发明的化合物可配制为混悬剂或固体、半固体或触变性液体，以提供活性化合物的修饰释放的植入式储槽形式来给药。这样的制剂的实例包括药物涂布的支架及包含负载药物的聚（DL- 乳酸 - 共乙醇酸 (coglycolic acid)）(PLGA) 微球的半固体及混悬剂。

[0317] 本发明的化合物（包括其药学上可接受的盐及其 N- 氧化物）还可向皮肤或黏膜局部、皮（内）或经皮给药。用于该目的的典型制剂包括凝胶剂、水凝胶、洗剂、溶液剂、乳膏剂、软膏剂、撒粉剂 (dusting powder)、敷料、泡沫剂、薄膜剂、皮肤贴剂、包药糯米纸剂 (wafer)、植入物、海绵、纤维、绷带及微乳剂。还可使用脂质体。典型载体包括醇、水、矿物油、液体石蜡、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.* 1999, 88, 955-958。

[0318] 局部给药的其它手段包括通过电穿孔、电离子透入疗法、超声透入疗法、超声促渗法及微针或无针（例如 Powderject™、Bioject™等）注射来递送。

[0319] 用于局部给药的制剂可配制为立即释放和 / 或修饰释放制剂。修饰释放制剂包括延迟释放、持续释放、脉冲释放、控制释放、靶向释放及程控释放制剂。

[0320] 本发明的化合物（包括其药学上可接受的盐及其 N- 氧化物）还可经鼻内或通过吸入来给药，其通常呈来自干粉吸入器的干粉形式（单独；呈混合物形式，例如与乳糖的干掺合物；或呈混合组分颗粒形式，例如与磷脂（诸如磷脂酰胆碱）混合），呈在使用或不使

用适合的抛射剂（诸如 1, 1, 1, 2- 四氟乙烷或 1, 1, 1, 2, 3, 3, 3- 七氟丙烷）下的来自加压容器、泵、喷雾器（spray）、雾化器（例如使用电流体动力学以产生精细薄雾的雾化器）或喷雾器（nebulizer）的气雾剂喷雾形式，或呈鼻滴剂形式。对鼻内使用而言，粉末可包含生物粘附剂，例如聚氨基葡萄糖或环糊精。

[0321] 加压容器、泵、喷雾器（spray）、雾化器或喷雾器（nebulizer）含有本发明的化合物的溶液或悬浮液，所述溶液或悬浮液包含例如乙醇、乙醇水溶液或适用于分散、增溶活性物质或延长活性物质的释放的其它供选择物质、作为溶剂的抛射剂及任选存在的表面活性剂（诸如三油酸山梨坦、油酸或寡聚乳酸（oligolactic acid））。

[0322] 在干粉或混悬剂制剂中使用之前，药品经微粒化为适合于通过吸入递送尺寸（通常小于 5 微米）。这可通过任何适当的粉碎方法来实现，诸如螺旋形喷射研磨、流化床喷射研磨、形成纳米颗粒的超临界流体处理、高压匀浆化或喷雾干燥。

[0323] 用于吸入器或吹入器的胶囊剂（例如自明胶或羟丙基甲基纤维素制得）、泡壳包装剂及药筒可配制为含有本发明的化合物、适合的粉末基质（诸如乳糖或淀粉）及效能调节剂（诸如 L- 亮氨酸、甘露醇或硬脂酸镁）的粉末混合物。乳糖可为无水的或呈一水合物形式。其它适合的赋形剂包括葡聚糖、葡萄糖、麦芽糖、山梨糖醇、木糖醇、果糖、蔗糖及海藻糖。

[0324] 适用于使用电流体动力学来产生精细薄雾的雾化器的溶液制剂可含有每次致动 1 μ g 至 20mg 的本发明的化合物，且致动体积可在 1 μ L 至 100 μ L 变化。典型制剂可包含式 I 的化合物或其药学上可接受的盐、丙二醇、无菌水、乙醇及氯化钠。可代替丙二醇使用的其它供选择溶剂包括甘油及聚乙二醇。

[0325] 可将适合的调味剂（诸如薄荷脑及左薄荷脑）或甜味剂（诸如糖精或糖精钠）添加至意图用于吸入 / 鼻内给药的本发明的那些制剂中。

[0326] 用于吸入 / 鼻内给药的制剂可使用例如 PGLA 配制为立即释放和 / 或修饰释放制剂。修饰释放制剂包括延迟释放、持续释放、脉冲释放、控制释放、靶向释放及程控释放制剂。

[0327] 在干粉吸入器及气雾剂的情况下，通过递送定量的阀门来确定剂量单位。本发明的单位通常经配置以给药含有 0.01-100mg 的式 I 的化合物的定量剂量或“喷一次剂量（puff）”。总日剂量通常会为 1 μ g 至 200mg，其可以单次剂量形式给药，或更通常在整日中以分次剂量形式给药。

[0328] 本发明的化合物可经直肠或经阴道给药，例如以栓剂、子宫托或灌肠剂形式给药。可可脂为传统栓剂基质，但适当时可使用多种替代物。

[0329] 用于经直肠 / 阴道给药的制剂可配制为立即释放和 / 或修饰释放制剂。修饰释放制剂包括延迟释放、持续释放、脉冲释放、控制释放、靶向释放及程控释放制剂。

[0330] 本发明的化合物还可直接向眼或耳给药，通常呈等渗、pH 经调节的无菌盐水中的微粒化悬浮液或溶液的滴剂的形式。适合于眼部及耳部给药的其它制剂包括软膏剂、凝胶剂、可生物降解植入物（例如可吸收凝胶海绵、胶原）及不可生物降解植入物（例如硅酮）、包药糯米纸剂、镜片及颗粒剂或囊泡系统（诸如泡囊（niosome）或脂质体）。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）或杂多醣聚合物（例如琼脂糖胶）的聚合物可与防腐剂（诸如苯扎氯铵）掺合在

一起。这样的制剂还可通过电离子透入疗法来递送。

[0331] 用于眼部 / 耳部给药的制剂可配制为立即释放和 / 或修饰释放制剂。修饰释放制剂包括延迟释放、持续释放、脉冲释放、控制释放、靶向释放或程控释放制剂。

[0332] 本发明的化合物可与可溶性高分子实体（诸如环糊精及其适合的衍生物，或含有聚乙二醇的聚合物）组合，以改良其在任何前述给药模式中使用时的溶解度、溶出率、味道掩蔽性、生物利用度和 / 或稳定性。

[0333] 例如，发现药物 - 环糊精络合物通常可用于多数剂型及给药途径。可使用包络合物及非包络合物。作为与药物直接络合的替代方案，环糊精可用作辅助添加剂，即用作载体、稀释剂或增溶剂。最常用于这些目的的为 α - 环糊精、 β - 环糊精及 γ - 环糊精，其实例可见于第 WO 91/11172 号、第 WO94/02518 号及第 WO 98/55148 号国际专利申请中。

[0334] 因为本发明的一个方面涉及用可分开给药的活性成分的组合来治疗本文中描述的疾病 / 病况，所以本发明还涉及以药盒形式来组合分开的药物组合物。所述药盒包含两种分开的药物组合物：式 I 的化合物、其前药或这样的化合物或前药的盐，及如上文所描述第二化合物。药盒包含用于容纳所述分开的组合物的手段，诸如容器、分开的瓶或分开的箔材包装。所述药盒通常包含用于给药分开的组分的指导。当分开的组分例如以不同剂型（例如经口及肠胃外）给药时、以不同的给药间隔给药时，或处方医师需要滴定组合的单独组分时，药盒形式是特别有益的。

[0335] 这样的药盒的实例为所谓的泡壳包装。泡壳包装在包装工业中为人所熟知，且广泛用于包装药物单位剂型（片剂、胶囊剂等）。泡壳包装通常由用透明塑料材料箔片覆盖的相对刚性材料的薄片组成。在包装过程期间，在塑料箔片中形成凹槽。所述凹槽具有待包装的片剂或胶囊剂的尺寸及形状。然后，将片剂或胶囊剂置放在凹槽中，且相对于塑料箔片，在箔片正面与形成凹槽的方向相反的一面密封相对刚性材料的薄片。因此，片剂或胶囊剂被密封在塑料箔片与薄片之间的凹槽中。在一些实施方案中，所述薄片的强度使得片剂或胶囊剂可从泡壳包装移出，其通过在凹槽上手动施加压力，从而在凹槽位置于薄片形成开口。然后，所述片剂或胶囊剂可通过所述开口来移出。

[0336] 药盒上可能需要提供记忆辅助，例如以紧邻片剂或胶囊剂的编号形式，其中编号对应于方案中应摄入所述指定的片剂或胶囊剂的天数。这样的记忆辅助的另一个实例为在卡上印刷的日历，例如如下“第一周，周一、周二等……第二周，周一、周二……”等。记忆辅助的其它变型会是显而易见的。“日剂量”可为于指定日期服用的单一片剂或胶囊剂，或数个丸剂或胶囊剂。此外，式 I 的化合物的日剂量可由一种片剂或胶囊剂组成，而第二化合物的日剂量可由数个片剂或胶囊剂组成，且反的还然。记忆辅助应反映此情况。

[0337] 在本发明的另一个具体实施方案中，提供经设计以按所期望使用的顺序一次分配日剂量的分配器。例如，所述分配器配备有记忆辅助，以进一步促进与方案的顺应性。这样的记忆辅助的一个实例为指示已分配的日剂量数目的机械计数器。这样的记忆辅助的另一个实例为与液晶读数器或音频提醒信号组合的电池供电的微芯片存储器，所述液晶读数器或音频提醒信号例如读出服用上一日剂量的日期和 / 或提醒何时服用下一剂量。

[0338] 通过具体实施例更详细地描述本发明。为了说明的目的而提供以下实施例，并不意图以任何方式限制本发明。本领域技术人员会容易识别可经改变或修改以产生基本相同的结果的多种非关键性参数。在以下实施例及制备中，“DMSO”意指二甲亚砜，在提及浓

度时“N”在指代浓度时意指当量浓度,“M”意指摩尔,“mL”意指毫升,“mmol”意指毫摩尔,“ μmol ”意指微摩尔,“eq.”意指当量,“ $^{\circ}\text{C}$ ”意指摄氏度,“MHz”意指兆赫兹,“HPLC”意指高效液相色谱法。

实施例

[0339] 实验通常在惰性氛围(氮气或氩气)下进行,特别是在其中采用对氧或水分敏感的试剂或中间体的情况下。商购溶剂及试剂通常不经进一步纯化即使用,适当时包括无水溶剂(通常为来自Aldrich Chemical Company, Milwaukee, Wisconsin的Sure-SealTM产品)。产物在继续进行进一步反应或提交用于进行生物测试之前通常在真空下干燥。质谱数据由液相色谱法-质谱法(LCMS)、大气压化学电离(APCI)或气相色谱法-质谱法(GCMS)探测报告。核磁共振(NMR)数据的化学位移参考来自所采用的氘化溶剂的残余峰以兆比率(ppm, δ)来表示。在一些实施例中,进行手性分离以分离本发明的某些化合物的阻转异构体(或阻转对映异构体)(在一些实施例中,根据其洗脱次序,将所分离的阻转异构体指定为ENT-1及ENT-2)。在一些实施例中,使用旋光计测量阻转异构体的旋光度。根据其所观测的旋转数据(或其具体旋转数据),具有顺时针旋光性的阻转异构体(或阻转对映异构体)指定为(+)-阻转异构体[或(+)-阻转对映异构体],具有逆时针旋光性的阻转异构体(或阻转对映异构体)指定为(-)-阻转异构体[或(-)-阻转对映异构体]。

[0340] 对参考其它实施例或方法中的方法的合成,反应条件(反应时间长度及温度)可变化。一般而言,在反应之后进行薄层色谱法或质谱法,且适当时进行后处理。在实验之间,纯化可变化:一般而言,选择用于洗脱液/梯度的溶剂及溶剂比率以提供适当 R_f 或保留时间。

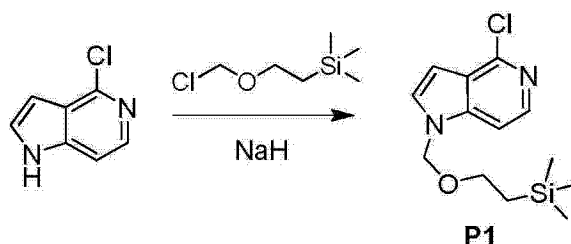
[0341] 制备

[0342] 制备P1-P8描述用于制备本发明的某些化合物的一些原料或中间体的制备。

[0343] 制备P1

[0344] 4-氯-1-{[2-(三甲基硅烷基)乙氧基]甲基}-1H-吡咯并[3,2-c]吡啶(P1)

[0345]



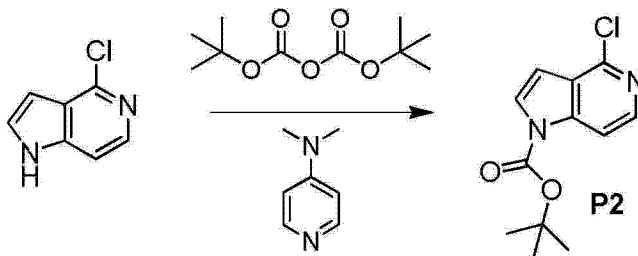
[0346] 将4-氯-1H-吡咯并[3,2-c]吡啶(98%, 2.0g, 13mmol)与四氢呋喃(20mL)的混合物冷却至 0°C 。经5分钟分批添加氢化钠(于油中60%, 1.03g, 25.8mmol),且在 0°C 下搅拌反应混合物10分钟。随后经5分钟逐滴添加2-(三甲基硅烷基)乙氧基甲基氯(3.40mL, 19.3mmol),且在 0°C 下继续搅拌15分钟。用饱和氯化铵水溶液淬灭反应混合物;用乙酸乙酯萃取水层两次,且用硫酸钠干燥合并的有机层,过滤,且在真空中浓缩。硅胶色谱法(梯度:庚烷中的10%至20%乙酸乙酯),得到呈无色油状的产物。收率:2.64g, 9.33mmol, 72%。LCMS m/z 283.0 $[\text{M}+\text{H}^+]$ 。 ^1H NMR(400MHz, CDCl_3) δ 8.13(d, $J = 5.8\text{Hz}$, 1H), 7.34(dd, $J = 5.8, 0.7\text{Hz}$, 1H), 7.25(d, $J = 3.3\text{Hz}$, 1H), 6.69(dd, $J = 3.3, 0.7\text{Hz}$, 1H), 5.48(s, 2H), 3.4

6 (dd, $J = 8.2, 8.1\text{Hz}$, 2H), 0.89 (dd, $J = 8.2, 8.1\text{Hz}$, 2H), -0.05 (s, 9H)。

[0347] 制备 P2

[0348] 4-氯-1H-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯 (P2)

[0349]

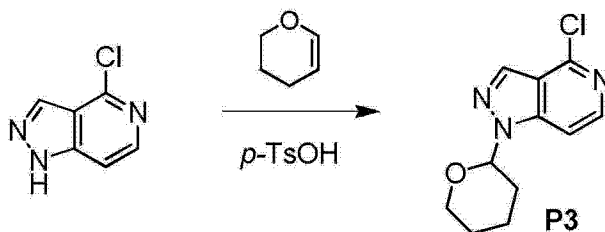


[0350] 向 4-氯-1H-吡咯并[3,2-c]吡啶 (300mg, 1.97mmol) 及 4-(二甲氨基)吡啶 (97%, 124mg, 0.984mmol) 于乙腈 (3mL) 中的溶液中添加二碳酸二叔丁酯 (99%, 650mg, 2.95mmol), 且在室温下搅拌反应混合物 18 小时。在真空中移除挥发物, 且通过硅胶色谱法 (梯度: 庚烷中的 0% 至 50% 乙酸乙酯) 来纯化残渣, 得到呈白色固体状的产物。收率: 410mg, 1.62mmol, 82%。LCMS m/z 253.0 $[M+H]^+$ 。 ^1H NMR (400MHz, CDCl_3) δ 8.24 (d, $J = 5.7\text{Hz}$, 1H), 7.95 (br d, $J = 5.7\text{Hz}$, 1H), 7.65 (d, $J = 3.7\text{Hz}$, 1H), 6.72 (dd, $J = 3.7, 0.8\text{Hz}$, 1H), 1.70 (s, 9H)。

[0351] 制备 P3

[0352] 4-氯-1-(四氢-2H-吡喃-2-基)-1H-吡唑并[4,3-c]吡啶 (P3)

[0353]

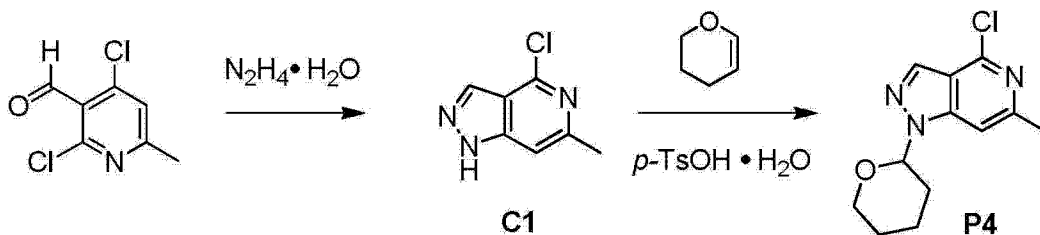


[0354] 向 4-氯-1H-吡唑并[4,3-c]吡啶 (20.0g, 130mmol) 于二氯甲烷 (400mL) 中的悬浮液中顺序添加对甲苯磺酸一水合物 (2.4g, 13mmol) 及 3,4-二氢-2H-吡喃 (99%, 45mL, 520mmol)。将反应混合物在室温下搅拌 24 小时, 此时用饱和碳酸氢钠水溶液洗涤。用硫酸钠干燥有机层, 过滤, 且在真空中浓缩。通过硅胶色谱法 (洗脱液: 庚烷中的 10%、随后 30%、随后 50% 乙酸乙酯) 来纯化, 得到呈白色固体状的产物。收率: 27.51g, 115.7mmol, 89%。LCMS m/z 238.1 $[M+H]^+$ 。 ^1H NMR (400MHz, CDCl_3) δ 8.19 (d, $J = 6.0\text{Hz}$, 1H), 8.16 (d, $J = 0.9\text{Hz}$, 1H), 7.47 (dd, $J = 6.0, 0.9\text{Hz}$, 1H), 5.73 (br dd, $J = 9.0, 2.7\text{Hz}$, 1H), 3.97-4.04 (m, 1H), 3.72-3.80 (m, 1H), 2.43-2.53 (m, 1H), 2.07-2.20 (m, 2H), 1.65-1.85 (m, 3H)。

[0355] 制备 P4

[0356] 4-氯-6-甲基-1-(四氢-2H-吡喃-2-基)-1H-吡唑并[4,3-c]吡啶 (P4)

[0357]



[0358] 步骤 1. 4-氯-6-甲基-1H-吡唑并[4,3-c]吡啶 (C1) 的合成

[0359] 向 2,4-二氯-6-甲基吡啶-3-甲醛 (12g, 63mmol) 于 1,2-二氯乙烷 (200mL) 中的溶液中添加肼一水合物 (9.52g, 0.190mol), 且在 80℃ 下加热反应混合物 18 小时。在真空中移除溶剂之后, 将残渣悬浮于水 (150mL) 中且搅拌 30 分钟。通过过滤来收集所得沉淀, 且用石油醚 (2×250mL) 洗涤, 随后悬浮于氯仿 (150mL) 中, 搅拌 30 分钟且过滤。重复氯仿悬浮两次, 得到呈白色固体状的产物。收率: 6.7g, 40mmol, 63%。LCMS m/z 168.1 $[M+H]^+$ 。¹H NMR (400MHz, DMSO- d_6) δ 13.70 (br s, 1H), 8.21 (s, 1H), 7.38 (s, 1H), 2.52 (s, 3H)。

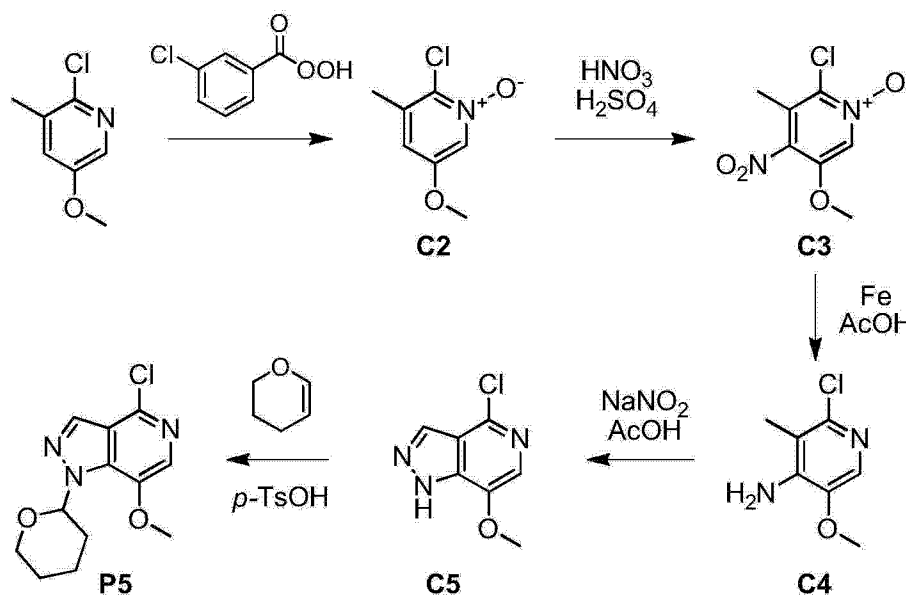
[0360] 步骤 2. P4 的合成

[0361] 向 C1 (250mg, 1.49mmol) 及 4Å 分子筛于二氯甲烷 (10mL) 中的悬浮液中顺序添加对甲苯磺酸一水合物 (29mg, 0.15mmol) 及 3,4-二氢-2H-吡喃 (99%, 205 μ L, 2.39mmol)。将反应混合物在室温下搅拌 4 小时, 此时过滤, 在真空中浓缩, 且用庚烷洗涤三次。通过硅胶色谱法 (梯度: 庚烷中的 20% 至 50% 乙酸乙酯) 来纯化, 得到呈无色油状的产物。收率: 65mg, 0.26mmol, 17%。LCMS m/z 252.1 $[M+H]^+$ 。¹H NMR (400MHz, $CDCl_3$), 特征峰: δ 8.08 (d, J = 0.9Hz, 1H), 7.26-7.27 (m, 1H), 5.67 (dd, J = 9.1, 2.8Hz, 1H), 3.99-4.05 (m, 1H), 3.71-3.79 (m, 1H), 2.65 (d, J = 0.8Hz, 3H), 2.06-2.2 (m, 2H)。

[0362] 制备 P5

[0363] 4-氯-7-甲氧基-1-(四氢-2H-吡喃-2-基)-1H-吡唑并[4,3-c]吡啶 (P5)

[0364]



[0365] 步骤 1. 2-氯-5-甲氧基-3-甲基吡啶 1-氧化物 (C2) 的合成

[0366] 向 2-氯-5-甲氧基-3-甲基吡啶 (370mg, 2.35mmol) 于二氯甲烷 (10mL) 中的溶液中添加 3-氯过氧苯甲酸 (70%, 695mg, 2.82mmol)。在室温下搅拌 18 小时之后, 在真空中

浓缩反应混合物,且通过硅胶色谱法(梯度:乙酸乙酯中的0%至10%甲醇)来纯化,得到呈白色固体状的产物。收率:370mg,2.13mmol,91%。¹H NMR(400MHz, CD₃OD) δ 8.14(d, J = 2.5Hz, 1H), 7.23(d, J = 2.3Hz, 1H), 3.88(s, 3H), 2.44(s, 3H)。

[0367] 步骤 2. 2-氯-5-甲氧基-3-甲基-4-硝基吡啶 1-氧化物(C3)的合成

[0368] 向 C2(350mg, 2.02mmol) 于浓硫酸(2.5mL) 中的 0℃ 溶液中逐滴添加浓硝酸(2.5mL)。在 90℃ 下加热反应混合物 1 小时,随后冷却至室温且倒在碎冰上。用饱和碳酸钠水溶液将所得混合物中和至 pH 6-7,且用乙酸乙酯萃取。用水洗涤合并的有机层,用饱和氯化钠水溶液洗涤,经硫酸镁干燥,过滤,且在真空中浓缩,得到呈淡黄色固体状的产物。收率:370mg, 1.69mmol, 84%。LCMS m/z 219.0, 221.1[M+H⁺]。¹H NMR(400MHz, DMSO-d₆) δ 8.65(s, 1H), 3.94(s, 3H), 2.31(s, 3H)。

[0369] 步骤 3. 2-氯-5-甲氧基-3-甲基吡啶-4-胺(C4)的合成

[0370] 向 C3(350mg, 1.60mmol) 于乙酸(8mL) 中的溶液中添加铁粉(700mg, 12mmol), 且在 100℃ 下加热反应混合物 1 小时,随后冷却至室温。在通过硅藻土过滤且用乙酸乙酯及甲醇彻底洗涤过滤垫之后,在真空中浓缩合并的滤液。用饱和碳酸氢钠水溶液稀释残渣,且用乙酸乙酯萃取。用水洗涤合并的有机层,用饱和氯化钠水溶液洗涤,经硫酸镁干燥,过滤,且在减压下浓缩。硅胶色谱法(梯度:庚烷中的 50%至 75%乙酸乙酯),得到呈白色固体状的产物。收率:240mg, 1.39mmol, 87%。LCMS m/z 173.0[M+H⁺]。¹H NMR(400MHz, CDCl₃) δ 7.65(s, 1H), 4.38(br s, 2H), 3.91(s, 3H), 2.20(s, 3H)。

[0371] 步骤 4. 4-氯-7-甲氧基-1H-吡唑并[4,3-c]吡啶(C5)的合成

[0372] 向 C4(200mg, 1.16mmol) 于乙酸(8mL) 中的溶液中添加亚硝酸钠(98%, 326mg, 4.63mmol) 于水(0.6mL) 中的溶液,且在 75℃ 下加热反应混合物 1 小时。在将反应混合物冷却至室温之后,在真空中浓缩,用饱和碳酸氢钠水溶液稀释,且用乙酸乙酯萃取。用饱和氯化钠水溶液洗涤合并的有机层,经硫酸镁干燥、过滤,且在减压下浓缩。硅胶色谱法(梯度:庚烷中的 25%至 50%乙酸乙酯),得到呈黄色固体状的产物。收率:140mg, 0.763mmol, 66%。LCMS m/z 184.0[M+H⁺]。¹H NMR(400MHz, CDCl₃) δ 8.17(s, 1H), 7.74(s, 1H), 4.06(s, 3H)。

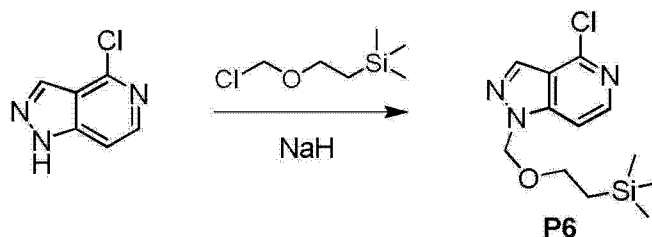
[0373] 步骤 5. P5 的合成

[0374] 使用在制备 P3 中合成 4-氯-1-(四氢-2H-吡喃-2-基)-1H-吡唑并[4,3-c]吡啶 P3 时所描述的方法来将 C5 转化为产物。获得呈淡黄色油状的产物,其在静置后固化。收率:120mg, 0.448mmol, 41%。LCMS m/z 268.1[M+H⁺]。¹H NMR(400MHz, CDCl₃) δ 8.11-8.12(m, 1H), 7.72(s, 1H), 6.12(dd, J = 10.0, 2.6Hz, 1H), 4.06(s, 3H), 4.04-4.10(m, 1H), 3.69-3.77(m, 1H), 2.51-2.62(m, 1H), 2.12-2.21(m, 1H), 2.00-2.08(m, 1H), 1.5-1.8(m, 3H)。

[0375] 制备 P6

[0376] 4-氯-1-{[2-(三甲基硅烷基)乙氧基]甲基}-1H-吡唑并[4,3-c]吡啶(P6)

[0377]

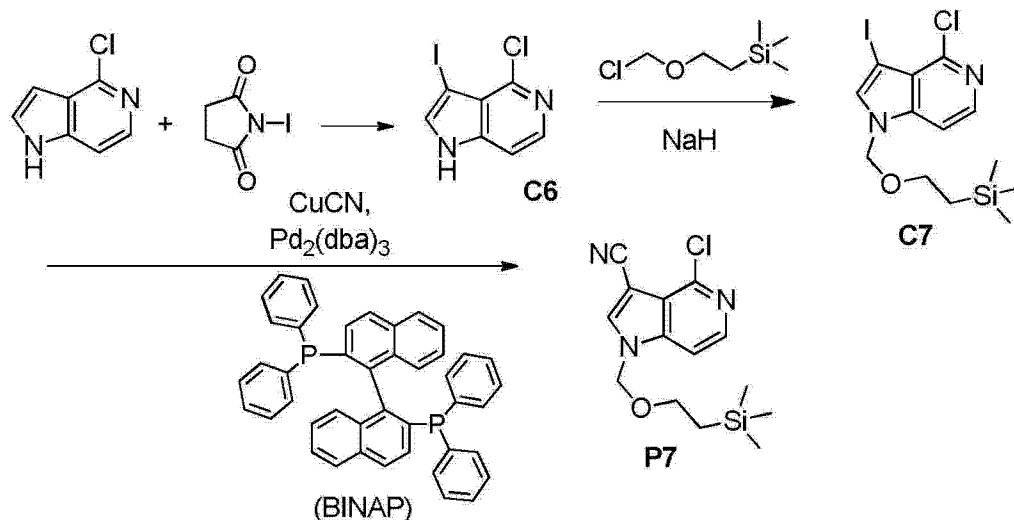


[0378] 使用制备 P1 中合成 P1 时所描述的方法来将 4-氯-1H-吡唑并[4,3-c]吡啶转化为产物。分离呈白色固体状的产物。收率:686mg, 2.42mmol, 50%。¹H NMR(400MHz, CDCl₃) δ 8.24(d, J = 5.8Hz, 1H), 8.17(s, 1H), 7.43(d, J = 5.8Hz, 1H), 5.74(s, 2H), 3.54-3.60(m, 2H), 0.86-0.92(m, 2H), -0.05(s, 9H)。

[0379] 制备 P7

[0380] 4-氯-1-{[2-(三甲基硅烷基)乙氧基]甲基}-1H-吡咯并[3,2-c]吡啶-3-甲腈(P7)

[0381]



[0382] 步骤 1. 4-氯-3-碘-1H-吡咯并[3,2-c]吡啶(C6)的合成

[0383] 向 4-氯-1H-吡咯并[3,2-c]吡啶(0.60g, 3.9mmol)于 N,N-二甲基甲酰胺(10mL)中的 0℃溶液中添加 N-碘丁二酰亚胺(1.3g, 5.8mmol)。在室温下搅拌反应混合物 18 小时,接着在真空中浓缩。通过硅胶色谱法(石油醚中的 0%至 50%乙酸乙酯)来纯化,得到呈黄色固体状的产物。收率:900mg, 3.2mmol, 82%。¹H NMR(400MHz, CDCl₃) δ 8.10(d, J = 5.5Hz, 1H), 7.42(d, J = 2.5Hz, 1H), 7.34(d, J = 5.8Hz, 1H)。

[0384] 步骤 2. 4-氯-3-碘-1-{[2-(三甲基硅烷基)乙氧基]甲基}-1H-吡咯并[3,2-c]吡啶(C7)的合成

[0385] 向 C6(900mg, 3.2mmol)于 N,N-二甲基甲酰胺(3mL)及四氢呋喃(70mL)中的 0℃溶液中添加氢化钠(矿物油中 60%, 168mg, 4.2mmol)。在 5 分钟之后,向冷混合物中添加 2-(三甲基硅烷基)乙氧基甲基氯(592mg, 3.55mmol)。在室温下搅拌反应混合物 3 小时,随后冷却至 0℃,且用额外的氢化钠(56mg, 1.4mmol)及 2-(三甲基硅烷基)乙氧基甲基氯(197mg, 1.18mmol)处理。在室温下搅拌 18 小时之后,用饱和氯化钠水溶液(100mL)稀释反应混合物,且用乙酸乙酯(2×100mL)萃取。干燥合并的有机层,过滤,且在真空中浓缩。硅

胶色谱法(梯度:石油醚中的0%至30%乙酸乙酯),得到呈黄色油状的产物。收率:650mg, 1.59mmol, 50%。¹H NMR(400MHz, CDCl₃) δ 8.14(d, J = 6.0Hz, 1H), 7.39(d, J = 6.0Hz, 1H), 7.38(s, 1H), 5.44(s, 2H), 3.44-3.50(m, 2H), 0.86-0.92(m, 2H), -0.03(s, 9H)。

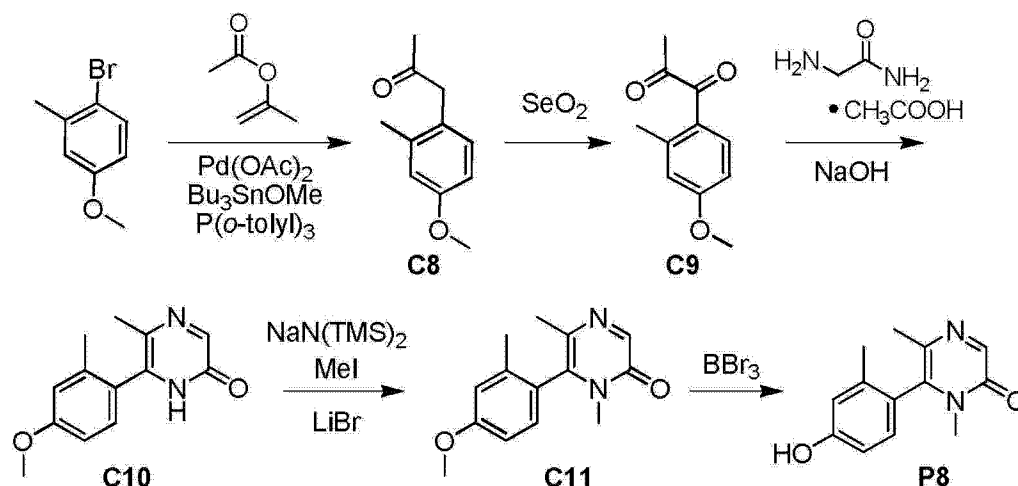
[0386] 步骤3.P7的合成

[0387] 向C7(1.2g, 2.9mmol)及氰化铜(I)(540mg, 6.0mmol)于1,4-二氧杂环己烷(40mL)中的混合物中添加三(二亚苄基丙酮)二钯(0)(275mg, 0.300mmol)及1,1'-联二萘-2,2'-二基双(二苯基磷烷)(BINAP, 540mg, 0.87mmol)。在110℃下搅拌反应混合物18小时之后,过滤且在减压下浓缩。通过硅胶色谱法(梯度:石油醚中的5%至20%乙酸乙酯)来纯化,得到呈黄色固体状的产物。收率:380mg, 1.2mmol, 41%。¹H NMR(400MHz, CDCl₃) δ 8.27(d, J = 5.8Hz, 1H), 7.80(s, 1H), 7.43(d, J = 5.8Hz, 1H), 5.52(s, 2H), 3.47-3.54(m, 2H), 0.88-0.95(m, 2H), -0.02(s, 9H)。

[0388] 制备P8

[0389] 6-(4-羟基-2-甲基苯基)-1,5-二甲基吡嗪-2(1H)-酮(P8)

[0390]



[0391] 步骤1.1-(4-甲氧基-2-甲基苯基)丙-2-酮(C8)的合成

[0392] 进行四批次该实验(4×250g底物)。在100℃下,将三丁基(甲氧基)锡烷(400g, 1.24mol)、1-溴-4-甲氧基-2-甲基苯(250g, 1.24mol)、乙酸丙-1-烯-2-基酯(187g, 1.87mol)、乙酸钯(II)(7.5g, 33mmol)及三(2-甲基苯基)磷烷(10g, 33mmol)于甲苯(2L)中一起搅拌18小时。在冷却至室温之后,用氟化钾水溶液(4M, 400mL)处理反应混合物,且在40℃下搅拌2小时。用甲苯(500mL)稀释所得混合物,且通过硅藻土过滤;用乙酸乙酯(2×1.5L)充分洗涤过滤垫。经硫酸钠干燥来自合并的滤液的有机相,过滤,且在真空中浓缩。通过硅胶色谱法(梯度:石油醚中的0%至5%乙酸乙酯)来纯化,得到呈黄色油状的产物。合并的收率:602g, 3.38mol, 68%。LCMS m/z 179.0[M+H]⁺。¹H NMR(400MHz, CDCl₃) δ 7.05(d, J = 8.3Hz, 1H), 6.70-6.77(m, 2H), 3.79(s, 3H), 3.65(s, 2H), 2.22(s, 3H), 2.14(s, 3H)。

[0393] 步骤2.1-(4-甲氧基-2-甲基苯基)丙烷-1,2-二酮(C9)的合成

[0394] 将C8(6.00g, 33.7mmol)及二氧化硒(7.47g, 67.3mmol)悬浮于1,4-二氧杂环己烷(50mL)中,且在100℃下加热18小时。将反应混合物冷却至室温,且通过硅藻土过滤;在真空中浓缩滤液。硅胶色谱法(洗脱液:庚烷中的10%乙酸乙酯),得到呈鲜黄色油状

的产物。收率:2.55g,13.3mmol,39%。LCMS m/z 193.1[M+H⁺]。¹H NMR(400MHz, CDCl₃) δ 7.66(d, J = 8.6Hz, 1H), 6.81(br d, AB 四重峰的一半, J = 2.5Hz, 1H), 6.78(br dd, ABX 模式的一半, J = 8.7, 2.6Hz, 1H), 3.87(s, 3H), 2.60(br s, 3H), 2.51(s, 3H)。

[0395] 步骤 3.6-(4-甲氧基-2-甲基苯基)-5-甲基吡嗪-2(1H)-酮(C10)的合成

[0396] 将 C9(4.0g,21mmol)及乙酸甘氨酸酰胺(2.79g,20.8mmol)溶解于甲醇(40mL)中,且冷却至-10℃。添加氢氧化钠水溶液(12N,3.5mL,42mmol),且将所得混合物缓慢升温至室温。在搅拌3天之后,在真空中浓缩反应混合物。用水稀释残渣,且添加1N盐酸水溶液直至pH为约7。用乙酸乙酯萃取水相,且用饱和氯化钠水溶液洗涤合并的有机萃取物,经硫酸镁干燥,过滤,且在减压下浓缩。将所得残渣用3:1乙酸乙酯/庚烷制成浆料,搅拌5分钟,过滤,且在真空中浓缩。硅胶色谱法(洗脱液:乙酸乙酯),得到呈褐色固体状的产物,该产物含有15%非所需的区域异构体;该物质不经进一步纯化即使用。收率:2.0g。LCMS m/z 231.1[M+H⁺]。¹H NMR(400MHz, CDCl₃) δ 8.09(s, 1H), 7.14(d, J = 8.2Hz, 1H), 6.82-6.87(m, 2H), 3.86(s, 3H), 2.20(s, 3H), 2.11(s, 3H)。

[0397] 步骤 4.6-(4-甲氧基-2-甲基苯基)-1,5-二甲基吡嗪-2(1H)-酮(C11)的合成

[0398] 将 C10(来自前述步骤,1.9g)溶解于N,N-二甲基甲酰胺(40mL)中。添加溴化锂(0.86g,9.9mmol)及双(三甲基硅烷基)氨化钠(95%,1.91g,9.89mmol),且搅拌所得溶液30分钟。添加碘代甲烷(0.635mL,10.2mmol),且在室温下继续搅拌18小时。随后用水稀释反应混合物,且通过缓慢分批添加1N盐酸水溶液来使pH值达到约7。用乙酸乙酯萃取水层,且用水洗涤合并的有机层数次,经硫酸镁干燥,过滤,且浓缩。硅胶色谱法(梯度:庚烷中的75%至100%乙酸乙酯),得到呈粘稠橙色油状的产物。两步后收率:1.67g,6.84mmol,33%。LCMS m/z 245.1[M+H⁺]。¹H NMR(400MHz, CDCl₃) δ 8.17(s, 1H), 7.03(br d, J = 8Hz, 1H), 6.85-6.90(m, 2H), 3.86(s, 3H), 3.18(s, 3H), 2.08(br s, 3H), 2.00(s, 3H)。

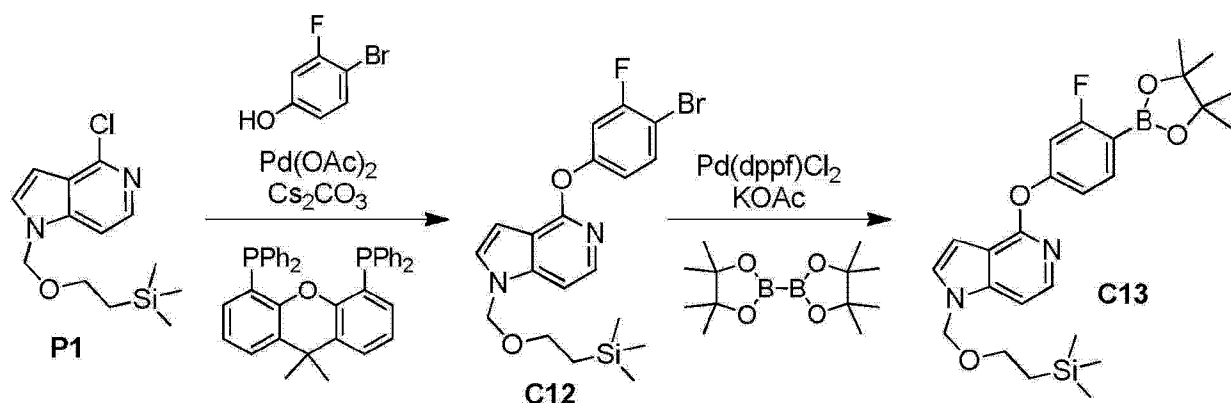
[0399] 步骤 5.P8的合成

[0400] 向 C11(1.8g,7.37mmol)于二氯甲烷(40mL)中的-78℃溶液中添加三溴化硼于二氯甲烷中的溶液(1M,22mL,22mmol)。在30分钟之后移除冷却浴,且使反应混合物升温至室温且搅拌18小时。将反应物冷却至-78℃,且缓慢添加甲醇(10mL);将所得混合物缓慢升温至室温。在真空中浓缩反应混合物,添加甲醇(20mL),且在减压下再次浓缩混合物。用乙酸乙酯(300mL)及水(200mL)稀释残渣,且通过分批添加饱和碳酸钠水溶液来使水层达到pH 7。用乙酸乙酯(3×200mL)萃取混合物。用水及饱和氯化钠水溶液洗涤合并的有机萃取物,经硫酸镁干燥,过滤,且在真空中浓缩,得到呈淡褐色固体状的产物。收率:1.4g,6.0mmol,81%。LCMS m/z 231.1[M+H⁺]。¹H NMR(400MHz, CDCl₃) δ 8.21(s, 1H), 6.98(d, J = 8.2Hz, 1H), 6.87-6.89(m, 1H), 6.85(br dd, J = 8.2, 2.5Hz, 1H), 3.22(s, 3H), 2.06(br s, 3H), 2.03(s, 3H)。

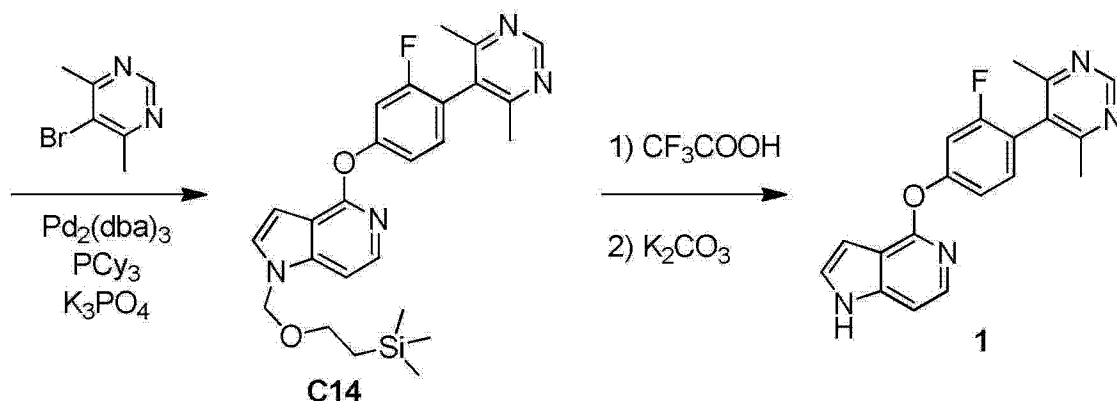
[0401] 实施例 1

[0402] 4-[4-(4,6-二甲基嘧啶-5-基)-3-氟苯氧基]-1H-吡咯并[3,2-c]吡啶(1)

[0403]



[0404]



[0405] 步骤 1. 4-(4-溴-3-氟苯氧基)-1-[[2-(三甲基硅烷基)乙氧基]甲基]-1H-吡咯并[3,2-c]吡啶 (C12) 的合成

[0406] 将 P1 (2.9g, 10mmol)、4-溴-3-氟苯酚 (3.4g, 18mmol)、乙酸钯 (II) (168mg, 0.748mmol)、4,5-双(二苯基膦基)-9,9-二甲基吨 (Xantphos, 0.87g, 1.5mmol) 及碳酸铯 (9.8g, 30mmol) 于 1,4-二氧杂环己烷 (60mL) 中的混合物在 120℃ 下搅拌 4 小时。过滤混合物, 在真空中浓缩滤液, 且通过硅胶色谱法 (洗脱液: 10:1 石油醚/乙酸乙酯) 来纯化残渣, 得到呈无色油状的产物。收率: 1.6g, 3.7mmol, 37%。¹H NMR (400MHz, CDCl₃) δ 7.90 (d, J = 5.8Hz, 1H), 7.55 (dd, J = 8.5, 8.0Hz, 1H), 7.17-7.21 (m, 2H), 7.08 (dd, J = 9.4, 2.6Hz, 1H), 6.94-6.99 (m, 1H), 6.68 (d, J = 3.3Hz, 1H), 5.49 (s, 2H), 3.50 (t, J = 8.0Hz, 2H), 0.91 (t, J = 8.1Hz, 2H), -0.04 (s, 9H)。

[0407] 步骤 2. 4-[3-氟-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼戊环-2-基)苯氧基]-1-[[2-(三甲基硅烷基)乙氧基]甲基]-1H-吡咯并[3,2-c]吡啶 (C13) 的合成

[0408] 将 C12 (1.2g, 2.7mmol)、4,4,4',4',5,5,5',5'-八甲基-2,2'-双-1,3,2-二氧杂硼戊环 (1.38g, 5.43mmol)、乙酸钾 (0.8g, 8mmol) 及 [1,1'-双(二苯基膦基)二茂铁]二氯化钯 (II) (150mg, 0.20mmol) 于 1,4-二氧杂环己烷 (20mL) 中的混合物在 120℃ 下搅拌 5 小时。在反应完成之后, 过滤混合物, 且在减压下浓缩滤液。使用硅胶色谱法 (洗脱液: 15:1 石油醚/乙酸乙酯) 来纯化, 得到呈橙色油状的产物。收率: 0.94g, 1.9mmol, 70%。¹H NMR (400MHz, CDCl₃) δ 7.92 (d, J = 5.8Hz, 1H), 7.77 (dd, J = 7.9, 7.2Hz, 1H), 7.19 (d, J = 5.9Hz, 1H), 7.17 (d, J = 3.3Hz, 1H), 6.99-7.03 (m, 1H), 6.90-6.94 (m, 1H), 6.62 (d, J = 3.3Hz, 1H), 5.49 (s, 2H), 3.49 (t, J = 8.1Hz, 2H), 1.36 (s, 12H), 0.90 (t, J = 8.2Hz, 2H), -0.04 (s, 9H)。

[0409] 步骤 3. 4-[4-(4,6-二甲基嘧啶-5-基)-3-氟苯氧基]-1-[[2-(三甲基硅烷基)乙氧基]甲基]-1H-吡咯并[3,2-c]吡啶(C14)的合成

[0410] 将 C13(427mg, 0.881mmol)、5-溴-4,6-二甲基嘧啶(150mg, 0.802mmol)、三(二亚苄基丙酮)二钯(0)(147mg, 0.160mmol)、三环己基膦(90mg, 0.32mmol)及磷酸钾(341mg, 1.61mmol)于含有 5 滴水的 1,4-二氧杂环己烷(4mL)中的混合物在微波照射下于 120℃ 下加热 2 小时。过滤混合物,在减压下浓缩滤液,且通过制备型硅胶薄层色谱法(洗脱液:乙酸乙酯)来纯化残渣,得到产物,该产物不经进一步纯化即使用。收率:180mg, 0.387mmol, 48%。LCMS m/z 465.3[M+H⁺]。

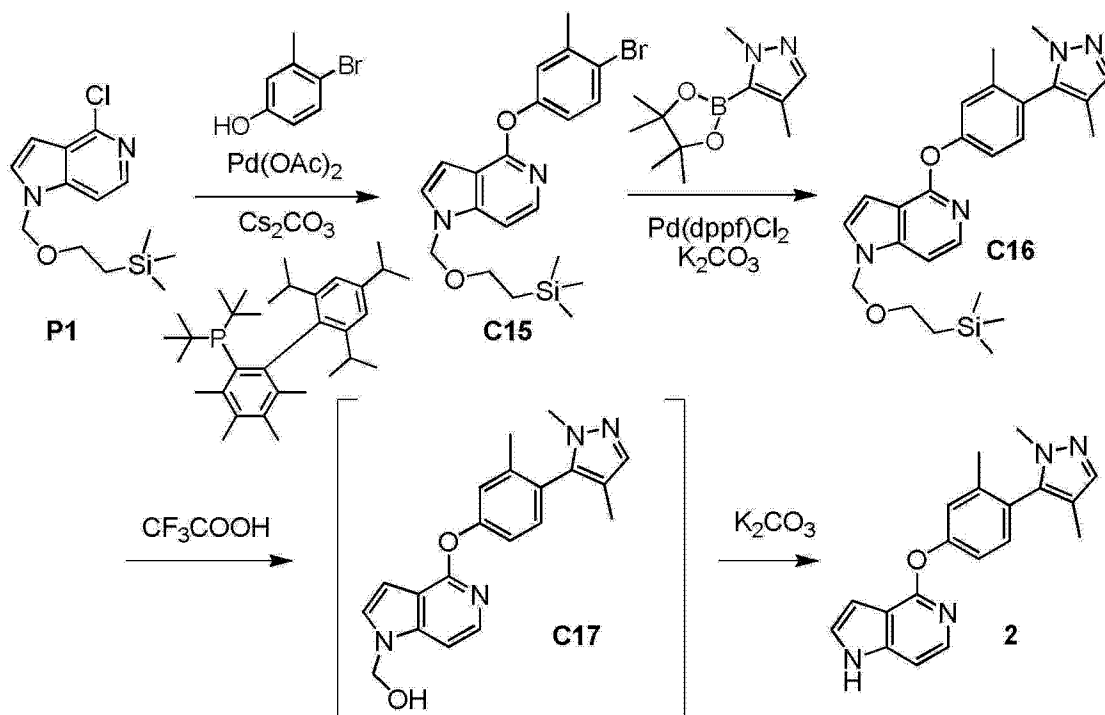
[0411] 步骤 4. 4-[4-(4,6-二甲基嘧啶-5-基)-3-氟苯氧基]-1H-吡咯并[3,2-c]吡啶(1)的合成

[0412] 将 C14(180mg, 0.387mmol)于三氟乙酸(6mL)中的溶液加热至 90℃,持续 2 小时。在减压下浓缩混合物,且将残渣溶解于乙腈(5mL)及水(1mL)中。添加固体碳酸钾(1g),且将混合物回流 2 小时。过滤悬浮液,且在真空中浓缩滤液。通过制备型反相高效液相色谱法(柱:Phenomenex Synergi C18, 4μm;流动相 A:水中的 0.1%甲酸;流动相 B:乙腈中的 0.1%甲酸;梯度:18%至 28% B)来纯化,得到呈白色固体状的产物。收率:114mg, 0.341mmol, 88%。LCMS m/z 334.9[M+H⁺]。¹H NMR(400MHz, CD₃OD) δ 8.96(s, 1H), 8.01(d, J = 6.5Hz, 1H), 7.67(d, J = 6.5Hz, 1H), 7.61(d, J = 3.0Hz, 1H), 7.47-7.58(m, 2H), 7.41(br d, J = 8.5Hz, 1H), 6.17(d, J = 3.0Hz, 1H), 2.39(s, 6H)。

[0413] 实施例 2

[0414] 4-[4-(1,4-二甲基-1H-吡唑-5-基)-3-甲基苯氧基]-1H-吡咯并[3,2-c]吡啶(2)

[0415]



[0416] 步骤 1. 4-(4-溴-3-甲基苯氧基)-1-[[2-(三甲基硅烷基)乙氧基]甲基]-1H-吡咯并[3,2-c]吡啶(C15)的合成

[0417] 在可密封的管中将 P1 (326mg, 1.15mmol)、4-溴-3-甲基苯酚 (216mg, 1.15mmol)、二叔丁基 [3,4,5,6-四甲基-2',4',6'-三(丙-2-基)联苯-2-基] 磷烷 (97%, 114mg, 0.230mmol)、乙酸铯 (II) (95%, 19.1mg, 80.8 μ mol) 及碳酸铯 (1.13g, 3.47mmol) 于 1,4-二氧杂环己烷 (7mL) 中合并, 且在 130℃ 下加热反应混合物 18 小时。添加乙酸乙酯, 且通过硅藻土过滤混合物, 在真空中浓缩且通过硅胶色谱法 (梯度: 庚烷中的 0% 至 50% 乙酸乙酯) 纯化两次。获得呈油状的产物, 其仍含有一些苯酚原料。收率: 395mg, <0.91mmol, <79%。LCMS m/z 434.9 [M+H]⁺。¹H NMR (500MHz, CDCl₃), 仅产物峰: δ 7.91 (d, J = 5.9Hz, 1H), 7.52 (d, J = 8.5Hz, 1H), 7.19-7.22 (m, 2H), 7.12 (br d, J = 2.7Hz, 1H), 6.94 (br dd, J = 8.7, 2.8Hz, 1H), 6.69 (br d, J = 3.2Hz, 1H), 5.51 (s, 2H), 3.51-3.56 (m, 2H), 2.36 (s, 3H), 0.92-0.97 (m, 2H), 0.01 (s, 9H)。

[0418] 步骤 2.4-[4-(1,4-二甲基-1H-吡唑-5-基)-3-甲基苯氧基]-1-[[2-(三甲基硅烷基)乙氧基]甲基]-1H-吡咯并 [3,2-c] 吡啶 (C16) 的合成

[0419] 在室温下向 C15 (100mg, 0.231mmol)、1,4-二氧杂环己烷 (2mL) 与水 (0.5mL) 的混合物中添加 1,4-二甲基-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼戊环-2-基)-1H-吡唑 (56mg, 0.25mmol)、[1,1'-双(二苯基膦基)二茂铁] 二氯化铯 (II) (25.6mg, 0.0350mmol) 及碳酸钾 (97mg, 0.70mmol)。在 120℃ 下搅拌反应混合物 1 小时; 在冷却至室温之后, 过滤混合物且在真空中浓缩滤液。通过制备型硅胶薄层色谱法 (洗脱液: 1:1 石油醚 / 乙酸乙酯) 来纯化, 得到呈红色油状的产物。收率: 51mg, 0.11mmol, 48%。¹H NMR (400MHz, CD₃OD) δ 7.80 (d, J = 6.0Hz, 1H), 7.43 (d, J = 3.3Hz, 1H), 7.37-7.40 (m, 2H), 7.21 (d, J = 8.3Hz, 1H), 7.16 (br d, J = 2.0Hz, 1H), 7.08 (br dd, J = 8.3, 2.5Hz, 1H), 6.61 (d, J = 3.3Hz, 1H), 5.60 (s, 2H), 3.61 (s, 3H), 3.51-3.57 (m, 2H), 2.09 (s, 3H), 1.91 (s, 3H), 0.85-0.91 (m, 2H), -0.06 (s, 9H)。

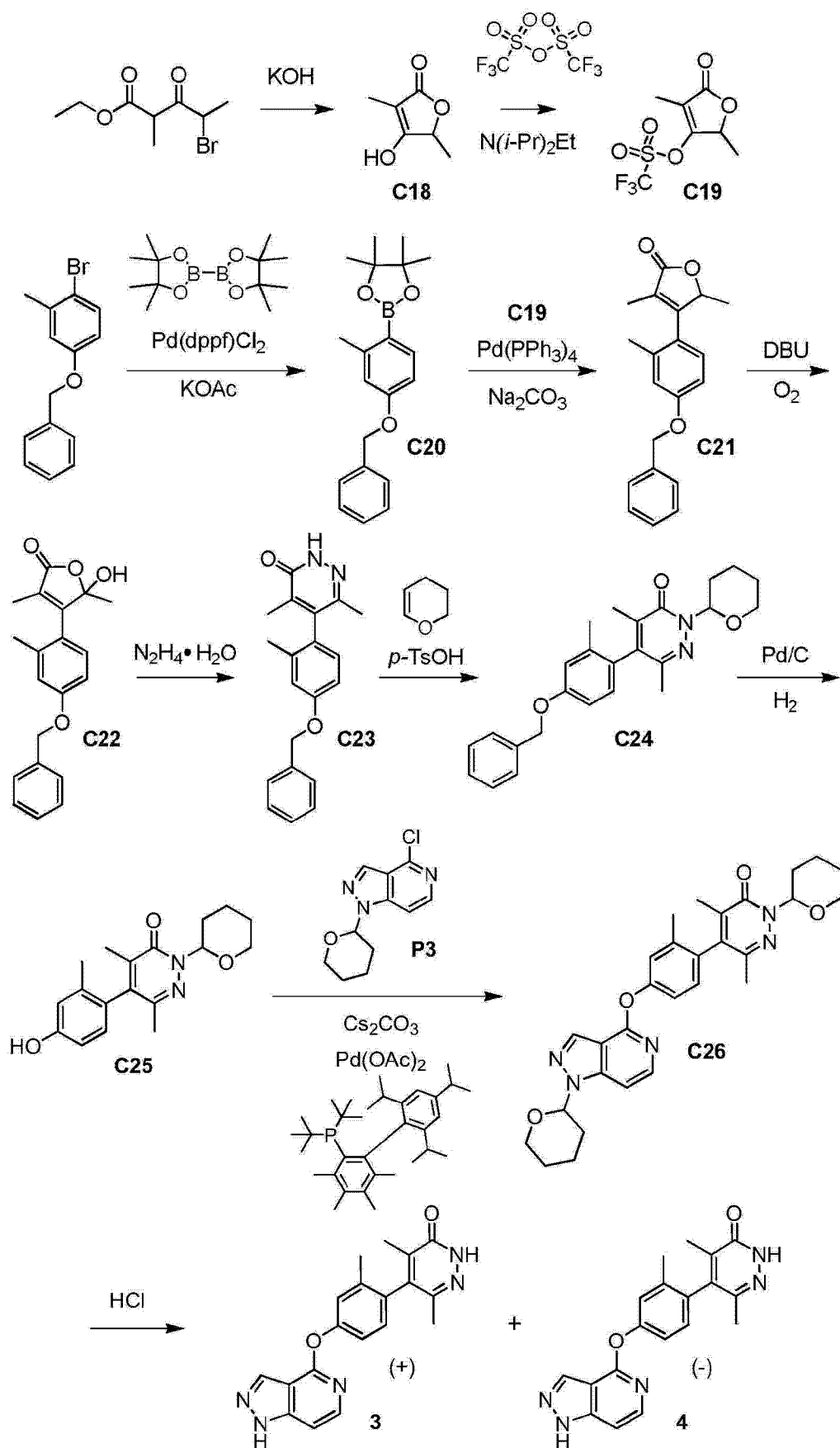
[0420] 步骤 3.4-[4-(1,4-二甲基-1H-吡唑-5-基)-3-甲基苯氧基]-1H-吡咯并 [3,2-c] 吡啶 (2) 的合成

[0421] 将 C16 (51mg, 0.11mmol) 于三氟乙酸 (2mL) 中的溶液在 80℃ 下搅拌 1 小时。在冷却至室温之后, 在真空中浓缩混合物, 得到 {4-[4-(1,4-二甲基-1H-吡唑-5-基)-3-甲基苯氧基]-1H-吡咯并 [3,2-c] 吡啶-1-基} 甲醇 (C17) (38mg, 100%), 将其与碳酸钾 (100mg)、乙腈 (2mL) 及水 (0.3mL) 合并。在 80℃ -85℃ 下搅拌此反应混合物 24 小时。将反应混合物冷却至室温, 且在减压下浓缩; 通过制备型硅胶薄层色谱法 (洗脱液: 1:3 石油醚 / 乙酸乙酯) 来纯化, 得到呈白色固体状的产物。收率: 16mg, 50 μ mol, 45%。LCMS m/z 318.9 [M+H]⁺。¹H NMR (400MHz, CD₃OD) δ 7.71 (d, J = 5.5Hz, 1H), 7.38 (s, 1H), 7.32 (d, J = 3.5Hz, 1H), 7.23 (d, J = 6.0Hz, 1H), 7.20 (d, J = 8.5Hz, 1H), 7.14 (d, J = 2.5Hz, 1H), 7.06 (dd, J = 8.3, 2.3Hz, 1H), 6.53 (d, J = 3.0Hz, 1H), 3.60 (s, 3H), 2.09 (s, 3H), 1.91 (s, 3H)。

[0422] 实施例 3 及 4

[0423] (+)-4,6-二甲基-5-[2-甲基-4-(1H-吡唑并 [4,3-c] 吡啶-4-基氧基) 苯基] 哒嗪-3(2H)-酮 (3) 及 (-)-4,6-二甲基-5-[2-甲基-4-(1H-吡唑并 [4,3-c] 吡啶-4-基氧基) 苯基] 哒嗪-3(2H)-酮 (4)

[0424]



[0425] 步骤 1. 4-羟基-3,5-二甲基呋喃-2(5H)-酮 (C18) 的合成

[0426] 根据 D. Kalaitzakis 等人, Tetrahedron:Asymmetry 2007, 18, 2418-2426 的方法

来使 3- 氧代戊酸乙酯甲基化, 得到 2- 甲基 -3- 氧代戊酸乙酯 ; 随后用氯仿中的 1 当量溴处理, 得到 4- 溴 -2- 甲基 -3- 氧代戊酸乙酯。将该粗物质 (139g, 586mmol) 缓慢添加至氢氧化钾 (98.7g, 1.76mol) 于水 (700mL) 中的 0℃ 溶液中。在添加期间, 内部反应温度升至 30℃。将反应混合物在冰浴中剧烈搅拌 4 小时, 此时通过缓慢添加浓盐酸来使其酸化。在用乙酸乙酯萃取之后, 用固体氯化钠使水层饱和, 且用乙酸乙酯再萃取三次。用饱和氯化钠水溶液洗涤合并的有机层, 经硫酸镁干燥, 过滤, 且在减压下浓缩, 得到油与固体的混合物 (81.3g)。将该物质悬浮于氯仿 (200mL) 中 ; 通过过滤来移除固体, 且用氯仿 (2×50mL) 洗涤。在真空中浓缩合并的滤液, 且用庚烷与乙醚 3:1 的混合物 (300mL) 处理。将混合物剧烈涡旋, 直至一些油开始固化。随后在减压下浓缩, 得到油状固体 (60.2g)。在添加庚烷与乙醚 3:1 的混合物 (300mL) 且剧烈搅拌 10 分钟之后, 通过过滤来收集固体, 得到呈灰白色固体状的产物。收率 : 28.0g, 219mmol, 37%。¹H NMR (400MHz, CDCl₃) δ 4.84 (br q, J = 6.8Hz, 1H), 1.74 (br s, 3H), 1.50 (d, J = 6.8Hz, 3H)。

[0427] 步骤 2. 三氟甲磺酸 2, 4- 二甲基 -5- 氧代 -2, 5- 二氢呋喃 -3- 基酯 (C19) 的合成

[0428] 在 -20℃ 下向 C18 (15.0g, 117mmol) 及 N, N- 二异丙基乙胺 (99%, 24.8mL, 140mmol) 于二氯甲烷 (500mL) 中的溶液中分批添加三氟甲磺酸酐 (23.7mL, 140mmol), 添加速率足以使内部反应温度维持在 -10℃ 以下。在 -20℃ 下搅拌反应混合物, 且使其经 5 小时逐渐升温至 0℃。随后使反应混合物穿过硅胶塞, 经硫酸镁干燥, 且在真空中浓缩。将残渣悬浮于乙醚中, 且过滤 ; 在减压下浓缩滤液。使用硅胶色谱法 (梯度 : 庚烷中的 0% 至 17% 乙酸乙酯) 来纯化, 得到呈浅黄色油状的产物。收率 : 21.06g, 80.94mmol, 69%。¹H NMR (400MHz, CDCl₃) δ 5.09-5.16 (m, 1H), 1.94-1.96 (m, 3H), 1.56 (d, J = 6.6Hz, 3H)。

[0429] 步骤 3. 2-[4-(苯甲氧基)-2- 甲基苯基]-4, 4, 5, 5- 四甲基 -1, 3, 2- 二氧杂硼戊环 (C20) 的合成

[0430] 将苯甲基 4- 溴 -3- 甲基苯基醚 (19g, 69mmol)、[1, 1'- 双 (二苯基膦基) 二茂铁] 二氯化钡 (II) (7.5g, 10.2mmol)、乙酸钾 (26.9g, 274mmol) 及 4, 4, 4', 4', 5, 5, 5', 5'- 八甲基 -2, 2'- 双 -1, 3, 2- 二氧杂硼戊环 (20g, 79mmol) 在 1, 4- 二氧杂环己烷 (500mL) 中合并, 且在回流下加热 2 小时。通过硅藻土过滤反应混合物 ; 在真空中浓缩滤液, 且通过硅胶色谱法 (梯度 : 石油醚中的 0% 至 1% 乙酸乙酯) 来纯化, 得到呈黄色凝胶状的产物。收率 : 15g, 46mmol, 67%。¹H NMR (400MHz, CDCl₃) δ 7.73 (d, J = 8.0Hz, 1H), 7.30-7.46 (m, 5H), 6.76-6.82 (m, 2H), 5.08 (s, 2H), 2.53 (s, 3H), 1.34 (s, 12H)。

[0431] 步骤 4. 4-[4-(苯甲氧基)-2- 甲基苯基]-3, 5- 二甲基呋喃 -2(5H)- 酮 (C21) 的合成

[0432] 将 C19 (5.0g, 19mmol)、C20 (7.48g, 23.1mmol)、四 (三苯基膦) 钯 (0) (2.22g, 1.92mmol) 及碳酸钠 (4.07g, 38.4mmol) 在 1, 4- 二氧杂环己烷 (100mL) 及水 (5mL) 中合并, 且在回流下加热 2 小时。过滤反应混合物, 且在真空中浓缩滤液。使用硅胶色谱法 (洗脱液 : 10:1, 随后 5:1 石油醚 / 乙酸乙酯) 来纯化, 得到呈白色固体状的产物。收率 : 5.8g, 19mmol, 100%。NMR (400MHz, CDCl₃) δ 7.33-7.49 (m, 5H), 6.98 (d, J = 8.5Hz, 1H), 6.94 (br d, J = 2.5Hz, 1H), 6.88 (br dd, J = 8.3, 2.5Hz, 1H), 5.20 (qq, J = 6.7, 1.8Hz, 1H), 5.09 (s, 2H), 2.21 (s, 3H), 1.78 (d, J = 1.8Hz, 3H), 1.31 (d, J = 6.8Hz, 3H)。

[0433] 步骤 5. 4-[4-(苯甲氧基)-2- 甲基苯基]-5- 羟基 -3, 5- 二甲基呋喃 -2(5H)- 酮

(C22) 的合成

[0434] 将 C21 (5.4g, 18mmol) 及 1,8-二氮杂双环 [5.4.0] 十一碳-7-烯 (DBU, 13.3g, 87.4mmol) 于乙腈 (100mL) 中的溶液冷却至 -60°C 。在 -60°C 下用氧气向反应混合物中鼓泡 20 分钟;随后在 50°C 下搅拌溶液 18 小时。在真空中浓缩反应混合物,且通过硅胶色谱法 (洗脱液:5:1 石油醚 / 乙酸乙酯) 来纯化,得到呈无色油状的产物。收率:3.5g, 11mmol, 61%。 ^1H NMR (400MHz, CDCl_3), 特征峰: δ 7.33-7.49 (m, 5H), 6.92-6.96 (m, 1H), 6.88 (dd, $J = 8.5, 2.5\text{Hz}$, 1H), 5.09 (s, 2H), 2.20 (s, 3H), 1.73 (s, 3H)。

[0435] 步骤 6.5-[4-(苯甲氧基)-2-甲基苯基]-4,6-二甲基哒嗪-3(2H)-酮 (C23) 的合成

[0436] 将 C22 (3.5g, 11mmol) 及水合肼 (水中的 85%, 1.9g, 32mmol) 于正丁醇 (60mL) 中的混合物在回流下加热 18 小时。在减压下移除挥发物之后,用乙酸乙酯 (20mL) 搅拌残渣 30 分钟,随后过滤,得到呈白色固体状的产物。收率:2.0g, 6.2mmol, 56%。 ^1H NMR (400MHz, CDCl_3) δ 10.93 (br s, 1H), 7.33-7.51 (m, 5H), 6.96 (s, 1H), 6.88-6.94 (m, 2H), 5.10 (s, 2H), 2.04 (s, 3H), 1.95 (s, 3H), 1.91 (s, 3H)。

[0437] 步骤 7.5-[4-(苯甲氧基)-2-甲基苯基]-4,6-二甲基-2-(四氢-2H-吡喃-2-基)哒嗪-3(2H)-酮 (C24) 的合成

[0438] 将 C23 (1.04g, 3.25mmol)、3,4-二氢-2H-吡喃 (12.3g, 1.46mmol) 及对甲苯磺酸 (59.4mg, 0.652mmol) 于四氢呋喃 (100mL) 中的混合物在回流下加热 24 小时。随后在真空中浓缩反应混合物,且在乙酸乙酯与水之间分配。用硫酸钠干燥有机层,过滤,且在减压下浓缩。硅胶色谱法 (梯度:庚烷中的 0% 至 40% 乙酸乙酯),得到呈胶状的产物,自 ^1H NMR 光谱推测该产物为非对映阻转异构体的混合物。收率:560mg, 1.38mmol, 42%。LCMS m/z 405.3 $[\text{M}+\text{H}^+]$ 。 ^1H NMR (400MHz, CDCl_3), 特征峰: δ 7.33-7.49 (m, 5H), 6.83-6.95 (m, 3H), 6.12-6.17 (m, 1H), 5.09 (s, 2H), 4.15-4.24 (m, 1H), 3.76-3.85 (m, 1H), 2.29-2.41 (m, 1H), 2.02 及 2.04 (2s, 总 3H), 1.98 及 1.98 (2s, 总 3H), 1.89 及 1.89 (2s, 总 3H)。

[0439] 步骤 8.5-(4-羟基-2-甲基苯基)-4,6-二甲基-2-(四氢-2H-吡喃-2-基)哒嗪-3(2H)-酮 (C25) 的合成

[0440] 向 C24 (1.47g, 3.63mmol) 于甲醇 (30mL) 及乙酸乙酯 (10mL) 中的溶液中添加钯 (10% 钯 / 碳, 1.16g, 1.09mmol),且在帕尔震荡器 (Parr shaker) 上于室温下使混合物氢化 (50psi) 18 小时。通过硅藻土过滤反应混合物,且用乙酸乙酯冲洗过滤垫;在真空中浓缩合并的滤液,且用庚烷研磨,得到呈白色固体状的产物,自 ^1H NMR 光谱判定该产物为非对映阻转异构体的混合物。收率:1.01g, 3.21mmol, 88%。 ^1H NMR (400MHz, CDCl_3), 特征峰: δ 6.74-6.85 (m, 3H), 6.12-6.17 (m, 1H), 4.15-4.23 (m, 1H), 3.76-3.84 (m, 1H), 2.28-2.41 (m, 1H), 1.99 及 2.01 (2s, 总 3H), 1.97 及 1.98 (2s, 总 3H), 1.89 及 1.89 (2s, 总 3H)。

[0441] 步骤 9.4,6-二甲基-5-(2-甲基-4-[[1-(四氢-2H-吡喃-2-基)-1H-吡唑并 [4,3-c] 吡啶-4-基] 氧基] 苯基)-2-(四氢-2H-吡喃-2-基)哒嗪-3(2H)-酮 (C26) 的合成

[0442] 向 P3 (550mg, 2.31mmol) 及 C25 (662mg, 2.10mmol) 于 1,4-二氧杂环己烷 (40mL) 中的溶液中添加碳酸铯 (2.06g, 6.32mmol)。在添加乙酸钯 (II) (48mg, 0.21mmol) 之后,用氮气吹扫反应混合物 10 分钟。引入二叔丁基 [3,4,5,6-四甲基-2',4',6'-三(丙-2-基)]

联苯-2-基]磷烷(97%, 210mg, 0.42mmol), 且用氮气短暂吹扫反应混合物, 随后在 100℃ 下加热 3.5 小时。在冷却反应混合物且通过硅藻土过滤之后, 用乙酸乙酯充分冲洗过滤垫, 且在真空中浓缩合并的滤液。硅胶色谱法(洗脱液: 庚烷中的 10%、随后 30%、随后 50%、随后 90% 乙酸乙酯), 得到呈褐色固体状的产物, 自其 ^1H NMR 光谱判定该产物为非对映阻转异构体的混合物。收率: 690mg, 1.34mmol, 58%。LCMS m/z 516.3 $[\text{M}+\text{H}]^+$ 。 ^1H NMR (400MHz, CDCl_3), 特征峰: δ 8.09 (s, 1H), 7.97 (d, $J = 6.0\text{Hz}$, 1H), 7.25 (d, $J = 6.0\text{Hz}$, 1H), 7.17–7.24 (m, 2H), [7.04 (d, $J = 8.2\text{Hz}$) 及 7.00 (d, $J = 8.2\text{Hz}$), 总 1H], 6.16 (br d, $J = 10.7\text{Hz}$, 1H), 5.72 (dd, $J = 9.4, 2.5\text{Hz}$, 1H), 4.16–4.24 (m, 1H), 4.03–4.10 (m, 2H), 3.73–3.85 (m, 2H), 2.48–2.59 (m, 1H), 2.29–2.43 (m, 1H), 2.04 (br s, 3H), 1.95 (2s, 总 3H)。

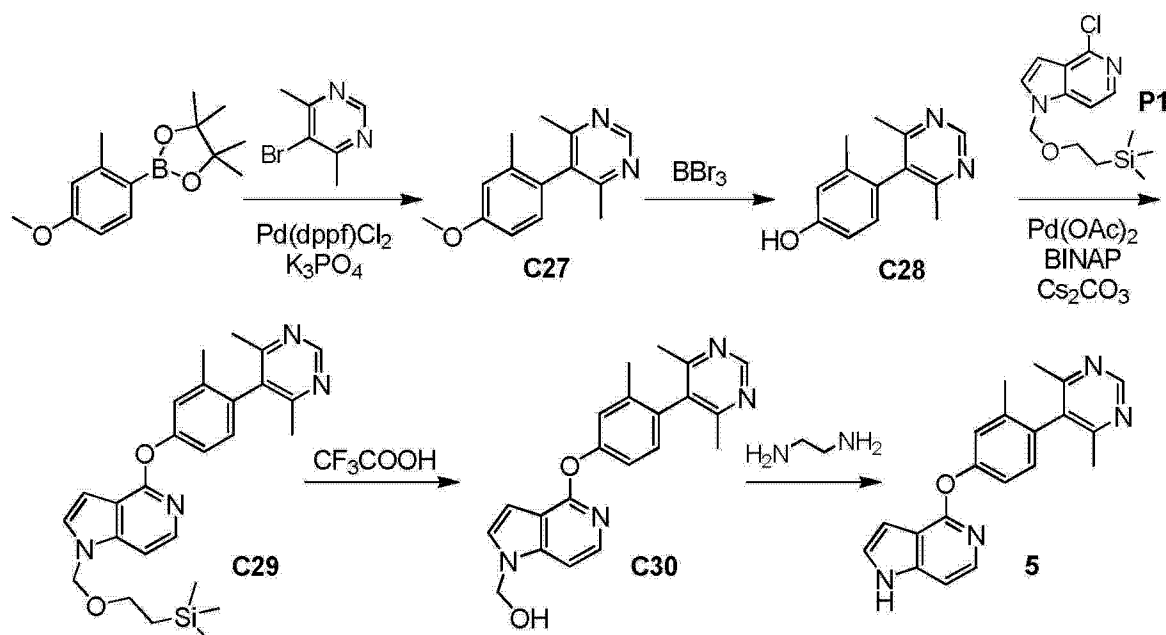
[0443] 步骤 10. (+)-4,6-二甲基-5-[2-甲基-4-(1H-吡唑并[4,3-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮 (3) 及 (-)-4,6-二甲基-5-[2-甲基-4-(1H-吡唑并[4,3-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮 (4) 的合成

[0444] 将 C26 (807mg, 1.56mmol) 溶解于 1,4-二氧杂环己烷 (80mL) 及二氯甲烷 (80mL) 中。添加氯化氢于 1,4-二氧杂环己烷中的溶液 (4M, 39.0mL, 156mmol), 且在室温下搅拌反应混合物 18 小时。在真空中移除溶剂之后, 将残渣在饱和碳酸氢钠水溶液与乙酸乙酯之间分配。用乙酸乙酯萃取水层两次, 且用硫酸钠干燥合并的有机层, 过滤, 且在减压下浓缩。用乙醚研磨, 得到呈白色固体状的外消旋 4,6-二甲基-5-[2-甲基-4-(1H-吡唑并[4,3-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮。收率: 396mg, 1.14mmol, 73%。LCMS m/z 348.1 $[\text{M}+\text{H}]^+$ 。使用超临界流体色谱法(柱: Chiral Technologies, Chiralcel OJ-H, $5\mu\text{m}$; 洗脱液: 1:3 甲醇/二氧化碳)分离阻转对映异构体。获得呈灰白色固体状的第一洗脱产物, 其展现正 (+) 旋光性, 指定为化合物实施例 3。收率: 155mg, 0.446mmol, 28%。LCMS m/z 348.2 $[\text{M}+\text{H}]^+$ 。 ^1H NMR (400MHz, CD_3OD) δ 8.08 (s, 1H), 7.86 (d, $J = 6.2\text{Hz}$, 1H), 7.26–7.30 (m, 2H), 7.22 (br dd, ABX 模式的一半, $J = 8.2, 2.3\text{Hz}$, 1H), 7.17 (d, AB 四重峰的一半, $J = 8.2\text{Hz}$, 1H), 2.11 (s, 3H), 2.03 (s, 3H), 1.93 (s, 3H)。保留时间: 5.47 分钟(柱: Chiral Technologies, Chiralcel OJ-H, $250 \times 4.6\text{mm}$, $5\mu\text{m}$; 洗脱液: 1:3 甲醇/二氧化碳; 流速: 2.5 毫升/分钟)。第二洗脱产物还为灰白色固体状, 其展现负 (-) 旋光性, 指定为化合物实施例 4。收率: 159mg, 0.458mmol, 29%。LCMS m/z 348.2 $[\text{M}+\text{H}]^+$ 。 ^1H NMR (400MHz, CD_3OD) δ 8.08 (s, 1H), 7.86 (d, $J = 6.0\text{Hz}$, 1H), 7.26–7.30 (m, 2H), 7.22 (br dd, ABX 模式的一半, $J = 8.2, 2.3\text{Hz}$, 1H), 7.17 (d, AB 四重峰的一半, $J = 8.2\text{Hz}$, 1H), 2.11 (s, 3H), 2.03 (s, 3H), 1.93 (s, 3H)。保留时间: 5.86 分钟 (HPLC 条件与用于以上实施例 3 的那些条件相同)。

[0445] 实施例 5

[0446] 4-[4-(4,6-二甲基嘧啶-5-基)-3-甲基苯氧基]-1H-吡咯并[3,2-c]吡啶 (5)

[0447]



[0448] 步骤 1. 5-(4-甲氧基-2-甲基苯基)-4,6-二甲基嘧啶 (C27) 的合成

[0449] 向 2-(4-甲氧基-2-甲基苯基)-4,4,5,5-四甲基-1,3,2-二氧杂硼戊环 (30g, 120mmol)、5-溴-4,6-二甲基嘧啶 (22.5g, 120mmol) 及磷酸钾 (76.3g, 359mmol) 于 1,4-二氧杂环己烷 (300mL) 及水 (150mL) 中的经脱气混合物中添加 1,1'-双(二苯基膦基)二茂铁] 二氯化钯 (II)-二氯甲烷络合物 (5g, 6mmol)。在回流下加热反应混合物 4 小时, 随后过滤, 且在真空中浓缩。通过硅胶色谱法 (梯度: 石油醚中乙酸乙酯) 来纯化, 得到呈棕色固体状的产物。收率: 25g, 110mmol, 92%。LCMS m/z 229.3 $[\text{M}+\text{H}^+]$ 。 ^1H NMR (300MHz, CDCl_3) δ 8.95 (s, 1H), 6.94 (d, $J = 8.2\text{Hz}$, 1H), 6.87-6.89 (m, 1H), 6.84 (dd, $J = 8.3, 2.5\text{Hz}$, 1H), 3.86 (s, 3H), 2.21 (s, 6H), 1.99 (s, 3H)。

[0450] 步骤 2. 4-(4,6-二甲基嘧啶-5-基)-3-甲基苯酚 (C28) 的合成

[0451] 在 -70°C 下向 C27 (3.0g, 13mmol) 于二氯甲烷 (150mL) 中的溶液中逐滴添加三溴化硼 (3.8mL, 40mmol)。在室温下搅拌反应混合物 16 小时, 随后用饱和碳酸氢钠水溶液调整至 pH 8。用二氯甲烷 ($3 \times 200\text{mL}$) 萃取水层, 且用硫酸钠干燥合并的有机层, 过滤, 且在真空中浓缩。硅胶色谱法 (梯度: 石油醚中的 60% 至 90% 乙酸乙酯), 得到呈黄色固体状的产物。收率: 1.2g, 5.6mmol, 43%。LCMS m/z 215.0 $[\text{M}+\text{H}^+]$ 。 ^1H NMR (400MHz, CDCl_3) δ 8.98 (s, 1H), 6.89 (d, $J = 8.0\text{Hz}$, 1H), 6.86 (d, $J = 2.3\text{Hz}$, 1H), 6.80 (dd, $J = 8.3, 2.5\text{Hz}$, 1H), 2.24 (s, 6H), 1.96 (s, 3H)。

[0452] 步骤 3. 4-[4-(4,6-二甲基嘧啶-5-基)-3-甲基苯氧基]-1-[[2-(三甲基硅烷基)乙氧基]甲基]-1H-吡咯并[3,2-c]吡啶 (C29) 的合成

[0453] 向 C28 (390mg, 1.82mmol) 与 1,4-二氧杂环己烷 (10mL) 的混合物中添加 P1 (566mg, 2.0mmol)、乙酸钯 (II) (40mg, 0.18mmol)、1,1'-联二萘-2,2'-二基双(二苯基膦烷) (224mg, 0.360mmol) 及碳酸铯 (1.76g, 5.40mmol)。在 120°C 下搅拌反应混合物 2 小时, 随后将其冷却至室温, 过滤, 且在真空中浓缩。硅胶色谱法 (洗脱液: 70:1 二氯甲烷/甲醇), 得到呈红色油状的产物。收率: 620mg, 1.35mmol, 74%。 ^1H NMR (400MHz, CD_3OD) δ 8.89 (s, 1H), 7.81 (d, $J = 6.0\text{Hz}$, 1H), 7.43 (d, $J = 3.3\text{Hz}$, 1H), 7.39 (br d, $J = 6\text{Hz}$, 1H),

7.18-7.20 (m, 1H), 7.15 (d, AB 四重峰的一半, $J = 8.3\text{Hz}$, 1H), 7.11 (dd, ABX 模式的一半, $J = 8.3, 2.3\text{Hz}$, 1H), 6.60 (d, $J = 3.3\text{Hz}$, 1H), 5.60 (s, 2H), 3.52-3.58 (m, 2H), 2.28 (s, 6H), 2.02 (s, 3H), 0.85-0.91 (m, 2H), -0.06 (s, 9H)。

[0454] 步骤 4. {4-[4-(4,6-二甲基嘧啶-5-基)-3-甲基苯氧基]-1H-吡咯并[3,2-c]吡啶-1-基} 甲醇 (C30) 的合成

[0455] 将 C29 (430mg, 0.93mmol) 于三氟乙酸 (3mL) 中的溶液在 80°C 下搅拌 1 小时。在冷却至室温之后, 过滤混合物, 且在真空中浓缩滤液。硅胶色谱法 (梯度: 二氯甲烷中的 3% 至 9% 甲醇), 得到呈黄色固体状的产物。收率: 330mg, 0.92mmol, 99%。

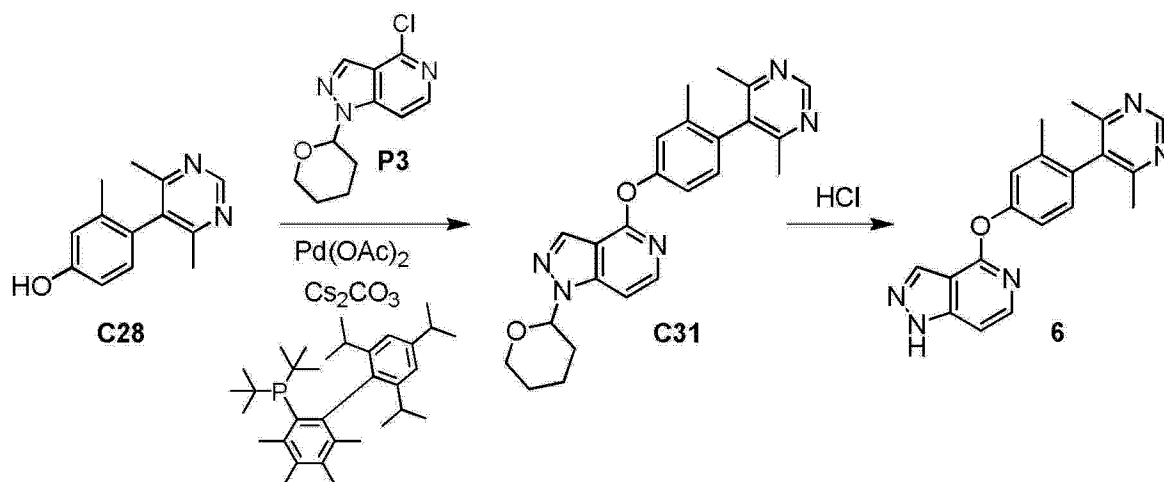
[0456] 步骤 5. 4-[4-(4,6-二甲基嘧啶-5-基)-3-甲基苯氧基]-1H-吡咯并[3,2-c]吡啶 (5) 的合成

[0457] 向 C30 (330mg, 0.92mmol) 于甲醇 (8mL) 中的溶液中添加乙烷-1,2-二胺 (300mg, 5.0mmol), 且在 45°C 搅拌反应混合物 1 小时。在冷却至室温之后, 在真空中浓缩混合物, 且使用硅胶色谱法 (洗脱液: 20:1 二氯甲烷 / 甲醇) 来纯化, 得到呈白色固体状的产物。收率: 256mg, 0.775mmol, 84%。LCMS m/z 331.1 $[\text{M}+\text{H}^+]$ 。 ^1H NMR (400MHz, CD_3OD) δ 8.89 (s, 1H), 7.73 (d, $J = 5.8\text{Hz}$, 1H), 7.32 (d, $J = 3.0\text{Hz}$, 1H), 7.23 (dd, $J = 5.9, 0.9\text{Hz}$, 1H), 7.17 (br d, $J = 2\text{Hz}$, 1H), 7.13 (d, AB 四重峰的一半, $J = 8.3\text{Hz}$, 1H), 7.09 (br dd, ABX 模式的一半, $J = 8.2, 2.4\text{Hz}$, 1H), 6.52 (dd, $J = 3.3, 0.8\text{Hz}$, 1H), 2.28 (s, 6H), 2.02 (br s, 3H)。

[0458] 实施例 6

[0459] 4-[4-(4,6-二甲基嘧啶-5-基)-3-甲基苯氧基]-1H-吡啶并[4,3-c]吡啶 (6)

[0460]



[0461] 步骤 1. 4-[4-(4,6-二甲基嘧啶-5-基)-3-甲基苯氧基]-1-(四氢-2H-吡喃-2-基)-1H-吡啶并[4,3-c]吡啶 (C31) 的合成

[0462] 在可密封反应容器中向 C28 (225mg, 1.05mmol) 及 P3 (250mg, 1.05mmol) 于 1,4-二氧杂环己烷 (10mL) 中的溶液中添加碳酸铯 (1.03g, 3.16mmol) 及乙酸钯 (II) (24mg, 0.11mmol), 且用氮气吹扫溶液 10 分钟。添加二叔丁基[3,4,5,6-四甲基-2',4',6'-三(丙-2-基)联苯-2-基]磷烷 (97%, 104mg, 0.210mmol), 且用氮气短暂吹扫反应混合物。密封容器, 且在 100°C 下搅拌反应混合物 3 小时。在冷却至室温之后, 通过硅藻土过滤混合物, 且用乙酸乙酯洗涤过滤垫; 在真空中浓缩合并的滤液, 且通过硅胶色谱法 (洗

脱液：庚烷中的 20%、随后 50%、随后 100% 乙酸乙酯）来纯化。获得呈灰白色固体状的产物。收率：272mg, 0.655mmol, 62%。LCMS m/z 416.5 $[M+H]^+$ 。 ^1H NMR (400MHz, $CDCl_3$) δ 8.99 (s, 1H), 8.11 (d, $J = 0.6$ Hz, 1H), 7.99 (d, $J = 6.0$ Hz, 1H), 7.25–7.27 (m, 2H, 假定部分被溶剂峰遮蔽), 7.20–7.24 (m, 1H), 7.10 (d, $J = 8.4$ Hz, 1H), 5.73 (dd, $J = 9.4, 2.5$ Hz, 1H), 4.04–4.10 (m, 1H), 3.74–3.82 (m, 1H), 2.49–2.59 (m, 1H), 2.28 (s, 6H), 2.08–2.21 (m, 2H), 2.04 (s, 3H), 1.66–1.84 (s, 3H)。

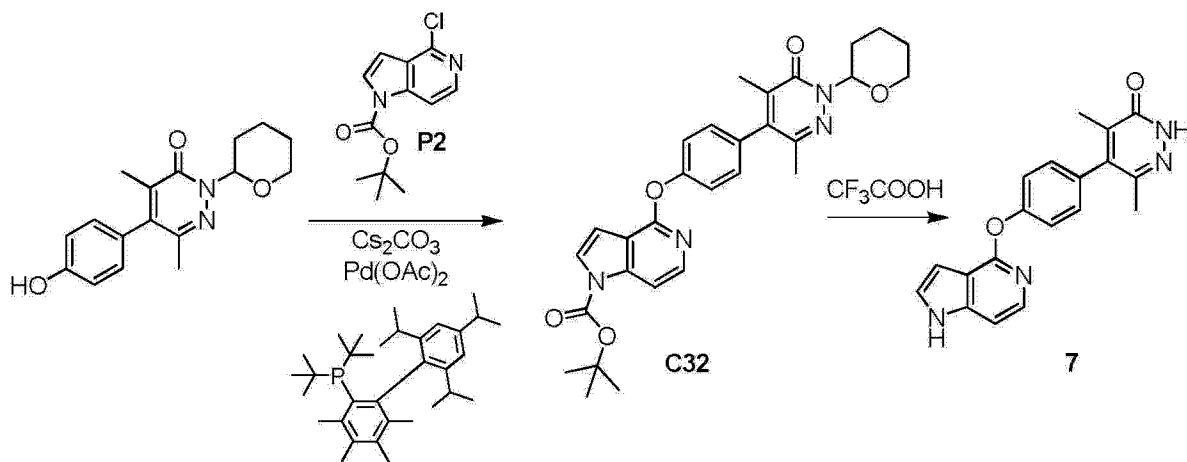
[0463] 步骤 2. 4-[4-(4,6-二甲基嘧啶-5-基)-3-甲基苯氧基]-1H-吡唑并[4,3-c]吡啶 (6) 的合成

[0464] 将 C31 (172mg, 0.414mmol) 溶解于 1,4-二氧杂环己烷 (5mL) 及二氯甲烷 (5mL) 中, 且冷却至 0℃。添加氯化氢于 1,4-二氧杂环己烷中的溶液 (4M, 1.04mL, 4.16mmol), 且在室温下搅拌反应混合物 45 小时。在真空中移除溶剂之后, 将残渣在饱和碳酸氢钠水溶液与二氯甲烷之间分配。用二氯甲烷萃取水层两次, 且用硫酸钠干燥合并的有机层, 过滤, 且在减压下浓缩, 得到呈灰白色固体状的产物。收率：130mg, 0.392mmol, 95%。LCMS m/z 332.3 $[M+H]^+$ 。 ^1H NMR (400MHz, $CDCl_3$) δ 9.00 (s, 1H), 8.20 (br s, 1H), 7.99 (d, $J = 6.0$ Hz, 1H), 7.28–7.30 (m, 1H), 7.23–7.27 (m, 1H), 7.16 (dd, $J = 6.0, 1.0$ Hz, 1H), 7.11 (d, $J = 8.2$ Hz, 1H), 2.28 (s, 6H), 2.05 (s, 3H)。

[0465] 实施例 7

[0466] 4,6-二甲基-5-[4-(1H-吡咯并[3,2-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮 (7)

[0467]



[0468] 步骤 1. 4-[4-[3,5-二甲基-6-氧代-1-(四氢-2H-吡喃-2-基)-1,6-二氢哒嗪-4-基]苯氧基]-1H-吡咯并[3,2-c]吡啶-1-甲酸叔丁酯 (C32) 的合成

[0469] 将 5-(4-羟基苯基)-4,6-二甲基-2-(四氢-2H-吡喃-2-基)哒嗪-3(2H)-酮 (以类似于实施例 3 及 4 中 C25 的方式制备) (600mg, 2.00mmol)、P2 (757mg, 3.00mmol)、碳酸铯 (1.95g, 5.99mmol)、乙酸钡 (II) (44mg, 0.20mmol) 及二叔丁基[3,4,5,6-四甲基-2',4',6'-三(丙-2-基)联苯-2-基]磷烷 (97%, 200mg, 0.40mmol) 于 1,4-二氧杂环己烷 (15mL) 中的混合物用氮气吹扫 10 分钟, 且随后在 80℃ 下加热 18 小时。在过滤之后, 用水稀释滤液, 且用乙酸乙酯萃取数次。用水洗涤合并的有机层, 用饱和氯化钠水溶液洗涤, 经硫酸镁干燥, 过滤, 且在真空中浓缩。通过硅胶色谱法 (梯度：庚烷中的 25% 至

50%乙酸乙酯)来纯化,得到呈白色固体状的产物。收率:860mg,1.66mmol,83%。LCMS m/z 517.1[M+H⁺]⁺。¹H NMR(400MHz, CDCl₃), 特征峰: δ 8.04(d, J = 5.8Hz, 1H), 7.80(br d, J = 5.8Hz, 1H), 7.62(d, J = 3.7Hz, 1H), 7.31-7.36(m, 2H), 7.11-7.19(m, 2H), 6.75(dd, J = 3.7, 0.6Hz, 1H), 6.15(dd, J = 10.7, 2.0Hz, 1H), 4.15-4.21(m, 1H), 3.76-3.84(m, 1H), 2.29-2.41(m, 1H), 2.12(s, 3H), 2.01(s, 3H), 1.71(s, 9H)。

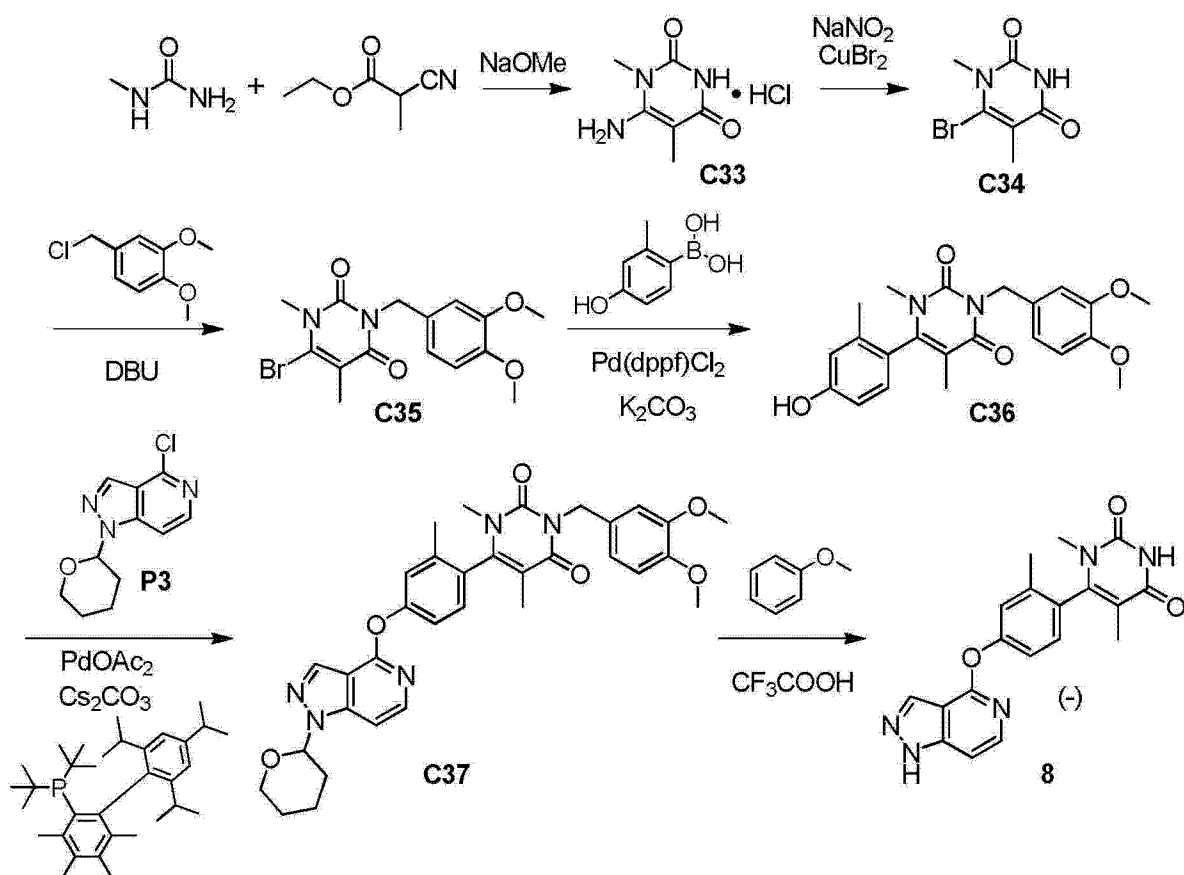
[0470] 步骤 2.4, 6-二甲基-5-[4-(1H-吡咯并[3,2-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮(7)的合成

[0471] 向 C32(850mg, 1.64mmol) 于二氯甲烷(15mL)中的溶液中添加三氟乙酸(5mL), 且在室温下搅拌反应混合物 18 小时。在减压下移除挥发物之后, 将残渣溶解于饱和碳酸氢钠水溶液中, 且用乙酸乙酯萃取数次。用水洗涤合并的有机层, 用饱和氯化钠水溶液洗涤, 经硫酸镁干燥, 过滤, 且在真空中浓缩。将所得物质悬浮于乙酸乙酯中, 搅拌 10 分钟且过滤, 得到呈白色固体状的产物。收率: 280mg, 0.842mmol, 51%。LCMS m/z 333.1[M+H⁺]⁺。¹H NMR(400MHz, DMSO-d₆) δ 12.77(br s, 1H), 11.69(br s, 1H), 7.72(d, J = 5.8Hz, 1H), 7.43(dd, J = 3.2, 2.3Hz, 1H), 7.29(s, 4H), 7.20(dd, J = 5.8, 0.9Hz, 1H), 6.55(ddd, J = 3.2, 2.0, 0.9Hz, 1H), 1.97(s, 3H), 1.83(s, 3H)。

[0472] 实施例 8

[0473] (-)-1,5-二甲基-6-[2-甲基-4-(1H-吡唑并[4,3-c]吡啶-4-基氧基)苯基]哒嗪-2,4(1H,3H)-二酮(8)

[0474]



[0475] 步骤 1.6-氨基-1,5-二甲基哒嗪-2,4(1H,3H)-二酮盐酸盐(C33)的合成

[0476] 向 2- 氰基 丙酸 乙酯 (95 %, 13.2mL, 99.6mmol) 及 1- 甲基 脲 (98 %, 8.26g, 109mmol) 于 甲醇 (75mL) 中的溶液中添加甲醇钠于甲醇中的溶液 (4.4M, 27mL, 119mmol), 且在回流下加热反应混合物 18 小时, 随后冷却至室温。在真空中移除溶剂之后, 用乙腈 (3×50mL) 在减压下反复蒸发残渣, 随后在乙腈 (100mL) 与水 (100mL) 之间分配。缓慢添加 6M 盐酸水溶液直至 pH 达到约 2; 搅拌所得混合物一小时。通过过滤来收集沉淀, 且用叔丁基甲基醚洗涤, 得到呈白色固体状的产物。收率: 15.2g, 79.3mmol, 80%。LCMS m/z 156.1 $[M+H]^+$ 。 ^1H NMR (400MHz, DMSO- d_6) δ 10.38 (br s, 1H), 6.39 (s, 2H), 3.22 (s, 3H), 1.67 (s, 3H)。

[0477] 步骤 2. 6- 溴 -1, 5- 二甲基嘧啶 -2, 4(1H, 3H)- 二酮 (C34) 的合成

[0478] 向 C33 (9.50g, 49.6mmol)、亚硝酸钠 (5.24g, 76mmol) 及溴化铜 (II) (22.4g, 100mmol) 的混合物中添加乙腈与水的 1:1 混合物 (120mL), 且在室温下搅拌反应混合物 66 小时。添加硫酸水溶液 (1N, 200mL) 及乙酸乙酯 (100mL), 得到沉淀, 通过过滤来收集该沉淀, 且用水及乙酸乙酯洗涤, 得到呈淡黄色固体状的产物 (7.70g)。将滤液的有机层浓缩至较小体积, 在此期间形成额外的沉淀; 通过过滤来分离此沉淀, 且用 1:1 乙酸乙酯 / 庚烷洗涤, 得到额外的产物 (0.4g)。总收率: 8.1g, 37mmol, 75%。LCMS m/z 217.9 $[M+H]^+$ 。 ^1H NMR (400MHz, DMSO- d_6) δ 11.58 (br s, 1H), 3.45 (s, 3H), 1.93 (s, 3H)。

[0479] 步骤 3. 6- 溴 -3-(3, 4- 二甲氧基苯甲基)-1, 5- 二甲基嘧啶 -2, 4(1H, 3H)- 二酮 (C35) 的合成

[0480] 向 C34 (4.00g, 18.3mmol) 及 4-(氯甲基)-1, 2- 二甲氧基苯 (5.16g, 27.6mmol) 于乙腈 (80mL) 中的悬浮液中添加 1, 8- 二氮杂双环 [5.4.0] 十一碳 -7- 烯 (98%, 5.57mL, 36.5mmol), 且在 60°C 下加热反应混合物 18 小时。在真空中移除溶剂之后, 通过硅胶色谱法 (梯度: 庚烷中的 25% 至 50% 乙酸乙酯) 来纯化残渣, 得到呈白色固体状的产物。收率: 5.70g, 15.4mmol, 84%。 ^1H NMR (400MHz, $CDCl_3$) δ 7.08-7.12 (m, 2H), 6.80 (d, J = 8.0Hz, 1H), 5.07 (s, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.65 (s, 3H), 2.14 (s, 3H)。

[0481] 还可使用其它适合的保护基来保护 C34 的“NH”基团。例如, 可使用 SEM、BOM 或 Boc 来代替 C35 中的二甲氧基苯甲基。

[0482] 步骤 4. 3-(3, 4- 二甲氧基苯甲基)-6-(4- 羟基 -2- 甲基苯基)-1, 5- 二甲基嘧啶 -2, 4(1H, 3H)- 二酮 (C36) 的合成

[0483] 向 C35 (1.20g, 3.25mmol)、(4- 羟基 -2- 甲基苯基) 硼酸 (988mg, 6.50mmol)、[1, 1'- 双 (二苯基膦基) 二茂铁] 二氯化钡 (II)- 二氯甲烷络合物 (98 %, 271mg, 0.325mmol) 及 1, 4- 二氧杂环己烷 (30mL) 的混合物中添加碳酸钾水溶液 (3.0M, 3.3mL, 9.9mmol)。在 100°C 下加热反应混合物 66 小时之后, 将其冷却至室温, 用乙酸乙酯及水稀释, 且通过硅藻土过滤。用饱和碳酸氢钠水溶液洗涤来自滤液的有机层, 用饱和氯化钠水溶液洗涤, 经硫酸镁干燥, 过滤, 且在真空中浓缩。使用硅胶色谱法 (梯度: 庚烷中的 25% 至 50% 乙酸乙酯) 来纯化, 得到呈白色泡沫状的产物。收率: 650mg, 1.64mmol, 50%。LCMS m/z 397.2 $[M+H]^+$ 。 ^1H NMR (400MHz, $CDCl_3$) δ 7.22 (d, J = 2.0Hz, 1H), 7.19 (dd, J = 8.2, 2.0Hz, 1H), 6.92 (d, J = 8.1Hz, 1H), 6.81-6.84 (m, 2H), 6.79 (br dd, J = 8.2, 2.5Hz, 1H), 5.53 (br s, 1H), 5.17 (AB 四重峰, J_{AB} = 13.4Hz, $\Delta \nu_{AB}$ = 18.8Hz, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.03 (s, 3H), 2.10 (br s, 3H), 1.66 (s, 3H)。

[0484] 或者, (4-羟基-2-甲基苯基) 硼酸的游离 OH 基团可由适合的保护基 (例如 MOM 或苯甲基) 保护, 随后将 (4-羟基-2-甲基苯基) 硼酸与 C35 偶联。在该情况下, 偶联反应的产物可经脱保护, 得到 C36。

[0485] 步骤 5. 3-(3,4-二甲氧基苯甲基)-1,5-二甲基-6-(2-甲基-4-[[1-(四氢-2H-吡喃-2-基)-1H-吡唑并[4,3-c]吡啶-4-基]氧基]苯基)嘧啶-2,4(1H,3H)-二酮 (C37) 的合成

[0486] 使用在实施例 3 及 4 中合成 C26 时所采用的方法来将 C36 转化为产物。在此情况下, 在通过硅藻土过滤且用乙酸乙酯冲洗过滤垫之后, 用水洗涤合并的滤液的有机层, 用饱和氯化钠水溶液洗涤, 经硫酸钠干燥, 过滤, 且在真空中浓缩。通过硅胶色谱法 (梯度: 庚烷中的 50% 至 100% 乙酸乙酯) 来纯化, 得到呈褐色固体状的产物。收率: 490mg, 0.820mmol, 63%。LCMS m/z 598.3 $[M+H]^+$ 。 ^1H NMR (400MHz, $CDCl_3$), 特征峰: δ 8.06-8.08 (m, 1H), 7.99 (d, $J = 6.2$ Hz, 1H), 7.32 (dd, $J = 6.2, 0.9$ Hz, 1H), 7.24 (br d, $J = 2.0$ Hz, 1H), 7.21 (br dd, $J = 8.1, 2.0$ Hz, 1H), 7.15 (d, $J = 8.2$ Hz, 1H), 6.84 (d, $J = 8.2$ Hz, 1H), 5.74 (dd, $J = 9.2, 2.5$ Hz, 1H), 5.18 (AB 四重峰, $J_{AB} = 13.4$ Hz, $\Delta v_{AB} = 19.1$ Hz, 2H), 4.03-4.09 (m, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.74-3.82 (m, 1H), 3.11 (s, 3H), 2.21 (br s, 3H), 1.71 (s, 3H)。

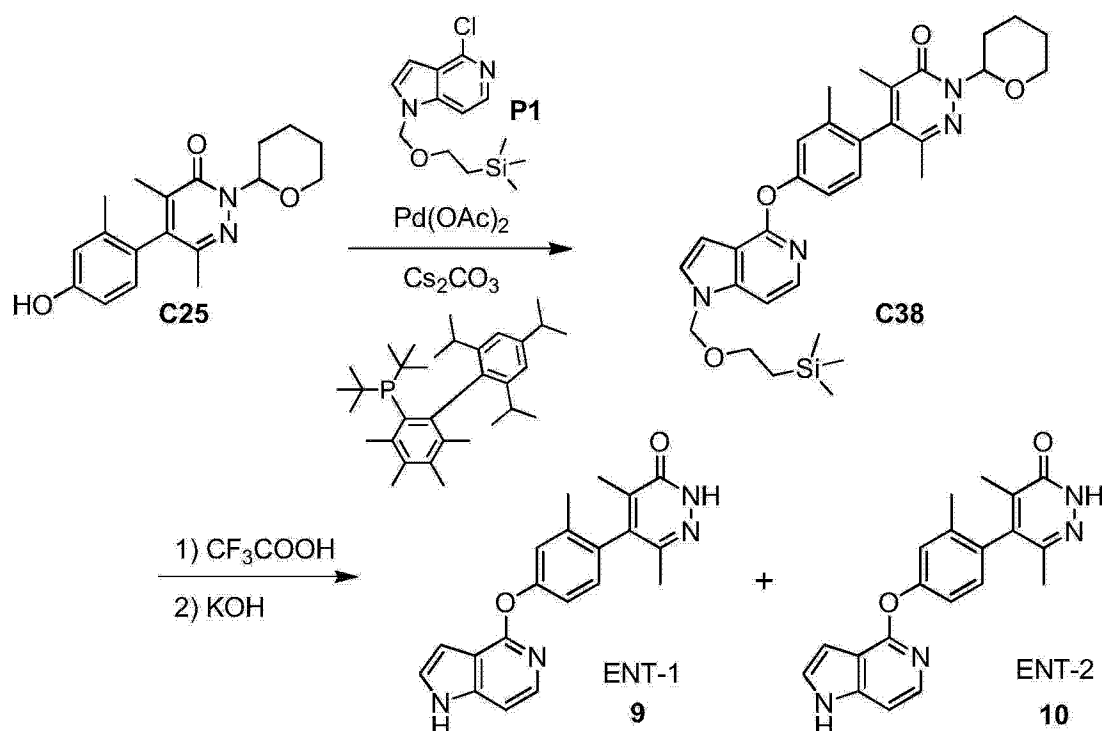
[0487] 步骤 6. (-)-1,5-二甲基-6-[2-甲基-4-(1H-吡唑并[4,3-c]吡啶-4-基氧基)苯基]嘧啶-2,4(1H,3H)-二酮 (8) 的合成

[0488] 在压力管中合并 C37 (490mg, 0.820mmol)、三氟乙酸 (8mL) 及甲氧基苯 (0.446mL, 4.10mmol); 密封管且在 120°C 下加热反应混合物 42 小时。在冷却至室温之后, 在真空中浓缩反应混合物, 且在乙酸乙酯 (100mL) 与饱和碳酸氢钠水溶液 (20mL) 之间分配。顺序用水 (10mL) 及用饱和氯化钠水溶液 (10mL) 洗涤有机层, 经硫酸镁干燥, 过滤, 且在减压下浓缩。在硅胶色谱法 (梯度: 庚烷中的 65% 至 100% 乙酸乙酯) 之后, 将产物在手性柱上进行超临界流体色谱法。收集一种阻转对映异构体, 提供呈固体状的产物; 此物质展现负 (-) 旋光性。收率: 95mg, 0.26mmol, 32%。LCMS m/z 364.2 $[M+H]^+$ 。 ^1H NMR (400MHz, $CDCl_3$) δ 8.33 (br s, 1H), 8.24 (br s, 1H), 7.98 (d, $J = 6.1$ Hz, 1H), 7.27-7.32 (m, 2H, 假定; 部分被溶剂峰遮蔽), 7.19 (dd, $J = 6.1, 1.0$ Hz, 1H), 7.18 (br d, $J = 8$ Hz, 1H), 3.08 (s, 3H), 2.23 (br s, 3H), 1.70 (s, 3H)。

[0489] 实施例 9 及 10

[0490] 4,6-二甲基-5-[2-甲基-4-(1H-吡咯并[3,2-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮, ENT-1 (9) 及 4,6-二甲基-5-[2-甲基-4-(1H-吡咯并[3,2-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮, ENT-2 (10)

[0491]



[0492] 步骤 1. 4,6-二甲基-5-{2-甲基-4-[(1-{[2-(三甲基硅烷基)乙氧基]甲基}-1H-吡咯并[3,2-c]吡啶-4-基)氧基]苯基}-2-(四氢-2H-吡喃-2-基)哒嗪-3(2H)-酮 (C38) 的合成

[0493] 使用在实施例 6 中合成 C31 时所描述的方法来使 C25 与 P1 反应。获得呈固体状的产物, 基于其 ¹H NMR 光谱推测所述产物为非对映阻转异构体的混合物。收率: 53mg, 94 μmol, 27%。LCMS m/z 561.4 [M+H]⁺。 ¹H NMR (400MHz, CDCl₃), 特征峰: δ 7.98 (br d, J = 6Hz, 1H), 6.96-7.04 (m, 1H), 6.13-6.18 (m, 1H), 5.51 (s, 2H), 4.16-4.24 (m, 1H), 3.77-3.85 (m, 1H), 3.48-3.54 (m, 2H), 2.04 (2s, 总 3H), 1.95 (2s, 总 3H), 0.89-0.94 (m, 2H), -0.03 (s, 9H)。

[0494] 步骤 2. 4,6-二甲基-5-[2-甲基-4-(1H-吡咯并[3,2-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮, ENT-1 (9) 及 4,6-二甲基-5-[2-甲基-4-(1H-吡咯并[3,2-c]吡啶-4-基氧基)苯基]哒嗪-3(2H)-酮, ENT-2 (10) 的合成

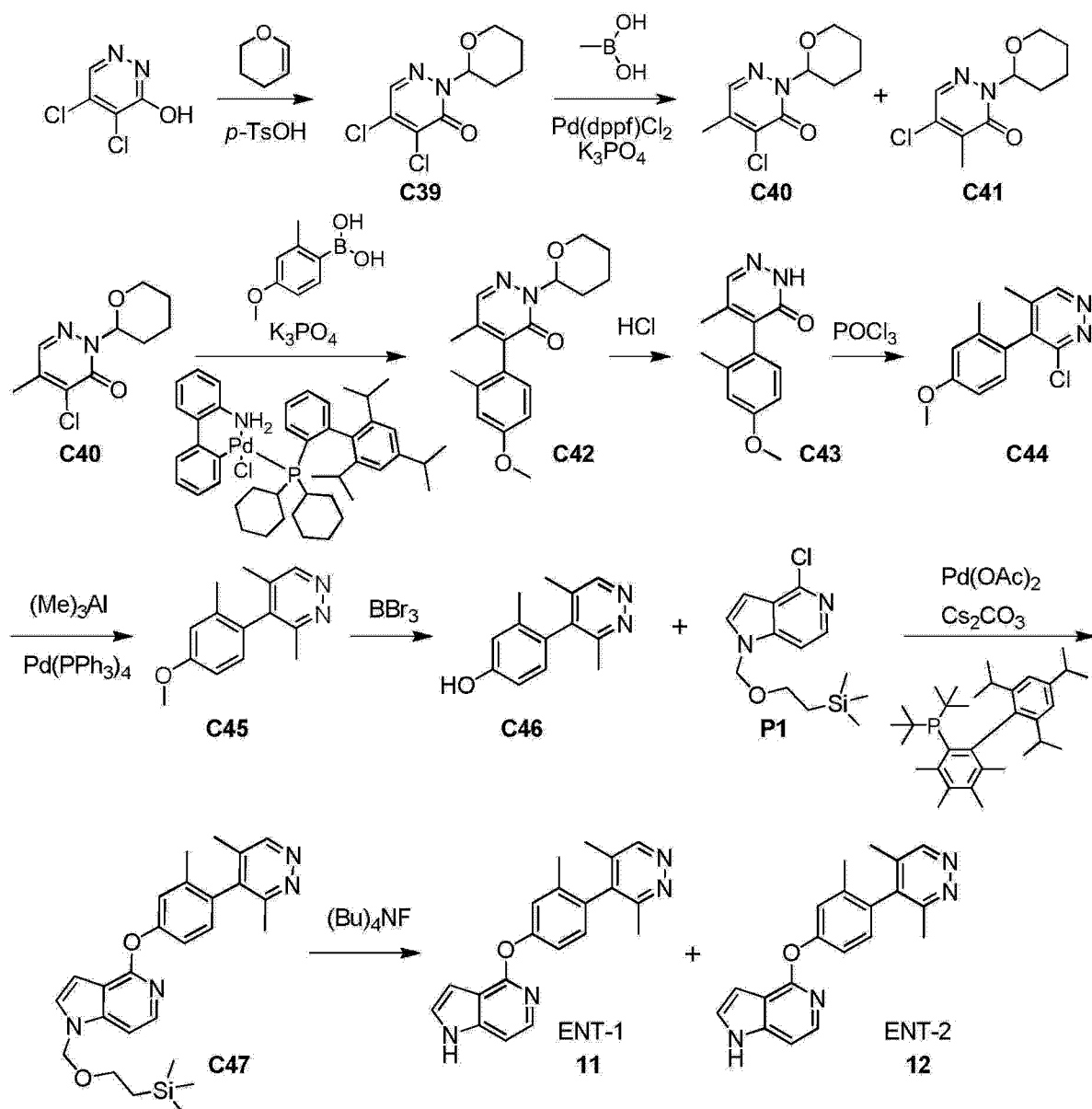
[0495] 向 C38 (53mg, 94 μmol) 于二氯甲烷 (3mL) 中的溶液中添加三氟乙酸 (1mL), 且在室温下搅拌反应混合物 18 小时。将溶液在乙酸乙酯与饱和碳酸氢钠水溶液之间分配; 用乙酸乙酯萃取水层三次, 且将合并的有机层合并, 干燥, 过滤, 且在真空中浓缩。在四氢呋喃 (5mL) 及水 (1mL) 中溶解残渣, 用氢氧化钾 (300mg, 5.3mmol) 处理, 且在室温下搅拌 18 小时。随后将反应混合物在乙酸乙酯与饱和氯化铵水溶液之间分配; 用乙酸乙酯萃取水层三次, 且干燥合并的有机层, 过滤, 且在减压下浓缩。使所得固体 (40mg) 进行超临界流体色谱法 (柱: Chiral Technologies, Chiralpak AS-H, 5 μm, 洗脱液: 7:3 二氧化碳/甲醇)。分离呈固体状的第一洗脱阻转对映异构体, 将其指定为化合物 9。收率: 8mg, 20 μmol, 20%。LCMS m/z 347.1 [M+H]⁺。 ¹H NMR (400MHz, CD₃OD) δ 7.78 (br d, J = 5.8Hz, 1H), 7.36 (d, J = 3.1Hz, 1H), 7.31 (d, J = 6.0Hz, 1H), 7.20-7.22 (m, 1H), 7.10-7.16 (m, 2H), 6.39 (d, J = 3.1Hz, 1H), 2.08 (s, 3H), 2.02 (s, 3H), 1.92 (s, 3H)。保留时间: 4.07 分钟 (柱: Chiral

Technologies, Chiralpak AS-H, $4.6 \times 250\text{mm}$, $5\ \mu\text{m}$; 洗脱液: 二氧化碳中的 5% 甲醇持续 1.0 分钟, 接着二氧化碳中的 5% 至 50% 甲醇经 6.0 分钟的梯度; 流速: 4.0 毫升/分钟)。还获得呈固体状的第二洗脱阻转对映异构体, 将其指定为化合物 10。收率: 8mg, $20\ \mu\text{mol}$, 20%。LCMS m/z 347.2 $[\text{M}+\text{H}]^+$ 。 ^1H NMR (400MHz, CD_3OD) δ 7.88 (br d, $J = 6.4\text{Hz}$, 1H), 7.47 (br d, $J = 6\text{Hz}$, 1H), 7.45 (d, $J = 3.3\text{Hz}$, 1H), 7.34 (br d, $J = 2\text{Hz}$, 1H), 7.27 (br dd, ABX 模式的一半, $J = 8.3, 2.2\text{Hz}$, 1H), 7.21 (d, AB 四重峰的一半, $J = 8.4\text{Hz}$, 1H), 6.16 (dd, $J = 3.3, 0.6\text{Hz}$, 1H), 2.11 (s, 3H), 2.02 (s, 3H), 1.92 (s, 3H)。保留时间: 5.47 分钟 (HPLC 条件与对化合物 9 所描述的那些条件相同)。

[0496] 实施例 11 及 12

[0497] 4-[4-(3,5-二甲基吡嗪-4-基)-3-甲基苯氧基]-1H-吡咯并[3,2-c]吡啶, ENT-1 (11) 及 4-[4-(3,5-二甲基吡嗪-4-基)-3-甲基苯氧基]-1H-吡咯并[3,2-c]吡啶, ENT-2 (12)

[0498]



[0499] 步骤 1. 4, 5- 二氯 -2-(四氢 -2H- 吡喃 -2- 基) 哒嗪 -3(2H)- 酮 (C39) 的合成

[0500] 将 4, 5- 二氯哒嗪 -3- 醇 (42g, 250mmol)、3, 4- 二氢 -2H- 吡喃 (168g, 2.00mol) 及对甲苯磺酸 (8.8g, 51mmol) 于四氢呋喃 (2L) 中的混合物在回流下加热 2 天。在冷却至室温之后, 在真空中浓缩反应混合物, 且通过硅胶色谱法 (梯度: 石油醚中的 3% 至 5% 乙酸乙酯) 来纯化。获得呈白色固体状的产物。收率: 42g, 170mmol, 68%。¹H NMR(400MHz, CDCl₃) δ 7.84(s, 1H), 6.01(br d, J = 11Hz, 1H), 4.10-4.16(m, 1H), 3.70-3.79(m, 1H), 1.99-2.19(m, 2H), 1.50-1.80(m, 4H)。

[0501] 步骤 2. 4- 氯 -5- 甲基 -2-(四氢 -2H- 吡喃 -2- 基) 哒嗪 -3(2H)- 酮 (C40) 及 5- 氯 -4- 甲基 -2-(四氢 -2H- 吡喃 -2- 基) 哒嗪 -3(2H)- 酮 (C41) 的合成

[0502] 向 C39(40g, 0.16mol)、甲基硼酸 (9.6g, 0.16mol) 及碳酸铯 (156g, 479mmol) 于 1, 4- 二氧杂环己烷 (500mL) 及水 (50mL) 中的混合物中添加 [1, 1'- 双 (二苯基膦基) 二茂铁] 二氯化钡 (II) (5g, 7mmol)。在 110℃ 下搅拌反应混合物 2 小时, 随后将其冷却至室温, 且在真空中浓缩。通过硅胶色谱法 (梯度: 石油醚中的 3% 至 6% 乙酸乙酯) 来纯化, 得到呈浅黄色固体状的化合物 C40。收率: 9.0g, 39mmol, 24%。LCMS m/z 250.8[M+Na⁺]¹H NMR(400MHz, CDCl₃) δ 7.71(s, 1H), 6.07(dd, J = 10.7, 2.1Hz, 1H), 4.10-4.18(m, 1H), 3.71-3.81(m, 1H), 2.30(s, 3H), 1.98-2.19(m, 2H), 1.53-1.81(m, 4H)。还获得呈浅黄色固体状的 C41。收率: 9.3g, 41mmol, 26%。LCMS m/z 250.7[M+Na⁺]¹H NMR(400MHz, CDCl₃) δ 7.77(s, 1H), 6.02(dd, J = 10.7, 2.1Hz, 1H), 4.10-4.17(m, 1H), 3.71-3.79(m, 1H), 2.27(s, 3H), 1.99-2.22(m, 2H), 1.51-1.79(m, 4H)。

[0503] 步骤 3. 4-(4- 甲氧基 -2- 甲基苯基) -5- 甲基 -2-(四氢 -2H- 吡喃 -2- 基) 哒嗪 -3(2H)- 酮 (C42) 的合成

[0504] 向 (4- 甲氧基 -2- 甲基苯基) 硼酸 (200mg, 1.20mmol)、C40(250mg, 1.09mmol) 及 [2'-(氮二基 (azanidyl)-κ N) 联苯 -2- 基 -κ C₂](氯) { 二环己基 [2', 4', 6'- 三 (丙 -2- 基) 联苯 -2- 基]-λ⁵- 磷烷基 } 钡 (22mg, 28 μmol) 于四氢呋喃 (4mL) 中的经脱气溶液中添加经脱气的磷酸钾水溶液 (0.5M, 4.37mL, 2.18mmol)。在室温下 4 小时之后, 用乙酸乙酯稀释反应混合物; 用饱和氯化钠水溶液洗涤有机层两次, 随后经硫酸镁干燥, 过滤, 且在真空中浓缩。硅胶色谱法 (洗脱液: 3:7 乙酸乙酯 / 庚烷), 得到呈胶状的产物。收率: 290mg, 0.922mmol, 85%。LCMS m/z 315.1[M+H⁺]¹H NMR(400MHz, CDCl₃), 推测为非对映阻转异构体的混合物; δ 7.76 及 7.77(2s, 总 1H), [6.92(d, J = 8.4Hz) 及 6.93(d, J = 8.4Hz), 总 1H], 6.79-6.82(m, 1H), 6.76(dd, J = 8.4, 2.5Hz, 1H), 6.06(dd, J = 10.7, 2.1Hz, 1H), 4.09-4.17(m, 1H), 3.78(s, 3H), 3.66-3.76(m, 1H), 2.09-2.26(m, 1H), 2.08 及 2.08(2s, 总 3H), 1.96-2.05(m, 1H), 1.93 及 1.94(2s, 总 3H), 1.63-1.80(m, 3H), 1.48-1.60(m, 1H)。

[0505] 步骤 4. 4-(4- 甲氧基 -2- 甲基苯基) -5- 甲基哒嗪 -3(2H)- 酮 (C43) 的合成

[0506] 将 C42(184mg, 0.585mmol) 与氯化氢于 1, 4- 二氧杂环己烷中的溶液 (4M, 8mL) 混合, 且搅拌 1 小时。在真空中浓缩, 得到呈固体状的产物 (140mg), 将其直接用于下一步骤。LCMS m/z 231.1[M+H⁺]¹H NMR(400MHz, CD₃OD) δ 7.98(br s, 1H), 6.98(d, J = 8.4Hz, 1H), 6.89(br d, J = 2.5Hz, 1H), 6.84(br dd, J = 8.4, 2.7Hz, 1H), 3.82(s, 3H), 2.09(br s, 3H), 2.01(s, 3H)。

[0507] 步骤 5. 3-氯-4-(4-甲氧基-2-甲基苯基)-5-甲基吡嗪 (C44) 的合成

[0508] 将 C43 (来自前述步骤, 140mg) 与氧氯化磷 (1.5mL, 16mmol) 的混合物在 90℃ 下搅拌 1.5 小时。在真空中移除氧氯化磷之后, 将残渣在二氯甲烷 (120mL) 与水 (20mL) 之间分配, 且用碳酸氢钠中和。顺序用碳酸氢钠水溶液 (2×50mL) 及水 (2×50mL) 洗涤有机层, 随后经硫酸镁干燥, 过滤, 且在减压下浓缩。获得呈胶状的产物。经两步收率: 133mg, 0.535mmol, 91%。LCMS m/z 249.1 $[M+H]^+$ 。 ^1H NMR (400MHz, $CDCl_3$) δ 9.03 (s, 1H), 6.94 (d, AB 四重峰的一半, $J = 8.2$ Hz, 1H), 6.84-6.91 (m, 2H), 3.87 (s, 3H), 2.11 (s, 3H), 2.03 (s, 3H)。

[0509] 步骤 6. 4-(4-甲氧基-2-甲基苯基)-3,5-二甲基吡嗪 (C45) 的合成

[0510] 用氮气向四(三苯基膦)钼 (0) (32mg, 28 μ mol) 及 C44 (133mg, 0.535mmol) 于 1,4-二氧杂环己烷 (5mL) 中的搅拌混合物中鼓泡 10 分钟。随后添加三甲基铝 (甲苯中的 2M, 0.5mL, 1.0mmol), 且在 95℃ 下加热反应混合物 1.5 小时。在冷却之后, 通过逐滴添加甲醇来淬灭反应混合物, 随后用甲醇稀释。通过硅藻土过滤混合物, 且在真空中浓缩滤液。硅胶色谱法 (洗脱液: 乙酸乙酯中的 5% 甲醇), 得到呈油状的产物。收率: 94mg, 0.41mmol, 77%。LCMS m/z 229.1 $[M+H]^+$ 。 ^1H NMR (400MHz, $CDCl_3$) δ 8.91 (s, 1H), 6.78-6.86 (m, 3H), 3.80 (s, 3H), 2.32 (s, 3H), 1.97 (s, 3H), 1.91 (s, 3H)。

[0511] 步骤 7. 4-(3,5-二甲基吡嗪-4-基)-3-甲基苯酚 (C46) 的合成

[0512] 向 C45 (740mg, 3.24mmol) 于二氯甲烷 (10mL) 中的 -78℃ 溶液中逐滴添加三溴化硼 (二氯甲烷中的 1M 溶液, 13.0mL, 13.0mmol)。在 -78℃ 下搅拌 15 分钟之后, 经 1 小时将反应混合物逐渐升温至室温, 且在室温下搅拌 2 小时。随后将其冷却至 -78℃, 用无水甲醇 (15mL) 淬灭, 且升温至室温。在真空中移除溶剂, 且用甲醇 (20mL) 处理残渣, 并在回流下加热 30 分钟。冷却反应混合物, 且在减压下浓缩; 将残渣在二氯甲烷与水之间分配。用 1N 氢氧化钠水溶液将水层调整至 pH 14, 随后再用二氯甲烷萃取。通过添加 1N 盐酸水溶液来使水层达到 pH 6-7, 且搅拌 10 分钟; 通过过滤来分离所得沉淀, 得到呈灰白色固体状的产物。收率: 599mg, 2.80mmol, 86%。LCMS m/z 215.1 $[M+H]^+$ 。 ^1H NMR (400MHz, CD_3OD) δ 8.97 (s, 1H), 6.74-6.89 (m, 3H), 2.33 (s, 3H), 2.07 (s, 3H), 1.91 (s, 3H)。

[0513] 步骤 8. 4-[4-(3,5-二甲基吡嗪-4-基)-3-甲基苯氧基]-1-[[2-(三甲基硅烷基)乙氧基]甲基]-1H-吡咯并 [3,2-c] 吡啶 (C47) 的合成

[0514] 使用实施例 2 中合成 C15 时所描述的方法来将 C46 转化为产物。在此情况下, 通过硅胶色谱法 (流动相 A: 二氯甲烷; 流动相 B: 80:20:1 二氯甲烷 / 甲醇 / 浓氢氧化铵溶液; 梯度: 0% 至 25% B) 来进行纯化。获得呈黄色胶状的产物。收率: 67mg, 0.15mmol, 65%。LCMS m/z 461.3 $[M+H]^+$ 。 ^1H NMR (400MHz, $CDCl_3$) δ 8.98 (s, 1H), 7.94 (d, $J = 5.7$ Hz, 1H), 7.16-7.26 (m, 4H), 7.00 (d, $J = 8.2$ Hz, 1H), 6.68-6.72 (m, 1H), 5.50 (s, 2H), 3.47-3.55 (m, 2H), 2.42 (s, 3H), 2.07 (s, 3H), 1.98 (s, 3H), 0.87-0.95 (m, 2H), -0.04 (s, 9H)。

[0515] 步骤 9. 4-[4-(3,5-二甲基吡嗪-4-基)-3-甲基苯氧基]-1H-吡咯并 [3,2-c] 吡啶, ENT-1 (11) 及 4-[4-(3,5-二甲基吡嗪-4-基)-3-甲基苯氧基]-1H-吡咯并 [3,2-c] 吡啶, ENT-2 (12) 的合成

[0516] 向 C47 (44.9mg, 97.5 μ mol) 于四氢呋喃 (1mL) 中的溶液中添加氟化四丁基铵 (四氢呋喃中的 1M 溶液, 1mL, 1mmol), 且在 80℃ 下加热反应混合物 2 小时。冷却反应混合物, 且用乙酸乙酯萃取。用水及饱和氯化钠水溶液洗涤合并的有机层, 随后经硫酸镁干燥, 过滤,

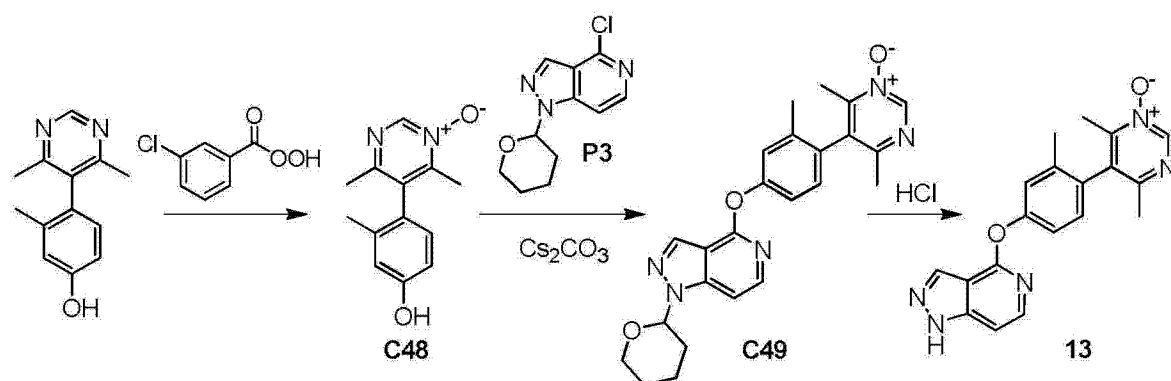
且在真空中浓缩。使用高效液相色谱法(柱:Princeton Silica, 5 μ m; 梯度:庚烷中的5%至100%乙醇)来纯化,接着通过超临界流体色谱法(柱:Chiral Technologies, Chiralpak AS-H, 5 μ m; 洗脱液:3:1 二氧化碳/甲醇)来进行阻转对映异构体分离。获得呈固体状的第一洗脱阻转对映异构体,指定为化合物11。收率:4.1mg, 12 μ mol, 12%。LCMS m/z 331.2 $[M+H]^+$ 。 ^1H NMR(400MHz, $CDCl_3$) δ 8.99(s, 1H), 8.72(br s, 1H), 7.91(d, J = 5.9Hz, 1H), 7.23-7.27(m, 2H), 7.21(br dd, J = 8.2, 2.3Hz, 1H), 7.14(dd, J = 5.8, 0.9Hz, 1H), 7.01(d, J = 8.2Hz, 1H), 6.72-6.74(m, 1H), 2.43(s, 3H), 2.07(s, 3H), 1.99(s, 3H)。保留时间:4.43分钟(柱:Chiral Technologies, Chiralpak AS-H, 250 $\times$ 4.6mm, 5 μ m; 洗脱液:3:1 二氧化碳/甲醇; 流速:2.5毫升/分钟)。

[0517] 还获得呈固体状的第二洗脱阻转对映异构体,指定为化合物12。收率:4.5mg, 14 μ mol, 14%。LCMS m/z 331.2 $[M+H]^+$ 。 ^1H NMR(400MHz, $CDCl_3$) δ 8.99(s, 1H), 8.73(br s, 1H), 7.91(d, J = 5.9Hz, 1H), 7.23-7.27(m, 2H), 7.21(br dd, J = 8.3, 2.4Hz, 1H), 7.14(dd, J = 5.9, 1.0Hz, 1H), 7.01(d, J = 8.2Hz, 1H), 6.71-6.74(m, 1H), 2.43(s, 3H), 2.07(s, 3H), 1.99(s, 3H)。保留时间:6.74分钟(HPLC条件与对化合物11所描述的那些条件相同)。

[0518] 实施例13

[0519] 4-[4-(4,6-二甲基-1-氧化嘧啶-5-基)-3-甲基苯氧基]-1H-吡唑并[4,3-c]吡啶(13)

[0520]



[0521] 步骤1. 4-(4,6-二甲基-1-氧化嘧啶-5-基)-3-甲基苯酚(C48)的合成

[0522] 在0℃下向4-(4,6-二甲基嘧啶-5-基)-3-甲基苯酚(1.0g, 4.7mmol)于二氯甲烷(25mL)中的溶液中添加3-氯过氧苯甲酸(887mg, 5.14mmol)。在0℃下搅拌反应2小时,随后在室温下持续搅拌14小时。在真空中移除溶剂之后,通过硅胶色谱法(梯度:石油醚中的0%至100%乙酸乙酯)来纯化,得到产物。收率:742mg, 3.22mmol, 69%。 ^1H NMR(400MHz, $CDCl_3$) δ 9.03(s, 1H), 6.82-6.91(m, 3H), 2.30(s, 3H), 2.22(s, 3H), 1.97(s, 3H)。

[0523] 步骤2. 4-[4-(4,6-二甲基-1-氧化嘧啶-5-基)-3-甲基苯氧基]-1-(四氢-2H-吡喃-2-基)-1H-吡唑并[4,3-c]吡啶(C49)的合成

[0524] 向C48(230mg, 1.0mmol)于乙腈(25mL)中的溶液中添加P3(238mg, 1.00mmol)及碳酸铯(650mg, 2.0mmol),且在110℃下搅拌反应混合物60小时。过滤反应混合物且在真空中浓缩;硅胶色谱法(梯度:二氯甲烷中的0%至5%甲醇),得到呈黄色固体状的产物。

收率:290mg,0.67mmol,67%。

[0525] 步骤 3.4-[4-(4,6-二甲基-1-氧化嘧啶-5-基)-3-甲基苯氧基]-1H-吡唑并[4,3-c]吡啶(13)的合成

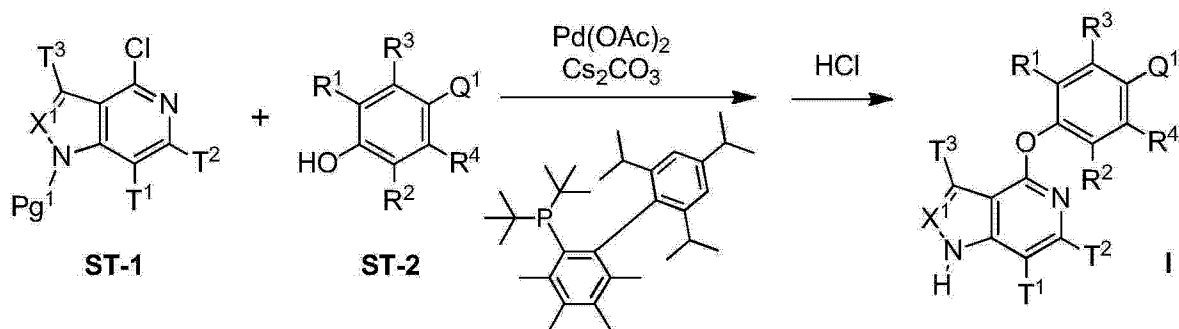
[0526] 在 0℃下向 C49(290mg,0.67mmol)中添加氯化氢于 1,4-二氧杂环己烷(10mL)中的溶液。在室温下搅拌反应混合物 2 小时,且随后在真空中浓缩。用氢氧化铵水溶液中和残渣,直至 pH 达到 9。在减压下移除溶剂之后,通过制备型硅胶薄层色谱法(洗脱液:10:1 二氯甲烷/甲醇)来进行纯化,得到呈白色固体状的产物。收率:70mg,0.20mmol,30%。LCMS m/z 347.9[M+H]⁺。¹H NMR(400MHz, CD₃OD) δ 9.05(s, 1H), 8.15(s, 1H), 7.85(d, J = 6.0Hz, 1H), 7.33(br s, 1H), 7.29(d, J = 5.5Hz, 1H), 7.24-7.26(m, 2H), 2.33(s, 3H), 2.30(s, 3H), 2.09(s, 3H)。

[0527] 方法 A

[0528] 将 N-保护的 4-氯-1H-吡咯并[3,2-c]吡啶或 4-氯-1H-吡唑并[4,3-c]吡啶与酚类偶联

[0529] 方法 A 描述用于制备本发明的某些化合物的具体方法。

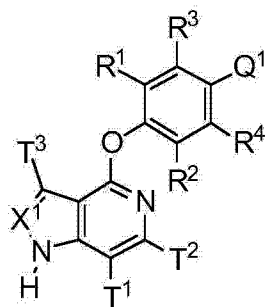
[0530]



[0531] 向 2 打兰(dram)小瓶中式 ST-2 的酚(0.1mmol)中添加经脱气的 1,4-二氧杂环己烷(1mL)中的其中 Pg¹为保护基的 N-保护的式 ST-1 的化合物(例如 P2 或 P3)(0.11mmol)。添加碳酸铯(约 98mg,0.3mmol)、乙酸铯(II)(约 2.5mg,10 μ mol)及二叔丁基[3,4,5,6-四甲基-2',4',6'-三(丙-2-基)联苯-2-基]磷烷(约 10mg,20 μ mol),且顺序使用真空及氮气填充使反应混合物脱气两次。振荡小瓶且在 80℃下加热 20 小时,随后冷却至室温。将反应混合物在水(1.5mL)与乙酸乙酯(2.5mL)之间分配,且通过硅藻土过滤;使有机层穿过用硫酸钠填充的 6mL 固相萃取柱。通过相同程序萃取水层两次,且在真空中浓缩来自硫酸钠柱的合并的滤液。将残渣溶解于二氯甲烷(0.5mL)中,且用 1,4-二氧杂环己烷中的氯化氢(4M,0.5mL,2mmol)处理。在室温下振荡此反应混合物 66 小时,随后用乙酸乙酯(2.5mL)稀释,且用氢氧化钠水溶液(6N,0.35mL)及水(1mL)淬灭。使有机层穿过经硫酸钠填充的 6mL 固相萃取柱。通过相同程序萃取水层两次,且在真空中浓缩来自硫酸钠柱的合并的滤液。使用反相高效液相色谱法(柱:Waters XBridge C18,5 μ m;流动相 A:水中的 0.03%氢氧化铵(v/v);流动相 B:乙腈中的 0.03%氢氧化铵(v/v);梯度:10%至 100% B)来进行纯化,得到产物。

[0532] 表 1. 实施例 14-29

[0533]



$X^1 = CT^4$;
 T^1, T^2, T^3 和 T^4 各自为H

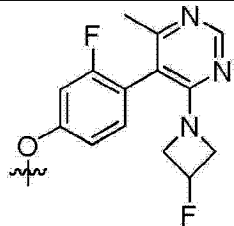
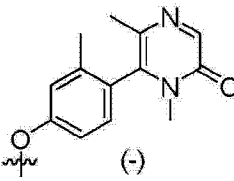
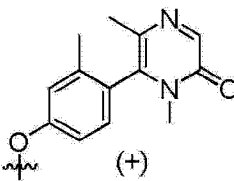
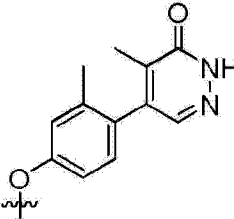
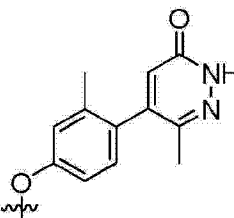
[0534]

实施例编号		制备方法; 非商购的原料	^1H NMR (400 MHz, $CDCl_3$), δ (ppm); 质谱, 观测离子 m/z [$M+H^+$]或HPLC保留时间(分钟); 质谱 m/z [$M+H^+$] (除非另外说明)
14		实施例 1 ^{1,2,3}	9.72 (br s, 1H), 9.07 (s, 1H), 7.88 (d, $J=5.8$ Hz, 1H), 7.71 (d, $J=1.0$ Hz, 1H), 7.32-7.34 (m, 1H), 7.27-7.29 (m, 2H), 7.26 (dd, $J=3.1, 2.3$ Hz, 1H), 7.15 (dd, $J=5.8, 0.8$ Hz, 1H), 7.07-7.09 (m, 1H), 6.73-6.76 (m, 1H), 2.34 (s, 3H), 2.03 (s, 3H); 356.0
15		实施例1 ⁴	9.62 (br s, 1H), 9.16 (s, 1H), 7.89 (d, $J=6.0$ Hz, 1H), 7.81-7.84 (m, 2H), 7.41 (d, $J=8.3$ Hz, 1H), 7.25-7.34 (m, 4H), 7.14 (d, $J=6.0$ Hz, 1H), 6.77-6.81 (m, 1H), 2.14 (s, 3H); 342.2
16		实施例2; C13	^1H NMR (400 MHz, CD_3OD) δ 9.19 (s, 1H), 7.79 (d, $J=5.8$ Hz, 1H), 7.51 (dd, $J=9.3, 8.0$ Hz, 1H), 7.36 (d, $J=3.0$ Hz, 1H), 7.30 (d, $J=6.0$ Hz, 1H), 7.14-7.20 (m, 2H), 6.57 (d, $J=3.3$ Hz, 1H), 2.53 (s, 3H); 345.9
17		实施例16	^1H NMR (400 MHz, CD_3OD) δ 9.18 (s, 1H), 7.76 (d, $J=5.8$ Hz, 1H), 7.31 (d, $J=3.3$ Hz, 1H), 7.25-7.28 (m, 2H), 7.20 (br d, $J=2.5$ Hz, 1H), 7.12 (br dd, $J=8.3, 2.3$ Hz, 1H), 6.47 (dd, $J=3.3, 0.8$ Hz, 1H), 2.44 (s, 3H), 2.10 (br s, 3H); 342.0

[0535]

18		实施例1 ^{1,2}	9.10 (s, 1H), 8.68 (br s, 1H), 7.95 (d, $J=5.8$ Hz, 1H), 7.75 (d, $J=1.0$ Hz 1H), 7.46 (dd, $J=8.8, 7.8$ Hz, 1H), 7.36-7.38 (m, 1H), 7.25-7.32 (m, 3H, 假定; 部分被溶剂峰遮蔽), 7.21 (dd, $J=5.8, 1.0$ Hz, 1H), 6.77-6.79 (m, 1H), 2.46 (s, 3H); 360.1
19		实施例5 ^{1,5}	9.11 (br s, 1H), 9.10 (s, 1H), 7.91 (d, $J=5.8$ Hz, 1H), 7.74 (br s, 1H), 7.49 (s, 4H), 7.40 (br s, 1H), 7.26-7.29 (m, 1H, 假定; 部分被溶剂峰遮蔽), 7.18 (br d, $J=5.8$ Hz, 1H), 6.74-6.78 (m, 1H), 2.46 (s, 3H); 342.0
20		实施例9及 10 ^{6,3}	9.64-9.80 (br m, 1H), 8.94 (s, 1H), 7.85 (br d, $J=5.8$ Hz, 1H), 7.36 (br d, $J=8.6$ Hz, 2H), 7.17-7.22 (m, 3H), 7.12 (br d, $J=5.7$ Hz, 1H), 6.65-6.68 (m, 1H), 2.29 (s, 6H); 317.1
21		实施例5 ⁷ ; P2 ⁸	9.04 (s, 1H), 8.72 (br s, 1H), 7.91 (d, $J=5.9$ Hz, 1H), 7.76 (dd, $J=2.5, 0.4$ Hz, 1H), 7.66 (dd, $J=8.5, 2.5$ Hz, 1H), 7.33 (dd, $J=8.5, 0.3$ Hz, 1H), 7.29 (dd, $J=3.3, 2.3$ Hz, 1H), 7.20 (dd, $J=5.9, 1.0$ Hz, 1H), 6.76 (ddd, $J=3.3, 2.0, 1.0$ Hz, 1H), 2.36 (s, 6H); 342.2
22		实施例5 ^{9,3}	¹ H NMR (600 MHz, DMSO- d_6) δ 8.96 (s, 1H), 7.69 (d, $J=5.7$ Hz, 1H), 7.55-7.60 (m, 2H), 7.48 (dd, $J=3.1, 2.6$ Hz, 1H), 7.23 (br d, $J=6$ Hz, 1H), 6.64-6.66 (m, 1H), 2.30 (s, 6H); 353.1
23		实施例6; P2 ¹⁰	¹ H NMR (600 MHz, DMSO- d_6) δ 8.98 (s, 1H), 7.69 (d, $J=5.7$ Hz, 1H), 7.48-7.50 (m, 1H), 7.36-7.40 (m, 1H), 7.27-7.31 (m, 1H), 7.24 (br d, $J=5.7$ Hz, 1H), 6.65-6.68 (m, 1H), 2.29 (s, 6H); 353.2
24		方法A	2.02分钟 ¹¹ ; 351.1, 353.1

[0536]

25		方法A	2.33分钟 ¹² ; 394.2
26		实施例6; P2, P8 ¹³	¹ H NMR (400 MHz, CD ₃ OD) δ 8.09 (s, 1H), 7.73 (d, <i>J</i> =5.9 Hz, 1H), 7.33 (d, <i>J</i> =3.2 Hz, 1H), 7.23-7.28 (m, 2H), 7.19-7.21 (m, 1H), 7.13 (br dd, <i>J</i> =8.2, 2.3 Hz, 1H), 6.54-6.56 (m, 1H), 3.28 (s, 3H), 2.12 (s, 3H), 2.06 (s, 3H); 347.1
27		实施例6; P2, P8 ¹⁴	¹ H NMR (400 MHz, CD ₃ OD) δ 8.09 (s, 1H), 7.73 (d, <i>J</i> =5.8 Hz, 1H), 7.33 (d, <i>J</i> =3.1 Hz, 1H), 7.23-7.28 (m, 2H), 7.19-7.21 (m, 1H), 7.13 (br dd, <i>J</i> =8.5, 2.4 Hz, 1H), 6.54-6.56 (m, 1H), 3.28 (s, 3H), 2.13 (s, 3H), 2.06 (s, 3H); 347.1
28		实施例6; P2, C41 ¹⁵	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ 7.70 (d, <i>J</i> =5.7 Hz, 1H), 7.68 (s, 1H), 7.42 (dd, <i>J</i> =2.8, 2.6 Hz, 1H), 7.18-7.20 (m, 2H), 7.17 (br d, <i>J</i> =2.2 Hz, 1H), 7.09 (dd, <i>J</i> =8.3, 2.4 Hz, 1H), 6.54-6.56 (m, 1H), 2.11 (s, 3H), 1.86 (s, 3H); 333.0
29		实施例3及 4 ¹⁶	¹ H NMR (400 MHz, CD ₃ OD) δ 7.72 (d, <i>J</i> =6.1 Hz, 1H), 7.32 (d, <i>J</i> =3.1 Hz, 1H), 7.23 (dd, <i>J</i> =6.0, 0.9 Hz, 1H), 7.18 (d, <i>J</i> =8.2 Hz, 1H), 7.10-7.12 (m, 1H), 7.05 (br dd, <i>J</i> =8.3, 2.4 Hz, 1H), 6.76 (d, <i>J</i> =0.4 Hz, 1H), 6.51 (dd, <i>J</i> =3.1, 1.0 Hz, 1H), 2.16 (br s, 3H), 2.11 (d, <i>J</i> =0.4 Hz, 3H); 333.2

[0537] 1. 通过A. R. Harris等人, Tetrahedron 2011, 67, 9063-9066的方法来制备必需的5-溴-6-甲基咪唑并[1,2-a]吡嗪。

[0538] 2. 在倒数第二个步骤中,使用四(三苯基膦)钯(0)及碳酸钠来进行偶联。

[0539] 3. 最终脱保护用氟化四丁基铵来实现。

[0540] 4. 通过实施例5中用于合成C28的通用方法来制备必需的4-(咪唑并[1,2-a]吡嗪-5-基)-3-甲基苯酚。

[0541] 5. 使用三氟乙酸来进行最终脱保护,随后用碳酸钾处理。

[0542] 6. 使用实施例5中所描述的方法来制备4-(4,6-二甲基咪唑-5-基)苯酚。

[0543] 7. 用三氟乙酸来进行最终脱保护。

[0544] 8. 使用实施例3及4中制备C20时所描述的通用方法来将5-溴-4,6-二甲基咪唑转化为4,6-二甲基-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼戊环-2-基)咪唑。根据实

实施例 5 中给出的合成 C28 的通用方法,此化合物通过与 2-溴-5-甲氧基苯甲腈的 Suzuki 反应及脱保护来转化为必需的 2-(4,6-二甲基嘧啶-5-基)-5-羟基苯甲腈。

[0545] 9. 通过 (2,5-二氟-4-甲氧基苯基)硼酸与 5-溴-4,6-二甲基嘧啶之间由四(三苯基膦)钯(0)介导的 Suzuki 反应,接着使用三溴化硼脱甲基化来制备必需的 4-(4,6-二甲基嘧啶-5-基)-2,5-二氟苯酚。

[0546] 10. 5-溴-4,6-二甲基嘧啶与 (2,3-二氟-4-甲氧基苯基)硼酸之间的 Suzuki 反应由三(二亚苄基丙酮)二钯(0)及三环己基膦介导;用三溴化硼脱保护,得到必需的 4-(4,6-二甲基嘧啶-5-基)-2,3-二氟苯酚。

[0547] 11. 用于分析型 HPLC 的条件。柱:Waters Atlantis dC18,4.6×50mm,5 μm;流动相 A:水中的 0.05%三氟乙酸(v/v);流动相 B:乙腈中的 0.05%三氟乙酸(v/v);梯度:5.0%至 95% B,经 4.0 分钟线性变化;流速:2 毫升/分钟。

[0548] 12. 用于分析型 HPLC 的条件。柱:Waters XBridge C18,4.6×50mm,5 μm;流动相 A:水中的 0.03%氢氧化铵(v/v);流动相 B:乙腈中的 0.03%氢氧化铵(v/v);梯度:5.0%至 95% B,经 4.0 分钟线性变化;流速:2 毫升/分钟。

[0549] 13. 使用超临界流体色谱法(柱:Chiral Technologies Chiralcel OJ-H,5 μm;洗脱液:1:4 甲醇/二氧化碳)来分离外消旋产物。阻转对映异构体实施例 26 为第一洗脱异构体,其展现负(-)旋光性及 4.28 分钟的保留时间(柱:Chiral Technologies Chiralcel OJ-H,4.6×250mm,5 μm;洗脱液:1:4 甲醇/二氧化碳;流速 2.5mL/min)。

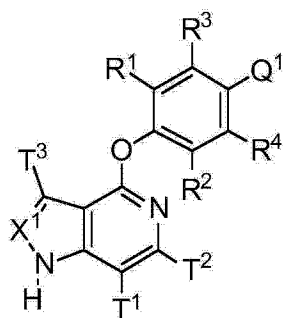
[0550] 14. 如脚注 13 中所描述来分离外消旋产物。阻转对映异构体实施例 27 为第二洗脱异构体,其展现正(+)旋光性及 4.97 分钟的保留时间(分析条件与脚注 13 中的那些条件相同)。

[0551] 15. 使用与实施例 5 中制备 C27 时所采用的那些条件类似的条件来使化合物 C41 与 C20 反应。所得 5-[4-(苯甲氧基)-2-甲基苯基]-4-甲基-2-(四氢-2H-吡喃-2-基)哒嗪-3(2H)-酮经氢化,得到 5-(4-羟基-2-甲基苯基)-4-甲基-2-(四氢-2H-吡喃-2-基)哒嗪-3(2H)-酮。

[0552] 16. 使用实施例 3 及 4 中制备 C19 时所概述的通用方法由 4-溴-3-氧代戊酸乙酯制备三氟甲磺酸 2-甲基-5-氧代-2,5-二氢呋喃-3-基酯。

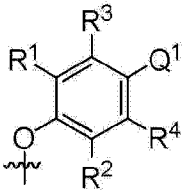
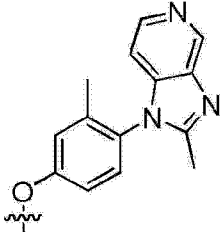
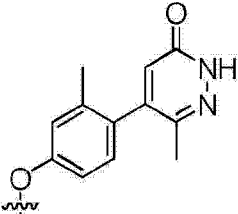
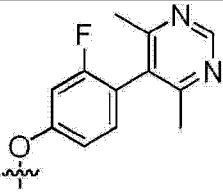
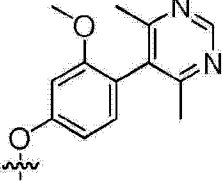
[0553] 表 2. 实施例 30-43

[0554]

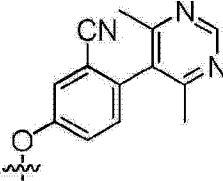
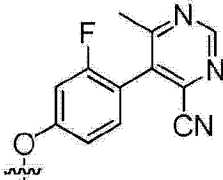
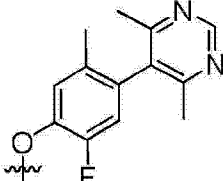
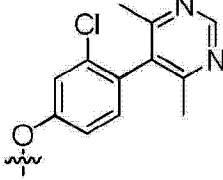
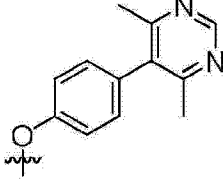
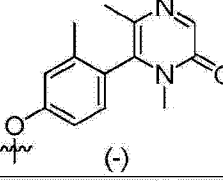
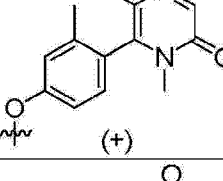
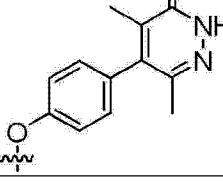


$X^1 = N$;
 T^1, T^2 和 T^3 各自为H

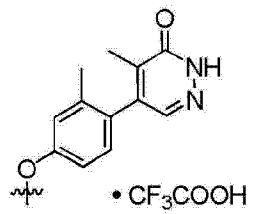
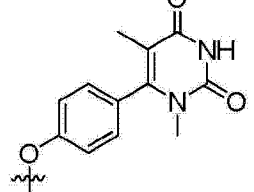
[0555]

实施例编号		制备方法；非商购的原料	¹ H NMR (400 MHz, CD ₃ OD), δ (ppm); 质谱, 观测离子 <i>m/z</i> [M+H] ⁺ 或 HPLC 保留时间(分钟); 质谱 <i>m/z</i> [M+H] ⁺ (除非另外说明)
30		实施例11及12 ¹ ; P6 ²	¹ H NMR (400 MHz, CDCl ₃), δ 9.10 (s, 1H), 8.41 (d, <i>J</i> =5.5 Hz, 1H), 8.26 (s, 1H), 7.94 (d, <i>J</i> =6.0 Hz, 1H), 7.40 (br d, <i>J</i> =2.5 Hz, 1H), 7.35 (br dd, ABX模式的一半, <i>J</i> =8.5, 2.4 Hz, 1H), 7.30 (d, AB四重峰的一半, <i>J</i> =8.6 Hz, 1H), 7.25-7.29 (m, 1H, 假定; 部分被溶剂峰遮蔽), 7.01 (dd, <i>J</i> =5.5, 0.8 Hz, 1H), 2.49 (s, 3H), 2.00 (s, 3H); 357.2
31		实施例3及4 ³	8.11 (br s, 1H), 7.83 (d, <i>J</i> =6.3 Hz, 1H), 7.23-7.28 (m, 3H), 7.17-7.21 (m, 1H), 6.79-6.80 (m, 1H), 2.20 (br s, 3H), 2.13 (d, <i>J</i> =0.4 Hz, 3H); 334.2
32		实施例5; P6 ⁴	¹ H NMR (400 MHz, CDCl ₃), δ 9.00 (s, 1H), 8.27 (s, 1H), 8.00 (d, <i>J</i> =6.0 Hz, 1H), 7.19-7.28 (m, 4H, 假定; 部分被溶剂峰遮蔽), 2.38 (s, 6H); 336.1
33		实施例5; P6 ⁵	9.27 (s, 1H), 8.08 (d, <i>J</i> =6.5 Hz, 1H), 7.62-7.69 (m, 1H), 7.58 (s, 1H), 7.45-7.55 (m, 2H), 7.27-7.33 (m, 1H), 3.84 (s, 3H), 2.55 (s, 6H); 348.1

[0556]

34		实施例5 ⁶ ; P6 ⁷	¹ H NMR (400 MHz, CDCl ₃), δ 9.05 (s, 1H), 8.30 (d, <i>J</i> =0.8 Hz, 1H), 7.97 (d, <i>J</i> =6.0 Hz, 1H), 7.84 (d, <i>J</i> =2.5 Hz, 1H), 7.70 (dd, <i>J</i> =8.5, 2.5 Hz, 1H), 7.39 (d, <i>J</i> =8.5 Hz, 1H), 7.24 (dd, <i>J</i> =6.0, 1.0 Hz, 1H), 2.37 (s, 6H); 343.1
35		实施例5 ⁸ ; P3 ⁹	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆), δ 9.33 (s, 1H), 8.31 (br s, 1H), 7.91 (dd, <i>J</i> =5.9, 0.4 Hz, 1H), 7.73 (dd, <i>J</i> =8.6, 8.6 Hz, 1H), 7.56 (dd, <i>J</i> =10.8, 2.2 Hz, 1H), 7.39 (dd, <i>J</i> =8.4, 2.2 Hz, 1H), 7.36 (br d, <i>J</i> =5.9 Hz, 1H), 2.48 (s, 3H); 347.2
36		方法A	2.33分钟; 350.1 ¹⁰
37		方法A	2.40分钟; 352.1 ¹⁰
38		实施例5; P6	¹ H NMR (400 MHz, CDCl ₃), δ 8.97 (s, 1H), 8.23 (s, 1H), 7.98 (d, <i>J</i> =6.0 Hz, 1H), 7.42 (br d, <i>J</i> =8.5 Hz, 2H), 7.24-7.29 (m, 2H, 假定; 部分被溶剂峰遮蔽), 7.17 (d, <i>J</i> =6.0 Hz, 1H), 2.35 (s, 6H); 318.1
39		实施例6; P8 ¹¹	8.18 (s, 1H), 8.10 (s, 1H), 7.85 (d, <i>J</i> =6.2 Hz, 1H), 7.32-7.36 (m, 2H), 7.25-7.30 (m, 2H), 3.29 (s, 3H), 2.16 (s, 3H), 2.07 (s, 3H); 348.4
40		实施例6; P8 ¹²	8.17-8.18 (m, 1H), 8.10 (s, 1H), 7.85 (d, <i>J</i> =6.1 Hz, 1H), 7.32-7.36 (m, 2H), 7.25-7.30 (m, 2H), 3.29 (s, 3H), 2.16 (s, 3H), 2.07 (s, 3H); 348.4
41		实施例3 及4	8.12 (s, 1H), 7.86 (d, <i>J</i> =6.2 Hz, 1H), 7.37 (br AB四重峰, <i>J</i> _{AB} =8.6 Hz, Δ <i>v</i> _{AB} =28 Hz, 4H), 7.28 (d, <i>J</i> =5.8 Hz, 1H), 2.11 (s, 3H), 1.99 (s, 3H); 334.2

[0557]

42		实施例3 及4 ^{13,14}	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆), δ 8.23 (br s, 1H), 7.84 (d, <i>J</i> =6.2 Hz, 1H), 7.72 (s, 1H), 7.26-7.30 (m, 2H), 7.25 (d, AB 四重峰的一半, <i>J</i> =7.9 Hz, 1H), 7.19 (dd, ABX模式的一半, <i>J</i> =7.9, 2.2 Hz, 1H), 2.13 (s, 3H), 1.86 (s, 3H); 334.0
43		实施例8	8.18 (d, <i>J</i> =1.0 Hz, 1H), 7.85 (d, <i>J</i> =6.1 Hz, 1H), 7.42-7.47 (m, 4H), 7.29 (dd, <i>J</i> =6.1, 1.0 Hz, 1H), 3.11 (s, 3H), 1.71 (s, 3H); 350.2

[0558] 1. 在倒数第二个步骤中,使用 4,5-双(二苯基膦基)-9,9-二甲基吨而非二叔丁基 [3,4,5,6-四甲基-2',4',6'-三(丙-2-基)联苯-2-基] 磷烷来进行偶联。

[0559] 2. 必需的 3-甲基-4-(2-甲基-1H-咪唑并[4,5-c]吡啶-1-基)苯酚按以下方式来制备:将 4-甲氧基-2-甲基苯胺与 4-氯-3-硝基吡啶反应,得到 N-(4-甲氧基-2-甲基苯基)-3-硝基吡啶-4-胺。在使硝基氢化之后,将所得胺用原乙酸乙酯及乙酸酐来环化,得到 1-(4-甲氧基-2-甲基苯基)-2-甲基-1H-咪唑并[4,5-c]吡啶,其用三溴化硼脱甲基化。

[0560] 3. 使用实施例 3 及 4 中制备 C19 时所概述的通用方法由 4-溴-3-氧代戊酸乙酯制备三氟甲磺酸 2-甲基-5-氧代-2,5-二氢呋喃-3-基酯。

[0561] 4. 使用实施例 1 中合成 C14 时所描述的方法来将 1-溴-2-氟-4-甲氧基苯转化为中间体 5-(2-氟-4-甲氧基苯基)-4,6-二甲基嘧啶。

[0562] 5. 将 4-溴-3-甲氧基苯酚以其 [三(丙-2-基)] 硅烷醚的形式进行保护,且随后用 [1,1'-双(二苯基膦基)二茂铁] 二氯化钯(II) 催化剂来将其转化为 [3-甲氧基-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼戊环-2-基)苯氧基][三(丙-2-基)] 硅烷。将其使用实施例 5 中合成 C27 时所描述的条件与 5-溴-4,6-二甲基嘧啶反应,得到 5-(2-甲氧基-4-[[三(丙-2-基)硅烷基]氧基]苯基)-4,6-二甲基嘧啶;用氟化四乙基铵来脱保护,得到必需的 4-(4,6-二甲基嘧啶-5-基)-3-甲氧基苯酚。

[0563] 6. 用三氟乙酸来进行最终脱保护,接着在甲醇中用乙酸钠处理。

[0564] 7. 将 2-溴-5-羟基苯甲腈以其 [三(丙-2-基)] 硅烷醚的形式进行保护。根据实施例 1 中用于制备 C14 的方法来与 4,6-二甲基-5-(4,4,5,5-四甲基-1,3,2-二氧杂硼戊环-2-基)嘧啶(使用实施例 1 中合成 C13 时所描述的条件由 5-溴-4,6-二甲基嘧啶制备)反应,得到必需的 2-(4,6-二甲基嘧啶-5-基)-5-羟基苯甲腈。

[0565] 8. 用盐酸来进行最终脱保护。

[0566] 9. 通过与氰化钾及 1,4,7,10,13,16-六氧杂环十八烷的反应由 5-溴-4-氯-6-甲基嘧啶制备 5-溴-6-甲基嘧啶-4-甲腈。使用脚注 5 中所概述的条件来将 4-溴-3-氟苯酚转化为 [3-氟-4-(4,4,5,5-四甲基-1,3,2-二氧杂硼戊环-2-基)苯氧基][三(丙-2-基)] 硅烷。使这两种试剂如脚注 5 中所描述进行 Suzuki 反应及脱硅烷基化,得到 5-(2-氟-4-羟基苯基)-6-甲基嘧啶-4-甲腈。

[0567] 10. 用于分析型 HPLC 的条件。柱:Waters Atlantis dC18, 4.6×50mm, 5 μm; 流动相 A:水中的 0.05% 三氟乙酸 (v/v); 流动相 B:乙腈中的 0.05% 三氟乙酸 (v/v); 梯度: 5.0% 至 95% B, 经 4.0 分钟线性变化; 流速:2 毫升/分钟。

[0568] 11. 使用超临界流体色谱法 (柱:Chiral Technologies Chiralcel OJ-H, 5 μm; 洗脱液:1:4 甲醇/二氧化碳) 来分离外消旋产物。阻转对映异构体实施例 39 为第一洗脱异构体, 其展现负 (-) 旋光性及 2.91 分钟的保留时间 (柱:Chiral Technologies Chiralcel OJ-H, 4.6×250mm, 5 μm; 洗脱液:1:4 甲醇/二氧化碳; 流速 2.5mL/min)。

[0569] 12. 如脚注 11 中所描述来分离外消旋产物。阻转对映异构体实施例 40 为第二洗脱异构体, 其展现正 (+) 旋光性及 3.28 分钟的保留时间 (分析条件与脚注 11 中的那些条件相同)。

[0570] 13. 在倒数第二个步骤中, 在吡啶中于 100°C 下使用碘化铜 (I) 及碳酸铯来进行偶联。

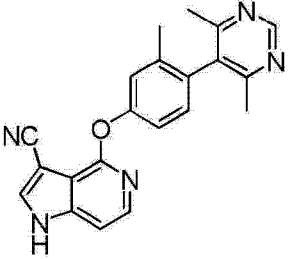
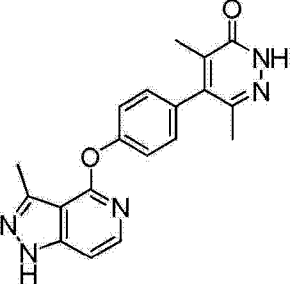
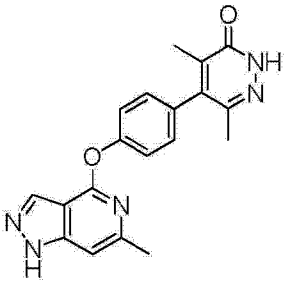
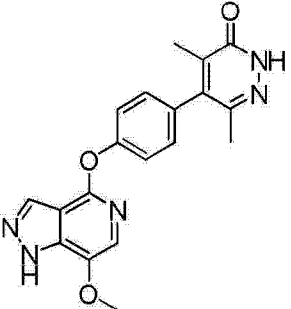
[0571] 14. 使用类似于实施例 5 中制备 C27 时所采用的那些条件来将化合物 C41 与 C20 反应。将所得 5-[4-(苯甲氧基)-2-甲基苯基]-4-甲基-2-(四氢-2H-吡喃-2-基) 哒嗪-3(2H)-酮氢化, 得到 5-(4-羟基-2-甲基苯基)-4-甲基-2-(四氢-2H-吡喃-2-基) 哒嗪-3(2H)-酮。

[0572] 表 3. 实施例 44-47

[0573]

实施例编号	结构	制备方法; 非商购的原料	¹ H NMR (400 MHz, CDCl ₃), δ (ppm) 质谱, 观测离子 <i>m/z</i> [M+H ⁺]
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[0574]

44		实施例5; P7 ¹	9.44 (br s, 1H), 8.98 (s, 1H), 8.00 (d, $J=5.5$ Hz, 1H), 7.79 (br d, $J=2$ Hz, 1H), 7.32-7.35 (m, 1H), 7.27-7.31 (m, 1H, 假定; 部分被溶剂峰遮蔽), 7.16 (d, $J=5.5$ Hz, 1H), 7.09 (d, $J=8.0$ Hz, 1H), 2.27 (s, 6H), 2.04 (s, 3H); 355.9
45		实施例3 及4 ²	7.78 (d, $J=6.2$ Hz, 1H), 7.35 (br AB四重峰, $J_{AB}=8.7$ Hz, $\Delta v_{AB}=25.9$ Hz, 4H), 7.18 (d, $J=6.2$ Hz, 1H), 2.73 (s, 3H), 2.10 (s, 3H), 1.99 (s, 3H); 348.3
46		实施例3 及4; P4	7.79 (d, $J=0.6$ Hz, 1H), 7.37 (br AB四重峰, $J_{AB}=8.8$ Hz, $\Delta v_{AB}=34.9$ Hz, 4H), 7.09-7.11 (m, 1H), 2.47 (d, $J=0.8$ Hz, 3H), 2.10 (s, 3H), 1.99 (s, 3H); 348.1
47		实施例3 及4; P5	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆), δ 8.16 (br s, 1H), 7.50 (s, 1H), 7.32 (br AB四重峰, $J_{AB}=8.3$ Hz, $\Delta v_{AB}=19.3$ Hz, 4H), 3.97 (s, 3H), 1.97 (s, 3H), 1.83 (s, 3H); 364.0

[0575] 1. 用三氟乙酸来进行最终脱保护,接着在甲醇中用乙酸钠处理。

[0576] 2. 使用制备 P3 中所描述的方法来制备 4-氯-3-甲基-1-(四氢-2H-吡喃-2-基)-1H-吡唑并[4,3-c]吡啶。

[0577] 实施例 AA:人 D1 受体结合测定及数据

[0578] 通过类似于 Ryman-Rasmussen 等人,“Differential activation of adenylate cyclase and receptor internalization by novel dopamine D1 receptor agonists”,Molecular Pharmacology 68(4):1039-1048(2005)中所描述的那些竞争结合测定法来测定本文中描述的化合物的亲和性。该放射性配体结合测定法使用 [³H]-SCH23390 (放射性标记的 D1 配体) 来评估当结合至 D1 受体上时,所测试的化合物与放射性配体竞争的能力。

[0579] 使用过度表达的 LTK 人细胞株来进行 D1 结合测定。为确定基本测定参数,自饱和结合研究来测定配体浓度,其中发现 [³H]-SCH23390 的 K_d 为 1.3nM。自组织浓度曲线研究得出,在使用 0.5nM 的 [³H]-SCH23390 的情况下,最优组织量测定为每 96 孔板 1.75mg/mL。这些

配体及组织浓度用于时程研究中,以测定结合的线性及平衡条件。结合在 30 分钟内于 37℃ 下与指定量的组织达到平衡。由这些参数,使用 Polytron 且在离心机中以 40,000×g 旋转 10 分钟来使指定量的各种组织在含有 2.0mM MgCl₂的 50mM Tris(在 4℃下 pH 7.4) 中均质化,由此测定 K_i值。将小丸再悬浮于测定缓冲剂 [含有 4mM MgSO₄及 0.5mM EDTA 的 50mM Tris(在室温下 pH 7.4) 中。通过向含有测试药物 (2.5 μL) 及 0.5nM [³H]-SCH23390 (50 μL) 的 96 孔板中添加 200 μL 组织 (最终体积为 250 μL) 来开始孵育。通过在饱和浓度的 (+)-布他拉莫 (D1 拮抗剂) (10 μM) 的存在下进行放射性配体结合来测定非特异性结合。在 37℃ 下 30 分钟孵育期之后,通过 Unifilter-96GF/B PEI 涂布的过滤板快速过滤测定样品,且用 50mM Tris 缓冲剂 (在 4℃下 pH 7.4) 冲洗。通过在 Ecolume 中进行过滤板液体闪烁计数来测定膜结合的 [³H]-SCH23390 水平。通过在 Microsoft Excel 中进行浓度-反应数据的线性回归来计算 IC₅₀值 (产生 50% 的特异性结合抑制的浓度)。根据 Cheng-Prusoff 方程来计算 K_i值。

$$K_i = \frac{IC_{50}}{1 + ([L]/K_d)}$$

[0580]

[0581] 其中 [L] = 游离放射性配体的浓度,并且 K_d = 对 D1 受体的放射性配体的解离常数 (对 [³H]-SCH23390 为 1.3nM)。

[0582] 实施例 BB :D1cAMP HTRF 测定及数据

[0583] 本文所使用及描述的 D1cAMP (环状腺苷单磷酸) HTRF (均相时间分辨荧光) 测定为在由细胞产生的天然 cAMP 与用 XL-665 标记的 cAMP 之间的竞争性免疫测定。该测定法用于测定测试化合物激动 (包括部分激动) D1 的能力。经 Mab 抗 cAMP 标记的穴状化合物使示踪剂可见。在样品不含有游离 cAMP 时获得最大信号,这是由于供体 (Eu- 穴状化合物) 与受体 (XL665) 实体的接近性。因此,信号与样品中 cAMP 的浓度成反比。时间分辨及参比测量 (em 665nm/em 620nm) 使培养基的干扰最小化。cAMP HTRF 测定为可商购的,例如来自 Cisbio Bioassays, IBA group。

[0584] 材料及方法

[0585] 材料:cAMP 动力学试剂盒获自 Cisbio International (Cisbio 62AM4PEJ)。Multidrop Combi (Thermo Scientific) 用于在测定中进行添加。EnVision (PerkinElmer) 读数器用于对 HTRF 读数。

[0586] 细胞培养:内部构建 HEK293T/hd1#1 稳定细胞系 (Pfizer Ann Arbor)。在 37℃ 下及 5% CO₂ 中,细胞在 Nunc T₅₀₀ 烧瓶中于高葡萄糖 DMEM (Invitrogen 11995-065)、10% 经透析的胎牛血清 (Invitrogen 26400-044)、1×MEM NEAA (Invitrogen 1140)、25mM HEPES (Invitrogen 15630)、1×青霉素/链霉素 (Invitrogen 15070-063) 及 500 μg/mL Genenticin (Invitrogen 10131-035) 中以黏着细胞形式生长。在生长 72 或 96 小时后,用 DPBS 冲洗细胞,且添加 0.25% 胰蛋白酶-EDTA 以使细胞移位。随后添加培养基,离心细胞,且移除培养基。将细胞小丸以 4e7 个细胞/mL 的密度再悬浮于细胞培养冷冻培养基 (Invitrogen 12648-056) 中。在低温小瓶中制得细胞的 1mL 等分部分,且在 -80℃ 下冷冻,供之后用于 D1HTRF 测定中。

[0587] D1cAMP HTRF 测定方法:将冷冻细胞快速解冻,再悬浮于 50mL 温热培养基中,且在

室温下静置 5 分钟,随后离心 (1000rpm)。移除培养基,且将细胞小丸再悬浮于 PBS/0.5 μ M IBMX 中,产生 2×10^5 个细胞 /mL。使用 Multidrop Combi 向已含有 5 μ L 测试化合物的测定板 (Greiner 784085) 上添加 5 μ L 细胞 / 孔。还在每一板上均包括化合物对照 [5 μ M 多巴胺 (最终) 及 0.5% DMSO (最终)] 以用于数据分析。在室温下孵育细胞及化合物 30 分钟。根据 Cisbio 说明书来制备 cAMP-D2 及抗 cAMP- 穴状化合物的工作溶液。使用 Multidrop 向含有测试化合物及细胞的测定板上添加 5 μ L cAMP-D2 工作溶液。使用 Multidrop 向含有测试化合物、细胞及 cAMP-D2 的测定板上添加 5 μ L 抗 cAMP- 穴状化合物工作溶液。在室温下孵育测定板 1 小时。在 EnVision 板读数器上使用 Cisbio 推荐设置来对测定板读数。使用在 Cisbio 药盒中所提供的 cAMP 储备溶液来生成 cAMP 标准曲线。

[0588] 数据分析 :使用计算机软件来进行数据分析。自化合物对照组来计算百分比效果。使用来自 EnVision 读数器的原始比率数据来测定比率 EC_{50} 。在分析程序中使用 cAMP 标准曲线来自原始比率数据测定 cAMP 浓度。使用所计算出的 cAMP 数据来测定 cAMP EC_{50} 。

[0589] 表 4. 实施例 1-47 的生物数据

[0590]

实施 例编 号	化合物IUPAC名称	人D1受体结 合, K_i (μM): 2-3次测定的 几何平均值	人D1 cAMP HTRF, EC_{50} (μM), 2-6次测 定的几何平均 值
1	4-[4-(4,6-二甲基嘧啶-5-基)-3-氟苯氧基]-1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶	0.0303 ^c	0.176 ^a
2	4-[4-(1,4-二甲基-1 <i>H</i> -吡唑-5-基)-3-甲基苯氧基]-1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶	0.0348 ^b	0.355
3	(+)-4,6-二甲基-5-[2-甲基-4-(1 <i>H</i> -吡唑并[4,3- <i>c</i>]吡啶-4-基氧基)苯基]哒嗪-3(2 <i>H</i>)-酮	0.00976	0.0151
4	(-)-4,6-二甲基-5-[2-甲基-4-(1 <i>H</i> -吡唑并[4,3- <i>c</i>]吡啶-4-基氧基)苯基]哒嗪-3(2 <i>H</i>)-酮	0.0104	0.0105
5	4-[4-(4,6-二甲基嘧啶-5-基)-3-甲基苯氧基]-1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶	0.0130 ^c	0.146 ^a
6	4-[4-(4,6-二甲基嘧啶-5-基)-3-甲基苯氧基]-1 <i>H</i> -吡唑并[4,3- <i>c</i>]吡啶	0.113 ^c	0.568 ^a
7	4,6-二甲基-5-[4-(1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶-4-基氧基)苯基]哒嗪-3(2 <i>H</i>)-酮	0.00412	0.0192 ^a
8	(-)-1,5-二甲基-6-[2-甲基-4-(1 <i>H</i> -吡唑并[4,3- <i>c</i>]吡啶-4-基氧基)苯基]嘧啶-2,4(1 <i>H</i> ,3 <i>H</i>)-二酮	0.00183	<0.00222 ^a
9	4,6-二甲基-5-[2-甲基-4-(1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶-4-基氧基)苯基]哒嗪-3(2 <i>H</i>)-酮, ENT-1	0.00487	0.00733 ^a
10	4,6-二甲基-5-[2-甲基-4-(1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶-4-基氧基)苯基]哒嗪-3(2 <i>H</i>)-酮, ENT-2	0.00504	0.00431
11	4-[4-(3,5-二甲基哒嗪-4-基)-3-甲基苯氧基]-1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶, ENT-1	0.0141 ^b	0.117
12	4-[4-(3,5-二甲基哒嗪-4-基)-3-甲基苯氧基]-1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶, ENT-2	0.0883 ^b	0.520
13	4-[4-(4,6-二甲基-1-氧化嘧啶-5-基)-3-甲基苯氧基]-1 <i>H</i> -吡唑并[4,3- <i>c</i>]吡啶	0.0931 ^b	0.260

[0591]

14	6-甲基-5-[2-甲基-4-(1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶-4-基氧基)苯基]咪唑并[1,2- <i>a</i>]吡嗪	0.00798 ^c	0.137
15	5-[2-甲基-4-(1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶-4-基氧基)苯基]咪唑并[1,2- <i>a</i>]吡嗪	0.0975	0.417
16	5-[2-氟-4-(1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶-4-基氧基)苯基]-6-甲基嘧啶-4-甲腈	0.0283	0.396
17	6-甲基-5-[2-甲基-4-(1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶-4-基氧基)苯基]嘧啶-4-甲腈	0.0392	0.374
18	5-[2-氟-4-(1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶-4-基氧基)苯基]-6-甲基咪唑并[1,2- <i>a</i>]吡嗪	0.0294 ^c	0.141
19	6-甲基-5-[4-(1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶-4-基氧基)苯基]咪唑并[1,2- <i>a</i>]吡嗪	0.0159	0.464 ^a
20	4-[4-(4,6-二甲基嘧啶-5-基)苯氧基]-1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶	0.0443	0.238
21	2-(4,6-二甲基嘧啶-5-基)-5-(1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶-4-基氧基)苯甲腈	0.102	0.247
22	4-[4-(4,6-二甲基嘧啶-5-基)-2,5-二氟苯氧基]-1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶	0.0548	0.538
23	4-[4-(4,6-二甲基嘧啶-5-基)-2,3-二氟苯氧基]-1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶	0.0538 ^c	0.590 ^a
24	4-[3-氯-4-(4,6-二甲基嘧啶-5-基)苯氧基]-1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶	0.00984	0.102
25	4-{3-氟-4-[4-(3-氟氮杂环丁烷-1-基)-6-甲基嘧啶-5-基]苯氧基}-1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶	0.00509	0.156
26	(-)-1,5-二甲基-6-[2-甲基-4-(1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶-4-基氧基)苯基]吡嗪-2(1 <i>H</i>)-酮	0.00456	0.0730
27	(+)-1,5-二甲基-6-[2-甲基-4-(1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶-4-基氧基)苯基]吡嗪-2(1 <i>H</i>)-酮	0.0106	0.0646
28	4-甲基-5-[2-甲基-4-(1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶-4-基氧基)苯基]哒嗪-3(2 <i>H</i>)-酮	0.0357	0.0549
29	6-甲基-5-[2-甲基-4-(1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶-4-基氧基)苯基]哒嗪-3(2 <i>H</i>)-酮	0.0679 ^b	0.119

[0592]

30	4-[3-甲基-4-(2-甲基-1 <i>H</i> -咪唑并[4,5- <i>c</i>]吡啶-1-基)苯氧基]-1 <i>H</i> -吡啶并[4,3- <i>c</i>]吡啶	0.268 ^b	2.76
31	6-甲基-5-[2-甲基-4-(1 <i>H</i> -吡啶并[4,3- <i>c</i>]吡啶-4-基氧基)苯基]哒嗪-3(2 <i>H</i>)-酮	0.287 ^b	0.548
32	4-[4-(4,6-二甲基嘧啶-5-基)-3-氟苯氧基]-1 <i>H</i> -吡啶并[4,3- <i>c</i>]吡啶	0.0723 ^b	0.903 ^a
33	4-[4-(4,6-二甲基嘧啶-5-基)-3-甲氧基苯氧基]-1 <i>H</i> -吡啶并[4,3- <i>c</i>]吡啶	0.124 ^b	2.08 ^a
34	2-(4,6-二甲基嘧啶-5-基)-5-(1 <i>H</i> -吡啶并[4,3- <i>c</i>]吡啶-4-基氧基)苯甲腈	0.391 ^b	2.38
35	5-[2-氟-4-(1 <i>H</i> -吡啶并[4,3- <i>c</i>]吡啶-4-基氧基)苯基]-6-甲基嘧啶-4-甲腈	0.0696 ^b	1.34
36	4-[4-(4,6-二甲基嘧啶-5-基)-2-氟-5-甲基苯氧基]-1 <i>H</i> -吡啶并[4,3- <i>c</i>]吡啶	0.118 ^b	0.733
37	4-[3-氯-4-(4,6-二甲基嘧啶-5-基)苯氧基]-1 <i>H</i> -吡啶并[4,3- <i>c</i>]吡啶	0.0523	0.248 ^a
38	4-[4-(4,6-二甲基嘧啶-5-基)苯氧基]-1 <i>H</i> -吡啶并[4,3- <i>c</i>]吡啶	0.129 ^b	2.52 ^a
39	(-)-1,5-二甲基-6-[2-甲基-4-(1 <i>H</i> -吡啶并[4,3- <i>c</i>]吡啶-4-基氧基)苯基]吡嗪-2(1 <i>H</i>)-酮	0.0418 ^c	0.168 ^a
40	(+)-1,5-二甲基-6-[2-甲基-4-(1 <i>H</i> -吡啶并[4,3- <i>c</i>]吡啶-4-基氧基)苯基]吡嗪-2(1 <i>H</i>)-酮	0.0281 ^b	0.674
41	4,6-二甲基-5-[4-(1 <i>H</i> -吡啶并[4,3- <i>c</i>]吡啶-4-基氧基)苯基]哒嗪-3(2 <i>H</i>)-酮	0.0409 ^c	0.127 ^a
42	4-甲基-5-[2-甲基-4-(1 <i>H</i> -吡啶并[4,3- <i>c</i>]吡啶-4-基氧基)苯基]哒嗪-3(2 <i>H</i>)-酮三氟乙酸盐	0.123	0.340
43	1,5-二甲基-6-[4-(1 <i>H</i> -吡啶并[4,3- <i>c</i>]吡啶-4-基氧基)苯基]嘧啶-2,4(1 <i>H</i> ,3 <i>H</i>)-二酮	0.0175	0.0282
44	4-[4-(4,6-二甲基嘧啶-5-基)-3-甲基苯氧基]-1 <i>H</i> -吡咯并[3,2- <i>c</i>]吡啶-3-甲腈	0.00460	0.0553 ^a
45	4,6-二甲基-5-{4-[(3-甲基-1 <i>H</i> -吡啶并[4,3- <i>c</i>]吡啶-4-基)氧基]苯基}哒嗪-3(2 <i>H</i>)-酮	0.0103	0.0663 ^a

[0593]

46	4,6-二甲基-5-{4-[(6-甲基-1 <i>H</i> -吡唑并[4,3- <i>c</i>]吡啶-4-基)氧基]苯基}哒嗪-3(2 <i>H</i>)-酮	0.0247	0.0891
47	5-{4-[(7-甲氧基-1 <i>H</i> -吡唑并[4,3- <i>c</i>]吡啶-4-基)氧基]苯基}-4,6-二甲基哒嗪-3(2 <i>H</i>)-酮	0.695 ^b	1.30

[0594] a. 值表示≥ 7 次测定的几何平均值。

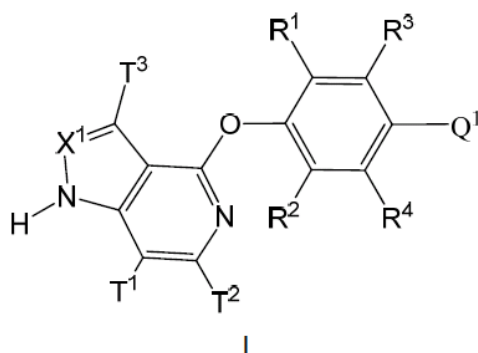
[0595] b. 值表示单次测定。

[0596] c. 值表示≥ 4 次测定的几何平均值。

[0597] 除本文中描述的那些外,根据前述描述,本发明的多种修改对本领域技术人员而言会是显而易见的。这样的修改也意图落入所附权利要求书的范围内。本申请中所引用的各参考文献(包括所有专利、专利申请、期刊文章、书籍及任何其它公开)均以其整体援引加入本文。

Abstract

The present invention provides, in part, compounds of Formula I:



and pharmaceutically acceptable salts thereof and *N*-oxides of the foregoing; processes for the preparation of; intermediates used in the preparation of; and compositions containing such compounds, salts or *N*-oxides, and their uses for treating D1-mediated (or D1-associated) disorders including, e.g., schizophrenia (e.g., its cognitive and negative symptoms), cognitive impairment (e.g., cognitive impairment associated with schizophrenia, AD, PD, or pharmacotherapy therapy), ADHD, impulsivity, compulsive gambling, overeating, autism spectrum disorder, MCI, age-related cognitive decline, dementia, RLS, Parkinson's disease, Huntington's chorea, anxiety, depression, MDD, TRD, and bipolar disorder.