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(54) Title: NOVEL JAK1 SELECTIVE INHIBITORS AND USES THEREOF

(57) Abstract: The new 1*H*-furo[3,2-*b*]imidazo[4,5-*d*]pyridine derivatives are selective Jak1 kinase inhibitors useful in treating disorders related to Jak1 activities such as autoimmune diseases or disorders, inflammatory diseases or disorders, and cancer or neoplastic diseases or disorders.

NOVEL JAK1 SELECTIVE INHIBITORS AND USES THEREOF

Cross-Reference to Related Applications

This application claims the priority of U.S. provisional application serial number 62/403,660, filed October 03, 2016, which is incorporated herein by reference in its entirety.

Technical Field of the Invention

This invention relates to novel 1*H*-furo[3,2-*b*]imidazo[4,5-*d*]pyridine derivatives, their pharmaceutically acceptable salts, solvates, hydrates and polymorphs thereof as selective Jak1 kinase inhibitors. The invention also provides compositions comprising a compound of this invention and the use of such compositions in methods of treating diseases and conditions associated with Jak1 and are useful in treating disorders related to Jak1 activities such as an autoimmune disease or disorder, an inflammatory disease or disorder, and a cancer or neoplastic disease or disorder.

Background of the Invention

The protein kinases represent a large family of proteins that play a central role in the regulation of a wide variety of cellular processes and maintenance of cellular function. A partial, non-limiting, list of these kinases include: non-receptor tyrosine kinases such as the Janus kinase family (Jak1, Jak2, Jak3 and Tyk2); receptor tyrosine kinases such as platelet-derived growth factor receptor kinase (PDGFR); and serine/threonine kinases such as b-RAF. Aberrant kinase activity has been observed in many disease states including benign and malignant proliferative disorders as well as diseases resulting from inappropriate activation of the immune and nervous systems. The compounds of this invention selectively inhibit the activity of one or more protein kinases over other related kinases, and are thus expected to be useful in the treatment of diseases mediated by the selectively inhibited kinase(s) while avoiding the undesirable side effects associated with the inhibition of the related kinase(s).

In particular, the Janus kinase family comprises 4 known family members: Jak l, 2, 3, and tyrosine kinase 2 (Tyk2). These cytoplasmic tyrosine kinases are associated with membrane cytokine receptors such as common gamma-chain receptors and the glycoprotein 130 (gp 130) trans-membrane proteins (Murray, *J. Immunol.* 178(5):2623-2629, **2007**). Almost 40 cytokine receptors signal through combinations of these 4 Jak family members and their 7 downstream substrates: the signal transduction activators of transcription (STAT) family members (Ghoreschi *et al.*, *Immunol Rev.* 228(1):273-287, **2009**). Cytokine binding to its receptor initiates Jak activation via trans- and auto-phosphorylation. The Jak family kinases in turn phosphorylate cytokine receptor residues, creating binding sites for sarcoma homology 2 (SH2) containing proteins, such as the STAT factors and other regulators, which are subsequently activated by Jak phosphorylation. Activated STATs enter the nucleus initiating expression of survival factors, cytokines, chemokines, and molecules that facilitate leukocyte cellular trafficking (Schindler *et al.*, *J. Biol. Chem.* 282(28):20059-20063, **2007**). Jak activation also results in cell proliferation via phosphoinositide 3-kinase (PI3K) and protein kinase B-mediated pathways.

Jak3 and Jak1 are components of the common gamma-chain cytokine receptor complexes, and blockade of either inhibits signaling by inflammatory cytokines: interleukin (IL) -2, 4, 7, 9, 15, and 21 (Ghoreschi *et al.*, *Immunol. Rev.* 228(1):273-287, **2009**). By contrast, other pathologically relevant cytokines, such as IL-6, depend uniquely on Jak1. Hence, Jak1 blockade inhibits signaling of many pro-inflammatory cytokines (Guschin *et al.*, EMBO J. 14(7):1421-1429, **1995**). Clinical efficacy in rheumatoid arthritis (RA) has been observed with the IL-6 receptor neutralizing antibody, tocilizumab (Maini *et al.*, *Arthritis Rheum.* 54(9):2817-2829, **2006**).

Humans deficient in Jak1 and Jak2 have not been described. Mice lacking Jak1 die perinatally (Schindler *et al.*, *J. Biol Chem.* 282(28):20059-20063, **2007**). Jak2 deficiency in mice is also lethal, with $Jak2^{-/-}$ embryos dying between Day 12 and Day 13 after conception because of deficits in erythropoiesis (Neubauer *et al.*, *Cell* 93(3):397-409, **1998**). Jak3 deficiency has been described in humans and presents as severe combined immunodeficiency in the first few months of life, with symptoms such as failure to thrive, severe and recurrent infections, thrush, and diarrhea. Infants with Jak3 deficiency have an absence of circulating T cells and NK cells and abnormal B cell function. Tyk2-deficiency additionally has been described in humans,

manifesting with impaired antimicrobial responses, elevated serum IgE, and atopic dermatitis (Minegishi *et al.*, *Immunity* 25(5):745-755, **2006**).

Given the high degree of structural similarity between Jak1 and Jak2 (Williams *et al.*, *J. Mal. Biol.* 387(1):219-232, **2009**), the literature suggests that the majority of Jak1 inhibitors also inhibit Jak2 (Incyte Corp. press release, 10 Nov. 2010; Changelian *et al.*, *Science* 302(5646):875-878, **2003**).

Anti-cytokine therapies have become standard in the treatment of RA. In humans, a growing body of evidence suggests that Jak1 inhibition is an effective therapy for the treatment of signs and symptoms of RA. Multiple clinical trials administering Pfizer's Jak 1/3 inhibitor tofacitinib (Kremer *et al.*, *Arthritis Rheum.* 60(7):1895-1905, **2009**; Riese *et al. Best Pract. Res. Clin. Rheumatol.* 24(4):513-526, **2010**), Incyte/Lilly's Jak1/2 inhibitor INCB-28050/LY3009104 (Incyte Corp. press release, 10 Nov 2010), or Galapagos' Jak1 inhibitor GLP0634 (Galapagos NV press release, 22 Nov 2011) have demonstrated statistically significant efficacy in this disease.

Tofacitinib, an inhibitor of Jak1, and Jak3, has been approved in the United States and additional countries around the world for the indication of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate (MTX), used as monotherapy or in combination with MTX or other non-biologic DMARDs. Safety data from Phase 2 and Phase 3 studies in patients (Fleischmann, *Curr. Opin. Rheumatol.* 24(3):335-341, **2012**; Kremer et al., *Arthritis Rheum.* 64(4):970-981, **2012**; Fleischmann *et al.*, *Arthritis Rheum.* 64(3):617-629, **2012**) with RA for tofacitinib compared with placebo have indicated that the most common serious adverse reactions are infections, including pneumonia, cellulitis, herpes zoster, and urinary tract infection. In addition, tuberculosis (including cases of disseminated tuberculosis) and opportunistic infections such as other mycobacterial infections, cryptococcus, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus, and BK virus were reported. Lymphoma and other malignancies have been observed in patients treated with tofacitinib. Epstein-Barr virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with tofacitinib and concomitant immunosuppressive medications. Gastrointestinal perforations in patients receiving tofacitinib also were reported. In addition, laboratory

abnormalities have been described, including dose-related decreases in absolute neutrophil counts as well as hemoglobin. Furthermore, small increases in liver transaminases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) and serum creatinine, and elevated LDL, HDL, and total cholesterol levels have been reported.

A Phase 2 study of VX-509 (inhibitor of Jak3) in patients with RA also has shown an increased risk of infections and increases in lipid levels (Fleischmann et al., Arthritis Rheum. 63:LB3, 2011).

A 52-week, open-label, long-term extension Phase 2b study of baricitinib - an orally administered selective Jak1 and Jak2 inhibitor - in 201 patients with active RA found no opportunistic infections, cases of tuberculosis, or lymphomas. Clinically significant laboratory abnormalities were infrequently observed (increased ALT, anemia, increased creatine kinase [CK], pancytopenia, reported in one subject each); one subject discontinued due to a laboratory abnormality (increased ALT). One death occurred and was attributed to presumed myocardial infarction (Keystone *et al.*, *Ann. Rheum. Dis.* 71(Suppl 3):152, **2012**; Genovese *et al.*, *Arthritis Rheum.* 64 (Suppl 10):2487, **2012**; Taylor *et al.*, abstract OP0047, EULAR **2013**, the Annual Congress of the European League Against Rheumatism. 2013 Jun 12-15; Madrid, Spain).

Despite the seemingly numerous treatment options, however, many RA patients fail to experience substantial decreases in disease activity. Although earlier studies have shown that Jak blockade may be effective in managing disease and achieving remission, the first generation Jak inhibitors (such as tofacitinib and baricitinib) have failed to reach their full potential, at least partly due to their tolerability and safety issues that limit dose.

Specifically, the first generation Jak inhibitors tofacitinib and baricitinib have been characterized as Jak1/Jak3 and Jak1/Jak2 inhibitors, respectively (Fridman *et al.*, *J. Immunol.*, 184:5298-5307, **2010**; Meyer *et al.*, *J. Inflamm.* (Lond.) 7:41, **2010**; and Taylor *et al.*, *Rheumatology* 52:i44-i55, **2013**). Despite the initial encouraging results, these first generation Jak inhibitors have failed to reach their full potential due to tolerability issues that limited dose (Fleischmann *et al.*, *Curr. Opin. Rheumatol.* 24:335-341, **2012**; Riese *et al.*, *Best Pract. Res. Clin. Rheumatol.* 24:513-526, **2010**). JAKs are known to play roles in the regulation of over forty pathways (Murray, *J. Immunol.* 178:2623-2629, **2007**). However, despite the high selectivity of these two compounds for JAKs over other kinase families, these inhibitors may not be optimally

selective for kinases within the JAK family. For instance, incidence of severe anemia was reported to be a dose limiting factor during Tofacitinib Phase II development in RA (Pfizer, Investigators Brochure. In FDA Advisory Board (Bethesda MD), 2012; Riese *et al.*, *Best Pract. Res. Clin. Rheumatol.* 24:513-526, **2010**). Moreover, increases in herpes virus infections, potentially secondary to decreases in NK cell counts, were reported in Phase III tofacitinib trials (O'Shea *et al.*, *Ann. Rheum. Dis.* 72(Suppl 2):ii111-115, **2013**; Pfizer, Investigators Brochure. In FDA Advisory Board (Bethesda MD), 2012). It is reasonable that these effects could arise due to inhibition of EPO and IL-15 signaling via Jak2 and Jak3 respectively (Jost and Altfeld, *Annu. Rev. Immunol.* 31:163-194, **2013**; Kennedy *et al.*, *J. Exp. Med.* 191:771-780, **2000**; and Richmond *et al.*, *Trends Cell Biol.* 15:146-155, **2005**). Indeed, failure of interventions to treat anemia associated with RA may limit chances for a fully successful response to treatment.

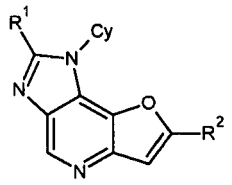
Thus, there is a medical need unmet by the current treatment options using Jak inhibitors. Efforts to identify Jak1 selective inhibitors are on-going (Zak et al. *J. Med. Chem.* **2013**, 56, 4764–4785; Menet et al. *Future Med. Chem.* **2015**, 7, 203–235; WO2013/007768). Prominent Jak1 selective compounds in development are GLP0634, ABT-494 (WO2015/061665), and the compound in a recent patent publication from Incyte (WO2015/168246), but no Jak1 selective inhibitor has been approved yet.

Herein, novel 1*H*-furo[3,2-*b*]imidazo[4,5-*d*]pyridine derivatives are described as Jak1 selective inhibitors. These compounds, and compositions comprising a compound of this invention are useful in treating disorders related to Jak1 activities such as an autoimmune disease or disorder, or an inflammatory disease or disorder, and a cancer or neoplastic disease or disorder.

Summary of the Invention

This invention discloses novel 1*H*-furo[3,2-*b*]imidazo[4,5-*d*]pyridine derivatives their pharmaceutically acceptable salts, solvates, hydrates and polymorphs thereof as selective Jak1 kinase inhibitors. The invention also provides compositions comprising a compound of this invention and the use of such compositions in methods of treating diseases and conditions associated with Jak1.

The present invention solves the problems set forth above by providing an isolated compound of Formula I:

I 

,

or a pharmaceutically acceptable salt thereof; or a prodrug, or a pharmaceutically acceptable salt of a prodrug thereof; or a hydrate, solvate, or polymorph thereof; wherein:

R^1 is H, halo, or C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, OH, CN, OR, NHR, NRR', N(R)C(=O)R', N(R)C(=O)(O)R', OC(=O)NRR', C(=O)R, C(=O)NRR', $N(R)S(O)_2R'$, $S(O)_2R$, and $S(O)_2NRR'$;

R^2 is H, halo, or C_{1-3} alkyl;

Cy is C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl, each optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of R^3, oxo, halo, OH, CN, OR, NHR, NRR', N(R)C(=O)R', N(R)C(=O)(O)R', OC(=O)NRR', C(=O)R, C(=O)NRR', $N(R)S(O)_2R'$, $S(O)_2R$, and $S(O)_2NRR'$, wherein R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, OH, CN, OR, NHR, NRR', N(R)C(=O)R', N(R)C(=O)(O)R', OC(=O)NRR', C(=O)R, C(=O)NRR', $N(R)S(O)_2R'$, $S(O)_2R$, and $S(O)_2NRR'$;

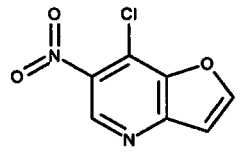
R, R' each is independently H, or C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, OH, and CN.

The compounds of this invention, and compositions comprising them, are useful for treating or lessening the severity of Jak1 modulated diseases, disorders, or symptoms thereof.

In another aspect, the invention relates to a method of treating a disease or disease symptom in a subject in need thereof including administering to the subject an effective amount of a compound of formula I herein, or pharmaceutically acceptable salt, solvate or hydrate thereof (or composition thereof). The disease or disease symptom can be any of those modulated

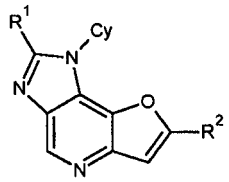
by Jak1. The disease or disease symptom can be, for example, an autoimmune disease or disorder such as rheumatoid arthritis or an inflammatory disease or disorder, and cancer or neoplastic proliferative disease or disorder (e.g., including those delineated herein).

In another aspect, the invention relates to a compound of formula A1-14:

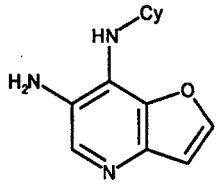
A1-14 

useful for the process of making compounds of formula I.

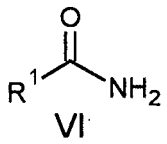
In another aspect, the invention relates to a process of preparing a compound of formula I:

I 

comprising contacting a compound of formula V:

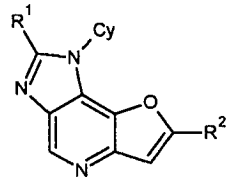
V 

and a compound of formula VI:



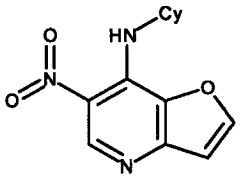
VI

in the presence of a $(C_{1-6})_3$ alkyloxonium tetrafluoroborate at sufficient temperature, and for sufficient time to produce a compound of formula I:

I 

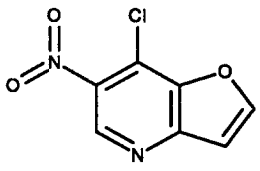
wherein R^2 is H, and R^1 and Cy are as defined above. The $(C_{1-6})_3$ alkyloxonium tetrafluoroborate can be triethyloxonium tetrafluoroborate.

In another aspect, the invention relates to a process of preparing compound of formula V comprising reducing a compound of formula VII:

VII 

in the presence of a hydrogenation catalyst and hydrogen gas at sufficient temperature, sufficient pressure and for sufficient time to produce a compound of formula V wherein Cy is as defined above. The hydrogenation catalyst can be palladium on carbon.

In another aspect, the invention relates to a process preparing compound of formula VII comprising contacting a compound of formula A1-14:

A1-14 

and a compound of formula VIII:

$$Cy—NH_2$$

VIII

in the presence of a base at sufficient temperature, and for sufficient time to produce a compound of formula VII wherein Cy is as defined above. The base can be N,N-Diisopropylethylamine.

Detailed Description of the Invention

Definitions

The terms "ameliorate" and "treat" are used interchangeably and both mean decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease (e.g., a disease or disorder delineated herein).

By "disease" is meant any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ.

By "marker" is meant any alteration that is associated with a disease or disorder. For example, any protein or polynucleotide having an alteration in expression level or activity that is associated with a disease or disorder.

In this disclosure, "comprises," "comprising," "containing" and "having" and the like can have the meaning ascribed to them in U.S. Patent law and can mean " includes," "including," and the like; "consisting essentially of" or "consists essentially" likewise has the meaning ascribed in U.S. Patent law and the term is open-ended, allowing for the presence of more than that which is recited so long as basic or novel characteristics of that which is recited is not changed by the presence of more than that which is recited, but excludes prior art embodiments.

The term "compound" as used herein, is also intended to include pharmaceutically acceptable salts, prodrugs, and prodrug salts of a compound of formulae herein. The term also includes any solvates, hydrates, and polymorphs of any of the foregoing. The specific recitation of "prodrug," "prodrug salt," "solvate," "hydrate," or "polymorph" in certain aspects of the invention described in this application shall not be interpreted as an intended omission of these forms in other aspects of the invention where the term "compound" is used without recitation of these other forms.

A salt of a compound of this invention is formed between an acid and a basic group of the compound, such as an amino functional group, or a base and an acidic group of the compound, such as a carboxyl functional group. According to another preferred embodiment, the compound is a pharmaceutically acceptable acid addition salt.

As used herein and unless otherwise indicated, the term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide a compound of this invention. Prodrugs may only become active upon such

reaction under biological conditions, or they may have activity in their unreacted forms. Examples of prodrugs contemplated in this invention include, but are not limited to, analogs or derivatives of compounds of any one of the formulae disclosed herein that comprise biohydrolyzable moieties such as amides, esters, carbamates, carbonates, and phosphate analogues. Prodrugs can typically be prepared using well-known methods, such as those described by Burger's Medicinal Chemistry and Drug Discovery (1995) 172-178, 949-982 (Manfred E. Wolff ed., 5th ed); see also Goodman and Gilman's, The Pharmacological basis of Therapeutics, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs".

As used herein and unless otherwise indicated, the term "biohydrolyzable moiety" means a functional group (e.g., amide, ester, carbamate, carbonate, or phosphate analogue, that either: 1) does not destroy the biological activity of the compound and confers upon that compound advantageous properties in vivo, such as uptake, duration of action, or onset of action; or 2) is itself biologically inactive but is converted in vivo to a biologically active compound.

A prodrug salt is a compound formed between an acid and a basic group of the prodrug, such as an amino functional group, or a base and an acidic group of the prodrug, such as a carboxyl functional group. In a one embodiment, the prodrug salt is a pharmaceutically acceptable salt.

Particularly favored prodrugs and prodrug salts are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or central nervous system) relative to the parent species. Preferred prodrugs include derivatives where a group that enhances aqueous solubility or active transport through the gut membrane is appended to the structure of formulae described herein. See, e.g., Alexander, J. et al. Journal of Medicinal Chemistry 1988, 31, 318-322; Bundgaard, H. Design of Prodrugs; Elsevier: Amsterdam, 1985; pp 1-92; Bundgaard, H.; Nielsen, N. M. Journal of Medicinal Chemistry 1987, 30, 451-454; Bundgaard, H. A Textbook of Drug Design and Development; Harwood Academic Publ.: Switzerland, 1991; pp 113-191; Digenis, G. A. et al. Handbook of Experimental Pharmacology 1975, 28, 86-112; Friis, G. J.; Bundgaard, H. A Textbook of Drug Design and Development; 2 ed.; Overseas Publ.: Amsterdam, 1996; pp 351-385; Pitman, I. H. Medicinal Research Reviews 1981, 1, 189-214.

The term "pharmaceutically acceptable," as used herein, refers to a component that is, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. A "pharmaceutically acceptable salt" means any non-toxic salt that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound or a prodrug of a compound of this invention.

Acids commonly employed to form pharmaceutically acceptable salts include inorganic acids such as hydrogen bisulfide, hydrochloric, hydrobromic, hydroiodic, sulfuric and phosphoric acid, as well as organic acids such as para-toluenesulfonic, salicylic, tartaric, bitartaric, ascorbic, maleic, besylic, fumaric, gluconic, glucuronic, formic, glutamic, methanesulfonic, ethanesulfonic, benzenesulfonic, lactic, oxalic, para-bromophenylsulfonic, carbonic, succinic, citric, benzoic and acetic acid, and related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-l,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, terephathalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, □-hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2- sulfonate, mandelate and the like salts. Preferred pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and especially those formed with organic acids such as maleic acid.

Suitable bases for forming pharmaceutically acceptable salts with acidic functional groups of prodrugs of this invention include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methyl,N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-lower alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-tert-butylamine, or tris-(hydroxymethyl)methylamine, N, N,-

di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N,N-dimethyl-N-(2-hydroxyethyl)amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like.

As used herein, the term "hydrate" means a compound which further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

As used herein, the term "solvate" means a compound which further includes a stoichiometric or non-stoichiometric amount of solvent such as water, acetone, ethanol, methanol, dichloromethane, 2-propanol, or the like, bound by non-covalent intermolecular forces.

As used herein, the term "polymorph" means solid crystalline forms of a compound or complex thereof which may be characterized by physical means such as, for instance, X-ray powder diffraction patterns or infrared spectroscopy. Different polymorphs of the same compound can exhibit different physical, chemical and/or spectroscopic properties. Different physical properties include, but are not limited to stability (e.g., to heat, light or moisture), compressibility and density (important in formulation and product manufacturing), hygroscopicity, solubility, and dissolution rates (which can affect bioavailability). Differences in stability can result from changes in chemical reactivity (e.g., differential oxidation, such that a dosage form discolors more rapidly when comprised of one polymorph than when comprised of another polymorph) or mechanical characteristics (e.g., tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically more stable polymorph) or both (e.g., tablets of one polymorph are more susceptible to breakdown at high humidity). Different physical properties of polymorphs can affect their processing. For example, one polymorph might be more likely to form solvates or might be more difficult to filter or wash free of impurities than another due to, for example, the shape or size distribution of particles of it.

The term "substantially free of other stereoisomers" as used herein means less than 25% of other stereoisomers, preferably less than 10% of other stereoisomers, more preferably less than 5% of other stereoisomers and most preferably less than 2% of other stereoisomers, or less than "X"% of other stereoisomers (wherein X is a number between 0 and 100, inclusive) are present. Methods of obtaining or synthesizing diastereomers are well known in the art and may be

applied as practicable to final compounds or to starting material or intermediates. Other embodiments are those wherein the compound is an isolated compound. The term "at least X% enantiomerically enriched" as used herein means that at least X% of the compound is a single enantiomeric form, wherein X is a number between 0 and 100, inclusive.

The term "stable compounds", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintain the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., formulation into therapeutic products, intermediates for use in production of therapeutic compounds, isolatable or storable intermediate compounds, treating a disease or condition responsive to therapeutic agents).

"Stereoisomer" refers to both enantiomers and diastereomers.

As used herein, the term "halo" or "halogen" refers to any radical of fluorine, chlorine, bromine or iodine.

The terms "alk" or "alkyl" refer to straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms. The expression "lower alkyl" refers to alkyl groups of 1 to 4 carbon atoms (inclusive).

The term "arylalkyl" refers to a moiety in which an alkyl hydrogen atom is replaced by an aryl group.

The term "alkenyl" refers to straight or branched chain hydrocarbon groups of 2 to 10, preferably 2 to 4, carbon atoms having at least one double bond. Where an alkenyl group is bonded to a nitrogen atom, it is preferred that such group not be bonded directly through a carbon bearing a double bond.

The term "alkoxy" refers to an -O-alkyl radical. The term "alkylenedioxo" refers to a divalent species of the structure -O-R-O-, in which R represents an alkylene.

The term "alkynyl" refers to straight or branched chain hydrocarbon groups of 2 to 10, preferably 2 to 4, carbon atoms having at least one triple bond. Where an alkynyl group is bonded to a nitrogen atom, it is preferred that such group not be bonded directly through a carbon bearing a triple bond.

The term "alkylene" refers to a divalent straight chain bridge of 1 to 5 carbon atoms connected by single bonds (e.g., $-(CH_2)_x-$, wherein x is 1 to 5), which may be substituted with 1 to 3 lower alkyl groups.

The term "alkenylene" refers to a straight chain bridge of 2 to 5 carbon atoms having one

or two double bonds that is connected by single bonds and may be substituted with 1 to 3 lower alkyl groups. Exemplary alkenylene groups are -CH=CH-CH=CH-, -CH_2-CH=CH-, -CH_2-CH=CH-CH_2-, -$C(CH_3)_2$CH=CH- and -$CH(C_2H_5)$-CH=CH-.

The term "alkynylene" refers to a straight chain bridge of 2 to 5 carbon atoms that has a triple bond therein, is connected by single bonds, and may be substituted with 1 to 3 lower alkyl groups. Exemplary alkynylene groups are –C≡C-, -CH_2-C≡C-, -$CH(CH_3)$C≡C- and –C≡C-$CH(C_2H_5)CH_2$-.

The terms “cycloalkyl” and "cycloalkenyl" as employed herein includes saturated and partially unsaturated cyclic, respectively, hydrocarbon groups having 3 to 12 carbons, preferably 3 to 8 carbons, and more preferably 3 to 6 carbons.

The terms "Ar" or "aryl" refer to aromatic cyclic groups (for example 6 membered monocyclic, 10 membered bicyclic or 14 membered tricyclic ring systems) which contain 6 to 14 carbon atoms. Exemplary aryl groups include phenyl, naphthyl, biphenyl and anthracene.

“Heteroaryl” refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group of 5 to 12 ring atoms containing one, two, three or four ring heteroatoms selected from N, O, or S, the remaining ring atoms being C, and, in addition, having a completely conjugated pi-electron system, wherein 0, 1, 2, 3, or 4 atoms of each ring may be substituted by a substituent.. Examples, without limitation, of heteroaryl groups are pyrrole, furan, thiophene, imidazole, oxazole, thiazole, pyrazole, pyridine, pyrimidine, quinoline, quinazoline, isoquinoline, purine and carbazole.

The terms "heterocycle", "heterocyclic"or "heterocyclo" refer to fully saturated or partially unsaturated cyclic groups, for example, 3 to 7 membered monocyclic, 7 to 12 membered bicyclic, or 10 to 15 membered tricyclic ring systems, which have at least one heteroatom in at least one ring, wherein 0, 1, 2 or 3 atoms of each ring may be substituted by a substituent. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system.

The term “heterocyclyl” refers to fully saturated or partially unsaturated cyclic groups, for example, 3 to 7 membered monocyclic, 7 to 12 membered bicyclic, or 10 to 15 membered

tricyclic ring systems, which have at least one heteroatom in at least one ring, wherein 0, 1, 2 or 3 atoms of each ring may be substituted by a substituent. Each ring of the heterocyclyl group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclyl group may be attached at any heteroatom or carbon atom of the ring or ring system.

The term "substituents" refers to a group "substituted" on any functional group delineated herein, e.g., alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heterocyclyl, or heteroaryl group at any atom of that group. Suitable substituents include, without limitation halogen, CN, NO_2, OR^{15}, SR^{15}, $S(O)_2OR^{15}$, $NR^{15}R^{16}$, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, 1,2-methylenedioxy, $C(O)OR^{15}$, $C(O)NR^{15}R^{16}$, $OC(O)NR^{15}R^{16}$, $NR^{15}C(O)NR^{15}R^{16}$, $C(NR^{16})NR^{15}R^{16}$, $NR^{15}C(NR^{16})NR^{15}R^{16}$, $S(O)_2NR^{15}R^{16}$, R^{17}, $C(O)R^{17}$, $NR^{15}C(O)R^{17}$, $S(O)R^{17}$, $S(O)_2R^{17}$, R^{16}, oxo, $C(O)R^{16}$, $C(O)(CH_2)nOH$, $(CH_2)nOR^{15}$, $(CH_2)nC(O)NR^{15}R^{16}$, $NR^{15}S(O)_2R^{17}$, where n is independently 0-6 inclusive. Each R^{15} is independently hydrogen, C_1-C_4 alkyl or C_3-C_6 cycloalkyl. Each R^{16} is independently hydrogen, alkenyl, alkynyl, C_3-C_6 cycloalkyl, aryl, heterocyclyl, heteroaryl, C_1-C_4 alkyl or C_1-C_4 alkyl substituted with C_3-C_6 cycloalkyl, aryl, heterocyclyl or heteroaryl. Each R^{17} is independently C_3-C_6 cycloalkyl, aryl, heterocyclyl, heteroaryl, C_1-C_4 alkyl or C_1-C_4 alkyl substituted with C_3-C_6 cycloalkyl, aryl, heterocyclyl or heteroaryl. Each C_3-C_6 cycloalkyl, aryl, heterocyclyl, heteroaryl and C_1-C_4 alkyl in each R^{15}, R^{16} and R^{17} can optionally be substituted with halogen, CN, C_1-C_4 alkyl, OH, C_1-C_4 alkoxy, NH_2, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, or 1,2-methylenedioxy.

The term "oxo" refers to an oxygen atom, which forms a carbonyl when attached to carbon, an N-oxide when attached to nitrogen, and a sulfoxide or sulfone when attached to sulfur.

The term "acyl" refers to an alkylcarbonyl, cycloalkylcarbonyl, arylcarbonyl, heterocyclylcarbonyl, or heteroarylcarbonyl substituent, any of which may be further substituted by substituents.

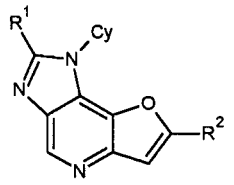
The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable herein includes that embodiment as any single embodiment or in

combination with any other embodiments or portions thereof.

The compounds of this invention may contain one or more asymmetric centers and thus occur as racemates and racemic mixtures, single enantiomers, individual diastereomers and diastereomeric mixtures, as well as cis and trans geometric isomers. All such isomeric forms of these compounds are expressly included in the present invention. The compounds of this invention may also be represented in multiple tautomeric forms, in such instances, the invention expressly includes all tautomeric forms of the compounds described herein. All such isomeric forms of such compounds are expressly included in the present invention. All crystal forms of the compounds described herein are expressly included in the present invention.

Compounds of the Invention

In one aspect, the present invention provides a compound of Formula **I**:

I 

,

or a pharmaceutically acceptable salt thereof; or a prodrug, or a pharmaceutically acceptable salt of a prodrug thereof; or a hydrate, solvate, or polymorph thereof; wherein:

R^1 is H, halo, or C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, OH, CN, OR, NHR, NRR', N(R)C(=O)R', N(R)C(=O)(O)R', OC(=O)NRR', C(=O)R, C(=O)NRR', $N(R)S(O)_2R'$, $S(O)_2R$, and $S(O)_2NRR'$;

R^2 is H, halo, or C_{1-3} alkyl;

Cy is C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl, each optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of R^3, oxo, halo, OH, CN, OR, NHR, NRR', N(R)C(=O)R', N(R)C(=O)(O)R', OC(=O)NRR', C(=O)R, C(=O)NRR', $N(R)S(O)_2R'$, $S(O)_2R$, and $S(O)_2NRR'$, wherein R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from the group

consisting of halo, OH, CN, OR, NHR, NRR', N(R)C(=O)R', N(R)C(=O)(O)R', OC(=O)NRR', C(=O)R, C(=O)NRR', $N(R)S(O)_2R'$, $S(O)_2R$, and $S(O)_2NRR'$;

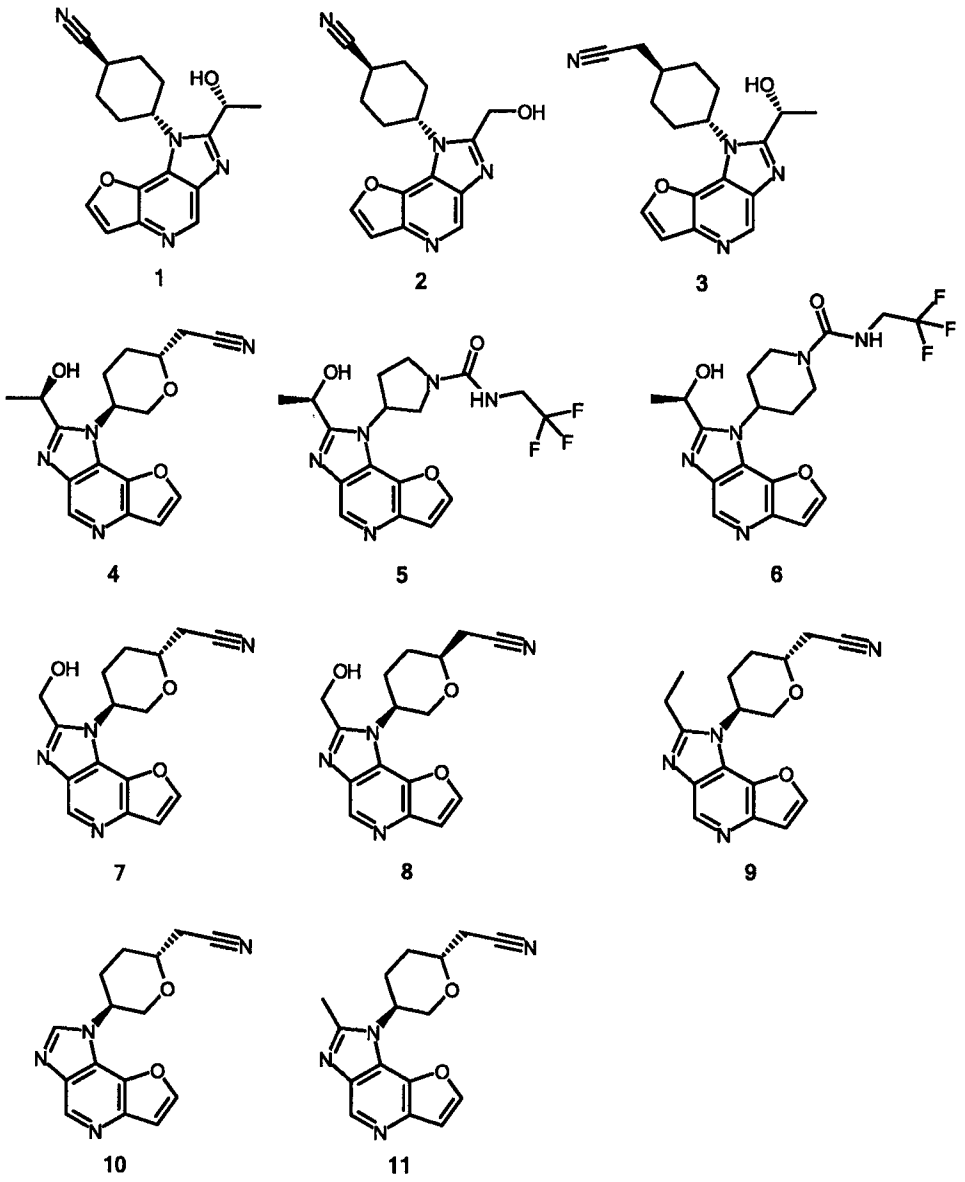
R, R' each is independently H, or C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, OH, and CN.

In another aspect Cy can be C_{5-7} cycloalkyl, or 5-7 membered heterocyclyl, each optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of R^3, oxo, halo, OH, CN, OR, NHR, NRR', N(R)C(=O)R', N(R)C(=O)(O)R', OC(=O)NRR', C(=O)R, C(=O)NRR', $N(R)S(O)_2R'$, $S(O)_2R$, and $S(O)_2NRR'$, wherein R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, OH, CN, OR, NHR, NRR', N(R)C(=O)R', N(R)C(=O)(O)R', OC(=O)NRR', C(=O)R, C(=O)NRR', $N(R)S(O)_2R'$, $S(O)_2R$, and $S(O)_2NRR'$.

In another aspect R^2 can be hydrogen.

Representative compounds of the invention are depicted in Table 1. In these examples the stereochemistry at the chiral carbon atoms is independently either *RS*, *R*, or *S*, unless specified. For compounds **4**, **7-11**, the stereochemistry shows only one of the *trans* or *cis* isomers, and the structures of their respective isomers are not shown. The structures depicted herein, including the Table 1 structures, may contain certain -NH-, $-NH_2$ (amino) and –OH (hydroxyl) groups where the corresponding hydrogen atom(s) do not explicitly appear; however they are to be read as –NH-, $-NH_2$ or –OH as the case may be. In certain structures, a stick bond is drawn and is meant to depict a methyl group.

Table 1



Representative compounds of the invention are listed below:

trans-4-[2-[(*R*)-1-Hydroxyethyl]-1H-furo[3,2-b] imidazo[4,5-d]pyridin-1-yl] cyclohexanecarbonitrile (**1**);

trans-4-[2-(Hydroxymethyl)furo[3,2-b]imidazo[4,5-d]pyridin-1-yl] cyclohexanecarbonitrile (**2**);

2-[*trans*-4-[2-[(*R*)-1-Hydroxyethyl]furo[3,2-b]imidazo[4,5-d]pyridin-1-yl]cyclohexyl] acetonitrile (**3**);

2-[(2*R*,5*S*)-5-[2-[(*R*)-1-Hydroxyethyl]furo[3,2-b]imidazo[4,5-d]pyridin-1-yl] tetrahydropyran-2-yl]acetonitrile (**4**);

3-[2-[(*R*)-1-Hydroxyethyl]-1H-furo[3,2-b]imidazo[4,5-d]pyridin-1-yl]-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide (**5**);

(*R*)-4-[2-(1-Hydroxyethyl)-1H-furo[3,2-b]imidazo[4,5-d]pyridin-1-yl]-N-(2,2,2-trifluoroethyl)piperidine-1-carboxamide (**6**);

2-[(2R,5S)-5-[2-(Hydroxymethyl)furo[3,2-b]imidazo[4,5-d]pyridin-1-yl]tetrahydropyran-2-yl]acetonitrile (7);

2-[(2S,5S)-5-[2-(Hydroxymethyl)furo[3,2-b]imidazo[4,5-d]pyridin-1-yl]tetrahydropyran-2-yl]acetonitrile (**8**),

2-[(2*R*,5*S*)-5-[2-Ethylfuro[3,2-b]imidazo[4,5-d] pyridin-1-yl] tetrahydropyran-2-yl]acetonitrile (**9**),

2-[(2*R*,5*S*)-5-[2-Furo[3,2-b]imidazo[4,5-d] pyridin-1-yl] tetrahydropyran-2-yl]acetonitrile (**10**),

2-[(2*R*,5*S*)-5-[2-Methylfuro[3,2-b]imidazo[4,5-d] pyridin-1-yl] tetrahydropyran-2-yl]acetonitrile (**11**).

The synthesis of compounds of the formulae herein can be readily effected by synthetic chemists of ordinary skill. Relevant procedures and intermediates are disclosed, for instance, herein. Each of the patents, patent applications, and publications, whether in traditional journals or available only through the internet, referred to herein, is incorporated in its entirety by reference.

Other approaches to synthesizing compounds of the formulae herein can readily be adapted from references cited herein. Variations of these procedures and their optimization are within the skill of the ordinary practitioner.

The specific approaches and compounds shown above are not intended to be limiting. The chemical structures in the schemes herein depict variables that are hereby defined

commensurately with chemical group definitions (moieties, atoms, etc.) of the corresponding position in the compound formulae herein, whether identified by the same variable name (e.g., R^1, R^2, R, R', X, etc.) or not. The suitability of a chemical group in a compound structure for use in synthesis of another compound structure is within the knowledge of one of ordinary skill in the art. Additional methods of synthesizing compounds of the formulae herein and their synthetic precursors, including those within routes not explicitly shown in schemes herein, are within the means of chemists of ordinary skill in the art. Methods for optimizing reaction conditions, if necessary minimizing competing by-products, are known in the art. The methods described herein may also additionally include steps, either before or after the steps described specifically herein, to add or remove suitable protecting groups in order to ultimately allow synthesis of the compounds herein. In addition, various synthetic steps may be performed in an alternate sequence or order to give the desired compounds. Synthetic chemistry transformations and protecting group methodologies (protection and deprotection) useful in synthesizing the applicable compounds are known in the art and include, for example, those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof.

The methods delineated herein contemplate converting compounds of one formula to compounds of another formula. The process of converting refers to one or more chemical transformations, which can be performed *in situ*, or with isolation of intermediate compounds. The transformations can include reacting the starting compounds or intermediates with additional reagents using techniques and protocols known in the art, including those in the references cited herein. Intermediates can be used with or without purification (e.g., filtration, distillation, sublimation, crystallization, trituration, solid phase extraction, and chromatography).

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds.

The invention also provides compositions comprising an effective amount of a compound of any of the formulae herein, or a pharmaceutically acceptable salt, solvate, hydrate, polymorph

or prodrug, if applicable, of said compound; and an acceptable carrier. Preferably, a composition of this invention is formulated for pharmaceutical use ("a pharmaceutical composition"), wherein the carrier is a pharmaceutically acceptable carrier. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and, in the case of a pharmaceutically acceptable carrier, not deleterious to the recipient thereof in amounts typically used in medicaments.

Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The pharmaceutical compositions of the invention include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. In certain embodiments, the compound of the formulae herein is administered transdermally (e.g., using a transdermal patch). Other formulations may conveniently be presented in unit dosage form, e.g., tablets and sustained release capsules, and in liposomes, and may be prepared by any methods well known in the art of pharmacy. See, for example, Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, PA (17th ed. 1985).

Such preparative methods include the step of bringing into association with the molecule to be administered ingredients such as the carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredients with liquid carriers, liposomes or finely divided solid carriers or both, and then if necessary shaping the product.

In certain preferred embodiments, the compound is administered orally. Compositions of the present invention suitable for oral administration may be presented as discrete units such as

capsules, sachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion, or packed in liposomes and as a bolus, etc. Soft gelatin capsules can be useful for containing such suspensions, which may beneficially increase the rate of compound absorption.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets optionally may be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. Methods of formulating such slow or controlled release compositions of pharmaceutically active ingredients, such as those herein and other compounds known in the art, are known in the art and described in several issued US Patents, some of which include, but are not limited to, US Patent Nos. 4,369,172; and 4,842,866, and references cited therein. Coatings can be used for delivery of compounds to the intestine (see, e.g., U.S. Patent Nos. 6,638,534, 5,217,720, and 6,569,457, 6,461,631, 6,528,080, 6,800,663, and references cited therein). A useful formulation for the compounds of this invention is the form of enteric pellets of which the enteric layer comprises hydroxypropylmethylcellulose acetate succinate.

In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

Compositions suitable for topical administration include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; and pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia.

Compositions suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampules and vials, and may be stored in a freeze dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets.

Such injection solutions may be in the form, for example, of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant.

The pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of

pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

Topical administration of the pharmaceutical compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches and iontophoretic administration are also included in this invention.

Particularly favored derivatives and prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a mammal (e.g., by allowing an orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or central nervous system) relative to the parent species. Preferred prodrugs include derivatives where a group that enhances aqueous solubility or active transport through the gut membrane is appended to the structure of formulae described herein. See, e.g., Alexander, J. et al. *Journal of Medicinal Chemistry* 1988, *31*, 318-322; Bundgaard, H. *Design of Prodrugs*; Elsevier: Amsterdam, 1985; pp 1-92; Bundgaard, H.; Nielsen, N. M. *Journal of Medicinal Chemistry* 1987, *30*, 451-454; Bundgaard, H. *A Textbook of Drug Design and Development*; Harwood Academic Publ.: Switzerland, 1991; pp 113-191; Digenis, G. A. et al. *Handbook of Experimental Pharmacology* 1975, *28*, 86-112; Friis, G. J.; Bundgaard, H. *A Textbook of Drug Design and Development*; 2

ed.; Overseas Publ.: Amsterdam, 1996; pp 351-385; Pitman, I. H. *Medicinal Research Reviews* 1981, *1*, 189-214.

Application of the subject therapeutics may be local, so as to be administered at the site of interest. Various techniques can be used for providing the subject compositions at the site of interest, such as injection, use of catheters, trocars, projectiles, pluronic gel, stents, sustained drug release polymers or other device which provides for internal access.

According to another embodiment, the invention provides a method of impregnating an implantable drug release device comprising the step of contacting said drug release device with a compound or composition of this invention. Implantable drug release devices include, but are not limited to, biodegradable polymer capsules or bullets, non-degradable, diffusible polymer capsules and biodegradable polymer wafers.

According to another embodiment, the invention provides an implantable medical device coated with a compound or a composition comprising a compound of this invention, such that said compound is therapeutically active.

In another embodiment, a composition of the present invention further comprises a second therapeutic agent. The second therapeutic agent includes any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered alone or with a compound of any of the formulae herein. Drugs that could be usefully combined with these compounds include other kinase inhibitors and/or other therapeutic agents for the treatment of the diseases and disorders discussed above.

Such agents are described in detail in the art. Preferably, the second therapeutic agent is an agent useful in the treatment or prevention of a disease or condition selected from cancer and neoplastic diseases or disorders, or autoimmune and inflammatory diseases or disorders.

In another embodiment, the invention provides separate dosage forms of a compound of this invention and a second therapeutic agent that are associated with one another. The term "associated with one another" as used herein means that the separate dosage forms are packaged together or otherwise attached to one another such that it is readily apparent that the separate dosage forms are intended to be sold and administered together (within less than 24 hours of one another, consecutively or simultaneously).

In the pharmaceutical compositions of the invention, the compound of the present invention is present in an effective amount. As used herein, the term "effective amount" refers to an amount which, when administered in a proper dosing regimen, is sufficient to reduce or ameliorate the severity, duration or progression of the disorder being treated, prevent the advancement of the disorder being treated, cause the regression of the disorder being treated, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy.

The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described in Freireich et al., (1966) Cancer Chemother Rep 50: 219. Body surface area may be approximately determined from height and weight of the patient. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardley, N.Y., 1970, 537. An effective amount of a compound of this invention can range from about 0.001 mg/kg to about 500 mg/kg, more preferably 0.01 mg/kg to about 50 mg/kg, more preferably 0.1 mg/kg to about 2.5 mg/kg. Effective doses will also vary, as recognized by those skilled in the art, depending on the diseases treated, the severity of the disease, the route of administration, the sex, age and general health condition of the patient, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents and the judgment of the treating physician.

For pharmaceutical compositions that comprise a second therapeutic agent, an effective amount of the second therapeutic agent is between about 20% and 100% of the dosage normally utilized in a monotherapy regime using just that agent. Preferably, an effective amount is between about 70% and 100% of the normal monotherapeutic dose. The normal monotherapeutic dosages of these second therapeutic agents are well known in the art. See, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), each of which references are entirely incorporated herein by reference.

It is expected that some of the second therapeutic agents referenced above will act synergistically with the compounds of this invention. When this occurs, it will allow the effective dosage of the second therapeutic agent and/or the compound of this invention to be reduced from that required in a monotherapy. This has the advantage of minimizing toxic side effects of either the second therapeutic agent of a compound of this invention, synergistic

improvements in efficacy, improved ease of administration or use and/or reduced overall expense of compound preparation or formulation.

Methods of Treatment

According to another embodiment, the invention provides a method of treating a subject suffering from or susceptible to a disease or disorder or symptom thereof (e.g., those delineated herein) comprising the step of administering to said subject an effective amount of a compound or a composition of this invention. Such diseases are well known in the art and are also disclosed herein.

In one aspect, the method of treating involves treatment of a disorder that is mediated by the Jak1 protein kinase.

In another aspect, the method of treating involves treatment of a disorder that is mediated primarily by the Jak1 protein kinase, but also to some extent by the Jak2 protein kinase.

In another aspect, the invention provides a method of treating a disease in a subject comprising administering to the subject a compound of any of the formulae herein.

In another aspect, invention provides a method of treating a disease in a subject comprising administering to the subject a composition comprising a compound of any of the formulae herein.

In certain embodiments, the disease is mediated by the Jak1 kinase. For example, the condition may be an inflammatory disease/disorder, an autoimmune disease/disorder, such as, but not limited to rheumatoid arthritis (RA), juvenile idiopathic arthritis, osteoarthritis, multiple sclerosis, allergic asthma, chronic obstructive pulmonary disease, bronchitis, experimental allergic encephalomyelitis, Crohn's disease, vasculitis, cardiomyopathy, ankylosing spondylitis (AS), glomerulonephritis, insulin-dependent diabetes, psoriatic arthritis, psoriasis, plaque psoriasis, ulcerative colitis, systemic lupus erythematosus (SLE), diabetic nephropathy, peripheral neuropathy, uveitis, fibrosing alveolitis, type I diabetes, juvenile diabetes, Castleman disease, neutropenia, endometriosis, autoimmune thyroid disease, sperm and testicular autoimmunity, scleroderma, axonal & neuronal neuropathies, allergic rhinitis, sinusitis,

hemolytic anemia, Graves, disease, Hashimoto's thyroiditis, IgA nephropathy, amyloidosis, Behcet's disease, sarcoidosis, vesiculobullous dermatosis, myositis, dry eye syndrome, primary biliary cirrhosis, polymyalgia rheumatic, Reiter's syndrome, autoimmune immunodeficiency, Chagas disease, Kawasaki syndrome, celiac sprue, myasthenia gravis, Sjogren's Syndrome, alopecia areata, vitiligo, atopic dermatitis, POEMS syndrome, lupus, inflammatory bowel disease, chronic obstructive pulmonary disease (COPD), pemphigus vulgris, bullous pemphigoid, chronic fatigue syndrome, organ transplant rejection (e.g., allograft rejection and graft versus host disease), viral diseases such as Epstein Barr virus, Hepatitis C, HIV, HTLV 1, Varicella-Zoster virus, and human papilloma virus, gouty arthritis, septic or infectious arthritis, reactive arthritis, reflext sympathetic dystrophy, algodystrophy, Tietze syndrome, costal athropathy, Mseleni disease, Handigodu disease, fibromyalgia, scleroderma, congentital cartilage malformations, and pulmonary arterial hypertension.

Further JAK-associated diseases include inflammation and inflammatory diseases or disorders, Examples include sarcoidosis, inflammatory diseases of the eye (e.g., iritis, uveitis, scleritis, conjunctivitis, blepharitis, or related disease), inflammatory diseases of the respiratory tract (e.g., the upper respiratory tract including the nose and sinuses such as rhinitis or sinusitis or the lowe respiratory tract including bronchitis, chronic obstructive pulmonary disease, and the like), inflammatory myopathy such as myocarditis and other inflammatory diseases.

In another embodiment, the disease is, cancer, a proliferative or other neoplastic disease, such as, but not limited to, breast cancer, Castleman's disease, colon and colorectal cancers, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor, glioblastoma, head and neck cancer, Kaposi's sarcoma, liver cancer, lung cancer, melanoma, pancreatic cancer, prostate cancer, renal cancer, rectal cancer, small intestine cancer, thyroid cancer, uterine leiomyosarcoma, lymphomas and leukemias such as acute lymphoblastic leukemia, acute myelogenous leukemia, multiple myeloma, cutaneous T cell lymphoma, cutaneous B cell lymphoma, myelodysplastic syndrome (MDS), myeloproliferative disorders (MPDs) such as polycythemia vera (PV), essential thrombocythemia (ET), myelofibrosis with myeloid metaplasia (MMM), primary myelofibrosis (PMF), chronic myelogenous leukemia (CML), chronic myelomonoytic leukemia (CMML), hypereosinophilic syndrome (HES), systemic mast cell disease (SMCD). In some embodiments, the myeloproliferative disorder is post-essential

thrombocythemia melofibrosis (Post-ET MF) or post-polycythemia versa myelofibrosis (Post-PV MF),

Further JAK-associated diseases include ischemia reperfusion injuries or a disease or condition related to an inflammatory ischemic event such as stroke or cardiac arrest, endotoxin-driven disease state (e.g., complications after bypass surgery of chronic endotoxin states contributing to chronic cardiac failure), anorexia, sclerodermitis, fibrosis, conditions associated with hypoxia or astrogliosis such as diabetic retinopathy, cancer, or neurodegeneration, and other inflammatory disease such as systemic inflammatory response syndrome and septic shock.

Other JAK-associated disease include gout and increased prostate size due to, e.g., benign prostate hypertrophy or benign prostatic hyperplasia, as well as bone resorption diseases such as osteoporosis or osteoarthritis, bone resorption diseases associated with: hormonal imbalance and/or hormonal therapy, autoimmune disease (e.g., osseous sarcoidosis).

Other examples of JAK-associated diseases or conditions include ameliorating the dermatological side effects of other pharmaceuticals by adminnstration of the compound of the invention. For example, numerous pharmaceutical agents result in unwanted allergic reaction which can manifest as acneiform rash or related dermatitis. Example pharmaceutical agents that have such undesirable side effects include anti-cancer drugs such as gefitinib, cetuximab, erlotinib, and the like. The compounds of the invention may be administered systemically or topically (e.g., localized to the vicinity of the dermatitis) in combination with pharmaceutical agent having the undesirable dermatological side effect. Accordingly, compositions of the invention include topical formulations containing the compound of the invention and a further pharmaceutical agent which can cause dermatitis, skin disorders, or related side effects.

In a one embodiment, the method of this invention is used to treat a subject suffering from or susceptible to a disease or condition. Such diseases, disorders or symptoms thereof include, for example, those modulated by the Jak1 protein kinase. The disease or disease symptom can be, for example, rheumatoid arthritis, cancer or proliferation disease or disorder. Methods delineated herein include those wherein the subject is identified as in need of a particular stated treatment. Identifying a subject in need of such treatment can be in the judgment of a subject or a health care professional and can be subjective (e.g. opinion) or objective (e.g. measurable by a test or diagnostic method).

In yet another embodiment, the compounds of the formulae herein (and compositions thereof) can be used to treat subjects having a disease or disorder who have been treated with and developed resistance to other therapeutic agents. In one aspect, the methods herein include those where a subject resistant to treatment with methotrexate or anti-TNF-alpha therapy.

In another embodiment, the invention provides a method of modulating the activity of the Jak1 protein kinase in a cell comprising contacting a cell with one or more compounds of any of the formulae herein.

In another embodiment, the above method of treatment comprises the further step of co-administering to said patient one or more second therapeutic agents. The choice of second therapeutic agent may be made from any therapeutic agent known to be useful for indications herein. One or more additional therapeutic may include chemotherapeutics, anti-inflammatory agents, steroids, immunosuppressants, as well as PI3Kdelta, mTOR, BCR-ABl, FLT-3, RAF and FAK kinase inhibitors, and the like. Additional therapeutic agents include but are not limited to agents for treatment of diseases, disorders or symptoms thereof including for example, (1) agents that modulate human immune system or are anti-inflammatory agents selected from the group consisting of, but not limited to, aspirin, acetaminophen, aminosalicylate, antithymoyte globulin, ciprofloxacin, corticosteroid, cyclosporine, deoxyspergualin, daclizuma, metronidazole, probiotic, tacrolimus, ibuprofen, naproxen, piroxicam, prednisolone, dexamethasone, anti-inflammatory steroid, methotrexate, chloroquine, azathioprine, hydroxychloroquine, mycophnolate, muromonab-CD3, penicillamine, sulfasalazine, leflunomide, tacrolimus, tocilzumab, anakinra, abatacept, certolizumab pegol, golimumab, rapamycin, vedolizumab, natalizumab, ustekinumab, rituximab, efalizumab, belimumab, etanercept, infliximab, adalimuman, immune modulator (e.g., activator) for CD4+CD25+ regulatory T cells, NSAIDs, analgesics, other non-biological disease-modifying anti-rheumatic drugs (DMARDs) and/or in combination with anti-TNF-alpha biological agents such as TNA antagnoists like chimeric, humanized or human TNF antibodies, adalimumab, infliximab, golimumab, CDP571 and soluble p55 or l75 TNA receptors, derivatives, thereof, etanerceptr pr lenercept (2) anti-cancer and anti-neoplastic agents, antiproliferative agents, antineoplastic agents, antitumor agents, antimetabolite-type/thymidilate synthase inhibitor antineoplastic agents, alkylating-type antineoplastic agents, antibiotic-type antineoplastic agents, or, any other agent typically

administered as a primary or adjuvant agent in cancer treatment protocols (e.g., antinausea, antianemia, etc.), including for example, vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, tamoxifen, toremifen, raloxifene, droloxifene, iodoxyfene, megestrol acetate, anastrozole, letrazole, borazole, exemestane, flutamide, nilutamide, bicalutamide, cyproterone acetate, goserelin acetate, luprolide, finasteride, herceptin, methotrexate, 5-fluorouracil, cytosine arabinoside, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin, mithramycin, cisplatin, carboplatin, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotephan, vincristine, taxol, taxotere, etoposide, teniposide, amsacrine, irinotecan, topotecan, an epothilone, Iressa, Avastin, OSI-774, angiogenesis inhibitors, EGFR inhibitors, MEK inhibitors, VEGFR inhibitors, CDK inhibitors, Her1 and Her2 inhibitors, monoclonal antibodies, proteosome inhibitors such as bortezomib, thalidomide, and revlimid; an apoptotic inducer such as ABT-737. A nucleic acid therapy such as antisense or RNAi; nuclear receptor ligands (e.g., agonists and/or antagonists. All-trans retinoic acid or boxarotene); epigenetic targeting agents such as histone deacetylase inhibitors (e.g., vorinostat), hypomethylating agents (e.g., decitabine), regulators of protein stability such as HSP90 inhibitors, ubiquitin and /or ubiquitin like conjugating or deconjugating molecules.

In some embodiments, the additional pharmaceutical agent is selected from IMiDs, an anti-IL-6 agent, an anti-TNF-alpha agent, a hypomethylating agent, and a biologic response modifier (RBM). RBM is generally a substance made from living organisms to treat disease. Examples of RBMs include IL-2, GM-CSF, CSF, monoclonal antibodies such as abciximab, etanercept, infliximab, rituximab, trastuzumab, and high dose ascorbate. The hypomethylating agent is a DNA methyltransferase inhibitor such as 5 azacytidine and decitabine. Examples of IMiDs include thalidomide, lenalidomide, pomalidomide, CC-11006, and CC-10015.

In some embodiments, the additional pharmaceutical agents include anti-thymocyte globulin, recombinant human granulocyte colony-stimulating factor (G-CSF), granulocyte-moncyte CSF (GM-CSF), a erythropoiesis-stimulating agent (ESA), and cyclosporine.

In some embodiments, the additional therapeutic agent is an additional JAK inhibitor. In some embodiments, the additional JAK inhibitor is tofacitinib, ruxolitinib or baricitinib.

In some embodiments, one or more JAK inhibitors of the invention can be used in combination with one or more other cancer therapeutic agents in the treatment of cancer, such as multiple myeloma, and may improve the treatment benefit as compared to the benefit shown by the other cancer therapeutic agents, without exacerbating of their toxic effects. Examples of additional pharmaceutical agents used in the treatment of multiple myeloma can include, without limition, melphalan, melphalan plus prednisone (MP), doxorubicin, dexamethasone, and bortezomib. Additional agents used in the treatment of multiple myeoloma include BRC-ABL, FLT-3, RAF, MEK, PI3K, mTOR inhibitors. Additive or synergistic effects are desirable outcomes of combining a JAK inhibitor of the current invention with an additional agent. Furthermore, resistance of multiple myeloma cells to agents such as dexamethasone or other agents may be reversible upon treatment with a JAK inhibitor of the present invention. The agents can be combined with the present compounds in a single or continuous dosage form, or the agents can be administered simultaneously or sequentially as separate dosage forms.

In some embodiments, a corticosteroid such as dexamethasone is administered to a patient in combination with at least one JAK inhibitor of the invention where the dexamethasone is administered intermittently as opposed to continuously.

In some embodiments, combinations of one or more JAK inhibitors of the invention with other therapeutic agents can be administered to a patient prior to, during, and/or after a bone marrow transplantation or stem cell transplantation.

In some embodiments, the additional therapeutic agent is fluocinolone acetonide or remexolone.

In some embodiments, the additional therapeutic is a corticosteroid such as triamcinolone, dexamethasone, fluocinolone, cortisone, prednisolone, or flumetholone.

In some embodimennts, the additional therapeutic agent includes Dehydrex, Civamide, sodium hyaluronate, cyclosporine, ARG101, AGR1012, ecabet sodium, gefarnate, 15-(s)-hydroxyeicosatetraenoic acid, cevilemine doxycycline, minocycline, iDestrin, cyclosporine A, oxytetracycline, voclosporin, ARG103, RX-10045, DYN15, rivoglitazone, TB4, OPH-01, PCS101, REV1-31, Lacritin, rebamipide, OT-551, PAI-2, pilocarpine, tacrolimus, pimercrolimus, loteprednol etabonate, rituximan, diquafosol tetrasodium, KLS-0611,

dehydroepiandrosterone, anakinra, efalizuma, mycophenolate sodium, etanercept, hydroxychloroquine, NGX267, actemra, or L-asparaginase.

In some embodiments, the additional therapeutic agent is an anti-angiogenic agent, cholinergic agent, TRP-1 receptor modulator, a calcium channel blocker, a mucin secretagogue, MUC1 stimulant, a calcineurin inhibitor, a P2Y2 receptor agonist, a muscarinic receptor agonist, and a tetracycline derivative.

In some embodimenbts, the additional therapeutic agents include demulcent eye drops, which include, but not limited to, compositions containing polyvinylalchol, hyroxypropyl methylcellulose, glycerin, polyethylene glycol (e.g., PEG400), or carboxymethyl cellose, In some embodiments, the additional therapeutic agent is a mucolytic drug, such as N-acetyl-systeine, which can interact with the mucoproteins and decrease the viscositiy of the tear film.

In some embodiments, the additional therapeutic agent includes an antibiotic, antiviral, antifungal, anesthetic, anti-inflammatory agents including steroidal and non-steroidal anti-inflammatories, and anti-allergic agents. Examples of suitable medicaments include aminoglycosides such as amikacin, gentamycin, tobramycin, streptomycin, netilmycin, and kanamycin; fluoroquinolones such as ciprofloxacin, norfloxacin, ofloxacin, trovafloxacin, lomefloxacin, levofloxacin, and enoxacin; naphthyridine; sulfonamides; polymyxin; chloramphenicol; neomycin; paramomycin; colistimethate; bacitracin, vanocomycin; tetracyclines; rifampin and its derivatives; cycloserine; beta-lactams; cephalosporins; emphotericins; fluconazole; flucytosine; natamycin; miconazole; ketoconazole; corticosteroids; dicloenac; flurbiprofen; ketorolac; suprofen; cromolyn; iodoxamide; levocabastin; naphazoline; antazoline; pheniramine; or azalide antibiotic.

The term "co-administered" as used herein means that the second therapeutic agent may be administered together with a compound of this invention as part of a single dosage form (such as a composition of this invention comprising a compound of the invention and an second therapeutic agent as described above) or as separate, multiple dosage forms. Alternatively, the additional agent may be administered prior to, consecutively with, or following the administration of a compound of this invention. In such combination therapy treatment, both the compounds of this invention and the second therapeutic agent(s) are administered by conventional methods. The administration of a composition of this invention comprising both a

compound of the invention and a second therapeutic agent to a subject does not preclude the separate administration of that same therapeutic agent, any other second therapeutic agent or any compound of this invention to said subject at another time during a course of treatment.

Effective amounts of these second therapeutic agents are well known to those skilled in the art and guidance for dosing may be found in patents and published patent applications referenced herein, as well as in Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, Conn. (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, Calif. (2000), and other medical texts. However, it is well within the skilled artisan's purview to determine the second therapeutic agent's optimal effective-amount range.

In one embodiment of the invention where a second therapeutic agent is administered to a subject, the effective amount of the compound of this invention is less than its effective amount would be where the second therapeutic agent is not administered. In another embodiment, the effective amount of the second therapeutic agent is less than its effective amount would be where the compound of this invention is not administered. In this way, undesired side effects associated with high doses of either agent may be minimized. Other potential advantages (including without limitation improved dosing regimens and/or reduced drug cost) will be apparent to those of skill in the art.

In yet another aspect, the invention provides the use of a compound of any of the formulae herein alone or together with one or more of the above-described second therapeutic agents in the manufacture of a medicament, either as a single composition or as separate dosage forms, for treatment or prevention in a subject of a disease, disorder or symptom set forth above. Another aspect of the invention is a compound of the formulae herein for use in the treatment or prevention in a subject of a disease, disorder or symptom thereof delineated herein.

In other aspects, the methods herein include those further comprising monitoring subject response to the treatment administrations. Such monitoring may include periodic sampling of subject tissue, fluids, specimens, cells, proteins, chemical markers, genetic materials, etc. as markers or indicators of the treatment regimen. In other methods, the subject is prescreened or identified as in need of such treatment by assessment for a relevant marker or indicator of suitability for such treatment.

In one embodiment, the invention provides a method of monitoring treatment progress. The method includes the step of determining a level of diagnostic marker (Marker) (e.g., any target or cell type delineated herein modulated by a compound herein) or diagnostic measurement (e.g., screen, assay) in a subject suffering from or susceptible to a disorder or symptoms thereof delineated herein, in which the subject has been administered a therapeutic amount of a compound herein sufficient to treat the disease or symptoms thereof. The level of Marker determined in the method can be compared to known levels of Marker in either healthy normal controls or in other afflicted patients to establish the subject's disease status. In preferred embodiments, a second level of Marker in the subject is determined at a time point later than the determination of the first level, and the two levels are compared to monitor the course of disease or the efficacy of the therapy. In certain preferred embodiments, a pre-treatment level of Marker in the subject is determined prior to beginning treatment according to this invention; this pre-treatment level of Marker can then be compared to the level of Marker in the subject after the treatment commences, to determine the efficacy of the treatment.

In certain method embodiments, a level of Marker or Marker activity in a subject is determined at least once. Comparison of Marker levels, e.g., to another measurement of Marker level obtained previously or subsequently from the same patient, another patient, or a normal subject, may be useful in determining whether therapy according to the invention is having the desired effect, and thereby permitting adjustment of dosage levels as appropriate. Determination of Marker levels may be performed using any suitable sampling/expression assay method known in the art or described herein. Preferably, a tissue or fluid sample is first removed from a subject. Examples of suitable samples include blood, urine, tissue, mouth or cheek cells, and hair samples containing roots. Other suitable samples would be known to the person skilled in the art. Determination of protein levels and/or mRNA levels (e.g., Marker levels) in the sample can be performed using any suitable technique known in the art, including, but not limited to, enzyme immunoassay, ELISA, radiolabelling/assay techniques, blotting/chemiluminescence methods, real-time PCR, and the like.

The present invention also provides kits for use to treat diseases, disorders, or symptoms thereof, including those delineated herein. These kits comprise: a) a pharmaceutical composition comprising a compound of any of the formula herein or a pharmaceutically

acceptable salt thereof; or a prodrug, or a pharmaceutically acceptable salt of a prodrug thereof; or a hydrate, solvate, or polymorph thereof, wherein said pharmaceutical composition is in a container; and b) instructions describing a method of using the pharmaceutical composition to treat the disease, disorder, or symptoms thereof, including those delineated herein.

The container may be any vessel or other sealed or sealable apparatus that can hold said pharmaceutical composition. Examples include bottles, divided or multi-chambered holders bottles, wherein each division or chamber comprises a single dose of said composition, a divided foil packet wherein each division comprises a single dose of said composition, or a dispenser that dispenses single doses of said composition. The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle, which is in turn contained within a box. Preferably, the container is a blister pack.

The kit may additionally comprising information and/or instructions for the physician, pharmacist or subject. Such memory aids include numbers printed on each chamber or division containing a dosage that corresponds with the days of the regimen which the tablets or capsules so specified should be ingested, or days of the week printed on each chamber or division, or a card which contains the same type of information.

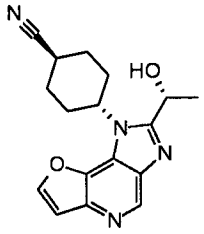
The compounds delineated herein can be assessed for their biological activity using protocols known in the art, including for example, those delineated herein. Certain of the compounds herein demonstrate unexpectedly superior attributes (e.g., inhibition of P450, metabolic stability, pharmacokinetic properties, etc.) making them superior candidates as potential therapeutic agents.

All references cited herein, whether in print, electronic, computer readable storage media or other form, are expressly incorporated by reference in their entirety, including but not limited

to, abstracts, articles, journals, publications, texts, treatises, technical data sheets, internet web sites, databases, patents, patent applications, and patent publications.

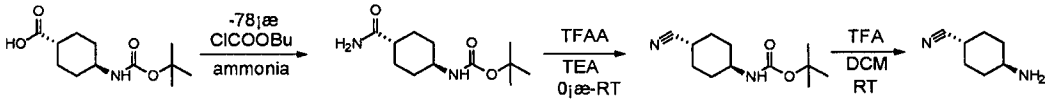
Examples

Example 1: Synthesis of *trans*-4-[2-[(*R*)-1-Hydroxyethyl]-1H-furo[3,2-b]imidazo[4,5-d] pyridin-1-yl]cyclohexanecarbonitrile (1)

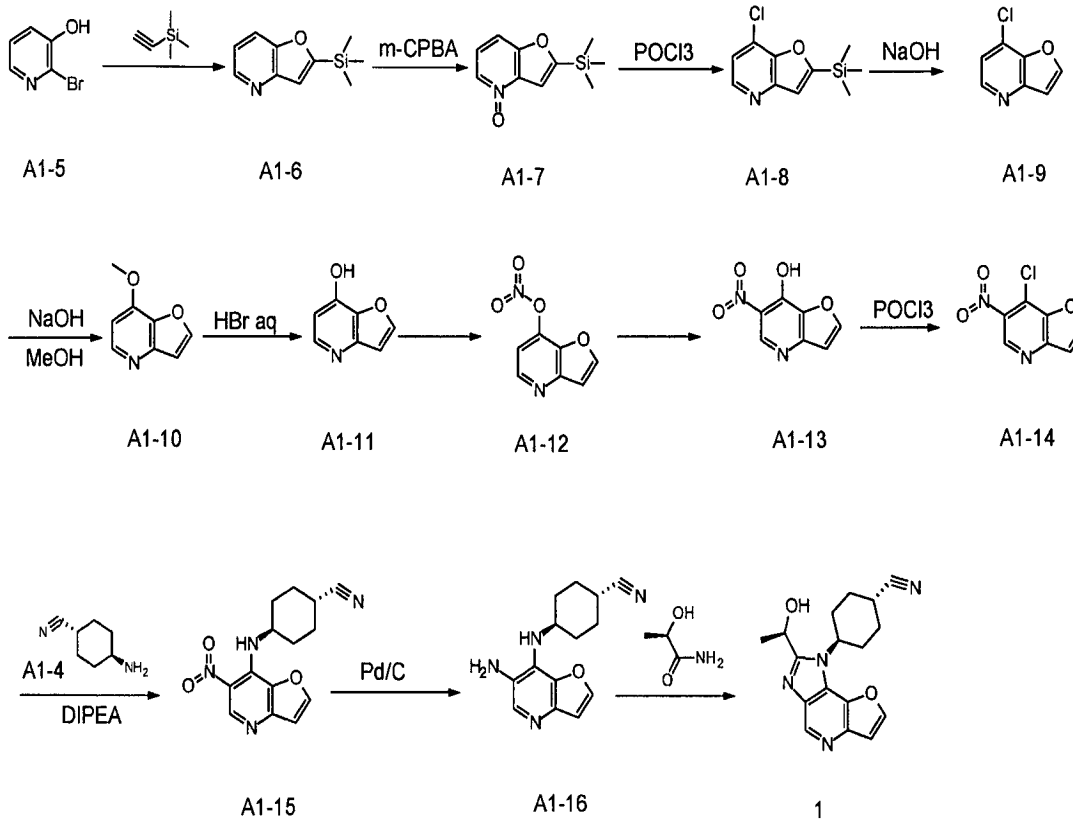


1

Scheme 1:



A1-1 A1-2 A1-3 A1-4



Step 1. A solution of trans-4-(Boc-amino)cyclohexane carboxylic acid (A1-1) (62g, 0.256mol,1.0eq) in THF (1500mL) was treated with NMM (64.6g, 0.64mol, 2.5eq) in nitrogen atmosphere. The mixture was cooled to -78°C, and isobutyl chloroformate (33.6g, 0.33mol, 1.3eq) was added dropwise. After stirring at -78°C for 1hr, NH_3(gas) was bubbled through the mixture for about 20mins. After that the reaction temperature rose to -30°C, then stirring at -30°C for 1hr. The resulting slurry was filtered, washed by water (3*200mL), and oven dried to give compound A1-2 as white powder (58g, yield 93.5%). MS-ESI:$[M+1]^+$: 243.1

^{1}H NMR(300MHz, d_6-DMSO): 7.192(s,1H),6.688-6.728(m,2H),3.122-3.147(m,1H), 1.92-1.959(m,1H),1.696-1.787(m,4H),1.382(s,9H),1.086-1.358(m,4H).

Step 2. A solution of compound A1-2 (74g, 0.306mol, 1.0eq) in DCM (1000mL) was treated with triethylamine (77.2g, 0.64mol, 2.5eq). The mixture was cooled to 0°C in ice-bath, and TFAA (80.9g, 0.383mol, 1.25eq) was added dropwise. The ice bath was removed after addition and the reaction temperature rose to 20°C, then stirring at 20°C for 2hrs, water (300mL) was added, and then the aqueous phase was extracted twice with DCM. The combined extracts was

washed with brine, dried over anhydrous sodium sulfate, concentrated and purified by silica gel column chromatography to give compound A1-3 as white powder (46g, yield 67.1%). MS-ESI:$[M+1]^+$: 225.1.

^{1}H NMR(300MHz, $CDCl_3$): 4.397(m, 1H), 3.467(m, 1H), 2.381-2.418(m, 1H), 2.079-2.147 (m, 4H), 1.613-1.757(m, 2H), 1.454(s, 9H), 1.114-1.232(m, 2H).

Step 3. To a solution of compound A1-3 (10g, 44.6mmol, 1.0eq) in DCM (50mL), was added TFA (20g). The reaction mixture was stirred for 2hrs at room temperature until TLC showed the reaction was complete, then concentrated under vacuum. Ice-water (30mL) was added and the solution was treated with aqueous sodium hydroxide solution (4mol/L) to pH 10. Then the aqueous phase was extracted six times with DCM/methanol (10/1). The combined extracts was dried over anhydrous sodium sulfate, concentrated to give compound A1-4 as an off-white solid (5.1g, yield 91.9%). MS-ESI:$[M+1]^+$: 125.1.

^{1}H NMR(300MHz, $CDCl_3$): 2.738-2.772(m, 1H), 2.370-2.421(m, 1H), 2.115-2.170(m, 2H), 1.923-1.977(m, 2H), 1.580-1.694(m, 2H), 1.075-1.197(m, 2H)

Step 4. In nitrogen atmosphere, to a solution of 2-Bromo-3-hydroxypyridine (A1-5) (225g, 1.293mol, 1.0eq), trimethylsilylacetylene (153.3g, 1.592mol, 1.23eq) in 1,4-dioxane (2500mL) was added CuI (25g) and $Pd(PPh3)_2Cl_2$(45g). The reaction mixture was stirred for 30mins at 25°C, then cooled to 10°C and triethylamine (363g, 3.594mol, 2.78eq) was added dropwise. After stirring for 4hrs at 60°C, the solution was cooled and concentrated under vacuum. The residue was added water (2000mL) and MTBE (200mL), stirring and filtered. The filtrate was extracted with MTBE (1000mL*2). The combined organic layers was washed with brine, dried over anhydrous sodium sulfate, concentrated and purified by silica gel column chromatography to give compound A1-6 as light brown liquid (150g, yield 60.7%). GC-MS: 191 (EI)

Step 5. To a solution of compound A1-6 (105g, 0.55mol, 1.0eq) in DCM (1000mL) was added m-chloroperoxybenzoic acid (85%, 230g, 1.13mol, 12.06eq) in portions below 25°C. After stirring overnight at room temperature, saturated sodium bicarbonate solution was added to pH 7-8 in ice-bath. The resulting mixture was filtered, and the filtrate was separate, and was extracted twice with DCM. The combined organic layers was washed with saturated sodium

bicarbonate solution and brine, dried over anhydrous sodium sulfate, concentrated to give compound A1-7 as a brown liquid (115g, yield 100%).

Step 6. A solution of compound A1-7 (115g, 0.55mol, 1.0eq) in toluene (400mL) was added to phosphorus oxychloride (400mL) in ice-bath below 30°C. The reaction mixture was stirred for 2hrs at 90°C, cooled to room temperature, and concentrated. The residue was slowly added saturated sodium bicarbonate solution to pH 7-8 below 20°C, and the mixture was extracted twice with MTBE. The combined organic layers was washed with brine, dried over anhydrous sodium sulfate, concentrated and purified by silica gel column chromatography to give compound A1-8 as a yellow liquid (73g, yield 58.7%). GC-MS: 225 (EI)

Step 7. To a solution of compound A1-8 (73g, 0.323mol, 1.0eq) in THF (400mL) was added aqueous sodium hydroxide solution (300mL, 4mol/L). After stirring for 1hr at 50°C, the reaction mixture was cooled to room temperature and 1000mL water was added. The mixture was extracted twice with MTBE. The combined organic layers was washed with brine, dried over anhydrous sodium sulfate, concentrated and recrystallized from ethyl acetate and petroleum ether to give compound A1-9 as an off-white powder (30g, yield 60.5%). GC-MS: 153 (EI) ^{1}H NMR(300MHz, $CDCl_3$):8.485(d, 1H),7.945(d, 1H),7.312(d, 1H),7.079(d, 1H).

Step 8. Compound A1-9 (9.21g, 60mmol, 1.0eq) was dissolved in methanol (150mL), then water (150mL) and sodium hydroxide (24g, 10eq) were added. After stirring for 1hr at 50°C, the reaction mixture was cooled to 20°C and concentrated. The residue was extracted three times with DCM, then the combined organic layers was dried over anhydrous sodium sulfate and concentrated to give compound A1-10 as a yellow liquid (5.5g, yield 61.5%). MS-ESI:$[M+1]^+$: 150

Step 9. Compound A1-10 (5.5g, 37mmol, 1.0eq) was added to 40% HBr aq (150mL). The reaction mixture was heated to reflux for 18hrs, cooled and concentrated. The residue was treated with saturated sodium bicarbonate solution (100mL) to pH 7-8. After stirring for 20min, the precipitate was filtered, washed with water, and oven dried to give compound A1-11 as an off-white powder (3.1g, yield 62%). MS-ESI:$[M+1]^+$: 136

Step 10. In nitrogen atmosphere, a mixture of compound A1-11 (1.68g, 12.4mmol, 1.0eq) in 120mL DCM was cooled to -5°C, and tetrabutyl-ammonium nitrate (5.17g, 17mmol, 1.36eq) in DCM (30mL) was added drop wise below 0°C, then TFAA (5.17g , 20mmol, 1.6eq) was added all at once. After addition, the reaction mixture was stirred at -5°C for 1hr and then warmed up to 25°C and stirred for 15hrs. The solvent was concentrated, and ether (200mL) was added to the residue, stirred and filtered. Collected filter-cake and saturated sodium bicarbonate solution (100mL) was added. The mixture was extracted twice with ethyl acetate, then the combined organic layers was dried over anhydrous sodium sulfate and concentrated to give compound A1-12 as a yellow powder (1.37g, yield 61.4%). MS-ESI:$[M+1]^+$: 181

Step 11. A mixture of compound A1-12 (1.37g, 7.61mmol, 1.0eq) and propionic acid (50mL) was heated to 110°C, then fuming nitric acid (0.65mL) was added dropwise at 110°C to 120°C. After stirring for 30mins at 125°C and cooled to room temperature, ether (100mL) was added, and the solid was filtered, washed with ether and dried under vacuum to give compound A1-13 as yellow a powder (1.2g, yield 87.6%). MS-ESI:$[M+1]^+$: 181.
^{1}H NMR(300MHz, d_6-DMSO): 13.149(s, 1H),9.024(s, 1H), 8.234(d, 1H), 6.966(d, 1H).

Step 12. To a solution of compound A1-13 (1.2g, 6.67mmol, 1.0eq) in 1,2-dichloroethane (50mL), was added phosphorus oxychloride (15mL) below 20°C, then stirred for 2hrs at 95°C in nitrogen atmosphere, cooled to 25°C and concentrated. The residue was slowly added saturated sodium bicarbonate solution to pH 7-8 below 20°C, and the mixture was extracted twice with MTBE. The combined organic layers was washed with brine, dried over anhydrous sodium sulfate, concentrated to give compound A1-14 as a light-yellow powder (0.8g, yield 60.4%),
^{1}H NMR(300MHz, $CDCl_3$): 9.250(s, 1H),8.189(d, 1H),7.191(d, 1H).

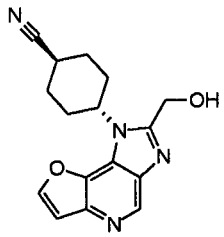
Step 13. To a solution of A1-14 (280mg, 1.41mmol, 1.0eq) in n-butanol (20mL) was added compound A1-4 (290mg, 2.34mmol,1.66eq) and DIPEA (403mg, 3.12mmol, 2.21eq). The reaction mixture was stirred for 1hr at 135°C, concentrated and purified by silica gel column chromatography to give A1-15 as a yellow powder (320mg, yield 79.4%). MS-ESI:$[M+1]^+$: 287.1.

^{1}H NMR(300MHz, $CDCl_3$):9.268(s, 1H), 8.653(d, 1H), 7.952(d, 1H), 7.034(d, 1H),4.423-4.511(m, 1H), 2.629-2.723(m, 1H), 2.241-2.355(m, 4H), 1.864-1.902(m, 2H),1.539-1.578(m, 2H).

Step 14. To a solution of A1-15 (320mg, 1.12mmol, 1.0eq) in methanol (15mL), was added 10% Pd/C(0.3g,50% wet). Hydrogenation was carried out under atmospheric pressure at room temperature until hydrogen uptake ceased. The catalyst was filtered and washed by methanol. The filtrates was concentrated under vacuum, and A1-16 was obtained as a yellow oil (286mg, yield 100%). MS-ESI: $[M+1]^+$: 257.1

Step 15. A solution of (R)-(+)-Lactamide (259mg, 2.8mmol, 5.0eq) and Et3O-BF4 (543mg, 2.8 mmol, 5.0eq) in THF(10mL) was stirred 30mins at room temperature in nitrogen atmosphere. Then the above solution was added to the mixture of A1-16 (143mg, 0.56mmol, 1.0eq) in ethanol (10mL). After stirring for 2hrs at 85°C, the mixture was concentrated, added water and extracted four times with ethyl acetate. The organic phase was discarded and the aqueous phase was treated with saturated sodium bicarbonate solution (100mL) to pH 8, extracted twice with ethyl acetate. The second organic phases was dried over anhydrous sodium sulfate, concentrated to give the title compound as a light-yellow powder (80mg, yield 46%). MS-ESI: $[M+1]^+$: 311.4 ^{1}H NMR(300MHz, $CDCl_3$): 9.005(s, 1H), 7.949(s, 1H),7.256(s, 1H),5.227-5.290(m, 1H), 4.766-4.843(m, 1H), 2.783-2.864(m, 1H), 2.438-2.527(m, 4H), 2.068-2.192(m, 2H), 1.913-2.003(m, 2H), 1.767-1.846(d, 3H).

Example 2: Synthesis of *trans*-4-[2-(Hydroxymethyl)furo[3,2-b]imidazo[4,5-d]pyridin-1-yl] cyclohexanecarbonitrile (2)



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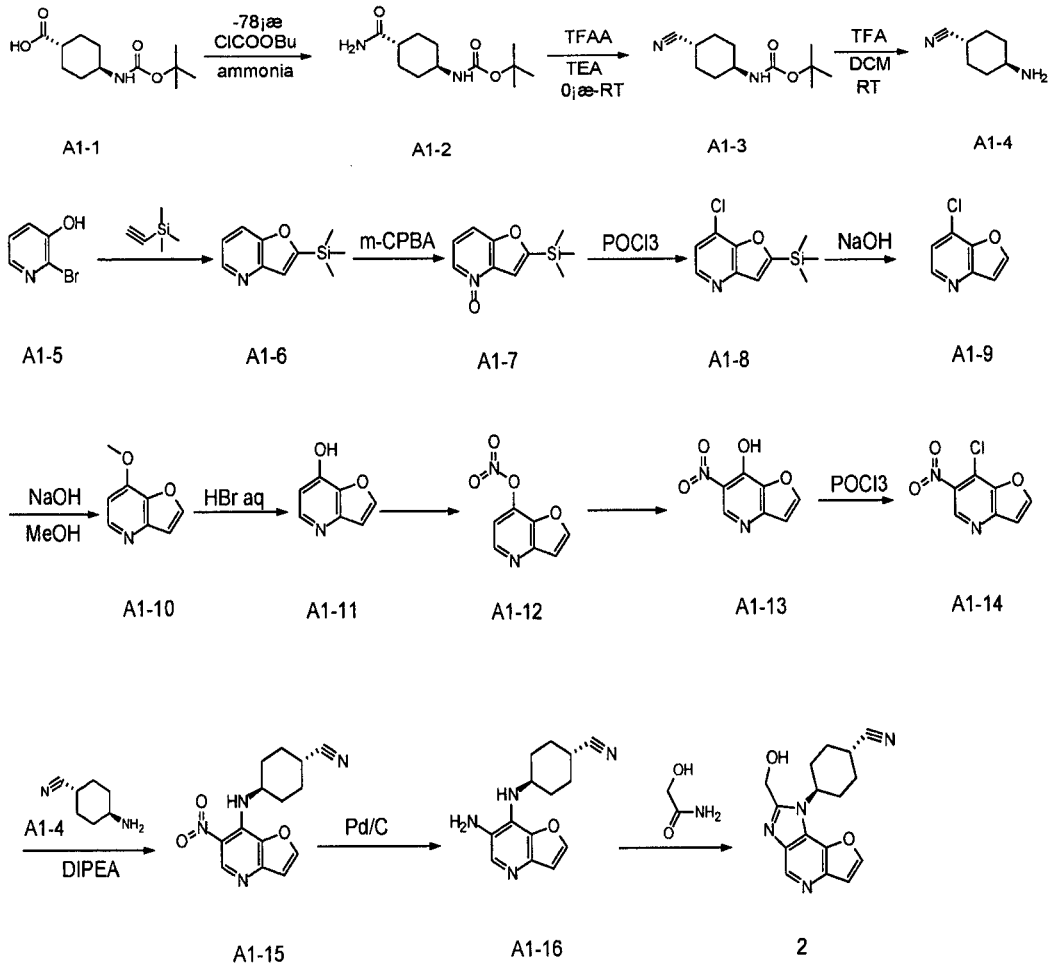
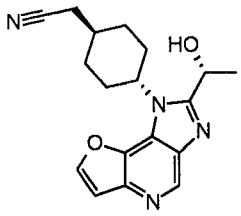
Scheme 2:



Example 2 was made using the same procedure as **Example 1** except that (R)-(+)-Lactamide is replaced by 2-hydroxyacetamide in step 15): 40mg of title compound as a light-yellow powder, MS-ESI: $[M+1]^+$: 297.4

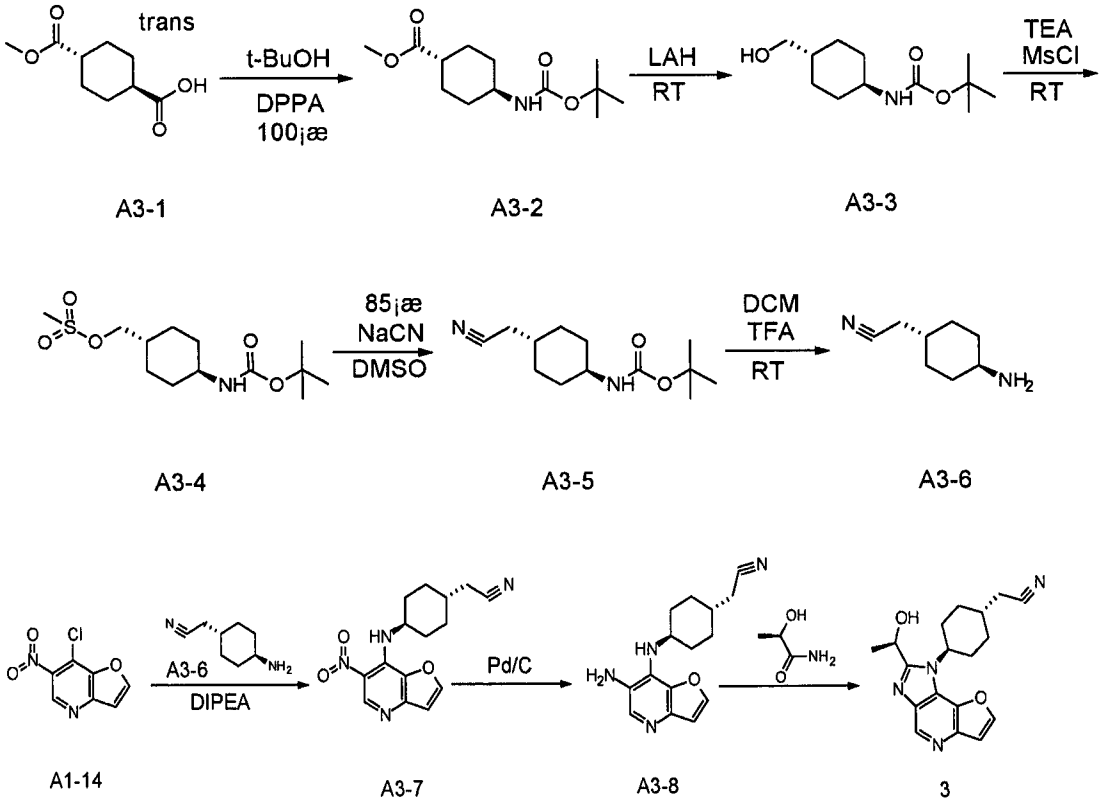
^{1}H NMR(300MHz, $CDCl_3$): 9.048(s, 1H), 7.965(s, 1H), 7.286(s, 1H), 5.049(s, 2H), 4.702-4.813(m, 1H), 2.753-2.873(m, 1H), 2.376-2.527(m, 4H), 2.087-2.226(m, 2H), 1.872-2.053(m, 2H).

Example 3: Synthesis of 2-[*trans*-4-[2-[(*R*)-1-Hydroxyethyl]furo[3,2-b]imidazo[4,5-d] pyridin-1-yl]cyclohexyl]acetonitrile (3)



3

Scheme 3:



Step 1. In nitrogen atmosphere, to a solution of trans-1,4-cyclohexane-dicarboxylic acid monomethyl ester (A3-1) (100g, 0.538mol, 1.0eq) and triethylamine (57.4g, 0.568mol, 1.055eq) in t-butyl alcohol (1000mL) was added dropwise diphenylphosphoryl azide (155g, 0.563mol, 1.047eq) at room temperature. The mixture was refluxed over 16hrs. Upon completion by TLC, the mixture was then cooled and concentrated. Water (1000mL) was added, and the mixture was extracted three times with MTBE. Then the organic layer was washed with saturated sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, concentrated and purified

by silica gel column chromatography to give compound A3-2 as an off-white powder (53g, yield 39.2%). MS-ESI:$[M+1]^+$: 257.1

Step 2. A suspension of $LiAlH_4$ (9.0g, 0.236mol, 1.12eq) in THF (500mL) was cooled to 0°C in ice-bath, and then added a solution of compound A3-2 (54.3g, 0.211mol, 1.0eq) in THF (200mL) while keeping the temperature below 10°C. The reaction mixture was stirred overnight at room temperature, and then quenched with sodium sulfate decahydrate (27g) at 15°C to 25°C, filtered and the filtrate was concentrated to give compound A3-3 as a white powder (43g, yield 89%). MS-ESI:$[M+1]^+$: 229.1

Step 3. A mixture of compound A3-3 (11.5g, 0.05mol, 1.0eq) and triethylamine (7.6g, 0.075mol, 1.5eq) in DCM (200mL), was added methylsufonyl chloride (6.9g, 0.06mol, 1.2eq) dropwise below 10°C. After stirring for 2hrs at room temperature, water (300mL) was added. The mixture was extracted twice with ethyl acetate. The combined extracts was washed with brine, dried over anhydrous sodium sulfate, concentrated to give compound A3-4 as yellow liquid (16.0g, yield 100%). MS-ESI:$[M+1]^+$: 307.1

Step 4. To a solution of compound A3-4 (16.0g, 0.05mol, 1.0eq) in DMSO (150mL) was added sodium cyanide (7.0g, 0.143mol, 2.86eq) in portions below 20°C. After stirring for 5hrs at 85°C, the mixture was cooled to room temperature, ice-water (500mL) was added. The mixture was extracted twice with MTBE. The combined extracts was washed three times with brine, dried over anhydrous sodium sulfate, concentrated and purified by silica gel column chromatography to give compound A3-5 as white powder (9.3g, yield 78%). MS-ESI:$[M+1]^+$: 238.1. ^1H NMR(300MHz, $CDCl_3$): 4.408(m, 1H), 3.405(m, 1H), 2.263-2.285(d, 2H), 2.064-2.096(m, 2H), 1.457(s, 9H), 1.122-1.281(m, 4H).

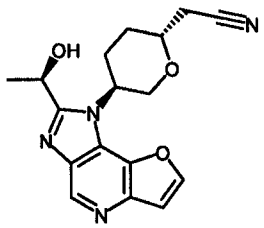
Step 5. To a solution of compound A3-5 (1.1g, 4.6mmol, 1.0eq) in DCM (10mL) was added TFA (6g). The reaction mixture was stirred for 2hrs at room temperature, then concentrated under vacuum. Ice-water (15mL) was added and the solution was treated with aqueous sodium hydroxide solution (4mol/L) to pH 10. Then the aqueous phase was extracted five times with DCM/methanol (10/1). The combined extracts was dried over anhydrous sodium sulfate,

concentrated to give compound A3-6 as a yellow oil (0.55g, yield 87.7%). MS-ESI:$[M+1]^+$: 138.1.

Step 6 to step 8 are the same as step 13 to step 15 in **Example 1** except that the amine A1-4 is replaced by A3-6 to make the title compound: 70mg of light-yellow powder (Yield: 0.565%). MS-ESI: $[M+1]^+$: 325.5

^{1}H NMR(300MHz, $CDCl_3$): 9.003(s, 1H), 7.965(s, 1H), 7.270(s, 1H), 5.255-5.298(m, 1H), 4.713-4.795(m, 1H), 2.439-2.611(m, 4H), 2.068-2.512(m, 5H), 1.808-1.829(d, 3H), 1.452-1.576(d, 2H).

Example 4: Synthesis of 2-[(2*R*,5*S*)-5-[2-[(*R*)-1-Hydroxyethyl]furo[3,2-b]imidazo[4,5-d] pyridin-1-yl]tetrahydropyran-2-yl]acetonitrile (4)



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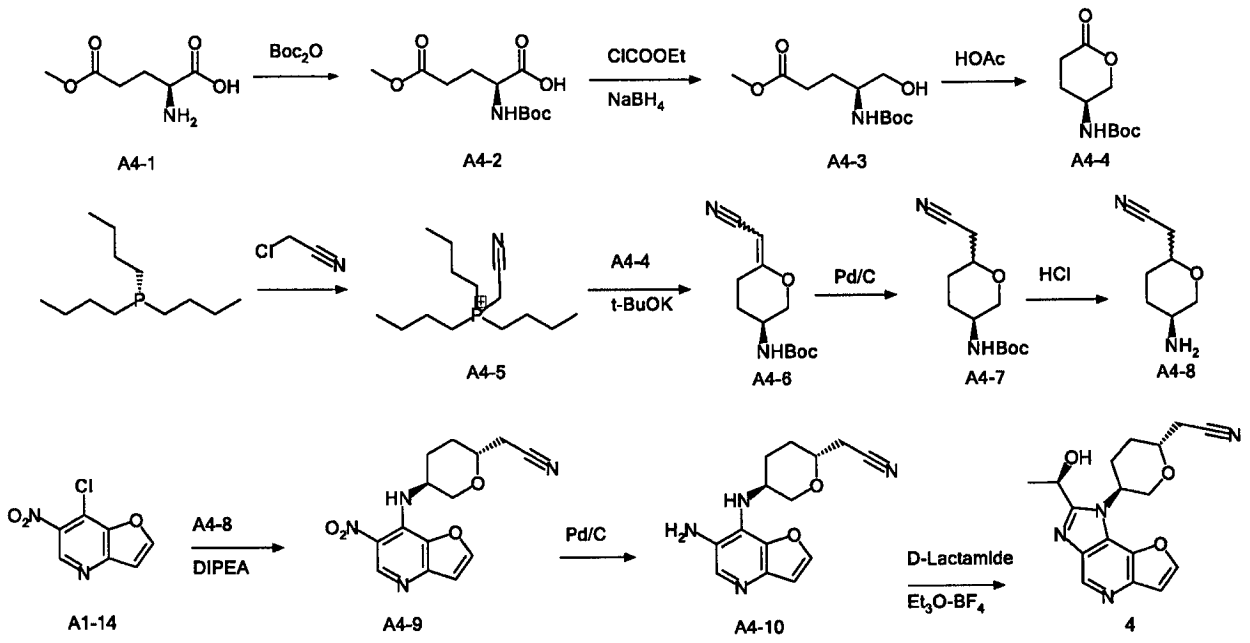
Scheme 4:



Step 1. In a round bottom flask, triethylamine (188g, 1.86mol, 1.0eq) was added dropwise to a stirred solution of di-tert-butyl dicarbonate (162g, 0.744mol, 1.2eq) and compound A4-1 (100g, 0.62mol, 1.0eq) in water (500mL) and 1,4-dioxane (500mL). After stirring for 18hrs at room temperature, the solution was extracted with MTBE (500mL*2) and the aqueous phase was cooled on ice and carefully acidified to pH 3 by slow addition of 10% citric acid solution. The urethane was then extracted twice with ethyl acetate, and the combined extracts was washed with brine, dried over anhydrous sodium sulfate, and concentrated to give compound A4-2 as clear viscous oil (180g, yield 100%). MS-ESI:$[M+1]^+$: 262.1

Step 2. A solution of compound A4-2 (40g, 0.153mmol, 1.0eq) in THF (600mL) was treated with 4-methylmorpholine (17g, 0.168, 1.1eq) at room temperature. The resulting mixture was cooled to 0°C before being treated with isobutyl chloroformate (22.7g, 0.166mmol, 1.08eq) dropwise. The resulting reaction mixture was stirred at 0°C for an addition 20mins before being filtered and washed with THF. Then the clear filtrate solution was cooed to 0°C, and treated with a solution of $NaBH_4$ (11.2g, 0.295mol, 1.93eq) in water (100mL). The resulting mixture was stirred overnight at room temperature, and then quenched with an aqueous HCl solution (1.0mol/L,200mL) dropwise, The mixture was extracted with ethyl acetate, and the combined

extracts was washed with brine, dried over anhydrous sodium sulfate, concentrated to give compound A4-3 as a yellow oil (25g, yield 66%). MS-ESI:$[M+1]^+$: 248.1

Step 3. A solution of compound of A4-3 (25g, 0.1mol, 1.0eq) in toluene (300mL) and acetic acid (150mL) was heated to reflux for 5hrs and then cooled, concentrated under vacuum. The residual was added saturated sodium bicarbonate solution to pH 7-8 in ice-bath. Then the mixture was extracted three times with ethyl acetate, and the combined extracts was washed with brine, dried over anhydrous sodium sulfate, concentrated and recrystallized by ethyl acetate and PE to give compound A4-4 as a white powder (8.0g, yield 37.2%). GC-MS: 215

Step 4. A solution of tributyl phosphine (72.9g, 0.36mol, 1.0eq) in nitromethane (500mL), was added dropwise chloroacetonitrile (27.2g, 0.36mol, 1.0eq) in nitrogen atmosphere. The resulting reaction mixture was stirred for 16hrs at room temperature, then concentrated. The residual oil solidified when a small amount of ethyl acetate was added. The solid was recrystallized by ethyl acetate and DCM to afford compound A4-5 as a white powder (95g, yield 95%).

Step 5. To a solution of dry compound A4-5 (8.3g, 30mmol, 3.0eq) in N,N-dimethylacetamide (30mL) in nitrogen atmosphere, was added solid Potassium tert-butoxide (3.1g, 28mmol, 2.8eq) in portions at 0°C. The resulting mixture was gradually warmed to 30°C and stirred for 2hrs. The resulting ylide solution was then treated with compound A4-4 (2.15g, 10mmol, 1.0eq), and stirred overnight at 70°C. After cooled to room temperature, the resulting slurry was poured into the mixture of ice-water (100mL) and saturated sodium bicarbonate solution (100mL). The mixture was extracted twice with ethyl acetate, and the combined extracts was washed three times with brine, dried over anhydrous sodium sulfate, concentrated to give compound A4-6 as yellow oil without purification (7.5g, yield 100%). MS-ESI:$[M+1]^+$: 239.1

Step 6. To a solution of compound A4-6 (7.5g, 10mmol, 1.0eq) in methanol (200mL), was added 10% Pd/C(0.5g,50% wet). Hydrogenation was carried out under atmospheric pressure at room temperature until hydrogen uptake ceased. The catalyst was filtered and washed by methanol. The filtrates was concentrated under vacuum, and purified by silica gel column chromatography to give compound A4-7 as off-white powder (1.6g, yield 66.7%). MS-ESI:$[M+1]^+$: 241.1

Step 7. To a solution of compound A4-7 (1.6g, 6.67mmol, 1.0eq) in DCM (20mL), was added TFA (10g, 88.5mmol, 13.2eq). The reaction mixture was stirred for 2 hrs at room temperature until TLC showed the reaction was complete, then concentrated under vacuum. Water (20mL) was added and the solution was treated with aqueous sodium hydroxide solution (4mol/L) to pH 10. Then the aqueous phase was extracted six times with DCM/methanol (10/1). The combined extracts was dried over anhydrous sodium sulfate, concentrated to give compound A4-8 as light-brown oil (950mg, yield 100%). MS-ESI:$[M+1]^+$: 141.1

Step 8. To a solution of compound A1-14 (prepared as step 4 to 12 in example 1) (600mg, 3.0mmol, 1.0eq) in n-butanol (15mL), was added compound A4-8 (950mg, 6.7mmol, 2.26eq) and DIPEA (1.36g, 10.5mmol, 3.5eq). The reaction mixture was stirred for 1hr at 135°C, concentrated and purified by silica gel column chromatography to give compound A4-9 (2R,5S) as light-yellow powder (254mg, yield 28.0%).MS-ESI: $[M+1]^+$: 303.1.
^{1}H NMR(300MHz, d_6-DMSO): 9.063(s, 1H), 8.503(d, 1H), 9.326(d, 1H), 7.176(d, 1H), 4.431-4.513(m, 1H), 4.128-4.156(m, 1H), 3.633-3.659(m, 1H), 3.448-3.518(m, 1H), 2.775-2.841(m,2H),2.205-2.312(m, 1H), 1.829-1.859(m, 2H), 1.501-1.521(m, 1H).

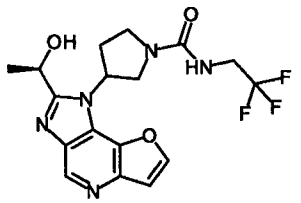
Step 9. To a solution of compound A4-9 (254g, 0.84mmol, 1.0eq) in methanol (20mL), was added 10% Pd/C(0.15g,50% wet). Hydrogenation was carried out under atmospheric pressure at room temperature until hydrogen uptake ceased. The catalyst was filtered and washed by methanol. The filtrates was concentrated under vacuum, and compound A4-10 was obtained as yellow oil (230mg, yield 100%). MS-ESI:$[M+1]^+$: 273.1

Step 10. A solution of D-Lactamide (388mg, 4.2mmol, 5.0eq) and Et_3O-BF_4 (1.3g, 6.72mmol, 8.0eq) in THF (10mL) was stirred for 30mins at room temperature in nitrogen atmosphere. Then the above solution was added to the mixture of compound A4-10 (230mg, 0.84mmol, 1.0eq) in ethanol (10mL). After stirring for 3hrs at 85°C until HPLC showed the reaction was complete, the mixture was concentrated, added water and extracted four times with ethyl acetate. The organic phases was discarded and the aqueous phase was treated with saturated sodium bicarbonate solution to pH 8, extracted twice with ethyl acetate. The second organic phases was

dried over anhydrous sodium sulfate, concentrated and purified by silica gel column chromatography to give the title compound as light-yellow powder (120mg, yield 43.8%). MS-ESI: $[M+1]^+$: 327.6,

^1H NMR(300MHz, $CDCl_3$): 9.039(s, 1H), 7.939(d, 1H), 7.196(d, 1H), 5.235-5.336(m, 1H), 4.806-4.973(m, 1H), 4.403-4.483(t, 1H), 4.096-6.116(m, 2H), 2.700-2.807(m, 4H), 2.105-2.312(m, 2H), 1.830-1.852(d, 3H).

Example 5: Synthesis of 3-[2-[(*R*)-1-Hydroxyethyl]-1H-furo[3,2-b]imidazo[4,5-d] pyridin-1-yl]-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide (5)



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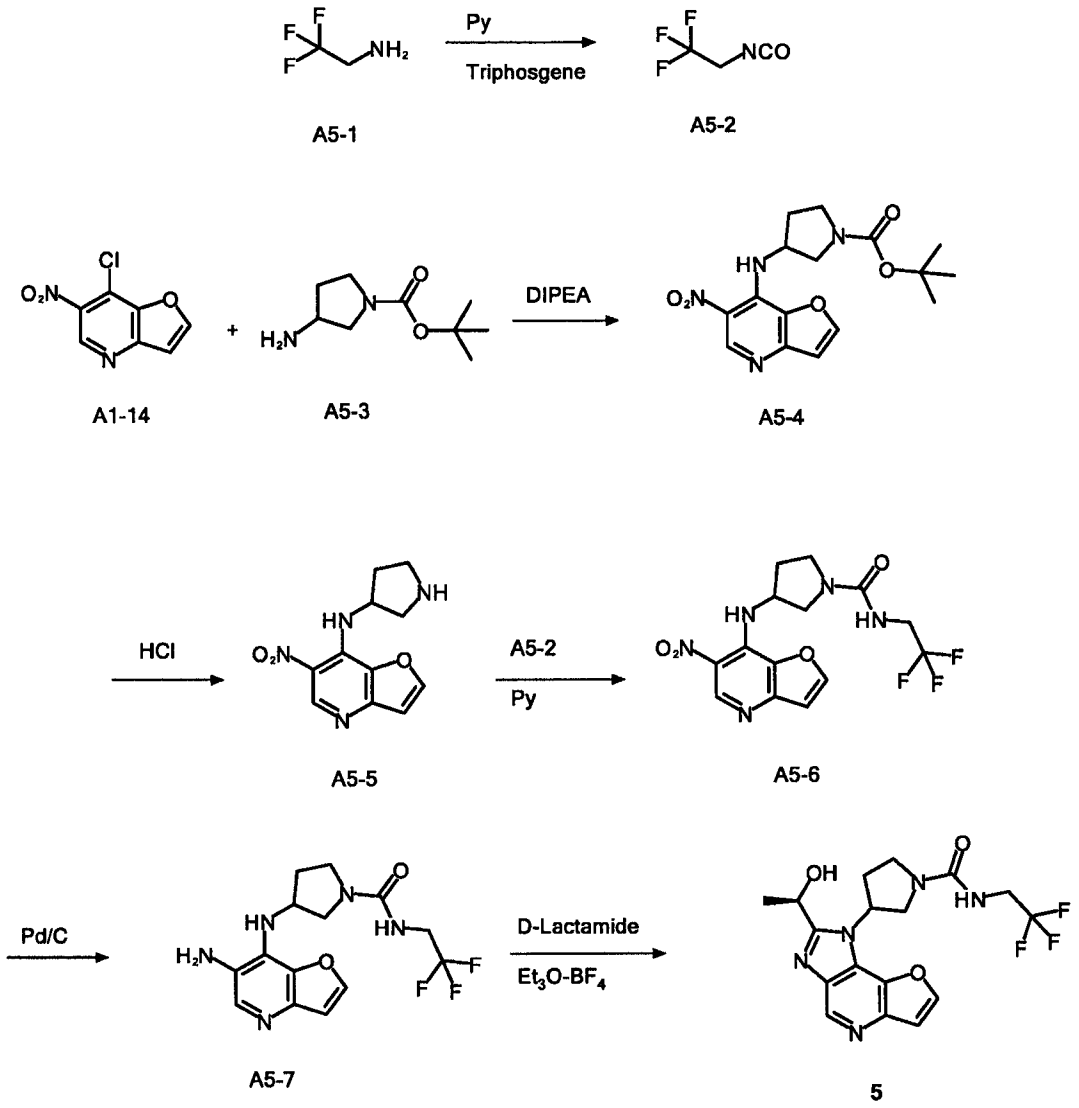
Scheme 5:



Step 1. To a solution of compound A1-14 (prepared as step 4 to 12 in example 1) (820mg, 4.13mmol, 1.0eq) in n-butanol (15mL), was added compound A5-3 (1.0g, 5.37mmol, 1.3eq) and DIPEA (1.6g, 12.4mmol, 3.0eq). The reaction mixture was stirred for 1hr at 135°C, concentrated and purified by silica gel column chromatography to give compound A5-4 as yellow powder (1.32g, yield 91.8%). MS-ESI:$[M+1]^+$: 349.1

Step 2. To a solution of compound A5-4 (1.32g, 3.8mmol, 1.0eq) in DCM (15mL), was added a solution of HCl in ethanol(30%w/w) (15mL). The reaction mixture was stirred for 2hrs at room temperature until TLC showed the reaction was complete, then concentrated under vacuum. Ice-

water (20mL) was added and the solution was treated with aqueous sodium hydroxide solution (4mol/L) to pH 10. Then the aqueous phase was extracted three times with DCM. The combined extracts was dried over anhydrous sodium sulfate, concentrated to give compound A5-5 as yellow powder (950mg, yield 100%). MS-ESI:$[M+1]^+$: 249.1

Step 3. A mixture of 2,2,2-trifluoroethylamine (A5-1) (1.21g, 12.2mmol, 1.0eq) and pyridine (2.4g, 30.5mmol, 2.5eq) in DCM (50mL) was cooled to 0°C, and treated with triphosgene (1.34g, 4.52mmol, 0.37eq) in DCM (50mL) dropwise below 5°C. After addition, the reaction mixture was stirred at 35 °Cfor 1hr and then 25°C for 2hrs. The isocyanate (A5-2) solution was used for next step without purification.

Step 4. A mixture of compound A5-5 (0.95g, 3.8mmol, 1.0eq) and pyridine (0.45g, 5.7mmol, 1.5eq) in DCM (60mL) was cooled to 10°C, and treated with the isocyanate (A5-2) solution (12.2mmol, 3.2eq) dropwise. The reaction mixture was heated to reflux for 3h, and then cooled. Saturated sodium bicarbonate solution (200mL) was added, the mixture was extracted twice with DCM. The combined extracts was washed brine, dried over anhydrous sodium sulfate, concentrated and purified by silica gel column chromatography to give compound A5-6 as yellow powder (850mg, yield 60%). MS-ESI:$[M+1]^+$: 374.3
^{1}H NMR(300MHz, d_6-DMSO): 9.282(s, 1H), 8.718(d, 1H), 7.962(d, 1H),7.024(d, 1H), 5.165-5.186(m, 1H), 4.642(m, 1H), 3.926-4.008(m, 3H), 3.517-3.675(m, 3H), 2.502-2.568(m, 1H), 2.206-2.267(m, 2H).

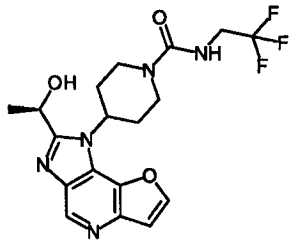
Step 5. To a solution of compound A5-6 (850mg, 2.28mmol, 1.0eq) in methanol (80mL), was added 10% Pd/C (0.45g, 50% wet). Hydrogenation was carried out under atmospheric pressure at room temperature until hydrogen uptake ceased. The catalyst was filtered and washed by methanol. The filtrate was concentrated under vacuum, and compound A5-7 was obtained as brown oil (800mg, yield 100%). MS-ESI:$[M+1]^+$: 344.3

Step 6. A solution of D-Lactamide(1.27g,13.68mmol,6.0eq) and Et3O-BF4 (3.53g, 18.24mmol, 8.0eq) in THF (20mL) was stirred 30min at room temperature in nitrogen atmosphere. Then the above solution was added to the mixture of compound A5-7 (800mg, 2.28mmol, 1.0eq) in

ethanol (20mL). After stirring for 5hrs at 85°C until HPLC showed the reaction was complete, the mixture was concentrated, added HCl (1mol/L,30mL) and extracted four times with ethyl acetate. The organic phases was discarded and the aqueous phase was treated with saturated sodium bicarbonate solution to pH 8, extracted three times with ethyl acetate. The second organic phase was dried over anhydrous sodium sulfate, concentrated and purified by silica gel column chromatography to give the title compound as light-yellow powder (530mg, yield 58.5%). MS-ESI:[M-1]$^-$: 396.5.

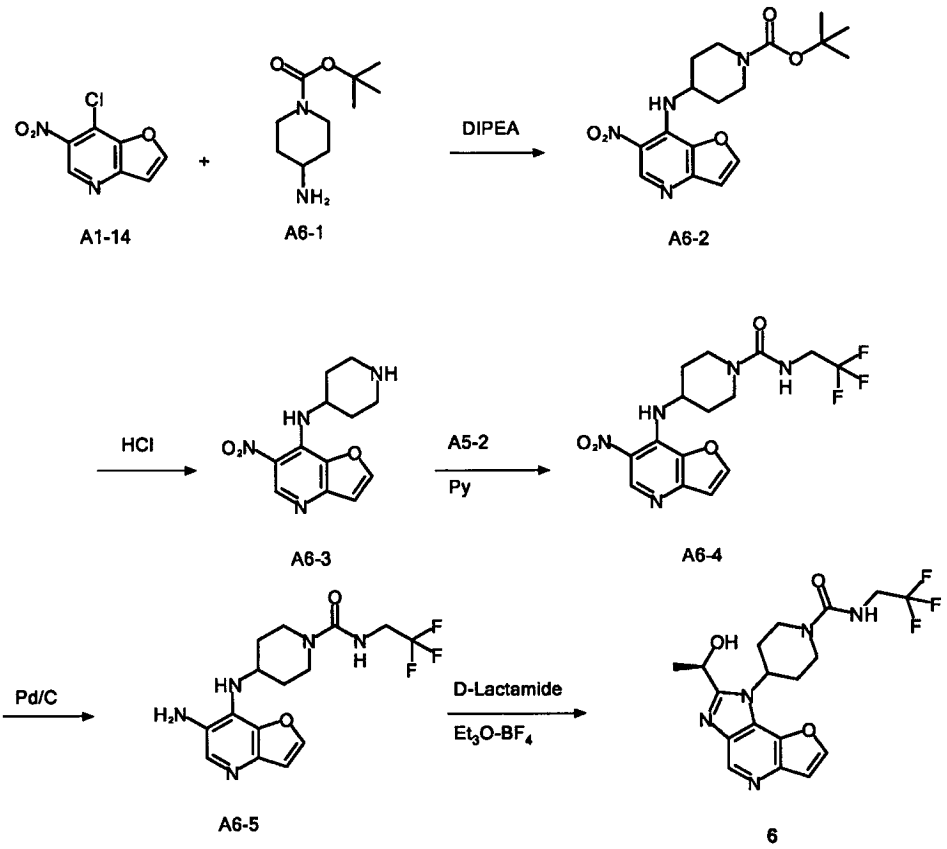
^{1}H NMR(300MHz, d_6-DMSO): 8.931(s, 1H), 8.338(d, 1H), 7.276(d, 1H), 7.007(m, 1H),5.889-5.910(m, 1H), 5.661-5.683(m, 1H), 5.251-5.273(m, 2H), 3.652-3.970(m, 5H), 3.435-3.505(m, 1H), 2.455-2.712(m, 2H), 1.672(d, 3H).

Example 6: Synthesis of (*R*)-4-[2-(1-Hydroxyethyl)-1H-furo[3,2-b]imidazo[4,5-d]pyridin-1-yl]-N-(2,2,2-trifluoroethyl)piperidine-1-carboxamide (6)



6

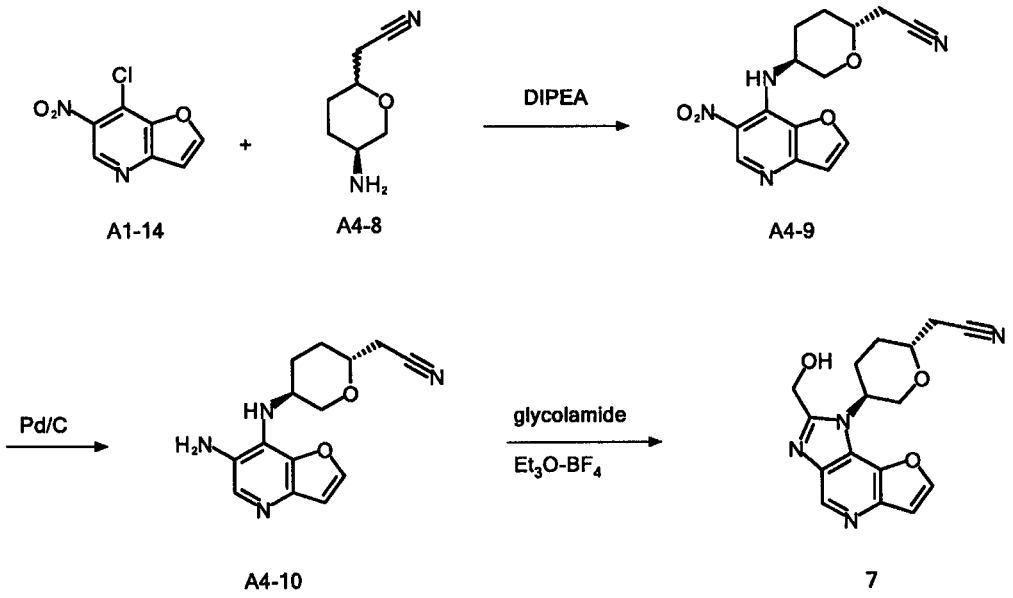
Scheme 6:



The procedures are similar to those in **Example 5** to produce the title compound as an off-white powder (21mg, Yield:6.7%), MS-ESI:[M-1]⁻:410.6.

^{1}H NMR(300MHz, CD3OD): 8.862(s, 1H), 8.046(d, 1H),7.150(d, 1H), 5.152-5.383(m, 2H), 4.325-4.386(m, 2H), 3.990-4.022(m, 2H), 3.110-3.192(m, 2H), 2.423-2.653(m, 2H), 1.984-2.117(m, 2H), 1.793-1.915(d, 3H).

Example 7: Synthesis of 2-[(2R,5S)-5-[2-(Hydroxymethyl)furo[3,2-b]imidazo[4,5-d]pyridin-1-yl]tetrahydropyran-2-yl]acetonitrile (7)



Step 1. In nitrogen atmosphere, to a solution of compound A1-14 (500mg, 2.0mmol, 1.0eq) in butyl alcohol (8mL), were added compound A4-8 (350mg, 2.5mmol, 1.0eq) and DIPEA (403mg, 8.25mmol, 3.3eq). The reaction mixture was stirred 2hrs at 135°C, then concentrated and purified by silica gel column chromatography to give compound A4-9 as yellow solid (194mg, yield 25.6%). MS-ESI:$[M+1]^+$: 302.3

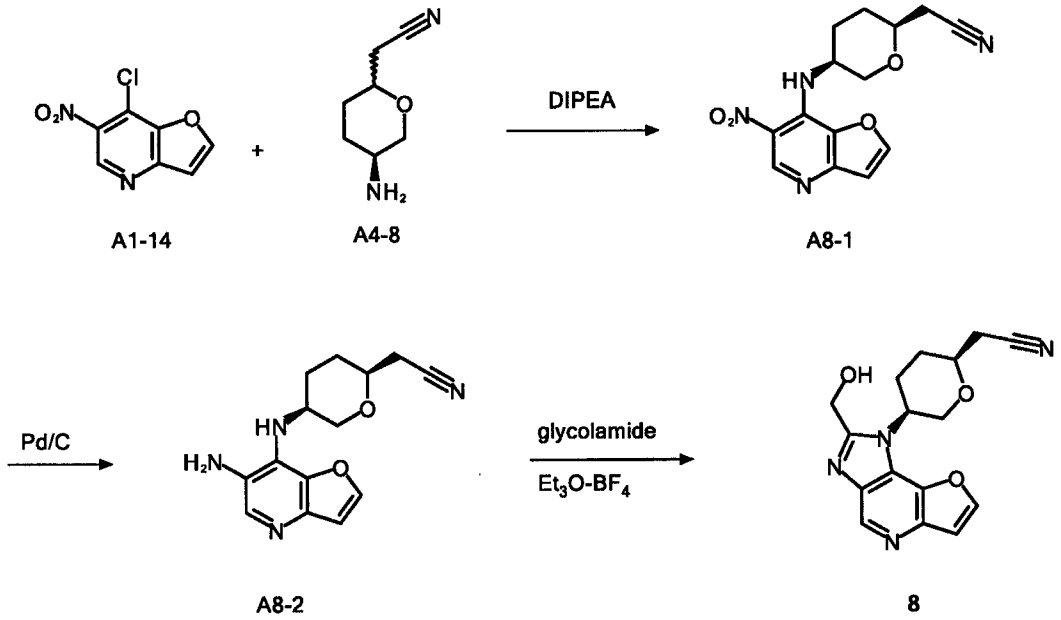
Step 2. To a solution of compound A4-9 (97mg, 1.0mmol) in methanol (15mL), was added 10% Pd/C (50mg, 50% wet). Hydrogenation was carried out under atmospheric pressure at room temperature until hydrogen uptake ceased. The catalyst was filtered and washed by methanol. The filtrate was concentrated to give compound A4-10 as yellow oil (535mg, yield: 100%). MS-ESI: $[M+1]^+$: 272.5

Step 3. A solution of glycolamide (126mg, 1.6mmol, 5.0eq) and Et3O-BF4 (310mg, 1.6mmol, 5.0eq) in THF (10mL) was stirred 30mins at room temperature in nitrogen atmosphere. Then the above solution was added to the mixture of compound A4-10 (88mg, 0.32mmol, 1.0eq) in ethanol (10mL). After stirring 12hrs at 85°C, the mixture was concentrated, added water and extracted three times with ethyl acetate. The organic phases were discarded and the aqueous phase was treated with saturated sodium bicarbonate solution (100mL) to pH: 8, then the mixture was extracted twice with ethyl acetate. The second organic phase was dried over anhydrous

sodium sulfate, concentrated and purified by silica gel column chromatography to give the title compound as an off-white powder (70mg, yield: 70%). MS-ESI: [M+1]+: 313.5

1H NMR(300MHz, $CDCl_3$): 9.00(s, 1H), 7.95(d, 1H),7.26(d, 1H),5.27-5.29(m, 1H), 4.76-4.84(m, 1H), 2.78-2.86(m, 1H), 2.43-2.52(m, 4H), 2.06-2.19(m, 2H), 1.91-2.00(m, 2H), 1.76-1.84(d, 3H).

Example 8: Synthesis of 2-[(2S,5S)-5-[2-(Hydroxymethyl)furo[3,2-b]imidazo[4,5-d]pyridin-1-yl]tetrahydropyran-2-yl]acetonitrile (8)



Step 1. In nitrogen atmosphere, to a solution of compound A1-14 (500mg, 2.0mmol, 1.0eq) in butyl alcohol (8mL), were added compound A4-8 (350mg, 2.5mmol, 1.0eq) and DIPEA (403mg, 8.25mmol, 3.3eq). The reaction mixture was stirred 2hrs at 135°C, then concentrated and purified by silica gel column chromatography to give compound A8-1 as yellow solid (67mg, yield 8.84%).

MS-ESI:$[M+1]^+$: 302.3

Step 2. To a solution of compound A8-1 (67mg, 1.0mmol) in methanol (10mL), was added 10% Pd/C (30mg,50% wet). Hydrogenation was carried out under atmospheric pressure at room temperature until hydrogen uptake ceased. The catalyst was filtered and washed by methanol. The filtrate was concentrated to give compound A8-2 as yellow oil (60mg, yield: 100%).

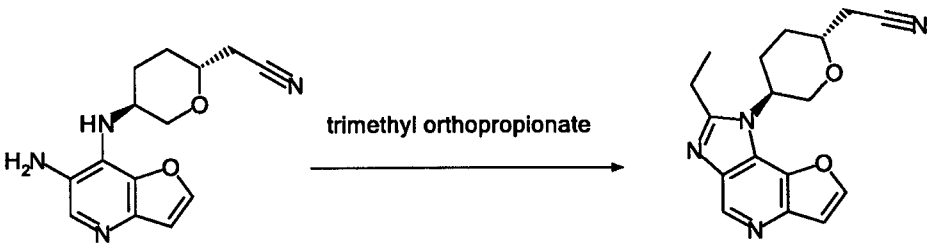
MS-ESI: $[M+1]^+$: 272.5

Step 3. A solution of glycolamide (105mg, 1.33mmol, 6.0eq) and Et_3O-BF_4 (258mg, 1.33mmol, 6.0eq) in THF (10mL) was stirred 30mins at room temperature in nitrogen atmosphere. Then the above solution was added to the mixture of compound A8-2 (60mg, 0.221mmol, 1.0eq) in ethanol (10mL). After stirring 12hrs at 85°C, the mixture was concentrated, added water and extracted three times with ethyl acetate. The organic phases was discarded and the aqueous phase was treated with saturated sodium bicarbonate solution (100mL) to pH: 8, then the mixture was extracted twice with ethyl acetate. The second organic phases was dried over anhydrous sodium sulfate, concentrated and purified by silica gel column chromatography to give the title compound as an off-white powder (21mg, yield: 30.5%).

MS-ESI: $[M+1]^+$: 313.5

^1H NMR(300MHz, CD_3OD): 8.85(s, 1H), 8.29(d, 1H), 7.18(d, 1H), 4.98 (d, 3H), 4.35-4.42 (m, 2H), 3.95-3.99 (m, 1H), 3.48-3.65 (m, 1H), 3.04-3.11 (m, 1H), 2.67-2.76 (m, 1H), 1.97-2.31 (m, 3H).

Example 9: Synthesis of 2-[(2*R*,5*S*)-5-[2-Ethylfuro[3,2-b]imidazo[4,5-d] pyridin-1-yl] tetrahydropyran-2-yl]acetonitrile (9)



A4-10 9

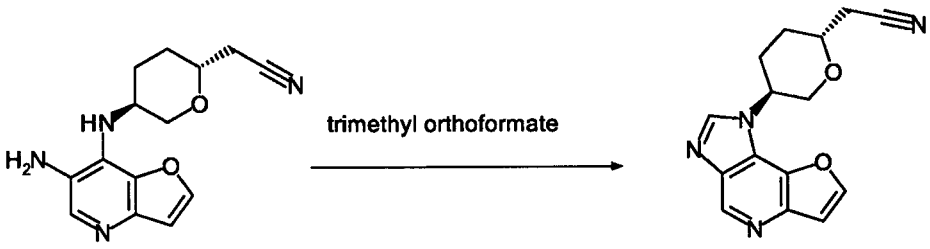
In nitrogen atmosphere, a solution of compound A4-10 (1.1g, 4.04mmol, 1.0eq) and trimethyl ortho-propionate(2.2mL) in 1,2-dichloroethane (50mL) was heated to reflux, and then added pyridine hydrochloride (200mg). The reaction mixture was stirred 2hrs at 80°C, concentrated, and treated with saturated sodium bicarbonate solution to pH: 8. The mixture was and extracted twice with ethyl acetate. The combined organic phases was dried over anhydrous sodium sulfate,

concentrated purified by silica gel column chromatography to give the title compound as a yellow solid (800mg, yield: 63.8%).

MS-ESI: $[M+1]^+$: 311.0

^1H NMR(300MHz, $CDCl_3$): 9.01(s, 1H), 7.91(d, 1H), 7.17(d, 1H), 4.54-4.59(m, 1H), 4.33-4.38(t, 1H), 4.05-4.09(m, 2H), 3.01-3.06(m, 2H), 2.70-2.83(m, 3H), 2.15-2.19(m, 2H), 1.85-1.92(m, 1H), 1.49-1.54(t, 3H).

Example 10: Synthesis of 2-[(2*R*,5*S*)-5-[2-Furo[3,2-b]imidazo[4,5-d] pyridin-1-yl] tetrahydropyran-2-yl]acetonitrile (10)



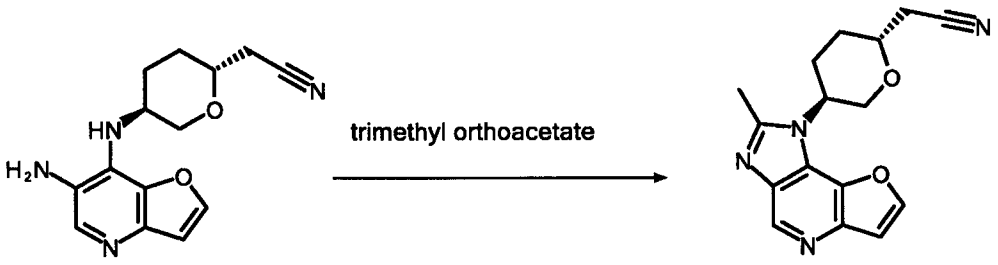
A4-10 10

In nitrogen atmosphere, to a solution of compound A4-10 (136mg, 0.5mmol, 1.0eq) in trimethyl ortho-formate(5.0mL), was added formic acid (1.0mL). The reaction mixture was stirred 1hr at 80°C, concentrated, and treated with saturated sodium bicarbonate solution (100mL) to pH: 8. The mixture was and extracted twice with ethyl acetate. The combined organic phases was dried over anhydrous sodium sulfate, concentrated purified by silica gel column chromatography to give the title compound as a yellow solid (400mg, yield: 28.4%).

MS-ESI: $[M+1]^+$: 282.9

^1H NMR(300MHz, $CDCl_3$): 9.10(s, 1H), 7.94(s, 1H), 7.92(d, 1H), 7.19(d, 1H), 4.76-4.79(m, 1H), 4.32-4.37(m, 1H), 3.92-4.03(m, 2H), 2.71-2.73(d, 2H), 2.46-2.51(m, 2H), 2.17-2.21(m, 1H), 1.89-1.91(m, 1H).

Example 11: Synthesis of 2-[(2*R*,5*S*)-5-[2-Methylfuro[3,2-b]imidazo[4,5-d] pyridin-1-yl] tetrahydropyran-2-yl]acetonitrile (11)



A4-10 11

In nitrogen atmosphere, a solution of compound A4-10 (1.0g, 3.67mmol, 1.0eq) and trimethyl ortho-acetate(2.0mL) in 1,2-dichloroethane (30mL) was heated to reflux, and then added pyridine hydrochloride (200mg). The reaction mixture was stirred 2hrs at 80°C, concentrated, and treated with saturated sodium bicarbonate solution to pH: 8. The mixture was and extracted twice with ethyl acetate. The combined organic phases was dried over anhydrous sodium sulfate, concentrated purified by silica gel column chromatography to give the title compound as yellow solid (500mg, yield: 46.0%).

MS-ESI: $[M+1]^+$: 296.9

^1H NMR(300MHz, $CDCl_3$): 8.98(s, 1H), 7.91(d, 1H), 7.16(d, 1H), 4.54-4.59(m, 1H), 4.31-4.38(t, 1H), 4.02-4.09(m, 2H), 2.71-2.82(m, 6H), 2.15-2.22(m, 2H), 1.85-1.92(m, 1H).

BIOLOGICAL TEST

EXAMPLE B1: Jak1, 2, 3, Tyk2 Biochemical Assays

Assays were performed by Reaction Biology Corp, Malvern, PA. The procedure is briefly described below.

Reagent:

Base Reaction buffer; 20 mM Hepes (pH 7.5), 10 mM $MgCl_2$, 1 mM EGTA, 0.02% Brij35, 0.02 mg/ml BSA, 0.1 mM Na_3VO_4, 2 mM DTT, 1% DMSO. Required cofactors are added individually to each kinase reaction

Reaction Procedure:

1. Prepare indicated substrate in freshly prepared Base Reaction Buffer

2. Deliver any required cofactors to the substrate solution above

3. Deliver indicated kinase into the substrate solution and gently mix

4. Deliver compounds in DMSO into the kinase reaction mixture by Acoustic technology (Echo550; nanoliter range), inclubate for 20 minutes at room temperature

5. Deliver ^{33}P-ATP (specific activity 10 μCi/μl) into the reaction mixture to initiate the reaction.

6. Incubate kinase reaction for 2 hours at room temperature

7. Reactions are spotted onto P81 ion exchange paper

8. Detect kinase activity by filter-binding method.

Activities of compounds are summarized below based on the range of IC50: +: >1 μM; ++: 0.1 – 1 μM; +++: 10 – 100 nM; ++++: <10nM; NT: not tested. Examples 3, 4, 7, 9 are potent and selective Jak1 inhibitors.

Example	Jak1	Jak2
1	++	NT
2	++	NT
3	++++	++
4	++++	++
5	+	+
6	+	+
7	++++	++
8	++	+
9	++++	++
11	++++	+++

EXAMPLE B2: Human Whole blood p-STAT3 assay

Materials and Reagents:

1. Whole blood samples from human donors

2. IL-6 (R&D systems; Cat#206-IL)

3. Thrombopoietin (TPO; R&D systems; Cat# 288-TP)

4. Red Blood Cell Lysis Buffer (Qiagen, Cat#79217)

5. ELISA kit for pSTAT3 (Invitrogen; Cat# KHO0481)

Instruments:

1. Centrifuge

2. Envision; absorbance at 450 nm

Procedure:

1. 150 µl heparinized blood sample/tube.

2. Compounds at various concentrations is added to the blood, incubate for 10 min at RT (10 doses, 2 replicates for each compound).

3. Add IL-6 (final concentration: 100 ng/ml) or TPO (final conc: 50ng/ml) to the blood for 15 min.

4. After the stimulation, add 0.6 mL RBC lysis buffer (Qiagen 79217) and mix and rock for 1-2 minutes at room temperature before centrifugation to remove lyzed RBCs. This step may be repeated once if RBCs are not lyzed completely. Harvest the WBCs.

5. Add 200 µl cell lysis buffer, ice 30min.

6. Centrifuge at 16,000 g, 10 min, 4℃.

7. Transfer the supernatant to a new tube as cell lysate.

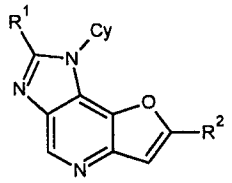
8. Run ELISA procedure according to the product instruction of ELIA kit.

In these assays, Examples 3, 4 and 7 showed selective inhibition of IL-6 induced STAT3 phosphorylation, but not TPO induced STAT3 phosphorylation as shown below based on the range of IC50: +: >100 µM; ++: 20 – 100 µM; +++: 5 – 20 µM; ++++: <5 µM. Example 11 also showed some activity in the TPO induced STAT3 phosphorylation assay.

Example	IL-6	TPO
3	++++	+
4	++++	+
7	++++	+
11	++++	++

What is claimed:

1. A compound of formula **I**:

I 

,

or a pharmaceutically acceptable salt thereof; or a prodrug, or a pharmaceutically acceptable salt of a prodrug thereof; or a hydrate, solvate, or polymorph thereof; wherein:

R^1 is H, halo, or C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, OH, CN, OR, NHR, NRR', N(R)C(=O)R', N(R)C(=O)(O)R', OC(=O)NRR', C(=O)R, C(=O)NRR', $N(R)S(O)_2R'$, $S(O)_2R$, and $S(O)_2NRR'$;

R^2 is H, halo, or C_{1-3} alkyl;

Cy is C_{3-7} cycloalkyl, 3-7 membered heterocyclyl, phenyl, or 5-6 membered heteroaryl, each optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of R^3, oxo, halo, OH, CN, OR, NHR, NRR', N(R)C(=O)R', N(R)C(=O)(O)R', OC(=O)NRR', C(=O)R, C(=O)NRR', $N(R)S(O)_2R'$, $S(O)_2R$, and $S(O)_2NRR'$, wherein R^3 is C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, OH, CN, OR, NHR, NRR', N(R)C(=O)R', N(R)C(=O)(O)R', OC(=O)NRR', C(=O)R, C(=O)NRR', $N(R)S(O)_2R'$, $S(O)_2R$, and $S(O)_2NRR'$;

R, R' each is independently H, or C_{1-3} alkyl optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, OH, and CN.

2. A compound of formula **I** in claim 1 wherein Cy is C_{5-7} cycloalkyl, or 5-7 membered heterocyclyl, each optionally substituted with 1, 2, or 3 substituents independently selected from the group consisting of R^3, oxo, halo, OH, CN, OR, NHR, NRR', N(R)C(=O)R', N(R)C(=O)(O)R', OC(=O)NRR', C(=O)R, C(=O)NRR', $N(R)S(O)_2R'$, $S(O)_2R$, and $S(O)_2NRR'$, wherein R^3 is C_{1-3} alkyl optionally substituted

with 1, 2, or 3 substituents independently selected from the group consisting of halo, OH, CN, OR, NHR, NRR', N(R)C(=O)R', N(R)C(=O)(O)R', OC(=O)NRR', C(=O)R, C(=O)NRR', $N(R)S(O)_2R'$, $S(O)_2R$, and $S(O)_2NRR'$.

3. A compound of formula **I** in claim 1 wherein R^2 is hydrogen.

4. A compound of claim 1 wherein the compound is selected from the group consisting of:

trans-4-[2-[(*R*)-1-Hydroxyethyl]-1H-furo[3,2-b]imidazo[4,5-d]pyridin-1-yl] cyclohexanecarbonitrile (**1**),

trans-4-[2-(Hydroxymethyl)furo[3,2-b]imidazo[4,5-d]pyridin-1-yl] cyclohexanecarbonitrile (**2**),

2-[*trans*-4-[2-[(*R*)-1-Hydroxyethyl]furo[3,2-b]imidazo[4,5-d]pyridin-1-yl]cyclohexyl] acetonitrile (**3**),

2-[(2*R*,5*S*)-5-[2-[(*R*)-1-Hydroxyethyl]furo[3,2-b]imidazo[4,5-d]pyridin-1-yl] tetrahydropyran-2-yl]acetonitrile (**4**),
3-[2-[(*R*)-1-Hydroxyethyl]-1H-furo[3,2-b]imidazo[4,5-d]pyridin-1-yl]-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide (**5**),
(*R*)-4-[2-(1-Hydroxyethyl)-1H-furo[3,2-b]imidazo[4,5-d]pyridin-1-yl]-N-(2,2,2-trifluoroethyl)piperidine-1-carboxamide (**6**),
2-[(2R,5S)-5-[2-(Hydroxymethyl)furo[3,2-b]imidazo[4,5-d]pyridin-1-yl]tetrahydropyran-2-yl]acetonitrile (**7**),
2-[(2S,5S)-5-[2-(Hydroxymethyl)furo[3,2-b]imidazo[4,5-d]pyridin-1-yl]tetrahydropyran-2-yl]acetonitrile (**8**),
2-[(2*R*,5*S*)-5-[2-Ethylfuro[3,2-b]imidazo[4,5-d] pyridin-1-yl] tetrahydropyran-2-yl]acetonitrile (**9**),
2-[(2*R*,5*S*)-5-[2-Furo[3,2-b]imidazo[4,5-d] pyridin-1-yl] tetrahydropyran-2-yl]acetonitrile (**10**),
and

2-[(2*R*,5*S*)-5-[2-Methylfuro[3,2-b]imidazo[4,5-d] pyridin-1-yl] tetrahydropyran-2-yl]acetonitrile (**11**).

5. A method of treating a disease in a subject comprising administering to the subject a compound of any one of claims 1-4.

6. A method of treating a disease in a subject comprising administering to the subject a composition comprising a compound of any one of claims 1-4.

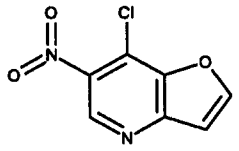
7. The method of claim 5, wherein the disease is mediated by the Jak1 protein kinase.

8. The method of claim 5, wherein the disease is mediated primarily by the Jak1 protein kinase, but also to some extent by the Jak2 protein kinase.

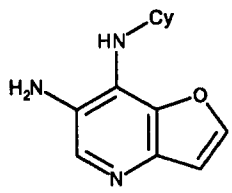
9. The method of any one of the claims 5-8, wherein the disease is an autoimmune disease or disorder, an inflammatory disease or disorder, a cancer or neoplastic disease or disorder.

10. The method of claim 9, wherein the disease is rheumatoid arthritis.

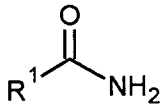
11. The compound of formula **A1-14** which can be used to make compounds of formula **I** in claim 1

A1-14 

12. A process for preparing a compound of claim 1, comprising contacting a compound of formula V:

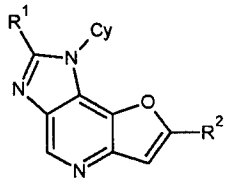
V 

and a compound of formula VI:



VI

in the presence of a $(C_{1-6})_3$ alkyloxonium tetrafluoroborate at sufficient temperature, and for sufficient time to produce a compound of formula I:

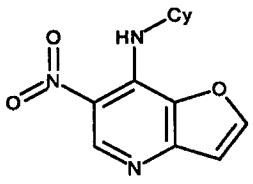


I

wherein R^2 is H, and R^1 and Cy are as defined in claim 1.

13. The process of claim 12, wherein the $(C_{1-6})_3$ alkyloxonium tetrafluoroborate reagent is triethyloxonium tetrafluoroborate.

14. The process of claim 12, wherein the compound of formula V is prepared by a process comprising reducing a compound of formula VII:

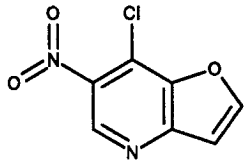


VII

in the presence of a hydrogenation catalyst and hydrogen gas at sufficient temperature, sufficient pressure and for sufficient time to produce a compound of formula V wherein Cy is as defined in claim 1.

15. The process of claim 14, wherein the hydrogenation catalyst is palladium on carbon.

16. The process of claim 14, wherein the compound of formula VII is prepared by a process comprising contacting a compound of formula A1-14:

A1-14 

and a compound of formula VIII:

$$Cy—NH_2$$

VIII

in the presence of a base at sufficient temperature, and for sufficient time to produce a compound of formula VII wherein Cy is as defined in claim 1.

17. The process of claim 16, wherein the base is N,N-Diisopropylethylamine.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/54668

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/4155, A61K 31/437, A61K 31/519 (2017.01)
CPC - A61K 9/0019, A61K 31/4155, A61K 31/437

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)
See Search History Document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/071031 A1 (INCYTE CORPORATION) 08 May 2014 (08.05.2014); pg. 47, ln 16-21, pg. 48, ln 1-5, pg. 57, ln 5-19, pg. 58, ln 21-24, pg. 82, ln 10, pg. 94, ln 1-5	1-8, 11-17
A	US 2015/344497 A1 (Incyte Corporation) 03 December 2015 (03.12.2015); entire document	1-8, 11-17
A	US 2012/0122846 A1 (Calderwood et al.) 17 May 2012 (17.05.2012); entire document	1-8, 11-17
A	WO 2013/024895 A1 (NISSAN CHEMICAL INDUSTRIES, LTD.) 21 February 2013 (21.02.2013); entire document	1-8, 11-17
A	US 2007/0185152 A1 (Yamashita et al.) 09 August 2007 (09.08.2007); para [0035]	1-8, 11-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 November 2017	15 DEC 2017

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 17/54668

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 9-10
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

(19)中华人民共和国国家知识产权局

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权利要求书3页 说明书37页

(54)发明名称

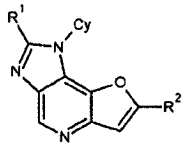
新型Jak1选择性抑制剂及其用途

(57)摘要

新型1H-呋喃并[3,2-b]咪唑并[4,5-d]吡啶衍生物，其是选择性Jak1激酶抑制剂，可用于治疗与Jak1活性有关的障碍，例如自身免疫性疾病或障碍、炎性疾病或障碍以及癌症或肿瘤疾病或障碍。

CN 108366994 A

1.一种式I的化合物：

I 

，

或其药学上可接受的盐；或前药或其前药的药学上可接受的盐；或其水合物、溶剂化物或多晶型物；

其中：

R^1是H、卤素或C_{1-3}烷基，所述C_{1-3}烷基任选被1、2或3个独立选自由卤素、OH、CN、OR、NHR、NRR'、N(R)C(=O)R'、N(R)C(=O)(O)R'、OC(=O)NRR'、C(=O)R、C(=O)NRR'、N(R)S(O)$_2$R'、S(O)$_2$R和S(O)$_2$NRR'组成的组的取代基所取代；

R^2是H、卤素或C_{1-3}烷基；

Cy是C_{3-7}环烷基、3-7元杂环基、苯基或5-6元杂芳基，各自任选被1、2或3个独立选自由R^3、氧代、卤素、OH、CN、OR、NHR、NRR'、N(R)C(=O)R'、N(R)C(=O)(O)R'、OC(=O)NRR'、C(=O)R、C(=O)NRR'、N(R)S(O)$_2$R'、S(O)$_2$R和S(O)$_2$NRR'组成的组的取代基所取代，其中R^3为C_{1-3}烷基，其任选被1、2或3个独立选自由卤素、OH、CN、OR、NHR、NRR'、N(R)C(=O)R'、N(R)C(=O)(O)R'、OC(=O)NRR'、C(=O)R、C(=O)NRR'、N(R)S(O)$_2$R'、S(O)$_2$R和S(O)$_2$NRR'组成的组的取代基所取代；

R、R'各自独立地为H或C_{1-3}烷基，所述C_{1-3}烷基任选被1、2或3个独立选自由卤素、OH和CN组成的组的取代基所取代。

2.根据权利要求1所述的式I化合物，其中Cy为C_{5-7}环烷基或5-7元杂环基，各自任选被1、2或3个独立选自由R^3、氧代、卤素、OH、CN、OR、NHR、NRR'、N(R)C(=O)R'、N(R)C(=O)(O)R'、OC(=O)NRR'、C(=O)R、C(=O)NRR'、N(R)S(O)$_2$R'、S(O)$_2$R和S(O)$_2$NRR'组成的组的取代基所取代，其中R^3为C_{1-3}烷基，所述C_{1-3}烷基任选被1、2或3个独立选自由卤素、OH、CN、OR、NHR、NRR'、N(R)C(=O)R'、N(R)C(=O)(O)R'、OC(=O)NRR'、C(=O)R、C(=O)NRR'、N(R)S(O)$_2$R'、S(O)$_2$R和S(O)$_2$NRR'组成的组的取代基所取代。

3.根据权利要求1所述的式I化合物，其中R^2是氢。

4.根据权利要求1所述的化合物，其中所述化合物选自由下列组成的组：

反式-4-[2-[(R)-1-羟乙基]-1H-呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]环己烷甲腈(1)，

反式-4-[2-(羟甲基)呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]环己烷甲腈(2)，

2-[反式-4-[2-(R)-1-羟乙基]呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]环己基]乙腈(3)，

2-[(2R,5S)-5-[2-[(R)-1-羟乙基]呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]四氢吡喃-2-基]乙腈(4)，

3-[2-[(R)-1-羟乙基]-1H-呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]-N-(2,2,2-三氟乙基)吡咯烷-1-甲酰胺(5)，

(R)-4-[2-(1-羟乙基)-1H-呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]-N-(2,2,2-三氟乙基)哌啶-1-甲酰胺(6)，

2-[(2R,5S)-5-[2-(羟甲基)呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]四氢吡喃-2-基]乙腈(7)，

2-[(2S,5S)-5-[2-(羟甲基)呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]四氢吡喃-2-基]乙腈(8)，

2-[(2R,5S)-5-[2-乙基呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]四氢吡喃-2-基]乙腈(9)，

2-[(2R,5S)-5-[2-呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]四氢吡喃-2-基]乙腈(10)，

和

2-[(2R,5S)-5-[2-甲基呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]四氢吡喃-2-基]乙腈(11)。

5.一种治疗受试者中疾病的方法，包括向所述受试者施用权利要求1-4中任一项所述的化合物。

6.一种治疗受试者中疾病的方法，包括向所述受试者施用包含权利要求1-4中任一项所述化合物的组合物。

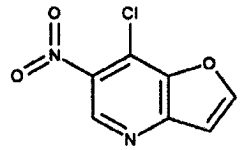
7.根据权利要求5所述的方法，其中所述疾病是由Jak1蛋白激酶介导的。

8.根据权利要求5所述的方法，其中所述疾病主要是由Jak1蛋白激酶介导的，但也在某种程度上由Jak2蛋白激酶介导。

9.根据权利要求5-8中任一项所述的方法，其中所述疾病是自身免疫性疾病或障碍、炎性疾病或障碍、癌症或肿瘤疾病或障碍。

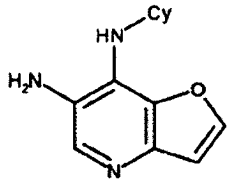
10.根据权利要求9所述的方法，其中所述疾病是类风湿性关节炎。

11.能够用于制备权利要求1中式I化合物的式A1-14化合物

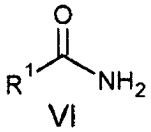
A1-14 

。

12.一种用于制备权利要求1的化合物的方法，包括使式V的化合物：

V 

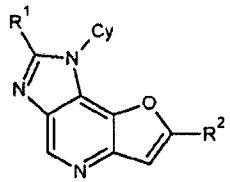
与式VI的化合物：



VI

接触，

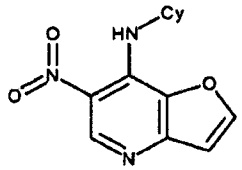
在$(C_{1-6})_3$烷基氧鎓四氟硼酸盐的存在下，在足够的温度下并进行足够的时间以产生式I的化合物：

I 

其中R^2是H，且R^1和Cy如权利要求1中所定义。

13.根据权利要求12所述的方法，其中所述$(C_{1-6})_3$烷基氧鎓四氟硼酸盐试剂是三乙基氧鎓四氟硼酸盐。

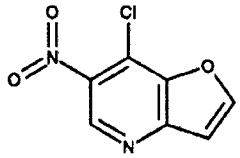
14.根据权利要求12所述的方法，其中式V的化合物通过以下方法制备，包括还原式VII的化合物：

VII 

在加氢催化剂和氢气存在下，在足够的温度、足够的压力下并进行足够的时间以产生式V的化合物，其中Cy如权利要求1所定义。

15.根据权利要求14所述的方法，其中所述加氢催化剂是钯碳。

16.根据权利要求14所述的方法，其中所述式VII的化合物通过以下方法制备，包括使式A1-14的化合物：

A1-14 

与式VIII的化合物：

$Cy-NH_2$

VIII

接触，

在碱的存在下，在足够的温度下进行足够的时间以产生式VII的化合物，其中Cy如权利要求1中所定义。

17.根据权利要求16所述的方法，其中所述碱是N,N-二异丙基乙胺。

新型Jak1选择性抑制剂及其用途

[0001] 相关申请的交叉引用

[0002] 本申请要求2016年10月3日提交的序列号为62/403,660的美国临时申请的优先权,其全部内容通过引用合并于此。

技术领域

[0003] 本发明涉及作为选择性Jak1激酶抑制剂的新型1H-呋喃并[3,2-b]咪唑并[4,5-d]吡啶衍生物,它们药学上可接受的盐、溶剂化物、水合物和多晶型物。本发明还提供了包含本发明化合物的组合物以及这些组合物在治疗与Jak1相关的疾病和病状的方法中的用途,并且可用于治疗与Jak1活性相关的障碍,例如自身免疫性疾病或障碍、炎性疾病或障碍以及癌症或者肿瘤疾病或障碍。

背景技术

[0004] 蛋白激酶代表了在调节多种细胞过程和维持细胞功能中发挥重要作用的一大家族的蛋白质。这些激酶的部分非限制性清单包括:非受体酪氨酸激酶,如Janus激酶家族(Jak1、Jak2、Jak3和Tyk2);受体酪氨酸激酶,如血小板衍生生长因子受体激酶(PDGFR);和丝氨酸/苏氨酸激酶,如b-RAF。在许多疾病状态中观察到异常的激酶活性,包括良性和恶性增殖性障碍以及免疫和神经系统的不适当激活导致的疾病。本发明化合物选择性抑制一种或多种蛋白激酶相对于其他相关激酶的活性,并且因此预计可用于治疗由选择性抑制的一种或多种激酶介导的疾病,同时避免与相关激酶的抑制有关的不良副作用。

[0005] 具体而言,Janus激酶家族包含4个已知的家族成员:Jak1、Jak2、Jak3和酪氨酸激酶2(Tyk2)。这些细胞质酪氨酸激酶与膜细胞因子受体(例如常见的γ-链受体和糖蛋白130(gp130)跨膜蛋白)相关(Murray,J.Immunol.178(5):2623-2629,2007)。几乎40种细胞因子受体通过这4种Jak家族成员及其7种下游底物的组合发出信号:转录(STAT)家族成员的信号转导激活剂(Ghoreschi等,Immunol Rev.228(1):273-287,2009)。与其受体结合的细胞因子经由相互和自身磷酸化启动Jak激活。Jak家族激酶反过来使细胞因子受体残基磷酸化,为含有肉瘤同源性2(SH2)的蛋白质(如STAT因子和其他调节剂)产生结合位点,随后由Jak磷酸化激活。活化的STAT进入细胞核,开始促进白细胞细胞运输的存活因子、细胞因子、趋化因子和分子的表达(Schindler等,J.Biol.Chem.282(28):20059-20063,2007)。Jak激活还经由磷酸肌醇3-激酶(PI3K)和蛋白激酶B介导的途径导致细胞增殖。

[0006] Jak3和Jak1是常见γ-链细胞因子受体复合物的组分,并且这两者任一种的阻断抑制炎性细胞因子(白细胞介素(IL)-2,4,7,9,15和21)的信号传导(Ghoreschi等,Immunol.Rev.228(1):273-287,2009)。相比之下,其他病理上相关的细胞因子(如IL-6)仅依赖于Jak1。因此,Jak1阻断抑制了许多促炎细胞因子的信号传导(Guschin et al,EMBO J.14(7):1421-1429,1995)。观察到IL-6受体中和抗体—托珠单抗在类风湿性关节炎(RA)中的临床疗效(Maini等,Arthritis Rheum.54(9):2817-2829,2006)。

[0007] 人类对Jak1和Jak2的缺乏尚未被描述。缺乏Jak1的小鼠在围产期死亡(Schindler

等,J.Biol Chem.282(28):20059-20063,2007)。小鼠中的Jak2缺陷也是致命的,由于红细胞生成缺陷,$Jak2^{-/-}$胚胎在受孕后第12天和第13天之间死亡(Neubauer等,Cell 93(3):397-409,1998)。已描述了在人类中的Jak3缺陷,并且在生命的最初几个月表现为严重的联合免疫缺陷,出现诸如发育停滞、严重和反复感染、鹅口疮和腹泻等症状。具有Jak3缺陷的婴儿缺乏循环T细胞和NK细胞并且具有不正常B细胞功能。另外,已描述了在人类中的Tyk2-缺陷,表现为抗微生物应答受损、血清IgE升高和特应性皮炎(Minegishi等,Immunity 25(5):745-755,2006)。

[0008] 鉴于Jak1和Jak2之间的高度结构相似性(Williams等,J.Mai.Biol.387(1):219-232,2009),文献表明大多数Jak1抑制剂也抑制Jak2(Incyte Corp.press release,10Nov.2010;Changelian等,Science 302(5646):875-878,2003)。

[0009] 抗细胞因子疗法已经成为RA治疗的标准。在人类中,越来越多的证据表明Jak1抑制是用于治疗RA的病征和症状的有效疗法。多个临床试验已经证明了施用Pfizer的Jak 1/3抑制剂—托法替尼(tofacitinib)(Kremer等,Arthritis Rheum.60(7):1895-1905,2009;Riese等Best Pract.Res.Clin.Rheumatol.24(4):513-526,2010)、Incyte/Lilly的Jak 1/2抑制剂—INCB-28050/LY3009104(Incyte Corp.press release,11月10日,2010)或者Galapagos的Jak1抑制剂—GLP0634(Galapagos NV press release,11月22日,2011)在这种疾病中有统计学意义的显著疗效。

[0010] 对于对甲氨蝶呤(MTX)不充分应答或不耐受的中度至严重活动性RA的成年患者,托法替尼—Jak1和Jak3的抑制剂,其用作单一疗法或者与MTX或其他非生物DMARD组合已在美国和世界其他国家被批准。与安慰剂相比,对于托法替尼的RA患者2期和3期研究的安全性数据(Fleischmann,Curr.Opin.Rheumatol.24(3):335-341,2012;Kremer等,Arthritis Rheum.64(4):970-981,2012;Fleischmann等,Arthritis Rheum.64(3):617-629,2012)表明,最常见的严重不良反应是感染,包括肺炎、蜂窝组织炎、带状疱疹和尿路感染。此外,还报告了结核病(包括播散性结核的病例)和机会性感染,如其他分枝杆菌感染、隐球菌、食道念珠菌、肺囊虫病、多发性带状疱疹、巨细胞病毒和BK病毒。在用托法替尼治疗的患者中观察到淋巴瘤和其他恶性肿瘤。在用托法替尼和伴随免疫抑制药物治疗的肾移植患者中观察到EB(Epstein-Barr)病毒相关的移植后淋巴组织增殖性障碍增加。也报告了接受托法替尼的患者胃肠穿孔。此外,还描述了实验室异常情况,包括与绝对中性粒细胞计数和血红蛋白剂量相关的下降。此外,报道了肝转氨酶(丙氨酸转氨酶[ALT]、天冬氨酸转氨酶[AST])和血清肌酸酐的小幅增加,以及LDL、HDL和总胆固醇水平的升高。

[0011] VX-509(Jak3的抑制剂)在RA患者中的2期研究也显示了感染风险的增加和血脂水平的增加(Fleischmann等,Arthritis Rheum.63:LB3,2011)。

[0012] 在201例活动期RA患者中,巴西替尼(baricitinib)(一种口服给药选择性Jak1和Jak2抑制剂)的长达52周的开放标签的长期延长的2b期研究中未发现机会性感染、结核病或淋巴瘤病例。偶尔观察到临床上显著的实验室异常(ALT增加、贫血、肌酸激酶[CK]增加、全血细胞减少,各自报告一个受试者);由于实验室异常(ALT升高),一个受试者终止。发生一例死亡并且归因于推测的心肌梗塞(Keystone等,Ann.Rheum.Dis.71(Suppl 3):152,2012;Genovese等,Arthritis Rheum.64(Suppl 10):2487,2012;Taylor等,abstract OP0047,EULAR 2013,the Annual Congress of the European League Against

Rheumatism.2013六月12-15;Madrid,Spain)。

[0013] 尽管看似有许多治疗选择,但是许多RA患者难以体会到疾病活动的实质性减少。尽管早期研究显示Jak阻断剂可能有效控制疾病并达到缓解,但第一代Jak抑制剂(如托法替尼和巴西替尼)未能达到其全部潜力,至少部分原因是其限制剂量的耐受性和安全性问题。

[0014] 具体而言,第一代Jak抑制剂托法替尼和巴西替尼分别表征为Jak1/Jak3抑制剂和Jak1/Jak2抑制剂(Fridman等,J.Immunol.,184:5298-5307,2010;Meyer等,J.Inflamm.(Lond.)7:41,2010;和Taylor等,Rheumatology 52:i44-i55,2013)。尽管有初步令人鼓舞的结果,但由于限制剂量的耐受性问题,这些第一代Jak抑制剂未能达到其全部潜力(Fleischmann等,Curr.Opin.Rheumatol.24:335-341,2012;Riese等,Best Pract.Res.Clin.Rheumatol.24:513-526,2010)。已知JAK在40多种途径的调控中发挥作用(Murray,J.Immunol.178:2623-2629,2007)。然而,尽管这两种化合物对JAK的选择性高于其他激酶家族,但这些抑制剂可能对JAK家族内的激酶没有最佳的选择性。例如,在RA中的托法替尼II期开发期间,严重贫血的发生率被报道为剂量限制因素(Pfizer,Investigators Brochure.In FDA Advisory Board(Bethesda MD),2012;Riese等,Best Pract.Res.Clin.Rheumatol.24:513-526,2010)。此外,在III期托法替尼试验中报道了疱疹病毒感染增加(可能继发于NK细胞计数降低)(O'Shea等,Ann.Rheum.Dis.72(Suppl 2):iil 11-115,2013;Pfizer,Investigators Brochure.In FDA Advisory Board(Bethesda MD),2012)。由于分别经由Jak2和Jak3抑制EPO和IL-15信号传导,出现这些现象是合理的(Jost和Altfeld,Annu.Rev.Immunol.31:163-194,2013;Kennedy等,J.Exp.Med.191:771-780,2000;和Richmond等,Trends Cell Biol.15:146-155,2005)。事实上,干预治疗与RA有关的贫血的失败可能会限制对治疗的完全成功反应的机会。

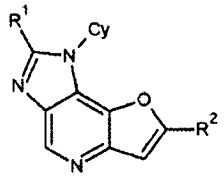
[0015] 因此,通过使用Jak抑制剂的当前治疗选择存在未满足的医疗需求。寻找Jak1选择性抑制剂的努力正在进行中(Zak等J.Med.Chem.2013,56,4764-4785;Menet等Future Med.Chem.2015,7,203-235;WO2013/007768)。突出的正在开发的Jak1选择性化合物有GLPO634、ABT-494(WO2015/061665),以及来自Incyte的最近专利公开(WO2015/168246)中的化合物,但是还没有Jak1选择性抑制剂被批准。

[0016] 本文中,新型1H-呋喃并[3,2-b]咪唑并[4,5-d]吡啶衍生物被描述为Jak1选择性抑制剂。这些化合物和包含本发明化合物的组合物可用于治疗与Jak1活性有关的障碍,例如自身免疫性疾病或障碍,或者炎性疾病或障碍,以及癌症或者肿瘤疾病或障碍。

发明内容

[0017] 本发明公开了作为选择性Jak1激酶抑制剂的新型1H-呋喃并[3,2-b]咪唑并[4,5-d]吡啶衍生物,它们药学上可接受的盐、溶剂化物、水合物和多晶型物。本发明还提供了包含本发明化合物的组合物以及这些组合物在治疗与Jak1相关的疾病和病状的方法中的用途。

[0018] 本发明通过提供单独的式I化合物解决了上述问题:

[0019] I 

[0020] 或其药学上可接受的盐;或前药或其前药的药学上可接受的盐;或其水合物、溶剂化物或多晶型物;

[0021] 其中:

[0022] R^1是H、卤素或C_{1-3}烷基,所述C_{1-3}烷基任选被1、2或3个独立选自由卤素、OH、CN、OR、NHR、NRR'、N(R)C(=O)R'、N(R)C(=O)(O)R'、OC(=O)NRR'、C(=O)R、C(=O)NRR'、N(R)S(O)$_2$R'、S(O)$_2$R和S(O)$_2$NRR'组成的组的取代基所取代;

[0023] R^2是H、卤素或C_{1-3}烷基;

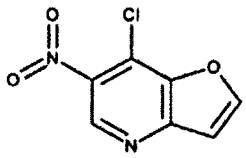
[0024] Cy是C_{3-7}环烷基、3-7元杂环基、苯基或5-6元杂芳基,各自任选被1、2或3个独立选自由R^3、氧代、卤素、OH、CN、OR、NHR、NRR'、N(R)C(=O)R'、N(R)C(=O)(O)R'、OC(=O)NRR'、C(=O)R、C(=O)NRR'、N(R)S(O)$_2$R'、S(O)$_2$R和S(O)$_2$NRR'组成的组的取代基所取代,其中R^3为C_{1-3}烷基,其任选被1、2或3个独立选自由卤素、OH、CN、OR、NHR、NRR'、N(R)C(=O)R'、N(R)C(=O)(O)R'、OC(=O)NRR'、C(=O)R、C(=O)NRR'、N(R)S(O)$_2$R'、S(O)$_2$R和S(O)$_2$NRR'组成的组的取代基所取代;

[0025] R、R'各自独立地为H或C_{1-3}烷基,所述C_{1-3}烷基任选被1、2或3个独立选自由卤素、OH和CN组成的组的取代基所取代。

[0026] 本发明的化合物和包含它们的组合物可用于治疗Jak1调节的疾病、障碍或其症状或者减轻它们的严重性。

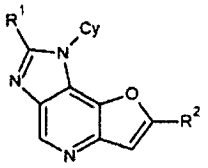
[0027] 在另一方面,本发明涉及治疗有需要的受试者的疾病或疾病症状的方法,包括向受试者施用有效量的本文的式I化合物或其药学上可接受的盐、溶剂化物或水合物(或其组合物)。该疾病或疾病症状可以是Jak1调节的任何疾病或疾病症状。例如,该疾病或疾病症状可以是自身免疫性疾病或障碍,例如类风湿性关节炎或炎症性疾病或障碍,以及癌症或肿瘤增殖性疾病或障碍(例如,包括本文中描述的那些)。

[0028] 在另一方面,本发明涉及式A1-14的化合物:

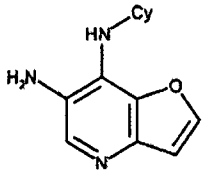
[0029] A1-14 

[0030] 其在用于制备式I化合物的方法中有用。

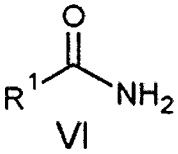
[0031] 在另一方面,本发明涉及制备式I化合物的方法:

[0032] I 

[0033] 包括将式V的化合物:

[0034] V 

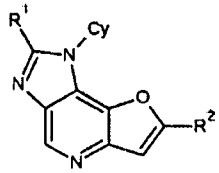
[0035] 和式VI的化合物：

[0036] 

VI

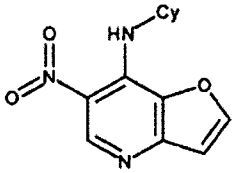
[0037] 接触，

[0038] 在$(C_{1-6})_3$烷基氧鎓四氟硼酸盐的存在下，在足够的温度下，进行足够的时间以产生式I的化合物：

[0039] I 

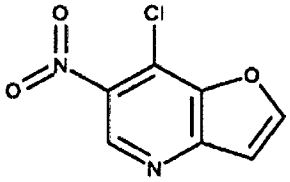
[0040] 其中R^2是H，并且R^1和Cy如上所定义。$(C_{1-6})_3$烷基氧鎓四氟硼酸盐可以是三乙基氧鎓四氟硼酸盐。

[0041] 在另一方面，本发明涉及制备式V化合物的方法，其包括还原式VII的化合物：

[0042] VII 

[0043] 在加氢催化剂和氢气存在下，在足够的温度、足够的压力下并进行足够的时间以产生式V的化合物，其中Cy如上所定义。加氢催化剂可以是钯碳。

[0044] 在另一方面，本发明涉及制备式VII化合物的方法，其包括使式A1-14的化合物：

[0045] A1-14 

[0046] 和式VIII的化合物：

[0047] $Cy-NH_2$

[0048] VIII

[0049] 接触，

[0050] 在碱存在下，在足够的温度下，进行足够的时间以产生式VII的化合物，其中Cy如上定义。碱可以是N,N-二异丙基乙胺。

具体实施方式

[0051] 定义

[0052] 术语“改善”和“治疗”可互换使用，并且均意味着降低、抑制、减弱、减少、阻止或稳

定疾病(例如,本文描述的疾病或障碍)的发展或进展。

[0053] “疾病”是指损害或干扰细胞、组织或器官的正常功能的任何状态或障碍。

[0054] “标记”是指与疾病或障碍相关的任何改变。例如,具有与疾病或障碍相关的表达水平或活性改变的任何蛋白质或多核苷酸。

[0055] 在本公开中,“包含(comprises、comprising)”、“含有(containing)”和“具有”等可以具有美国专利法中赋予它们的含义,并且可以表示“包括”(includes,including)等;“基本上由...组成(consisting essentially of或consists essentially)”同样具有美国专利法中所赋予的含义,并且该术语是开放式的,允许存在多于所叙述的内容,只要所叙述内容的基本或新颖特征是不会因存在多于所叙述的而改变,但不包括现有技术实施例。

[0056] 如本文所用,术语“化合物”还旨在包括本文式的化合物的药学上可接受的盐、前药和前药盐。该术语还包括前述任何溶剂化物、水合物和多晶型物。在本申请描述的本发明的某些方面中,“前药”、“前药盐”、“溶剂化物”、“水合物”或“多晶型物”的具体叙述不应被解释为在本发明的其他方面中(其中使用术语“化合物”而没有列举这些其他形式)意图省略这些形式。

[0057] 本发明化合物的盐在酸和该化合物的碱性基团(例如氨基官能团)之间形成,或者在碱和该化合物的酸性基团(例如羧基官能团)之间形成。根据另一个优选的实施方案,该化合物是药学上可接受的酸加成盐。

[0058] 如本文所用且除非另外指出,术语“前药”是指在生物条件下(体外或体内)可水解、氧化或以其他方式反应以提供本发明化合物的化合物的衍生物。在生物条件下前药只能在这种反应中变得活跃,或者它们可能具有未反应形式的活性。本发明所涉及的前药的实例包括但不限于本文公开的任何一个式的化合物的类似物或衍生物,其包含可生物水解的部分,例如酰胺、酯、氨基甲酸酯、碳酸酯和磷酸酯类似物。通常可以使用熟知的方法制备前药,例如由Burger's Medicinal Chemistry and Drug Discovery(1995)172-178,949-982(Manfred E.Wolff ed.,5th ed)所述的那些;也参见Goodman和Gilman's,The Pharmacological basis of Therapeutics,8th ed.,McGraw-Hill,Int.Ed.1992,“Biotransformation of Drugs”。

[0059] 如本文所用且除非另外指出,术语“生物可水解部分”是指官能团(例如,酰胺、酯、氨基甲酸酯、碳酸酯或磷酸酯类似物,其:1)不破坏化合物的生物活性并赋予该化合物在体内有利的性质,例如摄取、作用持续时间或起效;或2)本身是无生物活性的,但在体内转化为生物活性化合物。

[0060] 前药盐是在酸和该前药的碱性基团(例如氨基官能团)之间形成的化合物,或者是在碱和该前药的酸性基团(例如羧基官能团)之间形成的化合物。在一个实施方案中,前药盐是药学上可接受的盐。

[0061] 特别有利的前药和前药盐是这些:当将这样的化合物给予哺乳动物时增强本发明化合物的生物利用度(例如,通过使口服给药的化合物更容易被吸收到血液中),或者相对于亲本物种增强母体化合物向生物区室(例如脑或中枢神经系统)的递送。优选的前药包括衍生物,其中增强水溶性或通过肠膜的主动运输的基团附加到本文所述式的结构。例如参见Alexander,J.等Journal of Medicinal Chemistry 1988,31,318-322;Bundgaard,H.Design of Prodrugs;Elsevier:Amsterdam,1985;pp 1-92;Bundgaard,H.;Nielsen,

N.M.Journal of Medicinal Chemistry 1987,30,451-454;Bundgaard,H.A Textbook of Drug Design and Development;Harwood Academic Publ.:Switzerland,1991;pp 113-191;Digenis,G.A.等Handbook of Experimental Pharmacology 1975,28,86-112;Friis,G.J.;Bundgaard,H.A Textbook of Drug Design and Development;2ed.;Overseas Publ.:Amsterdam,1996;pp351-385;Pitman,I.H.Medicinal Research Reviews 1981,1,189-214。

[0062] 如本文所用,术语"药学上可接受的"是指在合理的医学判断范围内适合用于与人和其他哺乳动物的组织接触而没有不适当的毒性、刺激性、过敏反应等的组分,并且与合理的利益/风险比相称。"药学上可接受的盐"是指任何无毒的盐,其在给予接受者时能够直接或间接提供本发明的化合物或本发明的化合物的前药。

[0063] 通常用于形成药学上可接受的盐的酸包括:无机酸,如二硫化氢、盐酸、氢溴酸、氢碘酸、硫酸和磷酸;以及有机酸,如对甲苯磺酸、水杨酸、酒石酸、二酒石酸、抗坏血酸、马来酸、苯磺酸、富马酸、葡糖酸、葡糖醛酸、甲酸、谷氨酸、甲磺酸、乙磺酸、苯磺酸、乳酸、草酸、对溴苯磺酸、碳酸、琥珀酸、柠檬酸、苯甲酸和乙酸,以及相关的无机酸和有机酸。因此这些药学上可接受的盐包括:硫酸盐、焦硫酸盐、硫酸氢盐、亚硫酸盐、亚硫酸氢盐、磷酸盐、磷酸一氢盐、磷酸二氢盐、偏磷酸盐、焦磷酸盐、氯化物、溴化物、碘化物、乙酸盐、丙酸盐、癸酸盐(decanoate)、辛酸盐、丙烯酸盐、甲酸盐、异丁酸盐、癸酸盐(caprate)、庚酸盐、丙炔酸盐(propiolate)、草酸盐、丙二酸盐、琥珀酸盐、辛二酸盐、癸二酸盐、富马酸盐、马来酸盐、丁炔-1,4-二酸盐、己炔-1,6-二酸盐、苯甲酸盐、氯苯甲酸盐、苯甲酸甲盐、二硝基苯甲酸盐、羟基苯甲酸盐、甲氧基苯甲酸盐、邻苯二甲酸盐、对苯二甲酸盐、磺酸盐、二甲苯磺酸盐、苯乙酸盐、苯丙酸盐、苯丁酸盐、柠檬酸盐、乳酸盐、□-羟基丁酸盐、乙醇酸盐、马来酸盐、酒石酸盐、甲磺酸盐、丙磺酸盐、萘-1-磺酸盐、萘-2-磺酸盐、扁桃酸盐等。优选的药学上可接受的酸加成盐包括与无机酸(例如盐酸和氢溴酸)形成的那些,特别是与有机酸(例如马来酸)形成的那些盐。

[0064] 用于与本发明的前药的酸性官能团形成药学上可接受的盐的合适的碱包括但不限于:碱金属(如钠、钾和锂)的氢氧化物;碱土金属(如钙和镁)的氢氧化物;其他金属(如铝和锌)的氢氧化物;氨和有机胺,例如未取代或羟基取代的单-、二-或三烷基胺;二环己胺;三丁胺;吡啶;N-甲基,N-乙基胺;二乙胺;三乙胺;单-、双-或三-(2-羟基-低级烷基胺),如单-、双-或三-(2-羟乙基)胺、2-羟基-叔丁胺或三-(羟甲基)甲胺,N,N-二低级烷基-N-(羟基低级烷基)-胺,如N,N-二甲基-N-(2-羟乙基)胺或三-(2-羟乙基)胺;N-甲基-D-葡糖胺;和氨基酸如精氨酸、赖氨酸等。

[0065] 如本文所用,术语"水合物"是指还包括由非共价分子间力结合的化学计量或非化学计量量的水的化合物。

[0066] 如本文所用,术语"溶剂化物"是指还包括由非共价分子间力结合的化学计量或非化学计量量的溶剂(例如水、丙酮、乙醇、甲醇、二氯甲烷、2-丙醇等)的化合物。

[0067] 如本文所用,术语"多晶型物"是指化合物或其复合物的固体晶型,其可以通过物理手段(例如X射线粉末衍射图或红外光谱)来表征。相同化合物的不同多晶型物可以表现出不同的物理、化学和/或光谱性质。不同的物理性质包括但不限于:稳定性(例如,热、光或湿度)、可压缩性和密度(在制剂和产品制造中很重要)、吸湿性、溶解性和溶解速率(可影响

生物利用度)。稳定性的差异可以由化学反应性的变化(例如差别氧化,使得当包含一种多晶型物时,与包含另一种多晶型物相比,剂型更快地变色)造成,或者由机械特性(例如片剂在储存时破碎,因为动力学有利的多晶型物转化为热力学更稳定的多晶型物)造成,或者由它们两者(例如,一种多晶型物的片剂在高湿度下更容易分解)造成。多晶型物的不同物理性质可影响其加工。例如,由于例如粒子的形状或大小分布,一种多晶型物可能比另一种更可能形成溶剂化物,或者可能更难以过滤或清除杂质。

[0068] 如本文所用,术语"基本上不含其它立体异构体"是指存在少于25%的其他立体异构体,优选存在少于10%的其他立体异构体,更优选存在少于5%的其他立体异构体,并且最优选存在少于2%的其它立体异构体,或存在少于"X"%的其它立体异构体(其中X是0和100之间的数字,包括0和100)。获得或合成非对映异构体的方法在本领域中是公知的,并且可以可行地应用于最终化合物或原料或中间体。其他实施方式是其中化合物是分离的化合物的那些。如本文所用,术语"至少X%对映体富集"是指至少X%的化合物是单一对映体形式,其中X是0和100之间的数字,包括0和100。

[0069] 如本文所用,术语"稳定化合物"是指具有足够的稳定性以允许制造并且维持化合物的完整性持续足够的时间段以用于本文详述的目的的化合物(例如,配制成治疗产品、用于生产治疗化合物的中间体、可分离或可储存的中间体化合物、治疗对治疗剂有反应的疾病或病状)。

[0070] "立体异构体"是指对映异构体和非对映异构体。

[0071] 如本文所用,术语"卤代"或"卤素"是指氟、氯、溴或碘的任何自由基。

[0072] 术语"烷基(alk或alkyl)"是指具有1至12个碳原子、优选1至8个碳原子的直链或支链烃基。表述"低级烷基"是指1至4个(包括端值)碳原子的烷基。

[0073] 术语"芳基烷基"是指其中烷基氢原子被芳基替代的部分。

[0074] 术语"烯基"是指具有至少一个双键的2至10个碳原子、优选2至4个碳原子的直链或支链烃基。在烯基与氮原子键合的情况下,优选该基团不通过带有双键的碳直接键合。

[0075] 术语"烷氧基"是指-O-烷基自由基。术语"亚烷基二氧基"是指结构为-O-R-O-的二价类型,其中R表示亚烷基。

[0076] 术语"炔基"是指具有至少一个三键的2至10个碳原子、优选2至4个碳原子的直链或支链烃基。当炔基与氮原子键合时,优选该基团不通过带有三键的碳直接键合。

[0077] 术语"亚烷基"是指通过单键连接的1至5个碳原子的二价直链桥(例如-$(CH_2)_x$-,其中x为1至5),其可以被1至3个低级烷基基团取代。

[0078] 术语"亚烯基"是指具有一个或两个通过单键连接的双键的2至5个碳原子的直链桥,并且可以被1至3个低级烷基取代。示例性的亚烯基基团是-CH=CH-CH=CH-、-CH_2-CH=CH-、-CH_2-CH=CH-CH_2-、-C$(CH_3)_2$CH=CH-和-CH(C_2H_5)CH=CH-。

[0079] 术语"亚炔基"是指其中具有通过单键连接的三键的2至5个碳原子的直链桥,并且可以被1至3个低级烷基取代。示例性的亚炔基是-C≡C-、-CH_2-C≡C-、-CH(CH_3)C≡C-和-C-C≡C-CH$(C_2H_5)$$CH_2$。

[0080] 如本文使用,术语"环烷基"和"环烯基"分别包括饱和和部分不饱和的环状烃基,其具有3至12个碳、优选3至8个碳、更优选3至6个碳。

[0081] 术语"Ar"或"芳基"是指含有6至14个碳原子的芳族环状基团(例如6元单环、10元

双环或14元三环系统)。示例性的芳基包括苯基、萘基、联苯基和蒽。

[0082] "杂芳基"是指5至12个环原子的单环或稠合环(即,共享相邻原子对的环),含有1、2、3或4个选自N、O或S的环杂原子,剩余的环原子是C并且此外具有完全共轭的π电子体系,其中每个环的0、1、2、3或4个原子可以被取代基取代。杂芳基的非限制性实例为吡咯、呋喃、噻吩、咪唑、恶唑、噻唑、吡唑、吡啶、嘧啶、喹啉、喹唑啉、异喹啉、嘌呤和咔唑。

[0083] 术语"杂环(heterocycle)"、"杂环的(heterocyclic)"或"杂环(heterocyclo)"是指完全饱和或部分不饱和的环状基团,例如3至7元单环、7至12元双环或10至15元三环的环体系,其在至少一个环中具有至少一个杂原子,其中每个环的0、1、2或3个原子可以被取代基取代。含有杂原子的杂环基的每个环可以具有1、2、3或4个选自氮原子、氧原子和/或硫原子的杂原子,其中氮和硫杂原子可以任选地被氧化并且氮杂原子可以任选地被季铵化。杂环基团可以连接在环或环体系的任何杂原子或碳原子上。

[0084] 术语"杂环基(heterocyclyl)"是指完全饱和或部分不饱和的环状基团,例如3至7元单环、7至12元双环或10至15元三环的环体系,其在至少一个环中具有至少一个杂原子,其中每个环的0、1、2或3个原子可以被取代基取代。含有杂原子的杂环基的每个环可以具有1、2、3或4个选自氮原子、氧原子和/或硫原子的杂原子,其中氮和硫杂原子可以任选地被氧化并且氮杂原子可以任选地被季铵化。杂环基团可以连接在环或环体系的任何杂原子或碳原子上。

[0085] 术语"取代基"是指在本文描述的任何官能团上"取代"的基团,例如在该基团的任何原子上的烷基、烯基、炔基、环烷基、环烯基、芳基、杂环基或杂芳基。合适的取代基包括但不限于:卤素、CN、NO_2、OR^{15}、SR^{15}、$S(O)_2OR^{15}$、$NR^{15}R^{16}$、C_1-C_2全氟烷基、C_1-C_2全氟烷氧基、1,2-亚甲二氧基、$C(O)OR^{15}$、$C(O)NR^{15}R^{16}$、$OC(O)NR^{15}R^{16}$、$NR^{15}C(O)NR^{15}R^{16}$、$C(NR^{16})NR^{15}R^{16}$、$NR^{15}C(NR^{16})NR^{15}R^{16}$、$S(O)_2NR^{15}R^{16}$、$R^{17}$、$C(O)R^{17}$、$NR^{15}C(O)R^{17}$、$S(O)R^{17}$、$S(O)_2R^{17}$、$R^{16}$、氧代、$C(O)R^{16}$、$C(O)(CH_2)_nOH$、$(CH_2)_nOR^{15}$、$(CH_2)_nC(O)NR^{15}R^{16}$、$NR^{15}S(O)_2R^{17}$,其中n独立地为0-6,包含0和6。每个$R^{15}$独立地为氢、$C_1$-$C_4$烷基或$C_3$-$C_6$环烷基。每个$R^{16}$独立地为氢、烯基、炔基、$C_3$-$C_6$环烷基、芳基、杂环基、杂芳基、$C_1$-$C_4$烷基或被$C_3$-$C_6$环烷基、芳基、杂环基或杂芳基取代的$C_1$-$C_4$烷基。每个$R^{17}$独立地为$C_3$-$C_6$环烷基、芳基、杂环基、杂芳基、$C_1$-$C_4$烷基或被$C_3$-$C_6$环烷基、芳基、杂环基或杂芳基取代的$C_1$-$C_4$烷基。在每个$R^{15}$、$R^{16}$和$R^{17}$中的每个$C_3$-$C_6$环烷基、芳基、杂环基、杂芳基和$C_1$-$C_4$烷基可以任选被卤素、CN、$C_1$-$C_4$烷基、OH、$C_1$-$C_4$烷氧基、$NH_2$、$C_1$-$C_4$烷基氨基、$C_1$-$C_4$二烷基氨基、$C_1$-$C_2$全氟烷基、$C_1$-$C_2$全氟烷氧基或1,2-亚甲二氧基取代。

[0086] 术语"氧代"是指氧原子,当其连接到碳时形成羰基,当其连接至氮时形成N-氧化物,并且当其连接至硫时形成亚砜或砜。

[0087] 术语"酰基"是指烷基羰基、环烷基羰基、芳基羰基、杂环基羰基或杂芳基羰基取代基,它们中的任何一个可以被取代基进一步取代。

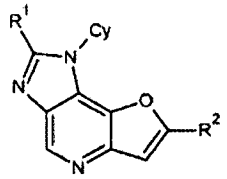
[0088] 在本文的变量的任何定义中化学基团列表的叙述包括该变量作为任何单个基团或所列基团组合的定义。本文对变量的实施方式的叙述包括该实施方式作为任何单个实施方式或与任何其他实施方式或其部分的组合。

[0089] 本发明的化合物可含有一个或多个不对称中心,因此作为外消旋体和外消旋混合物、单一对映异构体、单独非对映异构体和非对映异构体混合物以及顺式和反式几何异构体存在。这些化合物的所有这些异构形式都明确地包括在本发明中。本发明的化合物也可

以以多种互变异构形式表示，在这种情况下，本发明明确地包括本文所述化合物的所有互变异构形式。这些化合物的所有这些异构形式都明确地包括在本发明中。本文描述的化合物的所有晶型都明确地包括在本发明中。

[0090] 本发明的化合物

[0091] 在一方面，本发明提供了式I的化合物：

[0092] I 

[0093] 或其药学上可接受的盐；或前药或其前药的药学上可接受的盐；或其水合物、溶剂化物或多晶型物；其中：

[0094] R^1是H、卤素或C_{1-3}烷基，所述C_{1-3}烷基任选被1、2或3个独立选自由卤素、OH、CN、OR、NHR、NRR'、N(R)C(=O)R'、N(R)C(=O)(O)R'、OC(=O)NRR'、C(=O)R、C(=O)NRR'、N(R)S(O)$_2$R'、S(O)$_2$R和S(O)$_2$NRR'组成的组的取代基所取代；

[0095] R^2是H、卤素或C_{1-3}烷基；

[0096] Cy是C_{3-7}环烷基、3-7元杂环基、苯基或5-6元杂芳基，各自任选被1、2或3个独立选自由R^3、氧代、卤素、OH、CN、OR、NHR、NRR'、N(R)C(=O)R'、N(R)C(=O)(O)R'、OC(=O)NRR'、C(=O)R、C(=O)NRR'、N(R)S(O)$_2$R'、S(O)$_2$R和S(O)$_2$NRR'组成的组的取代基所取代，其中R^3为C_{1-3}烷基，其任选被1、2或3个独立选自由卤素、OH、CN、OR、NHR、NRR'、N(R)C(=O)R'、N(R)C(=O)(O)R'、OC(=O)NRR'、C(=O)R、C(=O)NRR'、N(R)S(O)$_2$R'、S(O)$_2$R和S(O)$_2$NRR'组成的组的取代基所取代；

[0097] R、R'各自独立地为H或C_{1-3}烷基，所述C_{1-3}烷基任选被1、2或3个独立选自由卤素、OH和CN组成的组的取代基所取代。

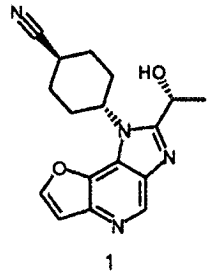
[0098] 在另一方面，Cy可以为C_{5-7}环烷基或5-7元杂环基，各自任选被1、2或3个独立选自由R^3、氧代、卤素、OH、CN、OR、NHR、NRR'、N(R)C(=O)R'、N(R)C(=O)(O)R'、OC(=O)NRR'、C(=O)R、C(=O)NRR'、N(R)S(O)$_2$R'、S(O)$_2$R和S(O)$_2$NRR'组成的组的取代基所取代，其中R^3为C_{1-3}烷基，所述C_{1-3}烷基任选被1、2或3个独立选自由卤素、OH、CN、OR、NHR、NRR'、N(R)C(=O)R'、N(R)C(=O)(O)R'、OC(=O)NRR'、C(=O)R、C(=O)NRR'、N(R)S(O)$_2$R'、S(O)$_2$R和S(O)$_2$NRR'组成的组的取代基所取代。

[0099] 在另一方面，R^2可以是氢。

[0100] 表1中描述了本发明的代表性化合物。除非特别说明，在这些实施例中，手性碳原子的立体化学独立地为RS、R或S。对于化合物4、7-11，立体化学仅显示反式或顺式异构体中的一种，并且未显示它们各自异构体的结构。本文所述的结构，包括表1结构，可包含某些-NH-、-NH_2(氨基)和-OH(羟基)基团，其中相应的氢原子并未明确出现；然而它们根据情况被视为-NH-、-NH_2或-OH。在某些结构中，绘制棒状键并用于描绘甲基。

[0101] 表1

[0102]



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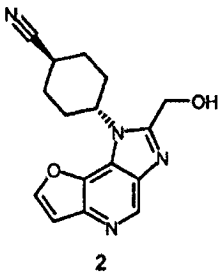

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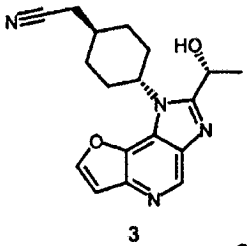

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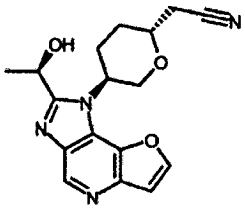

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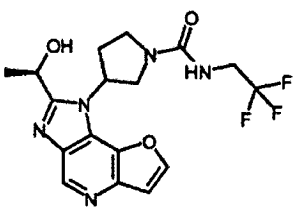

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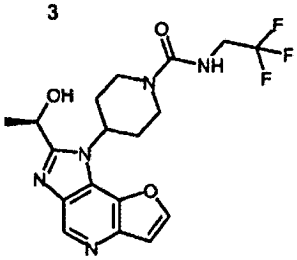

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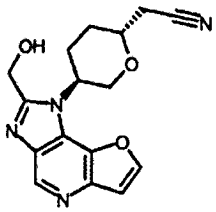

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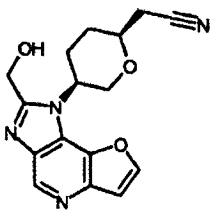

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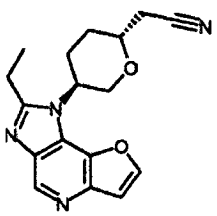

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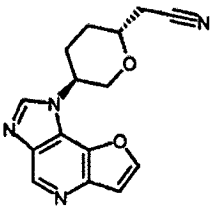

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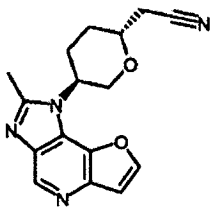


11

[0103] 以下列出了本发明的代表性化合物：

[0104] 反式-4-[2-[(R)-1-羟乙基]-1H-呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]环己烷甲腈(1)，

[0105] 反式-4-[2-(羟甲基)呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]环己烷甲腈(2)，

[0106] 2-[反式-4-[2-(R)-1-羟乙基]呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]环己基]乙腈(3)，

[0107] 2-[(2R,5S)-5-[2-[(R)-1-羟乙基]呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]四氢吡喃-2-基]乙腈(4)，

[0108] 3-[2-[(R)-1-羟乙基]-1H-呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]-N-(2,2,2-三氟乙基)吡咯烷-1-甲酰胺(5)，

[0109] (R)-4-[2-(1-羟乙基)-1H-呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]-N-(2,2,2-三氟乙基)哌啶-1-甲酰胺(6)，

[0110] 2-[(2R,5S)-5-[2-(羟甲基)呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]四氢吡喃-2-基]乙腈(7)，

[0111] 2-[(2S,5S)-5-[2-(羟甲基)呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]四氢吡喃-

2-基]乙腈(8)，

[0112] 2-[(2R,5S)-5-[2-乙基呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]四氢吡喃-2-基]乙腈(9)，

[0113] 2-[(2R,5S)-5-[2-呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]四氢吡喃-2-基]乙腈(10)，

[0114] 2-[(2R,5S)-5-[2-甲基呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]四氢吡喃-2-基]乙腈(11)。

[0115] 本文中式的化合物的合成可以由普通技术的合成化学家容易地进行。例如，在此公开了相关的程序和中间体。在此引用的无论是在传统期刊中还是仅通过因特网可获得的每个专利、专利申请和出版物，通过引用全部并入本文。

[0116] 合成本文式的化合物的其他方法可以容易地从本文引用的参考文献进行调整。这些程序的变化及其优化在普通从业者的技能范围内。

[0117] 以上所示的具体方法和化合物并非意在限制。本文的方案中的化学结构描绘了变量，这些变量因此与本文化合物式中的相应位置的化学基团定义(部分、原子等)相称地进行定义，而不管是否由相同的变量名称(例如R^1、R^2、R、R'、X等)确定。一种化合物结构中的化学基团用于合成另一种化合物结构的适用性在本领域普通技术人员的知识范围内。合成本文式的化合物及它们的合成前体的其他方法(包括本文方案中未明确示出的途径中的那些)在本领域普通化学技术人员的手段之内。如果需要，优化反应条件(其使竞争副产物最小化)的方法在本领域中是已知的。本文所述的方法还可以额外地包括在本文具体描述的步骤之前或之后的步骤，以添加或除去合适的保护基，以最终允许合成本文中的化合物。另外，各种合成步骤可以按照交替的顺序或次序进行以产生期望的化合物。用于合成适用化合物的合成化学转化和保护基的方法(保护和脱保护)是本领域已知的，并且例如包括以下描述的那些：R.Larock,Comprehensive Organic Transformations,VCH Publishers(1989)；T.W.Greene和P.G.M.Wuts,Protective Groups in Organic Synthesis,3rd Ed.,John Wiley and Sons(1999)；L.Fieser和M.Fieser,Fieser and Fieser's Reagents for Organic Synthesis,John Wiley and Sons(1994)；和L.Paquette,ed.,Encyclopedia of Reagents for Organic Synthesis,John Wiley and Sons(1995)及其后续版本。

[0118] 本文描述的方法考虑将一种通式的化合物转化为另一种通式的化合物。转化方法涉及一种或多种化学变化，其可以原位进行，或者具有中间体化合物的分离。变化可以包括使用本领域已知的技术和方案(包括本文引用的参考文献中的那些)，使起始化合物或中间体与另外的试剂反应。中间体可以在有或没有纯化(例如过滤、蒸馏、升华、结晶、研磨、固相萃取和色谱法)的情况下使用。

[0119] 本发明设想的取代基和变量的组合仅是导致形成稳定化合物的那些。

[0120] 本发明还提供了组合物，其包含有效量的任何本文式的化合物或所述化合物的药学上可接受的盐、溶剂化物、水合物、多晶型物或前药(如果适用的话)；和可接受的载体。优选地，配制本发明的组合物用于药物用途(“药物组合物”)，其中载体是药学上可接受的载体。就与制剂的其它成分相容的意义而言，载体必须是“可接受的”，在药学上可接受的载体的情况下，在药物通常的使用量下，对其受体无害。

[0121] 可用于本发明药物组合物中的药学上可接受的载体、佐剂和赋形剂(vehicle)包

括但不限于离子交换剂、氧化铝、硬脂酸铝、卵磷脂、血清蛋白(如人血清白蛋白)、缓冲物质(如磷酸盐)、甘氨酸、山梨酸、山梨酸钾、饱和植物脂肪酸的偏甘油酯混合物、水、盐或电解质(如硫酸鱼精蛋白、磷酸氢二钠、磷酸氢钾、氯化钠、锌盐)、胶体二氧化硅、三硅酸镁、聚乙烯吡咯烷酮、纤维素基物质、聚乙二醇、羧甲基纤维素钠、聚丙烯酸酯、蜡、聚乙烯-聚氧丙烯嵌段聚合物、聚乙二醇和羊毛脂。

[0122] 本发明的药物组合物包括适合于口服、直肠、鼻腔、局部(包括口腔和舌下)、阴道或肠胃外(包括皮下、肌内、静脉内和皮内)给药的那些。在某些实施方案中,本文式化合物经皮给药(例如使用透皮贴剂)。其他制剂可以方便地以单位剂量形式存在,例如片剂和缓释胶囊以及脂质体中,并且可以通过制药领域中公知的任何方法制备。例如参见Remington's Pharmaceutical Sciences,Mack Publishing Company,Philadelphia,PA(17th ed.1985)。

[0123] 这种制备方法包括使待施用分子与如构成一种或多种助剂的载体的成分结合的步骤。通常,组合物的制备通过使活性成分与液体载体、脂质体或细碎的固体载体或它们两者均匀且紧密地结合,然后如果需要使产物成形。

[0124] 在某些优选的实施方案中,该化合物口服给药。适用于口服给药的本发明组合物可以以离散单位形式存在,例如各自含有预定量的活性成分的胶囊、小药囊或片剂;以粉末或颗粒的形式存在;以水性液体或非水性液体中的溶液或悬浮液的形式存在;或者以水包油液体乳剂或油包水液体乳剂或者包装在脂质体中的形式存在以及以丸剂的形式存在等。软胶胶囊可以用于包含这种悬浮液,这可以有利地提高化合物吸收的比率。

[0125] 片剂可以通过压制或模制来制备,任选地具有一种或多种助剂。压制片剂可以通过在合适的机器中压制自由流动形式的活性成分(如粉末或颗粒),任选混合有粘合剂、润滑剂、惰性稀释剂、防腐剂、表面活性剂或分散剂来制备。模制片剂可以通过在合适的机器中模制用惰性液体稀释剂润湿的粉状化合物的混合物来制备。片剂任选可以被包衣或刻痕,并且可以被配制以提供其中的活性成分的缓慢或受控释放。配制药物活性成分(例如本文中的那些和本领域已知的其他化合物)的这种缓慢或受控释放组合物的方法在本领域中是已知的并且在几个发布的美国专利中进行了描述,其中一些包括但不限于美国专利第4,369,172号;和第4,842,866号,以及其中引用的参考文献。包衣可用于将化合物递送至肠内(参见例如美国专利第6,638,534、5,217,720号和第6,569,457、6,461,631、6,528,080、6,800,663号和其中引用的参考文献)。对于本发明化合物有用的制剂是其中肠溶层包含羟丙基甲基纤维素醋酸琥珀酸酯(hydroxypropylmethylcellulose acetate succinate)的肠溶微丸形式。

[0126] 在用于口服使用的片剂的情况下,通常使用的载体包括乳糖和玉米淀粉。通常还加入润滑剂,如硬脂酸镁。对于胶囊形式的口服给药,有用的稀释剂包括乳糖和干玉米淀粉。当口服给药水悬浮液时,活性成分与乳化剂和悬浮剂结合。如果需要,可加入某些甜味剂和/或调味剂和/或着色剂。

[0127] 适用于局部给药的组合物包括:锭剂(lozenge),该锭剂包含在调味基础(通常为蔗糖和阿拉伯胶或黄蓍胶)上的成分;以及锭剂(pastille),该锭剂包含在惰性基础(如明胶和甘油,或蔗糖和阿拉伯胶)上的活性成分。

[0128] 适用于胃肠外给药的组合物包括含水和无水的无菌注射溶液,其可含有抗氧化

剂、缓冲剂、抑菌剂和使制剂与预期接受者的血液等渗的溶质；以及含水和无水的无菌悬浮液，其可包含悬浮剂和增稠剂。制剂可以存在于单位剂量或多剂量容器中，例如密封安瓿和小瓶中，并且可以存储在冷冻干燥(冻干)条件下，仅需要在使用之前立刻添加无菌液体载体(例如注射用水)。临时注射溶液和悬浮液可以由无菌粉末、颗粒和片剂制备。

[0129] 这种注射溶液可以例如是无菌可注射含水或含油悬浮液的形式。该悬浮液可以根据本领域已知的技术使用合适的分散剂或湿润剂(例如吐温80)和悬浮剂配制。无菌注射制剂还可以是在无毒肠道外可接受的稀释剂或溶剂中的无菌注射溶液或悬浮液，例如作为1，3-丁二醇中的溶液。在可接受的载体和溶剂中可以使用的是甘露醇、水、林格氏溶液和等渗氯化钠溶液。另外，无菌的固定油通常用作溶剂或悬浮介质。为此目的，可使用任何温和的固定油，包括合成的甘油一酯或甘油二酯。脂肪酸(如油酸)及其甘油酯衍生物可用于制备注射剂，天然药学上可接受的油(如橄榄油或蓖麻油)，尤其是其聚氧乙烯化形式也是如此。这些油溶液或悬浮液还可以含有长链醇稀释剂或分散剂。

[0130] 本发明的药物组合物可以以用于直肠给药的栓剂形式给药。这些组合物可通过将本发明化合物与合适的无刺激性赋形剂混合来制备，所述赋形剂在室温下为固体，但在直肠温度下为液体，并且因此将在直肠中融化以释放活性组分。这样的材料包括但不限于可可脂、蜂蜡和聚乙二醇。

[0131] 本发明的药物组合物可以通过鼻腔气雾剂或吸入剂给药。这些组合物根据药物制剂领域熟知的技术制备，并且可以制备成生理盐水中的溶液，其使用苯甲醇或其他合适的防腐剂，使用吸收促进剂来增强生物利用度，使用碳氟化合物和/或其它本领域中已知的增溶剂或分散剂。

[0132] 当期望的治疗涉及通过局部应用容易接近的区域或器官时，本发明的药物组合物的局部给药是特别有用的。为了局部应用于皮肤，药物组合物应该用含有悬浮或溶解在载体中的活性组分的合适软膏配制。用于本发明化合物的局部给药的载体包括但不限于矿物油、液体凡士林、白凡士林、丙二醇、聚氧乙烯聚氧丙烯化合物、乳化蜡和水。或者，药物组合物可以用含有悬浮或溶解在载体中的活性化合物的合适洗剂或霜来配制。合适的载体包括但不限于矿物油、山梨醇酐单硬脂酸酯、聚山梨醇酯60、十六烷基酯蜡、十六硬脂酸酯、2-辛基十二烷醇、苯甲醇和水。本发明的药物组合物还可以通过直肠栓剂或适当的灌肠剂局部应用于下肠道。局部透皮贴剂和离子电渗给药也包括在本发明中。

[0133] 特别有利的衍生物和前药是这些：当将这样的化合物施用给哺乳动物时增强本发明化合物的生物利用度(例如，通过使口服给药的化合物更容易被吸收到血液中)，或者相对于亲本物种增强母体化合物向生物区室(例如脑或中枢神经系统)的递送。优选的前药包括衍生物，其中增强水溶性或通过肠膜的主动转运的基团附加到本文所述式的结构。例如参见Alexander,J.等Journal of Medicinal Chemistry 1988,31,318-322;Bundgaard,H.Design of Prodrugs;Elsevier:Amsterdam,1985;pp 1-92;Bundgaard,H.;Nielsen,N.M.Journal of Medicinal Chemistry 1987,30,451-454;Bundgaard,H.A Textbook of Drug Design and Development;Harwood Academic Publ.:Switzerland,1991;pp 113-191;Digenis,G.A.等Handbook of Experimental Pharmacology 1975,28,86-112;Friis,G.J.;Bundgaard,H.A Textbook of Drug Design and Development;2ed.;Overseas Publ.:Amsterdam,1996;pp351-385;Pitman,I.H.Medicinal Research Reviews 1981,1,

189-214。

[0134] 主题治疗剂的应用可以是局部的，以便在感兴趣的部位施用。可以使用各种技术在感兴趣的部位提供主题组合物，例如注射，使用导管、套针、抛射(projectile)、普流尼克凝胶、支架、持续药物释放聚合物或提供内部存取的其他装置。

[0135] 根据另一个实施方案，本发明提供浸渍可植入药物释放装置的方法，包括用本发明的化合物或组合物与所述药物释放装置接触的步骤。可植入药物释放装置包括但不限于可生物降解的聚合物胶囊或子弹、不可降解可扩散聚合物胶囊和可生物降解的聚合物薄片(wafer)。

[0136] 根据另一个实施方案，本发明提供涂覆有本发明化合物或包含本发明化合物的组合物的可植入医疗装置，使得所述化合物具有治疗活性。

[0137] 在另一个实施方案中，本发明的组合物还包含第二治疗剂。第二治疗剂包括已知当单独或与本文任何通式的化合物一起给药时具有或表现出有利性质的任何化合物或治疗剂。可以有效地与这些化合物结合的药物包括用于治疗上述疾病和障碍的其他激酶抑制剂和/或其他治疗剂。

[0138] 本领域中详细描述了这些药剂。优选地，第二治疗剂是在选自癌症和肿瘤疾病或障碍、或者自身免疫性和炎性疾病或障碍的疾病或病状的治疗和预防中有用的药剂。

[0139] 在另一个实施方案中，本发明提供了彼此联合的本发明化合物和第二种治疗剂的单独剂型。如本文所用，术语“彼此联合”是指将分开的剂型包装在一起或以其他方式彼此附加，使得显而易见的是该分开的剂型旨在一起出售和施用(在不到24小时内，连续或同时)。

[0140] 在本发明的药物组合物中，本发明的化合物以有效量存在。如本文所用，术语“有效量”是指：当以适当的给药方案施用时，足以降低或改善正在被治疗的障碍的严重性、持续时间或进展，防止正在被治疗的障碍的发展，引起所治疗障碍的消退，或者增强或改善另一种治疗的预防或治疗效果的量。

[0141] 在Freireich等，(1966)Cancer Chemother Rep 50:219中描述了用于动物和人的剂量之间的相互关系(基于每平方米身体表面积的毫克数)。身体表面积可以近似地由患者的身高和体重确定。例如参见Scientific Tables,Geigy Pharmaceuticals,Ardley,N.Y.,1970,537。本发明化合物的有效量可在约0.001mg/kg至约500mg/kg、更优选0.01mg/kg至约50mg/kg、更优选0.1mg/kg至约2.5mg/kg的范围内。正如本领域技术人员所认识的，有效剂量也会有所不同，这取决于：所治疗的疾病；疾病的严重程度；给药途径；患者的性别、年龄和一般健康状况；赋形剂用量；与其他治疗性处理(如使用其他药剂)共同使用的可能性以及治疗医师的判断。

[0142] 对于包含第二治疗剂的药物组合物，第二治疗剂的有效量为仅使用该药剂的单一治疗方案中正常使用剂量的约20%至100%。优选地，有效量在正常单一治疗剂量的约70%至100%之间。这些第二治疗剂的正常单治疗剂量在本领域中是公知的。例如参见Wells等，eds.,Pharmacotherapy Handbook,2nd Edition,Appleton and Lange,Stamford,Conn.(2000);PDR Pharmacopoeia,Tarascon Pocket Pharmacopoeia 2000,Deluxe Edition,Tarascon Publishing,Loma Linda,Calif.(2000)，其中每篇参考文献均通过引用整体并入本文。

[0143] 预期上面提到的一些第二治疗剂将与本发明的化合物协同作用。当这种情况发生时，它将允许第二治疗剂和/或本发明化合物的有效剂量与单一治疗所需的剂量相比减少。这具有如下优点：使本发明化合物的第二治疗剂的毒副作用最小化、疗效上协同改善、易于给药的改善或使用和/或减少化合物配制或制剂的整体费用。

[0144] 治疗方法

[0145] 根据另一个实施方案，本发明提供了治疗患有或易患有疾病或障碍或其症状(例如本文描述的那些)的受试者的方法，其包括向所述受试者施用有效量的本发明的化合物或组合物。这些疾病在本领域中是公知的，并且也在本文中公开。

[0146] 在一个方面，治疗方法涉及由Jak1蛋白激酶介导的障碍的治疗。

[0147] 在另一方面，治疗方法涉及主要由Jak1蛋白激酶介导、但也在某种程度上由Jak2蛋白激酶介导的障碍的治疗。

[0148] 在另一方面，本发明提供治疗受试者中疾病的方法，其包括向受试者施用本文任何式的化合物。

[0149] 在另一方面，本发明提供治疗受试者中疾病的方法，其包括向受试者施用包含本文任何式的化合物的组合物。

[0150] 在某些实施方案中，疾病由Jak1激酶介导。例如，所述病状可以是炎性疾病/障碍，自身免疫性疾病/障碍，例如但不限于：类风湿性关节炎(RA)、幼年特发性关节炎、骨关节炎、多发性硬化症、变应性哮喘、慢性阻塞性肺病、支气管炎、实验性变应性脑脊髓炎、克罗恩病、血管炎、心肌病、强直性脊柱炎(AS)、肾小球肾炎、胰岛素依赖型糖尿病、银屑病性关节炎、银屑病、斑块型银屑病、溃疡性结肠炎、全身性红斑狼疮(SLE)、糖尿病性肾病、周围神经病变、葡萄膜炎、纤维化肺泡炎、I型糖尿病、青少年糖尿病、Castleman病、嗜中性白血球减少症、子宫内膜异位症、自身免疫性甲状腺疾病、精子和睾丸自身免疫、硬皮病、轴突和神经元神经病变、过敏性鼻炎、鼻窦炎、溶血性贫血、格雷夫斯病(Graves)、桥本氏甲状腺炎、IgA肾病、淀粉样变性病、白塞氏病、结节病、囊泡状皮肤病、肌炎、干眼症、原发性胆汁性肝硬化、风湿性多肌痛、Reiter综合征、自身免疫性免疫缺陷、查加斯病、川崎综合征、口炎性腹泻、重症肌无力、干燥综合征、斑秃、白癜风、特应性皮炎、POEMS综合征、狼疮、炎症性肠病、慢性阻塞性肺病(COPD)、寻常型天疱疮、大疱性类天疱疮、慢性疲劳综合征、器官移植排斥(例如同种异体移植排斥和移植物抗宿主疾病)、病毒性疾病(例如EB病毒、丙型肝炎、HIV、HTLV 1、水痘带状疱疹病毒和人乳头瘤病毒)、痛风性关节炎、败血性或感染性关节炎、反应性关节炎、反射交感神经营养不良症、骨痛退化症、白化病综合征、肋软骨疾病、Mseleni病、Handigodu病、纤维肌痛症、硬皮病、先天性软骨畸形和肺动脉高压。

[0151] 进一步的JAK相关疾病包括炎症和炎性疾病或障碍，实例包括：结节病，眼部炎性疾病(例如虹膜炎、葡萄膜炎、巩膜炎、结膜炎、睑缘炎或相关疾病)，呼吸道炎性疾病(例如上呼吸道(包括鼻和鼻窦)，如鼻炎或鼻窦炎；或下呼吸道，包括支气管炎、慢性阻塞性肺病等)，炎性肌病(如心肌炎)以及其他炎性疾病。

[0152] 在另一个实施方案中，疾病是癌症、增殖性或其他肿瘤疾病，例如但不限于：乳腺癌、Castleman病、结肠癌和结肠直肠癌、胃癌、胃肠类癌瘤、胃肠道间质瘤、成胶质细胞瘤、头颈癌、卡波西氏肉瘤、肝癌、肺癌、黑素瘤、胰腺癌、前列腺癌、肾癌、直肠癌、小肠癌、甲状腺癌、子宫平滑肌肉瘤、淋巴瘤和白血病(例如急性淋巴细胞白血病、急性骨髓性白血病、多

发性骨髓瘤、皮肤T细胞淋巴瘤、皮肤B细胞淋巴瘤)、骨髓增生异常综合征(MDS)、骨髓增生障碍(MPD)(例如真性红细胞增多症(PV)、原发性血小板增多症(ET)、骨髓纤维化伴骨髓化生(MMM)、原发性骨髓纤维化)、慢性髓细胞性白血病(CML)、慢性骨髓单核细胞白血病(CMML)、嗜酸性粒细胞增多综合征(HES)、系统性肥大细胞病(SMCD)。在一些实施方案中,骨髓增殖性障碍是原发性血小板增多症后骨髓纤维化(Post-ET MF)或红血球增多症后相反骨髓纤维化(Post-PV MF)。

[0153] 进一步的JAK相关的疾病包括:缺血再灌注损伤、或者与炎性缺血事件(例如中风或心脏骤停)相关的疾病或病状、内毒素驱动的疾病状态(例如慢性内毒素状态的绕道手术后引起慢性心力衰竭的并发症)、厌食症、硬皮病、纤维化、与缺氧或星形胶质细胞增生有关的病状(如糖尿病视网膜病变、癌症或神经变性),以及其他炎性疾病(如全身炎症反应综合征和脓毒性休克)。

[0154] 其他JAK相关疾病包括:由于例如良性前列腺肥大或良性前列腺增生引起的痛风和增加的前列腺大小,以及骨吸收疾病(如骨质疏松症或骨关节炎),与以下相关的骨吸收疾病:激素失调和/或激素治疗,自身免疫性疾病(例如骨结节病)。

[0155] JAK相关疾病或病状的其它实例包括通过施用本发明化合物来改善其他药物的皮肤病副作用。例如,许多药剂导致不需要的过敏反应,其可表现为痤疮样皮疹或相关皮炎。具有不希望的副作用的示例性药剂包括抗癌药物,例如吉非替尼(gefitinib)、西妥昔单抗(cetuximab)、厄洛替尼(erlotinib)等。本发明的化合物可以与具有不希望的皮肤病副作用的药剂结合全身或局部给药(例如局限于皮炎附近)。因此,本发明的组合物包含含有本发明化合物和可引起皮炎,皮肤病或相关副作用的其他药剂的局部制剂。

[0156] 在一个实施方案中,本发明的方法用于治疗患有或易患疾病或病状的受试者。这些疾病、障碍或其症状包括例如由Jak1蛋白激酶调节的那些。疾病或疾病症状可以例如是类风湿性关节炎、癌症或增殖性疾病或障碍。本文描述的方法包括其中受试者被鉴定为需要特别定期治疗的那些。识别需要这种治疗的受试者可以在受试者或医疗保健专业人员的判断中,并且可以是主观的(例如意见)或客观的(例如通过测试或诊断方法可测量的)。

[0157] 在又一个实施方案中,本文式的化合物(及其组合物)可用于治疗患有已经用其他治疗剂治疗并产生了耐药性的疾病或障碍的受试者。在一个方面,本文的方法包括那些对用甲氨蝶呤或抗TNF-α疗法耐受的患者。

[0158] 在另一个实施方案中,本发明提供调节细胞中Jak1蛋白激酶活性的方法,其包括使细胞与本文任何通式的一种或多种化合物接触。

[0159] 在另一个实施方案中,上述治疗方法包括对所述患者共同施用一种或多种第二治疗剂的进一步步骤。第二治疗剂的选择可以为已知可用于本文适应症的任何治疗剂。一种或多种另外的治疗剂可以包括:化学治疗剂、抗炎剂、类固醇、免疫抑制剂以及PI3Kdelta、mTOR、BCR-AB1、FLT-3、RAF和FAK激酶抑制剂等。另外的治疗剂包括但不限于用于治疗疾病、障碍或其症状的药剂,例如包括:(1)调节人免疫系统的药剂或,其选自由以下组成的组、但不限于它们:阿司匹林、对乙酰氨基酚、氨基水杨酸盐、抗胸腺细胞球蛋白、环丙沙星、皮质类固醇、环孢素、脱氧精胍菌素、赛尼哌(daclizuma)、甲硝哒唑、益生素、他克莫司、布洛芬、萘普生、吡罗昔康、泼尼松龙、地塞米松、抗炎类固醇、甲氨喋呤、氯喹、硫唑嘌呤、羟氯喹、霉酚酸酯(mycophnolate)、莫罗单抗-CD3、青霉胺、柳氮磺胺吡啶、来氟米特、他克莫司、托珠

单抗(tocilzumab)、阿那白滞素、阿巴西普、塞妥珠单抗(certolizumab pegol)、高利单抗(golimumab)、雷帕霉素、维多珠单抗(vedolizumab)、那他珠单抗、优特克单抗(ustekinumab)、利妥昔单抗(rituximab)、依法利珠单抗(efalizumab)、贝利木单抗(belimumab)、依那西普、英夫利昔(infliximab)、阿达木单抗(adalimuman)、用于CD4+CD25+调节性T细胞的免疫调节剂(例如激活剂)、NSAID、止痛剂、其他非生物的缓解疾病的抗风湿性药物(DMARD)和/或与抗-TNF-α生物制剂(例如TNA拮抗剂(如嵌合抗体、人源化抗体或人TNF抗体)、阿达木单抗、英夫利昔、高利单抗、CDP571和可溶性p55或175TNA受体)、它们的衍生物、依那西普或来那西普联合;(2)抗癌和抗肿瘤剂,抗增殖剂,抗肿瘤剂(antineoplastic agent),抗肿瘤剂(antitumor agent),抗代谢型/胸苷酸合酶抑制剂抗肿瘤剂,烷化剂型抗肿瘤剂,抗生素型抗肿瘤剂,或在癌症治疗方案(例如止吐、抗贫血等)中通常施用为主剂或辅助剂的其它任何药剂,例如包括:硫酸长春碱、长春新碱、长春地辛、vinestramide、长春瑞滨、长春曲醇、长春利定、他莫昔芬、托瑞米芬、雷洛昔芬、屈洛昔芬、iodoxyfene、醋酸甲地孕酮、阿那曲唑、来曲唑、硼嗪、依西美坦、氟他胺、尼鲁米特、比卡鲁胺、醋酸环丙孕酮、醋酸戈舍瑞林、luprolide、非那雄胺、赫赛汀、氨甲蝶呤、5-氟尿嘧啶、阿糖胞苷、阿霉素、道诺霉素、表柔比星、伊达比星、丝裂霉素-C、更生霉素、光辉霉素、顺铂、卡铂、美法仑、苯丁酸氮芥、白消安、环磷酰胺、异环磷酰胺、亚硝基脲、thiotephan、长春新碱、紫杉酚、泰索帝、依托泊苷、替尼泊苷、安吖啶、伊立替康、拓扑替康、埃坡霉素、易瑞沙、阿瓦斯汀,OSI-774、血管生成抑制剂、EGFR抑制剂、MEK抑制剂、VEGFR抑制剂、CDK抑制剂、Her1和Her2抑制剂、单克隆抗体、蛋白酶体抑制剂(如硼替佐米、萨力多胺和雷利度胺)、凋亡诱导剂(如ABT-737)。核酸疗法,如反义或RNAi;核受体配体(例如激动剂和/或拮抗剂、全反式视黄酸或boxarotene);表观遗传靶向剂,如组蛋白脱乙酰酶抑制剂(例如伏立诺他)、低甲基化剂(例如地西他滨)、蛋白质稳定性调节剂,如HSP90抑制剂、泛素和/或类泛素共轭或解共轭分子。

[0160] 在一些实施方案中,另外的药剂选自IMiD、抗IL-6剂、抗TNF-α剂、低甲基化剂和生物反应调节剂(RBM)。RBM通常是由生物体制成以治疗疾病的物质。RBM的实例包括IL-2、GM-CSF、CSF、单克隆抗体(如阿昔单抗、依那西普、英夫利昔、利妥昔单抗、曲妥珠单抗)和高剂量抗坏血酸盐。低甲基化剂是DNA甲基转移酶抑制剂,例如5氮杂胞苷和地西他滨。IMiD的实例包括萨力多胺、来那度胺、泊马度胺、CC-11006和CC-10015。

[0161] 在一些实施方案中、另外的药剂包括抗胸腺细胞球蛋白、重组人粒细胞集落刺激因子(G-CSF)、粒细胞-单核细胞CSF(GM-CSF)、促红细胞生成剂(ESA)和环孢菌素。

[0162] 在一些实施方案中,另外的治疗剂是另外的JAK抑制剂。在一些实施方案中,另外的JAK抑制剂是托法替尼、鲁索替尼或巴西替尼。

[0163] 在一些实施方案中,在癌症(例如多发性骨髓瘤)的治疗中,本发明的一种或多种JAK抑制剂可以与一种或多种其他癌症治疗剂联合使用,并且与其他癌症治疗剂相比可以改善治疗益处,而不会加剧它们的毒性作用。用于治疗多发性骨髓瘤的其他药剂的实例可以包括但不限于美法仑、美法仑加泼尼松(MP)、阿霉素、地塞米松和硼替佐米。用于治疗多发性骨髓瘤的其他药剂包括BRC-ABL、FLT-3、RAF、MEK、PI3K、mTOR抑制剂。累加效应或协同效应是将本发明的JAK抑制剂与另外的药剂联合的理想结果。此外,用本发明的JAK抑制剂治疗时,多发性骨髓瘤细胞对诸如地塞米松或其它药物的药剂的抗性可能是可逆的。这些

药剂可以与单一或连续剂型的本发明化合物联合，或者这些药剂可以作为分开的剂型同时或相继施用。

[0164] 在一些实施方案中，将皮质类固醇(例如地塞米松)与至少一种本发明的JAK抑制剂联合施用于患者，其中间歇给药地塞米松而不是连续施用。

[0165] 在一些实施方案中，本发明的一种或多种JAK抑制剂与其他治疗剂的联合可以在骨髓移植或干细胞移植之前、期间和/或之后施用于患者。

[0166] 在一些实施方案中，另外的治疗剂是醋酸氟轻松(fluocinolone acetonide)或雷莫昔龙(remexolone)。

[0167] 在一些实施方案中，另外的治疗剂是皮质类固醇，例如去炎松、地塞米松、氟轻松、可的松、泼尼松龙或氟甲隆(flumetholone)。

[0168] 在一些实施方案中，另外的治疗剂包括:Dehydrex、Civamide、透明质酸钠、环孢菌素、ARGIOI、AGR1012、伊卡贝特钠、吉法酯、15-(s)-羟基二十碳四烯酸、cevilemine多西环素、米诺环素、iDestrin、环孢菌素A、土霉素、沃罗孢素(voclosporin)、ARG103、RX-10045、DYN15、来格列酮、TB4、OPH-01、PCS101、REV1-31、催泪蛋白(Lacritin)、瑞巴派特、OT-551、PAI-2、毛果芸香碱、他克莫司、吡美莫司(pimercrolimus)、依碳酸氯替泼诺、利妥昔单抗(rituximan)、地夸磷索四钠(diquafosol tetrasodium)、KLS-0611、脱氢表雄酮、阿那白滞素、依法利珠(efalizuma)、霉酚酸钠、依那西普、羟氯喹、NGX267、托珠单抗(actemra)或L-天冬酰胺酶。

[0169] 在一些实施方案中，另外的治疗剂是抗血管生成剂、胆碱能剂、TRP-1受体调节剂、钙通道阻断剂、粘蛋白促分泌素、MUC1兴奋剂、神经钙调蛋白抑制剂、P2Y2受体激动剂、毒蕈碱受体激动剂、和四环素衍生物。

[0170] 在一些实施方案中，另外的治疗剂包括缓和滴眼剂，其包括但不限于:含有聚乙烯醇，羟丙甲纤维素、甘油、聚乙二醇(例如PEG400)或羧甲基纤维素的组合物。在一些实施方案中，另外的治疗剂是一种粘液溶解药物，如N-乙酰基-半胱氨酸，其可以与粘蛋白相互作用并降低泪膜的粘性。

[0171] 在一些实施方案中，另外的治疗剂包括抗生素，抗病毒剂，抗真菌剂，麻醉剂，抗炎剂(包括甾体和非甾体抗炎药)以及抗过敏剂。合适药物的实例包括:氨基糖苷类，如阿米卡星、庆大霉素、妥布霉素、链霉素、奈替米星和卡那霉素;氟喹诺酮类，如环丙沙星、诺氟沙星、氧氟沙星、曲伐沙星、洛美沙星、左氧氟沙星和依诺沙星;萘啶;磺胺类药物;多粘菌素;氯霉素;新霉素;巴龙霉素;粘杆菌素;杆菌肽，万古霉素;四环素类;利福平及其衍生物;环丝氨酸;β-内酰胺类;头孢菌素类;两性霉素类(emphotericins);氟康唑;氟胞嘧啶;纳他霉素;咪康唑;酮康唑;皮质类固醇类;双氯芬酸(dicloenac);氟比洛芬;酮咯酸;舒洛芬;色甘酸;洛度沙胺;左卡巴司丁;萘甲唑啉;安他唑啉;苯吡胺;或氮杂内酯抗生素。

[0172] 如本文所用，术语“共同施用”是指第二治疗剂可与本发明化合物一起作为单一剂型的一部分(例如本发明的组合物，其包含本发明化合物和如上所述的第二治疗剂)或作为单独的多种剂型施用。

[0173] 或者，可以在施用本发明化合物之前、连续或之后施用另外的药剂。在这样的联合疗法治疗中，本发明的化合物和一种或多种第二治疗剂均通过常规方法施用。向受试者施用包含本发明化合物和第二治疗剂的本发明组合物不排除在一个疗程中在另一个时间将

相同治疗剂、任何其他第二治疗剂或任何本发明化合物分别施用于所述受试者。

[0174] 这些第二治疗剂的有效量对于本领域技术人员是公知的，并且用于剂量的指导可以在本文引用的专利和公开的专利申请以及Wells等，eds.，Pharmacotherapy Handbook，2nd Edition，Appleton and Lange，Stamford，Conn.(2000)；PDR Pharmacopoeia，Tarascon Pocket Pharmacopoeia 2000，Deluxe Edition，Tarascon Publishing，Loma Linda，Calif.(2000)以及其他医学文献中找到。然而，确定第二治疗剂的最佳有效量范围完全在技术人员的权限内。

[0175] 在将第二种治疗剂施用于受试者的本发明的一个实施方案中，本发明化合物的有效量小于其不施用第二种治疗剂时的有效量。在另一个实施方案中，第二治疗剂的有效量小于其不施用本发明化合物时的有效量。以这种方式，可以使与任何药剂的高剂量相关的不希望的副作用最小化。其他潜在的优点(包括但不限于改进的给药方案和/或降低的药物成本)对于本领域技术人员将是显而易见的。

[0176] 在又一方面，本发明提供单独或与一种或多种上述第二治疗剂一起的本文任何通式的化合物在制备药物中的用途，作为单一组合物或作为分开剂型，用于治疗或预防受试者中的上述疾病、障碍或症状。本发明的另一方面是本文式的化合物用于在治疗或预防本文描述受试者中的疾病、障碍或其症状的用途。

[0177] 在其他方面，本文的方法包括那些：进一步包含对治疗给药的受试者反应进行监测。这样的监测可以包括对受试者组织、液体，标品，细胞、蛋白质、化学标记、遗传物质等作为治疗方案的标记或指标的定期采样。在其他方法中，通过对适合于此类治疗的相关标记或指标进行评估，将受试者预先筛选或确定为需要此类治疗。

[0178] 在一个实施方案中，本发明提供了一种监测治疗进展的方法。该方法包括以下步骤：确定患有或易患本文描述的障碍或症状的受试者中的诊断标记(标记)(例如，由本文的化合物调节的本文描述的任何靶标或细胞类型)或诊断测量(例如筛选、测定)的水平，其中已向受试者施用足以治疗疾病或其症状的治疗量的本文的化合物。在该方法中确定的标记水平可以与健康正常对照或其他患病患者中已知的标记水平进行比较，以确定受试者的疾病状态。在优选的实施方式中，在比确定第一水平晚的时间点确定受试者中标记的第二水平，并且比较两个水平以监测疾病的过程或治疗的功效。在某些优选实施方案中，在开始根据本发明的治疗之前确定受试者中标记的预治疗水平；然后可以将该标记的预治疗水平与治疗开始后受试者中的标记水平进行比较，以确定治疗的功效。

[0179] 在某些方法实施方式中，受试者中的标记水平或标记活性至少确定一次。标记水平的比较，例如，与先前或随后从同一患者、另一患者或正常受试者获得的标记水平的另一测量值相比，可用于确定根据本发明的治疗是否具有期望的效果，从而允许酌情调整剂量水平。标记水平的确定可以使用本领域已知的或本文描述的任何合适的采样/表达测定方法进行。优选地，首先从受试者中取出组织或液体样品。合适的样品的实例包括血液、尿液、组织、口腔或脸颊细胞，以及含有根的头发样品。其他合适的样品对于本领域技术人员而言是已知的。样品中蛋白质水平和/或mRNA水平(例如标记水平)的确定可使用本领域已知的任何合适的技术进行，包括但不限于：酶免疫分析法、ELISA、放射性标记/测定技术、印迹/化学发光方法、实时PCR等。

[0180] 本发明还提供用于治疗疾病、障碍或其症状(包括本文描述的那些)的试剂盒。这

些试剂盒包含:a)药物组合物,其包含本文任何式的化合物或其药学上可接受的盐;或前药或其前药的药学上可接受的盐;或其水合物、溶剂化物或多晶型物,其中所述药物组合物在容器中;和b)描述使用该药物组合物来治疗疾病、障碍或其症状(包括本文描述的那些)的方法的说明书。

[0181] 该容器可以是可容纳所述药物组合物的任何容器或其他密封或可密封的装置。实例包括瓶子;分开的或多腔室持瓶,其中每个分区或腔室包含单一剂量的所述组合物;分开的箔包装,其中每个分装包含单一剂量的所述组合物;或分配单一剂量的所述组合物的分配器。该容器可以是本领域已知的任何常规形状或形式,其由药学上可接受的材料制成,例如纸或纸板盒、玻璃或塑料瓶或罐、可重新密封的袋(例如,保持片剂的"再填充"以放置到不同的容器中)或含有根据治疗时间表压出包装的个人剂量的泡罩包装。所使用的容器可以取决于所涉及的确切剂型,例如常规的纸板盒通常不会用于容纳液体悬浮液。可以将多于一个的容器一起用于单一包装中以销售单一剂型。例如,片剂可以装在一个瓶子里,而瓶子又装在一个盒子里。优选地,容器是泡罩包装。

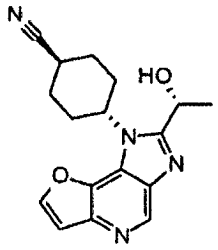
[0182] 该试剂盒可另外包含用于医师、药剂师或受试者的信息和/或说明。这种记忆辅助工具包括:印在每个腔室或分区上的数字,其中含有与方案(详细说明按方案应该摄入的片剂或胶囊)的天数相对应的剂量;或每个腔室或分区上印刷的每周的几天;或者包含相同类型信息的卡片。

[0183] 可以使用本领域已知的方案评估本文描述的化合物的生物活性,例如包括本文描述的那些方案。本文中的某些化合物表现出意料不到的优越属性(例如抑制P450、代谢稳定性、药代动力学性质等),使其成为潜在治疗剂的优选候选物。

[0184] 本文引用的所有参考文献,无论是印刷版、电子版、计算机可读存储介质还是其他形式,均通过引用整体明确地并入,包括但不限于摘要、文章、期刊、出版物、文本、论文、技术数据表、互联网网站、数据库、专利、专利申请和专利出版物。

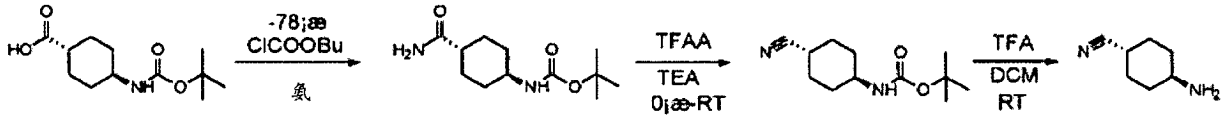
[0185] 实施例

[0186] 实施例1:反式-4-[2-[(R)-1-羟乙基]-1H-呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]环己烷甲腈(1)的合成

[0187] 

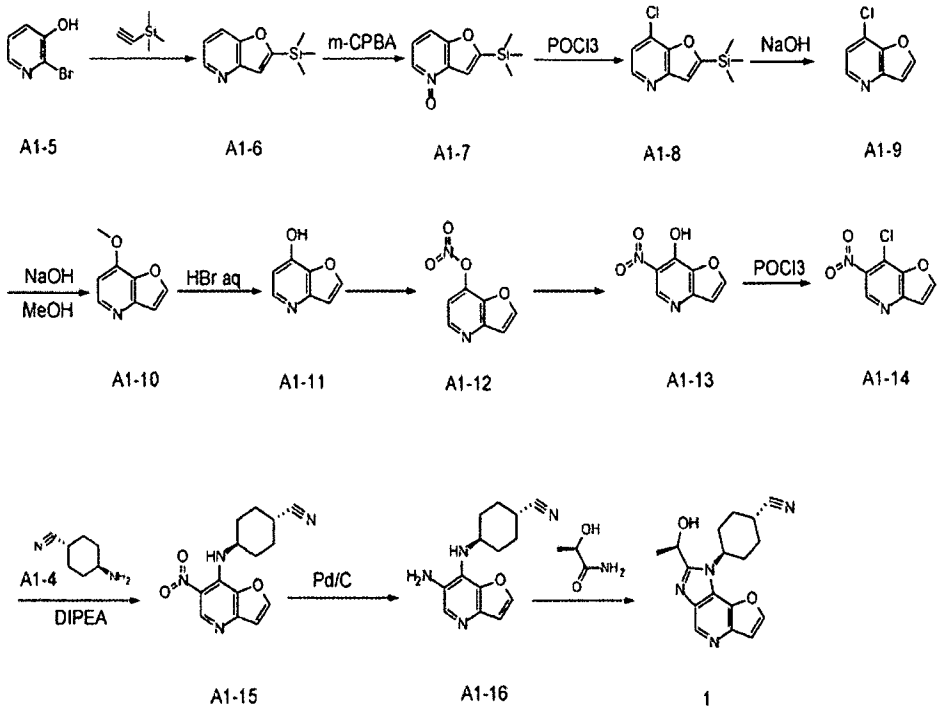
1

[0188] 方案1:

[0189] 

A1-1 A1-2 A1-3 A1-4

[0190]



A1-5 A1-6 A1-7 A1-8 A1-9 A1-10 A1-11 A1-12 A1-13 A1-14 A1-15 A1-16 1

[0191] 步骤1.将反式-4-(Boc-氨基)环己烷羧酸(A1-1)(62g,0.256mol,1.0当量)在THF(1500mL)中的溶液用NMM(64.6g,0.64mol,2.5当量)在氮气气氛下处理。将该混合物冷却至-78℃,逐逐滴加入氯甲酸异丁酯(33.6g,0.33mol,1.3当量)。在-78℃下搅拌1小时后,NH_3(气体)通过混合物鼓泡约20分钟。之后,反应温度升至-30℃,然后在-30℃搅拌1小时。过滤所得悬浮液,用水洗涤(3*200mL),烘干,得到白色粉末状的化合物A1-2(58g,收率93.5%)。MS-ESI:$[M+1]^+$:243.1

[0192] ^1H NMR(300MHz,d_6-DMSO):7.192(s,1H),6.688-6.728(m,2H),3.122-3.147(m,1H),1.92-1.959(m,1H),1.696-1.787(m,4H),1.382(s,9H),1.086-1.358(m,4H).

[0193] 步骤2.将化合物A1-2(74g,0.306mol,1.0当量)在DCM(1000mL)中的溶液用三乙胺(77.2g,0.64mol,2.5当量)处理。将混合物在冰浴中冷却至0℃,并逐滴加入TFAA(80.9g,0.383mol,1.25当量)。加入后除去冰浴并将反应温度升至20℃,然后在20℃下搅拌2小时,加入水(300mL),然后将水相用DCM萃取两次。将合并的萃取物用盐水洗涤,用无水硫酸钠干燥,浓缩并通过硅胶柱色谱法纯化,得到白色粉末状的化合物A1-3(46g,收率67.1%)。MS-ESI:[M+1]+:225.1。

[0194] ^1H NMR(300MHz,$CDCl_3$):4.397(m,1H),3.467(m,1H),2.381-2.418(m,1H),2.079-2.147(m,4H),1.613-1.757(m,2H),1.454(s,9H),1.114-1.232(m,2H).

[0195] 步骤3.向化合物A1-3(10g,44.6mmol,1.0当量)在DCM(50mL)中的溶液中加入TFA(20g)。将反应混合物在室温下搅拌2小时直至TLC显示反应完成,然后真空浓缩。加入冰水(30mL)并将溶液用氢氧化钠水溶液(4mol/L)处理至pH 10。然后用DCM/甲醇(10/1)萃取水相6次。合并的萃取物经无水硫酸钠干燥,浓缩,得到灰白色固体状的化合物A1-4,(5.1g,收率91.9%)。MS-ESI:[M+1]+:125.1。

[0196] ^1H NMR(300MHz,$CDCl_3$):2.738-2.772(m,1H),2.370-2.421(m,1H),2.115-2.170(m,2H),1.923-1.977(m,2H),1.580-1.694(m,2H),1.075-1.197(m,2H)

[0197] 步骤4.在氮气气氛下,向2-溴-3-羟基吡啶(A1-5)(225g,1.293mol,1.0当量)、三

甲基硅基乙炔(153.3g,1.592mol,1.23当量)在1,4-二氧杂环己烷(2500mL)中的溶液中加入CuI(25g)和Pd(PPh3)$_2$Cl$_2$(45g)。将反应混合物在25℃下搅拌30分钟,然后冷却至10℃,逐滴加入三乙胺(363g,3.594mol,2.78当量)。在60℃下搅拌4小时后,将溶液冷却并真空浓缩。向残余物中加入水(2000mL)和MTBE(200mL),搅拌并过滤。滤液用MTBE萃取(1000mL*2)。将合并的有机层用盐水洗涤,经无水硫酸钠干燥,浓缩并通过硅胶柱色谱法纯化,得到浅棕色液体状的化合物A1-6(150g,收率60.7%)。GC-MS:191(EI)

[0198] 步骤5.在25℃以下,向化合物A1-6(105g,0.55mol,1.0当量)在DCM(1000mL)中的溶液中分批加入间氯过氧苯甲酸(85%,230g,1.13mol,12.06当量)。在室温下搅拌过夜后,在冰浴中加入饱和碳酸氢钠溶液至pH 7-8。过滤得到的混合物,分离滤液,用DCM萃取两次。将合并的有机层用饱和碳酸氢钠溶液和盐水洗涤,经无水硫酸钠干燥,浓缩,得到褐色液体状的化合物A1-7(115g,产率100%)。

[0199] 步骤6.在30℃以下的冰浴中将化合物A1-7(115g,0.55mol,1.0当量)在甲苯(400mL)中的溶液加入到磷酰氯(400mL)中。将反应混合物在90℃下搅拌2小时,冷却至室温并浓缩。在20℃以下向残余物中缓慢加入饱和碳酸氢钠溶液至pH 7-8,并用MTBE将混合物萃取两次。将合并的有机层用盐水洗涤,经无水硫酸钠干燥,浓缩并通过硅胶柱色谱法纯化,得到黄色液体状化合物A1-8(73g,收率58.7%)。GC-MS:225(EI)

[0200] 步骤7.向化合物A1-8(73g,0.323mol,1.0当量)在THF(400mL)中的溶液中加入氢氧化钠水溶液(300mL,4mol/L)。在50℃下搅拌1小时后,将反应混合物冷却至室温并加入1000mL水。混合物用MTBE萃取两次。将合并的有机层用盐水洗涤,经无水硫酸钠干燥,浓缩并用乙酸乙酯和石油醚重结晶,得到灰白色粉末状的化合物A1-9(30g,收率60.5%)。GC-MS:153(EI)

[0201] ^{1}H NMR(300MHz,$CDCl_3$):8.485(d,1H),7.945(d,1H),7.312(d,1H),7.079(d,1H).

[0202] 步骤8.将化合物A1-9(9.21g,60mmol,1.0当量)溶于甲醇(150mL)中,然后加入水(150mL)和氢氧化钠(24g,10当量)。在50℃下搅拌1小时后,将反应混合物冷却至20℃并浓缩。残余物用DCM萃取三次,然后将合并的有机层经无水硫酸钠干燥并浓缩,得到黄色液体状的化合物A1-10(5.5g,收率61.5%)。MS-ESI:$[M+1]^+$:150

[0203] 步骤9.将化合物A1-10(5.5g,37mmol,1.0当量)加入到40%HBr水溶液(150mL)中。将反应混合物加热回流18小时,冷却并浓缩。残余物用饱和碳酸氢钠溶液(100mL)处理至pH 7-8。搅拌20分钟后,过滤沉淀物,用水洗涤,烘箱干燥,得到灰白色粉末状化合物A1-11(3.1g,收率62%)。MS-ESI:$[M+1]^+$:136

[0204] 步骤10.在氮气气氛下,将化合物A1-11(1.68g,12.4mmol,1.0当量)在120mL DCM中的混合物冷却至-5℃,在0℃下逐滴加入在DCM(30mL)中的四丁基硝酸铵(5.17g,17mmol,1.36当量),然后一次加入TFAA(5.17g,20mmol,1.6当量)。加入后,将反应混合物在-5℃下搅拌1小时,然后升温至25℃并搅拌15小时。浓缩溶剂,向残余物中加入乙醚(200mL),搅拌并过滤。收集滤饼并加入饱和碳酸氢钠溶液(100mL)。将混合物用乙酸乙酯萃取两次,然后将合并的有机层经无水硫酸钠干燥并浓缩,得到黄色粉末状的化合物A1-12,(1.37g,收率61.4%)。MS-ESI:$[M+1]^+$:181

[0205] 步骤11.将化合物A1-12(1.37g,7.61mmol,1.0当量)和丙酸(50mL)的混合物加热至110℃,然后在110℃至120℃下将发烟硝酸(0.65mL)逐滴加入。在125℃下搅拌30分钟并

冷却至室温后，加入乙醚(100mL)，过滤固体，用乙醚洗涤并真空干燥，得到黄色粉末状化合物A1-13(1.2g，收率87.6%)。MS-ESI:[M+1]$^+$:181。

[0206] ^{1}H NMR(300MHz，d_6-DMSO):13.149(s,1H)，9.024(s,1H)，8.234(d,1H)，6.966(d,1H)。

[0207] 步骤12.在20℃以下向化合物A1-13(1.2g，6.67mmol，1.0当量)在1,2-二氯乙烷(50mL)中的溶液中加入三氯氧磷(15mL)，然后在氮气气氛下在95℃搅拌2小时，冷却至25℃并浓缩。在20℃以下向残余物中缓慢加入饱和碳酸氢钠溶液至pH 7-8，并将混合物用MTBE萃取两次。合并的有机层用盐水洗涤，经无水硫酸钠干燥，浓缩，得到浅黄色粉末状的化合物A1-14(0.8g，收率60.4%)，^{1}H NMR(300MHz，$CDCl_3$):9.250(s,1H)，8.189(d,1H)，7.191(d,1H)。

[0208] 步骤13.向A1-14(280mg，1.41mmol，1.0当量)在正丁醇(20mL)中的溶液中加入化合物A1-4(290mg，2.34mmol，1.66当量)和DIPEA(403mg，3.12mmol，2.21当量)。将反应混合物在135℃下搅拌1小时，浓缩并通过硅胶柱色谱法纯化，得到黄色粉末状的A1-15(320mg，收率79.4%)。MS-ESI:[M+1]$^+$:287.1。

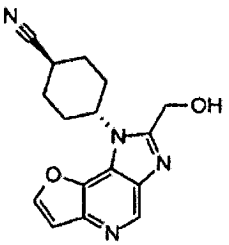
[0209] ^{1}H NMR(300MHz，$CDCl_3$):9.268(s,1H)，8.653(d,1H)，7.952(d,1H)，7.034(d,1H)，4.423-4.511(m,1H)，2.629-2.723(m,1H)，2.241-2.355(m,4H)，1.864-1.902(m,2H)，1.539-1.578(m,2H)。

[0210] 步骤14.向A1-15(320mg，1.12mmol，1.0当量)在甲醇(15mL)中的溶液中加入10%Pd/C(0.3g，50%湿)。在室温下在大气压力下进行氢化直到氢气吸收停止。将催化剂过滤并用甲醇洗涤。将滤液真空浓缩，得到黄色油状的A1-16，(286mg，收率100%)。MS-ESI:[M+1]$^+$:257.1

[0211] 步骤15.将(R)-(+)-乳酰胺(259mg，2.8mmol，5.0当量)和Et3O-BF4(543mg，2.8mmol，5.0当量)在THF(10mL)中的溶液在室温下在氮气气氛下搅拌30分钟。然后将上述溶液加入到A1-16(143mg，0.56mmol，1.0当量)在乙醇(10mL)中的混合物中。在85℃搅拌2小时后，浓缩混合物，加入水并用乙酸乙酯萃取四次。弃去有机相并用饱和碳酸氢钠溶液(100mL)将水相处理至pH 8，用乙酸乙酯萃取两次。第二有机相经无水硫酸钠干燥，浓缩，得到淡黄色粉末状的标题化合物(80mg，收率46%)。MS-ESI:[M+1]$^+$:311.4

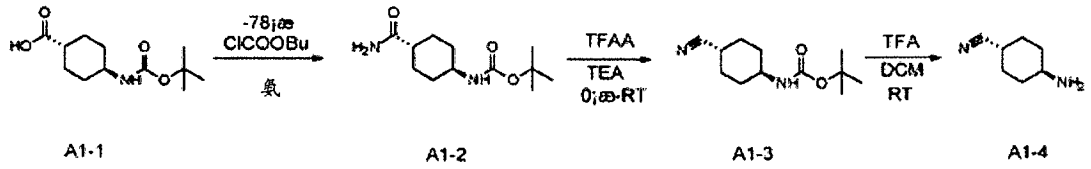
[0212] ^{1}H NMR(300MHz，$CDCl_3$):9.005(s,1H)，7.949(s,1H)，7.256(s,1H)，5.227-5.290(m,1H)，4.766-4.843(m,1H)，2.783-2.864(m,1H)，2.438-2.527(m,4H)，2.068-2.192(m,2H)，1.913-2.003(m,2H)，1.767-1.846(d,3H)。

[0213] 实施例2：反式-4-[2-(羟甲基)呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]环己烷甲腈(2)的合成

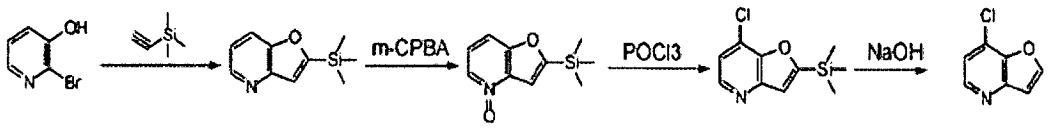
[0214] 

2

[0215] 方案2：

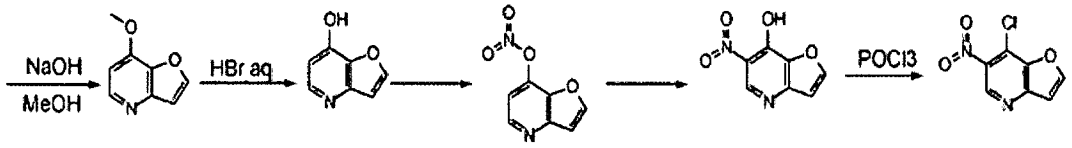


A1-1 A1-2 A1-3 A1-4

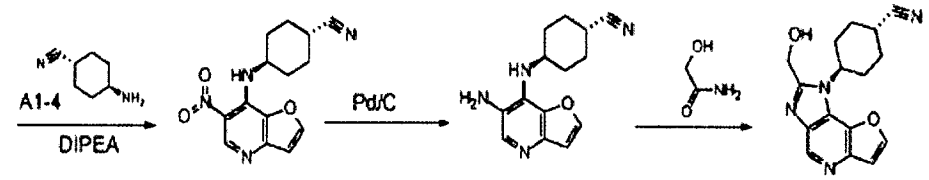


A1-5 A1-6 A1-7 A1-8 A1-9

[0216]



A1-10 A1-11 A1-12 A1-13 A1-14



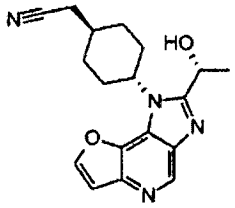
A1-15 A1-16 2

[0217] 实施例2使用与实施例1相同的步骤制备，不同之处在于：在步骤15)中用2-羟基乙酰胺代替(R)-(+)-乳酰胺：40mg浅黄色粉末状标题化合物，MS-ESI：[M+1]$^+$：297.4

[0218] ^{1}H NMR(300MHz，$CDCl_3$)：9.048(s，1H)，7.965(s，1H)，7.286(s，1H)，5.049(s，2H)，4.702-4.813(m，1H)，2.753-2.873(m，1H)，2.376-2.527(m，4H)，2.087-2.226(m，2H)，1.872-2.053(m，2H)。

[0219] 实施例3：2-[反式-4-[2-(R)-1-羟乙基]呋喃并[3，2-b]咪唑并[4，5-d]吡啶-1-基]环己基]乙腈(3)的合成

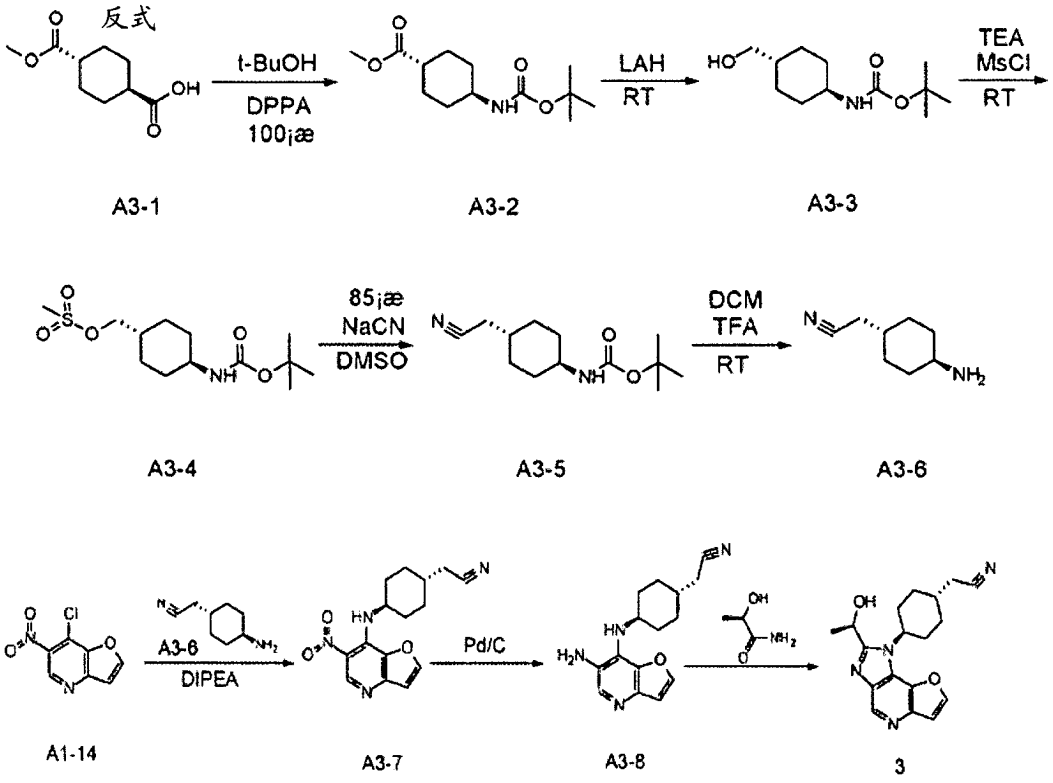
[0220]



3

[0221] 方案3：

[0222]



[0223] 步骤1.在氮气气氛下,在室温下向反式-1,4-环己烷-二羧酸单甲酯(A3-1)(100g,0.538mol,1.0当量)和三乙胺(57.4g,0.568mol,1.055当量)在叔丁醇(1000mL)中的溶液中逐滴加入二苯基磷酰基叠氮化物(155g,0.563mol,1.047当量)。混合物回流超过16小时。通过TLC完成后,将混合物冷却并浓缩。加入水(1000mL),并将混合物用MTBE萃取三次。然后将有机层用饱和碳酸氢钠溶液和盐水洗涤,经无水硫酸钠干燥,浓缩并通过硅胶柱色谱法纯化,得到灰白色粉末状的化合物A3-2,(53g,收率39.2%)。MS-ESI:$[M+1]^+$:257.1

[0224] 步骤2.将$LiAlH_4$(9.0g,0.236mol,1.12当量)在THF(500mL)中的悬浮液在冰浴中冷却至0℃,然后加入化合物A3-2(54.3g,0.211mol,1.0当量)在THF(200mL)中的溶液,同时保持温度在10℃以下。将反应混合物在室温下搅拌过夜,然后在15℃至25℃下用十水合硫酸钠(27g)猝灭,过滤并浓缩滤液,得到白色粉末状的化合物A3-3(43g,收率89%)。MS-ESI:$[M+1]^+$:229.1

[0225] 步骤3.在10℃以下向化合物A3-3(11.5g,0.05mol,1.0当量)和三乙胺(7.6g,0.075mol,1.5当量)在DCM(200mL)中的混合物中逐滴加入甲基磺酰氯(6.9g,0.06mol,1.2当量)。在室温下搅拌2小时后,加入水(300mL)。混合物用乙酸乙酯萃取两次。将合并的萃取物用盐水洗涤,经无水硫酸钠干燥,浓缩,得到黄色液体状的化合物A3-4(16.0g,收率100%)。MS-ESI:$[M+1]^+$:307.1

[0226] 步骤4.在20℃以下向化合物A3-4(16.0g,0.05mol,1.0当量)在DMSO(150mL)中的溶液中分批加入的氰化钠(7.0g,0.143mol,2.86当量)。在85℃搅拌5小时后,将混合物冷却至室温,加入冰水(500mL)。混合物用MTBE萃取两次。将合并的萃取物用盐水洗涤三次,经无水硫酸钠干燥,浓缩并通过硅胶柱色谱法纯化,得到白色粉末状化合物A3-5(9.3g,收率78%)。MS-ESI:$[M+1]^+$:238.1。

[0227] ^1H NMR(300MHz,$CDCl_3$):4.408(m,1H),3.405(m,1H),2.263-2.285(d,2H),2.064-

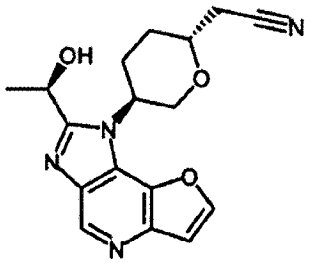
2.096(m,2H),1.457(s,9H),1.122-1.281(m,4H).

[0228] 步骤5.向化合物A3-5(1.1g,4.6mmol,1.0当量)在DCM(10mL)中的溶液中加入TFA(6g)。将反应混合物在室温下搅拌2小时,然后真空浓缩。加入冰水(15mL)并将溶液用氢氧化钠水溶液(4mol/L)处理至pH 10。然后将水相用DCM/甲醇(10/1)萃取5次。合并的萃取物经无水硫酸钠干燥,浓缩得到黄色油状的化合物A3-6(0.55g,收率87.7%)。MS-ESI:[M+1]$^+$:138.1。

[0229] 步骤6至步骤8与实施例1中的步骤13至步骤15相同,不同之处在于胺A-4被A3-6替代以制备标题化合物:70mg浅黄色粉末(收率:0.565%)。MS-ESI:[M+1]$^+$:325.5

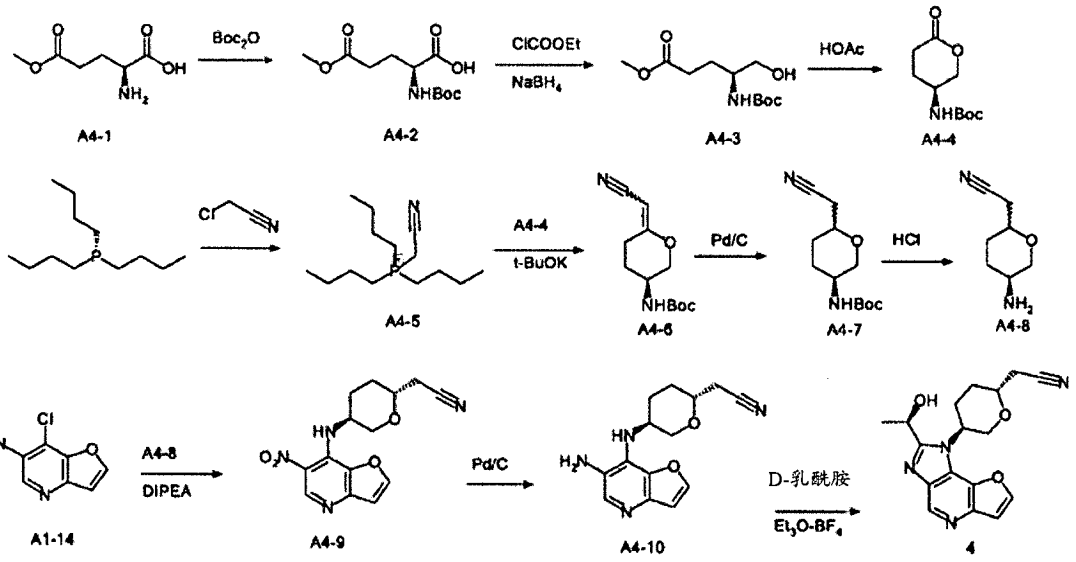
[0230] ^{1}H NMR(300MHz,$CDCl_3$):9.003(s,1H),7.965(s,1H),7.270(s,1H),5.255-5.298(m,1H),4.713-4.795(m,1H),2.439-2.611(m,4H),2.068-2.512(m,5H),1.808-1.829(d,3H),1.452-1.576(d,2H).

[0231] 实施例4:2-[(2R,5S)-5-[2-[(R)-1-羟乙基]呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]四氢吡喃-2-基]乙腈(4)的合成

[0232] 

4

[0233] 方案4:

[0234] 

[0235] 步骤1.在圆底烧瓶中,将三乙胺(188g,1.86mol,1.0当量)逐滴加入到二碳酸二叔丁酯(162g,0.744mol,1.2当量)和化合物A4-1(100g,0.62mol,1.0当量)在水(500mL)和1,4-二氧杂环己烷(500mL)中的搅拌溶液中。在室温下搅拌18小时后,将溶液用MTBE萃取(500mL*2)并将水相在冰上冷却并通过缓慢加入10%柠檬酸溶液小心地酸化至pH 3。然后用乙酸乙酯萃取氨基甲酸乙酯两次,合并的萃取物用盐水洗涤,经无水硫酸钠干燥,浓缩,得到澄清的粘稠油状的化合物A4-2(180g,收率100%)。MS-ESI:[M+1]$^+$:262.1

[0236] 步骤2.在室温下，用4-甲基吗啉(17g，0.168，1.L当量)处理化合物A4-2(40g，0.153mmol，1.0当量)在THF(600mL)中的溶液。将所得混合物冷却至0℃，然后逐滴用氯甲酸异丁酯(22.7g，0.166mmol，1.08当量)处理。将所得反应混合物在0℃另外搅拌20分钟，然后过滤并用THF洗涤。然后将清澈的滤液冷却至0℃，并用$NaBH_4$(11.2g，0.295mol，1.93当量)在水中的溶液(100mL)处理。将所得混合物在室温下搅拌过夜，然后逐滴用HCl水溶液(1.0mol/L，200mL)淬灭。混合物用乙酸乙酯萃取，合并的萃取物用盐水洗涤，经无水硫酸钠干燥，浓缩，得到黄色油状的化合物A4-3(25g，产率66％)。MS-ESI:$[M+1]^+$:248.1

[0237] 步骤3.将化合物A4-3(25g，0.1mol，1.0当量)在甲苯(300mL)和乙酸(150mL)中的溶液加热回流5小时，然后冷却，真空浓缩。在冰浴中将残余物加入饱和碳酸氢钠溶液至pH 7-8。然后用乙酸乙酯萃取混合物三次，合并的萃取物用盐水洗涤，经无水硫酸钠干燥，浓缩并用乙酸乙酯和PE重结晶，得到白色粉末状的化合物A4-4(8.0g，收率37.2％)。GC-MS:215

[0238] 步骤4.在氮气气氛下，将三丁基膦(72.9g，0.36mol，1.0当量)在硝基甲烷(500mL)中的溶液中逐滴加入氯乙腈(27.2g，0.36mol，1.0当量)。将所得反应混合物在室温下搅拌16小时，然后浓缩。当加入少量乙酸乙酯时，残余油固化。固体用乙酸乙酯和DCM重结晶，得到白色粉末状的化合物A4-5(95g，收率95％)。

[0239] 步骤5.在0℃下向氮气气氛下的干燥化合物A4-5(8.3g，30mmol，3.0当量)在N,N-二甲基乙酰胺(30mL)中的溶液中分批加入固体叔丁醇钾(3.1g，28mmol，2.8当量)。将所得混合物逐渐升温至30℃并搅拌2小时。然后将所得内鎓盐溶液用化合物A4-4(2.15g，10mmol，1.0当量)处理，并在70℃下搅拌过夜。冷却至室温后，将所得悬浮液倒入冰水(100mL)和饱和碳酸氢钠溶液(100mL)的混合物中。用乙酸乙酯萃取混合物两次，并将合并的萃取物用盐水洗涤三次，经无水硫酸钠干燥，浓缩，得到未经纯化的黄色油状的化合物A4-6(7.5g，收率100％)。MS-ESI:$[M+1]^+$:239.1

[0240] 步骤6.向化合物A4-6(7.5g，10mmol，1.0当量)在甲醇(200mL)中的溶液中加入10％Pd/C(0.5g，50％湿)。在室温下在大气压力下进行氢化直到氢气吸收停止。将催化剂过滤并用甲醇洗涤。将滤液真空浓缩，并通过硅胶柱色谱法纯化，得到灰白色粉末状的化合物A4-7(1.6g，收率66.7％)。MS-ESI:$[M+1]^+$:241.1

[0241] 步骤7.向化合物A4-7(1.6g，6.67mmol，1.0当量)在DCM(20mL)中的溶液中加入TFA(10g，88.5mmol，13.2当量)。将反应混合物在室温下搅拌2小时直到TLC显示反应完成，然后真空浓缩。加入水(20mL)并将溶液用氢氧化钠水溶液(4mol/L)处理至pH10。然后用DCM/甲醇(10/1)将水相萃取6次。将合并的萃取物经无水硫酸钠干燥，浓缩，得到浅棕色油状的化合物A4-8(950mg，收率100％)。MS-ESI:$[M+1]^+$:141.1

[0242] 步骤8.向化合物A1-14(如实施例1中步骤4至12制备)(600mg，3.0mmol，1.0当量)在正丁醇(15mL)中的溶液中加入化合物A4-8(950mg，6.7mmol，2.26当量)和DIPEA(1.36g，10.5mmol，3.5当量)。将反应混合物在135℃下搅拌1小时，浓缩并通过硅胶柱色谱法纯化，得到浅黄色粉末状的化合物A4-9(2R,5S)(254mg，收率28.0％)。MS-ESI:$[M+1]^+$:303.1。

[0243] ^1H NMR(300MHz，d_6-DMSO):9.063(s，1H)，8.503(d，1H)，9.326(d，1H)，7.176(d，1H)，4.431-4.513(m，1H)，4.128-4.156(m，1H)，3.633-3.659(m，1H)，3.448-3.518(m，1H)，2.775-2.841(m，2H)，2.205-2.312(m，1H)，1.829-1.859(m，2H)，1.501-1.521(m，1H)。

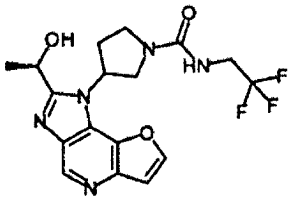
[0244] 步骤9.向化合物A4-9(254g，0.84mmol，1.0当量)在甲醇(20mL)中的溶液中加入

10%Pd/C(0.15g,50%湿)。在室温下在大气压力下进行氢化直到氢气吸收停止。将催化剂过滤并用甲醇洗涤。将滤液真空浓缩,得到黄色油状的化合物A4-10(230mg,收率100%)。MS-ESI:$[M+1]^+$:273.1

[0245] 步骤10.在室温和氮气气氛下,将D-乳酰胺(388mg,4.2mmol,5.0当量)和Et_3O-BF_4(1.3g,6.72mmol,8.0当量)在THF(10mL)中的溶液搅拌30分钟。然后将上述溶液加入到化合物A4-10(230mg,0.84mmol,1.0当量)在乙醇(10mL)中的混合物中。在85℃搅拌3小时直至HPLC显示反应完成后,浓缩混合物,加入水并用乙酸乙酯萃取四次。弃去有机相,将水相用饱和碳酸氢钠溶液处理至pH 8,用乙酸乙酯萃取两次。将第二有机相经无水硫酸钠干燥,浓缩并通过硅胶柱色谱法纯化,得到浅黄色粉末状标题化合物(120mg,收率43.8%)。MS-ESI:$[M+1]^+$:327.6,

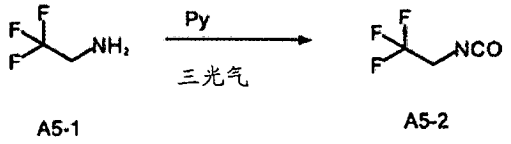
[0246] ^1H NMR(300MHz,$CDCl_3$):9.039(s,1H),7.939(d,1H),7.196(d,1H),5.235-5.336(m,1H),4.806-4.973(m,1H),4.403-4.483(t,1H),4.096-6.116(m,2H),2.700-2.807(m,4H),2.105-2.312(m,2H),1.830-1.852(d,3H).

[0247] 实施例5:3-[2-[(R)-1-羟乙基]-1H-呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]-N-(2,2,2-三氟乙基)吡咯烷-1-甲酰胺(5)的合成

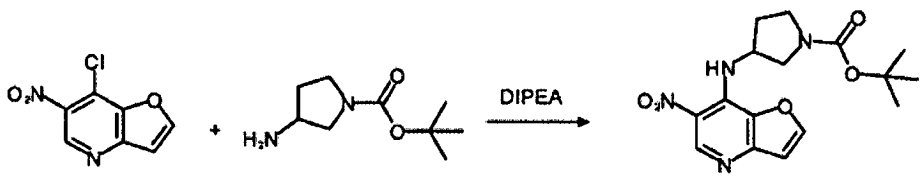
[0248] 

5

[0249] 方案5:

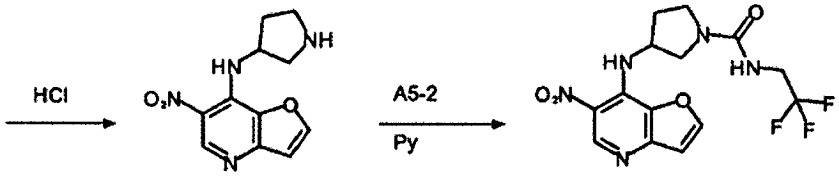


A5-1 A5-2

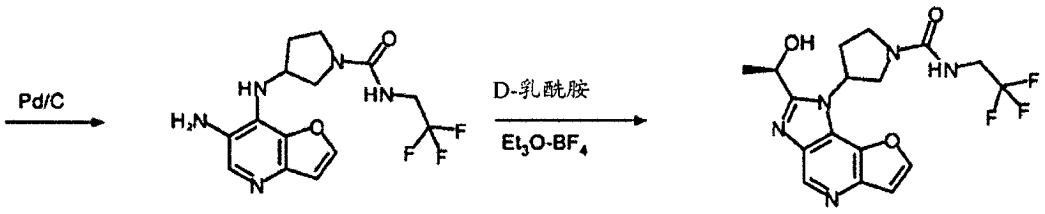


A1-14 A5-3 A5-4

[0250]



A5-5 A5-6



A5-7 5

[0251] 步骤1.向化合物A1-14(如实施例1中步骤4至12制备)(820mg,4.13mmol,1.0当量)在正丁醇(15mL)中的溶液中加入化合物A5-3(1.0g,5.37mmol,1.3当量)和DIPEA(1.6g,12.4mmol,3.0当量)。将反应混合物在135℃搅拌1小时,浓缩并通过硅胶柱色谱法纯化,得到黄色粉末状的化合物A5-4(1.32g,收率91.8%)。MS-ESI:$[M+1]^+$:349.1

[0252] 步骤2.向化合物A5-4(1.32g,3.8mmol,1.0当量)在DCM(15mL)中的溶液中加入HCl在乙醇(30%w/w)中的溶液(15mL)。将反应混合物在室温下搅拌2小时直至TLC显示反应完成,然后真空浓缩。加入冰水(20mL),并将溶液用氢氧化钠水溶液(4mol/L)处理至pH 10。然后将水相用DCM萃取三次。将合并的萃取物经无水硫酸钠干燥,浓缩,得到黄色粉末状的化合物A5-5(950mg,收率100%)。MS-ESI:$[M+1]^+$:249.1

[0253] 步骤3.将2,2,2-三氟乙胺(A5-1)(1.21g,12.2mmol,1.0当量)和吡啶(2.4g,30.5mmol,2.5当量)在DCM(50mL)中的混合物冷却至0℃,并在5℃以下用在DCM(50mL)中的三光气(1.34g,4.52mmol,0.37当量)逐滴处理。加入后,将反应混合物在35℃搅拌1小时,然后在25℃搅拌2小时。异氰酸酯(A5-2)溶液不经纯化用于下一步。

[0254] 步骤4.将化合物A5-5(0.95g,3.8mmol,1.0当量)和吡啶(0.45g,5.7mmol,1.5当量)在DCM(60mL)中的混合物冷却至10℃,并用异氰酸酯(A5-2)溶液(12.2mmol,3.2当量)逐滴处理。将反应混合物加热回流3小时,然后冷却。加入饱和碳酸氢钠溶液(200mL),混合物

用DCM萃取两次。将合并的萃取物用盐水洗涤，经无水硫酸钠干燥，浓缩并通过硅胶柱色谱法纯化，得到黄色粉末状的化合物A5-6(850mg，收率60%)。MS-ESI:$[M+1]^+$:374.3

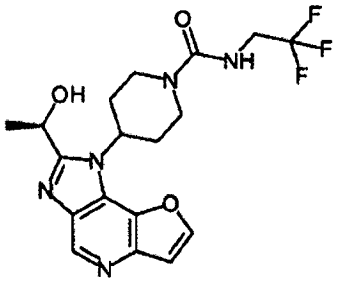
[0255] ^{1}H-NMR(300MHz，d_6-DMSO):9.282(s,1H)，8.718(d,1H)，7.962(d,1H)，7.024(d,1H)，5.165-5.186(m,1H)，4.642(m,1H)，3.926-4.008(m,3H)，3.517-3.675(m,3H)，2.502-2.568(m,1H)，2.206-2.267(m,2H)。

[0256] 步骤5.向化合物A5-6(850mg，2.28mmol，1.0当量)在甲醇(80mL)中的溶液中加入10%Pd/C(0.45g，50%湿)。在室温下在大气压力下进行氢化直到氢气吸收停止。将催化剂过滤并用甲醇洗涤。将滤液真空浓缩，得到棕色油状的化合物A5-7(800mg，收率100%)。MS-ESI:$[M+1]^+$:344.3

[0257] 步骤6.在室温下在氮气气氛中，将D-乳酰胺(1.27g，13.68mmol，6.0当量)和Et_3O-BF_4(3.53g，18.24mmol，8.0当量)在THF(20mL)中的溶液搅拌30分钟。然后将上述溶液加入到化合物A5-7(800mg，2.28mmol，1.0当量)在乙醇(20mL)中的混合物中。在85℃搅拌5小时直至HPLC显示反应完成后，浓缩混合物，加入HCl(1mol/L，30mL)并用乙酸乙酯萃取四次。弃去有机相，水相用饱和碳酸氢钠溶液处理至pH 8，用乙酸乙酯萃取三次。第二有机相经无水硫酸钠干燥，浓缩并用硅胶柱色谱纯化，得到浅黄色粉末状标题化合物(530mg，收率58.5%)。MS-ESI:$[M-1]^-$:396.5。

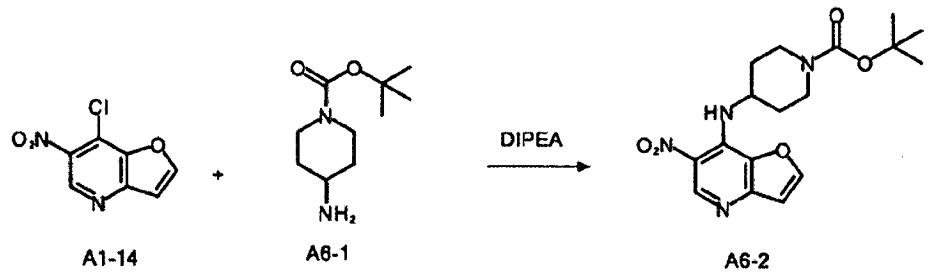
[0258] ^{1}H-NMR(300MHz，d_6-DMSO):8.931(s,1H)，8.338(d,1H)，7.276(d,1H)，7.007(m,1H)，5.889-5.910(m,1H)，5.661-5.683(m,1H)，5.251-5.273(m,2H)，3.652-3.970(m,5H)，3.435-3.505(m,1H)，2.455-2.712(m,2H)，1.672(d,3H)。

[0259] 实施例6：(R)-4-[2-(1-羟乙基)-1H-呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]-N-(2,2,2-三氟乙基)哌啶-1-甲酰胺(6)的合成

[0260] 

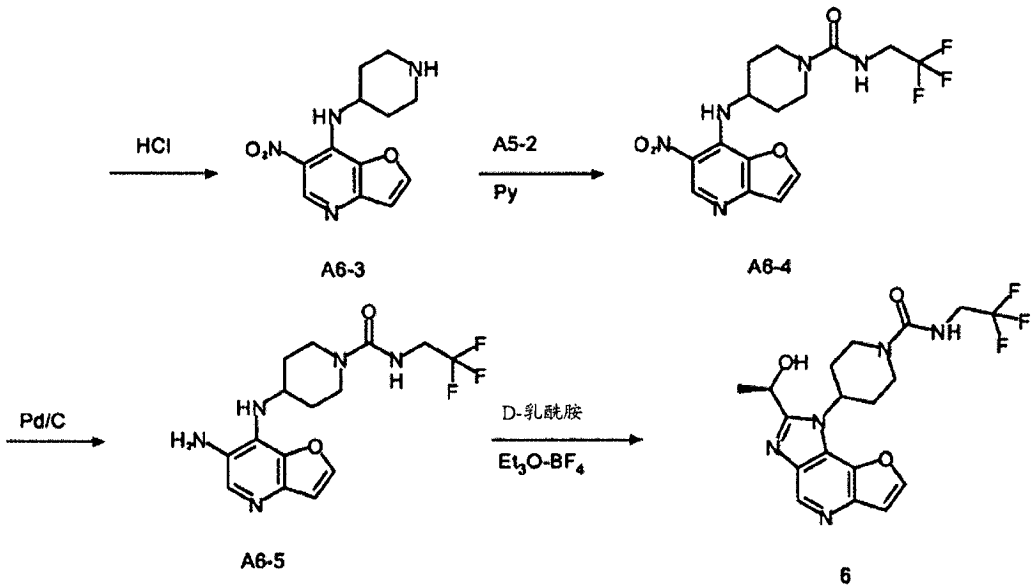
6

[0261] 方案6：



A1-14 A6-1 A6-2

[0262]

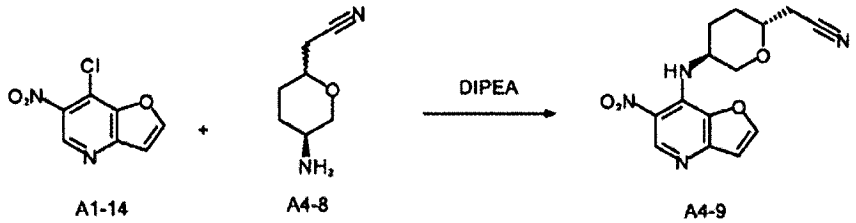


A6-3 A6-4 A6-5 6

[0263] 该步骤类似于实施例5中的那些，以产生灰白色粉末状标题化合物(21mg，收率：6.7%)，MS-ESI：[M-1]⁻：410.6。

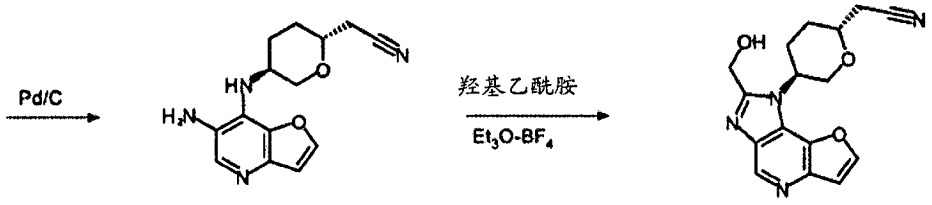
[0264] ^{1}H-NMR(300MHz，CD_3OD)：8.862(s，1H)，8.046(d，1H)，7.150(d，1H)，5.152-5.383(m，2H)，4.325-4.386(m，2H)，3.990-4.022(m，2H)，3.110-3.192(m，2H)，2.423-2.653(m，2H)，1.984-2.117(m，2H)，1.793-1.915(d，3H)。

[0265] 实施例7：2-[(2R，5S)-5-[2-(羟甲基)呋喃并[3，2-b]咪唑并[4，5-d]吡啶-1-基]四氢吡喃-2-基]乙腈(7)的合成



A1-14 A4-8 A4-9

[0266]



A4-10 7

[0267] 步骤1.在氮气气氛下，向化合物A1-14(500mg，2.0mmol，1.0当量)在丁醇(8mL)中

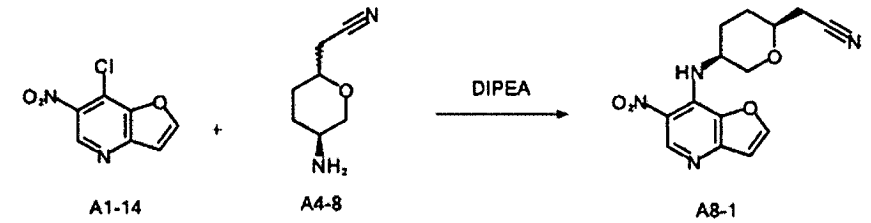
的溶液中加入化合物A4-8(350mg,2.5mmol,1.0当量)和DIPEA(403mg,8.25mmol,3.3当量)。将反应混合物在135℃下搅拌2小时,然后浓缩并通过硅胶柱色谱法纯化,得到黄色固体状的化合物A4-9(194mg,收率25.6%)。MS-ESI:[M+1]$^+$:302.3

[0268] 步骤2.向化合物A4-9(97mg,1.0mmol)在甲醇(15mL)中的溶液中加入10%Pd/C(50mg,50%湿)。在室温下在大气压力下进行氢化直到氢气吸收停止。将催化剂过滤并用甲醇洗涤。浓缩滤液,得到黄色油状的化合物A4-10(535mg,收率:100%)。MS-ESI:[M+1]$^+$:272.5

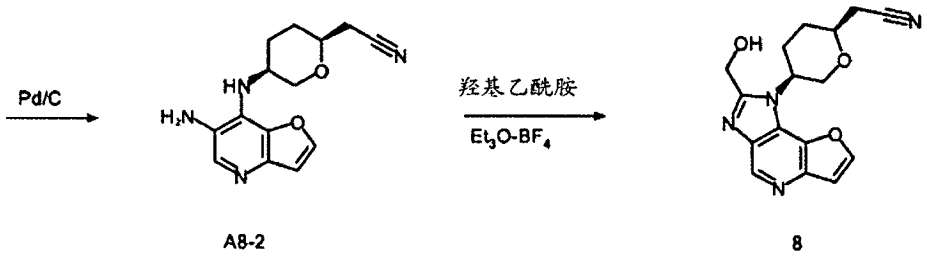
[0269] 步骤3.将羟基乙酰胺(126mg,1.6mmol,5.0当量)和Et_3O-BF_4(310mg,1.6mmol,5.0当量)在THF(10mL)中的溶液在室温下在氮气气氛中搅拌30分钟。然后将上述溶液加入到化合物A4-10(88mg,0.32mmol,1.0当量)在乙醇(10mL)中的混合物中。在85℃搅拌12小时后,浓缩混合物,加入水并用乙酸乙酯萃取三次。弃去有机相并将水相用饱和碳酸氢钠溶液(100mL)处理至pH:8,然后将混合物用乙酸乙酯萃取两次。第二有机相经无水硫酸钠干燥,浓缩并通过硅胶柱色谱法纯化,得到灰白色粉末状的标题化合物(70mg,收率:70%)。MS-ESI:[M+1]$^+$:313.5

[0270] ^{1}H NMR(300MHz,$CDCl_3$):9.00(s,1H),7.95(d,1H),7.26(d,1H),5.27-5.29(m,1H),4.76-4.84(m,1H),2.78-2.86(m,1H),2.43-2.52(m,4H),2.06-2.19(m,2H),1.91-2.00(m,2H),1.76-1.84(d,3H).

[0271] 实施例8:2-[(2S,5S)-5-[2-(羟甲基)呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]四氢吡喃-2-基]乙腈(8)的合成



[0272]



[0273] 步骤1.在氮气气氛下,向化合物A1-14(500mg,2.0mmol,1.0当量)在丁醇(8mL)中的溶液中加入化合物A4-8(350mg,2.5mmol,1.0当量)和DIPEA(403mg,8.25mmol,3.3当量)。将反应混合物在135℃下搅拌2小时,然后浓缩并通过硅胶柱色谱法纯化,得到黄色固体状的化合物A8-1(67mg,收率8.84%)。

[0274] MS-ESI:[M+1]$^+$:302.3

[0275] 步骤2.向化合物A8-1(67mg,1.0mmol)在甲醇(10mL)中的溶液中加入10%Pd/C(30mg,50%湿)。在室温下在大气压力下进行氢化直到氢气吸收停止。将催化剂过滤并用甲醇洗涤。浓缩滤液,得到黄色油状的化合物A8-2(60mg,收率:100%)。

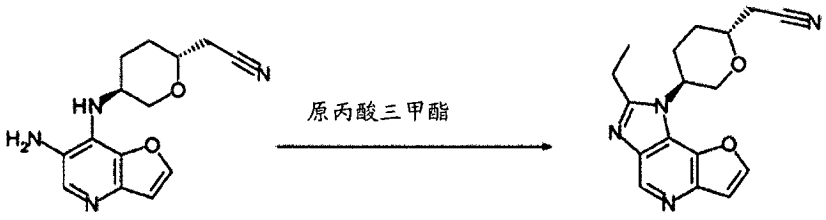
[0276] MS-ESI:[M+1]$^+$:272.5

[0277] 步骤3.将羟基乙酰胺(105mg,1.33mmol,6.0当量)和Et_3O-BF_4(258mg,1.33mmol,6.0当量)在THF(10mL)中的溶液在室温下在氮气气氛中搅拌30分钟。然后将上述溶液加入到化合物A8-2(60mg,0.221mmol,1.0当量)在乙醇中的(10mL)混合物中。在85℃搅拌12小时后,浓缩混合物,加入水并用乙酸乙酯萃取三次。弃去有机相并将水相用饱和碳酸氢钠溶液(100mL)处理至pH:8,然后用乙酸乙酯萃取混合物两次。第二有机相经无水硫酸钠干燥,浓缩并用硅胶柱色谱法纯化,得到灰白色粉末状的标题化合物(21mg,收率:30.5%)。

[0278] MS-ESI:[M+1]$^+$:313.5

[0279] ^{1}H-NMR(300MHz,CD_3OD):8.85(s,1H),8.29(d,1H),7.18(d,1H),4.98(d,3H),4.35-4.42(m,2H),3.95-3.99(m,1H),3.48-3.65(m,1H),3.04-3.11(m,1H),2.67-2.76(m,1H),1.97-2.31(m,3H).

[0280] 实施例9:2-[(2R,5S)-5-[2-乙基呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]四氢吡喃-2-基]乙腈(9)的合成

[0281] 

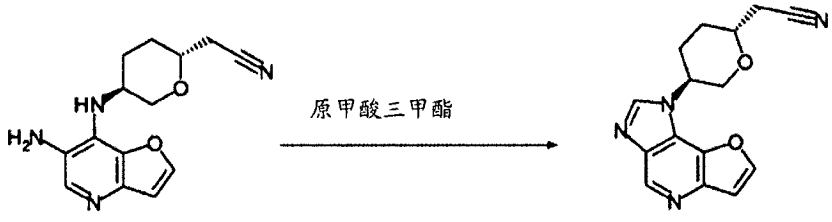
A4-10 9

[0282] 在氮气气氛中,将化合物A4-10(1.1g,4.04mmol,1.0当量)和原丙酸三甲酯(2.2mL)在1,2-二氯乙烷(50mL)中的溶液加热回流,然后加入吡啶盐酸盐(200mg)。将反应混合物在80℃下搅拌2小时,浓缩,并用饱和碳酸氢钠溶液处理至pH:8。混合物用乙酸乙酯萃取两次。将合并的有机相经无水硫酸钠干燥,通过硅胶柱色谱法浓缩纯化,得到黄色固体状标题化合物(800mg,收率:63.8%)。

[0283] MS-ESI:[M+1]$^+$:311.0

[0284] ^{1}H NMR(300MHz,$CDCl_3$):9.01(s,1H),7.91(d,1H),7.17(d,1H),4.54-4.59(m,1H),4.33-4.38(t,1H),4.05-4.09(m,2H),3.01-3.06(m,2H),2.70-2.83(m,3H),2.15-2.19(m,2H),1.85-1.92(m,1H),1.49-1.54(t,3H).

[0285] 实施例10:2-[(2R,5S)-5-[2-呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]四氢吡喃-2-基]乙腈(10)的合成

[0286] 

A4-10 10

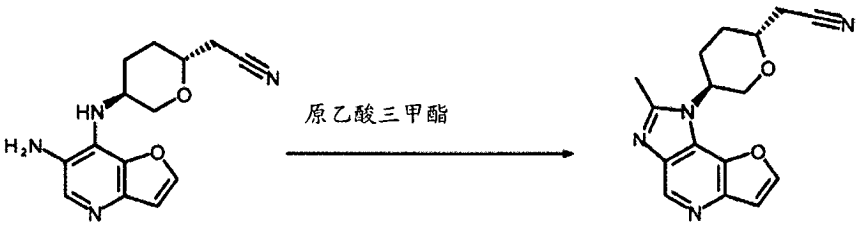
[0287] 在氮气气氛下,向化合物A4-10(136mg,0.5mmol,1.0当量)在原甲酸三甲酯(5.0mL)中的溶液中加入甲酸(1.0mL)。将反应混合物在80℃下搅拌1小时,浓缩,并用饱和

碳酸氢钠溶液(100mL)处理至pH:8。用乙酸乙酯萃取混合物两次。将合并的有机相经无水硫酸钠干燥，通过硅胶柱色谱法浓缩纯化，得到黄色固体状标题化合物(400mg，收率：28.4%)。

[0288] MS-ESI:$[M+1]^+$:282.9

[0289] ^1H NMR(300MHz,$CDCl_3$):9.10(s,1H),7.94(s,1H),7.92(d,1H),7.19(d,1H),4.76-4.79(m,1H),4.32-4.37(m,1H),3.92-4.03(m,2H),2.71-2.73(d,2H),2.46-2.51(m,2H),2.17-2.21(m,1H),1.89-1.91(m,1H).

[0290] 实施例11:2-[(2R,5S)-5-[2-甲基呋喃并[3,2-b]咪唑并[4,5-d]吡啶-1-基]四氢吡喃-2-基]乙腈(11)的合成

[0291] 

A4-10 11

[0292] 在氮气气氛下，将化合物A4-10(1.0g,3.67mmol,1.0当量)和原乙酸三甲酯(2.0mL)在1,2-二氯乙烷(30mL)中的溶液加热至回流，然后加入吡啶盐酸盐(200mg)。将反应混合物在80℃下搅拌2小时，浓缩，并用饱和碳酸氢钠溶液处理至pH:8。用乙酸乙酯萃取混合物两次。将合并的有机相经无水硫酸钠干燥，通过硅胶柱色谱法浓缩纯化，得到黄色固体状标题化合物(500mg，收率:46.0%)。

[0293] MS-ESI:$[M+1]^+$:296.9

[0294] ^1H NMR(300MHz,$CDCl_3$):8.98(s,1H),7.91(d,1H),7.16(d,1H),4.54-4.59(m,1H),4.31-4.38(t,1H),4.02-4.09(m,2H),2.71-2.82(m,6H),2.15-2.22(m,2H),1.85-1.92(m,1H).

[0295] 生物测试

[0296] 实施例B1:Jak1、Jak2、Jak3、Tyk2生物化学测定

[0297] 测定由Reaction Biology Corp,Malvern,PA进行。该步骤简要描述如下。

[0298] 试剂：

[0299] 基本反应缓冲液:20mM Hepes(pH 7.5),10mM $MgCl_2$,1mM EGTA,0.02%Brij35,0.02mg/ml BSA,0.1mM Na_3VO_4,2mM DTT,1%DMSO。分别向每个激酶反应添加所需的辅因子

[0300] 反应步骤：

[0301] 1.在新制备的基本反应缓冲液中制备指定的底物

[0302] 2.将所需的辅因子送入上述基质溶液

[0303] 3.将指定的激酶送入底物溶液并轻轻混匀

[0304] 4.通过Acoustic技术(Echo550;纳升范围)将DMSO中的化合物送入激酶反应混合物中，在室温下培养20分钟

[0305] 5.向反应混合物中送入^{33}P-ATP(比活性10μCi/μl)以引发反应。

[0306] 6.在室温下培养激酶反应2小时

[0307] 7.反应被点绘在P81离子交换纸上

[0308] 8.通过过滤结合法检测激酶活性。

[0309] 基于IC50的范围:+:＞1μM;++:0.1-1μM;+++:10-100nM;++++:＜10nM;NT:未经测试,化合物的活性总结如下。实施例3、4、7、9是有效和选择性的Jak1抑制剂。

[0310]

实施例	Jak1	Jak2
1	++	NT
2	++	NT
3	++++	++
4	++++	++
5	+	+
6	+	+
7	++++	++
8	++	+
9	++++	++
11	++++	+++

[0311] 实施例B2:人全血p-STAT3测定

[0312] 材料和试剂:

[0313] 1.来自人类提供者的全血样品

[0314] 2.IL-6(R&D系统;Cat#206-IL)

[0315] 3.血小板生成素(TPO;R&D系统;Cat#288-TP)

[0316] 4.红血细胞裂解缓冲液(Qiagen,Cat#79217)

[0317] 5.用于pSTAT3的ELISA试剂盒(Invitrogen;Cat#KH00481)

[0318] 仪器:

[0319] 1.离心机

[0320] 2.Envision;在450nm处吸收

[0321] 步骤:

[0322] 1. 150μl肝素化血液样品/管。

[0323] 2.将不同浓度的化合物加入血液中,在室温培养10分钟(10种剂量,每种化合物2次重复)。

[0324] 3.向血液中加入IL-6(终浓度:100ng/ml)或TPO(终浓度:50ng/ml)15分钟。

[0325] 4.刺激后,加入0.6mL红血细胞裂解缓冲液(Qiagen 79217),在室温下混合并摇动1-2分钟,然后离心去除溶解的红血细胞。如果红血细胞没有完全溶解,这一步可能会重复一次。收获WBC。

[0326] 5.加入200μl细胞裂解缓冲液,冰30分钟。

[0327] 6.在16,000g下离心,10分钟,4℃。

[0328] 7.将上清液作为细胞裂解液转移至新管中。

[0329] 8.根据ELIA试剂盒的产品说明运行ELISA步骤。

[0330] 在这些测定中,如下所示,基于IC 50的范围:+:＞100μM;++:20-100μM;+++:5-20μM;++++:＜5μM,实施例3、4和7显示出对IL-6诱导的STAT3磷酸化的选择性抑制,而不显示出

对TPO诱导的STAT3磷酸化的选择性抑制。实施例11在TPO诱导的STAT3磷酸化测定中也显示出一些活性。

[0331]

实施例	IL-6	TPO
3	++++	+
4	++++	+
7	++++	+
11	++++	++

Abstract:

The new 1*H*-furo[3,2-*b*]imidazo[4,5-*d*]pyridine derivatives are selective Jak1 kinase inhibitors useful in treating disorders related to Jak1 activities such as autoimmune diseases or disorders, inflammatory diseases or disorders, and cancer or neoplastic diseases or disorders.