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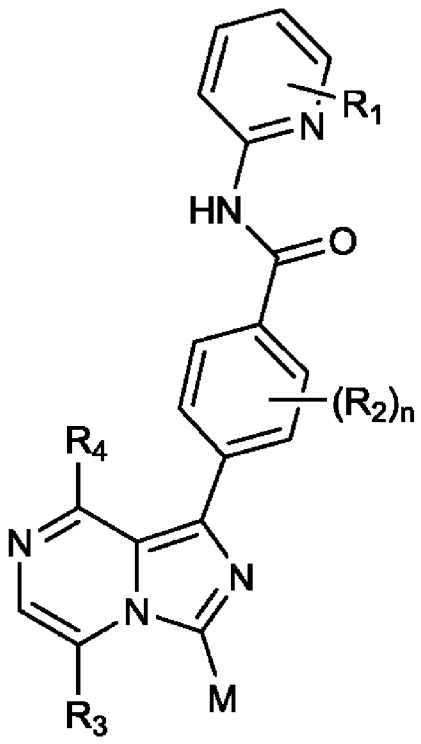
[Continued on next page]

(54) Title: BTK INHIBITORS

(57) Abstract: The present invention provides Bruton's Tyrosine Kinase (Btk) inhibitor compounds according to Formula (I), or pharmaceutically acceptable salts thereof, or to pharmaceutical compositions comprising these compounds and to their use in therapy. In particular, the present invention relates to the use of Btk inhibitor compounds of Formula (I) in the treatment of Btk mediated disorders.



(I)

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BTK INHIBITORS

FIELD OF THE INVENTION

The present invention relates to Btk inhibitor compounds, to pharmaceutical compositions comprising these compounds and to their use in therapy. In particular, the present invention relates to the use of Btk inhibitor compounds in the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

BACKGROUND OF THE INVENTION

B lymphocyte activation is key in the generation of adaptive immune responses. Derailed B lymphocyte activation is a hallmark of many autoimmune diseases and modulation of this immune response is therefore of therapeutic interest. Recently the success of B cell therapies in autoimmune diseases has been established. Treatment of rheumatoid arthritis (RA) patients with Rituximab (anti-CD20 therapy) is an accepted clinical therapy by now. More recent clinical trial studies show that treatment with Rituximab also ameliorates disease symptoms in relapsing remitting multiple sclerosis (RRMS) and systemic lupus erythematosus (SLE) patients. This success supports the potential for future therapies in autoimmune diseases targeting B cell immunity.

Bruton tyrosine kinase (Btk) is a Tec family non-receptor protein kinase, expressed in B cells and myeloid cells. The function of Btk in signaling pathways activated by the engagement of the B cell receptor (BCR) and FcεR1 on mast cells is well established. In addition, a function for Btk as a downstream target in Toll-like receptor signaling was suggested. Functional mutations in Btk in human results in the primary immunodeficiency disease called XLA which is characterized by a defect in B cell development with a block between pro- and pre-B cell stage. This results in an almost complete absence of B lymphocytes in human causing a pronounced reduction of serum immunoglobulin of all classes. These finding support the key role for Btk in the regulation of the production of auto-antibodies in autoimmune diseases. In addition, regulation of Btk may affect BCR-induced production of pro-inflammatory cytokines and chemokines by B cells, indicating a broad potential for Btk in the treatment of autoimmune diseases.

With the regulatory role reported for Btk in FcεR-mediated mast cell activation, Btk inhibitors may also show potential in the treatment of allergic responses [Gilfillan et al, Immunological Reviews **288** (2009) pp149-169].

Furthermore, Btk is also reported to be implicated in RANKL-induced osteoclast differentiation [Shinohara et al, Cell **132** (2008) pp794-806] and therefore may also be of interest for the treatment of bone resorption disorders.

Other diseases with an important role for dysfunctional B cells are B cell malignancies. Indeed anti-CD20 therapy is used effectively in the clinic for the treatment of follicular lymphoma, diffuse large B-cell lymphoma and chronic lymphocytic leukemia [Lim et al, Haematologica, **95** (2010) pp135-143]. The reported role for Btk in the regulation of proliferation and apoptosis of B cells indicates there is potential for Btk inhibitors in the treatment of B cell lymphomas as well. Inhibition of Btk seems to be relevant in particular for B cell lymphomas due to chronic active BCR signaling [Davis et al, Nature, **463** (2010) pp88-94].

Some classes of Btk inhibitor compounds have been described as kinase inhibitors, e.g. Imidazo[1,5-f][1,2,4]triazine compounds have been described in WO2005/097800 and WO2007/064993. Imidazo[1,5-a]pyrazine compounds have been described in WO2005/037836 and WO2001/019828 as IGF-1R enzyme inhibitors.

Some of the Btk inhibitors reported in the literature are not selective over Src-family kinases. With dramatic adverse effects reported for knockouts of Src-family kinases, especially for double and triple knockouts, this is seen as prohibitive for the development of Btk inhibitors that are not selective over the Src-family kinases.

Both Lyn-deficient and Fyn-deficient mice exhibit autoimmunity mimicking the phenotype of human lupus nephritis. In addition, Fyn-deficient mice also show pronounced neurological defects. Lyn knockout mice also show an allergic-like phenotype, indicating Lyn as a broad negative regulator of the IgE-mediated allergic response by controlling mast cell responsiveness and allergy-associated traits [Odom et al, J. Exp. Med., **199** (2004) pp1491-1502]. Furthermore, aged Lyn knock-out mice develop severe splenomegaly (myeloid expansion) and disseminated monocyte/macrophage tumors [Harder et al, Immunity, **15** (2001) pp603-615]. These observations are in line with hyperresponsive B cells, mast cells and myeloid cells, and increased Ig levels observed in Lyn-deficient mice. Female Src knockout mice are infertile due to reduced follicle development and ovulation [Roby et al, Endocrine, **26** (2005) pp169-176]. The double knockouts $Src^{-/-}Fyn^{-/-}$ and $Src^{-/-}Yes^{-/-}$ show a severe phenotype with effects on movement and breathing. The triple knockouts $Src^{-/-}Fyn^{-/-}Yes^{-/-}$ die at day 9.5 [Klinghoffer et al, EMBO J., **18** (1999) pp2459-2471]. For the double knockout $Src^{-/-}Hck^{-/-}$, two thirds of the mice die at birth, with surviving mice developing osteopetrosis, extramedullary hematopoiseis, anemia, leukopenia [Lowell et al, Blood, **87** (1996) pp1780-1792].

Hence, an inhibitor that inhibits multiple or all kinases of the Src-family kinases simultaneously may cause serious adverse effects.

SUMMARY OF THE INVENTION

The present invention provides compounds which inhibit Btk activity, their use for treatment of Btk mediated diseases and disorders, in particular autoimmune diseases and inflammatory diseases, as well as pharmaceutical compositions comprising such compounds and pharmaceutical carriers.

DETAILED DESCRIPTION

Definitions

The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding, and except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names, common names, and chemical structures may be used interchangeably to describe the same structure. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated.

As used herein, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

The term “alkoxy” as used herein, refers to an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. Non-limiting examples of alkoxy groups include methoxy and ethoxy.

The term "alkyl,” as used herein, refers to an aliphatic hydrocarbon group having one of its hydrogen atoms replaced with a bond having the specified number of carbon atoms. In different embodiments, an alkyl group contains, for example, from 1 to 3 carbon atoms (1-3C)alkyl. In one embodiment, an alkyl group is linear. In another embodiment, an alkyl group is branched. Non-limiting examples of alkyl groups include methyl, ethyl, n-propyl and isopropyl.

The term “amount effective” or "effective amount" as used herein, refers to an amount of the compound of Formula I and/or an additional therapeutic agent, or a composition thereof, that is effective in producing the desired therapeutic, ameliorative, inhibitory or preventative effect when administered to a subject suffering from a BTK-mediated disease or disorder. In the combination therapies of the present invention, an effective amount can refer to each individual agent or to the combination as a whole, wherein the amounts of all agents

administered are together effective, but wherein the component agent of the combination may not be present individually in an effective amount.

The term “halo”, as used herein, refers to fluorine, chlorine, bromine or iodine. Fluorine, chlorine or bromine are preferred halogens.Fluorine and chlorine are more preferred.

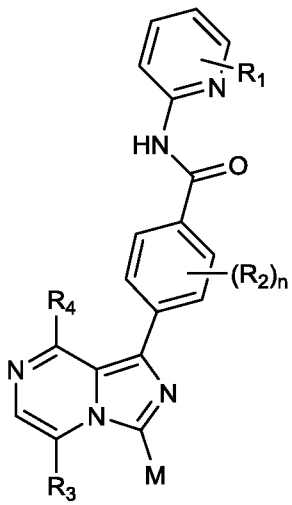
The term "purified" as used herein, refers to the physical state of a compound after the compound has been isolated through a synthetic process (e.g., from a reaction mixture), from a natural source, or a combination thereof. The term "purified" also refers to the physical state of a compound after the compound has been obtained from a purification process or processes described herein or well-known to the skilled artisan (e.g., chromatography, recrystallization, and the like), in sufficient purity to be characterizable by standard analytical techniques described herein or well-known to the skilled artisan.

A “subject” is a human or non-human mammal. In one embodiment, a subject is a human. In another embodiment, the subject is a chimpanzee.

It should be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and tables herein is assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

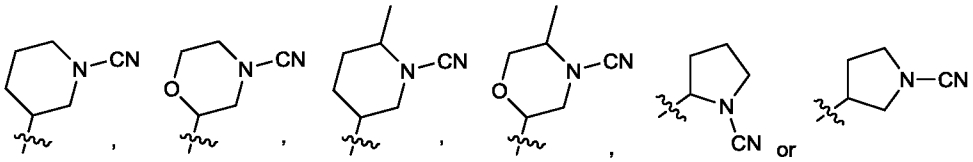
Compounds of the Invention

The present invention provides Btk inhibitor compounds according to Formula I or pharmaceutically acceptable salts thereof



Formula I

wherein:

M is  ;

n is 1 or 2;

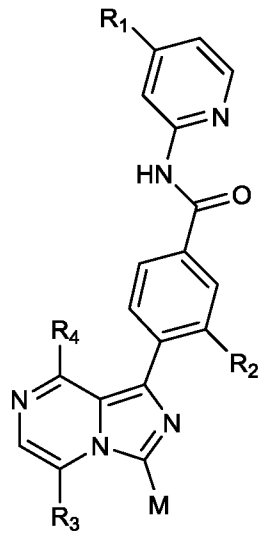
R_1 is optionally present and selected from the group consisting of halo, OH, CF_3, CHF_2, cyclopropyl, cyclobutyl, cyclopentyl, (1-3C)alkyl and (1-3C)alkoxy;

R_2 is optionally present and selected from the group consisting of halo, OH, CF_3, CHF_2, cyclopropyl, cyclobutyl, cyclopentyl, (1-3C)alkyl and (1-3C)alkoxy;

$R_3$is optionally present and selected from the group consisting of halo, OH, CF_3, CHF_2, cyclopropyl, cyclobutyl, cyclopentyl, (1-3C)alkyl, methoxy, methoxymethyl and ethoxy; and

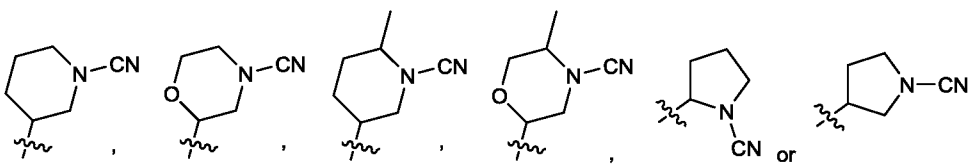
R_4 is methyl or NH_2.

In another embodiment the invention provides Btk inhibitor compounds according to Formula Ia or pharmaceutically acceptable salts thereof



Formula Ia

wherein:

M is  ;

R_1 is optionally present and selected from the group consisting of halo, OH, CF_3, CHF_2, cyclopropyl, cyclobutyl, cyclopentyl, (1-3C)alkyl and (1-3C)alkoxy;

R_2 is optionally present and selected from the group consisting of halo, OH, CF_3, CHF_2, cyclopropyl, cyclobutyl, cyclopentyl, (1-3C)alkyl and (1-3C)alkoxy;

R_3 is optionally present and selected from the group consisting of halo, OH, CF_3, CHF_2, cyclopropyl, cyclobutyl, cyclopentyl, (1-3C)alkyl, methoxy, methoxymethyl and ethoxy; and

R_4 is methyl or NH_2.

Non-limiting examples of the compounds of the present invention include:

4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;

4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-pyridin-2-ylbenzamide;

4-{8-amino-3-[(2S)-1-cyanopyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-N-pyridin-2-ylbenzamide;

4-{8-amino-3-[(2S)-1-cyanopyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(4-fluoropyridin-2-yl)benzamide;

4-{3-[(2S)-1-cyanopyrrolidin-2-yl]-8-methylimidazo[1,5-a]pyrazin-1-yl}-N-pyridin-2-ylbenzamide;

4-[8-amino-3-(4-cyanomorpholin-2-yl)imidazo[1,5-a]pyrazin-1-yl]-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;

4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(4-cyclopropylpyridin-2-yl)benzamide;

4-{3-[(3R)-1-cyanopiperidin-3-yl]-8-methylimidazo[1,5-a]pyrazin-1-yl}-N-(4-cyclopropylpyridin-2-yl)benzamide;

4-{8-amino-3-[(2S)-1-cyanopyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(4-cyclopropylpyridin-2-yl)benzamide;

4-{8-amino-3-[(3R,6S)-1-cyano-6-methylpiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-pyridin-2-ylbenzamide;

4-{8-amino-3-[(2R)-4-cyanomorpholin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;

4-{8-amino-3-[(2R)-4-cyanomorpholin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(4-cyclopropylpyridin-2-yl)benzamide;

4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-3-fluoro-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;

4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(4-methylpyridin-2-yl)benzamide;

4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(4-methoxypyridin-2-yl)benzamide;

4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-[4-(difluoromethyl)pyridin-2-yl]benzamide;

4-{8-amino-5-chloro-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;

4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]-5-(methoxymethyl)imidazo[1,5-a]pyrazin-1-yl}-3-fluoro-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;

4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-3-ethoxy-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;

4-{8-amino-5-chloro-3-[(2R,5S)-4-cyano-5-methylmorpholin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-3-fluoro-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;

4-{8-amino-5-chloro-3-[(2R,5S)-4-cyano-5-methylmorpholin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-3-ethoxy-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;

4-{8-amino-3-[(2R)-4-cyanomorpholin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-3-methoxy-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;

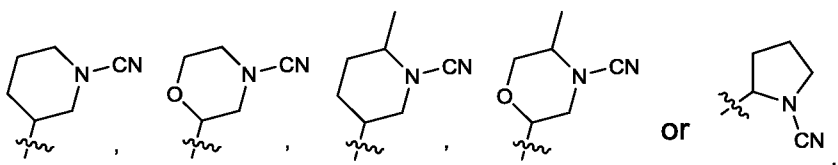
4-[8-amino-3-(8-cyano-8-azabicyclo[3.2.1]oct-2-en-3-yl)imidazo[1,5-a]pyrazin-1-yl]-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide; and

4-{8-amino-5-chloro-3-[(3R,6S)-1-cyano-6-methylpiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-3-ethoxy-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;

or a pharmaceutically acceptable salt thereof.

In another embodiment, n is 1.

In another embodiment, M is



In another embodiment, R_1 is optionally present and selected from the group consisting of F, CF_3, CHF_2, methyl, methoxy and cyclopropyl.

In another embodiment, $R_2$is optionally present and selected from the group consisting of ethoxy and methoxy.

In another embodiment, $R_3$is optionally present and selected from the group consisting of Cl and methoxymethyl.

In another embodiment, (1-3C)alkoxy is methoxy or ethoxy.

The compounds of this invention include the salts, solvates, hydrates or prodrugs of the compounds. The use of the terms "salt", "solvate", "hydrate", "prodrug" and the like, is intended to equally apply to the salt, solvate, hydrate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, or racemates of the inventive compounds.

Salts

The Btk inhibitor compoundsof the present invention, which can be in the form of a free base, may be isolated from the reaction mixture in the form of a pharmaceutically acceptable salt.

The compounds of Formula I can form salts which are also within the scope of this invention. Reference to a compound of Formula I herein is understood to include reference to pharmaceutically acceptable salts thereof, unless otherwise indicated. The term "pharmaceutically acceptable salt(s)" or "salt", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula I contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Such acidic and basic salts used within the scope of the invention are pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts. Salts of the compounds of Formula I may be formed, for example, by reacting a compound of Formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl et al, Camille G. (eds.) Handbook of Pharmaceutical Salts. Properties, Selection and Use. (2002) Zurich: Wiley-VCH; S. Berge et al, Journal of Pharmaceutical Sciences (1977) 66(1) 1-19; P. Gould, International J. of Pharmaceutics (1986) 33 201-217; Anderson et al, The Practice of Medicinal Chemistry (1996), Academic Press, New York; and in The Orange Book

(Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g., methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g., decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g., benzyl and phenethyl bromides), and others.

Crystals

The Btk inhibitor compoundsof the present invention may exist as amorphous forms or crystalline forms.

The compounds of Formula I may have the ability to crystallize in more than one form, a characteristic known as polymorphism, and it is understood that such polymorphic forms ("polymorphs") are within the scope of Formula I. Polymorphism generally can occur as a response to changes in temperature or pressure or both and can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics known in the art such as x-ray diffraction patterns, solubility and melting point.

Solvates

The compounds having Formula I or the pharmaceutically acceptable salts may form hydrates or solvates. It is known to those of skill in the art that charged compounds form hydrated species when lyophilized with water, or form solvated species when concentrated in a solution with an appropriate organic solvent. The compounds of this invention include the hydrates or solvates of the compounds listed.

One or more compounds of the invention having Formula I or the pharmaceutically acceptable salts or solvates thereof may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable

solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.* 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example IR spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

Optical Isomers

The compounds of Formula I may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of Formula I, as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound of Formula I incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Such stereoisomeric forms also include enantiomers and diastereoisomers, *etc.*

For chiral compounds, methods for asymmetric synthesis whereby the pure stereoisomers are obtained are well known in the art, *e.g.* synthesis with chiral induction, synthesis starting from chiral intermediates, enantioselective enzymatic conversions, separation of stereoisomers using chromatography on chiral media. Such methods are described in *Chirality in Industry* (edited by A.N. Collins, G.N. Sheldrake and J. Crosby, 1992; John Wiley). Likewise methods for synthesis of geometrical isomers are also well known in the art.

Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g. chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g. hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the compounds

of Formula I may be atropisomers (e.g. substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

It is also possible that the compounds of Formula I may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, esters and prodrugs of the compounds as well as the salts, solvates and esters of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations. The use of the terms "salt", "solvate", “ester”, "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

Prodrugs

A discussion of prodrugs is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems (1987) 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press. The term “prodrug” means a compound (e.g, a drug precursor) that is transformed in vivo to yield a compound of Formula I or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g. by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, “Pro-drugs as Novel Delivery Systems,” Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

Isotopes

In the compounds of Formula I, the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic

mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic Formula I. For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing in vivo half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within generic Formula I can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

Certain isotopically-labelled compounds of Formula I (e.g. those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labelled compounds of Formula I can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herinbelow, by substituting an appropriate isotopically labeled reagent for a non-isotopically labeled reagent.

Utilities

The compounds having Formula I and pharmaceutical compositions thereof can be used to treat or prevent a variety of conditions, diseases or disorders mediated by Bruton's Tyrosine kinase (Btk). Such Btk-mediated conditions, diseases or disorders include, but are not limited to: (1) arthritis, including rheumatoid arthritis, juvenile arthritis, psoriatic arthritis and osteoarthritis; (2) asthma and other obstructive airways diseases, including chronic asthma, late asthma, airway hyper-responsiveness, bronchitis, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, adult respiratory distress syndrome, recurrent airway obstruction, and chronic obstruction pulmonary disease including emphysema; (3) autoimmune diseases or disorders, including those designated as single organ or single cell-type autoimmune disorders, for example Hashimoto's thyroiditis, autoimmune hemolytic anemia, autoimmune atrophic gastritis of pernicious anemia, autoimmune encephalomyelitis, autoimmune orchitis, Goodpasture's disease, autoimmune thrombocytopenia including idiopathic thrombopenic purpura, sympathetic ophthalmia, myasthenia gravis, Graves' disease, primary biliary cirrhosis, chronic aggressive hepatitis, ulcerative colitis and membranous glomerulopathy, those

designated as involving systemic autoimmune disorder, for example systemic lupus erythematosis, immune thrombocytopenic purpura, rheumatoid arthritis, Sjogren's syndrome, Reiter's syndrome, polymyositis-dermatomyositis, systemic sclerosis, polyarteritis nodosa, multiple sclerosis and bullous pemphigoid, and additional autoimmune diseases, which can be B-cell (humoral) based or T-cell based, including Cogan's syndrome, ankylosing spondylitis, Wegener's granulomatosis, autoimmune alopecia, Type I or juvenile onset diabetes, and thyroiditis; (4) cancers or tumors, including alimentary/gastrointestinal tract cancer, colon cancer, liver cancer, skin cancer including mast cell tumor and squamous cell carcinoma, breast and mammary cancer, ovarian cancer, prostate cancer, lymphoma and leukemia (including but not limited to acute myelogenous leukemia, chronic myelogenous leukemia, mantle cell lymphoma, NHL B cell lymphomas (e.g. precursor B-ALL, marginal zone B cell lymphoma, chronic lymphocytic leukemia, diffuse large B cell lymphoma, Burkitt lymphoma, mediastinal large B-cell lymphoma), Hodgkin lymphoma, NK and T cell lymphomas; TEL-Syk and ITK-Syk fusion driven tumors, myelomas including multiple myeloma, myeloproliferative disorders kidney cancer, lung cancer, muscle cancer, bone cancer, bladder cancer, brain cancer, melanoma including oral and metastatic melanoma, Kaposi's sarcoma, proliferative diabetic retinopathy, and angiogenic-associated disorders including solid tumors, and pancreatic cancer; (5) diabetes, including Type I diabetes and complications from diabetes; (6) eye diseases, disorders or conditions including autoimmune diseases of the eye, keratoconjunctivitis, vernal conjunctivitis, uveitis including uveitis associated with Behcet's disease and lens-induced uveitis, keratitis, herpetic keratitis, conical keratitis, corneal epithelial dystrophy, keratoleukoma, ocular premphigus, Mooren's ulcer, scleritis, Grave's ophthalmopathy, Vogt-Koyanagi-Harada syndrome, keratoconjunctivitis sicca (dry eye), phlyctenule, iridocyclitis, sarcoidosis, endocrine ophthalmopathy, sympathetic ophthalmitis, allergic conjunctivitis, and ocular neovascularization; (7) intestinal inflammations, allergies or conditions including Crohn's disease and/or ulcerative colitis, inflammatory bowel disease, coeliac diseases, proctitis, eosinophilic gastroenteritis, and mastocytosis; (8) neurodegenerative diseases including motor neuron disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia, or neurodegenerative disease caused by traumatic injury, strike, glutamate neurotoxicity or hypoxia; ischemic/ reperfusion injury in stroke, myocardial ischemica, renal ischemia, heart attacks, cardiac hypertrophy, atherosclerosis and arteriosclerosis, organ hypoxia; (9) platelet aggregation and diseases associated with or caused by platelet activation, such as arteriosclerosis, thrombosis, intimal hyperplasia and restenosis following vascular injury; (10) conditions associated with cardiovascular diseases, including restenosis, acute coronary

syndrome, myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, a thrombotically mediated cerebrovascular syndrome, embolic stroke, thrombotic stroke, transient ischemic attacks, venous thrombosis, deep venous thrombosis, pulmonary embolus, coagulopathy, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, thromboangiitis obliterans, thrombotic disease associated with heparin-induced thrombocytopenia, thrombotic complications associated with extracorporeal circulation, thrombotic complications associated with instrumentation such as cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve, conditions requiring the fitting of prosthetic devices, and the like; (11) skin diseases, conditions or disorders including atopic dermatitis, eczema, psoriasis, scleroderma, pruritus and other pruritic conditions; (12) allergic reactions including anaphylaxis, allergic rhinitis, allergic dermatitis, allergic urticaria, angioedema, allergic asthma, or allergic reaction to insect bites, food, drugs, or pollen; (13) transplant rejection, including pancreas islet transplant rejection, bone marrow transplant rejection, graft- versus-host disease, organ and cell transplant rejection such as bone marrow, cartilage, cornea, heart, intervertebral disc, islet, kidney, limb, liver, lung, muscle, myoblast, nerve, pancreas, skin, small intestine, or trachea, and xeno transplantation; and (14) low grade scarring including scleroderma, increased fibrosis, keloids, post-surgical scars, pulmonary fibrosis, vascular spasms, migraine, reperfusion injury, and post-myocardial infarction.

The invention thus provides compounds of Formula I and salts thereof for use in therapy, and particularly in the treatment of disorders, diseases and conditions mediated by inappropriate Btk activity.

The inappropriate Btk activity referred to herein is any Btk activity that deviates from the normal Btk activity expected in a particular mammalian subject. Inappropriate Btk activity may take the form of, for instance, an abnormal increase in activity, or an aberration in the timing and or control of Btk activity. Such inappropriate activity may result then, for example, from overexpression or mutation of the protein kinase leading to inappropriate or uncontrolled activation.

In one embodiment, the present invention provides for the use of a compound of Formula I, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of a Btk-mediated disorder.

In another embodiment, the present invention provides methods of regulating, modulating, or inhibiting Btk for the prevention and/or treatment of disorders related to unregulated or inappropriate Btk activity.

In a further embodiment, the present invention provides a method for treating a subject suffering from a disorder mediated by Btk, which comprises administering to said subject a compound of Formula I or a pharmaceutically acceptable salt thereof in an amount effective to treat the Btk-mediated disorder.

A further aspect of the invention resides in the use of a compound of Formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament to be used for the treatment of chronic B cell disorders in which T cells play a prominent role.

Thus, the compounds according to the invention may be used in therapies to treat or prevent Bruton's Tyrosine Kinase (Btk) mediated diseases, conditions and disorders. Btk mediated diseases, conditions and disorders as used herein, mean any disease, condition or disorder in which B cells, mast cells, myeloid cells or osteoclasts play a central role. These diseases include but are not limited to, immune, autoimmune and inflammatory diseases, allergies, infectious diseases, bone resorption disorders and proliferative diseases.

Immune, autoimmune and inflammatory diseases that may be treated or prevented with the compounds of the present invention include rheumatic diseases (e.g. rheumatoid arthritis, psoriatic arthritis, infectious arthritis, progressive chronic arthritis, deforming arthritis, osteoarthritis, traumatic arthritis, gouty arthritis, Reiter's syndrome, polychondritis, acute synovitis and spondylitis), glomerulonephritis (with or without nephrotic syndrome), Goodpasture's syndrome, (and associated glomerulonephritis and pulmonary hemorrhage), atherosclerosis, autoimmune hematologic disorders (e.g. hemolytic anemia, aplasic anemia, idiopathic thrombocytopenia, chronic idiopathic thrombocytopenic purpura (ITP), and neutropenia), autoimmune gastritis, and autoimmune inflammatory bowel diseases (e.g. ulcerative colitis and Crohn's disease), irritable bowel syndrome, host versus graft disease, allograft rejection, chronic thyroiditis, Graves' disease, Sjorgren's disease, scleroderma, diabetes (type I and type II), active hepatitis (acute and chronic), pancreatitis, primary billiary cirrhosis, myasthenia gravis, multiple sclerosis, systemic lupus erythematosis, psoriasis, atopic dermatitis, dermatomyositis, contact dermatitis, eczema, skin sunburns, vasculitis (e.g. Behcet's disease), ANCA-associated and other vasculitudes, chronic renal insufficiency, Stevens-Johnson syndrome, inflammatory pain, idiopathic sprue, cachexia, sarcoidosis, Guillain-Barré syndrome, uveitis, conjunctivitis, kerato conjunctivitis, otitis media, periodontal disease, Addison's disease,

Parkinson's disease, Alzheimer's disease, diabetes, septic shock, myasthenia gravis, pulmonary interstitial fibrosis, asthma, bronchitis, rhinitis, sinusitis, pneumoconiosis, pulmonary insufficiency syndrome, pulmonary emphysema, pulmonary fibrosis, silicosis, chronic inflammatory pulmonary disease (e.g. chronic obstructive pulmonary disease) and other inflammatory or obstructive disease on airways.

Allergies that may be treated or prevented include, among others, allergies to foods, food additives, insect poisons, dust mites, pollen, animal materials and contact allergans, type I hypersensitivity allergic asthma, allergic rhinitis, allergic conjunctivitis.

Infectious diseases that may be treated or prevented include, among others, sepsis, septic shock, endotoxic shock, sepsis by Gram-negative bacteria, shigellosis, meningitis, cerebral malaria, pneumonia, tuberculosis, viral myocarditis, viral hepatitis (hepatitis A, hepatitis B and hepatitis C), HIV infection, retinitis caused by cytomegalovirus, influenza, herpes, treatment of infections associated with severe burns, myalgias caused by infections, cachexia secondary to infections, and veterinary viral infections such as lentivirus, caprine arthritic virus, visna-maedi virus, feline immunodeficiency virus, bovine immunodeficiency virus or canine immunodeficiency virus.

Bone resorption disorders that may be treated or prevented include, among others, osteoporosis, osteoarthritis, traumatic arthritis, gouty arthritis and bone disorders related with multiple myeloma.

Proliferative diseases that may be treated or prevented include, among others, non-Hodgkin lymphoma (in particular the subtypes diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL)), B cell chronic lymphocytic leukemia and acute lymphoblastic leukemia (ALL) with mature B cell, ALL in particular.

In particular the compounds of Formula I or pharmaceutically acceptable salts may be used for the treatment of B cell lymphomas resulting from chronic active B cell receptor signaling.

Yet another aspect of the present invention provides a method for treating diseases caused by or associated with Fc receptor signaling cascades, including FceRI and/or FcgRI-mediated degranulation as a therapeutic approach towards the treatment or prevention of diseases characterized by, caused by and/or associated with the release or synthesis of chemical mediators of such Fc receptor signaling cascades or degranulation. In addition, Btk is known to play a critical role in*immunotyrosine*-based activation motif (ITAM) singaling, B cell receptor signaling, T cell receptor signaling and is an essential component of integrin beta (1), beta (2), and beta (3) signaling in neutrophils. Thus, compounds of the present invention can be used to

regulate Fc receptor, ITAM, B cell receptor and integrin signaling cascades, as well as the cellular responses elicited through these signaling cascades. Non-limiting examples of cellular responses that may be regulated or inhibited include respiratory burst, cellular adhesion, cellular degranulation, cell spreading, cell migration, phagocytosis, calcium ion flux, platelet aggregation and cell maturation.

Combination Therapy

Included herein are methods of treatment and/ or pharmaceutical compositions in which at least one compound of Formula I or a pharmaceutically acceptable salt thereof is administered in combination with at least one other active agent. The other active agent is an anti-inflammatory agent, an immunosuppressant agent, an immunotherapy agent or a chemotherapeutic agent. Anti-inflammatory agents include but are not limited to NSAIDs, non-specific and COX-2 specific cyclooxgenase enzyme inhibitors, gold compounds, corticosteroids, methotrexate, tumor necrosis factor receptor (TNF) receptors antagonists, immunosuppressants and methotrexate.

Examples of NSAIDs include, but are not limited to, ibuprofen, flurbiprofen, naproxen and naproxen sodium, diclofenac, combinations of diclofenac sodium and misoprostol, sulindac, oxaprozin, diflunisal, piroxicam, indomethacin, etodolac, fenoprofen calcium, ketoprofen, sodium nabumetone, sulfasalazine, tolmetin sodium, and hydroxychloroquine. Examples of NSAIDs also include COX-2 specific inhibitors such as celecoxib, valdecoxib, lumiracoxib and/or etoricoxib.

In some embodiments, the anti-inflammatory agent is a salicylate. Salicylates include by are not limited to acetylsalicylic acid or aspirin, sodium salicylate, and choline and magnesium salicylates.

The anti-inflammatory agent may also be a corticosteroid. For example, the corticosteroid may be cortisone, dexamethasone, methylprednisolone, prednisolone, prednisolone sodium phosphate, or prednisone.

In additional embodiments the anti-inflammatory agent is a gold compound such as gold sodium thiomalate or auranofin.

The invention also includes embodiments in which the anti-inflammatory agent is a metabolic inhibitor such as a dihydrofolate reductase inhibitor, such as methotrexate or a dihydroorotate dehydrogenase inhibitor, such as leflunomide.

Other embodiments of the invention pertain to combinations in which at least one anti-inflammatory agent is an anti-C5 monoclonal antibody (such as eculizumab or pexelizumab),

a TNF antagonist, such as entanercept, or infliximab, which is an anti-TNF alpha monoclonal antibody.

Still other embodiments of the invention pertain to combinations in which at least one active agent is an immunosuppressant agent, such as an immunosuppressant compound chosen from methotrexate, leflunomide, cyclosporine, tacrolimus, azathioprine, and mycophenolate mofetil.

B-cells and B-cell precursors expressing BTK have been implicated in the pathology of B-cell malignancies, including, but not limited to, B-cell lymphoma, lymphoma (including Hodgkin's and non-Hodgkin's lymphoma), hairy cell lymphoma, multiple myeloma, chronic and acute myelogenous leukemia and chronic and acute lymphocytic leukemia.

BTK has been shown to be an inhibitor of the Fas/APO-1 (CD-95) death inducing signaling complex (DISC) in B-lineage lymphoid cells. The fate of leukemia/lymphoma cells may reside in the balance between the opposing proapoptotic effects of caspases activated by DISC and an upstream anti-apoptotic regulatory mechanism involving BTK and/or its substrates (Vassilev et al., J. Biol. Chem. 1998, 274, 1646-1656).

It has also been discovered that BTK inhibitors are useful as chemosensitizing agents, and, thus, are useful in combination with other chemotherapeutic agents, in particular, drugs that induce apoptosis. Examples of other chemotherapeutic agents that can be used in combination with chemosensitizing BTK inhibitors include topoisomerase I inhibitors (camptothecin or topotecan), topoisomerase II inhibitors (e.g. daunomycin and etoposide), alkylating agents (e.g. cyclophosphamide, melphalan and BCNU), tubulin directed agents (e.g. taxol and vinblastine), and biological agents (e.g. antibodies such as anti CD20 antibody, IDEC 8, immunotoxins, and cytokines).

Btk activity has also been associated with some leukemias expressing the bcr-abl fusion gene resulting from translocation of parts of chromosome 9 and 22. This abnormality is commonly observed in chronic myelogenous leukemia. Btk is constitutively phosphorylated by the bcr-abl kinase which initiates downstream survival signals which circumvents apoptosis in bcr-abl cells. (N. Feldhahn et al. J. Exp. Med. 2005 201(11):1837-1852).

The compound(s) of Formula I and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately this may occur simultaneously or sequentially in any order. The amounts of the compound(s) of Formula I and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

For the treatment of the inflammatory diseases, rheumatoid arthritis, psoriasis, inflammatory bowel disease, COPD, asthma and allergic rhinitis a compound of Formula I may be combined with one or more other active agents such as: (1) TNF-α inhibitors such as infliximab (Remicade®), etanercept (Enbrel®), adalimumab (Humira®), certolizumab pegol (Cimzia®), and golimumab (Simponi®); (2) non-selective COX-I/COX-2 inhibitors (such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, etodolac, azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin); (3) COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib and etoricoxib); (4) other agents for treatment of rheumatoid arthritis including methotrexate, leflunomide, sulfasalazine, azathioprine, cyclosporin, tacrolimus, penicillamine, bucillamine, actarit, mizoribine, lobenzarit, ciclesonide, hydroxychloroquine, d-penicillamine, aurothiomalate, auranofin or parenteral or oral gold, cyclophosphamide, Lymphostat-B, BAFF/APRIL inhibitors and CTLA-4-Ig or mimetics thereof; (5) leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as zileuton; (6) LTD4 receptor antagonist such as zafirlukast, montelukast and pranlukast; (7) PDE4 inhibitor such as roflumilast, cilomilast, AWD-12-281 (Elbion), and PD-168787 (Pfizer); (8) antihistaminic H1 receptor antagonists such as cetirizine, levocetirizine, loratadine, desloratadine, fexofenadine, astemizole, azelastine, levocabastine, olopatidine, methapyrilene and chlorpheniramine; (9) α1- and α2-adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, and ethylnorepinephrine hydrochloride; (10) anticholinergic agents such as ipratropium bromide, tiotropium bromide, oxitropium bromide, aclindinium bromide, glycopyrrolate, (R,R)-glycopyrrolate, pirenzepine, and telenzepine; (11) β-adrenoceptor agonists such as metaproterenol, isoproterenol, isoprenaline, albuterol, formoterol (particularly the fumarate salt), salmeterol (particularly the xinafoate salt), terbutaline, orciprenaline, bitolterol mesylate, fenoterol, and pirbuterol, or methylxanthanines including theophylline and aminophylline, sodium cromoglycate; (12) insulin-like growth factor type I (IGF-l) mimetic; (13) glucocorticosteroids, especially inhaled glucocorticoid with reduced systemic side effects, such as prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide and mometasone furoate; (14) kinase inhibitors such as inhibitors of the Janus Kinases (JAK 1 and/or JAK2 and/or JAK 3 and/or TYK2), p38 MAPK and IKK2; (15) B-cell targeting biologics such as rituximab (Rituxan®); (16) selective

costimulation modulators such as abatacept (Orencia); (17) interleukin inhibitors, such as IL-1 inhibitor anakinra (Kineret) and IL-6 inhibitor tocilizumab (Actemra).

The present invention also provides for "triple combination" therapy, comprising a compound of Formula I or a pharmaceutically acceptable salt thereof together with beta2-adrenoreceptor agonist and an anti-inflammatory corticosteroid. Preferably this combination is for treatment and/or prophylaxis of asthma, COPD or allergic rhinitis. The beta2-adrenoreceptor agonist and/or the anti-inflammatory corticosteroid can be as described above and/or as described in WO 03/030939 A1. Representative examples of such a "triple" combination are a compound of Formula I or a pharmaceutically acceptable salt thereof in combination with the components of Advair® (salmeterol xinafoate and fluticasone propionate), Symbicort® (budesonide and formoterol fumarate), or Dulera® (mometasone furoate and formoterol).

For the treatment of cancer a compound of Formula I may be combined with one or more of an anticancer agents. Examples of such agents can be found in *Cancer Principles and Practice of Oncology* by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Such anti-cancer agents include, but are not limited to, the following: (1) estrogen receptor modulator such as diethylstibestral, tamoxifen, raloxifene, idoxifene, LY353381, LY117081, toremifene, fluoxymestero, and SH646; (2) other hormonal agents including aromatase inhibitors (e.g., aminoglutethimide, tetrazole anastrozole, letrozole and exemestane), luteinizing hormone release hormone (LHRH) analogues, ketoconazole, goserelin acetate, leuprolide, megestrol acetate and mifepristone; (3) androgen receptor modulator such as finasteride and other 5α-reductase inhibitors, nilutamide, flutamide, bicalutamide, liarozole, and abiraterone acetate; (4) retinoid receptor modulator such as bexarotene, tretinoin, 13-cis-retinoic acid, 9-cis-retinoic acid, α-difluoromethylornithine, ILX23-7553, trans-N-(4'-hydroxyphenyl) retinamide, and N-4-carboxyphenyl retinamide; (5) antiproliferative agent such asantisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-fluoromethylene-2'-deoxycytidine, N6-[4-deoxy-4-[N2-[2(E),4(E)-tetradeca-dienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, aminopterin, 5-flurouracil, floxuridine, methotrexate, leucovarin, hydroxyurea,

thioguanine (6-TG), mercaptopurine (6-MP), cytarabine, pentostatin, fludarabine phosphate, cladribine (2-CDA), asparaginase, gemcitabine, alanosine, swainsonine, lometrexol, dexrazoxane, methioninase, and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone; (6) prenyl-protein transferase inhibitor including farnesyl-protein transferase (FPTase), geranylgeranyl-protein transferase type I (GGPTase-I), and geranylgeranyl-protein transferase type-II (GGPTase-II, also called Rab GGPTase); (7) HMG-CoA reductase inhibitor such as lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin and rosuvastatin; (8) angiogenesis inhibitor such as inhibitors of the tyrosine kinase receptors Flt-1 (VEGFR1) and Flk-1/KDR (VEGFR2), inhibitors of epidermal-derived, fibroblast-derived, or platelet derived growth factors, MMP (matrix metalloprotease) inhibitors, integrin blockers, interferon-α, interleukin-12, erythropoietin (epoietin-α), granulocyte-CSF (filgrastin), granulocyte, macrophage-CSF (sargramostim), pentosan polysulfate, cyclooxygenase inhibitors, steroidal anti-inflammatories, carboxyamidotriazole, combretastatin A-4, squalamine, 6-O-chloroacetyl-carbonyl)-fumagillol, thalidomide, angiostatin, troponin-1, angiotensin II antagonists, heparin, carboxypeptidase U inhibitors, and antibodies to VEGF, endostatin, ukrain, ranpirnase, IM862, acetyldinanaline, 5-amino-1-[[3,5-dichloro-4-(4-chlorobenzoyl)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide,CM101, squalamine, combretastatin, RPI4610, NX31838, sulfated mannopentaose phosphate, and 3-[(2,4-dimethylpyrrol-5-yl)methylene]-2-indolinone (SU5416); (9) PPAR-γ agonists, PPAR-δ agonists, thiazolidinediones (such as DRF2725, CS-011, troglitazone, rosiglitazone, and pioglitazone), fenofibrate, gemfibrozil, clofibrate, GW2570, SB219994, AR-H039242, JTT-501, MCC-555, GW2331, GW409544, NN2344, KRP297, NP0110, DRF4158, NN622, GI262570, PNU182716, DRF552926, 2-[(5,7-dipropyl-3-trifluoromethyl-1,2-benzisoxazol-6-yl)oxy]-2-methylpropionic acid (disclosed in USSN 09/782,856), and (2R)-7-(3-(2-chloro-4-(4-fluorophenoxy)phenoxy)propoxy)-2-ethylchromane-2-carboxylic acid (disclosed in USSN 60/235,708 and 60/244,697); (9) inhibitor of inherent multidrug resistance including inhibitors of p-glycoprotein (P-gp), such as LY335979, XR9576, OC144-093, R101922, VX853 and PSC833 (valspodar); (10) inhibitor of cell proliferation and survival signaling such as inhibitors of EGFR (for example gefitinib and erlotinib), inhibitors of ERB-2 (for example trastuzumab), inhibitors of IGF1R such as MK-0646 (dalotuzumab), inhibitors of CD20 (rituximab), inhibitors of cytokine receptors, inhibitors of MET, inhibitors of PI3K family kinase (for example LY294002), serine/threonine kinases (including but not limited to inhibitors of Akt such as described in (WO 03/086404, WO 03/086403, WO 03/086394, WO 03/086279, WO 02/083675, WO 02/083139, WO 02/083140 and WO 02/083138), inhibitors of Raf kinase (for example BAY-43-9006), inhibitors of MEK (for example CI-1040 and PD-098059) and

inhibitors of mTOR (for example Wyeth CCI-779 and Ariad AP23573); (11) a bisphosphonate such as etidronate, pamidronate, alendronate, risedronate, zoledronate, ibandronate, incadronate or cimadronate, clodronate, EB-1053, minodronate, neridronate, piridronate and tiludronate; (12) γ-secretase inhibitors, (13) agents that interfere with receptor tyrosine kinases (RTKs) including inhibitors of c-Kit, Eph, PDGF, Flt3 and c-Met; (14) agent that interferes with a cell cycle checkpoint including inhibitors of ATR, ATM, the Chk1 and Chk2 kinasesand cdk and cdc kinase inhibitors and are specifically exemplified by 7-hydroxystaurosporin, flavopiridol, CYC202 (Cyclacel) and BMS-387032; (15) BTK inhibitors such as PCI32765, AVL-292 and AVL-101; (16) PARP inhibitors including iniparib, olaparib, AGO14699, ABT888 and MK4827; (16) ERK inhibitors; (17) mTOR inhibitors such as sirolimus, ridaforolimus, temsirolimus, everolimus; (18) cytotoxic/cytostatic agents and (19) anti PD-1 and anti PD-L1 antibodies.

"Cytotoxic/cytostatic agents" refer to compounds which cause cell death or inhibit cell proliferation primarily by interfering directly with the cell's functioning or inhibit or interfere with cell mytosis, including alkylating agents, tumor necrosis factors, intercalators, hypoxia activatable compounds, microtubule inhibitors/microtubule-stabilizing agents, inhibitors of mitotic kinesins, inhibitors of histone deacetylase, inhibitors of kinases involved in mitotic progression, antimetabolites; biological response modifiers; hormonal/anti-hormonal therapeutic agents, haematopoietic growth factors, monoclonal antibody targeted therapeutic agents, topoisomerase inhibitors, proteasome inhibitors and ubiquitin ligase inhibitors.

Examples of cytotoxic agents include, but are not limited to, sertenef, cachectin, chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, uracil mustard, thiotepa, busulfan, carmustine, lomustine, streptozocin, tasonermin, lonidamine, carboplatin, altretamine, dacarbazine, procarbazine, prednimustine, dibromodulcitol, ranimustine, fotemustine, nedaplatin, oxaliplatin, temozolomide, heptaplatin, estramustine, improsulfan tosilate, trofosfamide, nimustine, dibrospidium chloride, pumitepa, lobaplatin, satraplatin, profiromycin, cisplatin, irofulven, dexifosfamide, cis-aminedichloro(2-methyl-pyridine)platinum, benzylguanine, glufosfamide, GPX100, (trans, trans, trans)-bis-mu-(hexane-1,6-diamine)-mu-[diamine-platinum(II)]bis[diamine(chloro)platinum (II)]tetrachloride, diarizidinylspermine, arsenic trioxide, 1-(11-dodecylamino-10-hydroxyundecyl)-3,7-dimethylxanthine, zorubicin, doxorubicin, daunorubicin, idarubicin, anthracenedione, bleomycin, mitomycin C, dactinomycin, plicatomycin, bisantrene, mitoxantrone, pirarubicin, pinafide, valrubicin, amrubicin, antineoplaston, 3'-deamino-3'-morpholino-13-deoxo-10-hydroxycarminomycin, annamycin, galarubicin, elinafide, MEN10755, and 4-demethoxy-3-deamino-3-aziridinyl-4-methylsulphonyl-daunorubicin.

An example of a hypoxia activatable compound is tirapazamine.

Examples of proteasome inhibitors include but are not limited to lactacystin and bortezomib.

Examples of microtubule inhibitors/microtubule-stabilising agents include vincristine, vinblastine, vindesine, vinzolidine, vinorelbine, vindesine sulfate, 3',4'-didehydro-4'-deoxy-8'-norvincaleukoblastine, podophyllotoxins (e.g., etoposide (VP-16) and teniposide (VM-26)), paclitaxel, docetaxol, rhizoxin, dolastatin, mivobulin isethionate, auristatin, cemadotin, RPR109881, BMS184476, vinflunine, cryptophycin, anhydrovinblastine, N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline-t-butylamide, TDX258, the epothilones (see for example U.S. Pat. Nos. 6,284,781 and 6,288,237) and BMS188797.

Some examples of topoisomerase inhibitors are topotecan, hycaptamine, irinotecan, rubitecan, 6-ethoxypropionyl-3',4'-O-exo-benzylidene-chartreusin, lurtotecan, 7-[2-(N-isopropylamino)ethyl]-(20S)camptothecin, BNP1350, BNPI1100, BN80915, BN80942, etoposide phosphate, teniposide, sobuzoxane, 2'-dimethylamino-2'-deoxy-etoposide, GL331, N-[2-(dimethylamino)ethyl]-9-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole-1-carboxamide, asulacrine, 2,3-(methylenedioxy)-5-methyl-7-hydroxy-8-methoxybenzo[c]-phenanthridinium, 5-(3-aminopropylamino)-7,10-dihydroxy-2-(2-hydroxyethylaminomethyl)-6H-pyrazolo[4,5,1-de]acridin-6-one, N-[1-[2-(diethylamino)ethylamino]-7-methoxy-9-oxo-9H-thioxanthen-4-ylmethyl]formamide, N-(2-(dimethylamino)ethyl)acridine-4-carboxamide, 6-[[2-(dimethylamino)ethyl]amino]-3-hydroxy-7H-indeno[2,1-c]quinolin-7-one, and dimesna.

Examples of inhibitors of mitotic kinesins include, but are not limited to inhibitors of KSP, inhibitors of MKLP1, inhibitors of CENP-E, inhibitors of MCAK, inhibitors of Kif14, inhibitors of Mphosph1 and inhibitors of Rab6-KIFL.

Examples of "histone deacetylase inhibitors" include, but are not limited to, vorinostat, trichostatin A, oxamflatin, PXD101, MG98, valproic acid and scriptaid.

"Inhibitors of kinases involved in mitotic progression" include, but are not limited to, inhibitors of aurora kinase, inhibitors of Polo-like kinases (PLK; in particular inhibitors of PLK-1), inhibitors of bub-1 and inhibitors of bub-R1. An example of an "aurora kinase inhibitor" is VX-680.

"Antiproliferative agents" includes antisense RNA and DNA oligonucleotides such as G3139, ODN698, RVASKRAS, GEM231, and INX3001, and antimetabolites such as enocitabine, carmofur, tegafur, pentostatin, doxifluridine, trimetrexate, fludarabine, capecitabine, galocitabine, cytarabine ocfosfate, fosteabine sodium hydrate, raltitrexed, paltitrexid, emitefur, tiazofurin, decitabine, nolatrexed, pemetrexed, nelzarabine, 2'-deoxy-2'-methylidenecytidine, 2'-

fluoromethylene-2'-deoxycytidine, N6-[4-deoxy-4-[N2-[2,4-tetradecadienoyl]glycylamino]-L-glycero-B-L-manno-heptopyranosyl]adenine, aplidine, ecteinascidin, troxacitabine, aminopterin, 5-flurouracil, floxuridine, methotrexate, leucovarin, hydroxyurea, thioguanine (6-TG), mercaptopurine (6-MP), cytarabine, pentostatin, fludarabine phosphate, cladribine (2-CDA), asparaginase, gemcitabine, alanosine, swainsonine, lometrexol, dexrazoxane, methioninase, and 3-aminopyridine-2-carboxaldehyde thiosemicarbazone.

Non-limiting examples of suitable agents used in cancer therapy that may be combined with compounds of Formula I include, but are not limited to, abarelix; aldesleukin; alemtuzumab; alitretinoin; allopurinol; altretamine; amifostine; anastrozole; arsenic trioxide; asparaginase; azacitidine; bendamustine; bevacuzimab; bexarotene; bleomycin; bortezomib; busulfan; calusterone; capecitabine; carboplatin; carmustine; cetuximab; chlorambucil; cisplatin; cladribine; clofarabine; cyclophosphamide; cytarabine; dacarbazine; dactinomycin, actinomycin D; dalteparin; darbepoetin alfa; dasatinib; daunorubicin; degarelix; denileukin diftitox; dexrazoxane; docetaxel; doxorubicin; dromostanolone propionate; eculizumab; Elliott's B Solution; eltrombopag; epirubicin; epoetin alfa; erlotinib; estramustine; etoposide phosphate; etoposide; everolimus; exemestane; filgrastim; floxuridine; fludarabine; fluorouracil; fulvestrant; gefitinib; gemcitabine; gemtuzumab ozogamicin; goserelin acetate; histrelin acetate; hydroxyurea; ibritumomab tiuxetan; idarubicin; ifosfamide; imatinib mesylate; interferon alfa 2a; interferon alfa-2b; irinotecan; ixabepilone; lapatinib; lenalidomide; letrozole; leucovorin; leuprolide acetate; levamisole; lomustine; meclorethamine, nitrogen mustard; megestrol acetate; melphalan, L-PAM; mercaptopurine; mesna; methotrexate; methoxsalen; mitomycin C; mitotane; mitoxantrone; nandrolone phenpropionate; nelarabine; nilotinib; Nofetumomab; ofatumumab; oprelvekin; oxaliplatin; paclitaxel; palifermin; pamidronat; panitumumab; pazopanib; pegademase; pegaspargase; Pegfilgrastim; pemetrexed disodium; pentostatin; pipobroman; plerixafor; plicamycin, mithramycin); porfimer sodium; pralatrexate; procarbazine; quinacrine; Rasburicase; raloxifene hydrochloride; Rituximab; romidepsin; romiplostim; sargramostim; sargramostim; satraplatin; sorafenib; streptozocin; sunitinib maleate; tamoxifen; temozolomide; temsirolimus; teniposide; testolactone; thioguanine; thiotepa; topotecan; toremifene; tositumomab; trastuzumab; tretinoin; uracil mustard; valrubicin; vinblastine; vincristine; vinorelbine; vorinostat; and zoledronate.

Non-limiting examples of suitable immunotherapy agents used in cancer therapy that may be combined with compounds of Formula I include, but are not limited to Nivolumab, Pembrolizumab, Pidilizumab, BMS-936559, MPDL3280A and MEDI-4736.

In particular the compounds of Formula I are useful for treating cancer when used in combination with Nivolumab or Pembrolizumab.

In particular the compounds of Formula I are useful for treating cancer when used in combination with Pembrolizumab.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, for example as alkali metal or amine salts or as acid addition salts, or prodrugs, or as esters, for example lower alkyl esters, or as solvates, for example hydrates, to optimise the activity and/or stability and/or physical characteristics, such as solubility, of the therapeutic ingredient. It will be clear also that, where appropriate, the therapeutic ingredients may be used in optically pure form.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical composition and thus pharmaceutical compositions comprising a combination as defined above together with a pharmaceutically acceptable diluent, carrier or excipient represent a further aspect of the invention. These combinations are of particular interest in respiratory diseases and are conveniently adapted for inhaled or intranasal delivery.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical compositions. Preferably, the individual compounds will be administered simultaneously in a combined pharmaceutical composition. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

Pharmaceutical Compositions

While it is possible that, for use in therapy, a compound of Formula I, as well as salts, solvates and physiological functional derivatives thereof, may be administered as the raw chemical, it is possible to present the active ingredient as a pharmaceutical composition. Accordingly, the invention further provides a pharmaceutical composition which comprises a compound of Formula I and salts, solvates and physiological functional derivatives thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. The compounds of the Formula I and salts, solvates and physiological functional derivatives thereof, are as described above. The carrier(s), diluent(s) or excipient(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. In accordance with another aspect of the invention there is also provided a process for the preparation of a pharmaceutical composition including admixing a compound of the Formula

I, or salts, solvates and physiological functional derivatives thereof, with one or more pharmaceutically acceptable carriers, diluents or excipients.

Routes of Administration

Pharmaceutical compositions of the present invention may be presented in unit dose forms containing a predetermined amount of active ingredient per unit dose. Such a unit may contain, for example, 5μg to 1 g, preferably 1 mg to 700 mg, more preferably 5 mg to 100 mg of a compound of the Formula I, depending on the condition being treated, the route of administration and the age, weight and condition of the patient. Such unit doses may therefore be administered more than once a day. Preferred unit dosage compositions are those containing a daily dose or sub-dose (for administration more than once a day), as herein above recited, or an appropriate fraction thereof, of an active ingredient. Furthermore, such pharmaceutical compositions may be prepared by any of the methods well known in the pharmacy art.

Pharmaceutical compositions of the present invention may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, topical, inhaled, nasal, ocular, sublingual, subcutaneous, local or parenteral (including intravenous and intramuscular) route, and the like, all in unit dosage forms for administration. Such compositions may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s). Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

In a further embodiment, the present invention provides a pharmaceutical composition adapted for administration by the oral route, for treating, for example, rheumatoid arthritis.

In a further embodiment, the present invention provides a pharmaceutical composition adapted for administration by the nasal route, for treating, for example, allergic rhinitis.

In a further embodiment, the present invention provides a pharmaceutical composition adapted for administration by the inhaled route, for treating, for example, asthma, Chronic Obstructive Pulmonary disease (COPD) or Acute Respiratory Distress Syndrome (ARDS).

In a further embodiment, the present invention provides a pharmaceutical composition adapted for administration by the ocular route, for treating, diseases of the eye, for example, conjunctivitis.

In a further embodiment, the present invention provides a pharmaceutical composition adapted for administration by the parenteral (including intravenous) route, for treating, for example, cancer.

For parenteral administration, the pharmaceutical composition of the invention may be presented in unit-dose or multi-dose containers, e.g. injection liquids in predetermined amounts, for example in sealed vials and ampoules, and may also be stored in a freeze dried (lyophilized) condition requiring only the addition of sterile liquid carrier, e.g. water, prior to use.

Mixed with such pharmaceutically acceptable auxiliaries, e.g. as described in the standard reference, Gennaro, A.R. et al., Remington: *The Science and Practice of Pharmacy* (20th Edition., Lippincott Williams & Wilkins, 2000, see especially Part 5: Pharmaceutical Manufacturing), the active agent may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically acceptable liquids the active agent can be applied as a fluid composition, e.g. as an injection preparation, in the form of a solution, suspension, emulsion, or as a spray, e.g. a nasal spray.

For making solid dosage units, the use of conventional additives such as fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. Suitable carriers with which the active agent of the invention can be administered as solid compositions include lactose, starch, cellulose derivatives and the like, or mixtures thereof, used in suitable amounts. For parenteral administration, aqueous suspensions, isotonic saline solutions and sterile injectable solutions may be used, containing pharmaceutically acceptable dispersing agents and/or wetting agents, such as propylene glycol or butylene glycol.

Pharmaceutical compositions of the present invention which are adapted for oral administration may be presented as discrete units such as capsules or tablets; powders or granules; solutions or suspensions in aqueous or non-aqueous liquids; edible foams or whips; or oil-in-water liquid emulsions or water-in-oil liquid emulsions.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules are made by preparing a powder mixture, as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate,

calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with a free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers, preservatives, flavor additive such as

peppermint oil or natural sweeteners or saccharin or other artificial sweeteners, and the like can also be added.

Where appropriate, dosage unit compositions for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release, for example, by coating or embedding particulate material in polymers, wax or the like.

The compounds of Formula I, and salts, solvates and physiological functional derivatives thereof, can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of Formula I and salts, solvates and physiological functional derivatives thereof may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

Dosage forms for inhaled administration may conveniently be formulated as aerosols or dry powders.

For compositions suitable and/or adapted for inhaled administration, it is preferred that the compound or salt of Formula I is in a particle-size-reduced form, and more preferably the size-reduced form is obtained or obtainable by micronisation. The preferable particle size of the size-reduced (e.g. micronised) compound or salt or solvate is defined by a D50 value of about 0.5 to about 10 microns (for example as measured using laser diffraction).

Aerosol formulations, e.g. for inhaled administration, can comprise a solution or fine suspension of the active substance in a pharmaceutically acceptable aqueous or non-aqueous solvent. Aerosol formulations can be presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomising device or inhaler. Alternatively the sealed container may be a unitary dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve (metered dose inhaler) which is intended for disposal once the contents of the container have been exhausted.

Where the dosage form comprises an aerosol dispenser, it preferably contains a suitable propellant under pressure such as compressed air, carbon dioxide or an organic propellant such as a hydrofluorocarbon (HFC). Suitable HFC propellants include 1,1,1,2,3,3,3-heptafluoropropane and 1,1,1,2-tetrafluoroethane. The aerosol dosage forms can also take the form of a pump-atomiser. The pressurised aerosol may contain a solution or a suspension of the active compound. This may require the incorporation of additional excipients e.g. co-solvents and/or surfactants to improve the dispersion characteristics and homogeneity of suspension formulations. Solution formulations may also require the addition of co-solvents such as ethanol. Other excipient modifiers may also be incorporated to improve, for example, the stability and/or taste and/or fine particle mass characteristics (amount and/or profile) of the formulation.

For pharmaceutical compositions suitable and/or adapted for inhaled administration, it is preferred that the pharmaceutical composition is a dry powder inhalable composition. Such a composition can comprise a powder base such as lactose, glucose, trehalose, mannitol or starch, the compound of Formula I or salt or solvate thereof (preferably in particle-size-reduced form, e.g. in micronised form), and optionally a performance modifier such as L-leucine or another amino acid, and/or metals salts of stearic acid such as magnesium or calcium stearate. Preferably, the dry powder inhalable composition comprises a dry powder blend of lactose and the compound of Formula I or salt thereof. The lactose is preferably lactose hydrate e.g. lactose monohydrate and/or is preferably inhalation-grade and/or fine-grade lactose. Preferably, the particle size of the lactose is defined by 90% or more (by weight or by volume) of the lactose particles being less than 1000 microns (micrometres) (e.g. 10-1000 microns e.g. 30-1000 microns) in diameter, and/or 50% or more of the lactose particles being less than 500 microns (e.g. 10-500 microns) in diameter. More preferably, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 300 microns (e.g. 10-300 microns e.g. 50-300 microns) in diameter, and/or 50% or more of the lactose particles being less than 100 microns in diameter. Optionally, the particle size of the lactose is defined by 90% or more of the lactose particles being less than 100-200 microns in diameter, and/or 50% or more of the lactose particles being less than 40-70 microns in diameter. It is preferable that about 3 to about 30% (e.g. about 10%) (by weight or by volume) of the particles are less than 50 microns or less than 20 microns in diameter. For example, without limitation, a suitable inhalation-grade lactose is E9334 lactose (10% fines) (Borculo Domo Ingredients, Hanzeplein 25, 8017 J D Zwolle, Netherlands).

Optionally, in particular for dry powder inhalable compositions, a pharmaceutical composition for inhaled administration can be incorporated into a plurality of sealed dose

containers (e.g. containing the dry powder composition) mounted longitudinally in a strip or ribbon inside a suitable inhalation device. The container is rupturable or peel-openable on demand and the dose of e.g. the dry powder composition can be administered by inhalation via the device such as the DISKUS® device(GlaxoSmithKline). Other dry powder inhalers are well known to those of ordinary skill in the art, and many such devices are commercially available, with representative devices including Aerolizer® (Novartis), Airmax™ (IVAX), ClickHaler® (Innovata Biomed), Diskhaler® (GlaxoSmithKline), Accuhaler (GlaxoSmithKline), Easyhaler® (Orion Pharma), Eclipse™ (Aventis), FlowCaps® (Hovione), Handihaler® (Boehringer Ingelheim), Pulvinal® (Chiesi), Rotahaler® (GlaxoSmithKline), SkyeHaler™ or Certihaler™ (SkyePharma), Twisthaler (Schering-Plough), Turbuhaler® (AstraZeneca), Ultrahaler® (Aventis), and the like.

Dosage forms for ocular administration may be formulated as solutions or suspensions with excipients suitable for ophthalmic use.

Dosage forms for nasal administration may conveniently be formulated as aerosols, solutions, drops, gels or dry powders.

Pharmaceutical compositions adapted for administration by inhalation include fine particle dusts or mists, which may be generated by means of various types of metered, dose pressurized aerosols, nebulizers or insufflators.

For pharmaceutical compositions suitable and/or adapted for intranasal administration, the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof may be formulated as a fluid formulation for delivery from a fluid dispenser. Such fluid dispensers may have, for example, a dispensing nozzle or dispensing orifice through which a metered dose of the fluid formulation is dispensed upon the application of a user-applied force to a pump mechanism of the fluid dispenser. Such fluid dispensers are generally provided with a reservoir of multiple metered doses of the fluid formulation, the doses being dispensable upon sequential pump actuations. The dispensing nozzle or orifice may be configured for insertion into the nostrils of the user for spray dispensing of the fluid formulation into the nasal cavity. A fluid dispenser of the aforementioned type is described and illustrated in WO-A-2005/044354, the entire content of which is hereby incorporated herein by reference. The dispenser has a housing which houses a fluid discharge device having a compression pump mounted on a container for containing a fluid formulation. The housing has at least one finger-operable side lever which is movable inwardly with respect to the housing to cam the container upwardly in the housing to cause the pump to compress and pump a metered dose of the formulation out of a

pump stem through a nasal nozzle of the housing. A particularly preferred fluid dispenser is of the general type illustrated in FIGS. 30-40 of WO-A-2005/044354.

The invention further includes a pharmaceutical composition of a compound of Formula I or pharmaceutically acceptable salts thereof, as hereinbefore described, in combination with packaging material suitable for said composition, said packaging material including instructions for the use of the composition for the use as hereinbefore described.

The following are examples of representative pharmaceutical dosage forms for the compounds of this invention:

Injectable Suspension (I.M.)	mg/ml
Compound of Formula I	10
Methylcellulose	5.0
Tween 80	0.5
Benzyl alcohol	9.0
Benzalkonium chloride	1.0
Water for injection to a total volume of 1 ml	

Tablet	mg/tablet
Compound of Formula I	25
Microcrystalline Cellulose	415
Providone	14.0
Pregelatinized Starch	43.5
Magnesium Stearate	2.5
	500

Capsule	mg/capsule
Compound of Formula I	25
Lactose Powder	573.5
Magnesium Stearate	1.5
	600

Aerosol	Per canister
Compound of Formula I	24 mg
Lecithin, NF Liquid Concentrate	1.2 mg

Trichlorofluoromethane, NF	4.025 gm
Dichlorodifluoromethane, NF	12.15 gm

It will be appreciated that when the compound of the present invention is administered in combination with other therapeutic agents normally administered by the inhaled, intravenous, oral or intranasal route, that the resultant pharmaceutical composition may be administered by the same routes.

It should be understood that in addition to the ingredients particularly mentioned above, the compositions may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

A therapeutically effective amount of a compound of the present invention will depend upon a number of factors including, for example, the age and weight of the animal, the precise condition requiring treatment and its severity, the particular compound having Formula I, the nature of the formulation, and the route of administration, and will ultimately be at the discretion of the attendant physician or veterinarian. However, an effective amount of a compound of Formula I for the treatment of diseases or conditions associated with inappropriate Btk activity, will generally be in the range of 5 μg to 100 mg/kg body weight of recipient (mammal) per day and more usually in the range of 5 μg to 10 mg/kg body weight per day. This amount may be given in a single dose per day or more usually in a number (such as two, three, four, five or six) of sub-doses per day such that the total daily dose is the same. An effective amount of a salt or solvate, thereof, may be determined as a proportion of the effective amount of the compound of Formula I per se.

In general parenteral administration requires lower dosages than other methods of administration which are more dependent upon absorption. However, a dosage for humans preferably contains 0.0001-25 mg of a compound of Formula I or pharmaceutically acceptable salts thereof per kg body weight. The desired dose may be presented as one dose or as multiple subdoses administered at appropriate intervals throughout the day, or, in case of female recipients, as doses to be administered at appropriate daily intervals throughout the menstrual cycle. The dosage as well as the regimen of administration may differ between a female and a male recipient.

General Synthesis

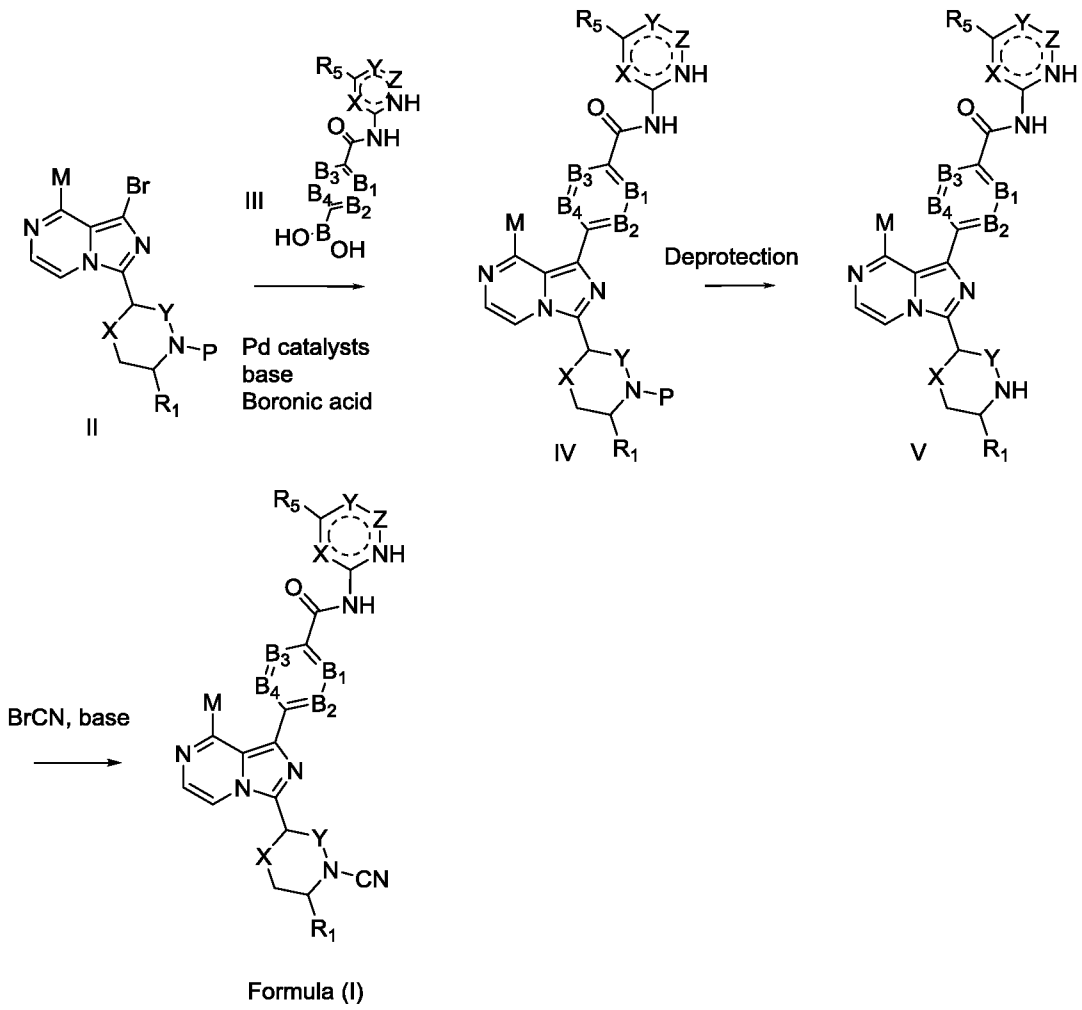
The 8-amino-imidazo[1,5-*a*]pyrazine derivatives of the present invention can be prepared by methods well known in the art of organic chemistry. See, for example, J. March,

'*Advanced Organic Chemistry*' 4th Edition, John Wiley and Sons. During synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This is achieved by means of conventional protecting groups, such as those described in T.W. Greene and P.G.M. Wutts '*Protective Groups in Organic Synthesis*' 3rd Edition, John Wiley and Sons, 1999. The protective groups are optionally removed at a convenient subsequent stage using methods well known in the art.

The products of the reactions are optionally isolated and purified, if desired, using conventional techniques, but not limited to, filtration, distillation, crystallization, chromatography and the like. Such materials are optionally characterized using conventional means, including physical constants and spectral data.

8-amino-imidazo[1,5-*a*]pyrazine compounds of formula I, can be prepared by the general synthetic route shown in scheme I.

Scheme 1



The preparation of intermediates II and III were described in patent applications WO2013/010380, WO2013/010868, WO2013/010869 and US2014/0206681. Suzuki coupling of

intermediate II with boronic acid or ester III catalyzed by palladium with base generates product IV with different protection on the amine. Deprotection of the amine under appropriate conditions for the protecting groups leads to product V. The freed amine is then converted to cyanimide by reaction with cyanobromide with base to provide the final product with formula (I).

Examples

The following Examples are illustrative embodiments of the invention, not limiting the scope of the invention in any way. Reagents are commercially available or are prepared according to procedures in the literature.

Mass Spectrometry: Electron Spray spectra were recorded on the Applied Biosystems API-165 single quad mass spectrometer in alternating positive and negative ion mode using Flow Injection. The mass range was 120-2000 Da. and scanned with a step rate of 0.2 Da. and the capillary voltage was set to 5000 V. N_2gas was used for nebulisation.

LC-MS spectrometer (Waters) Detector: PDA (200-320 nm), Mass detector: ZQ and Eluent : A: acetonitrile with 0.05% trifluoroacetic acid , B: acetronitrile/water = 1/9 (v/v) with 0.05% trifluoroacetic acid.

Method A:

Sample Info : Easy-Access Method: '1-Short_TFA_Pos'

Method Info : B222 Column Agilent SBC (3.0x50 mm, 1.8 μm); Flow 1.0 mL/min; solvent A: H_2O-0.1% TFA;

solvent B: MeCN-0.1% TFA;

GRADIENT TABLE: 0 min:10% B, 0.3 min:10%B, 1.5min: 95% B, 2.70min: 95% B, 2.76 min:10% B

stop time 3.60 min, PostTime 0.70 min.

Method B:

Sample Info : Easy-Access Method: '1_Fast'

Method Info : A330 Column Agilent Zorbax SB-C18 (2.1x30 mm, 3.5 μm); Flow 2.0 mL/min; solvent A: H_2O-0.1% TFA;

solvent B: MeCN-0.1% TFA;

GRADIENT TABLE: 0.01 min:10% B, 1.01 min:95% B, 1.37 min:95% B, 1.38 min:10% B, stop time 1.7min, PostTime=OFF

The following abbreviations are used throughout the application with respect to chemical terminology:

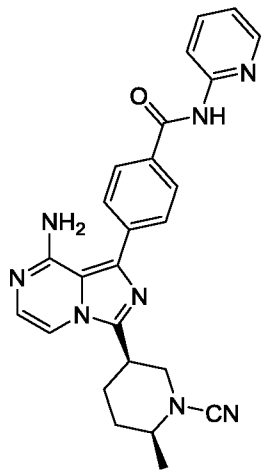
HATU	O-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluoro phosphate
Cbz	Benzyloxycarbonyl

D	Deuterated hydrogen
DMF	N,N-Dimethylformamide
DCM	Dichloromethane
EA	Ethyl acetate
EtOAc	Ethyl acetate
DIPEA	N,N-Diisopropylethylamine
THF	Tetrahydrofuran
EtOH	Ethanol
EDCI.HCl	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
4-DMAP	4-Dimethylaminopyridine
PyBOP	O-Benzotriazole-1-yl-oxy-trispyrrolidinophosphonium hexafluorophosphate
TBTU	O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate
HBr	Hydrogen bromide
HCl	Hydrogen chloride
HOAc	Acetic acid
$POCl_3$	Phosphorous oxychloride
HPLC	High Pressure Liquid Chromatography
UPLC	Ultra Performance Liquid Chromatography
LiHMDS	Lithium hexamethyldisilazide
MeOH	Methanol
DCM	Dichloromethane
n-BuLi	n-Butyllithium
CO_2	Carbondioxide
$NaHCO_3$	Sodium bicarbonate
K_3PO_4	Potassium phosphate
$P(Cy)_3$	Tricyclohexylphosphine
$Pd(OAc)_2$	Palladium(II) acetate
Na_2SO_4	Sodium sulfate
Na_2CO_3	Sodium carbonate
DAST	Diethylaminosulfur trifluoride
Cs_2CO_3	Cesium carbonate
Et_2O	Diethylether
$Na_2S_2O_3$	Sodium thiosulfate

$Na_2S_2O_4$	Sodium hydrosulfite
$NaCNBH_3$	Sodium cyanoborohydride
NH_4Cl	Ammonium chloride
$MgSO_4$	Magnesium sulfate
LiOH	Lithium hydroxide
IPA	Isopropylamine
TFA	Trifluoroacetic acid
Cbz-Cl	Benzylchloroformate
PE	Petroleum ether
EA	Ethyl acetate
NaHMDS	Sodium hexamethyldisilazide
10% Pd/C	10% Palladium on carbon
TEA	Triethylamine
CDI	1,1'-Carbonyl diimidazole
DMI	1,3-Dimethyl-2-imidazolidinone
NBS	N-Bromosuccinimide
i-PrOH	2-Propanol
K_2CO_3	Potassium carbonate
$Pd(dppf)Cl_2$	1,1'-Bis(diphenylphosphino)ferrocene palladium (II) chloride, complex withdichloromethane
Et_3N	Triethylamine
2-BuOH	2-Butanol
LCMS	Liquid Chromatography / Mass Spectrometry
MeCN	Acetonitrile
NH_3	Ammonia
CD_3I	Trideuteromethyl iodide
CD_3OD	Tetradeuteromethanol
CH_3I	Iodomethane
CBr_4	Carbon tetrabromide
Tris-HCl	Tris(hydroxymethyl)aminomethane hydrochloride
$MgCl_2$	Magnesium chloride
NaN_3	Sodium azide
DTT	Dithiothreitol
DMSO	Dimethyl sulfoxide

IMAP	Immobilized Metal Ion Affinity-Based Fluorescence Polarization
ATP	Adenosine triphosphate
$MnCl_2$	Manganese(II) chloride
DMA	Dimethylacetamide
IPA	Isopropyl alcohol
TPP	triphenylphosphine
DIAD	Diisopropyl azodicarboxylate
DMB	2,4-dimethoxybenzyl
DCE	Dichloroethane
DEAD	Diethyl azodicarboxylate
ACN	Acetonitrile
Ret. Time	Retention Time
RT (rt)	Room Temperature
Aq	Aqueous
EtOH	Ethanol
MPLC	Medium Pressure Liquid Chromoatography
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
X-phos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Example 10



4-(8-amino-3-((3R,6S)-1-cyano-6-methylpiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

Step 1: benzyl (2S,5R)-5-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-2-methylpiperidine-1-carboxylate

The reaction mixture of compoundN-(pyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide (1.2 mmol, preparation described in WO2013/01038),benzyl

(2S,5R)-5-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)-2-methylpiperidine-1-carboxylate (1 mmol, preparation described in WO2013/010380), $Pd(dppf)Cl_2$ (80 mg) and K_2CO_3 (480 mg, 3.5 mmol) in mixed solvent of dioxane (10 mL) and H_2O (2 mL) was stirred at 125°C for 20 minutes by micro wave condition. After cooling, the resulting mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by preparative TLC to give compound benzyl (2S,5R)-5-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-2-methylpiperidine-1-carboxylate. LC-MS: (M+H)+: 562.2

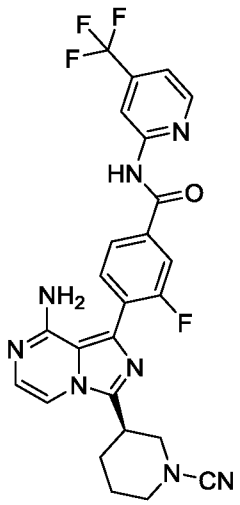
Step 2: 4-(8-amino-3-((3R,6S)-6-methylpiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

The reaction mixture of compoundbenzyl (2S,5R)-5-(8-amino-1-(4-(pyridin-2-ylcarbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-2-methylpiperidine-1-carboxylate (1 mmol) in HBr/AcOH (3 mL) was stirred at room temperature for 2 *hrs*, then diluted with MTBE (60 mL) and filtered. The white solid was dissolved into water, basified with 2 *M aq.* NaOH and extracted with DCM. The combined organic layer was dried over $MgSO_4$ and concentrated under vacuum to give compound4-(8-amino-3-((3R,6S)-6-methylpiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide.MS-ESI(m/z): 453 $(M+1)^+$: 428.2.

Step 3: 4-(8-amino-3-((3R,6S)-1-cyano-6-methylpiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide

To a solution of compound4-(8-amino-3-((3R,6S)-6-methylpiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide (150 mg, 0.35 mmol) and K_2CO_3 (193 mg, 1.4 mmol) in DMF (2.5 mL) was added BrCN (37 mg, 0.35 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 hour. The resulting mixture was diluted with methanol, filtered and purified by preparative HPLC to give compound4-(8-amino-3-((3R,6S)-1-cyano-6-methylpiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide.^{1}HNMR (DMSO 400 MHz): δ 10.93 (s, 1H),8.39 (d, J = 3.6 Hz, 1H), 8.19 (d, J = 8.4 Hz, 3H), 7.99 (d, J = 6.0 Hz, 1H), 7.83-7.88 (m, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.13-7.19 (m, 2H), 3.45-3.59 (m, 4H), 1.79-1.99 (m, 4H), 1.24 (d, J = 6.8 Hz, 3H) ppm. MS-ESI(m/z): 453 $(M+1)^+$.

Example 13



(R)-4-(8-amino-3-(1-cyanopiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

Step 1: benzyl (R)-3-(8-amino-1-(2-fluoro-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate

The mixture of compound benzyl (R)-3-(8-amino-1-bromoimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate (2.5 g, 7.6 mmol, prepared following the procedure described in WO2013/010380), (2-fluoro-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)boronic acid (3 g, 7.0 mmol, pepared following the procedure descibed in WO2013010380(A1)), $Pd(PPh_3)_2Cl_2$ (240 mg, 0.34 mmol) and Na_2CO_3 (1.5 g, 14 mmol) in dioxane/H_2O (16 mL/4 mL)was stirred for 2 h at 90 °C under nitrogen atmosphere. Then to the mixture was added water and extracted with DCM. The combined organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. After concentrated in *vacuo*, the residue was purified by column chromatography (DCM/MeOH = 20/1 v/v%) on silica gel to afford compound benzyl (R)-3-(8-amino-1-(2-fluoro-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate (2.5 g) as a solid. MS-ESI (m/z): 634 $(M+1)^+$ (Method B; Rt: 1.36 min).

Step 2: (R)-4-(8-amino-3-(piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

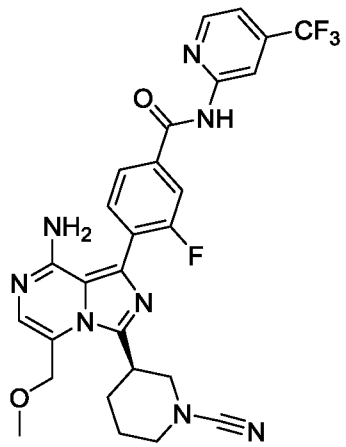
The solution of compound benzyl (R)-3-(8-amino-1-(2-fluoro-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate (2.5 g, 3.9 mmol) in HBr/AcOH (10 mL) was stirred for 2 h at room temperature. Tert-butylmethyl ether was added to the solution and stirred for 30 minutes, filtered and the cake was washed with TBME, then water was added to the residue, adjust to PH = 8 by 1 M Na_2CO_3solution. Filtered and rextracted with DCM twice, washed with brine, dried over

anhydrous Na_2SO_4, concentrated to give the product compound (R)-4-(8-amino-3-(piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (1.8 g).

Step 3: (R)-4-(8-amino-3-(1-cyanopiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

To a stirring solution of compound (R)-4-(8-amino-3-(piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (70 mg, 0.186 mmol) and BrCN (14 mg, 0.14 mmol) in DMF (2 mL) was added K_2CO_3 (38 mg, 0.28 mmol) with ice-bath. The reaction mixture was stirred at room temperature for 40 minutes, diluted with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative HPLC to give compound (R)-4-(8-amino-3-(1-cyanopiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide.^{1}H NMR (400MHz, METHANOL-d_4) δ 8.61 (br. s., 1H), 7.94 (s, 2H), 7.85 - 7.74 (m, 1H), 7.47 - 7.38 (m, 1H), 7.08 - 6.98 (m, 1H), 3.52 (br. s., 4H), 3.26 - 3.14 (m, 1H), 2.18 (d, *J*=11.3 Hz, 1H), 1.92 (br. s., 3H) ppm.MS-ESI (m/z): 525 $(M+1)^+$.

Example 18



(R)-4-(8-amino-3-(1-cyanopiperidin-3-yl)-5-(methoxymethyl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

Step 1: Benzyl (R)-3-(8-chloro-5-(methoxymethyl)imidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate

To a solution of benzyl (R)-3-(8-chloroimidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate (10.7 g, 29.1 mmol, prepared following the procedure described in WO2013/010380) in THF (70 ml) was cooled to -65 ^{0}C, then added dropwise n-BuLi (17.4 ml, 2.5 M in THF) over 15 minutes and stirred at this temperature for 10 minutes. A solution of iodo-methoxy-methane (10 g, 58.1 mmol) in THF (20 ml) was added dropwise over 15 minutes and stirred at -65 ^{0}C for 10 minutes. The reaction mixture was quenched with NH_4Cl solution, and extracted with EA and water. The organic layer was dried and concentrated, and the residue was purified by

column chromatography on silica gel eluted with (PE/EA =3/1 v/v%) to give the target product benzyl (R)-3-(8-chloro-5-(methoxymethyl)imidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate.MS-ESI (m/z): 415 $(M+1)^+$ (Method B; Rt: 1.167 min).

Step 2: benzyl (R)-3-(1-bromo-8-chloro-5-(methoxymethyl)imidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate

To a solution of benzyl (R)-3-(8-chloro-5-(methoxymethyl)imidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate (7.48 g, 18.1 mmol) in DMF (50 ml) was added a solution of NBS (3.5 g, 19.9 mmol) in DMF (10 ml) at 0 ^oC. The mixture was stirred at room temperature for 1 hrs. The reaction solution was poured into water (800 ml) and filtered. The solid was dissolved with DCM and extracted, and the organic layer was dried over Na_2SO_4, concentrated to give the productbenzyl (R)-3-(1-bromo-8-chloro-5-(methoxymethyl)imidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate, which was used in next step without further purification.MS-ESI (m/z): 495 $(M+1)^+$ (Method B; Rt: 1.310 min).

Step 3: benzyl (R)-3-(1-bromo-8-((2,4-dimethoxybenzyl)amino)-5-(methoxymethyl)imidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate

To a solution of benzyl (R)-3-(1-bromo-8-chloro-5-(methoxymethyl)imidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate (8.8 g, 17.8 mmol) in DMF (50 ml) was added K_2CO_3 (4.9 g, 35.7 mmol) and 2,4-Dimethoxy-benzylamine (3.3 g, 19.6 mmol). The mixture was stirred at 110 ^oC for 6 hrs. The reaction mixture was extracted with EA and water. The organic layer was dried and concentrated. The residue was purified by column chromatography on silica gel eluted with (PE/EA =3/1 v/v%) to give the target productbenzyl (R)-3-(1-bromo-8-((2,4-dimethoxybenzyl)amino)-5-(methoxymethyl)imidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate.MS-ESI (m/z): 626 $(M+1)^+$ (Method B; Rt: 1.118 min).

Step 4: benzyl (R)-3-(8-((2,4-dimethoxybenzyl)amino)-1-(2-fluoro-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)-5-(methoxymethyl)imidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate

To a solution ofbenzyl (R)-3-(1-bromo-8-((2,4-dimethoxybenzyl)amino)-5-(methoxymethyl)imidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate (2.3 g, 3.7 mmol) in dioxane/water (20 ml/4 ml) was added (2-fluoro-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)boronic acid (2 g, 4.9 mmol), Na_2CO_3 (1.2 g, 11.1 mmol) and $Pd(PPh_3)_2Cl_2$(131 mg). The mixture was stirred at 100 ^0C overnight. The reaction mixture was concentrated and purified by column chromatography on silica gel eluted with (DCM/MeOH =50/1 v/v%) to give the target productbenzyl (R)-3-(8-((2,4-dimethoxybenzyl)amino)-1-(2-

fluoro-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)-5-(methoxymethyl)imidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate.MS-ESI (m/z): 828 $(M+1)^+$ (Method B; Rt: 1.445 min).

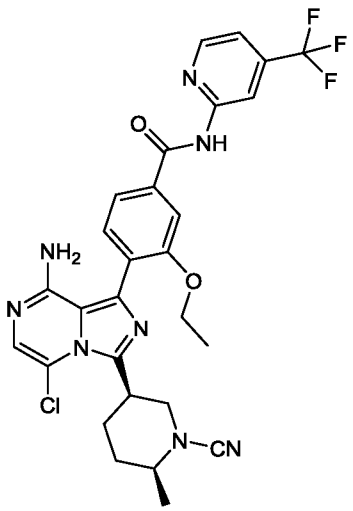
Step 5: (R)-4-(8-amino-5-(methoxymethyl)-3-(piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

To a solution of benzyl (R)-3-(8-((2,4-dimethoxybenzyl)amino)-1-(2-fluoro-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)-5-(methoxymethyl)imidazo[1,5-a]pyrazin-3-yl)piperidine-1-carboxylate (1.1 g, 1.3 mmol) in TFA (6 ml) was stirred at 110 ^{0}C for 2 hrs. The solvent was evaporated and extracted with DCM and Na_2CO_3 solution. The organic layer was dried and concentrated. The residue was purified by column chromatography on silica gel eluted with (DCM/MeOH =20/1 v/v%) to give the target product(R)-4-(8-amino-5-(methoxymethyl)-3-(piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide.MS-ESI (m/z): 544 $(M+1)^+$ (Method B; Rt: 1.048 min).

Step 6: (R)-4-(8-amino-3-(1-cyanopiperidin-3-yl)-5-(methoxymethyl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

To a solution of (R)-4-(8-amino-5-(methoxymethyl)-3-(piperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (70 mg, 0.13 mmol) in DMF (2 ml) was added K_2CO_3 (36 mg, 0.26 mmol). To the mixture was added cyanogen bromide (14 mg, 0.13 mmol) at 0-5 ^{o}C, and stirred at room temperature for 10 minutes. The reaction mixture was purified by Pre-HPLC to give the target product(R)-4-(8-amino-3-(1-cyanopiperidin-3-yl)-5-(methoxymethyl)imidazo[1,5-a]pyrazin-1-yl)-3-fluoro-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide. ^{1}H-NMR(400 MHz, MeOD) δ ppm 8.64 (s, 2H), 7.98~8.06 (m, 2H), 7.82 (t, *J*= 7.6 Hz, 1H), 7.48 (d, *J*= 5.2 Hz, 1H), 7.16 (d, *J*= 5.6 Hz, 1H), 4.32~4.80 (m, 2H), 3.50~4.08 (m, 7H), 3.18~3.28 (m, 1H), 1.70~2.30 (m, 4H). MS-ESI(m/z): 569 $(M+1)^+$.

Example 23



4-(8-amino-5-chloro-3-((3R,6S)-1-cyano-6-methylpiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-ethoxy-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

Step 1: benzyl (2S,5R)-5-(8-amino-5-chloro-1-(2-ethoxy-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-2-methylpiperidine-1-carboxylate

A solution of(2S,5R)-benzyl 5-(8-amino-1-bromo-5-chloroimidazo[1,5-a]pyrazin-3-yl)-2-methylpiperidine-1-carboxylate (200 mg, 0.418 mmol, preparation described in WO2013/010380),3-ethoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (182 mg, 0.418 mmol, preparation described in US2014/0206681),K_2CO_3 (173 mg, 1.253 mmol) in 1,4-dioxane (3 ml) and water (1mL) was addedPdCl_2(dppf) (3.06 mg, 4.18 μmol) at 20°C under nitrogen, the mixture was stirred at 80°C for 1 hour under nitrogen. H_2O (10mL) was added to the mixture, the mixture was extracted by EA (20 mL). The organic layer was washed with H_2O (10mL) and brine (10mL), dried over Na_2SO_4, concentrated to afford the crude product which was purified by pre-HPLC to give compoundbenzyl (2S,5R)-5-(8-amino-5-chloro-1-(2-ethoxy-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-2-methylpiperidine-1-carboxylate (100 mg, 0.141 mmol).^{1}H NMR(400MHz, chloroform-d) δ = 8.71 (br. s., 1H), 8.44 (d, *J*=4.7 Hz, 1H), 7.58 (br. s., 1H), 7.54 - 7.46 (m, 2H), 7.35 - 7.22 (m, 5H), 6.91 (br. s., 1H), 5.23 - 4.87 (m, 4H), 4.60 - 4.31 (m, 2H), 4.10 (d, *J*=6.3 Hz, 2H), 3.84 (d, *J*=11.3 Hz, 1H), 3.42 - 3.22 (m, 1H), 1.36 (s, 2H), 1.27 (d, *J*=6.7 Hz, 3H), 1.19 (t, *J*=6.8 Hz, 3H) ppm.

Step 2: 4-(8-amino-5-chloro-3-((3R,6S)-6-methylpiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-ethoxy-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

A solution of compoundbenzyl (2S,5R)-5-(8-amino-5-chloro-1-(2-ethoxy-4-((4-(trifluoromethyl)pyridin-2-yl)carbamoyl)phenyl)imidazo[1,5-a]pyrazin-3-yl)-2-methylpiperidine-1-carboxylate (100 mg, 0.141 mmol) in 2,2,2-trifluoroacetic acid (2 ml, 0.141 mmol) was heated at 80℃ for 1 hour, after the reaction, the mixture was evaporated to get the crude product compound4-(8-amino-5-chloro-3-((3R,6S)-6-methylpiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-ethoxy-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide (80 mg, 0.139 mmol). LCMS: Method A, RT = 2.38 min, (M+H)+ m/z： 574.2.

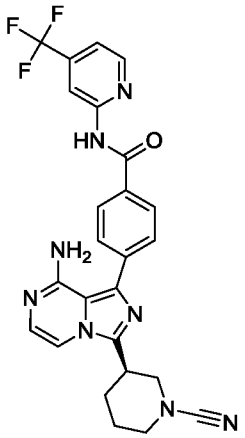
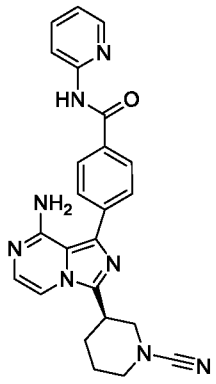
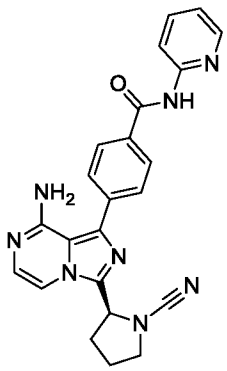
Step 3: 4-(8-amino-5-chloro-3-((3R,6S)-1-cyano-6-methylpiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-ethoxy-N-(4-(trifluoromethyl)pyridin-2-yl)benzamide

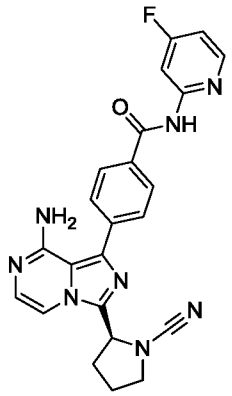
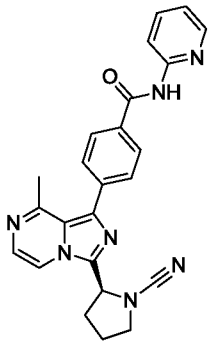
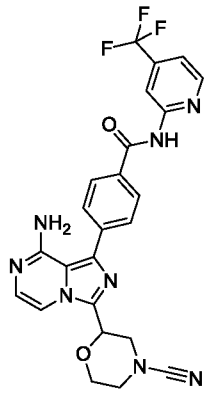
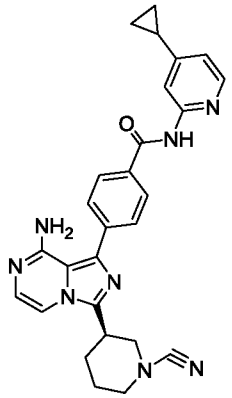
To a solution of Compound 3 (80 mg, 0.139 mmol) in DMF (2 ml) was added cyanic bromide (14.76 mg, 0.139 mmol) at 0°C. The mixture was stirred at 25°C for 16hours. The mixture was purified by pre-HPLC to give 4-(8-amino-5-chloro-3-((3R,6S)-1-cyano-6-methylpiperidin-3-yl)imidazo[1,5-a]pyrazin-1-yl)-3-ethoxy-N-(4-(trifluoromethyl)pyridin-2-

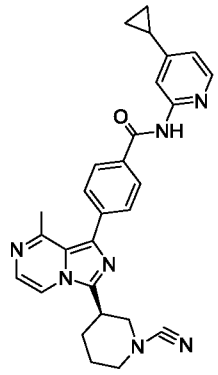
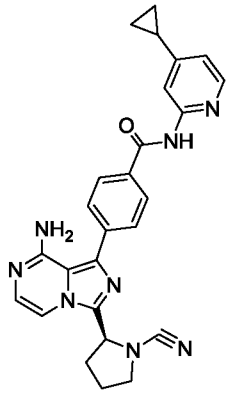
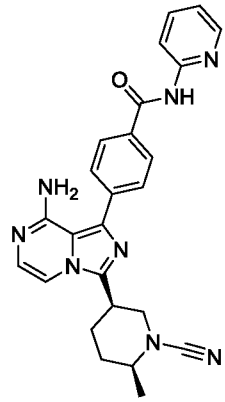
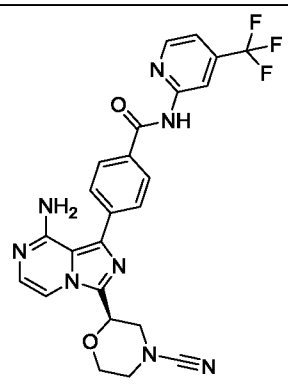
yl)benzamideas a solid. LCMS: Method A: RT = 2.47min, (M+H)+ m/z : 599.1. ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.47 (s, 1H), 8.69 (d, *J*=4.7 Hz, 1H), 8.57 (s, 1H), 7.84 (s, 1H), 7.78 (d, *J*=8.2 Hz, 1H), 7.62 - 7.53 (m, 2H), 7.24 (s, 1H), 4.27 - 4.17 (m, 4H), 4.05 (br. s., 2H), 3.64 - 3.50 (m, 3H), 2.00 (br. s., 2H), 1.82 (br. s., 1H), 1.36 - 1.13 (m, 6H) ppm.

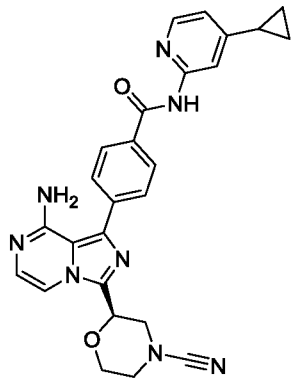
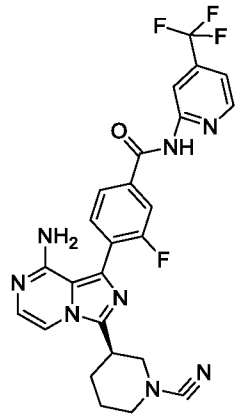
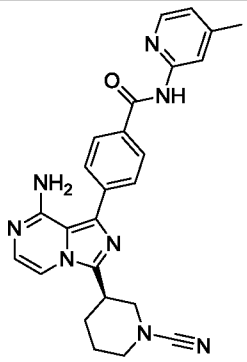
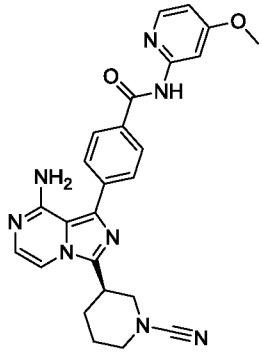
The following Examples were prepared with similar procedures for Examples 13, 18 and 23. The amines for the last step formation of cyanimide were described in patent applications WO2013/010380, WO2013/010868 and WO2013/010869.

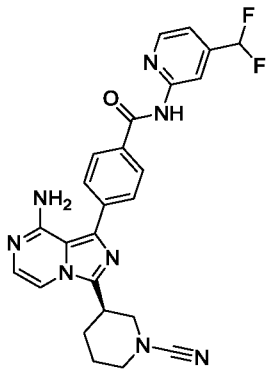
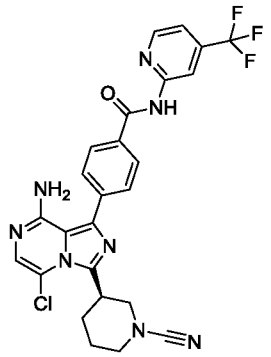
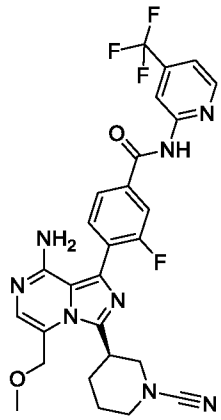
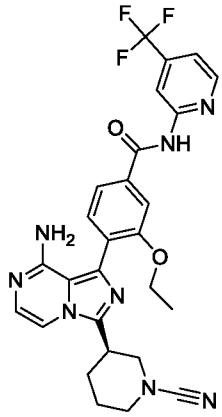
Table 1

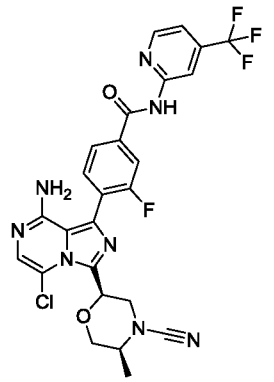
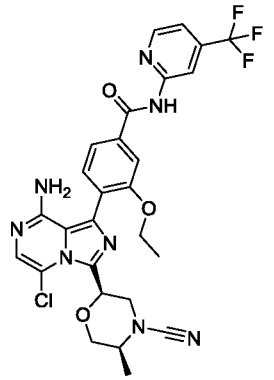
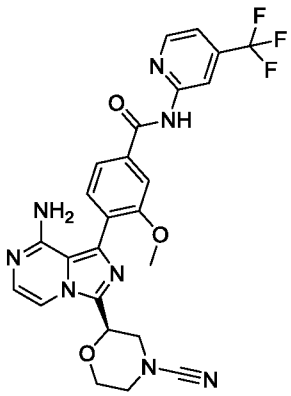
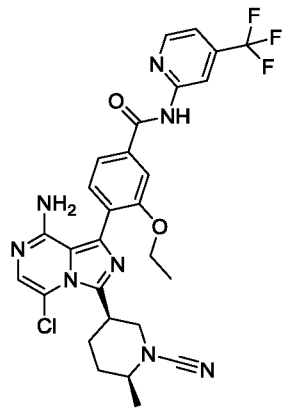
Example Number	**Structure**	**IUPAC Name**	**Exact Mass [M+H]+**
Example 1		4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide	Calc'd 507.2, found 507.3
Example 2		4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-pyridin-2-ylbenzamide	Calc'd 439.2, found 439.1
Example 3		4-{8-amino-3-[(2S)-1-cyanopyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-N-pyridin-2-ylbenzamide	Calc'd 425.2, found 425.2

Example Number	Structure	IUPAC Name	Exact Mass [M+H]+
Example 4		4-{8-amino-3-[(2S)-1-cyanopyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(4-fluoropyridin-2-yl)benzamide	Calc'd 443.2, found
Example 5		4-{3-[(2S)-1-cyanopyrrolidin-2-yl]-8-methylimidazo[1,5-a]pyrazin-1-yl}-N-pyridin-2-ylbenzamide	Calc'd 424.2, found 424.2
Example 6		4-[8-amino-3-(4-cyanomorpholin-2-yl)imidazo[1,5-a]pyrazin-1-yl]-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide	Calc'd 509.2, found 509.1
Example 7		4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(4-cyclopropylpyridin-2-yl)benzamide	Calc'd 479.2, found 479.3

Example Number	Structure	IUPAC Name	Exact Mass [M+H]+
Example 8		4-{3-[(3R)-1-cyanopiperidin-3-yl]-8-methylimidazo[1,5-a]pyrazin-1-yl}-N-(4-cyclopropylpyridin-2-yl)benzamide	Calc'd 478.2, found 478.2
Example 9		4-{8-amino-3-[(2S)-1-cyanopyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(4-cyclopropylpyridin-2-yl)benzamide	Calc'd 465.2, found 465.2
Example 10		4-{8-amino-3-[(3R,6S)-1-cyano-6-methylpiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-pyridin-2-ylbenzamide	Calc'd 453.2, found 453.1
Example 11		4-{8-amino-3-[(2R)-4-cyanomorpholin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide	Calc'd 509.2, found 509.1

Example Number	Structure	IUPAC Name	Exact Mass [M+H]+
Example 12		4-{8-amino-3-[(2R)-4-cyanomorpholin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(4-cyclopropylpyridin-2-yl)benzamide	Calc'd 481.2, found 481.2
Example 13		4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-3-fluoro-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide	Calc'd 525.2, found 525.2
Example 14		4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(4-methylpyridin-2-yl)benzamide	Calc'd 453.2, found 453.2
Example 15		4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(4-methoxypyridin-2-yl)benzamide	Calc'd 469.2, found 469.1

Example Number	Structure	IUPAC Name	Exact Mass [M+H]+
Example 16		4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-[4-(difluoromethyl)pyridin-2-yl]benzamide	Calc'd 489.2, found 489.2
Example 17		4-{8-amino-5-chloro-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide	Calc'd 541.1, found 541.0
Example 18		4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]-5-(methoxymethyl)imidazo[1,5-a]pyrazin-1-yl}-3-fluoro-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide	Calc'd 569.2, found 569.2
Example 19		4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-3-ethoxy-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide	Calc'd 551.2, found 551.2

Example Number	Structure	IUPAC Name	Exact Mass [M+H]+
Example 20		4-{8-amino-5-chloro-3-[(2R,5S)-4-cyano-5-methylmorpholin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-3-fluoro-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide	Calc'd 575.1, found 575.1
Example 21		4-{8-amino-5-chloro-3-[(2R,5S)-4-cyano-5-methylmorpholin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-3-ethoxy-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide	Calc'd 601.2, found 601.2
Example 22		4-{8-amino-3-[(2R)-4-cyanomorpholin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-3-methoxy-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide	Calc'd 539.2, found 539.1
Example 23		4-{8-amino-5-chloro-3-[(3R,6S)-1-cyano-6-methylpiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-3-ethoxy-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide	Calc'd 599.2, found 599.1

Biological Activity

The Btk inhibitor compounds of the invention having Formula I inhibit the Btk kinase activity. All compounds of the invention have an IC50 of 10 μM or lower. In another aspect the invention relates to compounds of Formula I which have an IC50 of less than 100 nM. In yet another aspect the invention relates to compounds of Formula I which have an IC50 of less than 10 nM.

The term IC50 means the concentration of the test compound that is required for 50% inhibition of its maximum effect *in vitro*.

Btk enzyme activity Assay Methods

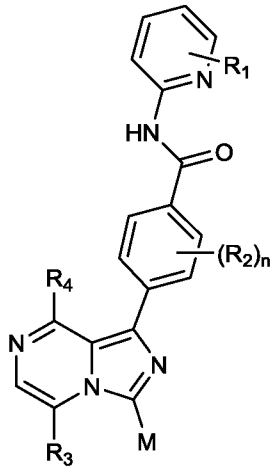
BTK enzymatic activity was determined with the LANCE (Lanthanide Chelate Excite) TR-FRET (Time-resolved fluorescence resonance energy transfer) assay. In this assay, the potency (IC_{50}) of each compound was determined from an eleven point (1:3 serial dilution; final compound concentration range in assay from 1 μM to 0.017 nM) titration curve using the following outlined procedure. To each well of a black non-binding surface Corning 384-well microplate (Corning Catalog #3820), 5 nL of compound (2000 fold dilution in final assay volume of 10 μL) was dispensed, followed by the addition of 7.5 μL of 1x kinase buffer (50 mM Hepes 7.5, 10 mM $MgCl_2$, 0.01% Brij-35, 1 mM EGTA, 0.05% BSA & 1 mM DTT) containing 5.09 pg/μL (66.67 pM) of BTK enzyme (recombinant protein from baculovirus-transfected *Sf9* cells: full-length BTK, 6HIS-tag cleaved). Following a 60 minute compound & enzyme incubation, each reaction was initiated by the addition of 2.5 μL 1x kinase buffer containing 8 μM biotinylated "A5" peptide (Biotin-EQEDEPEGDYFEWLE-NH2), and 100 μM ATP. The final reaction in each well of 10 μL consists of 50 pM *h*BTK, 2 μM biotin-A5-peptide, and 25 μM ATP. Phosphorylation reactions were allowed to proceed for 120 minutes. Reactions were immediately quenched by the addition of 20 uL of 1x quench buffer (15 mM EDTA, 25 mM Hepes 7.3, and 0.1% Triton X-100) containing detection reagents (0.626 nM of LANCE-Eu-W1024-anti-phosphoTyrosine antibody, PerkinElmer and 86.8 nM of Streptavidin-conjugated Dylight 650, Dyomics/ThermoFisher Scientific). After 60 minutes incubation with detection reagents, reaction plates were read on a PerkinElmer EnVision plate reader using standard TR-FRET protocol. Briefly, excitation of donor molecules (Eu-chelate:anti-phospho-antibody) with a laser light source at 337 nm produces energy that can be transferred to Dylight-650 acceptor molecules if this donor:acceptor pair is within close proximity. Fluorescence intensity at both 665 nm (acceptor) and 615 nm (donor) are measured and a TR-FRET ratio calculated for each well (acceptor intensity/donor intensity). IC_{50} values were determined by 4 parameter robust fit of TR-FRET ratio values vs. (Log_{10}) compound concentrations.

Table 2 Compounds BTK binding potency

Example number	BTK binding IC50 (nM)	Example number	BTK binding IC50 (nM)
Example 1	3.6	Example 13	0.36
Example 2	1.5	Example 14	0.24
Example 3	60.3	Example 15	0.41
Example 4	49	Example 16	0.29
Example 5	371	Example 17	0.19
Example 6	3.9	Example 18	0.92
Example 7	1.8	Example 19	0.68
Example 8	46.8	Example 20	0.48
Example 9	67.6	Example 21	1.5
Example 10	3.1	Example 22	0.60
Example 11	0.78	Example 23	2.2
Example 12	1.0		

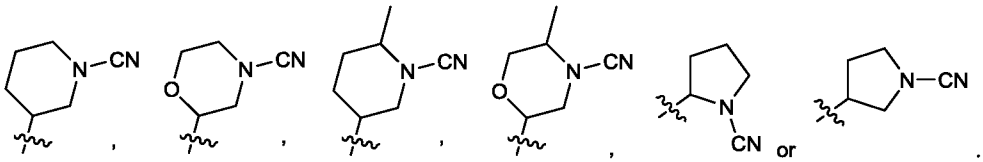
CLAIMS

1. A compound according to Formula I or pharmaceutically acceptable salts thereof



Formula I

wherein:

M is  ;

n is 1 or 2;

R_1 is optionally present and selected from the group consisting of halo, OH, CF_3, CHF_2, cyclopropyl, cyclobutyl, cyclopentyl, (1-3C)alkyl and (1-3C)alkoxy;

R_2 is optionally present and selected from the group consisting of halo, OH, CF_3, CHF_2, cyclopropyl, cyclobutyl, cyclopentyl, (1-3C)alkyl and (1-3C)alkoxy;

R_3 is optionally present and selected from the group consisting of halo, OH, CF_3, CHF_2, cyclopropyl, cyclobutyl, cyclopentyl, (1-3C)alkyl, methoxy, methoxymethyl and ethoxy; and

R_4 is methyl or NH_2.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein

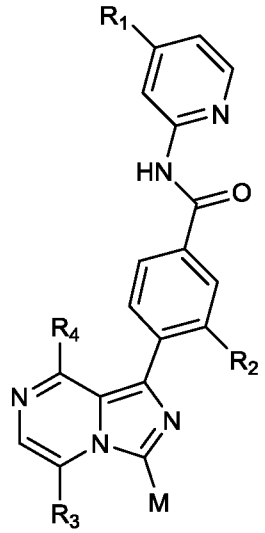
n is 1;

R_1 is optionally present and selected from the group consisting of F, CF_3, CHF_2, methyl, methoxy and cyclopropyl;

R_2 is is optionally present and selected from the group consisting of ethoxy and methoxy; and

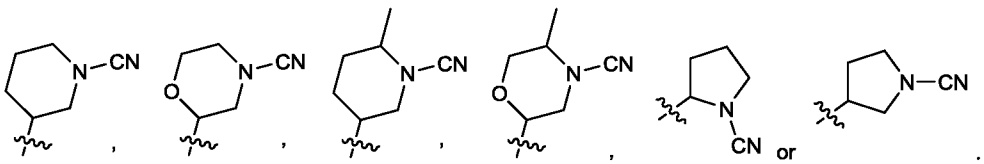
R_3 is is optionally present and selected from the group consisting of Cl and methoxymethyl.

3. The compound of claim 1, having Formula Ia



Formula Ia

wherein:

M is  ;

R_1 is optionally present and selected from the group consisting of halo, OH, CF_3, CHF_2, cyclopropyl, cyclobutyl, cyclopentyl, (1-3C)alkyl and (1-3C)alkoxy;

R_2 is optionally present and selected from the group consisting of halo, OH, CF_3, CHF_2, cyclopropyl, cyclobutyl, cyclopentyl, (1-3C)alkyl and (1-3C)alkoxy;

R_3 is optionally present and selected from the group consisting of halo, OH, CF_3, CHF_2, cyclopropyl, cyclobutyl, cyclopentyl, (1-3C)alkyl, methoxy, methoxymethyl and ethoxy; and

R_4 is methyl or NH_2.

or a pharmaceutically acceptable salt thereof.

4. The compound of claim 3, or a pharmaceutically acceptable salt thereof, wherein R_1 is optionally present and selected from the group consisting of F, CF_3, CHF_2, methyl, methoxy and cyclopropyl;

R_2 is optionally present and selected from the group consisting of ethoxy and methoxy; and

R_3 is optionally present and selected from the group consisting of Cl and methoxymethyl.

5. The compound of claim 1 selected from the group consisting of:
4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;
4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-pyridin-2-ylbenzamide;
4-{8-amino-3-[(2S)-1-cyanopyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-N-pyridin-2-ylbenzamide;
4-{8-amino-3-[(2S)-1-cyanopyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(4-fluoropyridin-2-yl)benzamide;
4-{3-[(2S)-1-cyanopyrrolidin-2-yl]-8-methylimidazo[1,5-a]pyrazin-1-yl}-N-pyridin-2-ylbenzamide;
4-[8-amino-3-(4-cyanomorpholin-2-yl)imidazo[1,5-a]pyrazin-1-yl]-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;
4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(4-cyclopropylpyridin-2-yl)benzamide;
4-{3-[(3R)-1-cyanopiperidin-3-yl]-8-methylimidazo[1,5-a]pyrazin-1-yl}-N-(4-cyclopropylpyridin-2-yl)benzamide;
4-{8-amino-3-[(2S)-1-cyanopyrrolidin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(4-cyclopropylpyridin-2-yl)benzamide;
4-{8-amino-3-[(3R,6S)-1-cyano-6-methylpiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-pyridin-2-ylbenzamide;
4-{8-amino-3-[(2R)-4-cyanomorpholin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;
4-{8-amino-3-[(2R)-4-cyanomorpholin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(4-cyclopropylpyridin-2-yl)benzamide;
4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-3-fluoro-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;
4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(4-methylpyridin-2-yl)benzamide;
4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-(4-methoxypyridin-2-yl)benzamide;

4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-[4-(difluoromethyl)pyridin-2-yl]benzamide;
4-{8-amino-5-chloro-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;
4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]-5-(methoxymethyl)imidazo[1,5-a]pyrazin-1-yl}-3-fluoro-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;
4-{8-amino-3-[(3R)-1-cyanopiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-3-ethoxy-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;
4-{8-amino-5-chloro-3-[(2R,5S)-4-cyano-5-methylmorpholin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-3-fluoro-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;
4-{8-amino-5-chloro-3-[(2R,5S)-4-cyano-5-methylmorpholin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-3-ethoxy-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;
4-{8-amino-3-[(2R)-4-cyanomorpholin-2-yl]imidazo[1,5-a]pyrazin-1-yl}-3-methoxy-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;
4-[8-amino-3-(8-cyano-8-azabicyclo[3.2.1]oct-2-en-3-yl)imidazo[1,5-a]pyrazin-1-yl]-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide; and
4-{8-amino-5-chloro-3-[(3R,6S)-1-cyano-6-methylpiperidin-3-yl]imidazo[1,5-a]pyrazin-1-yl}-3-ethoxy-N-[4-(trifluoromethyl)pyridin-2-yl]benzamide;
or a pharmaceutically acceptable salt thereof.

6. A pharmaceutical composition which comprises the compound of claim 1 or a pharmaceutically acceptable salt thereof and one or more pharmaceutically acceptable carriers.

7. The pharmaceutical composition of claim 6, which further comprises at least one additional therapeutically active agent.

8. The compound of claim 1 or a pharmaceutically acceptable salt thereof for use in therapy.

9. The compound of claim 1 or a pharmaceutically acceptable salt thereof for use in the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

10. Use of the compound of Formula I according to claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of Bruton's Tyrosine Kinase (Btk) mediated disorders.

11. A method for treating a subject suffering with a Bruton's Tyrosine Kinase (Btk) mediated disorder comprising administering to the subject the compound of claim 1 or a pharmaceutically acceptable salt thereof in an amount effective to treat the Btk mediated disorder, thereby treating the subject.

12. The method of claim 11, wherein the Btk mediated disorder is selected from the group consisting of rheumatoid arthritis, psoriatic arthritis, infectious arthritis, progressive chronic arthritis, deforming arthritis, osteoarthritis, traumatic arthritis, gouty arthritis, Reiter's syndrome, polychondritis, acute synovitis and spondylitis, glomerulonephritis (with or without nephrotic syndrome), autoimmune hematologic disorders, hemolytic anemia, aplasic anemia, idiopathic thrombocytopenia, and neutropenia, autoimmune gastritis, and autoimmune inflammatory bowel diseases, ulcerative colitis, Crohn's disease, host versus graft disease, allograft rejection, chronic thyroiditis, Graves' disease, schleroderma, diabetes (type I and type II), active hepatitis (acute and chronic), pancreatitis, primary billiary cirrhosis, myasthenia gravis, multiple sclerosis, systemic lupus erythematosis, psoriasis, atopic dermatitis, contact dermatitis, eczema, skin sunburns, vasculitis (e.g. Behcet's disease) chronic renal insufficiency, Stevens-Johnson syndrome, inflammatory pain, idiopathic sprue, cachexia, sarcoidosis, Guillain-Barré syndrome, uveitis, conjunctivitis, kerato conjunctivitis, otitis media, periodontal disease, pulmonary interstitial fibrosis, asthma, bronchitis, rhinitis, sinusitis, pneumoconiosis, pulmonary insufficiency syndrome, pulmonary emphysema, pulmonary fibrosis, silicosis, chronic inflammatory pulmonary disease, and chronic obstructive pulmonary disease.

13. The method of claim 12, wherein the Btk mediated disorder is rheumatoid arthritis, psoriatic arthritis, or osteoarthritis.

14. The method of claim 11, wherein the Btk mediated disorder is a proliferative disease.

15. The method of claim 14, wherein the proliferative disease is non-Hodgkin lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL)), B cell chronic lymphocytic leukemia and acute lymphoblastic leukemia (ALL).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2015/080754

A. CLASSIFICATION OF SUBJECT MATTER

C07D 487/04(2006.01)i; A61K 31/4985(2006.01)i; A61P 29/00(2006.01)i; A61P 31/00(2006.01)i; A61P 35/00(2006.01)i; A61P 37/00(2006.01)i

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)

C07D487; A61K31; A61P29; A61P31; A61P35; A61P37

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

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

DWPI, SIPOABS, CNABS, CPRSABS, CNKI, CAPLUS, REGISTRY(STN) merck, bruton tyrosine kinnase, Btk, pyrazin, imidazol, pyrazolo, arthriti+, autoimmune, infection, proliferative, pyrimidin, pyrazine, search according to the structure of Formula I in claim 1

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2013010380 A1 (MERCK SHARP & DOHME) 24 January 2013 (2013-01-24) see the whole document, especially examples 531-533, claims 1, 32 and 33	1-10
X	WO 2013010868 A1 (MSD OSS BV) 24 January 2013 (2013-01-24) see the whole document, especially example 94	1-10
X	WO 2013010869 A1 (MSD OSS BV) 24 January 2013 (2013-01-24) see the whole document, especially claim 1	1-10
X	WO 2015057992 A1 (IZUMI RAQUEL) 23 April 2015 (2015-04-23) see the whole document, especially compound 94 in table A, claim 1	1-10
A	WO 2014113942 A1 (MERCK SHARP & DOHME) 31 July 2014 (2014-07-31) see the whole document, especially claims 1-23	1-10

☐ 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
26 February 2016	**15 March 2016**
Name and mailing address of the ISA/CN **STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China** Facsimile No. **(86-10)62019451**	Authorized officer **MA,Jin** Telephone No. **(86-10)62084479**

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2015/080754

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.: **11-15**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 11-15 relate to the method of diseases treatment, which do not comply with the requirement of PCT rule 39.

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

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

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2015/080754

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
WO	2013010380	A1	24 January 2013	JP	2014520866	A	25 August 2014
				AU	2012286426	A1	30 January 2014
				MX	2014000747	A	15 October 2014
				EP	2548877	A1	23 January 2013
				EP	2734529	A4	03 June 2015
				KR	20140068020	A	05 June 2014
				CN	103917545	A	09 July 2014
				CA	2841899	A1	24 January 2013
				EP	2734529	A1	28 May 2014
				RU	2014106020	A	27 August 2015
				US	2014221333	A1	07 August 2014
WO	2013010868	A1	24 January 2013	CR	20140030	A	03 June 2014
				MA	35348	B1	01 August 2014
				EP	2734522	A1	28 May 2014
				KR	20140036324	A	25 March 2014
				CO	6940411	A2	09 May 2014
				CA	2841886	A1	24 January 2013
				CN	103889987	A	25 June 2014
				PE	16812014	A1	14 November 2014
				US	2014155385	A1	05 June 2014
				JP	5826931	B2	02 December 2015
				EC	SP14013217	A	31 March 2015
				MX	2014000746	A	07 May 2014
				CL	2014000130	A1	22 August 2014
				JP	2014520870	A	25 August 2014
				AU	2012285987	A1	06 February 2014
				DO	P2014000008	A	30 April 2014
				EA	201490300	A1	30 May 2014
				IN	408CHN2014	A	03 April 2015
				IL	230511	D0	31 March 2014
WO	2013010869	A1	24 January 2013	US	2014155406	A1	05 June 2014
				CA	2841887	A1	24 January 2013
				AU	2012285988	A1	30 January 2014
				JP	2014522860	A	08 September 2014
				EP	2734523	A1	28 May 2014
WO	2015057992	A1	23 April 2015		None		
WO	2014113942	A1	31 July 2014	WO	2014116504	A1	31 July 2014
				US	2015353565	A1	10 December 2015
				EP	2948431	A1	02 December 2015