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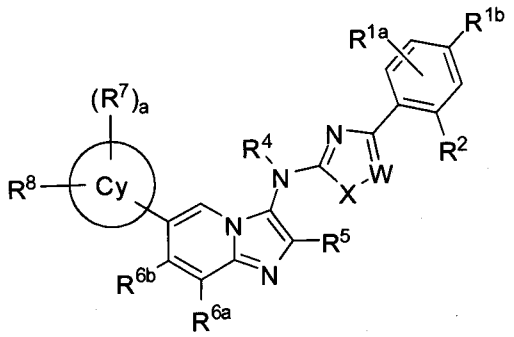
[57] Abstract:

The present invention discloses compounds according to Formula I: Wherein R1a, R1b, R2, R4, R5, R6a, R6b, R7, R8, W, X, Cy, and the subscript a are as defined herein. The present invention relates to compounds inhibiting autotaxin (NPP2 or ENPP2), methods for their production, pharmaceutical compositions comprising the same, and methods of treatment using the same, for the prophylaxis and/or treatment of diseases involving fibrotic diseases, proliferative diseases, inflammatory diseases, autoimmune diseases, respiratory diseases, cardiovascular diseases, neurodegenerative diseases, dermatological disorders, and/or abnormal angiogenesis associated diseasesby administering the compound of the invention.

dermatological disorders, and/or abnormal angiogenesis associated diseases by administering the compounds of the invention.

Accordingly, in a first aspect of the invention, the compounds of the invention are provided having a Formula (I):



I

wherein

R^{1a} is H, halo or C_{1-4} alkyl;

R^{1b} is:

- halo,
- C_{1-4} alkyl (which alkyl is optionally substituted with one or more independently selected halo), or
- C_{1-4} alkoxy (which alkoxy is optionally substituted with one or more independently selected halo);

X is –S-, -O-, –N=CH-, –CH=N- or –CH=CH-;

W is N, or CR^3

when W is N, R^2 is:

- H,
- -CN,
- halo,
- C_{1-4} alkyl (which alkyl is optionally substituted with one or more independently selected OH, or CN),
- $-C(=O)CH_3$,
- $-C(=O)CF_3$,
- $-C(=O)OCH_3$,
- $-C(=O)NH_2$, or
- $-NHC(=O)CH_3$, or

when W is CR^3, one of R^2 or R^3 is:

- H,
- -CN,

- halo,
- C_{1-4} alkyl (which alkyl is optionally substituted with one or more independently selected OH, or CN),
- $-C(=O)CH_3$,
- $-C(=O)CF_3$,
- $-C(=O)OCH_3$,
- $-C(=O)NH_2$, or
- $-NHC(=O)CH_3$,

and the other is H, or C_{1-4} alkyl;

R^4 is C_{1-4} alkyl;

R^5 is C_{1-4} alkyl optionally substituted with one or more independently selected CN, OH, halo, or $-C(=O)NH_2$;

one of R^{6a} or R^{6b} is selected from H, $-CH_3$, and halo, and the other is H;

Cy is:

- C_{4-10} cycloalkyl,
- 4-10 membered mono or bicyclic heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S, or
- 4-7 membered heterocycloalkenyl containing 1 double bond, containing one or more heteroatoms independently selected from O, N, and S;

each R^7 is independently selected from:

- OH,
- oxo,
- halo, and
- C_{1-4} alkyl (which alkyl is optionally substituted with one or more independently selected OH, or C_{1-4} alkoxy);

the subscript a is 0, 1 or 2;

R^8 is $-(L_1-W_1)_m-L_2-G_1$,

wherein

- L_1 is absent , or is -O-, -C(=O)-, $-NR^i$, $-NR^hC(=O)$-, or $-SO_2$-;
- W_1 is C_{1-4} alkylene;
- the subscript m is 0, or 1;
- L_2 is absent , or is -O-, -C(=O)-, -C(=O)O-, -OC(=O) -, -C(=O)-C(=O)-, -C(=O)-C(=O)NR^a-, $-NR^b$-, -C(=O)NR^c-, $-NR^dC(=O)$-, $-NR^jC(=O)O$-, $-SO_2$-, $-SO_2NR^e$- or $-NR^fSO_2$-;
- G_1 is
  - H,
  - -CN,

- C_{1-4} alkyl (which alkyl is optionally substituted with one or more independently selected –CN, OH, halo or phenyl),
- C_{3-7} cycloalkyl (which cycloalkyl is optionally substituted with $–NH_2$),
- 5-6 membered heterocycloalkenyl containing 1 double bond containing one or more heteroatoms independently selected from O, N, and S (which heterocycloalkenyl is optionally substituted with one or more independently selected R^9 groups),
- 4-10 membered mono, bi or spirocyclic heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S (which heterocycloalkyl is optionally substituted with one or more independently selected R^9 groups), or
- 5-6 membered heteroaryl containing one or more heteroatoms independently selected from O, N, and S (which heteroaryl is optionally substituted with one or more independently selected R^{10} groups),

each R^9 is oxo, or R^{10};

each R^{10} is:

- -OH,
- halo,
- -CN,
- C_{1-4} alkyl (which alkyl is optionally substituted with one or more independently selected OH, halo, or phenyl),
- C_{1-4} alkoxy,
- C_{3-7} cycloalkyl,
- phenyl,
- $-SO_2CH_3$,
- $-C(=O)C_{1-4}$ alkoxy,
- $-C(=O)C_{1-4}$ alkyl, or
- $-NR^gC(=O)C_{1-4}$ alkyl; and

each R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, R^i, and R^j is independently selected from H and C_{1-4} alkyl.

In one aspect, the compounds of the invention are inhibitors of autotaxin. Furthermore, the compounds of the invention may exhibit low clearance, possibly resulting in low therapeutic dose levels.

In a more particular aspect, the compounds of the invention are active *in vivo* against IPF and/or COPD.

In a particular aspect, the compounds of the invention are provided for use in the prophylaxis and/or treatment of fibrotic diseases, proliferative diseases, inflammatory diseases,

autoimmune diseases, respiratory diseases, cardiovascular diseases, neurodegenerative diseases, dermatological disorders, and/or abnormal angiogenesis associated diseases.

In a further aspect, the present invention provides pharmaceutical compositions comprising a compound of the invention, and a pharmaceutical carrier, excipient or diluent. In a particular aspect, the pharmaceutical composition may additionally comprise further therapeutically active ingredients suitable for use in combination with the compounds of the invention. In a more particular aspect, the further therapeutically active ingredient is an agent for the treatment of fibrotic diseases, proliferative diseases, inflammatory diseases, autoimmune diseases, respiratory diseases, cardiovascular diseases, neurodegenerative diseases, dermatological disorders, and/or abnormal angiogenesis associated diseases.

Moreover, the compounds of the invention, useful in the pharmaceutical compositions and treatment methods disclosed herein, are pharmaceutically acceptable as prepared and used.

In a further aspect of the invention, this invention provides a method of treating a mammal, in particular humans, afflicted with a condition selected from among those listed herein, and particularly fibrotic diseases, proliferative diseases, inflammatory diseases, autoimmune diseases, respiratory diseases, cardiovascular diseases, neurodegenerative diseases, dermatological disorders, and/or abnormal angiogenesis associated diseases, which method comprises administering an effective amount of the pharmaceutical composition or compounds of the invention as described herein.

The present invention also provides pharmaceutical compositions comprising a compound of the invention, and a suitable pharmaceutical carrier, excipient or diluent for use in medicine. In a particular aspect, the pharmaceutical composition is for use in the prophylaxis and/or treatment of fibrotic diseases, proliferative diseases, inflammatory diseases, autoimmune diseases, respiratory diseases, cardiovascular diseases, neurodegenerative diseases, dermatological disorders, and/or abnormal angiogenesis associated diseases.

In additional aspects, this invention provides methods for synthesizing the compounds of the invention, with representative synthetic protocols and pathways disclosed later on herein.

Other objects and advantages will become apparent to those skilled in the art from a consideration of the ensuing detailed description.

It will be appreciated that compounds of the invention may be metabolized to yield biologically active metabolites.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present invention.

When describing the invention, which may include compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. It should also be understood that when described herein any of the moieties defined forth below may be substituted with a variety of substituents, and that the respective definitions are intended to include such substituted moieties within their scope as set out below. Unless otherwise stated, the term 'substituted' is to be defined as set out below. It should be further understood that the terms 'groups' and 'radicals' can be considered interchangeable when used herein.

The articles 'a' and 'an' may be used herein to refer to one or to more than one (*i.e.* at least one) of the grammatical objects of the article. By way of example 'an analogue' means one analogue or more than one analogue.

As used herein the term 'LPA' relates to lysophosphatidic acid which is a member of the membrane-derived bioactive lipid mediators, further comprising sphingosine-1-phosphate (S1P), lysophosphatidylcholine (LPC), and sphingosylphosphorylcholine (SPC). LPA interacts with specific G protein-coupled receptors (GPCRs), namely LPA_1, LPA_2, LPA_3, LPA_4, LPA_5, LPA_6, LPA_7, LPA_8, in an autocrine and paracrine fashion, to activate intracellular signaling pathways, and in turn produce a variety of biological responses.

'Alkyl' means straight or branched aliphatic hydrocarbon with the number of carbon atoms specified. Particular alkyl groups have 1 to 8 carbon atoms. More particular is lower alkyl which has 1 to 6 carbon atoms. A further particular group has 1 to 4 carbon atoms. Exemplary straight chained groups include methyl, ethyl n-propyl, and n-butyl. Branched means that one or more lower alkyl groups such as methyl, ethyl, propyl or butyl is attached to a linear alkyl chain, exemplary branched chain groups include isopropyl, iso-butyl, t-butyl and isoamyl.

'Alkoxy' refers to the group $-OR^{26}$ where R^{26} is alkyl with the number of carbon atoms specified. Particular alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, and 1,2-dimethylbutoxy. Particular alkoxy groups are lower alkoxy, *i.e.* with between 1 and 6 carbon atoms. Further particular alkoxy groups have between 1 and 4 carbon atoms.

'Alkylene' refers to divalent alkene radical groups having the number of carbon atoms specified, in particular having 1 to 6 carbon atoms and more particularly 1 to 4 carbon atoms which can be straight-chained or branched. This term is exemplified by groups such as methylene ($-CH_2-$), ethylene ($-CH_2-CH_2-$), or $-CH(CH_3)-$ and the like.

'Alkenyl' refers to monovalent olefinically (unsaturated) hydrocarbon groups with the number of carbon atoms specified. Particular alkenyl has 2 to 8 carbon atoms, and more particularly, from 2 to 6 carbon atoms, which can be straight-chained or branched and having at least 1 and particularly from 1 to 2 sites of olefinic unsaturation. Particular alkenyl groups

include ethenyl (-CH=CH_2), n-propenyl (-CH_2CH=CH_2), isopropenyl (-C(CH_3)=CH_2) and the like.

'Amino' refers to the radical -NH_2.

'Aryl' refers to a monovalent aromatic hydrocarbon group derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. In particular aryl refers to an aromatic ring structure, monocyclic or polycyclic, with the number of ring atoms specified. Specifically, the term includes groups that include from 6 to 10 ring members. Where the aryl group is a monocyclic ring system it preferentially contains 6 carbon atoms. Particularly aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl.

'Cycloalkyl'refers to a non-aromatic hydrocarbyl ring structure, monocyclic or polycyclic, with the number of ring atoms specified. A cycloalkyl may have from 3 to 10 carbon atoms, and in particular from 3 to 7 carbon atoms. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

'Cyano' refers to the radical -CN.

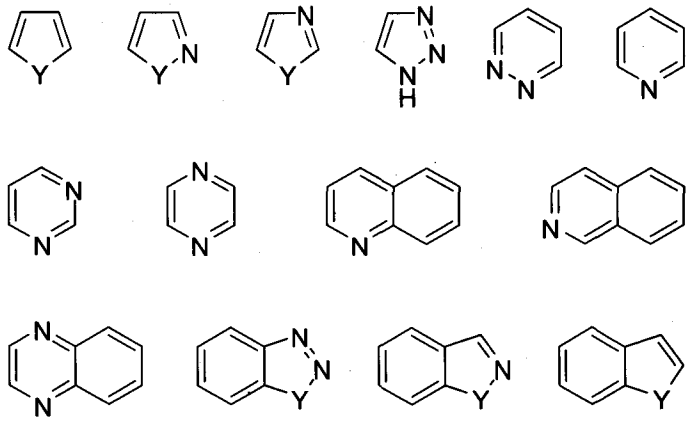
'Halo' or 'halogen' refers to fluoro (F), chloro (Cl), bromo (Br) and iodo (I). Particular halo groups are either fluoro or chloro.

'Hetero' when used to describe a compound or a group present on a compound means that one or more carbon atoms in the compound or group have been replaced by a nitrogen, oxygen, or sulfur heteroatom. Hetero may be applied to any of the hydrocarbyl groups described above such as alkyl, *e.g.* heteroalkyl, cycloalkyl, *e.g.* heterocycloalkyl, aryl, *e.g.* heteroaryl, and the like having from 1 to 4, and particularly from 1 to 3 heteroatoms, more typically 1 or 2 heteroatoms, for example a single heteroatom.

'Heteroaryl' means an aromatic ring structure, monocyclic or polycyclic, that includes one or more heteroatoms independently selected from O, N and S and the number of ring atoms specified. In particular, the aromatic ring structure may have from 5 to 10 ring members. The heteroaryl group can be, for example, a five membered or six membered monocyclic ring or a bicyclic structure formed from fused five and six membered rings or two fused six membered rings or, by way of a further example, two fused five membered rings. Each ring may contain up to four heteroatoms typically selected from nitrogen, sulphur and oxygen. Typically the heteroaryl ring will contain up to 4 heteroatoms, more typically up to 3 heteroatoms, more usually up to 2, for example a single heteroatom. In one embodiment, the heteroaryl ring contains at least one ring nitrogen atom. The nitrogen atoms in the heteroaryl rings can be basic, as in the case of an imidazole or pyridine, or essentially non-basic as in the case of an indole or pyrrole nitrogen. In general the number of basic nitrogen atoms present in the heteroaryl group, including any amino group substituents of the ring, will be less than five. Examples of five membered monocyclic heteroaryl groups include but are not limited to pyrrole, furan, thiophene, imidazole,

furazan, oxazole, oxadiazole, oxatriazole, isoxazole, thiazole, isothiazole, thiadiazole, pyrazole, triazole and tetrazole groups. Examples of six membered monocyclic heteroaryl groups include but are not limited to pyridine, pyrazine, pyridazine, pyrimidine and triazine. Particular examples of bicyclic heteroaryl groups containing a five membered ring fused to another five membered ring include but are not limited to imidazothiazole and imidazoimidazole. Particular examples of bicyclic heteroaryl groups containing a six membered ring fused to a five membered ring include but are not limited to benzofuran, benzothiophene, benzoimidazole, benzoxazole, isobenzoxazole, benzisoxazole, benzthiazole, benzisothiazole, isobenzofuran, indole, isoindole, isoindolone, indolizine, indoline, isoindoline, purine (*e.g.* adenine, guanine), indazole, imidazopyridines, imidazopyrimidines, imidazopyrazines, pyrazolopyrimidine, triazolopyrimidine, benzodioxole and pyrazolopyridine groups. Particular examples of bicyclic heteroaryl groups containing two fused six membered rings include but are not limited to quinoline, isoquinoline, chroman, thiochroman, chromene, isochromene, chroman, isochroman, benzodioxan, quinolizine, benzoxazine, benzodiazine, pyridopyridine, quinoxaline, quinazoline, cinnoline, phthalazine, naphthyridine and pteridine groups. Particular heteroaryl groups are those derived from thiophene, pyrrole, benzothiophene, benzofuran, indole, pyridine, quinoline, imidazole, thiazole, oxazole and pyrazine.

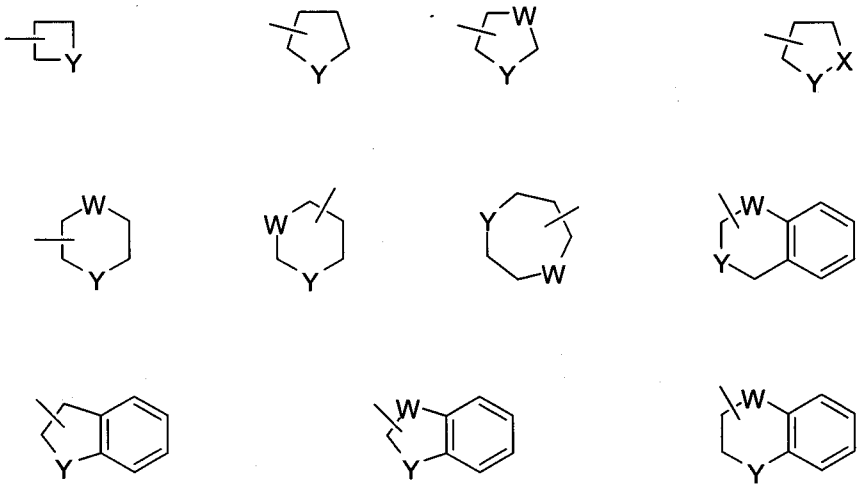
Examples of representative heteroaryls include the following:



wherein each Y is selected from >C(=O), NH, O and S.

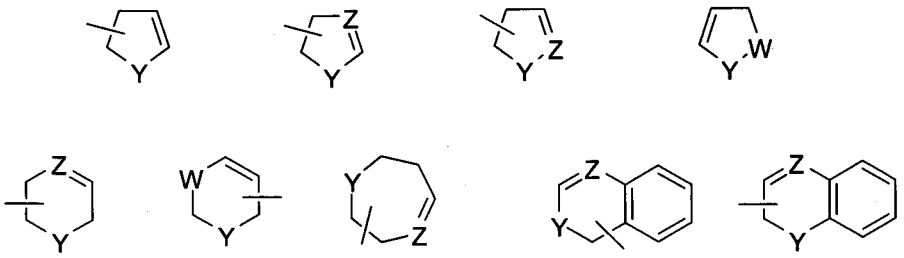
As used herein, the term 'heterocycloalkyl' means a stable non-aromatic ring structure, mono-cyclic or polycyclic, that includes one or more heteroatoms independently selected from O, N and S and the number of ring atoms specified. The non-aromatic ring structure may have from 4 to 10 ring members, and in particular from 4 to 7 ring members. A fused heterocyclic ring system may include carbocyclic rings and need only to include one heterocyclic ring. Examples of heterocyclic rings include, but are not limited to, morpholine, piperidine (*e.g.* 1-piperidinyl, 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), pyrrolidine (*e.g.* 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidone, pyran, , tetrahydrofuran, tetrahydrothiophene, dioxane, tetrahydropyran (*e.g.* 4-tetrahydro pyranyl), imidazoline,

imidazolidinone, oxazoline, thiazoline, 2-pyrazoline, pyrazolidine, piperazine, and N-alkyl piperazines such as N-methyl piperazine. Further examples include thiomorpholine and its S-oxide and S,S-dioxide (particularly thiomorpholine). Still further examples include azetidine, piperidone, piperazone, and N-alkyl piperidines such as N-methyl piperidine. Particular examples of heterocycloalkyl groups are shown in the following illustrative examples:



wherein each W is selected from CH_2, NH, O and S; and each Y is selected from NH, O, C(=O), SO_2, and S.

As used herein, the term 'heterocycloalkenyl' means a 'heterocycloalkyl', which comprises at least one double bond. Particular examples of heterocycloalkenyl groups are shown in the following illustrative examples:



wherein each W is selected from CH_2, NH, O and S; each Y is selected from NH, O, C(=O), SO_2, and S; and each Z is selected from N or CH.

'Hydroxyl' refers to the radical -OH.

'Oxo' refers to the radical =O.

'Substituted' refers to a group in which one or more hydrogen atoms are each independently replaced with the same or different substituent(s).

'Sulfo' or 'sulfonic acid' refers to a radical such as $-SO_3H$.

'Thiol' refers to the group -SH.

As used herein, term 'substituted with one or more' refers to one to four substituents. In one embodiment it refers to one to three substituents. In further embodiments it refers to one or two substituents. In a yet further embodiment it refers to one substituent.

'Thioalkoxy' refers to the group $-SR^{26}$ where R^{26} is alkyl with the number of carbon atoms specified. Particular thioalkoxy groups are thiomethoxy, thioethoxy, n-thiopropoxy, isothiopropoxy, n-thiobutoxy, tert-thiobutoxy, sec-thiobutoxy, n-thiopentoxy, n-thiohexoxy, and 1,2-dimethylthiobutoxy. More particular thioalkoxy groups are lower thioalkoxy, *i.e.* with between 1 and 6 carbon atoms. Further particular alkoxy groups have between 1 and 4 carbon atoms.

One having ordinary skill in the art of organic synthesis will recognize that the maximum number of heteroatoms in a stable, chemically feasible heterocyclic ring, whether it is aromatic or non aromatic, is determined by the size of the ring, the degree of unsaturation and the valence of the heteroatoms. In general, a heterocyclic ring may have one to four heteroatoms so long as the heteroaromatic ring is chemically feasible and stable.

'Pharmaceutically acceptable' means approved or approvable by a regulatory agency of the Federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly, in humans.

'Pharmaceutically acceptable salt' refers to a salt of a compound of the invention that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular, such salts are non-toxic may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl) benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.* an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the

compound contains a basic functionality, salts of non toxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like. The term 'pharmaceutically acceptable cation' refers to an acceptable cationic counter-ion of an acidic functional group. Such cations are exemplified by sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium cations, and the like.

'Pharmaceutically acceptable vehicle' refers to a diluent, adjuvant, excipient or carrier with which a compound of the invention is administered.

'Prodrugs' refers to compounds, including derivatives of the compounds of the invention,which have cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active *in vivo*. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like.

'Solvate' refers to forms of the compound that are associated with a solvent, usually by a solvolysis reaction. This physical association includes hydrogen bonding. Conventional solvents include water, ethanol, acetic acid and the like. The compounds of the invention may be prepared *e.g.* in crystalline form and may be solvated or hydrated. Suitable solvates include pharmaceutically acceptable solvates, such as hydrates, and further include both stoichiometric solvates and non-stoichiometric solvates. 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 isolable solvates. Representative solvates include hydrates, ethanolates and methanolates.

'Subject' includes humans. The terms 'human', 'patient' and 'subject' are used interchangeably herein.

'Effective amount' means the amount of a compound of the invention that, when administered to a subject for treating a disease, is sufficient to effect such treatment for the disease. The 'effective amount' can vary depending on the compound, the disease and its severity, and the age, weight, etc., of the subject to be treated.

'Preventing' or 'prevention' refers to a reduction in risk of acquiring or developing a disease or disorder (*i.e.* causing at least one of the clinical symptoms of the disease not to develop in a subject that may be exposed to a disease-causing agent, or predisposed to the disease in advance of disease onset).

The term 'prophylaxis' is related to 'prevention', and refers to a measure or procedure the purpose of which is to prevent, rather than to treat or cure a disease. Non-limiting examples of prophylactic measures may include the administration of vaccines; the administration of low molecular weight heparin to hospital patients at risk for thrombosis due, for example, to immobilization; and the administration of an anti-malarial agent such as chloroquine, in advance

of a visit to a geographical region where malaria is endemic or the risk of contracting malaria is high.

'Treating' or 'treatment' of any disease or disorder refers, in one embodiment, to ameliorating the disease or disorder (*i.e.* arresting the disease or reducing the manifestation, extent or severity of at least one of the clinical symptoms thereof). In another embodiment 'treating' or 'treatment' refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In yet another embodiment, 'treating' or 'treatment' refers to modulating the disease or disorder, either physically (*e.g.* stabilization of a discernible symptom), physiologically (*e.g.* stabilization of a physical parameter), or both. In a further embodiment, 'treating' or 'treatment' relates to slowing the progression of the disease.

As used herein the term 'fibrotic diseases' refers to diseases characterized by excessive scarring due to excessive production, deposition, and contraction of extracellular matrix, and are that are associated with the abnormal accumulation of cells and/or fibronectin and/or collagen and/or increased fibroblast recruitment and include but are not limited to fibrosis of individual organs or tissues such as the heart, kidney, liver, joints, lung, pleural tissue, peritoneal tissue, skin, cornea, retina, musculoskeletal and digestive tract. In particular, the term fibrotic diseases refers to idiopathic pulmonary fibrosis (IPF); cystic fibrosis, other diffuse parenchymal lung diseases of different etiologies including iatrogenic drug-induced fibrosis, occupational and/or environmental induced fibrosis, granulomatous diseases (sarcoidosis, hypersensitivity pneumonia), collagen vascular disease, alveolar proteinosis, langerhans cell granulomatosis, lymphangioleiomyomatosis, inherited diseases (Hermansky-Pudlak Syndrome, tuberous sclerosis, neurofibromatosis, metabolic storage disorders, familial interstitial lung disease); radiation induced fibrosis; chronic obstructive pulmonary disease (COPD); scleroderma; bleomycin induced pulmonary fibrosis; chronic asthma; silicosis; asbestos induced pulmonary fibrosis; acute respiratory distress syndrome (ARDS); kidney fibrosis; tubulointerstitium fibrosis; glomerular nephritis; focal segmental glomerular sclerosis; IgA nephropathy; hypertension; Alport; gut fibrosis; liver fibrosis; cirrhosis; alcohol induced liver fibrosis; toxic/drug induced liver fibrosis; hemochromatosis; nonalcoholic steatohepatitis (NASH); biliary duct injury; primary biliary cirrhosis; infection induced liver fibrosis; viral induced liver fibrosis; and autoimmune hepatitis; corneal scarring; hypertrophic scarring; Dupuytren disease, keloids, cutaneous fibrosis; cutaneous scleroderma; systemic sclerosis, spinal cord injury/fibrosis; myelofibrosis; vascular restenosis; atherosclerosis; arteriosclerosis; Wegener's granulomatosis; Peyronie's disease, or chronic lymphocytic. More particularly, the term 'fibrotic diseases' refers to idiopathic pulmonary fibrosis (IPF).

As used herein the term 'proliferative disease(s)' refers to conditions such as cancer (*e.g.* uterine leiomyosarcoma or prostate cancer), myeloproliferative disorders (*e.g.* polycythemia vera, essential thrombocytosis and myelofibrosis), leukemia (*e.g.* acute myeloid leukaemia, acute

and chronic lymphoblastic leukemia), multiple myeloma, psoriasis, restenosis, scleroderma or fibrosis. In particular the term refers to cancer, leukemia, multiple myeloma and psoriasis.

As used herein, the term 'cancer' refers to a malignant or benign growth of cells in skin or in body organs, for example but without limitation, breast, prostate, lung, kidney, pancreas, stomach or bowel. A cancer tends to infiltrate into adjacent tissue and spread (metastasise) to distant organs, for example to bone, liver, lung or the brain. As used herein the term cancer includes both metastatic tumour cell types (such as but not limited to, melanoma, lymphoma, leukaemia, fibrosarcoma, rhabdomyosarcoma, and mastocytoma) and types of tissue carcinoma (such as but not limited to, colorectal cancer, prostate cancer, small cell lung cancer and non-small cell lung cancer, breast cancer, pancreatic cancer, bladder cancer, renal cancer, gastric cancer, glioblastoma, primary liver cancer, ovarian cancer, prostate cancer and uterine leiomyosarcoma). In particular, the term ''cancer' refers to acute lymphoblastic leukemia, acute myeloidleukemia, adrenocortical carcinoma, anal cancer, appendix cancer, astrocytomas, atypical teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer (osteosarcoma and malignant fibrous histiocytoma), brain stem glioma, brain tumors, brain and spinal cord tumors, breast cancer, bronchial tumors, Burkitt lymphoma, cervical cancer, chronic lymphocytic leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-Cell lymphoma, embryonal tumors, endometrial cancer, ependymoblastoma, ependymoma, esophageal cancer, ewing sarcoma family of tumors, eye cancer, retinoblastoma, gallbladder cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), gastrointestinal stromal cell tumor, germ cell tumor, glioma, hairy cell leukemia, head and neck cancer, hepatocellular (liver) cancer, hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors (endocrine pancreas), Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, leukemia, Acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, hairy cell leukemia, liver cancer, non-small cell lung cancer, small cell lung cancer, Burkitt lymphoma, cutaneous T-celllymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, lymphoma, Waldenstrom macroglobulinemia, medulloblastoma, medulloepithelioma, melanoma, mesothelioma, mouth cancer, chronic myelogenous leukemia, myeloid leukemia, multiple myeloma, asopharyngeal cancer, neuroblastoma, non-small cell lung cancer, oral cancer, oropharyngeal cancer, osteosarcoma, malignant fibrous histiocytoma of bone, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor, pancreatic cancer, papillomatosis, parathyroid cancer, penile cancer, pharyngeal cancer, pineal parenchymal tumors of intermediate differentiation, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm/multiple myeloma, pleuropulmonary blastoma, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell (kidney) cancer, retinoblastoma, rhabdomyosarcoma, salivary

gland cancer, sarcoma, Ewing sarcoma family of tumors, sarcoma, kaposi, Sezary syndrome, skin cancer, small cell Lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, stomach (gastric) cancer, supratentorial primitive neuroectodermal tumors, T -cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenstrom macroglobulinemia, and Wilms tumor

As used herein the term 'leukemia' refers to neoplastic diseases of the blood and blood forming organs. Such diseases can cause bone marrow and immune system dysfunction, which renders the host highly susceptible to infection and bleeding. In particular the term leukemia refers to acute myeloid leukaemia (AML), and acute lymphoblastic leukemia (ALL) and chronic lymphoblastic leukaemia (CLL).

As used herein the term 'inflammatory diseases' refers to the group of conditions including, rheumatoid arthritis, osteoarthritis, juvenile idiopathic arthritis, psoriasis, psoriatic arthritis, allergic airway disease (*e.g.* asthma, rhinitis), chronic obstructive pulmonary disease (COPD), inflammatory bowel diseases (*e.g.* Crohn's disease, ulcerative colitis), endotoxin-driven disease states (*e.g.* complications after bypass surgery or chronic endotoxin states contributing to *e.g.* chronic cardiac failure), and related diseases involving cartilage, such as that of the joints. Particularly the term refers to rheumatoid arthritis, osteoarthritis, allergic airway disease (*e.g.* asthma), chronic obstructive pulmonary disease (COPD) and inflammatory bowel diseases (*e.g.* Crohn's disease and ulcerative colitis). More particularly the term refers to rheumatoid arthritis, and chronic obstructive pulmonary disease (COPD).

As used herein the term 'autoimmune disease(s)' refers to the group of diseases including obstructive airways disease, including conditions such as COPD, asthma (e.g intrinsic asthma, extrinsic asthma, dust asthma, infantile asthma) particularly chronic or inveterate asthma (for example late asthma and airway hyperreponsiveness), bronchitis, including bronchial asthma, systemic lupus erythematosus (SLE), cutaneous lupus erythrematosis, lupus nephritis, dermatomyositis, Sjogren's syndrome, multiple sclerosis, psoriasis, dry eye disease, type I diabetes mellitus and complications associated therewith, atopic eczema (atopic dermatitis), thyroiditis (Hashimoto's and autoimmune thyroiditis), contact dermatitis and further eczematous dermatitis, inflammatory bowel disease (*e.g.* Crohn's disease and ulcerative colitis), atherosclerosis and amyotrophic lateral sclerosis. Particularly the term refers to COPD, asthma, systemic lupus erythematosis, type I diabetes mellitus and inflammatory bowel disease.

As used herein , the term 'respiratory disease' refers to diseases affecting the organs that are involved in breathing, such as the nose, throat, larynx, eustachian tubes, trachea, bronchi, lungs, related muscles (*e.g.*, diaphram and intercostals), and nerves. In particular, examples of respiratory diseases include asthma, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma,

nocturnal asthma, allerGen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma, seasonal allergic rhinitis, perennial allergic rhinitis, chronic obstructive pulmonary disease, including chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation, cystic fibrosis, and hypoxia.

As used herein the term 'allergy' refers to the group of conditions characterized by a hypersensitivity disorder of the immune system including, allergic airway disease (*e.g.* asthma, rhinitis), sinusitis, eczema and hives, as well as food allergies or allergies to insect venom.

As used herein the term 'asthma' as used herein refers to any disorder of the lungs characterized by variations in pulmonary gas flow associated with airway constriction of whatever cause (intrinsic, extrinsic, or both; allergic or non-allergic). The term asthma may be used with one or more adjectives to indicate the cause.

As used herein the term 'cardiovascular disease' refers to diseases affecting the heart or blood vessels or both. In particular, cardiovascular disease includes arrhythmia (atrial or ventricular or both); atherosclerosis and its sequelae; angina; cardiac rhythm disturbances; myocardial ischemia; myocardial infarction; cardiac or vascular aneurysm; vasculitis, stroke; peripheral obstructive arteriopathy of a limb, an organ, or a tissue; reperfusion injury following ischemia of the brain, heart, kidney or other organ or tissue; endotoxic, surgical, or traumatic shock; hypertension, valvular heart disease, heart failure, abnormal blood pressure, vasoconstriction (including that associated with migraines); vascular abnormality, inflammation, insufficiency limited to a single organ or tissue.

As used herein the term 'neurodegenerative diseases' refers to disorders that are associated with atrophy of the affected central or peripheral structures of the nervous system. In particular, the term 'neurodegenerative diseases' refers to diseases such as Alzheimer's disease and other dementias, degenerative nerve diseases, encephalitis, epilepsy, genetic brain disorders, head and brain malformations, hydrocephalus, stroke, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS or Lou Gehrig's Disease), Huntington's disease, and prion diseases.

As used herein the term 'dermatological disorder' refers to a skin disorder. In particular, dermatological disorders include proliferative or inflammatory disorders of the skin such as, atopic dermatitis, bullous disorders, collagenoses, psoriasis, psoriatic lesions, dermatitis, contact dermatitis, eczema, pruritus, urticaria, rosacea, scleroderma, wound healing, scarring, hypertrophic scarring, keloids, Kawasaki Disease, rosacea, Sjogren-Larsso Syndrome, or urticaria.

As used herein the term 'abnormal angiogenesis associated disease' refers to diseases caused by the dysregulation of the processes mediating angiogenesis. In particular, abnormal

angiogenesis associated disease refers to atherosclerosis, hypertension, tumor growth, inflammation, rheumatoid arthritis, wet-form macular degeneration, choroidal neovascularization, retinal neovascularization, and diabetic retinopathy.

'Compound(s) of the invention', and equivalent expressions, are meant to embrace compounds of the Formula(e) as herein described, which expression includes the pharmaceutically acceptable salts, and the solvates, *e.g.* hydrates, and the solvates of the pharmaceutically acceptable salts where the context so permits. Similarly, reference to intermediates, whether or not they themselves are claimed, is meant to embrace their salts, and solvates, where the context so permits.

When ranges are referred to herein, for example but without limitation, C_{1-8} alkyl, the citation of a range should be considered a representation of each member of said range.

Other derivatives of the compounds of this invention have activity in both their acid and acid derivative forms, but in the acid sensitive form often offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (Bundgard, H, 1985). Prodrugs include acid derivatives well know to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides and anhydrides derived from acidic groups pendant on the compounds of this invention are particularly useful prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. Particular such prodrugs are the C_{1-8} alkyl, C_{2-8} alkenyl, C_{6-10} optionally substituted aryl, and (C_{6-10} aryl)-(C_{1-4} alkyl) esters of the compounds of the invention.

As used herein, the term 'isotopic variant' refers to a compound that contains unnatural proportions of isotopes at one or more of the atoms that constitute such compound. For example, an 'isotopic variant' of a compound can contain one or more non-radioactive isotopes, such as for example, deuterium (^{2}H or D), carbon-13 (^{13}C), nitroGen-15 (^{15}N), or the like. It will be understood that, in a compound where such isotopic substitution is made, the following atoms, where present, may vary, so that for example, any hydrogen may be ^{2}H/D, any carbon may be ^{13}C, or any nitrogen may be ^{15}N, and that the presence and placement of such atoms may be determined within the skill of the art. Likewise, the invention may include the preparation of isotopic variants with radioisotopes, in the instance for example, where the resulting compounds may be used for drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Further, compounds may be prepared that are substituted with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and

^{13}N, and would be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

All isotopic variants of the compounds provided herein, radioactive or not, are intended to be encompassed within the scope of the invention.

It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed 'isomers'. Isomers that differ in the arrangement of their atoms in space are termed 'stereoisomers'.

Stereoisomers that are not mirror images of one another are termed 'diastereomers' and those that are non-superimposable mirror images of each other are termed 'enantiomers'. When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R- and S-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (*i.e.* as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a 'racemic mixture'.

'Tautomers' refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci- and nitro- forms of phenylnitromethane, that are likewise formed by treatment with acid or base.

Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

The compounds of the invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (R)- or (S)- stereoisomers or as mixtures thereof.

Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

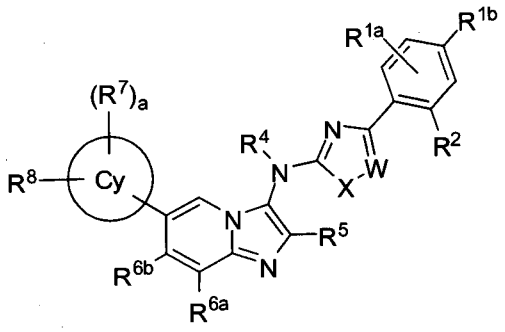
It will be appreciated that compounds of the invention may be metabolized to yield biologically active metabolites.

THE INVENTION

The present invention is based on the identification of novel compounds, and their ability to act as inhibitors of autotaxin and that they may be useful for the treatment of fibrotic diseases, proliferative diseases, inflammatory diseases, autoimmune diseases, respiratory diseases, cardiovascular diseases, neurodegenerative diseases, dermatological disorders, and/or abnormal angiogenesis associated diseases.

The present invention also provides methods for the production of these compounds, pharmaceutical compositions comprising these compounds and methods of treatment for fibrotic diseases, proliferative diseases, inflammatory diseases, autoimmune diseases, respiratory diseases, cardiovascular diseases, neurodegenerative diseases, dermatological disorders, and/or abnormal angiogenesis associated diseases by administering the compounds of the invention.

Accordingly, in a first aspect of the invention, the compounds of the invention are provided having a Formula (I):



I

wherein

R^{1a} is H, halo or C_{1-4} alkyl;

R^{1b} is:

- halo,
- C_{1-4} alkyl (which alkyl is optionally substituted with one or more independently selected halo), or
- C_{1-4} alkoxy (which alkoxy is optionally substituted with one or more independently selected halo);

X is –S-, -O-, –N=CH-, –CH=N- or –CH=CH-;

W is N, or CR^3

when W is N, R^2 is:

- H,
- -CN,
- halo,
- C_{1-4} alkyl (which alkyl is optionally substituted with one or more independently selected OH, or CN),
- $-C(=O)CH_3$,

- -C(=O)CF_3,
- -C(=O)OCH_3,
- -C(=O)NH_2, or
- -NHC(=O)CH_3, or

when W is CR^3, one of R^2 or R^3 is:

- H,
- -CN,
- halo,
- C_{1-4} alkyl (which alkyl is optionally substituted with one or more independently selected OH, or CN)
- -C(=O)CH_3,
- -C(=O)CF_3,
- -C(=O)OCH_3,
- -C(=O)NH_2, or
- -NHC(=O)CH_3,

and the other is H, or C_{1-4} alkyl;

R^4 is C_{1-4} alkyl;

R^5 is C_{1-4} alkyl optionally substituted with one or more independently selected CN, OH, halo, or -C(=O)NH_2;

one of R^{6a} or R^{6b} is selected from H, -CH_3, and halo, and the other is H;

Cy is:

- C_{4-10} cycloalkyl,
- 4-10 membered mono or bicyclic heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S, or
- 4-7 membered heterocycloalkenyl containing 1 double bond, containing one or more heteroatoms independently selected from O, N, and S;

each R^7 is independently selected from:

- OH,
- oxo,
- halo, and
- C_{1-4} alkyl (which alkyl is optionally substituted with one or more independently selected OH, or C_{1-4} alkoxy);

the subscript a is 0, 1 or 2;

R^8 is $-(L_1-W_1)_m-L_2-G_1$,

wherein

- L_1 is absent , or is -O-, -C(=O)-, $-NR^i$, $-NR^hC(=O)$-, or $-SO_2$-;
- W_1 is C_{1-4} alkylene;

- the subscript m is 0, or 1;
- L_2 is absent , or is -O-, -C(=O)-, -C(=O)O-, -OC(=O) -, -C(=O)-C(=O)-, -C(=O)-C(=O)NR^a-, -NR^b-, -C(=O)NR^c-, -NR^dC(=O)-, -NR^jC(=O)O-, -SO_2-, -SO_2NR^e- or –NR^fSO_2-;
- G_1 is
  - H,
  - -CN,
  - C_{1-4} alkyl (which alkyl is optionally substituted with one or more independently selected –CN, OH, halo or phenyl),
  - C_{3-7} cycloalkyl (which cycloalkyl is optionally substituted with –NH_2),
  - 5-6 membered heterocycloalkenyl containing 1 double bond containing one or more heteroatoms independently selected from O, N, and S (which heterocycloalkenyl is optionally substituted with one or more independently selected R^9 groups),
  - 4-10 membered mono, bi or spirocyclic heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S (which heterocycloalkyl is optionally substituted with one or more independently selected R^9 groups), or
  - 5-6 membered heteroaryl containing one or more heteroatoms independently selected from O, N, and S (which heteroaryl is optionally substituted with one or more independently selected R^{10} groups),

each R^9 is oxo, or R^{10};

each R^{10} is:

- -OH,
- halo,
- -CN,
- C_{1-4} alkyl (which alkyl is optionally substituted with one or more independently selected OH, halo, or phenyl),
- C_{1-4} alkoxy,
- C_{3-7} cycloalkyl,
- phenyl,
- -SO_2CH_3,
- -C(=O)C_{1-4} alkoxy,
- -C(=O)C_{1-4} alkyl, or
- -NR^gC(=O)C_{1-4} alkyl; and

each R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, R^i, and R^j is independently selected from H and C_{1-4} alkyl.

In one embodiment, a compound of the invention is according to Formula I, wherein R^{1a} is H.

In one embodiment, a compound of the invention is according to Formula I, wherein R^{1a} is halo. In a particular embodiment, R^{1a} is F, Cl, or Br. In a more particular embodiment, R^{1a} is F, or Cl. In a most particular embodiment, R^{1a} is F.

In one embodiment, a compound of the invention is according to Formula I, wherein R^{1a} is C_{1-4} alkyl. In a particular embodiment, R^{1a} is $-CH_3$, $-CH_2-CH_3$, $-CH_2-CH_2-CH_3$, $-CH(CH_3)_2$. In a more particular embodiment, R^{1a} is $-CH_3$, or $-CH_2-CH_3$.

In one embodiment, a compound of the invention is according to Formula I, wherein R^{1b} is halo. In a particular embodiment, R^{1b} is F, Cl, or Br. In a more particular embodiment, R^{1b} is F, or Cl. In a most particular embodiment, R^{1b} is F.

In one embodiment, a compound of the invention is according to Formula I, wherein R^{1b} is C_{1-4} alkyl. In a particular embodiment, R^{1b} is $-CH_3$, $-CH_2-CH_3$, $-CH_2-CH_2-CH_3$, $-CH(CH_3)_2$. In a more particular embodiment, R^{1b} is $-CH_3$, or $-CH_2-CH_3$.

In one embodiment, a compound of the invention is according to Formula I, wherein R^{1b} is C_{1-4} alkyl substituted with one or more independently selected halo. In a particular embodiment, R^{1b} is $-CF_3$, or $-CH_2-CF_3$. In a more particular embodiment, R^{1b} is $-CF_3$.

In one embodiment, a compound of the invention is according to Formula I, wherein R^{1b} is C_{1-4} alkoxy. In a particular embodiment, R^{1b} is $-OCH_3$, $-OCH_2-CH_3$, $-OCH_2-CH_2-CH_3$, $-OCH(CH_3)_2$. In a more particular embodiment, R^{1b} is $-OCH_3$, or $-OCH_2-CH_3$. In a most particular embodiment, R^{1b} is $-OCH_3$.

In one embodiment, a compound of the invention is according to Formula I, wherein R^{1b} is C_{1-4} alkoxy substituted with one or more independently selected halo. In a more particular embodiment, R^{1b} is $-OCF_3$, $-OCH_2-CHF_2$ or $-OCH_2-CF_3$. In a most particular embodiment, R^{1b} is $-OCF_3$.

In one embodiment, a compound of the invention is according to Formula I, wherein X is –S-, -O-, –N=CH-, –CH=N- or –CH=CH-. In a particular embodiment, X is -S-, or -O-. In another particular embodiment, X is -N=CH-.

In one embodiment, a compound of the invention is according to Formula I, wherein W is N, and R^2 is as previously defined. In a particular embodiment, R^2 is H, -CN, $-C(=O)CH_3$, $-C(=O)CF_3$, $-C(=O)OCH_3$, $-C(=O)NH_2$, or $-NHC(=O)CH_3$. In a more particular embodiment, R^2 is –CN.

In one embodiment, a compound of the invention is according to Formula I, wherein W is N, and R^2 is as previously defined. In a particular embodiment, R^2 is halo. In a more particular embodiment, R^2 is F, Cl, or Br. In a most particular embodiment, R^2 is F, or Cl.

In one embodiment, a compound of the invention is according to Formula I, wherein W is N, and R^2 is as previously defined. In a particular embodiment, R^2 is C_{1-4} alkyl. In another

COMPOUNDS AND PHARMACEUTICAL COMPOSITIONS THEREOF FOR THE TREATMENT OF INFLAMMATORY DISORDERS

FIELD OF THE INVENTION

The present invention relates to compounds that are inhibitors of autotaxin, also known as ectonucleotide pyrophosphatase/phosphodiesterase 2 (NPP2 or ENPP2), that is involved in fibrotic diseases, proliferative diseases, inflammatory diseases, autoimmune diseases, respiratory diseases, cardiovascular diseases, neurodegenerative diseases, dermatological disorders, and/or abnormal angiogenesis associated diseases. The present invention also provides methods for the production of a compound of the invention, pharmaceutical compositions comprising a compound of the invention, methods for the prophylaxis and/or treatment of diseases involving fibrotic diseases, proliferative diseases, inflammatory diseases, autoimmune diseases, respiratory diseases, cardiovascular diseases, neurodegenerative diseases, dermatological disorders, and/or abnormal angiogenesis associated diseases by administering a compound of the invention.

BACKGROUND OF THE INVENTION

Autotaxin (ATX; also known as ENPP2 (ectonucleotide pyrophosphatase / phosphodiesterase 2) or lysophospholipase D) is a ~120 kDa protein that belongs to the ENPP family of enzymes which is composed of seven members, out of which ENPP1 and ENPP3 are the closest to ATX. Whereas ENPP1 and ENPP3 are active in converting ATP into pyrophosphate (a regulator of mineralization and calcification processes in bone), ATX is the only ENPP enzyme with lysophospholipase D (lysoPLD) activity and is responsible for the hydrolysis of lysophosphatidylcholine (LPC) to produce the bioactive lipid lysophosphatidic acid (LPA). Several pieces of evidence have established ATX as the main source of LPA in blood. For example, blood LPA and ATX levels have been shown to be strongly correlated in humans. In addition, LPA levels are reduced by 50% in mice carrying a heterozygous null mutation of ATX (Tanaka, et al., 2006).

Due to the importance of LPA as a biological mediator, the levels of bio-active LPA are expected to be strictly spatially and temporally controlled. The relatively short half life of circulating LPA (~ 3 min) in mice is in line with this expectation. In the circulation, where LPC levels are very high (100–200 μM, mainly albumin-bound), ATX is constitutively active but newly produced LPA is rapidly degraded by membrane-bound phosphatases and levels of plasma LPA are thereby kept low (in the low μM range). This is confirmed by the fact that in cell-free plasma *ex vivo*, LPA levels increase at a steady rate. In addition, LPA in blood is bound to serum albumin, which might further reduce the levels of bio-active LPA. Besides this first level of

particular embodiment, R^2 is C_{1-4} alkyl substituted with one or more independently selected OH, and CN. In yet another particular embodiment, R^2 is C_{1-4} alkyl substituted with one OH, or CN. In a more particular embodiment, R^2 is $-CH_3$, $-CH_2-CH_3$, $-CH_2-OH$, or $-CH_2-CN$. In a most particular embodiment, R^2 is $-CH_2-OH$, or $-CH_2-CN$.

In another embodiment, a compound of the invention is according to Formula I, wherein W is CR^3, and R^2 and R^3 are as previously defined. In a particular embodiment, R^2 is H, -CN, $-C(=O)CH_3$, $-C(=O)CF_3$, $-C(=O)OCH_3$, $-C(=O)NH_2$, or $-NHC(=O)CH_3$, and R^3 is H, or C_{1-4} alkyl. In another particular embodiment, R^2 is H, or C_{1-4} alkyl, and R^3 is H, -CN, $-C(=O)CH_3$, $-C(=O)CF_3$, $-C(=O)OCH_3$, $-C(=O)NH_2$, or $-NHC(=O)CH_3$. In a more particular embodiment, R^2 is H, -CN, $-C(=O)CH_3$, $-C(=O)CF_3$, $-C(=O)OCH_3$, $-C(=O)NH_2$, or $-NHC(=O)CH_3$, and R^3 is H, $-CH_3$, or $-CH_2-CH_3$. In another more particular embodiment, R^2 is H, $-CH_3$, or $-CH_2-CH_3$, and R^3 is H, -CN, $-C(=O)CH_3$, $-C(=O)CF_3$, $-C(=O)OCH_3$, $-C(=O)NH_2$, or $-NHC(=O)CH_3$. In a most particular embodiment, R^2 is –CN, and R^3 is H, $-CH_3$, or $-CH_2-CH_3$. In another most particular embodiment, R^2 is H, $-CH_3$, or $-CH_2-CH_3$, and R^3 is –CN.

In another embodiment, a compound of the invention is according to Formula I, wherein W is CR^3, and R^2 and R^3 are as previously defined. In a particular embodiment, R^2 is halo, and R^3 is H, or C_{1-4} alkyl. In another particular embodiment, R^2 is H, or C_{1-4} alkyl, and R^3 is halo. In a more particular embodiment, R^2 is F, Cl, or Br, and R^3 is H, $-CH_3$, or $-CH_2-CH_3$. In another more particular embodiment, R^2 is H, $-CH_3$, or $-CH_2-CH_3$, and R^3 is F, Cl, or Br. In a most particular embodiment, R^2 is F, or Cl, and R^3 is H, $-CH_3$, or $-CH_2-CH_3$. In another most particular embodiment, R^2 is H, $-CH_3$, or $-CH_2-CH_3$, and R^3 is F, or Cl.

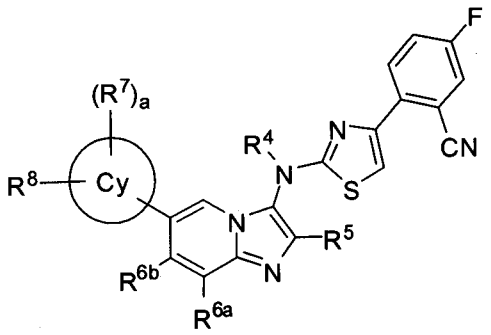
In another embodiment, a compound of the invention is according to Formula I, wherein W is CR^3, and R^2 and R^3 are as previously defined. In a particular embodiment, R^2 is C_{1-4} alkyl, and R^3 is H, or C_{1-4} alkyl. In another particular embodiment, R^2 is H, or C_{1-4} alkyl, and R^3 is C_{1-4} alkyl. In a more particular embodiment, R^2 is $-CH_3$, or $-CH_2-CH_3$, and R^3 is H, $-CH_3$, or $-CH_2-CH_3$. In another more particular embodiment, R^2 is H, $-CH_3$, or $-CH_2-CH_3$, and R^3 is $-CH_3$, or $-CH_2-CH_3$.

In another embodiment, a compound of the invention is according to Formula I, wherein W is CR^3, and R^2 and R^3 are as previously defined. In a particular embodiment, R^2 is C_{1-4} alkyl substituted with OH, or CN, and R^3 is H, or C_{1-4} alkyl. In another particular embodiment, R^2 is H, or C_{1-4} alkyl, and R^3 is C_{1-4} alkyl substituted with OH, or CN. In a more particular embodiment, R^2 is $-CH_2-OH$, or $-CH_2-CN$, and R^3 is H, $-CH_3$, or $-CH_2-CH_3$. In another more particular embodiment, R^2 is H, -

CH_3, or

$-CH_2-CH_3$, and R^3 is $-CH_2-OH$, or $-CH_2-CN$.

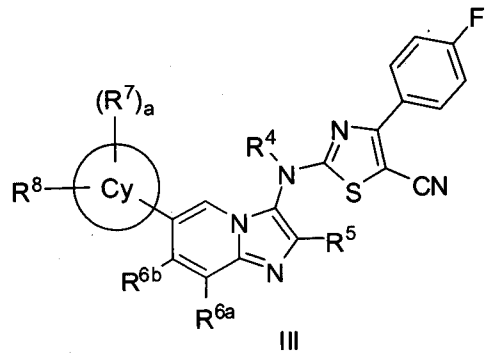
In one embodiment, a compound of the invention is according to Formula II:



II

wherein the subscript a, R^4, R^5, R^{6a}, R^{6b}, R^7 and R^8 are as described above.

In another embodiment, a compound of the invention is according to Formula III:



III

wherein the subscript a, R^4, R^5, R^{6a}, R^{6b}, R^7 and R^8 are as described above.

In one embodiment, a compound of the invention is according to Formula I, II or III, wherein R^4 is C_{1-4} alkyl. In a particular embodiment, R^4 is $-CH_3$, or $-CH_2-CH_3$. In a more particular embodiment, R^4 is $-CH_3$.

In one embodiment, a compound of the invention is according to Formula I, II or III, wherein R^5 is C_{1-4} alkyl. In a particular embodiment, R^5 is $-CH_3$, $-CH_2-CH_3$ or $-CH_2-CH_2-CH_3$. In a more particular embodiment, R^5 is $-CH_3$, or $-CH_2-CH_3$. In a most particular embodiment, R^5 is $-CH_2-CH_3$.

In one embodiment, a compound of the invention is according to Formula I, II or III, wherein R^5 is C_{1-4} alkyl substituted with one or more independently selected CN, OH, halo, and $-C(=O)NH_2$. In a particular embodiment, R^5 is C_{1-4} alkyl substituted with one CN, OH, halo, or $-C(=O)NH_2$. In a more particular embodiment, R^5 is $-CH_3$, $-CH_2-CH_3$, $-CH_2-CH_2-CH_3$, $-CH_2-CH_2-CH_2-CH_3$, $-CH(CH_3)_2$, or $-CH_2-CH(CH_3)_2$, each of which is substituted with one CN, OH, halo, or $-C(=O)NH_2$. In another more particular embodiment, R^5 is $-CH_3$, $-CH_2-CH_3$, $-CH_2-CH_2-CH_3$, $-CH_2-CH_2-CH_2-CH_3$, or -

CH_2-$CH(CH_3)_2$, each of which is substituted with one -CN, OH, F, or -C(=O)NH_2. In a most particular embodiment, R^5 is -CH_2-CH_2-CN, -CH_2-CH_2-OH, -CH_2-CF_3, or -CH_2-CH_2-C(=O)NH_2.

In one embodiment, a compound of the invention is according to Formula I, II or III, wherein Cy is C_{3-10} cycloalkyl. In a particular embodiment, Cy is cyclobutyl, cyclopentyl or cyclohexyl. In a more particular embodiment, Cy is cyclohexyl.

In one embodiment, a compound of the invention is according to Formula I, II or III, wherein Cy is 4-10 membered mono or bicyclic heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S. In a particular embodiment, Cy is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl. In a more particular embodiment, Cy is piperidinyl. In another more particular embodiment, Cy is piperazinyl.

In one embodiment, a compound of the invention is according to Formula I, II or III, wherein Cy is 4-7 membered heterocycloalkenyl containing 1 double bond, containing one or more heteroatoms independently selected from O, N, and S. In a particular embodiment, Cy is dihydrofuranyl, dihydrothiazolyl, dihydrooxazolyl, dihydropyranyl, tetrahydropyridinyl, or dihydrothiopyranyl. In a more particular embodiment, Cy is dihydrooxazolyl.

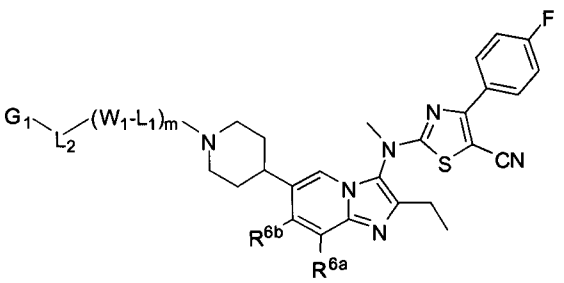
In one embodiment, a compound of the invention is according to Formula I, II or III, wherein the subscript a is 1 or 2, and R^7 is OH, oxo, or halo. In a particular embodiment, R^7 is OH, oxo, F, or Cl.

In one embodiment, a compound of the invention is according to Formula I, II or III, wherein the subscript a is 1 or 2, and R^7 is C_{1-4} alkyl. In a particular embodiment, R^7 is -CH_3, -CH_2-CH_3, or -$CH(CH_3)_2$. In a more particular embodiment, R^7 is -CH_3.

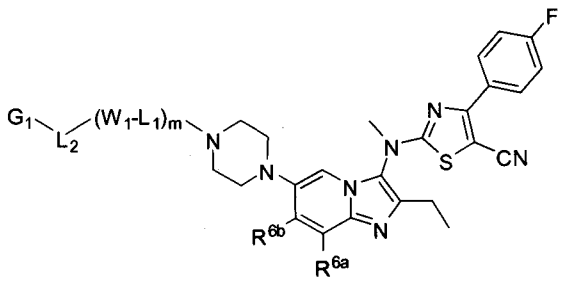
In one embodiment, a compound of the invention is according to Formula I, II or III, wherein the subscript a is 1 or 2, and R^7 is C_{1-4} alkyl substituted with OH, or C_{1-4} alkoxy. In a particular embodiment, R^7 is -CH_3, -CH_2-CH_3, or -$CH(CH_3)_2$, each of which is substituted with OH, or C_{1-4} alkoxy. In a more particular embodiment, R^7 is –CH_2-OH, or –CH_2-OCH_3.

In one embodiment, a compound of the invention is according to Formula I, II or III, wherein the subscript a is 0.

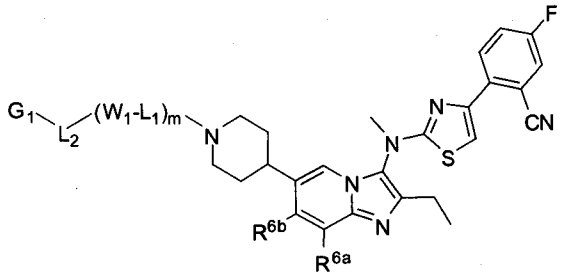
In one embodiment, a compound of the invention is according to Formula IVa, IVb, IVc or IVd:



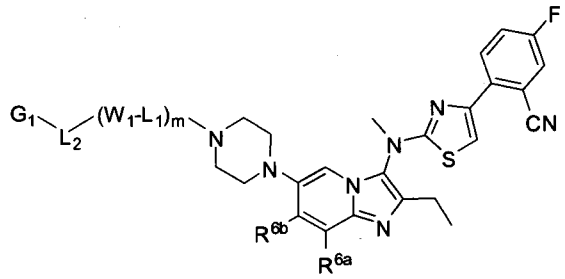
IVa,



IVb,



IVc, or



IVd

wherein R^{6a}, R^{6b}, L_1, W_1, L_2, G_1 and the subscript m are as previously described.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein the subscript m is 1, and L_1 is absent.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein the subscript m is 1, L_1 is -NR^i-, and R^i is as previously described. In a particular embodiment, R^i is H. In another particular embodiment, R^i is $-CH_3$, $-CH_2-CH_3$, or $-CH(CH_3)_2$.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein the subscript m is 1, L_1 is -$NR^hC(=O)$-, and R^h is as previously described. In a particular embodiment, R^h is H. In another particular embodiment, R^h is $-CH_3$, $-CH_2-CH_3$, or $-CH(CH_3)_2$.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein the subscript m is 1, and L_1 is -C(=O)-, or $-SO_2$-.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein the subscript m is 1, and W_1 is C_{1-4} alkylene. In a particular embodiment, W_1 is $-CH_2$-, $-CH_2-CH_2$-,

$-C(CH_3)H$-, $-CH_2-CH_2-CH_2$- or $-CH_2-C(CH_3)H$-. In a more particular embodiment, W_1 is $-CH_2$-, or

$-C(CH_3)H$-.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein the subscript m is 0.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein L_2 is absent.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein L_2 is -O-.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein L_2 is -O-, -C(=O)-, -C(=O)O-, -OC(=O) -, -C(=O)-C(=O)-, or $-SO_2-$.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein L_2 is -C(=O)-C(=O)NR^a-, and R^a is as previously described. In a particular embodiment, R^a is H. In another particular embodiment, R^a is $-CH_3$, $-CH_2-CH_3$, or $-CH(CH_3)_2$.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein L_2 is -NR^b-, and R^b is as previously described. In a particular embodiment, R^b is H. In another particular embodiment, R^b is $-CH_3$, $-CH_2-CH_3$, or $-CH(CH_3)_2$.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein L_2 is -C(=O)NR^c-, and R^c is as previously described. In a particular embodiment, R^c is H. In another particular embodiment, R^c is $-CH_3$, $-CH_2-CH_3$, or $-CH(CH_3)_2$.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein L_2 is -NR^dC(=O)- , and R^d is as previously described. In a particular embodiment, R^d is H. In another particular embodiment, R^d is $-CH_3$, $-CH_2-CH_3$, or $-CH(CH_3)_2$.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein L_2 is -NR^jC(=O)O-, and R^j is as previously described. In a particular embodiment, R^j is H. In another particular embodiment, R^j is $-CH_3$, $-CH_2-CH_3$, or $-CH(CH_3)_2$.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein L_2 is -SO_2NR^e-, and R^e is as previously described. In a particular embodiment, R^e is H. In another particular embodiment, R^e is $-CH_3$, $-CH_2-CH_3$, or $-CH(CH_3)_2$.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein L_2 is–NR^fSO_2-, and R^f is as previously described. In a particular embodiment, R^f is H. In another particular embodiment, R^f is $-CH_3$, $-CH_2-CH_3$, or $-CH(CH_3)_2$.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein G_1 is H, or CN.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein G_1 is C_{1-4} alkyl. In a particular embodiment, G_1 is $-CH_3$, or $-CH_2-CH_3$.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein G_1 is C_{1-4} alkyl substituted with –CN, OH, halo or phenyl. In a particular embodiment, G_1 is $-CH_3$, $-CH_2-CH_3$, or $-CH(CH_3)_2$, each of which is substituted with –CN, OH, halo or phenyl. In a more particular embodiment, G_1 is $-CF_3$, $-CH_2-Cl$, $-CH_2-CN$, $-CH_2-OH$ or $-CH_2-Ph$.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein G_1 is C_{3-7} cycloalkyl. In a particular embodiment, G_1 is cyclopropyl, cyclobutyl, cyclopropyl, or cyclohexyl.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein G_1 is C_{3-7} cycloalkyl substituted with $-NH_2$. In a particular embodiment, G_1 is cyclopropyl, cyclobutyl, cyclopropyl, or cyclohexyl, each of which is substituted with $-NH_2$.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein G_1 is 5-6 membered heterocycloalkenyl containing 1 double bond, containing one to three heteroatoms independently selected from O, N, and S. In a particular embodiment, G_1 is dihydrofuranyl, dihydrothiazolyl, dihydrooxazolyl, dihydropyranyl, or dihydrothiopyranyl.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein G_1 is 5-6 membered heterocycloalkenyl containing 1 double bond, containing one to three heteroatoms independently selected from O, N, and S, substituted with one or more independently selected R^9, and R^9 is as previously defined. In another embodiment, G_1 is 5-6 membered heterocycloalkenyl containing 1 double bond, containing one to three heteroatoms independently selected from O, N, and S, substituted with one or two independently selected R^9, and R^9 is as previously defined. In a particular embodiment, G_1 is dihydrofuranyl, dihydrothiazolyl, dihydrooxazolyl, dihydropyranyl, or dihydrothiopyranyl, each of which is substituted with one or two independently selected R^9, and R^9 is as previously defined.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein G_1 is 4-10 membered mono, bi or spirocyclic heterocycloalkyl containing one to three heteroatoms independently selected from O, N, and S. In a particular embodiment, G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, or 2,6-diaza-spiro[3.3]heptane.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein G_1 is 4-10 membered mono, bi or spirocyclic heterocycloalkyl containing one to three heteroatoms independently selected from O, N, and S, substituted with one or more independently selected R^9, and R^9 is as previously defined. In another embodiment, G_1 is 4-10 membered mono, bi or spirocyclic heterocycloalkyl containing one to three heteroatoms independently selected from O, N, and S, substituted with one or two independently selected R^9, and R^9 is as previously defined. In a particular embodiment, G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, or 2,6-diaza-spiro[3.3]heptanes, each of which is substituted with one or two independently selected R^9, and R^9 is as previously defined.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein R^9 is oxo.

In another embodiment, a compound of the invention is according to Formula I-IVd, wherein R^9 is R^{10}.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein R^{10} is selected from OH, F, Cl, and -CN.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein R^{10} is C_{1-4} alkyl. In a particular embodiment, R^{10} is selected from $-CH_3$, $-CH_2-CH_3$, and $-CH(CH_3)_2$. In a more particular embodiment, R^{10} is selected from $-CH_3$, and $-CH_2-CH_3$.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein R^{10} is C_{1-4} alkyl substituted with one or more independently selected OH, halo, phenyl. In a further embodiment, R^{10} is C_{1-4} alkyl substituted with one to three independently selected OH, halo, and phenyl. In a more particular embodiment, R^{10} is $-CH_3$, $-CH_2-CH_3$, and $-CH(CH_3)_2$, each of which is substituted with one to three independently selected OH, halo, and phenyl. In a most particular embodiment, R^{10} is $-CF_3$, $-CH_2-CH_2-OH$, and $-CH_2$-phenyl.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein R^{10} is C_{1-4} alkoxy. In a particular embodiment, R^{10} is selected from $-OCH_3$, $-OCH_2-CH_3$, and $-OC(CH_3)_3$. In a particular embodiment, R^{10} is $-OCH_3$.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein R^{10} is selected from $-SO_2CH_3$, $-C(=O)C_{1-4}$ alkoxy, and $-C(=O)C_{1-4}$ alkyl. In a particular embodiment, R^{10} is selected from $-SO_2CH_3$, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, $-C(=O)OCH(CH_3)_2$, $-C(=O)CH_3$, $-C(=O)CH_2CH_3$, and $-C(=O)OCH(CH_3)_2$. In a most particular embodiment, R^{10} is selected from $-SO_2CH_3$, $-C(=O)OCH_3$, and $-C(=O)CH_3$.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein R^{10} is $-NR^gC(=O)C_{1-4}$ alkyl, and R^g is as described previously. In a particular embodiment, R^{10} is $-NR^gC(=O)CH_3$, or $-NR^gC(=O)CH_2CH_3$, and R^g is as described previously. In a more particular embodiment, R^{10} is $-NR^gC(=O)CH_3$, or $-NR^gC(=O)CH_2CH_3$, and R^g is H, $-CH_3$, or $-CH_2CH_3$. In a most particular embodiment, R^{10} is $-NHC(=O)CH_3$, or $-NHC(=O)CH_2CH_3$.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein G_1 is 4-7 membered heterocycloalkyl containing one or more heteroatoms independently selected selected from O, N, and S, each of which is substituted with one or two independently selected R^9 groups, and R^9 is oxo. In a further particular embodiment, G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, or 2,6-diaza-spiro[3.3]heptane, each of which is substituted with one or two independently selected R^9 groups, and R^9 is oxo.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein G_1 is 4-7 membered heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a further embodiment, G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, or 2,6-diaza-spiro[3.3]heptane, each of which is substituted with

one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a particular embodiment, R^{10} is selected from OH, F, Cl, and -CN.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein G_1 is 4-7 membered heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a further embodiment, G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, or 2,6-diaza-spiro[3.3]heptane, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a particular embodiment, R^{10} is selected C_{1-4} alkyl. In a more particular embodiment, R^{10} is selected from $-CH_3$, $-CH_2-CH_3$, and $-CH(CH_3)_2$. In a most particular embodiment, R^{10} is selected from $-CH_3$, and $-CH_2-CH_3$.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein G_1 is 4-7 membered heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a further embodiment, G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, or 2,6-Diaza-spiro[3.3]heptane, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a particular embodiment, R^{10} is C_{1-4} alkyl substituted with one or more independently selected OH, halo, or phenyl. In a further embodiment, R^{10} is C_{1-4} alkyl substituted with one to three independently selected OH, halo, or phenyl. In a more particular embodiment, R^{10} is $-CH_3$, $-CH_2-CH_3$, or $-CH(CH_3)_2$, each of which is substituted with one to three independently selected OH, halo, or phenyl. In a most particular embodiment, R^{10} is $-CF_3$, $-CH_2-CH_2-OH$, or $-CH_2$-phenyl.

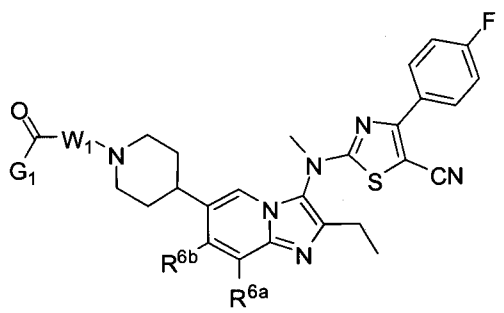
In one embodiment, a compound of the invention is according to Formula I-IVd, wherein G_1 is 4-7 membered heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a further embodiment, G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, or 2,6-diaza-spiro[3.3]heptane, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a particular embodiment, R^{10} is C_{1-4} alkoxy. In a more particular embodiment, R^{10} is selected from $-OCH_3$, $-OCH_2-CH_3$, and $-OC(CH_3)_3$. In a most particular embodiment, R^{10} is $-OCH_3$.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein G_1 is 4-7 membered heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S, each of which is substituted with one or two independently selected

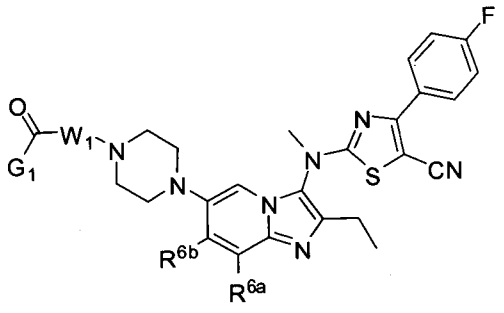
R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a further embodiment, G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, or 2,6-Diaza-spiro[3.3]heptane, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a particular embodiment, R^{10} is selected from $-SO_2CH_3$, $-C(=O)C_{1-4}$ alkoxy, and $-C(=O)C_{1-4}$ alkyl. In a more particular embodiment, R^{10} is selected from $-SO_2CH_3$, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, $-C(=O)OCH(CH_3)_2$, $-C(=O)CH_3$, $-C(=O)CH_2CH_3$, and $-C(=O)OCH(CH_3)_2$. In a most particular embodiment, R^{10} is selected from $-SO_2CH_3$, $-C(=O)OCH_3$, and $-C(=O)CH_3$.

In one embodiment, a compound of the invention is according to Formula I-IVd, wherein G_1 is 4-7 membered heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a further embodiment, G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, or 2,6-Diaza-spiro[3.3]heptane, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a particular embodiment, R^{10} is $-NR^gC(=O)C_{1-4}$ alkyl, and R^g is as described previously. In a particular embodiment, R^{10} is $-NR^gC(=O)CH_3$, or $-NR^gC(=O)CH_2CH_3$, and R^g is as described previously. In a more particular embodiment, R^{10} is $-NR^gC(=O)CH_3$, or $-NR^gC(=O)CH_2CH_3$, and R^g is H, $-CH_3$, or $-CH_2CH_3$. In a most particular embodiment, R^{10} is $-NHC(=O)CH_3$, or $-NHC(=O)CH_2CH_3$.

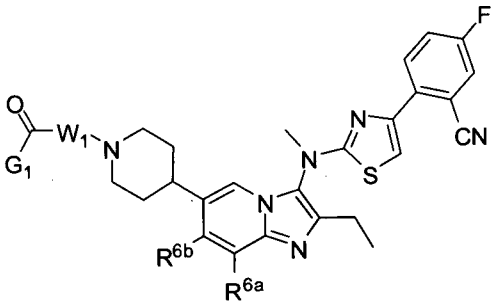
In one embodiment, a compound of the invention is according to Formula Va, Vb, Vc, or Vd:



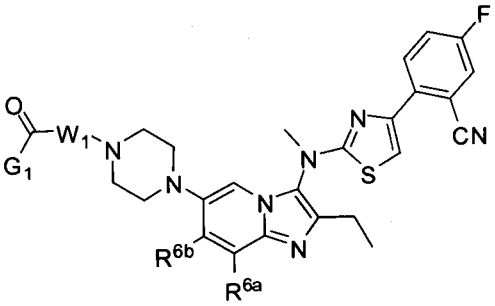
Va,



Vb,



Vc, or



Vd

wherein R^{6a}, R^{6b}, W_1, and G_1 are as described above.

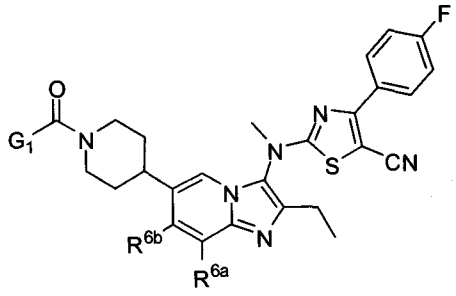
In one embodiment, a compound of the invention is according to Formula Va-Vd, wherein W_1 is C_{1-4} alkylene. In a particular embodiment, W_1 is $-CH_2-$, $-CH_2-CH_2-$, $-C(CH_3)H-$, $-CH_2-CH_2-CH_2-$ or $-CH_2-C(CH_3)H-$. In a more particular embodiment, W_1 is $-CH_2-$, or $-C(CH_3)H-$. In a most particular embodiment, W_1 is $-CH_2-$.

control of LPA levels, the spatial control of LPA production is ensured by the capacity of ATX to bind to cell surface molecules such as integrins and heparan sulphate proteoglycans (HSPs) to facilitate LPA release near to its cognate receptors. Several pieces of evidence support this hypothesis. First, the structural studies of ATX are supporting the fact that the ATX structure is compatible with such a process (Hausmann, J, 2011). In addition, several reports indicated how ATX is involved in lymphocyte homing through the interaction with cell surface integrins (Kanda, 2008). It was shown, for example, that ATX can be induced on high endothelial venules (HEVs) on sites of inflammation. This ATX expressed by HEVs acts on HEVs *in situ* to facilitate lymphocyte binding to endothelial cells (Nakasaki, et al., 2008). As such, ATX not only drives the formation of LPA but, through these cellular interactions, also ensures specificity in LPA signaling.

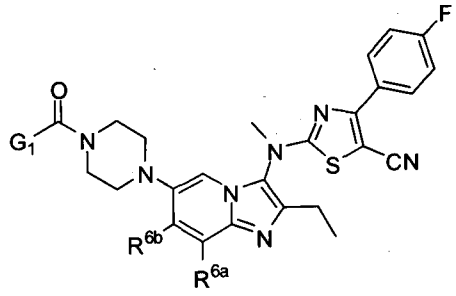
ATX is widely expressed, with highest mRNA levels detected in brain, lymph nodes, kidney, and testis. Originally discovered as 'autocrine motility factor' in melanoma cells, ATX has emerged as the key LPA-producing enzyme in plasma and tissues. Unfortunately, embryonic lethality has hampered studies of the importance of ATX in adult life. This embryonic lethality reflects the key role of LPA in various developmental processes, vasculogenesis in particular. Knock-out studies of the LPA receptors have been more informative in terms of unraveling the physiological role of LPA. LPA acts through at least six distinct (G protein)-coupled receptors (LPA1–6) found on the surface of different cell types, three of which belong to the edg receptor family and three to the non-edg receptor family. LPA interacts with specific G protein-coupled receptors (GPCRs), namely LPA1 (also known as EDG2), LPA2 (also known as EDG4), LPA3 (also known as EDG7), LPA4 (also known as GPR23/p2y9), LPA5 (also known as GPR92/93), LPA6 (also known as p2y5). LPA has also been described to interact with three other GPCRs (GPR87, p2y10, GPR35). In addition, a preference of LPA receptors for specific LPA species has been demonstrated (Bandoh, et al., 2000). As such, the specificity of the LPA activities is controlled by the expression pattern of the LPA receptors and their downstream signaling route.

The main part of the LPA responses are mediated through trimeric G-proteins and include but are not limited to mitogen-activated protein kinase (MAPK) activation, adenylyl cyclase (AC) inhibition/activation, phospholipase C (PLC) activation/Ca^{2+} mobilization, arachidonic acid release, Akt/PKB activation, and the activation of small GTPases, Rho, ROCK, Rac, and Ras. Other pathways that are affected by LPA receptor activation include cell division cycle 42/GTP-binding protein (Cdc42), proto-oncogene serine/threonine-protein kinase Raf (c-RAF), proto-oncogene tyrosine-protein kinase Src (c-src), extracellular signal-regulated kinase (ERK), focal adhesion kinase (FAK), guanine nucleotide exchange factor (GEF), glycogen synthase kinase 3b (GSK3b), c-jun amino-terminal kinase (JNK), MEK, myosin light chain II (MLC II), nuclear factor kB (NF-kB), N-methyl-D-aspartate (NMDA) receptor activation, phosphatidylinositol3-kinase (PI3K), protein kinase A (PKA), protein kinase C (PKC), and ras-

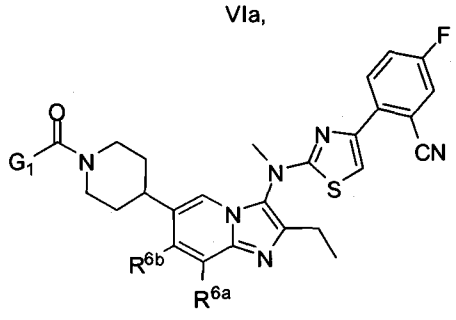
In one embodiment, a compound of the invention is according to Formula VIa, VIb, VIc, or VId:



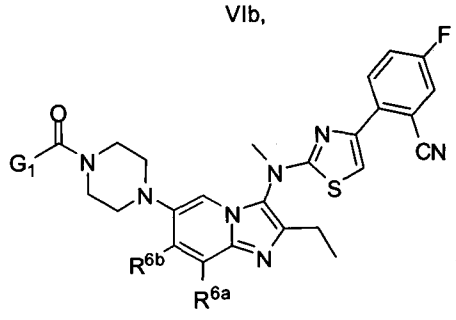
VIa,



VIb,



VIc, or



VId

wherein R^{6a}, R^{6b}, and G_1 are as described above.

In one embodiment, a compound of the invention is according to Formula Va-VId, wherein G_1 is 4-7 membered heterocycloalkyl containing one or more heteroatoms independently selected selected from O, N, and S. In a particular embodiment, G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl. In a more particular embodiment, G_1 is azetidinyl.

In one embodiment, a compound of the invention is according to Formula Va-VId, wherein G_1 is 4-7 membered heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S, which heterocycle is substituted with one or more independently selected R^9 groups. In a further embodiment, G_1 is 4-7 membered heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S, which heterocycle is substituted with one or two independently selected R^9 groups. In a particular embodiment, G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl, each of which is substituted with one or two independently selected R^9 groups. In a more particular embodiment, G_1 is azetidinyl substituted with one or two independently selected R^9 groups.

In one embodiment, a compound of the invention is according to Formula Va-VId, wherein G_1 is 4-7 membered heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S, each of which is substituted with one or two independently selected R^9 groups, and R^9 is oxo. In a further particular embodiment, G_1 is oxetanyl, azetidinyl,

tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl, each of which is substituted with one or two independently selected R^9 groups, and R^9 is oxo.

In one embodiment, a compound of the invention is according to Formula Va-VId, wherein G_1 is 4-7 membered heterocycloalkyl containing one or more heteroatoms independently selected selected from O, N, and S, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a further embodiment, G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a particular embodiment, R^{10} is selected from OH, F, Cl, and -CN. In a more particular embodiment, G_1 is azetidinyl substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a most particular embodiment, R^{10} is selected from OH, F, Cl, and -CN.

In one embodiment, a compound of the invention is according to Formula Va-VId, wherein G_1 is 4-7 membered heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a further embodiment, G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a particular embodiment, R^{10} is selected C_{1-4} alkyl. In a more particular embodiment, R^{10} is selected from $-CH_3$, $-CH_2-CH_3$, and $-CH(CH_3)_2$. In a most particular embodiment, R^{10} is selected from $-CH_3$, and $-CH_2-CH_3$.

In one embodiment, a compound of the invention is according to Formula Va-VId, wherein G_1 is 4-7 membered heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a further embodiment, G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a particular embodiment, R^{10} is C_{1-4} alkyl substituted with one or more independently selected OH, halo, phenyl. In a further embodiment, R^{10} is C_{1-4} alkyl substituted with one to three independently selected OH, halo, and phenyl. In a more particular embodiment, R^{10} is $-CH_3$, $-CH_2-CH_3$, and $-CH(CH_3)_2$, each of which is substituted with one to three independently selected OH, halo, and phenyl. In a most particular embodiment, R^{10} is $-CF_3$, $-CH_2-CH_2-OH$, and $-CH_2$-phenyl.

In one embodiment, a compound of the invention is according to Formula Va-VId, wherein G_1 is 4-7 membered heterocycloalkyl containing one or more heteroatoms independently

selected from O, N, and S, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a further embodiment, G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a particular embodiment, R^{10} is C_{1-4} alkoxy. In a more particular embodiment, R^{10} is selected from $-OCH_3$, $-OCH_2-CH_3$, and $-OC(CH_3)_3$. In a most particular embodiment, R^{10} is $-OCH_3$.

In one embodiment, a compound of the invention is according to Formula Va-VId, wherein G_1 is 4-7 membered heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a further embodiment, G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a particular embodiment, R^{10} is selected from $-SO_2CH_3$, $-C(=O)C_{1-4}$ alkoxy, and $-C(=O)C_{1-4}$ alkyl. In a more particular embodiment, R^{10} is selected from $-SO_2CH_3$, $-C(=O)OCH_3$, $-C(=O)OCH_2CH_3$, $-C(=O)OCH(CH_3)_2$, $-C(=O)CH_3$, $-C(=O)CH_2CH_3$, and $-C(=O)OCH(CH_3)_2$. In a most particular embodiment, R^{10} is selected from $-SO_2CH_3$, $-C(=O)OCH_3$, and $-C(=O)CH_3$.

In one embodiment, a compound of the invention is according to Formula Va-VId, wherein G_1 is 4-7 membered heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a further embodiment, G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl, each of which is substituted with one or two independently selected R^9 groups, R^9 is R^{10}, and R^{10} is as previously described. In a particular embodiment, R^{10} is $-NR^gC(=O)C_{1-4}$ alkyl, and R^g is as described previously. In a particular embodiment, R^{10} is $-NR^gC(=O)CH_3$, or $-NR^gC(=O)CH_2CH_3$, and R^g is as described previously. In a more particular embodiment, R^{10} is $-NR^gC(=O)CH_3$, or $-NR^gC(=O)CH_2CH_3$, and R^g is H, $-CH_3$, or $-CH_2CH_3$. In a most particular embodiment, R^{10} is $-NHC(=O)CH_3$, or $-NHC(=O)CH_2CH_3$.

In one embodiment, a compound of the invention is according to Formula I-VId, wherein R^{6a} is H, $-CH_3$ or halo, and R^{6b} is H. In a particular embodiment, R^{6a} is H, $-CH_3$, F, or Cl, and R^{6b} is H. In a more particular embodiment, R^{6a} is H, $-CH_3$, or F, and R^{6b} is H.

In one embodiment, a compound of the invention is according to Formula I-VId, wherein R^{6a} is H, and R^{6b} is H, $-CH_3$ or halo. In a particular embodiment, R^{6a} is H, and R^{6b} is H, $-CH_3$, F, or Cl. In a more particular embodiment, R^{6a} is H, and R^{6b} is H, $-CH_3$, or F.

In another embodiment, R^{6a} and R^{6b} are both H.

In one embodiment, a compound of the invention according to Formula I is selected from:

2-((2-ethyl-8-methyl-6-(piperazin-1-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile,

2-((2-ethyl-6-(4-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)piperazin-1-yl)-8-methylimidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile,

2-((2-ethyl-6-(4-(2-(3-hydroxy-3-methylazetidin-1-yl)-2-oxoethyl)piperazin-1-yl)-8-methylimidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile,

(R)-2-((2-ethyl-6-(4-(2-(3-hydroxypyrrolidin-1-yl)-2-oxoethyl)piperazin-1-yl)-8-methylimidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile,

(S)-2-((2-ethyl-6-(4-(2-(3-hydroxypyrrolidin-1-yl)-2-oxoethyl)piperazin-1-yl)-8-methylimidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile,

2-((2-ethyl-6-(4-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)-3,3-dimethylpiperazin-1-yl)-8-methylimidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)-8-methylimidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-1-(3-hydroxyazetidin-1-yl)ethanone,

(R)-2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)-8-methylimidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-1-(3-hydroxypyrrolidin-1-yl)ethanone,

(S)-2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)-8-methylimidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-1-(3-hydroxypyrrolidin-1-yl)ethanone,

2-((2-ethyl-6-(1-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)piperidin-4-yl)-8-methylimidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile,

2-(ethyl(2-ethyl-8-methyl-6-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridin-3-yl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile,

2-((2-ethyl-8-fluoro-6-(4-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)piperazin-1-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile,

2-(4-(3-((5-cyano-4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)-2-ethyl-8-fluoroimidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-N-methylacetamide,

2-(4-(2-ethyl-8-fluoro-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-1-(3-hydroxyazetidin-1-yl)ethanone,

(S)-2-(4-(2-ethyl-8-fluoro-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-1-(3-hydroxypyrrolidin-1-yl)ethanone,

(R)-2-(4-(2-ethyl-8-fluoro-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-1-(3-hydroxypyrrolidin-1-yl)ethanone,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)-7-methylimidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-1-(3-hydroxyazetidin-1-yl)ethanone,

2-[(2-Ethyl-7-fluoro-6-{4-[2-(3-hydroxy-azetidin-1-yl)-2-oxo-ethyl]-piperazin-1-yl}-imidazo[1,2-a]pyridin-3-yl)-methyl-amino]-4-(4-fluoro-phenyl)-thiazole-5-carbonitrile,

2-[4-(2-Ethyl-7-fluoro-3-{[4-(4-fluoro-phenyl)-thiazol-2-yl]-methyl-amino}-imidazo[1,2-a]pyridin-6-yl)-piperazin-1-yl]-1-(3-hydroxy-azetidin-1-yl)-ethanone,

2-[4-(2-Ethyl-7-fluoro-3-{[4-(4-fluoro-phenyl)-thiazol-2-yl]-methyl-amino}-imidazo[1,2-a]pyridin-6-yl)-piperazin-1-yl]-1-(3-hydroxy-pyrrolidin-1-yl)-ethanone,

2-[4-(2-Ethyl-7-fluoro-3-{[4-(4-fluoro-phenyl)-thiazol-2-yl]-methyl-amino}-imidazo[1,2-a]pyridin-6-yl)-piperazin-1-yl]-1-(3-hydroxy-pyrrolidin-1-yl)-ethanone,

2-(4-(3-((5-cyano-4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)-2-ethylimidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-N-methylacetamide,

tert-butyl 4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazine-1-carboxylate,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-1-(3-hydroxyazetidin-1-yl)ethanone,

(S)-2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-1-(3-hydroxypyrrolidin-1-yl)ethanone,

(R)-2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-1-(3-hydroxypyrrolidin-1-yl)ethanone,

N-(1-(2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)acetoyl)pyrrolidin-3-yl)acetamide,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-1-(3-fluoroazetidin-1-yl)ethanone,

1-(3,3-difluoroazetidin-1-yl)-2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)ethanone,

1-(azetidin-1-yl)-2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)ethanone,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-1-(pyrrolidin-1-yl)ethanone,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-1-morpholinoethanone,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)acetamide,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-1-(3-(hydroxymethyl)azetidin-1-yl)ethanone,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-N,N-dimethylacetamide,

ethyl 2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)acetate,

ethyl 2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)propanoate,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)acetonitrile,

N-(6-(4-((1-cyclopropyl-1H-tetrazol-5-yl)methyl)piperazin-1-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

N-(2-ethyl-6-(4-(oxazol-2-ylmethyl)piperazin-1-yl)imidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

N-(6-(4-((1,2,4-oxadiazol-3-yl)methyl)piperazin-1-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)acetic acid,

2-hydroxyethyl 4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazine-1-carboxylate,

tert-butyl 2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazine-1-carbonyl)pyrrolidine-1-carboxylate,

tert-butyl 3-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazine-1-carbonyl)pyrrolidine-1-carboxylate,

(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)(pyrrolidin-2-yl)methanone,

(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)(pyrrolidin-3-yl)methanone,

1-(3-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazine-1-carbonyl)pyrrolidin-1-yl)ethanone,

(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)(1-(methylsulfonyl)pyrrolidin-3-yl)methanone,

1-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-2-hydroxyethanone,

1-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)propan-1-one,

1-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-4-hydroxybutan-1-one,

4-(dimethylamino)-1-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)butan-1-one,

N-(2-ethyl-6-(4-(methylsulfonyl)piperazin-1-yl)imidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

N-(6-(4-(3-chloropropylsulfonyl)piperazin-1-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

N-(6-(4-(3-(dimethylamino)propylsulfonyl)piperazin-1-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

N-(2-ethyl-6-(4-(3-(pyrrolidin-1-yl)propylsulfonyl)piperazin-1-yl)imidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

3-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-ylsulfonyl)propan-1-ol,

methyl 2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-ylsulfonyl)acetate,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-ylsulfonyl)acetic acid,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-ylsulfonyl)acetamide,

tert-butyl 4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)-3-oxopiperazine-1-carboxylate,

tert-butyl 4-(3-((4-(4-chlorophenyl)thiazol-2-yl)(methyl)amino)-2-ethylimidazo[1,2-a]pyridin-6-yl)-3-oxopiperazine-1-carboxylate,

ethyl 2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)-3-oxopiperazin-1-yl)acetate,

1-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)-4-(methylsulfonyl)piperazin-2-one,

N-(2-ethyl-6-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

N-(6-(1-(chloromethylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

4-(4-chlorophenyl)-N-(2-ethyl-6-(1-(methylsulfonyl)-2,5-dihydro-1H-pyrrol-3-yl)imidazo[1,2-a]pyridin-3-yl)-N-methylthiazol-2-amine,

4-(4-chlorophenyl)-N-(2-ethyl-6-(1-(methylsulfonyl)-1,4,5,6-tetrahydropyridin-3-yl)imidazo[1,2-a]pyridin-3-yl)-N-methylthiazol-2-amine,

4-(4-tert-butylphenyl)-N-(2-ethyl-6-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridin-3-yl)-N-methylthiazol-2-amine,

N-(2-ethyl-6-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridin-3-yl)-4-(4-methoxyphenyl)-N-methylthiazol-2-amine,

N-(2-ethyl-6-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridin-3-yl)-N-methyl-4-(4-(trifluoromethoxy)phenyl)thiazol-2-amine,

4-(3,4-difluorophenyl)-N-(2-ethyl-6-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridin-3-yl)-N-methylthiazol-2-amine,

3-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)-5,6-dihydropyridin-1(2H)-ylsulfonyl)propyl acetate,

3-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)-5,6-dihydropyridin-1(2H)-ylsulfonyl)propan-1-ol,

4-(2-ethyl-3-((4-(4-chlorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)-3,6-dihydro-2H-thiopyran 1,1-dioxide,

N-(2-ethyl-6-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridin-3-yl)-5-fluoro-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

tert-butyl 4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)-3-hydroxypiperidine-1-carboxylate,

4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)-1-(methylsulfonyl)piperidin-3-ol,

N-(2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

4-(4-tert-butylphenyl)-N-(2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)-N-methylthiazol-2-amine,

N-(2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)-4-(4-methoxyphenyl)-N-methylthiazol-2-amine,

4-(3,4-difluorophenyl)-N-(2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)-N-methylthiazol-2-amine,

N-(2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)-N-methyl-4-(4-(trifluoromethyl)phenyl)thiazol-2-amine,

N-(2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)-N-methyl-4-(4-(trifluoromethoxy)phenyl)thiazol-2-amine,

N-(6-(1-(3-chloropropylsulfonyl)piperidin-4-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

N-(6-(1-(3-(dimethylamino)propylsulfonyl)piperidin-4-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

N-(2-ethyl-6-(1-(3-morpholinopropylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

N-(2-ethyl-6-(1-(3-(pyrrolidin-1-yl)propylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

N-(6-(1-(3-aminopropylsulfonyl)piperidin-4-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

N-(2-ethyl-6-(1-(2-morpholinoethylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidine-1-sulfonamide,

3-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-ylsulfonyl)propyl acetate,

3-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-ylsulfonyl)propan-1-ol,

3-(4-(2-ethyl-3-((5-fluoro-4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-ylsulfonyl)propan-1-ol,

2-(2-((2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)thiazol-4-yl)-5-fluorobenzonitrile,

2-(2-((2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-5-methylthiazol-4-yl)-5-fluorobenzonitrile,

N-(2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)-4-(4-fluoro-2-methylphenyl)-N-methylthiazol-2-amine,

4-(2-chloro-4-fluorophenyl)-N-(2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)-N-methylthiazol-2-amine,

4-(2,4-difluorophenyl)-N-(2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)-N-methylthiazol-2-amine,

N-(2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N,5-dimethylthiazol-2-amine,

4-(4-fluorophenyl)-N-(2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)-N-(d3-methyl)thiazol-2-amine,

4-(4-fluorophenyl)-N-(2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)-N-(d3-methyl)-(d-thiazol-2)-amine,

methyl 2-((2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carboxylate,

1-(2-((2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazol-5-yl)ethanone,

N-(2-(2-((2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)thiazol-4-yl)-5-fluorophenyl)acetamide,

(2-(2-((2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)thiazol-4-yl)-5-fluorophenyl)methanol,

ethyl 2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)-5,6-dihydropyridin-1(2H)-yl)acetate,

ethyl 2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)acetate,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-1-(3-hydroxyazetidin-1-yl)ethanone,

(R)-2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-1-(3-hydroxypyrrolidin-1-yl)ethanone,

(S)-2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-1-(3-hydroxypyrrolidin-1-yl)ethanone,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-1-(3-(hydroxymethyl)azetidin-1-yl)ethanone,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-N,N-dimethylacetamide,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-1-(pyrrolidin-1-yl)ethanone,

(S)-1-(2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)acetoyl)pyrrolidine-3-carbonitrile,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-1-(3-(hydroxymethyl)pyrrolidin-1-yl)ethanone,

4-((4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)methyl)-1,3-dioxolan-2-one,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-N-(2-hydroxyethyl)-N-methylacetamide,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-N-methoxy-N-methylacetamide,

N-(cyanomethyl)-2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-N-methylacetamide,

5-((4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)methyl)oxazolidin-2-one,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-N-(3-hydroxypropyl)acetamide,

related C3 botulinum toxin substrate 1 (RAC1). The actual pathway is influenced by cell type, expression level of a receptor or signaling protein, receptor usage, and LPA concentration (Tania, Khan, Zhang, Li, & Song, 2010). LPA has a broad range of physiological actions and various cellular effects (for example blood pressure regulation, platelet activation, smooth muscle contraction, cell growth, cell rounding, neurite retraction, actin stress fiber formation and cell migration).In addition, a preference of LPA receptors for specific LPA species has been demonstrated (Bandoh, et al., 2000). The knock-out studies for these receptors indicated a role in bone development (Gennero, et al., 2011), and neurogenesis (Matas-Rico, et al., 2008), embryo implantation (Ye, et al., 2005) and the formation of blood and lymphatic vessels (Sumida, et al., 2010).

With regard to pathophysiology, a role for LPA and LPA receptors has been claimed in various patho-physiological conditions such as proliferative diseases, neuropathic pain, inflammation, autoimmune diseases, fibrosis, lymphocyte tracking in lymph nodes, obesity, diabetes, or embryonic blood vessel formation.

The role of LPA in lung fibrosis has been well described in literature and also an involvement in asthma has been claimed. The present inventors however are the first to report a link to chronic obstructive pulmonary disease (COPD).

Several lines of evidence suggest a role for ATX in the control of lung function in disease through effects on lung epithelial cells, fibroblasts and smooth muscle cells. In general, inflammatory conditions in the lung are often described as associated with increased ATX and LPA levels. Instillation of LPS in mice, for example, induces increased ATX and LPA levels in the broncho-alveolar lavage (BAL) fluid (Zhao, et al., 2011). Also in humans, a segmental LPS challenge led to increased LPA levels (Georas, et al., 2007). Overall, the role of LPA in activating lung epithelial cells, the first line of defense to inhaled noxious stimuli, towards increased cytokine and chemokine production and migration have been extensively described (Zhao & Natarajan, 2013). Exogenous LPA promotes inflammatory responses by regulating the expression of chemokines, cytokines, and cytokine receptors in lung epithelial cells. In addition to the modulation of inflammatory responses, LPA regulates cytoskeleton rearrangement and confers protection against lung injury by enhancing lung epithelial cell barrier integrity and remodeling.

In the asthmatic individual, the release of normal repair mediators, including LPA, is exaggerated or the actions of the repair mediators are inappropriately prolonged leading to inappropriate airway remodeling. Major structural features of the remodeled airway observed in asthma include a thickened lamina reticularis (the basement membrane-like structure just beneath the airway epithelial cells), increased numbers and activation of myofibroblasts, thickening of the smooth muscle layer, increased numbers of mucus glands and mucus secretions, and alterations in the connective tissue and capillary bed throughout the airway wall. ATX and/ or LPA may

1-(3,3-difluoroazetidin-1-yl)-2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)ethanone,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)acetamide,

1-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-2-(pyrrolidin-1-yl)ethanone,

1-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-2-(methylamino)ethanone,

1-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-2-(3-hydroxyazetidin-1-yl)ethanone,

2-(dimethylamino)-1-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)ethanone,

3-(dimethylamino)-1-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)propan-1-one,

2-(3,3-difluoroazetidin-1-yl)-1-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)ethanone,

1-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-3-(methylamino)propan-1-one,

1-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-2-(3-fluoroazetidin-1-yl)ethanone,

1-(3-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)azetidin-1-yl)ethanone,

5-bromo-N-(2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

2-((2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile,

2-((2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carboxamide,

2-((2-ethyl-6-(4-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)piperazin-1-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile,

2-((2-ethyl-6-(4-(2-(3-(hydroxymethyl)azetidin-1-yl)-2-oxoethyl)piperazin-1-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile,

2-(4-(3-((5-cyano-4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)-2-ethylimidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-N,N-dimethylacetamide,

2-((2-ethyl-6-(1-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile,

(R)-2-((2-ethyl-6-(1-(2-(3-hydroxypyrrolidin-1-yl)-2-oxoethyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile,

(S)-2-((2-ethyl-6-(1-(2-(3-hydroxypyrrolidin-1-yl)-2-oxoethyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile,

2-((2-ethyl-6-(1-(2-(3-(hydroxymethyl)azetidin-1-yl)-2-oxoethyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile,

2-(4-(3-((5-cyano-4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)-2-ethylimidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-N,N-dimethylacetamide,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)-5-(hydroxymethyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-1-(3-(hydroxymethyl)azetidin-1-yl)ethanone,

(2-((2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazol-5-yl)methanol,

(2-((2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-(trifluoromethoxy)phenyl)thiazol-5-yl)methanol,

(2-((6-(1-(3-(dimethylamino)propylsulfonyl)piperidin-4-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazol-5-yl),

(2-((2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-(trifluoromethyl)phenyl)thiazol-5-yl)methanol,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)-5-(hydroxymethyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-1-(pyrrolidin-1-yl)ethanone,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)-5-(hydroxymethyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-1-(3-(hydroxymethyl)azetidin-1-yl)ethanone,

2-(dimethylamino)-1-(4-(2-ethyl-3-((4-(4-fluorophenyl)-5-(hydroxymethyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)ethanone,

1-(4-(2-ethyl-3-((4-(4-fluorophenyl)-5-(hydroxymethyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)propan-1-one,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)-5-(hydroxymethyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-N,N-dimethylacetamide,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)-5-(hydroxymethyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-1-(3-hydroxyazetidin-1-yl)ethanone,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)-5-(hydroxymethyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-N,N-dimethylacetamide,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)-5-(2,2,2-trifluoroacetoyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-N,N-dimethylacetamide,

1-(2-((2-ethyl-6-(1-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazol-5-yl)-2,2,2-trifluoroethanone,

1-(2-((2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazol-5-yl)-2,2,2-trifluoroethanone,

2-(2-((2-ethyl-6-(piperazin-1-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-5-methylthiazol-4-yl)-5-fluorobenzonitrile,

2-(2-((2-ethyl-6-(4-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)piperazin-1-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-5-methylthiazol-4-yl)-5-fluorobenzonitrile,

2-(4-(3-((4-(2-cyano-4-fluorophenyl)-5-methylthiazol-2-yl)(methyl)amino)-2-ethylimidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-N-methylacetamide,

2-(2-((2-ethyl-6-(4-(2-(3-fluoroazetidin-1-yl)-2-oxoethyl)piperazin-1-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)thiazol-4-yl)-5-fluorobenzonitrile,

2-(2-((6-(4-(2-(3,3-difluoroazetidin-1-yl)-2-oxoethyl)piperazin-1-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)(methyl)amino)thiazol-4-yl)-5-fluorobenzonitrile,

2-(2-((2-ethyl-6-(4-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)piperazin-1-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)thiazol-4-yl)-5-fluorobenzonitrile,

2-(2-((6-(4-(2-(azetidin-1-yl)-2-oxoethyl)piperazin-1-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)(methyl)amino)thiazol-4-yl)-5-fluorobenzonitrile,

2-(4-(3-((4-(2-cyano-4-fluorophenyl)thiazol-2-yl)(methyl)amino)-2-ethylimidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-N,N-dimethylacetamide,

2-(4-(3-((4-(2-cyano-4-fluorophenyl)thiazol-2-yl)(methyl)amino)-2-ethylimidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-N-methylacetamide,

2-(2-((2-ethyl-6-(1-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)thiazol-4-yl)-5-fluorobenzonitrile,

2-(4-(3-((4-(2-cyano-4-fluorophenyl)thiazol-2-yl)(methyl)amino)-2-ethylimidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-N,N-dimethylacetamide,

2-(2-((2-ethyl-6-(1-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-5-methylthiazol-4-yl)-5-fluorobenzonitrile,

2-(5-((2-ethyl-6-(1-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-1,2,4-thiadiazol-3-yl)-5-fluorobenzonitrile,

2-(4-(2-(2-cyanoethyl)-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-N,N-dimethylacetamide,

3-(3-((4-(4-fluorophenyl)-5-(hydroxymethyl)thiazol-2-yl)(methyl)amino)-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-2-yl)propanenitrile,

3-(6-(1-(2-(dimethylamino)-2-oxoethyl)piperidin-4-yl)-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-2-yl)propanamide,

N-(6-(3-aminoazetidin-1-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

2-(1-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)azetidin-3-ylamino)-1-(3-hydroxyazetidin-1-yl)ethanone,

N-(1-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)azetidin-3-yl)-2-(3-hydroxyazetidin-1-yl)acetamide,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)ethanol,

N-(2-ethyl-6-morpholinoimidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)-thiomorpholine 1,1-dioxide,

1-(3-((4-(4-chlorophenyl)thiazol-2-yl)(methyl)amino)-2-ethylimidazo[1,2-a]pyridin-6-yl)imidazolidin-2-one,

ethyl 2-(3-(3-((4-(4-chlorophenyl)thiazol-2-yl)(methyl)amino)-2-ethylimidazo[1,2-a]pyridin-6-yl)-2-oxoimidazolidin-1-yl)acetate,

4-(4-chlorophenyl)-N-methyl-N-(6-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)-2-(2,2,2-trifluoroethyl)imidazo[1,2-a]pyridin-3-yl)thiazol-2-amine,

2-(2-((2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazol-5-yl)acetonitrile,

2-ethyl-N-(4-(4-fluorophenyl)pyrimidin-2-yl)-N-methyl-6-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridin-3-amine,

3-(4-chlorophenyl)-N-(2-ethyl-6-(4-(methylsulfonyl)piperazin-1-yl)imidazo[1,2-a]pyridin-3-yl)-N-methyl-1,2,4-thiadiazol-5-amine,

N-(2-ethyl-6-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridin-3-yl)-3-(4-fluorophenyl)-N-methyl-1,2,4-oxadiazol-5-amine,

2-(4-(2-ethyl-3-((3-(4-fluorophenyl)-1,2,4-thiadiazol-5-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)-5,6-dihydropyridin-1(2H)-yl)-N,N-dimethylacetamide,

2-(4-(2-ethyl-3-((3-(4-fluorophenyl)-1,2,4-thiadiazol-5-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-N,N-dimethylacetamide,

N-(6-(4-((1H-imidazol-5-yl)methyl)piperazin-1-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

N-(2-ethyl-6-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridin-3-yl)-N-methyl-4-(4-(trifluoromethyl)phenyl)thiazol-2-amine,

N-cyclopropyl-2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)acetamide,

5-((4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)methyl)-3-methyloxazolidin-2-one,

(R)-5-((4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)methyl)oxazolidin-2-one,

(S)-5-((4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)methyl)oxazolidin-2-one,

4-((4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)methyl)oxazolidin-2-one,

N-(2-ethyl-6-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridin-3-yl)-3-(4-fluorophenyl)-N-methyl-1,2,4-thiadiazol-5-amine,

1-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)propane-1,2-dione,

5-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazine-1-carbonyl)pyrrolidin-2-one,

(1-aminocyclopropyl)(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)methanone,

(S)-1-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-2-hydroxypropan-1-one,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-2-oxoacetamide,

1-benzyl-4-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazine-1-carbonyl)pyrrolidin-2-one,

3-(3-((4-(4-chlorophenyl)thiazol-2-yl)(methyl)amino)-2-ethylimidazo[1,2-a]pyridin-6-yl)oxazolidin-2-one,

2-(2-ethyl-3-((4-(4-chlorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)-1-[1,2]thiazinane-1,1-dioxide,

4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)-N-(thiophen-2-yl)-5,6-dihydropyridine-1(2H)-carboxamide,

4-(4-chlorophenyl)-N-(2-ethyl-6-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridin-3-yl)-N-methylthiazol-2-amine,

4-(4-chlorophenyl)-N-(2-ethyl-6-(1-(trifluoromethylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridin-3-yl)-N-methylthiazol-2-amine,

1-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-4-ol,

2-(4-(3-((4-(4-chlorophenyl)thiazol-2-yl)(methyl)amino)-2-ethylimidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)ethanol,

4-(2-ethyl-3-((4-(4-chlorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)-thiomorpholine-1,1-dioxide,

tert-butyl 4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)-5,6-dihydropyridine-1(2H)-carboxylate,

1-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)propan-1-one,

N-(2-ethyl-6-(piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

N-(6-(1-benzylpiperidin-4-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

N-(2-ethyl-6-(1-isopropylpiperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

tert-butyl 4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidine-1-carboxylate,

N-(6-(3,6-dihydro-2H-pyran-4-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

4-(4-chlorophenyl)-N-(6-(3,6-dihydro-2H-pyran-4-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)-N-methylthiazol-2-amine,

(2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-4,5-dihydrooxazol-5-yl)methanol,

2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperidin-1-yl)-1-(3-hydroxypyrrolidin-1-yl)ethanone,

2-(2-((2-ethyl-6-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)(methyl)amino)thiazol-4-yl)-5-fluorophenol,

tert-butyl 4-(3-((3-(4-chlorophenyl)-1,2,4-thiadiazol-5-yl)(methyl)amino)-2-ethylimidazo[1,2-a]pyridin-6-yl)piperazine-1-carboxylate,

N-(6-(4-((1H-imidazol-2-yl)methyl)piperazin-1-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

cyclopropyl(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)methanone,

ethyl 2-(4-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)piperazin-1-yl)-2-oxoacetate,

[6-(1,1-Dioxo-isothiazolidin-2-yl)-2-ethyl-imidazo[1,2-a]pyridin-3-yl]-[4-(4-fluoro-phenyl)-thiazol-2-yl]-methyl-amine,

tert-butyl 4-(3-((4-(4-chlorophenyl)thiazol-2-yl)(methyl)amino)-2-ethylimidazo[1,2-a]pyridin-6-yl)-5,6-dihydropyridine-1(2H)-carboxylate,

4-(4-chlorophenyl)-N-(6-(3,6-dihydro-2H-thiopyran-4-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)-N-methylthiazol-2-amine,

N-(6-(4,4-difluoropiperidin-1-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

N-(6-(1-(3-chloropropylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

tert-butyl 4-(3-((4-(4-chlorophenyl)thiazol-2-yl)(methyl)amino)-2-ethylimidazo[1,2-a]pyridin-6-yl)piperazine-1-carboxylate,

N-(6-(1-(cyclohexylmethyl)piperidin-4-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

N-(2-ethyl-6-(5-methyl-4,5-dihydrooxazol-2-yl)imidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

N-(2-ethyl-6-(4-methyl-4,5-dihydrooxazol-2-yl)imidazo[1,2-a]pyridin-3-yl)-4-(4-fluorophenyl)-N-methylthiazol-2-amine,

2-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)-4,5-dihydrooxazole-4-carboxylic acid,

(2-(2-ethyl-3-((4-(4-fluorophenyl)thiazol-2-yl)(methyl)amino)imidazo[1,2-a]pyridin-6-yl)-4,5-dihydrooxazol-4-yl)methanol, and

4-(4-chlorophenyl)-N-(6-(4,5-dihydrooxazol-2-yl)-2-ethylimidazo[1,2-a]pyridin-3-yl)-N-methylthiazol-2-amine.

In one embodiment, a compound of the invention according to Formula I is 2-((2-ethyl-6-(4-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)piperazin-1-yl)-8-methylimidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile.

In another embodiment, a compound of the invention according to Formula I is not 2-((2-ethyl-6-(4-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)piperazin-1-yl)-8-methylimidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile.

In one embodiment a compound of the invention is not an isotopic variant.

In one aspect a compound of the invention according to any one of the embodiments herein described is present as the free base.

In one aspect a compound of the invention according to any one of the embodiments herein described is a pharmaceutically acceptable salt.

In one aspect a compound of the invention according to any one of the embodiments herein described is a solvate of the compound.

In one aspect a compound of the invention according to any one of the embodiments herein described is a solvate of a pharmaceutically acceptable salt of a compound.

While specified groups for each embodiment have generally been listed above separately, a compound of the invention includes one in which several or each embodiment in the above Formula, as well as other formulae presented herein, is selected from one or more of

particular members or groups designated respectively, for each variable. Therefore, this invention is intended to include all combinations of such embodiments within its scope.

While specified groups for each embodiment have generally been listed above separately, a compound of the invention may be one for which one or more variables (for example, R groups) is selected from one or more embodiments according to any of the Formula(e) listed above. Therefore, the present invention is intended to include all combinations of variables from any of the disclosed embodiments within its scope.

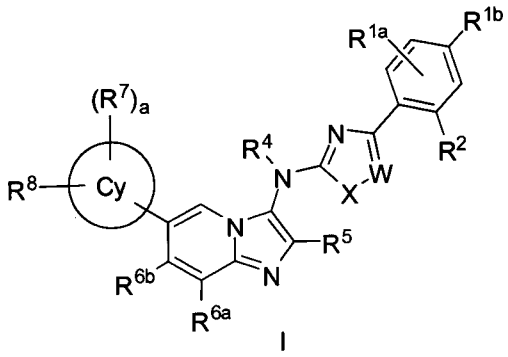
Alternatively, the exclusion of one or more of the specified variables from a group or an embodiment, or combinations thereof is also contemplated by the present invention.

In certain aspects, the present invention provides prodrugs and derivatives of the compounds according to the formulae above. Prodrugs are derivatives of the compounds of the invention, which have metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention, which are pharmaceutically active, *in vivo*. Such examples include, but are not limited to, choline ester derivatives and the like, N-alkylmorpholine esters and the like.

Other derivatives of the compounds of this invention have activity in both their acid and acid derivative forms, but the acid sensitive form often offers advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (Bundgard, H, 1985). Prodrugs include acid derivatives well know to practitioners of the art, such as, for example, esters prepared by reaction of the parent acid with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a substituted or unsubstituted amine, or acid anhydrides, or mixed anhydrides. Simple aliphatic or aromatic esters, amides and anhydrides derived from acidic groups pendant on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy)alkyl esters or ((alkoxycarbonyl)oxy)alkylesters. Particularly useful are the C_1 to C_8 alkyl, C_2-C_8 alkenyl, aryl, C_7-C_{12} substituted aryl, and C_7-C_{12} arylalkyl esters of the compounds of the invention.

CLAUSES

1) A compound according to Formula I:



I

wherein

R^{1a} is H, halo or C_{1-4} alkyl;

R^{1b} is:

- halo,
- C_{1-4} alkyl (which alkyl is optionally substituted with one or more independently selected halo), or
- C_{1-4} alkoxy (which alkoxy is optionally substituted with one or more independently selected halo);

X is –S-, -O-, –N=CH-, –CH=N- or –CH=CH-;

W is N, or CR^3

when W is N, R^2 is:

- H,
- -CN,
- halo,
- C_{1-4} alkyl (which alkyl is optionally substituted with one or more independently selected OH, or CN)
- $-C(=O)CH_3$,
- $-C(=O)CF_3$,
- $-C(=O)OCH_3$,
- $-C(=O)NH_2$,
- $-NHC(=O)CH_3$, or

when W is CR^3, one of R^2 or R^3 is:

- H,
- -CN,
- halo,
- C_{1-4} alkyl (which alkyl is optionally substituted with one or more independently selected OH, or CN)
- $-C(=O)CH_3$,
- $-C(=O)CF_3$,

- $-C(=O)OCH_3$,
- $-C(=O)NH_2$,
- $-NHC(=O)CH_3$,

and the other is H, or C_{1-4} alkyl;

R^4 is C_{1-4} alkyl;

R^5 is C_{1-4} alkyl optionally substituted with one or more independently selected CN, OH, halo, or $-C(=O)NH_2$;

one of R^{6a} or R^{6b} is selected from H, $-CH_3$, and halo, and the other is H;

Cy is:

- C_{4-10} cycloalkyl,
- 4-10 membered mono or bicyclic heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S, or
- 4-7 membered heterocycloalkenyl containing 1 double bond, containing one or more heteroatoms independently selected from O, N, and S;

each R^7 is independently selected from:

- OH,
- oxo,
- halo, and
- C_{1-4} alkyl (which alkyl is optionally substituted with one or more independently selected OH, or C_{1-4} alkoxy);

the subscript a is 0, 1 or 2;

R^8 is $-(L_1\text{-}W_1)_m\text{-}L_2\text{-}G_1$,

wherein

- L_1 is absent , or is -O-, -C(=O)-, $-NR^i$, $-NR^hC(=O)$-, or $-SO_2$-;
- W_1 is C_{1-4} alkylene;
- the subscript m is 0, or 1;
- L_2 is absent , or is -O-, -C(=O)-, -C(=O)O-, -OC(=O) -, -C(=O)-C(=O)-, -C(=O)-C(=O)NR^a-, $-NR^b$-, -C(=O)NR^c-, $-NR^dC(=O)$-, $-NR^jC(=O)O$-, $-SO_2$-, $-SO_2NR^e$- or $-NR^fSO_2$-;
- G_1 is
  - H,
  - -CN,
  - C_{1-4} alkyl (which alkyl is optionally substituted with one or more independently selected –CN, OH, halo or phenyl),
  - C_{3-7} cycloalkyl (which cycloalkyl is optionally substituted with $–NH_2$),
  - 5-6 membered heterocycloalkenyl containing 1 double bond containing one or more heteroatoms independently selected from O, N, and S (which

contribute to these structural changes in the airway, for example ATX and/ or LPA are involved in acute airway hyperresponsiveness in asthma. The lumen of the remodeled asthmatic airway is narrower due to the thickening of the airway wall, thus decreasing airflow. Additionally, LPA contributes to the long-term structural remodeling and the acute hyperresponsiveness of the asthmatic airway, for example LPA contributes to the hyper-responsiveness that is a primary feature of acute exacerbations of asthma. Reports describing the role of LPA in asthma generated different conclusions, ranging from a protective role (Zhao, et al., 2009) to a negative role (Emo, et al., 2012). The testing of autotaxin inhibitors in models for airway diseases as described herein allows for the clarification of the potential of this enzyme as a drug target.

Fibroblast proliferation and contraction and extracellular matrix secretion stimulated by LPA contributes to the fibroproliferative features of other airway diseases, such as the peribronchiolar fibrosis present in chronic bronchitis, and interstitial lung diseases and severe asthma. LPA plays a role in the fibrotic interstitial lung diseases and obliterative bronchiolitis, where both collagen and myofibroblasts are increased. Studies related to IPF (idiopathic pulmonary fibrosis) indicated an increase in LPA levels in the BAL fluid of patients (Tager, et al., 2008). Further LPA1 knock-out and inhibitor studies revealed a key role for LPA in fibrotic processes in lung and were complemented by studies using cell-specific knock-out mice lacking ATX in bronchial epithelial cells and macrophages. These mice were shown to be less sensitive to models of lung fibrosis (Oikonomou, et al., 2012). A role for LPA in other fibrotic diseases (kidney and skin) was based on similar types of observations (Pradère, et al., 2007), (Castelino, et al., 2011). The role of LPA in lung remodeling relates to the effects of LPA on both lung fibroblasts (through LPA1) and epithelial cells (through LPA2) (Xu, et al., 2009) have demonstrated that LPA2 plays a key role in the activation of TGFβ in epithelial cells under fibrotic conditions. The role of LPA in remodeling and fibrosis is relevant to COPD, IPF and asthma, diseases in which lung remodeling as a long term outcome will limit lung function. Finally, of interest towards lung diseases, in mice, ATX is one of the three main QTLs that appear to be associated with differences in lung function (Ganguly, et al., 2007).

One prominent area of research interest is the role of ATX–LPA signaling in cancer (Braddock, 2010). Although cancer-specific mutations in ATX have not been identified so far, overexpression of ATX or individual LPA receptors in xenografted and transgenic mice promotes tumour formation, angiogenesis and metastasis. Conversely, ATX knockdown in mammary carcinoma cells reduces their metastatic spread to bone. Several human cancers show elevated ATX and/or aberrant LPA receptor expression patterns, as revealed by microarray analyses. Autotaxin is viewed as a pro-metastatic enzyme. It has initially been isolated from the conditioned medium of human melanoma cells that stimulates a myriad of biological activities, including angiogenesis and the promotion of cell growth, migration, survival, and differentiation through the production of LPA (Lin M. E., 2010). LPA contributes to tumorigenesis by

heterocycloalkenyl is optionally substituted with one or more independently selected R^9 groups),

- 4-10 membered mono, bi or spirocyclic heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S (which heterocycloalkyl is optionally substituted with one or more independently selected R^9 groups), or
- 5-6 membered heteroaryl containing one or more heteroatoms independently selected from O, N, and S (which heteroaryl is optionally substituted with one or more independently selected R^{10} groups),

each R^9 is oxo, or R^{10};

each R^{10} is:

- -OH,
- halo,
- -CN,
- C_{1-4} alkyl (which alkyl is optionally substituted with one or more independently selected OH, halo, or phenyl),
- C_{1-4} alkoxy,
- C_{3-7} cycloalkyl,
- phenyl,
- $-SO_2CH_3$,
- $-C(=O)C_{1-4}$ alkoxy,
- $-C(=O)C_{1-4}$ alkyl, or
- $-NR^gC(=O)C_{1-4}$ alkyl; and

each R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, R^i, and R^j is independently selected from H and C_{1-4} alkyl;

or a pharmaceutically acceptable salt, or a solvate, or a pharmaceutically acceptable salt of a solvate thereof; or a biologically active metabolite thereof.

2) A compound or pharmaceutically acceptable salt thereof, according to clause 1, wherein R^{1a} is F, Cl, $-CH_3$ or $-C_2H_5$.

3) A compound or pharmaceutically acceptable salt thereof, according to clause 1, wherein R^{1a} is H.

4) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-3, wherein R^{1b} is F, Cl, $-CH_3$, $-C_2H_5$, $-CF_3$, $-OCH_3$, or $-OCF_3$.

5) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-3, wherein R^{1b} is F.

6) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-5, wherein X is –S- or -O-.

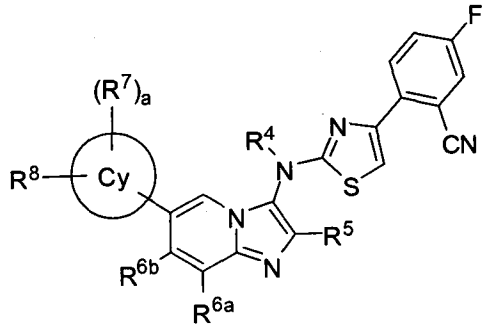
7) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-5, wherein X is –S-.

8) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-5, wherein W is N.

9) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-5, wherein W is CR^3.

10) A compound or pharmaceutically acceptable salt thereof, according to clause 9, wherein R^3 is H, CN, F, or Cl.

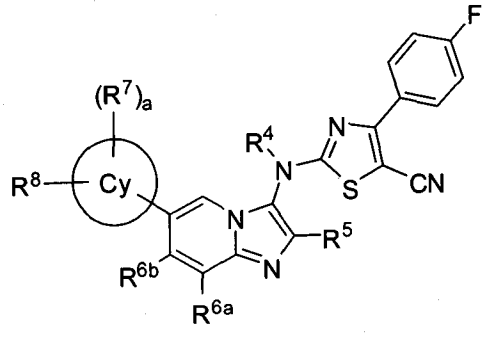
11) A compound or pharmaceutically acceptable salt thereof, according to clause 1, wherein the compound is according to Formula II:



II

wherein R^4, R^5, R^{6a}, R^{6b}, R^7, R^8 and the subscript a are according to clause 1.

12) A compound or pharmaceutically acceptable salt thereof, according to clause 1, wherein the compound is according to Formula III:



III

wherein R^4, R^5, R^{6a}, R^{6b}, R^7, R^8 and the subscript a are according to clause 1.

13) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-12, wherein R^4 is $-CH_3$, or $-C_2H_5$.

14) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-12, wherein R^4 is $-CH_3$.

15) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-14, wherein R^5 is C_{1-4} alkyl.

16) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-14, wherein R^5 is $-CH_3$, or $-C_2H_5$.

17) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-14, wherein R^5 is C_{1-4} alkyl substituted with one CN, OH, halo, or $-C(=O)NH_2$.

18) A compound or pharmaceutically acceptable salt thereof, according to clause 17, wherein R^5 is $-CH_3$, $-C_2H_5$ or $-C_3H_7$ substituted with one CN, OH, halo, or $-C(=O)NH_2$.

19) A compound or pharmaceutically acceptable salt thereof, according to clause 17, wherein R^5 is $-CH_2-CH_2-CN$, $-CH_2-CH_2-OH$, $-CH_2-CF_3$, or $-CH_2-CH_2-C(=O)NH_2$.

20) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-19, wherein Cy is C_{4-10} cycloalkyl.

21) A compound or pharmaceutically acceptable salt thereof, according to clause 20, wherein Cy is cyclobutyl, cyclopentyl or cyclohexyl.

22) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-19, wherein Cy is 4-10 membered mono or bicyclic heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S.

23) A compound or pharmaceutically acceptable salt thereof, according to clause 22, wherein Cy is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl.

24) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-19, wherein Cy is 4-7 membered heterocycloalkenyl containing 1 double bond, containing one or more heteroatoms independently selected from O, N, and S.

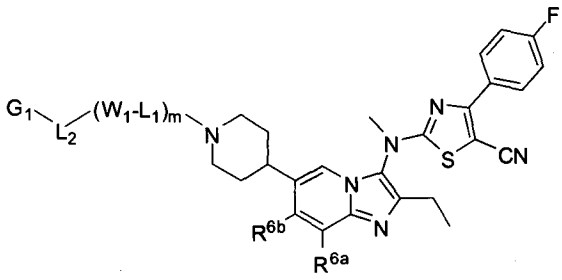
25) A compound or pharmaceutically acceptable salt thereof, according to clause 24, wherein Cy is dihydrofuranyl, dihydrothiazolyl, dihydrooxazolyl, dihydropyranyl, tetrahydropyridinyl, or dihydrothiopyranyl.

26) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-25, wherein the subscript a is 1 or 2, and R^7 is OH, oxo, F, Cl, or $-CH_3$.

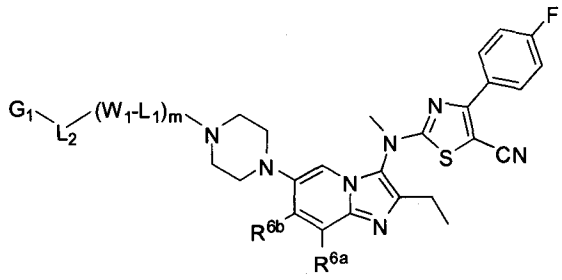
27) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-25, wherein the subscript a is 0.

28) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-27, wherein R^8 is $-(L_1-W_1)_m-L_2-G_1$.

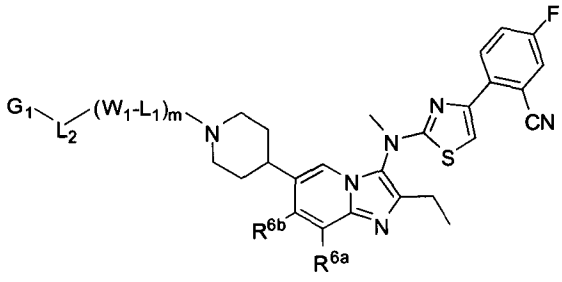
29) A compound according to Formula I, II, or III, wherein the compound is according to Formula IVa, IVb, IVc or IVd:



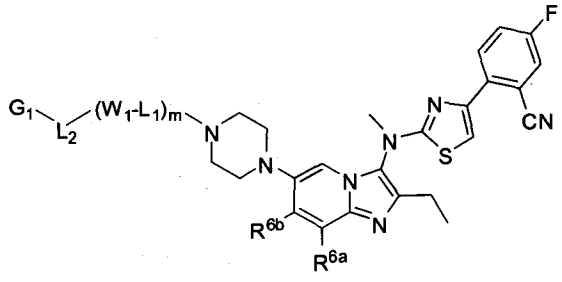
IVa,



IVb,



IVc, or



IVd

wherein R^{6a}, R^{6b}, L_1, W_1, L_2, G_1 and the subscript m are according to clause 1.

30) A compound or pharmaceutically acceptable salt thereof, according to clause 28, or 29, wherein the subscript m is 1, L_1 is absent.

31) A compound or pharmaceutically acceptable salt thereof, according to clause 28, or 29, wherein the subscript m is 1, L_1 is -C(=O)-, or -SO_2-.

32) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-31, wherein the subscript m is 1, and W_1 is C_{1-4} alkylene.

33) A compound or pharmaceutically acceptable salt thereof, according to clause 32, wherein the subscript m is 1, L_1 is as defined above and W_1 is -CH_2-, -CH_2-CH_2-, -$C(CH_3)H$-, -CH_2-CH_2-CH_2- or -CH_2-$C(CH_3)H$-.

34) A compound or pharmaceutically acceptable salt thereof, according to clause 28, or 29, wherein the subscript m is 0.

35) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-34, wherein L_2 is absent.

36) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-34, wherein L_2 is -O-.

37) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-34, wherein L_2 is –C(=O)-.

38) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-34, wherein L_2 is –C(=O)O- or -OC(=O)-.

39) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-34, wherein L_2 is -C(=O)-C(=O)NR^a-.

40) A compound or pharmaceutically acceptable salt thereof, according to clause 39, wherein R^a is H.

41) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-34, wherein L_2 is $-NR^b-$.

42) A compound or pharmaceutically acceptable salt thereof, according to clause 41, wherein R^b is H.

43) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-34, wherein L_2 is $-C(=O)NR^c-$.

44) A compound or pharmaceutically acceptable salt thereof, according to clause 41, wherein R^c is H, $-CH_3$, or $-CH_2-CH_3$.

45) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-34, wherein L_2 is $-NR^dC(=O)-$.

46) A compound or pharmaceutically acceptable salt thereof, according to clause 45, wherein R^d is H, $-CH_3$, or $-CH_2-CH_3$.

47) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-34, wherein L_2 is $-SO_2-$.

48) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-34, wherein L_2 is $-SO_2NR^e-$.

49) A compound or pharmaceutically acceptable salt thereof, according to clause 48, wherein R^e is H, $-CH_3$, or $-CH_2-CH_3$.

50) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-34, wherein L_2 is $-NR^fSO_2-$.

51) A compound or pharmaceutically acceptable salt thereof, according to clause 50, wherein R^f is H, $-CH_3$, or $-CH_2-CH_3$.

52) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-51, wherein G_1 is H, or CN.

53) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-51, wherein G_1 is C_{1-4} alkyl.

54) A compound or pharmaceutically acceptable salt thereof, according to clause 53, wherein G_1 is $-CH_3$, or $-CH_2-CH_3$.

55) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-51, wherein G_1 is C_{1-4} alkyl substituted with –CN, OH, halo or phenyl.

56) A compound or pharmaceutically acceptable salt thereof, according to clause 55, wherein G_1 is $-CF_3$, $-CH_2-Cl$, $-CH_2-CN$, $-CH_2-OH$ or $-CH_2-Ph$.

57) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-51, wherein G_1 is C_{3-7} cycloalkyl.

58) A compound or pharmaceutically acceptable salt thereof, according to clause 57, wherein G_1 is cyclopropyl, cyclobutyl, cyclopropyl, or cyclohexyl.

59) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-51, wherein G_1 is C_{3-7} cycloalkyl substituted with $-NH_2$.

60) A compound or pharmaceutically acceptable salt thereof, according to clause 59, wherein G_1 is cyclopropyl, cyclobutyl, cyclopropyl, or cyclohexyl, each of which is substituted with $-NH_2$.

61) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-51, wherein G_1 is 5-6 membered heterocycloalkenyl containing 1 double bond containing one to three heteroatoms independently selected from O, N, and S.

62) A compound or pharmaceutically acceptable salt thereof, according to clause 61, wherein G_1 is dihydrofuranyl, dihydrothiazolyl, dihydrooxazolyl, dihydropyranyl, or dihydrothiopyranyl.

63) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-51, wherein G_1 is 4-10 membered mono, bi or spirocyclic heterocycloalkyl containing one to three heteroatoms independently selected from O, N, and S.

64) A compound or pharmaceutically acceptable salt thereof, according to clause 63, wherein G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, or 2,6-Diaza-spiro[3.3]heptane.

65) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-51, wherein G_1 is 4-10 membered mono, bi or spirocyclic heterocycloalkyl containing one to three heteroatoms independently selected from O, N, and S, substituted with one or two independently selected R^9.

66) A compound or pharmaceutically acceptable salt thereof, according to clause 65, wherein G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, or 2,6-Diaza-spiro[3.3]heptane, each of which is substituted with one or two independently selected R^9.

67) A compound or pharmaceutically acceptable salt thereof, according to clause 65 or 66, wherein R^9 is oxo.

68) A compound or pharmaceutically acceptable salt thereof, according to clause 65 or 66, wherein R^9 is R^{10} and R^{10} is selected from OH, F, Cl, and -CN.

69) A compound or pharmaceutically acceptable salt thereof, according to clause 65 or 66, wherein R^9 is R^{10} and R^{10} is selected from $-CH_3$, $-CH_2-CH_3$, $-CF_3$, $-CH_2-CH_2-OH$, $-CH_2-$phenyl,

70) A compound or pharmaceutically acceptable salt thereof, according to clause 65 or 66, wherein R^9 is R^{10} and R^{10} is selected from $-OCH_3$, $-OCH_2-CH_3$, and $-OC(CH_3)_3$.

71) A compound or pharmaceutically acceptable salt thereof, according to clause 65 or 66, wherein R^9 is R^{10} and R^{10} is selected from $-SO_2CH_3$, $-C(=O)OCH_3$, and $-C(=O)CH_3$.

72) A compound or pharmaceutically acceptable salt thereof, according to clause 65 or 66, wherein each R^9 is R^{10} and R^{10} is $-NR^gC(=O)CH_3$, or $-NR^gC(=O)CH_2CH_3$.

73) A compound or pharmaceutically acceptable salt thereof, according to clause 72, wherein each R^g is H, $-CH_3$, or $-CH_2CH_3$.

74) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-51, wherein G_1 is 5-6 membered heteroaryl containing one to three heteroatoms independently selected from O, N, and S.

75) A compound or pharmaceutically acceptable salt thereof, according to clause 74, wherein G_1 is furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyrazinyl, or pyrimidyl.

76) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 28-51, wherein G_1 is 5-6 membered heteroaryl containing one to three heteroatoms independently selected from O, N, and S, substituted with one or two independently selected R^{10}.

77) A compound or pharmaceutically acceptable salt thereof, according to clause 76, wherein G_1 is furanyl, thienyl, pyrolyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, pyridyl, pyrazinyl, or pyrimidyl, each of which is substituted with one or two independently selected R^{10}.

78) A compound or pharmaceutically acceptable salt thereof, according to clause 77, wherein R^{10} is selected from OH, F, Cl, and -CN.

79) A compound or pharmaceutically acceptable salt thereof, according to clause 77, wherein R^{10} is selected from $-CH_3$, $-CH_2-CH_3$, $-CF_3$, $-CH_2-CH_2-OH$, and $-CH_2$-phenyl.

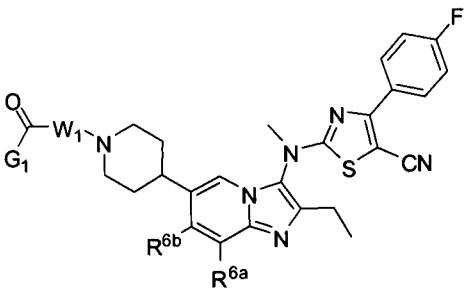
80) A compound or pharmaceutically acceptable salt thereof, according to clause 77, wherein R^{10} is selected from $-OCH_3$, $-OCH_2-CH_3$, and $-OC(CH_3)_3$.

81) A compound or pharmaceutically acceptable salt thereof, according to clause 77, wherein R^{10} is selected from $-SO_2CH_3$, $-C(=O)OCH_3$, and $-C(=O)CH_3$.

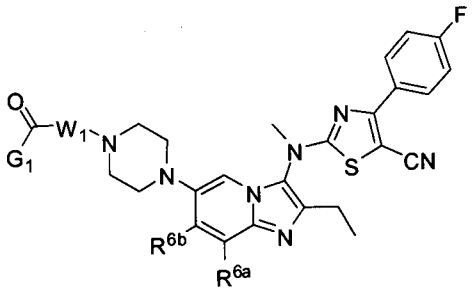
82) A compound or pharmaceutically acceptable salt thereof, according to clause 77, wherein each R^{10} is $-NR^gC(=O)CH_3$, or $-NR^gC(=O)CH_2CH_3$.

83) A compound or pharmaceutically acceptable salt thereof, according to clause 82, wherein each R^g is H, $-CH_3$, or $-CH_2CH_3$.

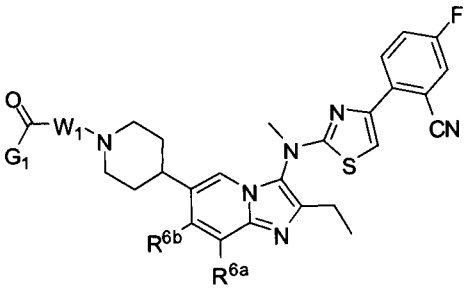
84) A compound according to clause 1, wherein the compound is according to Formula Va, Vb, Vc, or Vd:



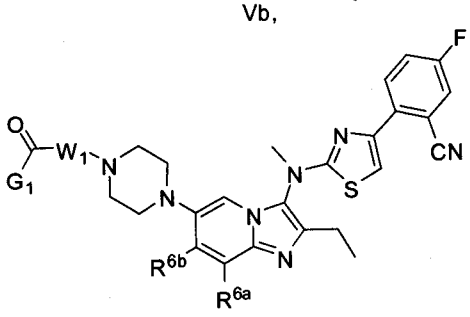
Va,



Vb,



Vc, or



Vd

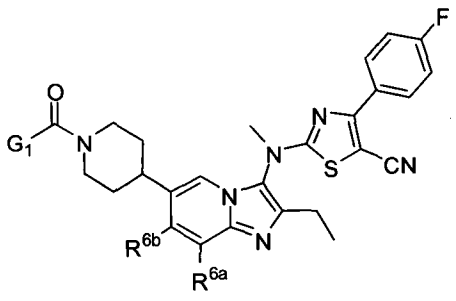
wherein R^{6a}, R^{6b}, W_1, and G_1 are according to clause 1.

85) A compound or pharmaceutically acceptable salt thereof, according to clause 84, wherein W_1 is

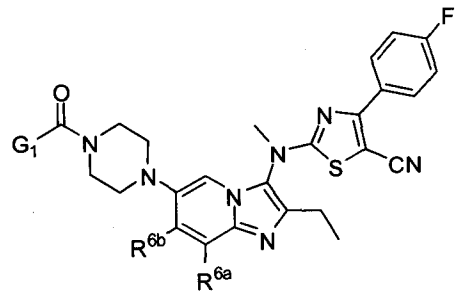
$C_{1\text{-}4}$ alkylene.

86) A compound or pharmaceutically acceptable salt thereof, according to clause 85, wherein W_1 is $-CH_2-$, $-CH_2-CH_2-$, $-C(CH_3)H-$, $-CH_2-CH_2-CH_2-$ or $-CH_2-C(CH_3)H-$.

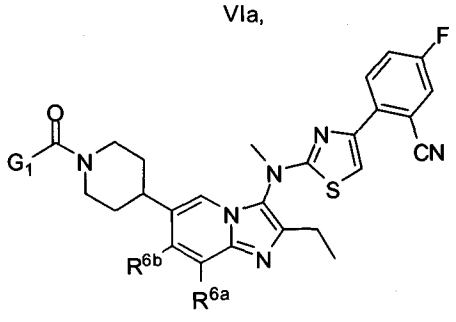
87) A compound according to to clause 1, wherein the compound is according to Formula VIa, VIb, VIc, or VId:



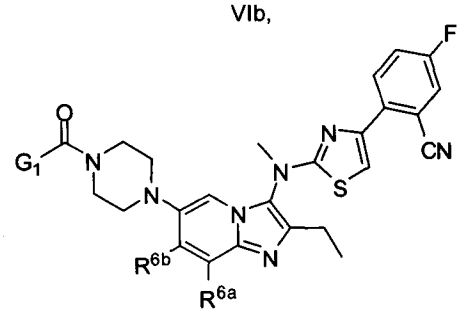
VIa,



VIb,



VIc, or



VId

wherein R^{6a}, R^{6b}, and G_1 are according to clause 1.

88) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 84-87, wherein G_1 is 4-7 membered heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S.

89) A compound or pharmaceutically acceptable salt thereof, according to clause 88, wherein G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl.

90) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 84-87, wherein G_1 is 4-7 membered heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S, which heterocycloalkyl is substituted with one or two independently selected R^9 groups.

91) A compound or pharmaceutically acceptable salt thereof, according to clause 90, wherein G_1 is oxetanyl, azetidinyl, tetrahydrofuranyl, pyrolidinyl, tetrahydropyranyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl, each of which is substituted with one or two independently selected R^9 groups.

92) A compound or pharmaceutically acceptable salt thereof, according to clause 90 or 91, wherein R^9 is oxo.

93) A compound or pharmaceutically acceptable salt thereof, according to clause 90 or 91, wherein R^9 is R^{10} and R^{10} is selected from OH, F, Cl, and -CN.

94) A compound or pharmaceutically acceptable salt thereof, according to clause 90 or 91, wherein R^9 is R^{10} and R^{10} is selected from $-CH_3$, $-CH_2-CH_3$, $-CF_3$, $-CH_2-CH_2-OH$, and $-CH_2$-phenyl.

95) A compound or pharmaceutically acceptable salt thereof, according to clause 90 or 91, wherein R^9 is R^{10} and R^{10} is selected from $-OCH_3$, $-OCH_2-CH_3$, and $-OC(CH_3)_3$.

96) A compound or pharmaceutically acceptable salt thereof, according to clause 90 or 91, wherein R^9 is R^{10} and R^{10} is selected from $-SO_2CH_3$, $-C(=O)OCH_3$, and $-C(=O)CH_3$.

97) A compound or pharmaceutically acceptable salt thereof, according to clause 90 or 91, wherein R^9 is R^{10} and R^{10} is $-NR^gC(=O)CH_3$, or $-NR^gC(=O)CH_2CH_3$.

98) A compound or pharmaceutically acceptable salt thereof, according to clause 90 or 91, wherein each R^g is H, $-CH_3$, or $-CH_2CH_3$.

99) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-98, wherein R^{6a} is H, $-CH_3$ or F, and R^{6b} is H.

100) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-98, wherein R^{6a} is CH_3, and R^{6b} is H.

101) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-98, wherein R^{6a} is H, and R^{6b} is H, $-CH_3$ or F.

102) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-98, wherein R^{6a} and R^{6b} are H.

103) A compound or pharmaceutically acceptable salt thereof, wherein the compound is selected from the compounds of Table III.

104) A compound or pharmaceutically acceptable salt thereof, wherein the compound is 2-((2-ethyl-6-(4-(2-(3-hydroxyazetidin-1-yl)-2-oxoethyl)piperazin-1-yl)-8-methylimidazo[1,2-a]pyridin-3-yl)(methyl)amino)-4-(4-fluorophenyl)thiazole-5-carbonitrile.

105) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound according to any one of clauses 1-104.

106) A pharmaceutical composition according to clause 105, comprising a further therapeutic agent.

107) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-104, or a pharmaceutical composition according to clause 105 or 106, for use in medicine.

108) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-104, or a pharmaceutical composition according to clause 105 or 106, for use in the treatment of fibrotic diseases, proliferative diseases, inflammatory diseases, autoimmune diseases, respiratory diseases, cardiovascular diseases, neurodegenerative diseases, dermatological disorders, and/or abnormal angiogenesis associated diseases.

109) A compound or pharmaceutically acceptable salt thereof, according to any one of clauses 1-104, or a pharmaceutical composition according to clause 105 or 106, for use in the treatment of idiopathic pulmonary fibrosis.

increasing motility and invasiveness of cells. The initiation, progression and metastasis of cancer involve several concurrent and sequential processes including cell proliferation and growth, survival and anti-apoptosis, migration of cells, penetration of foreign cells into defined tissues and/ or organs, and promotion of angiogenesis.

Therefore, the control of each of these processes by LPA signaling in physiological and pathophysiological conditions underscores the potential therapeutic usefulness of modulating LPA signaling pathways for the treatment of cancer. In particular, LPA has been implicated in the initiation or progression of ovarian cancer, prostate cancer, breast cancer, melanoma, head and neck cancer, bowel cancer (colorectal cancer), thyroid cancer, glioblastoma, follicular lymphoma and other cancers (Gardell, 2006) (Murph, Nguyen, Radhakrishna, & Mills, 2008) (Kishi, 2006).

Furthermore, autotaxin is implicated in the invasive and metastatic process of tumor cells, since ectopic overexpression of autotaxin is frequently observed in malignant tumor tissues such as ovarian cancer (Vidot, et al., 2010), breast cancer (Panupinthu, Lee, & Mills, 2010) (Zhang, et al., 2009), prostate cancer (Nouh, et al., 2009), renal cancer, Hodgkin lymphoma (Baumforth, 2005), hepatocellular carcinoma (Wu, et al., 2010), lung cancer (Xu & Prestwich, 2010), and glioblastoma (Kishi, 2006). Autotaxin overexpression has also been found in a variety of tumors such as malignant melanoma, teratocarcinoma, neuroblastoma, non-small-cell lung cancer, renal cell carcinoma (Stassar, et al., 2001).

Furthermore, expression of autotaxin by cancer cells controls osteolytic bone metastasis formation. In particular, LPA stimulates directly cancer growth and metastasis, and osteoclast differentiation. Therefore, targeting the autotaxin/LPA signaling route has also been found to be beneficial in patients with bone metastases (David, 2010). Finally, the inhibition of autotaxin seems to provide a beneficial adjuvant to chemotherapy for preventing tumor growth and metastasis in patients with high autotaxin expression in their tumors (Gaetano, 2009).

Upregulation of the autotaxin-LPA signaling pathway has been observed in a variety of inflammatory conditions. For example, pro-inflammatory effects of LPA include degranulation of mast cells, contraction of smooth-muscle cells and release of cytokines from dendritic cells.As an indication for its general role in inflammation, LPA and autotaxin activity have been shown to be induced by carageenan injection into the mouse air pouch model, which is used to develop anti-inflammatory drugs, including cyclooxygenase inhibitors for arthritis. Furthermore, a reduction in plasma and air pouch LPA has been observed in this rat air pouch model using an autotaxin inhibitor, confirming the role of autotaxin during inflammation as a major source of LPA (Gierse, 2010). It has been observed that autotaxin inhibitors reduce LPA and PGE2 and also reduce inflammatory pain.

As another general role in inflammatory diseases, LPA has been shown to induce chemokinesis in T-cells. Intravenous injection of enzymatically inactive autotaxin has been

110) The use of a compound or pharmaceutically acceptable salt thereof or the pharmaceutical composition according to clause 108 or 109, wherein said compound or pharmaceutical composition is administered in combination with a further therapeutic agent.

111) A method for the treatment, or prevention of diseases or conditions selected from fibrotic diseases, proliferative diseases, inflammatory diseases, autoimmune diseases, respiratory diseases, cardiovascular diseases, neurodegenerative diseases, dermatological disorders, and/or abnormal angiogenesis associated diseases, comprising administering an amount of compound according to any one of clauses 1-104, or the pharmaceutical composition according any one of clauses 105 or 106, sufficient to effect said treatment, or prevention.

112) A method for the treatment, or prevention of diseases or conditions selected from idiopathic pulmonary fibrosis, comprising administering an amount of compound according to any one of clauses 1-104, or the pharmaceutical composition according any one of clauses 105 or 106, sufficient to effect said treatment, or prevention.

113) The method according to clause 111 or 112, wherein the compound, or the pharmaceutical composition, is administered in combination with a further therapeutic agent.

114) The pharmaceutical composition according to clause 106, or the use according to clause 110, or the method according to clause 113, wherein the further therapeutic agent is for the treatment of fibrotic diseases, proliferative diseases, inflammatory diseases, autoimmune diseases, respiratory diseases, cardiovascular diseases, neurodegenerative diseases, dermatological disorders, and/or abnormal angiogenesis associated diseases.

115) The pharmaceutical composition according to clause 106, or the use according to clause 110, or the method according to clause 113, wherein the further therapeutic agent is for the treatment of idiopathic pulmonary fibrosis.

PHARMACEUTICAL COMPOSITIONS

When employed as a pharmaceutical, a compound of the invention is typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound of the invention according to Formula I. Generally, a compound of the invention is administered in a pharmaceutically effective amount. The amount of compound of the invention actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound of the invention administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

The pharmaceutical compositions of this invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intra-articular, intravenous,

intramuscular, and intranasal. Depending on the intended route of delivery, a compound of the invention is preferably formulated as either injectable or oral compositions or as salves, as lotions or as patches all for transdermal administration.

The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term 'unit dosage forms' refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient, vehicle or carrier. Typical unit dosage forms include prefilled, premeasured ampules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the compound of the invention according to Formula I is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

Liquid forms suitable for oral administration may include a suitable aqueous or non-aqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compound of the inventions of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint or orange flavoring.

Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As before, the active compound of the invention according to Formula I in such compositions is typically a minor component, often being from about 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

Transdermal compositions are typically formulated as a topical ointment or cream containing the active ingredient(s), generally in an amount ranging from about 0.01 to about 20% by weight, preferably from about 0.1 to about 20% by weight, preferably from about 0.1 to about 10% by weight, and more preferably from about 0.5 to about 15% by weight. When formulated as an ointment, the active ingredients will typically be combined with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with, for example an oil-in-water cream base. Such transdermal formulations are well-known in the art and generally include additional ingredients to enhance the dermal penetration

of stability of the active ingredients or the formulation. All such known transdermal formulations and ingredients are included within the scope of this invention.

A compound of the invention can also be administered by a transdermal device. Accordingly, transdermal administration can be accomplished using a patch either of the reservoir or porous membrane type, or of a solid matrix variety.

The above-described components for orally administrable, injectable or topically administrable compositions are merely representative. Other materials as well as processing techniques and the like are set forth in Part 8 of Remington's Pharmaceutical Sciences, 17th edition, 1985, Mack Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference.

A compound of the invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can be found in Remington's Pharmaceutical Sciences.

The following formulation examples illustrate representative pharmaceutical compositions that may be prepared in accordance with this invention. The present invention, however, is not limited to the following pharmaceutical compositions.

Formulation 1 - Tablets

A compound of the invention according to Formula I may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate may be added as a lubricant. The mixture may be formed into 240-270 mg tablets (80-90 mg of active compound of the invention according to Formula I per tablet) in a tablet press.

Formulation 2 - Capsules

A compound of the invention according to Formula I may be admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture may be filled into 250 mg capsules (125 mg of active compound of the invention according to Formula I per capsule).

Formulation 3 - Liquid

A compound of the invention according to Formula I (125 mg), may be admixed with sucrose (1.75 g) and xanthan gum (4 mg) and the resultant mixture may be blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89, 50 mg) in water. Sodium benzoate (10 mg), flavor, and color may be diluted with water and added with stirring. Sufficient

water may then be added with stirring. Further sufficient water may be then added to produce a total volume of 5 mL.

Formulation 4 - Tablets

A compound of the invention according to Formula I may be admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate may be added as a lubricant. The mixture may be formed into 450-900 mg tablets (150-300 mg of active compound of the invention according to Formula I) in a tablet press.

Formulation 5 - Injection

A compound of the invention according to Formula I may be dissolved or suspended in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/mL.

Formulation 6 - Topical

Stearyl alcohol (250 g) and a white petrolatum (250 g) may be melted at about 75°C and then a mixture of A compound of the invention according to Formula I (50 g) methylparaben (0.25 g), propylparaben (0.15 g), sodium lauryl sulfate (10 g), and propylene glycol (120 g) dissolved in water (about 370 g) may be added and the resulting mixture may be stirred until it congeals.

METHODS OF TREATMENT

In one embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention, for use in medicine. In a particular embodiment, the present invention provides compounds of the invention or pharmaceutical compositions comprising a compound of the invention, for use in the prophylaxis and/or treatment of fibrotic diseases, proliferative diseases, inflammatory diseases, autoimmune diseases, respiratory diseases, cardiovascular diseases, neurodegenerative diseases, dermatological disorders, and/or abnormal angiogenesis associated diseases.

In another embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of fibrotic diseases, proliferative diseases, inflammatory diseases, autoimmune diseases, respiratory diseases, cardiovascular diseases, neurodegenerative diseases, dermatological disorders, and/or abnormal angiogenesis associated diseases.

In one embodiment, the present invention provides pharmaceutical compositions comprising a compound of the invention, and another therapeutic agent. In a particular embodiment, the other therapeutic agent is a fibrotic diseases, proliferative diseases, inflammatory diseases, autoimmune diseases, respiratory diseases, cardiovascular diseases, neurodegenerative diseases, dermatological disorders, and/or abnormal angiogenesis associated diseases treatment agent.

In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with fibrotic diseases, proliferative diseases, inflammatory diseases, autoimmune diseases, respiratory diseases, cardiovascular diseases, neurodegenerative diseases, dermatological disorders, and/or abnormal angiogenesis associated diseases, which methods comprise the administration of an effective amount of a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition.

In one embodiment, the present invention provides compounds of the invention or pharmaceutical compositions comprising a compound of the invention, for use in the prophylaxis and/or treatment of fibrotic diseases. In a particular embodiment, the fibrotic disease is selected from idiopathic pulmonary fibrosis (IPF), cystic fibrosis, other diffuse parenchymal lung diseases of different etiologies including iatrogenic drug-induced fibrosis, occupational and/or environmental induced fibrosis, granulomatous diseases (sarcoidosis, hypersensitivity pneumonia), collagen vascular disease, alveolar proteinosis, langerhans cell granulomatosis, lymphangioleiomyomatosis, inherited diseases (Hermansky-Pudlak Syndrome, tuberous sclerosis, neurofibromatosis, metabolic storage disorders, familial interstitial lung disease), radiation induced fibrosis, chronic obstructive pulmonary disease (COPD), scleroderma, bleomycin induced pulmonary fibrosis, chronic asthma, silicosis, asbestos induced pulmonary fibrosis, acute respiratory distress syndrome (ARDS), kidney fibrosis, tubulointerstitium fibrosis, glomerular nephritis, focal segmental glomerular sclerosis, IgA nephropathy, hypertension, Alport, gut fibrosis, liver fibrosis, cirrhosis, alcohol induced liver fibrosis, toxic/drug induced liver fibrosis, hemochromatosis, nonalcoholic steatohepatitis (NASH), biliary duct injury, primary biliary cirrhosis, infection induced liver fibrosis, viral induced liver fibrosis, and autoimmune hepatitis, corneal scarring, hypertrophic scarring, Dupuytren disease, keloids, cutaneous fibrosis, cutaneous scleroderma, systemic sclerosis, spinal cord injury/fibrosis, myelofibrosis, vascular restenosis, atherosclerosis, arteriosclerosis, Wegener's granulomatosis, Peyronie's disease, or chronic lymphocytic. More particularly, the fibrotic diseases is idiopathic pulmonary fibrosis (IPF).

In another embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of fibrotic diseases. In

a particular embodiment, the fibrotic disease is selected from idiopathic pulmonary fibrosis (IPF), cystic fibrosis, other diffuse parenchymal lung diseases of different etiologies including iatrogenic drug-induced fibrosis, occupational and/or environmental induced fibrosis, granulomatous diseases (sarcoidosis, hypersensitivity pneumonia), collagen vascular disease, alveolar proteinosis, langerhans cell granulomatosis, lymphangioleiomyomatosis, inherited diseases (Hermansky-Pudlak Syndrome, tuberous sclerosis, neurofibromatosis, metabolic storage disorders, familial interstitial lung disease), radiation induced fibrosis, chronic obstructive pulmonary disease (COPD), scleroderma, bleomycin induced pulmonary fibrosis, chronic asthma, silicosis, asbestos induced pulmonary fibrosis, acute respiratory distress syndrome (ARDS), kidney fibrosis, tubulointerstitium fibrosis, glomerular nephritis, focal segmental glomerular sclerosis, IgA nephropathy, hypertension, Alport, gut fibrosis, liver fibrosis, cirrhosis, alcohol induced liver fibrosis, toxic/drug induced liver fibrosis, hemochromatosis, nonalcoholic steatohepatitis (NASH), biliary duct injury, primary biliary cirrhosis, infection induced liver fibrosis, viral induced liver fibrosis, and autoimmune hepatitis, corneal scarring, hypertrophic scarring, Dupuytren disease, keloids, cutaneous fibrosis, cutaneous scleroderma, systemic sclerosis, spinal cord injury/fibrosis, myelofibrosis, vascular restenosis, atherosclerosis, arteriosclerosis, Wegener's granulomatosis, Peyronie's disease, or chronic lymphocytic. More particularly, the fibrotic disease is idiopathic pulmonary fibrosis (IPF).

In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with fibrotic diseases, which methods comprise the administration of an effective amount of a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition. In a particular embodiment, the fibrotic disease is selected from idiopathic pulmonary fibrosis (IPF), cystic fibrosis, other diffuse parenchymal lung diseases of different etiologies including iatrogenic drug-induced fibrosis, occupational and/or environmental induced fibrosis, granulomatous diseases (sarcoidosis, hypersensitivity pneumonia), collagen vascular disease, alveolar proteinosis, langerhans cell granulomatosis, lymphangioleiomyomatosis, inherited diseases (Hermansky-Pudlak Syndrome, tuberous sclerosis, neurofibromatosis, metabolic storage disorders, familial interstitial lung disease), radiation induced fibrosis, chronic obstructive pulmonary disease (COPD), scleroderma, bleomycin induced pulmonary fibrosis, chronic asthma, silicosis, asbestos induced pulmonary fibrosis, acute respiratory distress syndrome (ARDS), kidney fibrosis, tubulointerstitium fibrosis, glomerular nephritis, focal segmental glomerular sclerosis, IgA nephropathy, hypertension, Alport, gut fibrosis, liver fibrosis, cirrhosis, alcohol induced liver fibrosis, toxic/drug induced liver fibrosis, hemochromatosis, nonalcoholic steatohepatitis (NASH), biliary duct injury, primary biliary cirrhosis, infection induced liver fibrosis, viral induced liver fibrosis, and autoimmune hepatitis, corneal scarring, hypertrophic scarring, Dupuytren disease, keloids, cutaneous fibrosis, cutaneous

scleroderma, systemic sclerosis, spinal cord injury/fibrosis, myelofibrosis, vascular restenosis, atherosclerosis, arteriosclerosis, Wegener's granulomatosis, Peyronie's disease, or chronic lymphocytic. More particularly, the fibrotic disease is idiopathic pulmonary fibrosis (IPF).

A particular regimen of the present method comprises the administration to a subject suffering from a fibrotic disease of an effective amount of a compound of the invention according to Formula I for a period of time sufficient to reduce the level of fibrosis in the subject, and preferably terminate the processes responsible for said fibrosis. A special embodiment of the method comprises administering of an effective amount of a compound of the invention according to Formula I to a subject patient suffering from to the development of idiopathic pulmonary fibrosis, for a period of time sufficient to reduce or prevent idiopathic pulmonary fibrosis of said patient, and preferably terminate, the processes responsible for said idiopathic pulmonary fibrosis.

In one embodiment, the present invention provides compounds of the invention or pharmaceutical compositions comprising a compound of the invention, for use in the prophylaxis and/or treatment of proliferative diseases. In a particular embodiment, the proliferative disease is selected from cancer, leukemia, multiple myeloma and psoriasis.

In another embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of proliferative diseases. In a particular embodiment, the proliferative disease is selected from cancer, leukemia, multiple myeloma and psoriasis.

In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with proliferative diseases, which methods comprise the administration of an effective amount of a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition. In a particular embodiment, the proliferative disease is selected from cancer, leukemia, multiple myeloma and psoriasis.

In one embodiment, the present invention provides compounds of the invention or pharmaceutical compositions comprising a compound of the invention, for use in the prophylaxis and/or treatment of inflammatory diseases. In a particular embodiment, the inflammatory disease is selected from rheumatoid arthritis, osteoarthritis, allergic airway disease (*e.g.* asthma), chronic obstructive pulmonary disease (COPD) and inflammatory bowel diseases (*e.g.* Crohn's disease and ulcerative colitis). More particularly, the inflammatory disease is selected from rheumatoid arthritis, and chronic obstructive pulmonary disease (COPD).

In another embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of inflammatory

diseases. In a particular embodiment, the inflammatory disease is selected from rheumatoid arthritis, osteoarthritis, allergic airway disease (*e.g.* asthma), chronic obstructive pulmonary disease (COPD) and inflammatory bowel diseases (*e.g.* Crohn's disease and ulcerative colitis). More particularly, the inflammatory disease is selected from rheumatoid arthritis, and chronic obstructive pulmonary disease (COPD).

In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with inflammatory diseases, which methods comprise the administration of an effective amount of a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition. In a particular embodiment, the inflammatory disease is selected from rheumatoid arthritis, osteoarthritis, allergic airway disease (*e.g.* asthma), chronic obstructive pulmonary disease (COPD) and inflammatory bowel diseases (*e.g.* Crohn's disease and ulcerative colitis). More particularly the inflammatory disease is selected from rheumatoid arthritis, and chronic obstructive pulmonary disease (COPD).

In one embodiment, the present invention provides compounds of the invention or pharmaceutical compositions comprising a compound of the invention, for use in the prophylaxis and/or treatment of autoimmune diseases. In a particular embodiment, the autoimmune disease is selected from COPD, asthma (e.g intrinsic asthma, extrinsic asthma, dust asthma, infantily asthma) particularly chronic or inveterate asthma (for example late asthma and airway hyperreponsiveness), bronchitis, including bronchial asthma, systemic lupus erythematosus (SLE), cutaneous lupus erythrematosis, lupus nephritis, dermatomyositis, Sjogren's syndrome, multiple sclerosis, psoriasis, dry eye disease, type I diabetes mellitus and complications associated therewith, atopic eczema (atopic dermatitis), thyroiditis (Hashimoto's and autoimmune thyroiditis), contact dermatitis and further eczematous dermatitis, inflammatory bowel disease (*e.g.* Crohn's disease and ulcerative colitis), atherosclerosis and amyotrophic lateral sclerosis. Particularly, the autoimmune disease is selected from COPD, asthma, systemic lupus erythematosis, type I diabetes mellitus and inflammatory bowel disease.

In another embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of autoimmune diseases. In a particular embodiment, the autoimmune disease is selected from COPD, asthma (e.g intrinsic asthma, extrinsic asthma, dust asthma, infantily asthma) particularly chronic or inveterate asthma (for example late asthma and airway hyperreponsiveness), bronchitis, including bronchial asthma, systemic lupus erythematosus (SLE), cutaneous lupus erythrematosis, lupus nephritis, dermatomyositis, Sjogren's syndrome, multiple sclerosis, psoriasis, dry eye disease, type I diabetes mellitus and complications associated therewith, atopic eczema (atopic dermatitis), thyroiditis (Hashimoto's and autoimmune thyroiditis), contact

dermatitis and further eczematous dermatitis, inflammatory bowel disease (*e.g.* Crohn's disease and ulcerative colitis), atherosclerosis and amyotrophic lateral sclerosis. Particularly, the autoimmune disease is selected from COPD, asthma, systemic lupus erythematosis, type I diabetes mellitus and inflammatory bowel disease.

In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with autoimmune diseases, which methods comprise the administration of an effective amount of a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition. In a particular embodiment, the autoimmune disease is selected from COPD, asthma (e.g intrinsic asthma, extrinsic asthma, dust asthma, infantily asthma) particularly chronic or inveterate asthma (for example late asthma and airway hyperreponsiveness), bronchitis, including bronchial asthma, systemic lupus erythematosus (SLE), cutaneous lupus erythrematosis, lupus nephritis, dermatomyositis, Sjogren's syndrome, multiple sclerosis, psoriasis, dry eye disease, type I diabetes mellitus and complications associated therewith, atopic eczema (atopic dermatitis), thyroiditis (Hashimoto's and autoimmune thyroiditis), contact dermatitis and further eczematous dermatitis, inflammatory bowel disease (*e.g.* Crohn's disease and ulcerative colitis), atherosclerosis and amyotrophic lateral sclerosis. Particularly, the autoimmune disease is selected from COPD, asthma, systemic lupus erythematosis, type I diabetes mellitus and inflammatory bowel disease.

In one embodiment, the present invention provides compounds of the invention or pharmaceutical compositions comprising a compound of the invention, for use in the prophylaxis and/or treatment of respiratory diseases. In a particular embodiment, the respiratory disease is selected from asthma, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma, seasonal allergic rhinitis, perennial allergic rhinitis, chronic obstructive pulmonary disease, including chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation and cystic fibrosis, and hypoxia.

In another embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of respiratory diseases. In a particular embodiment, the respiratory disease is selected from asthma, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child onset asthma, adult-

onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma, seasonal allergic rhinitis, perennial allergic rhinitis, chronic obstructive pulmonary disease, including chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation and cystic fibrosis, and hypoxia.

In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with respiratory diseases, which methods comprise the administration of an effective amount of a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition. In a particular embodiment, the respiratory disease is selected from asthma, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma, seasonal allergic rhinitis, perennial allergic rhinitis, chronic obstructive pulmonary disease, including chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation and cystic fibrosis, and hypoxia.

In one embodiment, the present invention provides compounds of the invention or pharmaceutical compositions comprising a compound of the invention, for use in the prophylaxis and/or treatment of cardiovascular diseases. In a particular embodiment, the cardiovascular disease is selected from arrhythmia (atrial or ventricular or both), atherosclerosis and its sequelae, angina, cardiac rhythm disturbances, myocardial ischemia, myocardial infarction, cardiac or vascular aneurysm, vasculitis, stroke, peripheral obstructive arteriopathy of a limb, an organ, or a tissue, reperfusion injury following ischemia of the brain, heart, kidney or other organ or tissue, endotoxic, surgical, or traumatic shock, hypertension, valvular heart disease, heart failure, abnormal blood pressure, shock, vasoconstriction (including that associated with migraines), vascular abnormality, inflammation, insufficiency limited to a single organ or tissue.

In another embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of cardiovascular diseases. In a particular embodiment, the cardiovascular disease is selected from arrhythmia (atrial or ventricular or both), atherosclerosis and its sequelae, angina, cardiac rhythm disturbances, myocardial ischemia, myocardial infarction, cardiac or vascular aneurysm, vasculitis, stroke, peripheral obstructive arteriopathy of a limb, an organ, or a tissue, reperfusion injury following ischemia of the brain, heart, kidney or other organ or tissue, endotoxic, surgical, or traumatic shock, hypertension, valvular heart disease, heart failure, abnormal blood pressure, shock, vasoconstriction (including that associated with migraines), vascular abnormality, inflammation, insufficiency limited to a single organ or tissue.

shown to attenuate the homing of T-cells to lymphoid tissues, likely by competing with endogenous autotaxin and exerting a dominant-negative effect. In certain instances, autotaxin facilitates lymphocyte entry into lymphoid organs (Kanda, 2008). Therefore an autotaxin inhibitor may block lymphocyte migration into secondary lymphoid organs and be of benefit in autoimmune diseases.

Specifically in rheumatoid arthritis, an increased expression of ATX in synovial fibroblasts from RA patients was demonstrated and ablation of ATX expression in mesenchymal cells (including synovial fibroblasts) resulted in attenuated symptoms in mouse models for rheumatoid arthritis (Nikitopoulou, et al., 2012). As such, the role of autotaxin in rheumatoid arthritis has been strongly established.

Several lines of evidence suggest a role for LPA in vascular injury and atherosclerosis. These relate to the role of LPA in modulating endothelial barrier function and the phenotype of vascular smooth muscle cells and the action of LPA as a weak platelet agonist. Platelets have been identified as important participants in LPA production in the circulation in some settings, mainly by providing sufficient LPC amounts. Plasma autotaxin associates with platelets during aggregation and concentrates in arterial thrombus, and activated but not resting platelets bind recombinant autotaxin in an integrin-dependent manner. Experimental induction of thrombocytopenia in rats, using an anti-platelet antibody, decreases the production of LPA in serum by almost 50%, which suggests a role for LPA during clotting. In some instances, transgenic overexpression of autotaxin elevates circulating LPA levels and induces a bleeding diathesis and attenuation of thrombosis in mice. Intravascular administration of exogenous LPA recapitulates the prolonged bleeding time observed in autotaxin-Tg mice. Finally, autotaxin$^{+/-}$ mice, which have ~50% normal plasma LPA levels, are more prone to thrombosis.

In addition to a role in blood clotting, LPA has multiple effects on the endothelial monolayer permeability increase, and endothelial cells, in particular in critical aspects of angiogenesis such as cell migration stimulation and invasion. Furthermore, LPA also exerts migratory and contractile effects on vascular smooth muscle cells: autotaxin-mediated LPA production and subsequent LPA signaling contributes to vascular development by stimulating endothelial cell migration and invasion as well as regulating adhesive interactions with the extracellular matrix and smooth muscle cells. For example, similar vascular defects have been observed in autotaxin-deficient mice and in mice lacking genes involved in cell migration and adhesion (Van Meeteren, et al., 2006). Therefore an autotaxin inhibitor may have benefit in some diseases involving dysregulated angiogenesis.

LPA induces neuropathic pain as well as demyelination and pain-related protein expression changes via LPA1 (Inoue, et al., 2008). ATX heterozygous knockout mice show about 50% recovery of nerve injury-induced neuropathic pain compared to wild type mice. Lysophosphatidylcholine (LPC), also known as lyso-lecithin, is known to induce neuropathic

In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with cardiovascular diseases, which methods comprise the administration of an effective amount of a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition. In a particular embodiment, the cardiovascular disease is selected from arrhythmia (atrial or ventricular or both), atherosclerosis and its sequelae, angina, cardiac rhythm disturbances, myocardial ischemia, myocardial infarction, cardiac or vascular aneurysm, vasculitis, stroke, peripheral obstructive arteriopathy of a limb, an organ, or a tissue, reperfusion injury following ischemia of the brain, heart, kidney or other organ or tissue, endotoxic, surgical, or traumatic shock, hypertension, valvular heart disease, heart failure, abnormal blood pressure, shock, vasoconstriction (including that associated with migraines), vascular abnormality, inflammation, insufficiency limited to a single organ or tissue.

In one embodiment, the present invention provides compounds of the invention or pharmaceutical compositions comprising a compound of the invention, for use in the prophylaxis and/or treatment of neurodegenerative diseases. In a particular embodiment, the neurodegenerative disease is selected from Alzheimer's disease and other dementias, brain cancer, degenerative nerve diseases, encephalitis, epilepsy, genetic brain disorders, head and brain malformations, hydrocephalus, stroke, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS or Lou Gehrig's Disease), Huntington's disease, and prion diseases.

In another embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of neurodegenerative diseases. In a particular embodiment, the neurodegenerative disease is selected from Alzheimer's disease and other dementias, brain cancer, degenerative nerve diseases, encephalitis, epilepsy, genetic brain disorders, head and brain malformations, hydrocephalus, stroke, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS or Lou Gehrig's Disease), Huntington's disease, and prion diseases.

In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with neurodegenerative diseases, which methods comprise the administration of an effective amount of a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition. In a particular embodiment, the neurodegenerative disease is selected from Alzheimer's disease and other dementias, brain cancer, degenerative nerve diseases, encephalitis, epilepsy, genetic brain disorders, head and brain malformations, hydrocephalus, stroke, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis (ALS or Lou Gehrig's Disease), Huntington's disease, and prion diseases.

In one embodiment, the present invention provides compounds of the invention or pharmaceutical compositions comprising a compound of the invention, for use in the prophylaxis and/or treatment of dermatological disorders. In a particular embodiment, the dermatological disease is selected from atopic dermatitis, bullous disorders, collagenoses, psoriasis, psoriatic lesions, dermatitis, contact dermatitis, eczema, pruritus, urticaria, rosacea, scleroderma, wound healing, scarring, hypertrophic scarring, keloids, Kawasaki Disease, rosacea, or Sjogren-Larsso Syndrome.

In another embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of dermatological disorders. In a particular embodiment, the dermatological disease is selected from atopic dermatitis, bullous disorders, collagenoses, psoriasis, psoriatic lesions, dermatitis, contact dermatitis, eczema, pruritus, urticaria, rosacea, scleroderma, wound healing, scarring, hypertrophic scarring, keloids, Kawasaki Disease, rosacea, or Sjogren-Larsso Syndrome.

In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with dermatological disorders, which methods comprise the administration of an effective amount of a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition. In a particular embodiment, the dermatological disease is selected from atopic dermatitis, bullous disorders, collagenoses, psoriasis, psoriatic lesions, dermatitis, contact dermatitis, eczema, pruritus, urticaria, rosacea, scleroderma, wound healing, scarring, hypertrophic scarring, keloids, Kawasaki Disease, rosacea, or Sjogren-Larsso Syndrome.

In one embodiment, the present invention provides compounds of the invention or pharmaceutical compositions comprising a compound of the invention, for use in the prophylaxis and/or treatment of abnormal angiogenesis associated diseases. In a particular embodiment, the abnormal angiogenesis associated disease is selected from atherosclerosis, hypertension, tumor growth, inflammation, rheumatoid arthritis, wet-form macular degeneration, choroidal neovascularization, retinal neovascularization, diabetic retinopathy, and glioblastoma multiforma.

In another embodiment, the present invention provides compounds of the invention, or pharmaceutical compositions comprising a compound of the invention for use in the manufacture of a medicament for use in the prophylaxis and/or treatment of abnormal angiogenesis associated diseases. In a particular embodiment, the abnormal angiogenesis associated disease is selected from atherosclerosis, hypertension, tumor growth, inflammation, rheumatoid arthritis, wet-form macular degeneration, choroidal neovascularization, retinal neovascularization, diabetic retinopathy, and glioblastoma multiforma.

In additional method of treatment aspects, this invention provides methods of prophylaxis and/or treatment of a mammal afflicted with abnormal angiogenesis associated diseases, which methods comprise the administration of an effective amount of a compound of the invention or one or more of the pharmaceutical compositions herein described for the treatment or prophylaxis of said condition. In a particular embodiment, the abnormal angiogenesis associated disease is selected from atherosclerosis, hypertension, tumor growth, inflammation, rheumatoid arthritis, wet-form macular degeneration, choroidal neovascularization, retinal neovascularization, diabetic retinopathy, and glioblastoma multiforma.

Injection dose levels range from about 0.1 mg/kg/h to at least 10 mg/kg/h, all for from about 1 to about 120 h and especially 24 to 96 h. A preloading bolus of from about 0.1 mg/kg to about 10 mg/kg or more may also be administered to achieve adequate steady state levels. The maximum total dose is not expected to exceed about 1 g/day for a 40 to 80 kg human patient.

For the prophylaxis and/or treatment of long-term conditions, such as degenerative conditions, the regimen for treatment usually stretches over many months or years so oral dosing is preferred for patient convenience and tolerance. With oral dosing, one to four (1-4) regular doses daily, especially one to three (1-3) regular doses daily, typically one to two (1-2) regular doses daily, and most typically one (1) regular dose daily are representative regimens. Alternatively for long lasting effect drugs, with oral dosing, once every other week, once weekly, and once a day are representative regimens. In particular, dosage regimen can be every 1-14 days, more particularly 1-10 days, even more particularly 1-7 days, and most particularly 1-3 days.

Using these dosing patterns, each dose provides from about 1 to about 1000 mg of a compound of the invention, with particular doses each providing from about 10 to about 500 mg and especially about 30 to about 250 mg.

Transdermal doses are generally selected to provide similar or lower blood levels than are achieved using injection doses.

When used to prevent the onset of a condition, a compound of the invention will be administered to a patient at risk for developing the condition, typically on the advice and under the supervision of a physician, at the dosage levels described above. Patients at risk for developing a particular condition generally include those that have a family history of the condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the condition.

A compound of the invention can be administered as the sole active agent or it can be administered in combination with other therapeutic agents, including other compound of the inventions that demonstrate the same or a similar therapeutic activity and that are determined to be safe and efficacious for such combined administration. In a specific embodiment, co-

administration of two (or more) agents allows for significantly lower doses of each to be used, thereby reducing the side effects seen.

In one embodiment, a compound of the invention or a pharmaceutical composition comprising a compound of the invention is administered as a medicament. In a specific embodiment, said pharmaceutical composition additionally comprises a further active ingredient.

In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of a disease involving inflammation, particular agents include, but are not limited to, immunoregulatory agents *e.g.* azathioprine, corticosteroids (*e.g.* prednisolone or dexamethasone), cyclophosphamide, cyclosporin A, tacrolimus, mycophenolate, mofetil, muromonab-CD3 (OKT3, *e.g.* Orthocolone®), ATG, aspirin, acetaminophen, ibuprofen, naproxen, and piroxicam.

In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of arthritis (*e.g.* rheumatoid arthritis), particular agents include but are not limited to analgesics, non-steroidal anti-inflammatory drugs (NSAIDS), steroids, synthetic DMARDS (for example but without limitation methotrexate, leflunomide, sulfasalazine, auranofin, sodium aurothiomalate, penicillamine, chloroquine, hydroxychloroquine, azathioprine, tofacitinib, baricitinib, fostamatinib, and cyclosporin), and biological DMARDS (for example but without limitation infliximab, etanercept, adalimumab, rituximab, and abatacept).

In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of proliferative disorders, particular agents include but are not limited to: methotrexate, leukovorin, adriamycin, prednisone, bleomycin, cyclophosphamide, 5-fluorouracil, paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, doxorubicin, tamoxifen, toremifene, megestrol acetate, anastrozole, goserelin, anti-HER2 monoclonal antibody (*e.g.* Herceptin™), capecitabine, raloxifene hydrochloride, EGFR inhibitors (*e.g.* Iressa®, Tarceva™, Erbitux™), VEGF inhibitors (*e.g.* Avastin™), proteasome inhibitors (*e.g.* Velcade™), Glivec® and hsp90 inhibitors (*e.g.* 17-AAG). Additionally, the compound of the invention according to Formula I may be administered in combination with other therapies including, but not limited to, radiotherapy or surgery. In a specific embodiment the proliferative disorder is selected from cancer, myeloproliferative disease or leukaemia.

In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of autoimmune diseases, particular agents include but are not limited to: glucocorticoids, cytostatic agents (*e.g.* purine analogs), alkylating agents (e.g nitrogen mustards (cyclophosphamide), nitrosoureas, platinum compound of the inventions, and others), antimetabolites (*e.g.* methotrexate, azathioprine and mercaptopurine), cytotoxic antibiotics (*e.g.* dactinomycin anthracyclines, mitomycin C, bleomycin, and mithramycin), antibodies (*e.g.* anti-CD20, anti-CD25 or anti-CD3 (OTK3) monoclonal

antibodies, Atgam® and Thymoglobuline®), cyclosporin, tacrolimus, rapamycin (sirolimus), interferons (*e.g.* IFN-β), TNF binding proteins (*e.g.* infliximab, etanercept, or adalimumab), mycophenolate, fingolimod and myriocin..

In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of transplant rejection, particular agents include but are not limited to: calcineurin inhibitors (*e.g.* cyclosporin or tacrolimus (FK506)), mTOR inhibitors (*e.g.* sirolimus, everolimus), anti-proliferatives (*e.g.* azathioprine, mycophenolic acid), corticosteroids (*e.g.* prednisolone, hydrocortisone), antibodies (*e.g.* monoclonal anti-IL-2Rα receptor antibodies, basiliximab, daclizumab), polyclonal anti-T-cell antibodies (*e.g.* anti-thymocyte globulin (ATG), anti-lymphocyte globulin (ALG)).

In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of asthma and/or rhinitis and/or COPD, particular agents include but are not limited to: beta2-adrenoceptor agonists (*e.g.* salbutamol, levalbuterol, terbutaline and bitolterol), epinephrine (inhaled or tablets), anticholinergics (*e.g.* ipratropium bromide), glucocorticoids (oral or inhaled). Long-acting β2-agonists (*e.g.* salmeterol, formoterol, bambuterol, and sustained-release oral albuterol), combinations of inhaled steroids and long-acting bronchodilators (*e.g.* fluticasone/salmeterol, budesonide/formoterol), leukotriene antagonists and synthesis inhibitors (*e.g.* montelukast, zafirlukast and zileuton), inhibitors of mediator release (*e.g.* cromoglycate and ketotifen), biological regulators of IgE response (*e.g.* omalizumab), antihistamines (*e.g.* ceterizine, cinnarizine, fexofenadine) and vasoconstrictors (*e.g.* oxymethazoline, xylomethazoline, nafazoline and tramazoline).

Additionally, a compound of the invention may be administered in combination with emergency therapies for asthma and/or COPD, such therapies include oxygen or heliox administration, nebulized salbutamol or terbutaline (optionally combined with an anticholinergic (*e.g.* ipratropium), systemic steroids (oral or intravenous, *e.g.* prednisone, prednisolone, methylprednisolone, dexamethasone, or hydrocortisone), intravenous salbutamol, non-specific beta-agonists, injected or inhaled (*e.g.* epinephrine, isoetharine, isoproterenol, metaproterenol), anticholinergics (IV or nebulized, *e.g.* glycopyrrolate, atropine, ipratropium), methylxanthines (theophylline, aminophylline, bamiphylline), inhalation anesthetics that have a bronchodilatory effect (*e.g.* isoflurane, halothane, enflurane), ketamine and intravenous magnesium sulfate.

In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of inflammatory bowel disease (IBD), particular agents include but are not limited to: glucocorticoids (*e.g.* prednisone, budesonide) synthetic disease modifying, immunomodulatory agents (*e.g.* methotrexate, leflunomide, sulfasalazine, mesalazine, azathioprine, 6-mercaptopurine and cyclosporin) and biological

disease modifying, immunomodulatory agents (infliximab, adalimumab, rituximab, and abatacept).

In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of SLE, particular agents include but are not limited to: human monoclonal antibodies (belimumab (Benlysta)), Disease-modifying antirheumatic drugs (DMARDs) such as antimalarials (*e.g.* plaquenil, hydroxychloroquine), immunosuppressants (*e.g.* methotrexate and azathioprine), cyclophosphamide and mycophenolic acid, immunosuppressive drugs and analgesics, such as nonsteroidal anti-inflammatory drugs, opiates (*e.g.* dextropropoxyphene and co-codamol), opioids (*e.g.* hydrocodone, oxycodone, MS Contin, or methadone) and the fentanyl duragesic transdermal patch.

In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of psoriasis, particular agents include but are not limited to: topical treatments such as bath solutions, moisturizers, medicated creams and ointments containing coal tar, dithranol (anthralin), corticosteroids like desoximetasone (Topicort™), fluocinonide, vitamin D3 analogues (for example, calcipotriol), argan oil and retinoids (etretinate, acitretin, tazarotene), systemic treatments such as methotrexate, cyclosporine, retinoids, tioguanine, hydroxyurea, sulfasalazine, mycophenolate mofetil, azathioprine, tacrolimus, fumaric acid esters or biologics such as Amevive™, Enbrel™, Humira™, Remicade™, Raptiva™ and ustekinumab (a IL-12 and IL-23 blocker). Additionally, a compound of the invention may be administered in combination with other therapies including, but not limited to phototherapy, or photochemotherapy (*e.g.* psoralen and ultraviolet A phototherapy (PUVA)).

In one embodiment, a compound of the invention is co-administered with another therapeutic agent for the treatment and/or prophylaxis of allergic reaction, particular agents include but are not limited to: antihistamines (*e.g.* cetirizine, diphenhydramine, fexofenadine, levocetirizine), glucocorticoids (*e.g.* prednisone, betamethasone, beclomethasone, dexamethasone), epinephrine, theophylline or anti-leukotrienes (*e.g.* montelukast or zafirlukast), anti-cholinergics and decongestants.

By co-administration is included any means of delivering two or more therapeutic agents to the patient as part of the same treatment regime, as will be apparent to the skilled person. Whilst the two or more agents may be administered simultaneously in a single formulation, *i.e.* as a single pharmaceutical composition, this is not essential. The agents may be administered in different formulations and at different times.

CHEMICAL SYNTHETIC PROCEDURES

General

The compound of the invention can be prepared from readily available starting materials using the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (*i.e.* reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art (Greene, T W; Wuts, P G M;, 1991).

The following methods are presented with details as to the preparation of a compound of the invention as defined hereinabove and the comparative examples. A compound of the invention may be prepared from known or commercially available starting materials and reagents by one skilled in the art of organic synthesis.

All reagents were of commercial grade and were used as received without further purification, unless otherwise stated. Commercially available anhydrous solvents were used for reactions conducted under inert atmosphere. Reagent grade solvents were used in all other cases, unless otherwise specified. Column chromatography was performed on silica gel 60 (35-70 μm). Thin layer chromatography was carried out using pre-coated silica gel F-254 plates (thickness 0.25 mm). ^{1}H NMR spectra were recorded on a Bruker DPX 400 NMR spectrometer (400 MHz or a Bruker Advance 300 NMR spectrometer (300 MHz). Chemical shifts (δ) for 1H NMR spectra are reported in parts per million (ppm) relative to tetramethylsilane (δ 0.00) or the appropriate residual solvent peak, i.e. $CHCl_3$ (δ 7.27), as internal reference. Multiplicities are given as singlet (s), doublet (d), triplet (t), quartet (q), quintuplet (quin), multiplet (m) and broad (br). Electrospray MS spectra were obtained on a Waters platform LC/MS spectrometer or with Waters Acquity UPLC with Waters Acquity PDA detector and SQD mass spectrometer. Columns used: UPLC BEH C18 1.7μm 2.1x5 mm VanGuard Pre-column with Acquity UPLC BEH C18 1.7μm 2.1x30 mm Column or Acquity UPLC BEH C18 1.7μm 2.1x50 mm Column. All the methods are using MeCN/H_2O gradients. MeCN and H_2O contain either 0.1% Formic Acid or NH_3 (10 mM). LC-MS columns used: Waters XBridge Prep OBD C18 5 μm 30 mm ID × 100 mm L (preparative column) and Waters XBridge BEH C18 5 μm 4.6 mm ID × 100 mm L (analytical column). All the methods are using either MeOH/H_2O or MeCN/H_2O gradients. MeOH, MeCN and H_2O contain either 0.1% Formic Acid or 0.1% Diethylamine. Microwave heating was performed with a Biotage Initiator. Celpure® P65 is a filtration aid, commercial product (cas number 61790-53-2).

List of abbreviations used in the experimental section:

µL	microliter
APMA	4-aminophenylmercuric acetate
app t	Apparent triplet
AUC	Area Under the Curve
BAL	Broncho-alveolar lavage
BALF	Broncho-alveolar lavage fluid
bd	Broad doublet
Boc	tert-Butyloxy-carbonyl
bs	Broad singlet
BSA	Bovine serum albumine
bt	Broad triplet
Cat.	Catalytic amount
cDNA	copy deoxyribonucleic acid
d	doublet
DavePhos	2-Dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
Desc'd	Described in details
DIAD	Diisopropyl azodicarboxylate
DIPE	Diisopropylether
DIPEA	N,N-diisopropylethylamine
DMA	Dimethylacetamide
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
dppf	1,1'- Bis(diphenylphosphino) ferrocene
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide)
EDC.HCl	N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride

eq.	Equivalent
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
FBS	Fetal bovine serum
FITC	Fluorescein Isothiocyanate
Fmoc	9-Fluorenylmethoxycarbonyl
g	gram
h	hour
HOBt	Hydroxybenzotriazole
HPLC	High pressure liquid chromatography
HRP	horseradish peroxydase
Int	Intermediate
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
kg	kilogram
L	liter
LC-MS	Liquid Chromatography-Mass Spectrometry
LPC	lysophosphatidylcholine
m	multiplet
MeCN	Acetonitrile
MeOH	Methanol
mg	milligram
min	minute
mL	millilitre
mmol	millimoles
MMP	Matrix Metallo Proteinase
MS Ms'd	Mass measured by LC-MS
MW	Molecular weight
N.A.	Not available
NBS	N-Bromosuccinimide
nBuOH	n-Butanol
NMR	Nuclear Magnetic Resonance

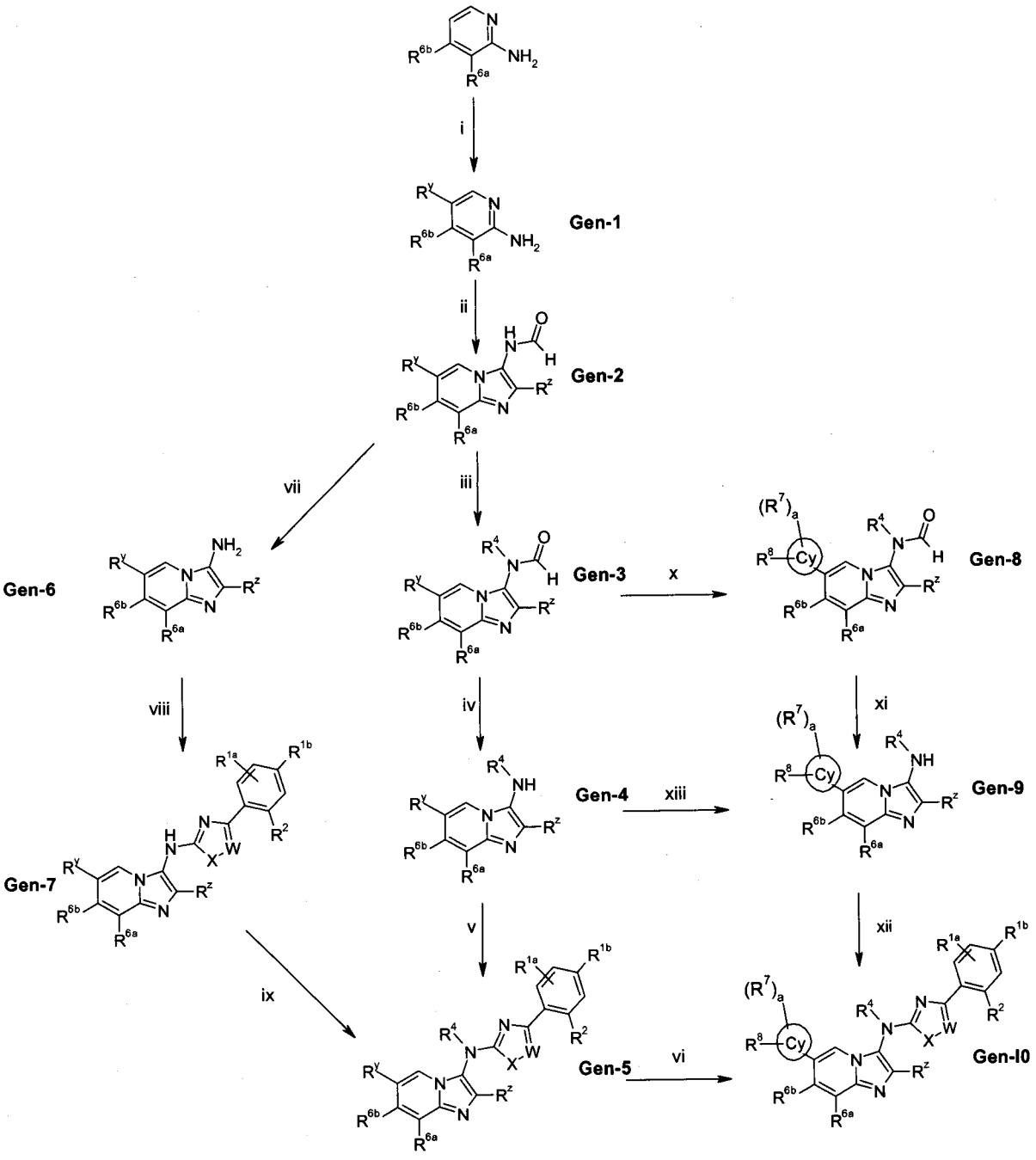
PBF	phosphate buffered formalin
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
Pd/C	Palladium on Carbon 10%
$Pd_2(dba)_3$	Tris(dibenzylideneacetone) dipalladium(0)
$PdCl_2dppf$	[1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II)
PEG	Polyethylene glycol
ppm	part-per-million
q	quartet
QrtPCR	quantitative real-time PCR
QTL	quantitative trait loci

r.t.	Room temperature
RNA	Ribonucleic acid
Rt	retention time
s	singlet
sept	septuplet
t	triplet
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TOOS	(N-ethyl-N-(2-hydroxy-3-sulfopropyl)-3-methylaniline, sodium salt dihydrate
TS	Tobacco smoke
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

SYNTHETIC PREPARATION OF THE COMPOUNDS OF THE INVENTION

Example 1. General Synthetic Methods

1.1. Synthetic methods overview



Where R^y is halo, NO_2, or - C(=O)Oalkyl, R^Z is R^5 or an alkyl, alkenyl or carbonyl group optionally substituted.

Step i : method A

Step ii : consists in one of the following methods

pain. It has been observed that LPC-induced neuropathic pain is partially reduced in ATX heterozygous knockout mice. These results support the idea that LPA is produced by autotaxin resulting in neuropathic pain (Lin M. E., 2010).

Autotaxin is also implicated in metabolic diseases, in particular obesity and diabetes (Federico, et al., 2012). In some instances, autotaxin is responsible for the lysoPLD activity released by adipocytes and exerts a paracrine control on preadipocyte growth via an LPA-dependent mechanism. In addition, autotaxin is upregulated during adipocyte differentiation and in genetic obesity. In certain instances, autotaxin mRNA is upregulated in adipocytes from db/db mice suggesting that the upregulation of autotaxin is related to the severe type 2 diabetes phenotype and adipocyte insuline resistance. In some instances, upregulation of adipocyte autotaxin is associated with type 2 diabetes in human (Ferry, 2003). The relationship between adipocyte and autotaxin biology suggests the use of an autotaxin inhibitor for the treatment of metabolic diseases.

Finally, two other conditions clearly related to autotaxin biology are cholestatic pruritus (Kremer, et al., 2010) and regulation of ocular pressure (Iyer, et al., 2012).

The current therapies are not satisfactory and therefore there remains a need to identify further compounds that may be of use in the treatment of fibrotic diseases, proliferative diseases, inflammatory diseases, autoimmune diseases, respiratory diseases, cardiovascular diseases, neurodegenerative diseases, dermatological disorders, and/or abnormal angiogenesis associated diseases. The present invention therefore provides compounds, methods for their manufacture and pharmaceutical compositions comprising a compound of the invention together with a suitable pharmaceutical carrier. The present invention also provides for the use of a compound of the invention in the preparation of a medicament for the treatment of fibrotic diseases, proliferative diseases, inflammatory diseases, autoimmune diseases, respiratory diseases, cardiovascular diseases, neurodegenerative diseases, dermatological disorders, and/or abnormal angiogenesis associated diseases.

SUMMARY OF THE INVENTION

The present invention is based on the identification of novel compounds, and their ability to act as inhibitors of autotaxin and that they may be useful for the treatment of fibrotic diseases, proliferative diseases, inflammatory diseases, autoimmune diseases, respiratory diseases, cardiovascular diseases, neurodegenerative diseases, dermatological disorders, and/or abnormal angiogenesis associated diseases. The present invention also provides methods for the production of these compounds, pharmaceutical compositions comprising these compounds and methods of treatment for fibrotic diseases, proliferative diseases, inflammatory diseases, autoimmune diseases, respiratory diseases, cardiovascular diseases, neurodegenerative diseases,

B1 (2 steps) : Route using isonitrile reagent then reaction with HCOOH

B2 (2 steps) : Route using KCN then reaction with HCOOH

Step iii : consists in one of the following methods

C1 : Alkylation with NaH as base in DMF

C2 : Alkylation with K_2CO_3 as base in acetone

Step iv : consists in one of the following methods

D1 : Deformylation under acid conditions

D2 : Deformylation under basic conditions

Step v : consists in one of the following methods

E1 (2 steps) : formation of thiourea then cyclisation to give thiazole derivative

E2 : Aromatic or heteroaromatic nucleophilic substitution

E3 (3steps) : formation of thiourea, methylation , then cyclisation to give oxadiazole derivative

C1 : NaH, DMF

Step vi : consists in one or several of the following methods

F1 : Buchwald coupling

F2 : Suzuki coupling

F3 : Negishi coupling

F4 : Copper mediated coupling

F5 : Boc deprotection

F6 : Reduction with (H_2) in presence of transition metal catalyst

F7 : Boc protection

F8 : Alkylation

F9a and F9b : Amide bond forming reaction

F10 : Reductive amination

F11 : Sulfonylation

F12a and F12b : Nucleophilic substitution

F13 : Saponification

F14 : Introduction of hydroxymethyl group

F15 : Introduction of trifluoroacetyl group

F16a and F16b : Halogenation

F17 : Copper mediated cyanation

F18 : Reduction with lithium borohydride

F19 : Synthesis of oxazoline

Step vii : consists in one of methods D

Step viii : consists in one of methods E or method H

Step ix : consists in one of methods C

Step x : consists in one or several methods F

Step xi : consists in one of methods D

Step xii : consists in one or several methods E and F

E1 (2 steps) : formation of thiourea then cyclisation to give thiazole derivative

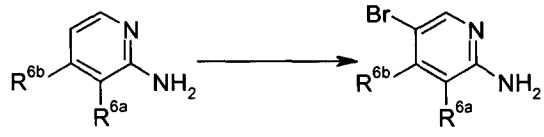
E4 : Buchwald coupling

E5 (2 steps) : SNAr then Suzuki coupling

Step xiii : consists in one or several methods F

1.2. ***General methods***

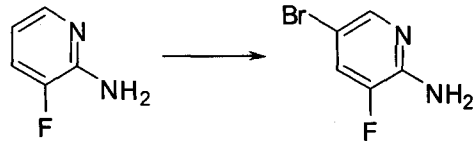
1.2.1. General method A: Synthesis of Intermediate Gen-1



Gen-1

To a solution of amino-pyridine derivative (1 eq.) in MeCN under argon at 0°C is added NBS (0.5 eq.). The reaction mixture is stirred at r.t. for 1 h then cooled to 0°C before introducing additional NBS (0.5 eq.). The reaction mixture is stirred at r.t. for 1 h then diluted in EtOAc. The organic layer is washed with a saturated $NaHCO_3$ solution, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue is diluted in DCM, washed with a 1 M NaOH solution. The organic phase is dried over Na_2SO_4, filtered and concentrated *in vacuo* to give Intermediate Gen-1.

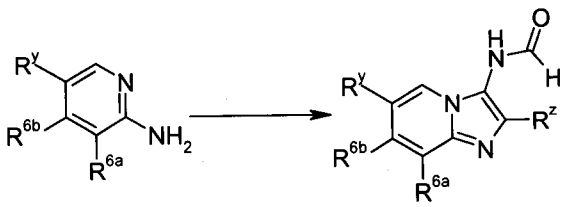
1.2.2. Illustrative synthesis of Intermediate Gen-1-a : 2-amino-5-bromo-3-fluoropyridine



To a solution of 2-amino-3-fluoro-pyridine (9.4 g, 83.1 mmol, 1 eq.) in MeCN (470 mL) under argon at 0°C was added NBS (7.4 g, 41.5 mmol, 0.5 eq.). The reaction mixture was stirred at r.t. for 1 h then cooled to 0°C before introducing additional NBS (7.39 g, 41.5 mmol, 0.5 eq.). The reaction mixture was stirred at r.t. for 1 h then diluted in EtOAc. The organic layer was washed with a saturated $NaHCO_3$ solution, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was diluted in DCM, washed with a 1 N NaOH solution. The organic phase was dried over Na_2SO_4, filtered and concentrated in vacuo to afford Intermediate Gen-1-a (2-amino-5-bromo-3-fluoropyridine).

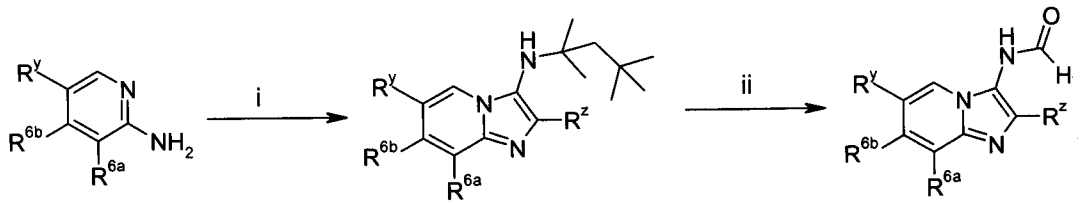
LC-MS: MW (calcd): 190 (^{79}Br), 192 (^{81}Br); m/z MW (obsd): 191 (^{79}Br M+1), 193 (^{81}Br M+1)

1.2.3. General methods B1 and B2: Synthesis of Intermediate Gen-2



Gen-1 **Gen-2**

1.2.3.1. General method B1



Gen-1 **Gen-2**

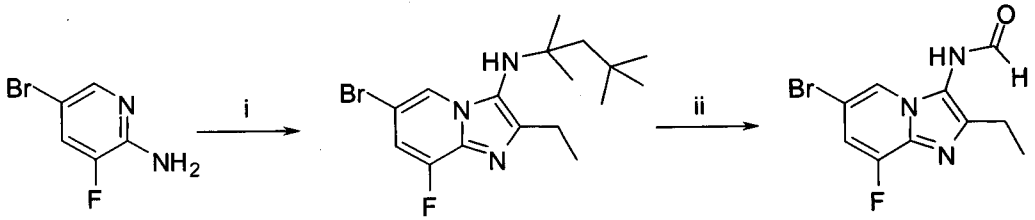
Step i)

To a solution of amino-pyridine derivative Gen-1 (1 eq.) in nBuOH under argon are added successively the aldehyde R^zCHO (2.5 eq.), $MgCl_2$ (0.04 eq.) and 1,1,3,3-tetramethylbutyl isocyanide (1.15 eq.). The reaction mixture is heated at 130 °C for 3.5 h, and then concentrated *in vacuo*. The residue is partitioned between heptane and water, stirred for 15 min and filtered on Celpure® P65. The resulting solid is then dissolved with DCM, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the expected amine.

Step ii)

A solution of the above prepared compound (1 eq.) in formic acid is heated at 80°C for 1 h. The reaction mixture is concentrated *in vacuo*. The residue is then triturated in Et_2O. The formed precipitate is filtered, rinsed and dried to afford Intermediate Gen-2.

1.2.3.2. Illustrative synthesis of Intermediate Gen-2-a: N-(6-Bromo-2-ethyl-8-fluoro-imidazo[1,2-a]pyridin-3-yl)-formamide



Step i)

To a solution of 2-amino-3-Fluoro-4-bromo-pyridine (Gen-1-a) (2 g, 10.5 mmol, 1 eq.) in nBuOH (12 mL) under argon were added successively propionaldehyde (1.9 mL, 26.2

mmol, 2.5 eq.), $MgCl_2$ (40 mg, 0.42 mmol, 0.04 eq.) and 1,1,3,3-tetramethylbutyl isocyanide (2.1 mL, 12 mmol, 1.15 eq.). The reaction mixture was heated at 130 °C for 3.5 h, then concentrated *in vacuo*.

The residue was partitioned between heptane (10 mL) and water (20 mL), stirred for 15 min and filtered on Celpure® P65. The resulting solid was then dissolved with DCM, dried over over Na_2SO_4, filtered and concentrated *in vacuo* to afford the corresponding amine. The filtrate was further extracted with DCM, the combined organic layers were washed with water, a 1 M NaOH solution, and brine dried over Na_2SO_4, filtered and concentrated *in vacuo* to deliver a second batch of the expected amine.

^{1}H NMR δ (ppm) (400 MHz, $CDCl_3$): 8.11 (1 H, s), 6.90 (1 H, d), 2.85-2.80 (1 H, m), 2.76 (2 H, q), 1.67 (2 H, s), 1.37 (3 H, t), 1.16 (6 H, s), 1.11 (9 H, s).

LC-MS: MW (calcd): 369 (^{79}Br), 371 (^{81}Br); m/z MW (obsd): 370 (^{79}Br M+1), 372 (^{81}Br M+1)

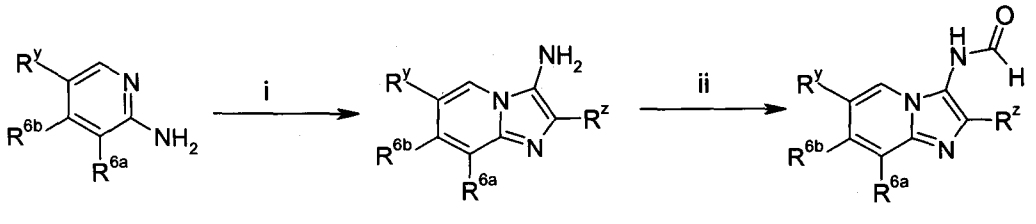
Step ii)

A solution of amine (2.9 g, 7.83 mmol, 1 eq.) in formic acid (23 mL) was heated at 80°C for 1 h. The reaction mixture was then concentrated *in vacuo*. The residue was triturated in toluene and evaporated twice. The resulting solid was taken up in Et_2O, stirred for 45 min, then filtered, rinsed and dried to afford Intermediate Gen-2-a.

^{1}H NMR δ (ppm) (400 MHz, $CDCl_3$): 2 rotamers 8.55 (1 H, s), 8.15 (1 H, d), 7.95 (1 H, s), 7.76 (1 H, s), 7.54-7.44 (1 H, m), 7.13-6.96 (3 H, m), 2.80 (2 H, q), 2.74 (2 H, q), 1.33 (3 H, t), 1.31 (3 H, t).

LC-MS: MW (calcd): 285 (^{79}Br), 287 (^{81}Br); m/z MW (obsd): 286 (^{79}Br M+1), 288 (^{81}Br M+1)

1.2.3.3. General method B2



Gen-1 **Gen-2**

Step i)

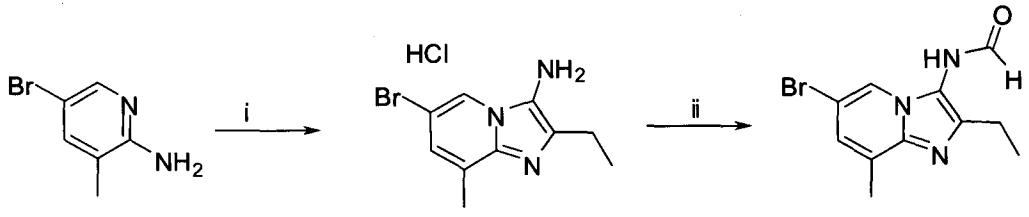
To a suspension of amino-pyridine derivative Gen-1 (1 eq.) in toluene are added the aldehyde R^zCHO (1 eq.) and benzotriazole (1 eq.). The mixture is stirred at r.t. overnight. Additional aldehyde reagent (0.06 eq.) and benzotriazole (0.06 eq.) are added. After 4 h stirring, potassium cyanide (1.2 eq.) is added, followed by EtOH. The reaction mixture is stirred at r.t.

for 5 days. The crude product mixture is then quenched with a 3 M NaOH solution. Solvents are evaporated carefully *in vacuo*. The residue is diluted with water and EtOAc. The aqueous layer is extracted with EtOAc. The combined organic layers are washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product mixture is dissolved in EtOH and carefully added to a solution of acetyl chloride (2.1 eq.) in EtOH at 0°C. The resulting reaction mixture is stirred at r.t. overnight and then concentrated to dryness to afford the corresponding imidazo[1,2-a]pyridin-3-ylamine as hydrochloride salt.

Step ii)

A solution of the above prepared imidazo[1,2-a]pyridin-3-ylamine hydrochloride salt (1 eq.) in formic acid is heated at 90°C for 2 h. Solvents are evaporated *in vacuo*. The residue is dissolved in water. The mixture is carefully basified with a saturated $NaHCO_3$ solution until pH 8-9 is reached. The formed solid is filtered, washed with water and DIPE and dried to afford Intermediate Gen-2.

1.2.3.4. Illustrative synthesis of Intermediate Gen-2-d : N-(6-Bromo-2-ethyl-8-methyl-imidazo[1,2-a]pyridin-3-yl)-formamide



Step i)

To a suspension of 2-amino-5-bromo-3-methylpyridine (420 g, 2.24 mol, 1 eq.) previously washed with a saturated $NaHCO_3$ solution before use in 1.5 L of toluene under nitrogen were added propionaldehyde (248 mL, 3.36 mol, 1.5 eq.) and 1H-benzotriazole (281 g, 2.36 mol, 1.05 eq.). The resulting mixture was stirred 4 h at r.t. before adding 3.5 L of EtOH and potassium cyanide (175 g, 2.70 mol, 1.2 eq.). The reaction mixture was further stirred overnight at r.t. and 2 h at 78°C. After cooling to r.t., the mixture was quenched by addition of a 2.5 M NaOH solution (3 L).

This experiment was performed in four batches with the same quantities of reagents, the crude mixture were then pooled together and concentrated *in vacuo*. The remaining oil was diluted with EtOAc (15 L) and washed with a 2 M NaOH solution (2 × 2 L). The aqueous layer was extracted twice with EtOAc (2 × 1 L). The combined organic layers were then dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was dissolved in EtOH (2 L) and carefully added to a solution of acetyl chloride (1 L, 14.0 mol, 1.6 eq.) in EtOH (6 L). The resulting reaction mixture was stirred at r.t. overnight and then concentrated to dryness. The

residue was triturated in DCM (7 L) for 3 days, the precipitate formed was collected, washed with DCM (2 × 500 mL) and dried to afford 6-Bromo-2-ethyl-8-methyl-imidazo[1,2-a]pyridin-3-ylamine as a hydrochloride salt.

^{1}H NMR δ (ppm) (400 MHz, DMSO): 8.70 (1 H, s), 7.75 (1 H, s), 4.86 (3 H, bs), 2.81 (2 H, q), 2.56 (3 H, s), 1.56 (3 H, s).

LC-MS: MW (calcd): 253 (^{79}Br), 255 (^{81}Br); m/z MW (obsd): 254 (^{79}Br M+1), 256 (^{81}Br M+1)

Step ii)

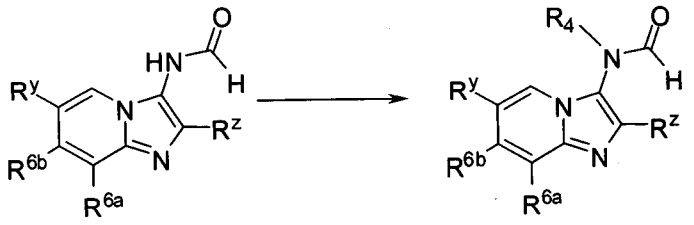
A suspension of the above prepared 6-bromo-2-ethyl-8-methyl-imidazo[1,2-a]pyridin-3-ylamine hydrochloride (785 g, 2.70 mol, 1 eq.) in formic acid (713 mL, 18.9 mol, 7 eq.) was heated to 80°C for 2 h. The crude mixture was concentrated *in vacuo* to low volume (about 400 mL). The residue was brought up in water (1 L) and a 3 M solution of NaOH (2 L), and further basified with a saturated $NaHCO_3$ solution until foaming ceased and pH reached 8-9. After homogenization for 1 h, the precipitate was filtered and washed with water (2 × 300 mL). Purification was achieved by dissolution in a mixture of toluene and MeOH 3:1 (4 L) followed by concentration *in vacuo*. Trituration of the residue in a mixture of 200 mL of MeOH and 5 L of DIPE, decantation and filtration of the resulting suspension afforded N-(6-bromo-2-ethyl-8-methylimidazo[1,2-a]pyridin-3-yl)formamide (Intermediate Gen-2-d).

Rotamer A: ^{1}H NMR δ (ppm) (400 MHz, DMSO): 10.2 (1 H, bs), 8.36 (1 H, s), 8.11 (1 H, s), 7.21 (1 H, s), 2.63-2.60 (2 H, m), 2.56 (3 H, s), 1.24-1.17 (3 H, m)

Rotamer B: ^{1}H NMR δ (ppm) (400 MHz, DMSO): 8.51 (1 H, s), 8.23 (1 H, s), 8.11 (1 H, s), 7.23 (1 H, s), 2.63-2.60 (2 H, m), 2.58 (3 H, s), 1.24-1.17 (3 H, m)

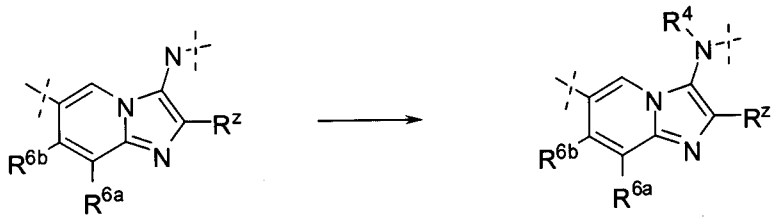
LC-MS: MW (calcd): 281 (^{79}Br), 283 (^{81}Br); m/z MW (obsd): 282 (^{79}Br M+1), 284 (^{81}Br M+1)

1.2.4. General methods C1 and C2 : Synthesis of Intermediate Gen-3



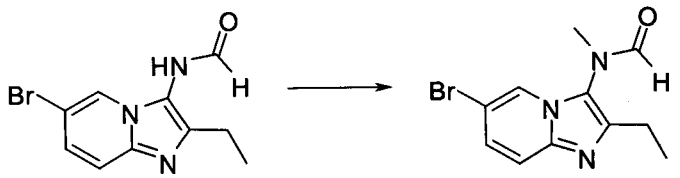
Gen-2 Gen-3

1.2.4.1. General method C1



To a solution of imidazo[1,2-a]pyridine-3-ylamine derivative (1 eq.) in DMF is added NaH (1.5 eq.) portionwise, then alkyl iodide (1.4 eq.). The reaction mixture is stirred for 1 h then quenched with water and diluted with EtOAc. The aqueous layer is extracted with EtOAc. The combined organic layers are washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue is triturated with DIPE. The solid is filtered, rinsed with DIPE and dried to give the expected intermediate.

1.2.4.2. Illustrative synthesis of Intermediate Gen3-b : N-(6-bromo-2-ethylimidazo[1,2-a]pyridin-3-yl)-N-methylformamide

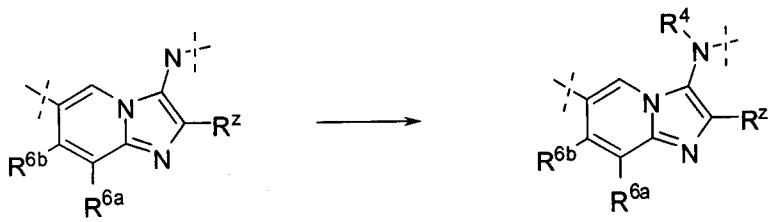


NaH (60% suspension in oil, 151 g, 3.76 mol, 1.5 eq.) was added portionwise at r.t. over a period of 30 min. to a solution of Intermediate Gen-2-b (673 g, 2.51 mol, 1 eq.) in DMF (6 L). The internal temperature increased to 35°C during the addition and the reaction mixture was directly cooled to 15°C. Methyl iodide (502 g, 3.53 mol, 1.4 eq.) was added dropwise over a period of 1 h. The reaction mixture was kept below 20°C, stirred for 1 h then quenched with water (220 mL). Solvents were evaporated *in vacuo*. The residue was diluted with water (3 L) and EtOAc (4 L). The aqueous layer was extracted with EtOAc (3 × 1 L). The combined organic layers were washed with water (2x 3 L) and brine (1.5 L), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was triturated with DIPE (2 L). The solids were filtered, rinsed with DIPE (2 × 1 L) and dried to give Intermediate Gen3-b.

^{1}H NMR δ (ppm) (400 MHz, $CDCl_3$): 7.92 (1 H, s), 7.78 (1 H, s), 7.33 (1 H, d), 7.30 (1 H, d), 3.25 (3 H, s), 2.72 (2 H, q), 1.35 (3 H, t).

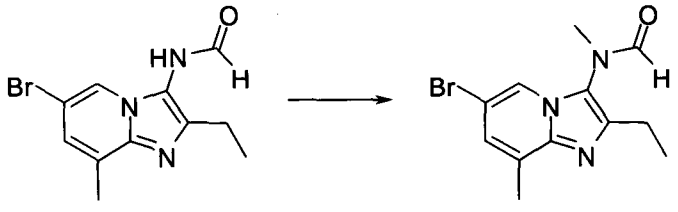
LC-MS: MW (calcd): 281 (^{79}Br), 283 (^{81}Br); m/z MW (obsd): 284 (^{81}Br M+1)

1.2.4.3. General method C2



To a suspension of imidazo[1,2-a]pyridine-3-ylamine derivative (1 eq.) in acetone are added potassium carbonate (3 eq.) and alkyl iodide (1.5 eq. to 1.9 eq.). The reaction mixture is stirred at a temperature comprised between r.t. and refluxing temperature. If after stirring overnight, the reaction is not complete, additional alkyl iodide (0.07 eq.) is then introduced and stirring is continued for 1 h. The reaction mixture is filtered and washed with acetone and DCM. The filtrate is concentrated *in vacuo* and the residue is partitioned between DCM and water. The aqueous layer is further extracted with DCM. The combined organic layers are then washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The solid is triturated with Et_2O at r.t. for 1 h, filtered off and dried to afford the expected Intermediate.

1.2.4.4. Illustrative synthesis of Intermediate Gen-3-e: N-(6-bromo-2-ethyl-8-methylimidazo[1,2-a]pyridin-3-yl)-N-methylformamide



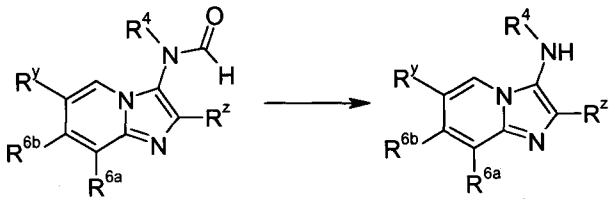
To a suspension of formamide Gen-2-d (720 g, 2.55 mol, 1 eq.) in 5 L of acetone were added potassium carbonate (1 kg, 7.66 mol, 3 eq.) and methyl iodide (700 g, 4.93 mol, 1.9 eq.). The reaction mixture was heated to 40°C overnight. Additional methyl iodide (25 g, 0.18 mol, 0.07 eq.) was then introduced and stirring continued for 1 h at 40°C. The reaction mixture was filtered and washed with acetone (2 × 300 mL) and DCM (2 × 300 mL). The filtrate was concentrated *in vacuo* and the residue was partitioned between DCM (3 L) and water (1 L). The aqueous layer was further extracted with DCM. The combined organic layers were then washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The solid was triturated with Et_2O (1 L) at r.t. for 1 h, filtered off and dried to afford Intermediate Gen-3-e.

Rotamer A (Major): ^{1}H NMR δ (ppm) (400 MHz, $CDCl_3$): 8.19 (1 H, s), 7.78 (1 H, s), 7.15 (1 H, s), 3.24 (3 H, s), 2.72 (2 H, q), 2.59 (3 H, s), 1.31 (3 H, t)

Rotamer B (Minor): ^{1}H NMR δ (ppm) (400 MHz, $CDCl_3$): 8.49 (1 H, s), 7.65 (1 H, s), 7.08 (1 H, s), 3.36 (3 H, s), 2.72 (2 H, q), 2.59 (3 H, s), 1.31 (3 H, t)

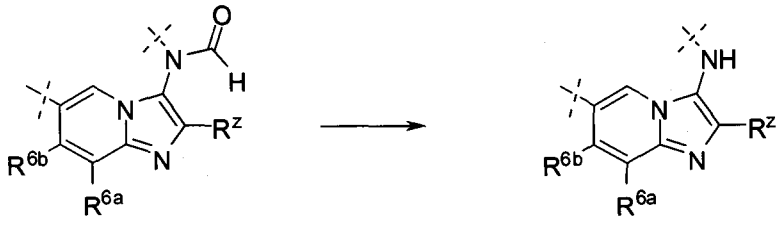
LC-MS: MW (calcd): 295 (^{79}Br), 297 (^{81}Br); m/z MW (obsd): 296 (^{79}Br M+1), 298 (^{81}Br M+1)

1.2.5. General methods D1 and D2: Synthesis of Intermediate Gen-4



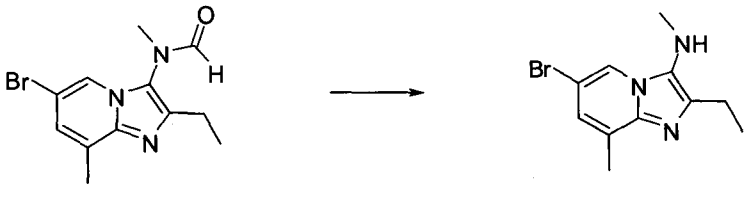
Gen-3 **Gen-4**

1.2.5.1. General method D1



A 4 M HCl solution in dioxane or 1.25 M HCl solution in MeOH (9 eq.) is added to a solution of imidazo[1,2-a]pyridine-3-yl formamide derivative (1 eq.) in MeOH. The reaction mixture is stirred at a room temperature or refluxed for 3 h. Additional 4 M HCl solution (1.5 eq.) is added and stirring is continued until completion of the reaction. The reaction mixture is then concentrated in vacuo to afford the expected intermediate.

1.2.5.2. Illustrative synthesis of Intermediate Gen-4-d : (6-Bromo-2-ethyl-8-methyl-imidazo[1,2-a]pyridin-3-yl)-methyl-amine

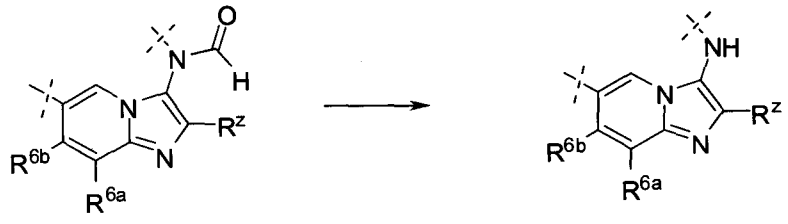


Intermediate Gen-3-e (80 g, 270 mmol, 1 eq.) was dissolved in a 1.25 M HCl solution in MeOH (540 mL, 2.5 eq.) and the resulting mixture was refluxed overnight. 270 mL of 1.25 M HCl solution in MeOH were added and heating continued overnight. After 48 h, additional 70 mL of the 1.25 M HCl solution in MeOH were introduced in the reaction mixture. Heating was maintained overnight until conversion was complete. The crude mixture was then concentrated *in vacuo* and the residue was partitioned between EtOAc (300 mL) and water (700 mL). A saturated $NaHCO_3$ solution was added until pH reached 8-9. The aqueous layer was extracted twice with EtOAc (2 × 300 mL). The combined organic layers were then washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give Intermediate Gen-4-d (6-bromo-2-ethyl-8-methyl-imidazo[1,2-a]pyridin-3-yl)-methyl-amine) as a free base.

^1H NMR δ (ppm) (400 MHz, $CDCl_3$): 8.05 (1 H, s), 7.04 (1 H, s), 2.84-2.78 (5 H, m), 2.60 (3 H, s), 1.35 (3 H, t)

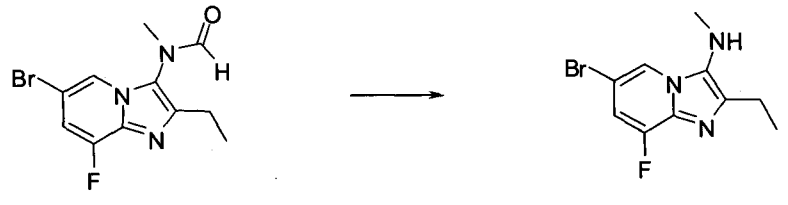
LC-MS: MW (calcd): 267 (^{79}Br), 269 (^{81}Br); m/z MW (obsd): 268 (^{79}Br M+1), 270 (^{81}Br M+1)

1.2.5.3. General method D2



A 10 M aqueous KOH solution (15 eq.) is added to a solution of imidazo[1,2-a]pyridine-3-yl formamide derivative (1 eq.) in MeOH. The reaction mixture is stirred at r.t. for 3 h, then quenched with brine and MeOH is removed *in vacuo*. The remaining aqueous phase is extracted with DCM three times. The combined organic layers are washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the expected intermediate as a free base.

1.2.5.4. Illustrative synthesis of Intermediate Gen-4-a: (6-Bromo-2-ethyl-8-fluoro-imidazo[1,2-a]pyridin-3-yl)-methyl-amine



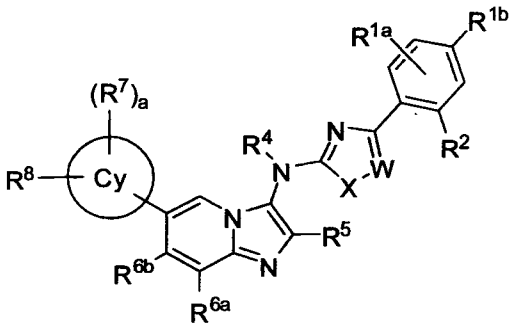
A 10 M aqueous KOH solution (25 mL, 250 mmol, 15 eq.) was added to a solution of imidazo-pyridine Intermediate Gen-3-a (5 g, 16.67 mmol, 1 eq.) in 25 mL of MeOH. The reaction mixture was stirred at r.t. for 3 h, then quenched with brine and MeOH was removed *in vacuo*. The remaining aqueous phase was extracted with DCM three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford Intermediate Gen-4-a as a free base.

LC-MS: MW (calcd): 271 (^{79}Br), 273 (^{81}Br); m/z (obsd): 272 (^{79}Br M+1), 274(^{81}Br M+1)

1.2.6. General Methods E1, E2, E3 and C: Synthesis of Intermediate Gen-5

CLAIMS

1) A compound according to Formula I:



I

wherein

R^{1a} is H, halo or C_{1-4} alkyl;

R^{1b} is:

- halo,
- C_{1-4} alkyl (which alkyl is optionally substituted with one or more independently selected halo), or
- C_{1-4} alkoxy (which alkoxy is optionally substituted with one or more independently selected halo);

X is –S-, -O-, –N=CH-, –CH=N- or –CH=CH-;

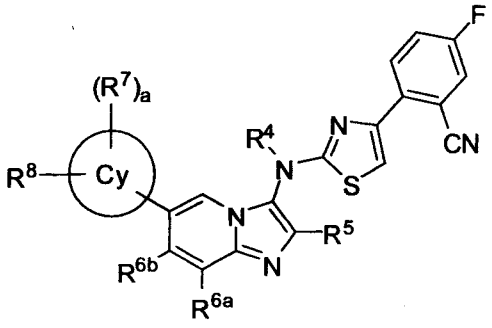
W is N, or CR^3

when W is N, R^2 is:

- H,
- -CN,
- halo,
- C_{1-4} alkyl (which alkyl is optionally substituted with one or more independently selected OH, or CN)
- $-C(=O)CH_3$,
- $-C(=O)CF_3$,
- $-C(=O)OCH_3$,
- $-C(=O)NH_2$, or
- $-NHC(=O)CH_3$, or

when W is CR^3, one of R^2 or R^3 is:

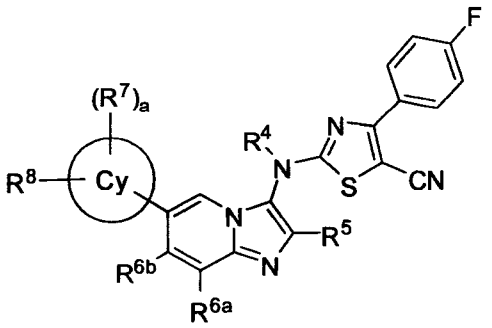
- H,
- -CN,
- halo,



II

wherein Cy, R^4, R^5, R^{6a}, R^{6b}, R^7, R^8 and the subscript a are according to claim 1.

4) A compound or pharmaceutically acceptable salt thereof, according to claim 1, wherein the compound is according to Formula III:



III

wherein Cy, R^4, R^5, R^{6a}, R^{6b}, R^7, R^8 and the subscript a are according to claim 1.

5) A compound or pharmaceutically acceptable salt thereof, according to claim 1, wherein R^5 is $-CH_3$, or $-C_2H_5$.

6) A compound or pharmaceutically acceptable salt thereof, according to claim 4, wherein R^5 is $-CH_2-CH_2-CN$, $-CH_2-CH_2-OH$, $-CH_2-CF_3$, or $-CH_2-CH_2-C(=O)NH_2$.

7) A compound or pharmaceutically acceptable salt thereof, according to claim 1, wherein Cy is 4-10 membered mono or bicyclic heterocycloalkyl containing one or more heteroatoms independently selected from O, N, and S.

8) A compound or pharmaceutically acceptable salt thereof, according to claim 1, wherein the subscript a is 0.