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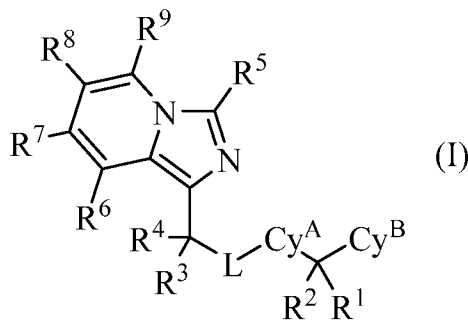
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(54) Titre : IMIDAZOPYRIDINES SUBSTITUEES EN TANT QU'INHIBITEURS DE LA KALLICREINE PLASMATIQUE ET
LEURS UTILISATIONS

(54) Title: SUBSTITUTED IMIDAZOPYRIDINES AS INHIBITORS OF PLASMA KALLIKREIN AND USES THEREOF



(57) **Abrégé/Abstract:**

The present invention provides compounds and compositions thereof which are useful as inhibitors of plasma kallikrein and which exhibit desirable characteristics for the same.

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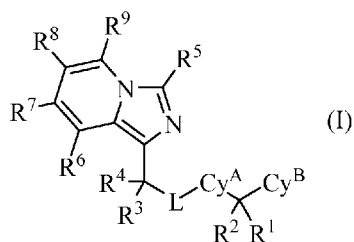
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(54) Title: SUBSTITUTED IMIDAZOPYRIDINES AS INHIBITORS OF PLASMA KALLIKREIN AND USES THEREOF



(57) Abstract: The present invention provides compounds and compositions thereof which are useful as inhibitors of plasma kallikrein and which exhibit desirable characteristics for the same.



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DEMANDE OU BREVET VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVET COMPREND PLUS D'UN TOME.

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SUBSTITUTED IMIDAZOPYRIDINES AS INHIBITORS OF PLASMA KALLIKREIN AND USES THEREOF

I. BACKGROUND OF THE INVENTION

[0001] Plasma Kallikrein (pKal) is a serine protease zymogen in blood that is converted to its catalytically active form by coagulation factor XIIa, and contributes to the innate inflammatory response and intrinsic cascade of blood coagulation. The mechanisms that lead to the activation of this pathway *in vivo* include interactions with polyphosphates released from activated platelets and deficiency of C1 inhibitor (C1-INH), the primary physiological inhibitor of pKal. pKal-mediated cleavage of high-molecular weight kininogen generates the potent vasodilator and pro-inflammatory nonapeptide bradykinin (BK), which activates the bradykinin 2 receptor. Subsequent cleavage of BK by carboxypeptidases generates des-Arg9-BK, which activates the B1 receptor. Both B1 and B2 receptors are expressed by vascular, glial, and neuronal cell types, with the highest levels of retinal expression detected in the ganglion cell layer and inner and outer nuclear layers. Activation of B1 and B2 receptors causes vasodilation and increases vascular permeability.

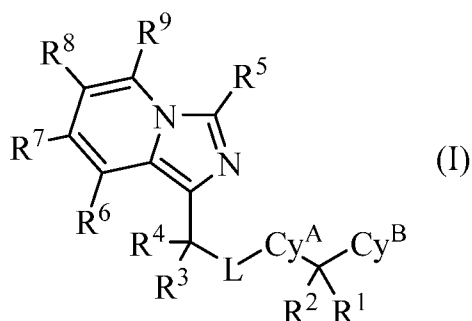
[0002] pKal is also associated with a number of disorders, such as hereditary angioedema (HAE), an autosomal dominant disease characterized by painful, unpredictable, recurrent attacks of inflammation affecting the hands, feet, face, abdomen, urogenital tract, and the larynx. Prevalence for HAE is uncertain but is estimated to be approximately 1 case per 50,000 persons without known differences among ethnic groups. HAE is caused by deficient (Type I) or dysfunctional (Type II) levels of C1-INH, which inhibits pKal, bradykinin, and other serine proteases in the blood. Individuals with hereditary angioedema (HAE) are deficient in C1-INH and consequently undergo excessive bradykinin generation, which in turn cause painful, debilitating, and potentially fatal swelling attacks. If left untreated, HAE can result in a mortality rate as high as 40% primarily due to upper airway obstruction.

II. SUMMARY OF THE INVENTION

[0003] The present disclosure is based on, at least in part, the development of a number of compounds which bind to plasma kallikrein and effectively inhibit its activity. Accordingly,

provided herein are compounds and uses thereof for targeting pKal and/or treating pKal-mediated diseases and disorders.

[0004] In some embodiments, the present invention provides a compound of Formula (I):



or a pharmaceutically acceptable salt thereof, wherein each of Cy^A , Cy^B , L , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 is defined and described in classes and subclasses herein. In certain embodiments, the present invention provides compounds of Formulae (I)-(V), as defined and described in classes and subclasses herein.

[0005] In some embodiments, the present invention also provides methods of using compounds of Formulae (I)-(V).

III. DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

A. Definitions

[0006] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in “Organic Chemistry”, Thomas Sorrell, University Science Books, Sausalito: 1999, and “March’s Advanced Organic Chemistry”, 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0007] The abbreviations used herein have their conventional meaning within the chemical and biological arts. The chemical structures and formulae set forth herein are constructed according to the standard rules of chemical valency known in the chemical arts.

[0008] The term “aliphatic” or “aliphatic group”, as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as “carbocyclyl,” “cycloaliphatic” or “cycloalkyl”), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, “cycloaliphatic” (or “carbocyclyl” or “cycloalkyl”) refers to a monocyclic C₃-C₇ hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0009] The term “heteroatom” means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR⁺ (as in N-substituted pyrrolidinyl)).

[0010] The term “unsaturated,” as used herein, means that a moiety has one or more units of unsaturation.

[0011] The term “alkylene” refers to a bivalent alkyl group. An “alkylene chain” is a polymethylene group, i.e., -(CH₂)_n-, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene

group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0012] The term “halogen” means F, Cl, Br, or I.

[0013] The term “aryl” refers to monocyclic and bicyclic ring systems having a total of five to 10 ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains three to seven ring members. The term “aryl” may be used interchangeably with the term “aryl ring”. In some embodiments, an 8-10 membered bicyclic aryl group is an optionally substituted naphthyl ring. In certain embodiments of the present invention, “aryl” refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term “aryl,” as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

[0014] The terms “heteroaryl” and “heteroar-” refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indoliziny, purinyl, naphthyridinyl, and pteridinyl. The terms “heteroaryl” and “heteroar-”, as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnoliny, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*-quinoliziny, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinoliny, tetrahydroisoquinoliny, and pyrido[2,3-*b*]-1,4-oxazin-3(4*H*)-one. A heteroaryl group may be mono- or bicyclic. The term “heteroaryl” may be used interchangeably with the terms “heteroaryl ring,” “heteroaryl group,” or “heteroaromatic,” any of which terms include rings that are optionally substituted.

[0015] As used herein, the terms “heterocyclyl,” “heterocyclic radical,” and “heterocyclic ring” are used interchangeably and refer to a stable 5- to 7-membered monocyclic or 7-10-

membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in this context in reference to a ring atom, the term “nitrogen” includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl), or ⁺NR (as in *N*-substituted pyrrolidinyl).

[0016] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothiophenyl pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms “heterocyclyl,” “heterocyclyl ring,” “heterocyclic group,” “heterocyclic moiety,” and “heterocyclic radical,” are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*-indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl, where the radical or point of attachment is on the heterocyclyl ring. A heterocyclyl group may be mono- or bicyclic. The term “heterocyclylalkyl” refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[0017] As used herein, the term “partially unsaturated” refers to a ring moiety that includes at least one double or triple bond. The term “partially unsaturated” is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0018] As used herein and unless otherwise specified, the suffix “-ene” is used to describe a bivalent group. Thus, any of the terms above can be modified with the suffix “-ene” to describe a bivalent version of that moiety. For example, a bivalent carbocycle is “carbocyclylene”, a bivalent aryl ring is “arylene”, a bivalent benzene ring is “phenylene”, a bivalent heterocycle is “heterocyclylene”, a bivalent heteroaryl ring is “heteroarylene”, a bivalent alkyl chain is “alkylene”, a bivalent alkenyl chain is “alkenylene”, a bivalent alkynyl chain is “alkynylene”, and so forth.

[0019] As described herein, compounds of the invention may, when specified, contain “optionally substituted” moieties. In general, the term “substituted,” whether preceded by the term “optionally” or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an “optionally substituted” group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term “stable,” as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0020] Suitable monovalent substituents on a substitutable carbon atom of an “optionally substituted” group are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$; $-O(CH_2)_{0-4}C(O)OR^\circ$; $-O(CH_2)_{0-4}OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R° ; $-CH=CHPh$, which may be substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}$ -pyridyl which may be substituted with R° ; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; SiR°_3 ; $-(C_{1-4}$ straight or branched alkylene) $O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene) $C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$ -(5-6 membered heteroaryl ring), or a 5-6 membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition

above, two independent occurrences of R° , taken together with their intervening atom(s), form a 3-12 membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[0021] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^\bullet$, $-(haloR^\bullet)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$, $-O(haloR^\bullet)$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^\bullet$, $-(CH_2)_{0-2}SR^\bullet$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^\bullet$, $-(CH_2)_{0-2}NR^\bullet_2$, $-NO_2$, $-SiR^\bullet_3$, $-OSiR^\bullet_3$, $-C(O)SR^\bullet$, $-(C_{1-4}$ straight or branched alkylene) $C(O)OR^\bullet$, or $-SSR^\bullet$ wherein each $R^\bullet$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include $=O$ and $=S$.

[0022] Suitable divalent substituents on a saturated carbon atom of an “optionally substituted” group include the following: $=O$, $=S$, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6 membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an “optionally substituted” group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0023] Suitable substituents on the aliphatic group of R^* include halogen, $-R^\bullet$, $-(haloR^\bullet)$, $-OH$, $-OR^\bullet$, $-O(haloR^\bullet)$, $-CN$, $-C(O)OH$, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6 membered

saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0024] Suitable substituents on a substitutable nitrogen of an “optionally substituted” group include $-R^{\dagger}$, $-NR^{\dagger}_2$, $-C(O)R^{\dagger}$, $-C(O)OR^{\dagger}$, $-C(O)C(O)R^{\dagger}$, $-C(O)CH_2C(O)R^{\dagger}$, $-S(O)_2R^{\dagger}$, $-S(O)_2NR^{\dagger}_2$, $-C(S)NR^{\dagger}_2$, $-C(NH)NR^{\dagger}_2$, or $-N(R^{\dagger})S(O)_2R^{\dagger}$; wherein each $R^{\dagger}$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted $-OPh$, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^{\dagger}$, taken together with their intervening atom(s) form an unsubstituted 3-12 membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0025] Suitable substituents on the aliphatic group of $R^{\dagger}$ are independently halogen, $-R^{\bullet}$, $-(haloR^{\bullet})$, $-OH$, $-OR^{\bullet}$, $-O(haloR^{\bullet})$, $-CN$, $-C(O)OH$, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or $-NO_2$, wherein each $R^{\bullet}$ is unsubstituted or where preceded by “halo” is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0026] As used herein, the term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1-19, incorporated herein by reference.

[0027] In certain embodiments, the neutral forms of the compounds are regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. In some embodiments, the parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0028] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the

structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention.

[0029] The term “oxo,” as used herein, means an oxygen that is double bonded to a carbon atom, thereby forming a carbonyl.

[0030] The symbol “”, except when used as a bond to depict unknown or mixed stereochemistry, denotes the point of attachment of a chemical moiety to the remainder of a molecule or chemical formula.

[0031] The articles “a” and “an” are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

[0032] A “dosing regimen” (or “therapeutic regimen”), as that term is used herein, is a set of unit doses (typically more than one) that are administered individually to a subject, typically separated by periods of time. In some embodiments, a given therapeutic agent has a recommended dosing regimen, which may involve one or more doses. In some embodiments, a dosing regimen comprises a plurality of doses each of which are separated from one another by a time period of the same length; in some embodiments, a dosing regimen comprises a plurality of doses and at least two different time periods separating individual doses.

[0033] As will be understood from context, a “reference” sample or subject is one that is sufficiently similar to a particular sample or subject of interest to permit a relevant comparison. In some embodiments, information about a reference sample is obtained simultaneously with information about a particular sample. In some embodiments, information about a reference

sample is historical. In some embodiments, information about a reference sample is stored, for example in a computer-readable medium. In some embodiments, comparison of a particular sample of interest with a reference sample establishes identity with, similarity to, or difference of the particular sample of interest relative to the reference.

[0034] As used herein, the term “sample” refers to a biological sample obtained or derived from a source of interest, as described herein. In some embodiments, a source of interest comprises an organism, such as an animal or human. In some embodiments, a biological sample comprises biological tissue or fluid. In some embodiments, a biological sample may be or comprise bone marrow; blood, e.g., whole blood; blood cells; ascites; tissue or fine needle biopsy samples; cell-containing body fluids; free floating nucleic acids; sputum; saliva; urine; cerebrospinal fluid, peritoneal fluid; pleural fluid; feces; lymph; gynecological fluids; skin swabs; vaginal swabs; oral swabs; nasal swabs; washings or lavages such as a ductal lavages or bronchoalveolar lavages; aspirates; scrapings; bone marrow specimens; tissue biopsy specimens; surgical specimens; feces, other body fluids, secretions, and/or excretions; and/or cells therefrom, *etc.* In some embodiments, a biological sample is or comprises cells obtained from a subject. In some embodiments, obtained cells are or include cells from a subject from whom the sample is obtained. In some embodiments, a sample is a “primary sample” obtained directly from a source of interest by any appropriate means. For example, in some embodiments, a primary biological sample is obtained by methods selected from the group consisting of biopsy (*e.g.*, fine needle aspiration or tissue biopsy), surgery, collection of body fluid (*e.g.*, blood (*e.g.*, whole blood), lymph, feces *etc.*), *etc.* In some embodiments, as will be clear from context, the term “sample” refers to a preparation that is obtained by processing (*e.g.*, by removing one or more components of and/or by adding one or more agents to) a primary sample. For example, filtering using a semi-permeable membrane. Such a “processed sample” may comprise, for example nucleic acids or proteins extracted from a sample or obtained by subjecting a primary sample to techniques such as amplification or reverse transcription of mRNA, isolation and/or purification of certain components, *etc.*

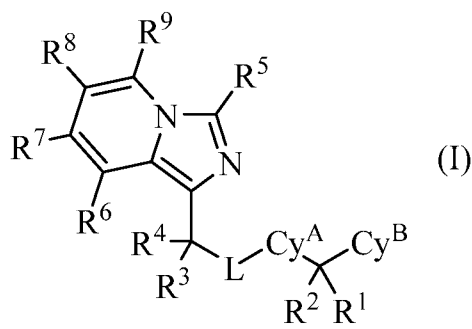
[0035] As used herein, the phrase “therapeutic agent” refers to any agent that has a therapeutic effect and/or elicits a desired biological and/or pharmacological effect, when administered to a subject.

[0036] As used herein, the term “therapeutically effective amount” refers to an amount of a therapeutic agent that confers a therapeutic effect on the treated subject, at a reasonable benefit/risk ratio applicable to any medical treatment. The therapeutic effect may be objective (i.e., measurable by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect). In particular, the “therapeutically effective amount” refers to an amount of a therapeutic agent effective to treat, ameliorate, or prevent a desired disease or condition, or to exhibit a detectable therapeutic or preventative effect, such as by ameliorating symptoms associated with the disease, preventing or delaying the onset of the disease, and/or also lessening the severity or frequency of symptoms of the disease. A therapeutically effective amount is commonly administered in a dosing regimen that may comprise multiple unit doses. For any particular therapeutic agent, a therapeutically effective amount (and/or an appropriate unit dose within an effective dosing regimen) may vary, for example, depending on route of administration, on combination with other pharmaceutical agents. Also, the specific therapeutically effective amount (and/or unit dose) for any particular subject may depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific therapeutic agent employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and/or rate of excretion or metabolism of the specific therapeutic agent employed; the duration of the treatment; and like factors as is well known in the medical arts.

[0037] As used herein, the term “treatment” (also “treat” or “treating”) refers to any administration of a substance (e.g., provided compositions) that partially or completely alleviates, ameliorates, relieves, inhibits, delays onset of, reduces severity of, and/or reduces incidence of one or more symptoms, features, and/or causes of a particular disease, disorder, and/or condition. Such treatment may be of a subject who does not exhibit signs of the relevant disease, disorder and/or condition and/or of a subject who exhibits only early signs of the disease, disorder, and/or condition. Alternatively or additionally, such treatment may be of a subject who exhibits one or more established signs of the relevant disease, disorder and/or condition. In some embodiments, treatment may be of a subject who has been diagnosed as suffering from the relevant disease, disorder, and/or condition. In some embodiments, treatment may be of a subject known to have one or more susceptibility factors that are statistically correlated with increased risk of development of the relevant disease, disorder, and/or condition.

B. Compounds

[0038] In some embodiments, a provided compound is of Formula (I):



or a pharmaceutically acceptable salt thereof,

wherein:

Cy^A is selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclene having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, and 7- to 10-membered bicyclic heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^A is substituted with 0-4 R^A groups;

each R^A is independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

Cy^B is selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-

membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, and 7- to 10-membered bicyclic heteroaryl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^B is substituted with 0-5 R^B groups;

each R^B is independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

L is selected from -QC(R)₂-, -C(R)₂Q-, -QC(Q)-, -C(Q)Q-, -C(R)₂QC(O)-, and -C(O)QC(R)₂-, wherein each Q is independently a monovalent or divalent group as valency allows, selected from the group consisting of O, N(R), or (S);

R¹, R², R³, and R⁴ are independently selected from hydrogen and C₁₋₆ aliphatic;

R⁵, R⁶, R⁷, R⁸, and R⁹ are independently selected from hydrogen, halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

each R is independently hydrogen, -CN, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur;

with the proviso that the compound is other than N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((3-chloroquinolin-6-yl)methyl)isonicotinamide.

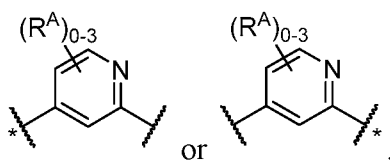
[0039] In some embodiments, a provided compound, or a pharmaceutically acceptable salt thereof, has a structure of Formula (I), with the proviso that Cy^A is a group other than pyridinediyl and the compound is other than N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((3-chloroquinolin-6-yl)methyl)isonicotinamide.

[0040] In some embodiments, Cy^A is selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclylene having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, and 7- to 10-membered bicyclic heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^A is substituted with 0-4 R^A groups.

[0041] In some embodiments, Cy^A is selected from 5- to 6-membered heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, and 7- to 10-membered bicyclic heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur wherein Cy^A is substituted with 0-4 R^A groups.

[0042] In some embodiments, Cy^A is a 5- to 6-membered heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur.

[0043] In some embodiments, Cy^A is a 6-membered heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^A is substituted with 0-3 R^A groups. In some embodiments, Cy^A is a 6-membered heteroarylene having 1 nitrogen, wherein Cy^A is substituted with 0-3 R^A groups. In some embodiments, Cy^A is pyridinediyl. In some embodiments, Cy^A is selected from either:

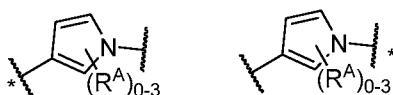


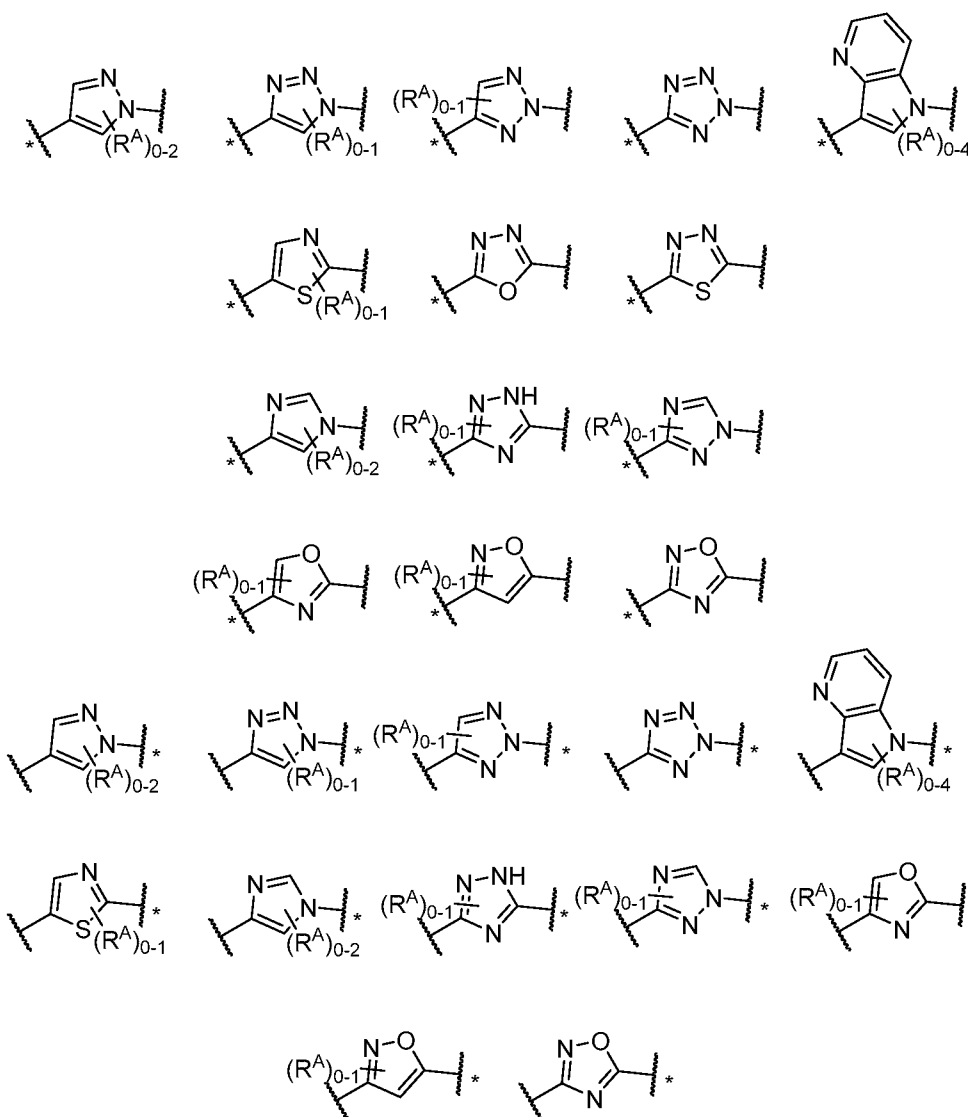
wherein * represents to point of attachment to L.

[0044] In some embodiments, Cy^A is a 5-membered heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^A is substituted with 0-2 R^A groups. In some embodiments, Cy^A is a pyrrolediyl substituted with 0-3 R^A groups. In some embodiments, Cy^A is a pyrazole-diyl substituted with 0-2 R^A groups. In some embodiments, Cy^A is a triazole-diyl substituted with 0-1 R^A groups. In some embodiments, Cy^A is a thiazole-diyl substituted with 0-1 R^A groups. In some embodiments, Cy^A is an unsubstituted tetrazole-diyl. In some embodiments, Cy^A is an unsubstituted oxadiazole-diyl. In some embodiments, Cy^A is an unsubstituted thiadiazole-diyl. In some embodiments, Cy^A is an imidazole-diyl substituted with 0-2 R^A groups. In some embodiments, Cy^A is a oxazole-diyl substituted with 0-1 R^A groups. In some embodiments, Cy^A is a isoxazole-diyl substituted with 0-1 R^A groups.

[0045] In some embodiments, Cy^A is a 7- to 10-membered bicyclic heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur wherein Cy^A is substituted with 0-4 R^A groups. In some embodiments, Cy^A is a 9-membered bicyclic heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur wherein Cy^A is substituted with 0-4 R^A groups. In some embodiments, Cy^A is a 9-membered bicyclic heteroarylene having 2 nitrogens wherein Cy^A is substituted with 0-4 R^A groups. In some embodiments, Cy^A is a pyrrolopyridinediyl substituted with 0-4 R^A groups.

[0046] In some embodiments, Cy^A is selected from the group consisting of:





wherein * represents to point of attachment to L.

[0047] In some embodiments, each R^A is independently selected from an optionally substituted group selected from C_{1-6} aliphatic, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur.

[0048] In some embodiments, substituents on an optionally substituted R^A group are independently halogen, $(CH_2)_{0-4}R^\circ$, $-(CH_2)_{0-4}OR^\circ$; and $-(CH_2)_{0-4}C(O)OR^\circ$, wherein each R° is independently hydrogen, C_{1-6} aliphatic, or a 5-6 membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0049] In some embodiments, a single instance of R^A is C_{1-6} aliphatic substituted with halogen.

[0050] In some embodiments, a single instance of R^A is C_{1-6} aliphatic substituted with $-(CH_2)_{0-4}OR^\circ$, wherein R° is hydrogen or C_{1-6} aliphatic.

[0051] In some embodiments, a single instance of R^A is C_{1-6} aliphatic substituted with $-(CH_2)_{0-4}C(O)OR^\circ$, wherein R° is hydrogen or C_{1-6} aliphatic.

[0052] In some embodiments, a single instance of R^A is C_{1-6} aliphatic is substituted with 5-6 membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0053] In some embodiments, a single instance of R^A is optionally substituted 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl. In some embodiments, a single instance of R^A is optionally substituted cyclopropyl. In some embodiments, a single instance of R^A is cyclopropyl substituted with $-(CH_2)_{0-4}C(O)OR^\circ$ and R° is hydrogen or C_{1-6} aliphatic.

[0054] In some embodiments, Cy^B is selected from phenyl, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, and 7- to 10-membered bicyclic heteroaryl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^B is substituted with 0-5 R^B groups. In some embodiments, Cy^B is selected from phenyl and 7- to 10-membered bicyclic heteroaryl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^B is substituted with 0-5 R^B groups.

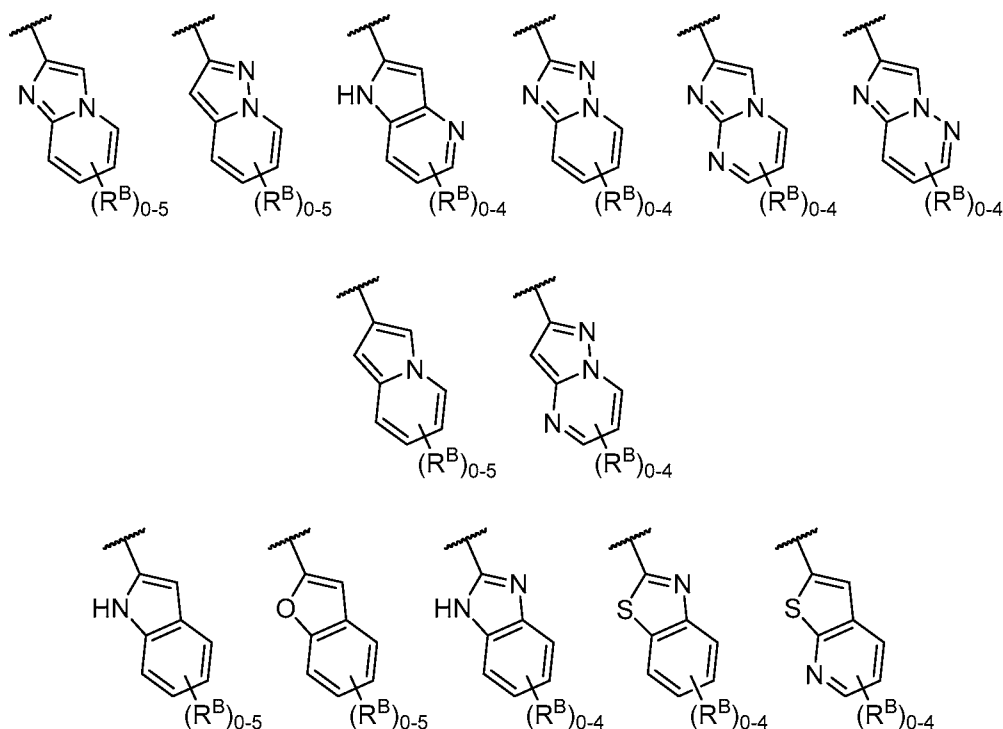
[0055] In some embodiments, Cy^B is a 7- to 10-membered bicyclic heteroaryl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^B is substituted with 0-5 R^B groups.

[0056] In some embodiments, Cy^B is a 9-membered bicyclic heteroaryl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^B is substituted with 0-5 R^B groups. In some embodiments, Cy^B is a 9-membered bicyclic heteroaryl having 2-3 nitrogens, wherein Cy^B is substituted with 0-5 R^B groups. In some embodiments, Cy^B is an imidazopyridinyl group substituted with 0-5 R^B groups. In some embodiments, Cy^B is a

pyrazolopyridinyl group substituted with 0-5 R^B groups. In some embodiments, Cy^B is a pyrrolopyridinyl group substituted with 0-4 R^B groups. In some embodiments, Cy^B is a triazolopyridinyl group substituted with 0-4 R^B groups. In some embodiments, Cy^B is an imidazopyrimidinyl group substituted with 0-4 R^B groups. In some embodiments, Cy^B is an imidazopyridazinyl group substituted with 0-4 R^B groups. In some embodiments, Cy^B is an indolizinyl group substituted with 0-5 R^B groups. In some embodiments, Cy^B is a pyrazolopyrimidinyl group substituted with 0-4 R^B groups.

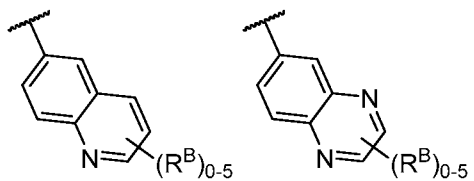
[0057] In some embodiments, Cy^B is an indolyl group substituted with 0-5 R^B groups. In some embodiments, Cy^B is a benzofuranyl group substituted with 0-5 R^B groups. In some embodiments, Cy^B is a pyrazolopyrimidinyl group substituted with 0-4 R^B groups. In some embodiments, Cy^B is a benzimidazolyl group substituted with 0-4 R^B groups. In some embodiments, Cy^B is a thienopyridinyl group substituted with 0-4 R^B groups.

[0058] In some embodiments, Cy^B is selected from the group consisting of:



[0059] In some embodiments, Cy^B is a 10-membered bicyclic heteroaryl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^B is substituted with 0-5 R^B

groups. In some embodiments, Cy^{B} is a 10-membered bicyclic heteroaryl having 1 nitrogen, wherein Cy^{B} is substituted with 0-5 R^{B} groups. In some embodiments, Cy^{B} is a quinolonyl group substituted with 0-5 R^{B} groups. In some embodiments, Cy^{B} is a quinoxalinyll group substituted with 0-5 R^{B} groups. In some embodiments, Cy^{B} is selected from the group consisting of:



[0060] In some embodiments, each R^{B} is independently selected from halogen, $-\text{CN}$, $-\text{C}(\text{O})\text{R}$, $-\text{C}(\text{O})_2\text{R}$, $-\text{N}(\text{R})_2$, $-\text{OR}$, or an optionally substituted group selected from C_{1-6} aliphatic, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein each R is independently hydrogen or C_{1-6} aliphatic.

[0061] In some embodiments, substituents on an optionally substituted R^{B} group are independently selected from halogen, $-(\text{CH}_2)_{0-4}\text{OR}^\circ$, $-\text{O}(\text{CH}_2)_{0-4}\text{OR}^\circ$, $-(\text{CH}_2)_{0-4}\text{C}(\text{O})\text{OR}^\circ$, and $-(\text{CH}_2)_{0-4}\text{N}(\text{R}^\circ)_2$ wherein each R° is independently hydrogen, C_{1-6} aliphatic, or two independent occurrences of R° , taken together with their intervening atom(s), form an optionally substituted 3-12 membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be further substituted.

[0062] In some embodiments, a single instance of R^{B} is halogen. In some embodiments, a single instance of R^{B} is $-\text{CN}$. In some embodiments, a single instance of R^{B} is $-\text{C}(\text{O})\text{R}$, wherein R is hydrogen or C_{1-6} aliphatic. In some embodiments, a single instance of R^{B} is $-\text{C}(\text{O})_2\text{R}$, wherein R is hydrogen or C_{1-6} aliphatic. In some embodiments, a single instance of R^{B} is $-\text{N}(\text{R})_2$, wherein R is hydrogen or C_{1-6} aliphatic. In some embodiments, a single instance of R^{B} is $-\text{OR}$, wherein R is hydrogen or C_{1-6} aliphatic.

[0063] In some embodiments, a single instance of R^{B} is C_{1-6} aliphatic substituted with $-(\text{CH}_2)_{0-4}\text{OR}^\circ$, wherein R° is hydrogen or C_{1-6} aliphatic.

[0064] In some embodiments, a single instance of R^B is C_{1-6} aliphatic substituted with $-O(CH_2)_{0-4}OR^\circ$, wherein R° is hydrogen or C_{1-6} aliphatic.

[0065] In some embodiments, a single instance of R^B is C_{1-6} aliphatic substituted with $-(CH_2)_{0-4}C(O)OR^\circ$, wherein R° is hydrogen or C_{1-6} aliphatic.

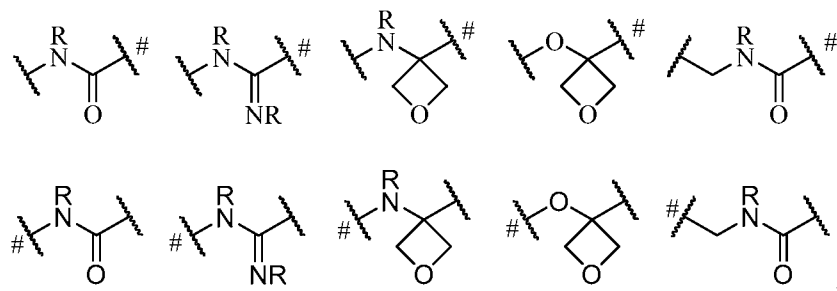
[0066] In some embodiments, a single instance of R^B is optionally substituted 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl. In some embodiments, a single instance of R^B is optionally substituted cyclopropyl. In some embodiments, a single instance of R^B is cyclopropyl is substituted with $-(CH_2)_{0-4}OR^\circ$ and R° is hydrogen or C_{1-6} aliphatic. In some embodiments, a single instance of R^B is cyclopropyl is substituted with $-(CH_2)_{0-4}C(O)OR^\circ$ and R° is hydrogen or C_{1-6} aliphatic.

[0067] In some embodiments, a single instance of R^B is optionally substituted 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur. In some embodiments, a single instance of R^B is optionally substituted 4-membered saturated monocyclic heterocyclyl having 1 oxygen. In some embodiments, a single instance of R^B is 4-membered saturated monocyclic heterocyclyl having 1 oxygen, and substituted with $-(CH_2)_{0-4}OR^\circ$, wherein R° is hydrogen or C_{1-6} aliphatic.

[0068] In some embodiments, a single instance of R^B is C_{1-6} aliphatic is substituted with $-(CH_2)_{0-4}N(R^\circ)_2$, wherein two independent occurrences of R° , taken together with their intervening atom(s), form an optionally substituted 3-12 membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be further substituted. In some embodiments, a single instance of R^B is C_{1-6} aliphatic substituted with $-(CH_2)_{0-4}N(R^\circ)_2$, wherein two independent occurrences of R° , taken together with their intervening atom(s), form an optionally substituted 5-membered saturated monocyclic ring further substituted with $=O$.

[0069] In some embodiments, L is selected from $-QC(R)_2-$, $-C(R)_2Q-$, $-C(Q)Q-$, or $-C(R)_2QC(O)-$, wherein Q is independently a monovalent or divalent group as valency allows, selected from O, N(R), or (S). In some embodiments, L is selected from $-QC(R)_2-$, $-C(R)_2Q-$, $-C(Q)Q-$, or $-C(R)_2QC(O)-$, wherein Q is independently a monovalent or divalent group as

valency allows, selected from O or N(R). In some embodiments, L is selected from the group consisting of:



wherein # represents to point of attachment to CyA.

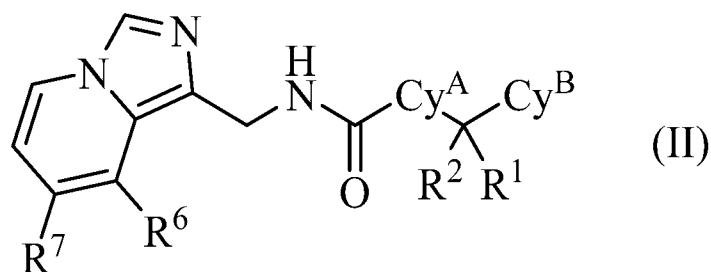
In some embodiments, L is -N(H)C(O)- . In some embodiments, L is -C(O)N(H)- .

[0070] In some embodiments, R^5 , R^6 , R^7 , R^8 , and R^9 are independently selected from hydrogen, halogen, -CN , -N(R)_2 , -OR , or an optionally substituted group selected from C_{1-6} aliphatic, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, wherein each R is independently hydrogen or C_{1-6} aliphatic. In some embodiments, R^5 , R^8 , and R^9 are hydrogen.

[0071] In some embodiments, R^6 is selected from hydrogen or halogen. In some embodiments, R^6 is hydrogen. In some embodiments R^6 is halogen. In some embodiments R^6 is F. In some embodiments R^6 is Cl. In some embodiments R^6 is Br. In some embodiments R^6 is I.

[0072] In some embodiments, R^7 is selected from halogen or an optionally substituted C_{1-6} aliphatic. In some embodiments R^7 is halogen. In some embodiments R^7 is F. In some embodiments R^7 is Cl. In some embodiments R^7 is Br. In some embodiments R^7 is I. In some embodiments, R^7 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^7 is optionally substituted C_{1-5} aliphatic. In some embodiments, R^7 is optionally substituted C_{1-4} aliphatic. In some embodiments, R^7 is optionally substituted C_{1-3} aliphatic. In some embodiments, R^7 is optionally substituted C_{1-2} aliphatic. In some embodiments, R^7 is alkynyl.

[0073] In some embodiments, a provided compound is of Formula (II):



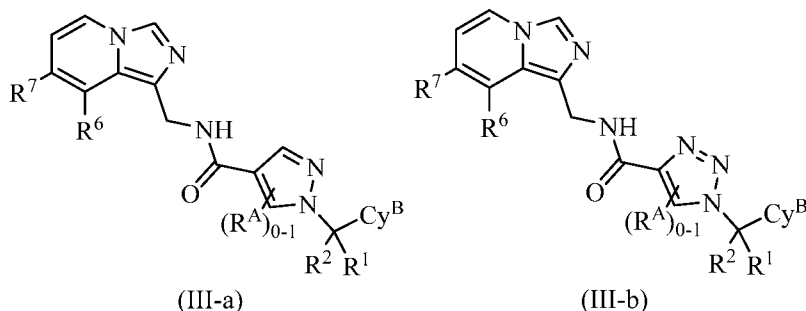
or a pharmaceutically acceptable salt thereof, wherein each of Cy^A , Cy^B , R^1 , R^2 , R^6 , and R^7 is defined and described in classes and subclasses herein;

with the proviso that the compound is other than N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((3-chloroquinolin-6-yl)methyl)isonicotinamide.

[0074] It will be understood that, unless otherwise specified or prohibited by the foregoing definition of Formula (II), embodiments of variables Cy^A , Cy^B , R^1 , R^2 , R^6 , and R^7 as defined above and described in classes and subclasses herein, also apply to compounds of Formula (II), both singly and in combination.

[0075] In some embodiments, a provided compound, or a pharmaceutically acceptable salt thereof, has a structure of Formula (II), with the proviso that Cy^A is a group other than pyridinediyl and the compound is other than N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((3-chloroquinolin-6-yl)methyl)isonicotinamide.

[0076] In some embodiments, a provided compound, or a pharmaceutically acceptable salt thereof, has a structure of Formula (III-a), Formula (III-b), Formula (III-c), Formula (III-d),





[0078] In some embodiments of Formulae (I), (II), (III-a), (III-b), (III-c), and (III-d), Cy^B is



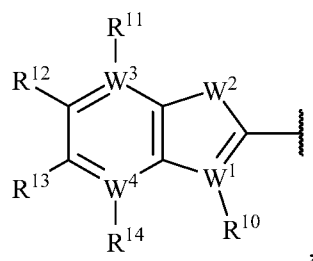
R¹⁰, R¹¹, R¹², R¹³, and R¹⁴ are each optionally present when attached to a carbon atom, and if present correspond to an occurrence of R^B independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic

carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

each R is independently hydrogen, -CN, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur.

[0079] In some embodiments, W¹ is nitrogen and W², W³ and W⁴ are carbon. In some embodiments, W² is nitrogen and W¹, W³ and W⁴ are carbon. In some embodiments, W² and W³ are nitrogen and W¹ and W⁴ are carbon. In some embodiments, W² and W⁴ are nitrogen and W¹ and W³ are carbon.

[0080] In some embodiments of Formulae (I), (II), (III-a), (III-b), (III-c), and (III-d), Cy^B is



wherein:

W² is selected from carbon, nitrogen, oxygen, and sulfur;

W¹, W³, and W⁴ are independently selected from carbon and nitrogen;

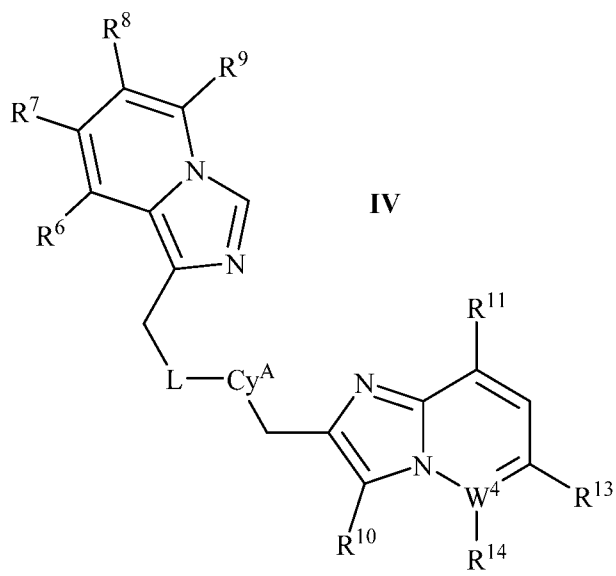
R¹⁰, R¹¹, R¹², R¹³, and R¹⁴ are each optionally present when attached to a carbon atom, and if present correspond to an occurrence of R^B independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -

$N(R)C(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)S(O)_2R$, $-OR$, $-OC(O)R$, $-OC(O)N(R)_2$, $-SR$, $-S(O)R$, $-S(O)_2R$, $-S(O)N(R)_2$, $-S(O)_2N(R)_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

each R is independently hydrogen, $-CN$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur.

[0081] In some embodiments, a provided compound is of Formula (IV):



or a pharmaceutically acceptable salt thereof,

wherein:

Cy^A is a 5-membered heteroarylene having 1-4 heteroatoms selected from oxygen or nitrogen, wherein Cy^A is substituted with 0-3 R^A groups;

each R^A is independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

L is selected from -NC(O)- and -C(O)N-;

R⁶, R⁸, and R⁹ are independently selected from hydrogen, halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R⁷ is -F, -Cl, or -Br;

W⁴ is carbon or nitrogen;

R¹⁰ and R¹¹ are each optionally present, and if present are independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R^{13} is selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₂₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R^{14} is optionally present, and if present and is selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₃₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

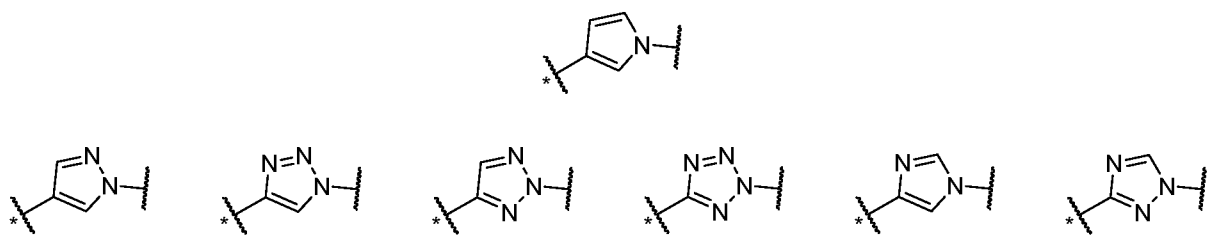
each R is independently hydrogen, -CN, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur.

[0082] In some embodiments, Cy^A is a 5-membered heteroarylene having 1-4 heteroatoms selected from oxygen or nitrogen. In some embodiments, Cy^A is a 5-membered heteroarylene having 1-4 nitrogens. In some embodiments, Cy^A is a 5-membered heteroarylene having 1-4 nitrogens, wherein when Cy^A comprises 3 nitrogens, it is not a 1,2,4-triazolediyl. In some embodiments, Cy^A is a 5-membered heteroarylene having 1-3 nitrogens. In some

embodiments, Cy^A is a 5-membered heteroarylene having 1-2 nitrogens. In some embodiments, Cy^A is a 5-membered heteroarylene having 1 nitrogen. In some embodiments, Cy^A is a 5-membered heteroarylene having 2 nitrogens. In some embodiments, Cy^A is a 5-membered heteroarylene having 3 nitrogens. In some embodiments, Cy^A is a 5-membered heteroarylene having 4 nitrogens.

[0083] In some embodiments, Cy^A is selected from the group consisting of:



wherein * represents to point of attachment to L.

[0084] In some embodiments, W⁴ is carbon. In some embodiments W⁴ is nitrogen.

[0085] In some embodiments, R¹¹ is optionally present, and if present is independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur.

[0086] In some embodiments, R¹³ is selected from -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur.

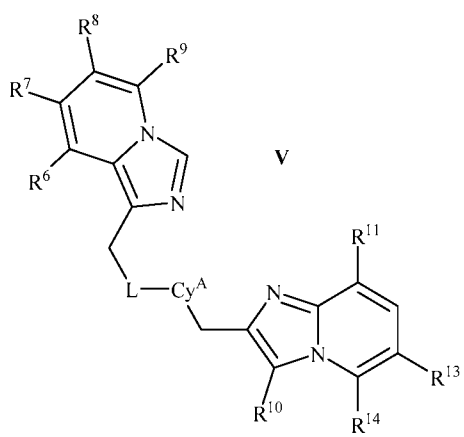
[0087] In some embodiments, R^{13} is selected from halogen, optionally substituted C_{1-6} aliphatic, and optionally substituted 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl.

[0088] In some embodiments, R^{13} is halogen. In some embodiments, R^{13} is -F. In some embodiments, R^{13} is -Cl. In some embodiments, R^{13} is -Br. In some embodiments, R^{13} is -I.

[0089] In some embodiments, R^{13} is optionally substituted C_{1-6} aliphatic. In some embodiments, R^{13} is optionally substituted C_{1-5} aliphatic. In some embodiments, R^{13} is optionally substituted C_{1-4} aliphatic. In some embodiments, R^{13} is optionally substituted C_{1-3} aliphatic. In some embodiments, R^{13} is optionally substituted C_{1-2} aliphatic.

[0090] In some embodiments, R^{13} is an optionally substituted 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl. In some embodiments, R^{13} is an optionally substituted 3- or 5-7-membered saturated or partially unsaturated monocyclic carbocyclyl. In some embodiments, R^{13} is an optionally substituted 7-membered saturated or partially unsaturated monocyclic carbocyclyl. In some embodiments, R^{13} is an optionally substituted 6-membered saturated or partially unsaturated monocyclic carbocyclyl. In some embodiments, R^{13} is an optionally substituted 5-membered saturated or partially unsaturated monocyclic carbocyclyl. In some embodiments, R^{13} is an optionally substituted 4-membered saturated or partially unsaturated monocyclic carbocyclyl. In some embodiments, R^{13} is an optionally substituted 3-membered saturated or partially unsaturated monocyclic carbocyclyl. In some embodiments, R^{13} is an optionally substituted cyclopropyl.

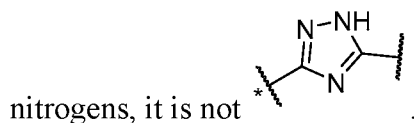
[0091] In some embodiments, a provided compound is of Formula (V):



or a pharmaceutically acceptable salt thereof,

wherein:

Cy^A is a 5-membered heteroarylene having 1-4 nitrogens, wherein when Cy^A comprises 3



L is selected from -NC(O)- and -C(O)N-;

R⁶, R⁸, and R⁹ are independently selected from hydrogen, halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R⁷ is -F, -Cl, or -Br;

R¹⁰ is optionally present, and if present is selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R¹¹ is optionally present, and if present is selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-

membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R¹³ is selected from -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- or 5-7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R¹⁴ is optionally present, and if present and is selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₃₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

each R is independently hydrogen, -CN, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur.

[0092] In some embodiments, a provided compound is selected from the group consisting of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((3-chloroquinolin-6-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-

chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((3-chloroquinolin-6-yl)methyl)isonicotinamide, 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-methylimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, 1-((6-chloro-5-methylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-isopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-(1-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxamide, 1-((7-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((6-methoxyimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-7-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-7-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-7-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-7-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, 1-((5-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, 1-((7-chloro-6-

cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((7-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5,6-dimethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, 1-((5-bromoimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, 1-((6-bromo-7-methylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrrolo[3,2-b]pyridine-3-carboxamide, N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrrolo[3,2-b]pyridine-3-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(methoxymethyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-5-(methoxymethyl)-1H-pyrazole-4-carboxamide, N-((7,8-dichloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, 1-((6-chloro-5-ethylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloro-8-methylimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, 1-((6-bromo-7-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, 1-((6-bromo-7-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)thiazole-5-carboxamide, 1-((6-bromo-5-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, 1-((6-bromo-5-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((7-(2,2-dimethylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((7-(2-methylprop-1-en-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-(2-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-

bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-(2-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-iodoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-ethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, (Z)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-(prop-1-en-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-cyclopropylimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((7-(2,2-dimethylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyclopropylpyrazolo[1,5-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide, N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide, N-((6-aminoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyanoimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyanoimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyclopropylpyrazolo[1,5-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((5-amino-7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclobutylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-methoxyimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-

pyrazole-4-carboxamide, methyl 3-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-3-yl)propanoate, 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-ethynylimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-ethylimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-(imidazo[1,2-a]pyridin-2-ylmethyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-thiadiazole-2-carboxamide, ethyl 2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carboxylate, 2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carboxylic acid, 3-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-3-yl)propanoic acid, N-(1-(7-bromoimidazo[1,5-a]pyridin-1-yl)ethyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyrimidin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-(methylamino)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-3-cyclopropyl-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-ethynylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, methyl 2-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetate, methyl 3-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-5-yl)propanoate, N-((7-bromo-3-(difluoromethyl)imidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-1H-pyrrolo[3,2-b]pyridin-2-

yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-3-cyclopropyl-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, 2-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetic acid, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxyethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, 1-((5-amino-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, 1-((5-amino-8-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-d2)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, methyl 2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)imidazo[1,2-a]pyridine-6-carboxylate, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, ethyl 3-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-3-yl)propanoate, N-(2-(7-chloroimidazo[1,5-a]pyridin-1-yl)ethyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamide, 2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)imidazo[1,2-a]pyridine-6-carboxylic acid, N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-N-((7-ethynylimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamide, ethyl 3-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acrylate, ethyl 3-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)propanoate, 3-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)propanoic acid, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(morpholinomethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-

cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(oxetan-3-yl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2-methoxyethoxy)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, 1-((8-acetyl-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2-hydroxypropan-2-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, ethyl 2-(2-((4-(((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetate, 2-(2-((4-(((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetic acid, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(3-hydroxypropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2-hydroxy-2-methylpropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-tetrazole-5-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, ethyl 2-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-3-yl)cyclopropane-1-carboxylate, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2-oxopyrrolidin-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, ethyl 1-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)imidazo[1,2-a]pyridin-8-yl)cyclopropane-1-carboxylate, 1-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)imidazo[1,2-a]pyridin-8-yl)cyclopropane-1-carboxylic acid, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-(1-(hydroxymethyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-vinylimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(3-hydroxy-3-methylbutyl)imidazo[1,2-a]pyridin-2-yl)methyl)-

1H-pyrazole-4-carboxamide, 2-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-3-yl)cyclopropane-1-carboxylic acid, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-1,2,3-triazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N'-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-N-cyano-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboximidamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-(1-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)ethyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2-methoxyethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, 3-((2H-tetrazol-5-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, ethyl 2-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)cyclopropane-1-carboxylate, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide, and N-((7-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-1-((5,6-dimethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(oxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, 2-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)cyclopropane-1-carboxylic acid, N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-tetrazole-5-carboxamide, N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide, N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide, N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-

carboxamide, N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxy(oxetan-3-yl)methyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-methoxyimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-bromo-6-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,4-triazole-3-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide, 1-((8-((1,3,4-oxadiazol-2-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide, ethyl 2-(2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetate, 2-(2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-

yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetic acid, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(methylsulfonyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1-methyl-1H-1,2,4-triazole-3-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-4H-1,2,4-triazole-3-carboxamide, ethyl 3-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)-2,2-dimethylpropanoate, ethyl 3-(2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)propanoate, 3-(2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)propanoic acid, N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyrimidin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, ethyl 2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carboxylate, 2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carboxylic acid, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(3-fluorooxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, ethyl 3-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)-2,2-dimethylpropanoate, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(oxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, 3-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)-2,2-dimethylpropanoic acid, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, 1-((6-chloro-5-methylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-

yl)methyl)-1-((6-cyclopropyl-8-morpholinoimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2H-tetrazol-5-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyclopropylpyrazolo[1,5-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)isoxazole-3-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,2,4-oxadiazole-3-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((7-cyclopropyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(1H-tetrazol-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(4H-1,2,4-triazol-4-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-formylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, 1-((8-(3-amino-3-oxopropyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-(2-cyanoethyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(oxetan-3-yl)methyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, 1-((6-chloro-8-(oxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6,7-dichloroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyclopropylthieno[2,3-b]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-3-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,2,4-oxadiazole-5-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyclopropylbenzofuran-2-yl)methyl)-

1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(difluoromethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, 1-((2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methyl)-1H-pyrazole-4-carboxylic acid, 1-((8-(2-(1H-tetrazol-5-yl)ethyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)oxazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-chlorobenzofuran-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-(1-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)ethyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2-oxotetrahydrofuran-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, 1-((8-((1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, 1-((2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methyl)-1H-pyrazole-3-carboxylic acid, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2-oxopyrrolidin-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, 1-((8-bromo-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, ethyl 3-(2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)-2,2-dimethylpropanoate, 3-(2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)-2,2-dimethylpropanoic acid, ethyl 2-((2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)oxy)acetate, 2-((2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)oxy)acetic acid, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylpyrazolo[1,5-a]pyrimidin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, ethyl 5-((2-((4-(((7-chloro-8-fluoroimidazo[1,5-

a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methyl)-1,3,4-oxadiazole-2-carboxylate, 1-((8-((1,3,4-oxadiazol-2-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyclopropyl-3-(trifluoromethyl)-1H-indol-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, 2-((2-((4-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)oxy)-2-methylpropanoic acid, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(1-fluoroethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, 1-((8-((1,3,4-oxadiazol-2-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(oxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2-oxooxazolidin-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((7-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyclopropylbenzo[b]thiophen-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylbenzofuran-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(1H-pyrazol-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, methyl 1-((2-((4-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methyl)cyclopentane-1-carboxylate, 1-((2-((4-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methyl)cyclopentane-1-carboxylic acid, 1-((2-((4-((7-chloro-8-ethoxyimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methyl)cyclopentane-1-carboxylic acid, 1-((6-chloro-1H-indol-2-yl)methyl)-N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, ethyl 2-((2-((4-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)oxy)-2-methylpropanoate, methyl 3-(2-((4-((7-chloro-8-

fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)-2-fluoropropanoate, 3-(2-(((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)-2-fluoropropanoic acid, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(isoxazol-4-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, 1-(2-(((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)-1H-imidazole-4-carboxylic acid, ethyl 3-(4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)-3-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)propanoate, 3-(4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)-3-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)propanoic acid, 3-(4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)-3-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)propanoic acid, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylbenzo[b]thiophen-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, 1-(2-(((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)-1H-pyrazole-4-carboxylic acid, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyclopropyl-7-(trifluoromethyl)pyrazolo[1,5-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyclopropyl-1H-indol-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyclopropyl-1-methyl-1H-indol-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-chlorobenzo[b]thiophen-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-1H-indol-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyclopropyl-1H-benzo[d]imidazol-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-(2-cyano-2-methylpropyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2-methyl-2-(2H-tetrazol-5-yl)propyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-7-fluoroimidazo[1,2-a]pyridin-2-

yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-3-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, ethyl 3-(2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)-3-hydroxy-2,2-dimethylpropanoate, 3-(2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)-3-hydroxy-2,2-dimethylpropanoic acid, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(1-ethyl-5,6-dioxo-5,6-dihydro-1,2,4-triazin-4(1H)-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)difluoromethyl)-1,3,4-oxadiazole-2-carboxamide, 2-(2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-5-cyclopropyl-1H-indol-1-yl)acetic acid, ethyl 3-(2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)-2-methylpropanoate, 3-(2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)-2-methylpropanoic acid, methyl 2-(2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-5-cyclopropyl-1H-indol-1-yl)acetate, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(5,6-dioxo-5,6-dihydro-1,2,4-triazin-4(1H)-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, ethyl 4-(2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)-4H-1,2,4-triazole-3-carboxylate, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(3-methyl-4H-1,2,4-triazol-4-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2-oxa-6-azaspiro[3.3]heptan-6-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, ethyl 3-(2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-5-cyclopropyl-1H-indol-1-yl)propanoate, 3-(2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-5-cyclopropyl-1H-indol-1-yl)propanoic acid, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylbenzo[d]thiazol-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-

fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(3,5-dimethyl-4H-1,2,4-triazol-4-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, methyl 4-(2-(((4-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-5-cyclopropyl-1H-indol-1-yl)benzoate, 1-((5-chloro-7-cyclopropyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)methyl)-N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylindolizin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2-methylthiazol-5-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(3-methyl-1H-1,2,4-triazol-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, 4-(2-(((4-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-5-cyclopropyl-1H-indol-1-yl)benzoic acid, ethyl 4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-imidazole-2-carboxylate, 4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-imidazole-2-carboxylic acid, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyclopropyl-7-(2-oxopyrrolidin-1-yl)pyrazolo[1,5-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(thiazol-5-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, 4-(2-(((4-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)morpholine-2-carboxylic acid, methyl 1-(2-(((4-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-b]pyridazin-8-yl)azetidine-3-carboxylate, 1-(2-(((4-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-b]pyridazin-8-yl)azetidine-3-carboxylic acid, methyl 1-(2-(((4-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-b]pyridazin-8-yl)pyrrolidine-3-carboxylate, 1-(2-(((4-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-b]pyridazin-8-yl)pyrrolidine-3-carboxylic acid, ethyl 2-(((4-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-

cyclopropylindolizine-3-carboxylate, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((1,2,3-trimethyl-1H-indol-5-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, methyl 4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrrole-2-carboxylate, 4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrrole-2-carboxylic acid, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-imidazole-4-carboxamide, methyl 2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropyl-1H-indole-3-carboxylate, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxy(3-(hydroxymethyl)oxetan-3-yl)methyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-cyano-3-cyclopropylquinolin-6-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, 2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropyl-1H-indole-3-carboxylic acid, 6-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-3-cyclopropylquinoline-8-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrrole-3-carboxamide, N-((7-chloro-6-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-(1-(7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)ethyl)-1-(1-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)ethyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxy(oxetan-3-yl)methyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-(1-(7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)ethyl)-1-((6-cyclopropyl-8-(hydroxy(oxetan-3-yl)methyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-((N-(2,2,2-trifluoroethyl)sulfamoyl)methyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, 1-([1,2,4]triazolo[1,5-a]pyridin-2-yl)methyl)-N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-tetrazole-5-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-(imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-

1-yl)methyl)-1-(imidazo[1,2-b]pyridazin-2-ylmethyl)-1H-pyrazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-(imidazo[1,2-a]pyridin-2-ylmethyl)-1H-1,2,3-triazole-4-carboxamide, 1-([1,2,4]triazolo[1,5-a]pyridin-2-ylmethyl)-N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-imidazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-2H-tetrazole-5-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-(imidazo[1,2-b]pyridazin-2-ylmethyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-(imidazo[1,2-b]pyridazin-2-ylmethyl)-1H-imidazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-(quinoxalin-6-ylmethyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-(quinoxalin-6-ylmethyl)-1H-pyrazole-4-carboxamide, 1-((8-(4H-1,2,4-triazol-4-yl)imidazo[1,2-b]pyridazin-2-yl)methyl)-N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(pyrrolidin-1-ylmethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-(oxetan-3-ylmethyl)imidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-(imidazo[1,2-a]pyridin-2-ylmethyl)-1H-imidazole-4-carboxamide, 1-((8-(aminomethyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-((2-(dimethylamino)ethoxy)methyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(((3,3,3-trifluoro-2-hydroxypropyl)amino)methyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-((2-hydroxyethoxy)methyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, 1-((8-((2-aminoethoxy)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-

a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide, or a pharmaceutically acceptable salt thereof.

C. Pharmaceutical Compositions

[0093] In another aspect, the present invention provides pharmaceutical compositions comprising a compound of Formulae (I)-(V) or a compound of Formulae (I)-(V) in combination with a pharmaceutically acceptable excipient (e.g., carrier).

[0094] The pharmaceutical compositions include optical isomers, diastereomers, or pharmaceutically acceptable salts of the inhibitors disclosed herein. A compound of Formulae (I)-(III-d) included in the pharmaceutical composition may be covalently attached to a carrier moiety, as described above. Alternatively, a compound of Formulae (I)-(V) included in the pharmaceutical composition is not covalently linked to a carrier moiety.

[0095] A “pharmaceutically acceptable carrier,” as used herein refers to pharmaceutical excipients, for example, pharmaceutically, physiologically, acceptable organic or inorganic carrier substances suitable for enteral or parenteral application that do not deleteriously react with the active agent. Suitable pharmaceutically acceptable carriers include water, salt solutions (such as Ringer's solution), alcohols, oils, gelatins, and carbohydrates such as lactose, amylose or starch, fatty acid esters, hydroxymethylcellulose, and polyvinyl pyrrolidone. Such preparations can be sterilized and, if desired, mixed with auxiliary agents such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, and/or aromatic substances and the like that do not deleteriously react with the compounds of the invention.

[0096] The compounds of the invention can be administered alone or can be coadministered to the subject. Coadministration is meant to include simultaneous or sequential administration of the compounds individually or in combination (more than one compound). The preparations can also be combined, when desired, with other active substances (e.g. to reduce metabolic degradation).

[0097] In some embodiments, a test agent as described herein can be incorporated into a pharmaceutical composition for administration by methods known to those skilled in the art and described herein for provided compounds.

D. Formulations

[0098] Compounds of the present invention can be prepared and administered in a wide variety of oral, parenteral, and topical dosage forms. Thus, the compounds of the present invention can be administered by injection (e.g. intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally). Also, the compounds described herein can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It is also envisioned that multiple routes of administration (e.g., intramuscular, oral, transdermal) can be used to administer the compounds of the invention. Accordingly, the present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier or excipient and one or more compounds of the invention.

[0099] For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substance that may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

[0100] In powders, the carrier is a finely divided solid in a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

[0101] The powders and tablets preferably contain from 5% to 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is

thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0102] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

[0103] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

[0104] When parenteral application is needed or desired, particularly suitable admixtures for the compounds of the invention are injectable, sterile solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suppositories. In particular, carriers for parenteral administration include aqueous solutions of dextrose, saline, pure water, ethanol, glycerol, propylene glycol, peanut oil, sesame oil, polyoxyethylene-block polymers, and the like. Ampoules are convenient unit dosages. The compounds of the invention can also be incorporated into liposomes or administered via transdermal pumps or patches. Pharmaceutical admixtures suitable for use in the present invention include those described, for example, in *Pharmaceutical Sciences* (17th Ed., Mack Pub. Co., Easton, PA) and WO 96/05309, the teachings of both of which are hereby incorporated by reference.

[0105] Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

[0106] Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0107] The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0108] The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 10000 mg, more typically 1.0 mg to 1000 mg, most typically 10 mg to 500 mg, according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

[0109] Some compounds may have limited solubility in water and therefore may require a surfactant or other appropriate co-solvent in the composition. Such co-solvents include: Polysorbate 20, 60, and 80; Pluronic F-68, F-84, and P-103; cyclodextrin; and polyoxyl 35 castor oil. Such co-solvents are typically employed at a level between about 0.01 % and about 2% by weight.

[0110] Viscosity greater than that of simple aqueous solutions may be desirable to decrease variability in dispensing the formulations, to decrease physical separation of components of a suspension or emulsion of formulation, and/or otherwise to improve the formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose, chondroitin sulfate and salts thereof, hyaluronic acid and salts thereof, and combinations of the foregoing. Such agents are typically employed at a level between about 0.01% and about 2% by weight.

[0111] The compositions of the present invention may additionally include components to provide sustained release and/or comfort. Such components include high molecular weight, anionic mucomimetic polymers, gelling polysaccharides, and finely-divided drug carrier substrates. These components are discussed in greater detail in U.S. Pat. Nos. 4,911,920; 5,403,841; 5,212,162; and 4,861,760. The entire contents of these patents are incorporated herein by reference in their entirety for all purposes.

E. Effective Dosages

[0112] Pharmaceutical compositions provided by the present invention include compositions wherein the active ingredient is contained in a therapeutically effective amount, i.e., in an amount effective to achieve its intended purpose. The actual amount effective for a particular application will depend, *inter alia*, on the condition being treated. For example, when administered in methods to treat HAE, such compositions will contain an amount of active ingredient effective to achieve the desired result (e.g. inhibiting pKal and/or decreasing the amount of bradykinin in a subject).

[0113] The dosage and frequency (single or multiple doses) of compound administered can vary depending upon a variety of factors, including route of administration; size, age, sex, health, body weight, body mass index, and diet of the recipient; nature and extent of symptoms of the disease being treated (e.g., the disease responsive to pKal inhibition); presence of other diseases or other health-related problems; kind of concurrent treatment; and complications from any disease or treatment regimen. Other therapeutic regimens or agents can be used in conjunction with the methods and compounds of the invention.

[0114] For any provided compound or test agent, the therapeutically effective amount can be initially determined from cell culture assays. Target concentrations will be those concentrations of active compound(s) that are capable of decreasing pKal enzymatic activity as measured, for example, using the methods described.

[0115] Therapeutically effective amounts for use in humans may be determined from animal models. For example, a dose for humans can be formulated to achieve a concentration that has been found to be effective in animals. The dosage in humans can be adjusted by monitoring pKal inhibition and adjusting the dosage upwards or downwards, as described above.

[0116] Dosages may be varied depending upon the requirements of the patient and the compound being employed. The dose administered to a patient, in the context of the present invention, should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side effects. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the

optimum effect under circumstances is reached. In some embodiments, the dosage range is 0.001% to 10% (w/v). In some embodiments, the dosage range is 0.1% to 5% (w/v).

[0117] Dosage amounts and intervals can be adjusted individually to provide levels of the administered compound effective for the particular clinical indication being treated. This will provide a therapeutic regimen that is commensurate with the severity of the individual's disease state.

F. Methods of Treatment

[0118] The present disclosure provides compounds for use in medicine. The present disclosure further provides the use of any compounds described herein for inhibiting the activity of pKal, which would be beneficial to treatment of pKal-mediated diseases and conditions. Exemplary pKal-mediated disorders include edema, which refers to swelling in the whole body of a subject or a part thereof due to inflammation or injury when small blood vessels become leaky and releases fluid into nearby tissues. In some examples, the edema is HAE. In other examples, the edema occurs in eyes, *e.g.*, diabetic macular edema (DME). The present disclosure provides methods of inhibiting the activity of pKal. In certain embodiments, the application provides a method of inhibiting the activity of pKal *in vitro* via contacting any of the compounds described herein with pKal molecules in a sample, such as a biological sample. In certain embodiments, the application provides a method of inhibiting the activity of pKal *in vivo* via delivering an effective amount of any of the compounds described herein to a subject in need of the treatment through a suitable route.

[0119] In certain embodiments, the methods comprise administering to a subject in need thereof (*e.g.*, a subject such as a human patient with edema) any of the compounds described herein or a pharmaceutically acceptable salt thereof. In certain embodiments, the methods comprise administering a compound of Formulae (I)-(V), or a pharmaceutically acceptable salt or composition thereof, to a subject in need thereof. In some embodiments, the method comprises administering a pharmaceutical composition comprising a compound of Formulae (I)-(V), or a pharmaceutically acceptable salt to a subject in need thereof.

[0120] In certain embodiments, the subject to be treated by any of the methods described herein is a human patient having, suspected of having, or at risk for edema, for example, HAE or diabetic macular edema (DME). A subject having an edema can be identified by routine medical examination, *e.g.*, laboratory tests. A subject suspected of having an edema might show one or more symptoms of the disease/disorder. A subject at risk for edema can be a subject having one or more of the risk factors associated with the disease, for example, deficiency in C1-INH as for HAE.

[0121] In certain embodiments, provided herein are methods of alleviating one or more symptoms of HAE in a human patient who is suffering from an HAE attack. Such a patient can be identified by routine medical procedures. An effective amount of one or more of the provided compounds can be given to the human patient via a suitable route, for example, those described herein. The compounds described herein may be used alone, or may be used in combination with other anti-HAE agents, for example, a C1 esterase inhibitor (*e.g.*, Cinryze[®] or Berinert[®]), a pKal inhibitor (*e.g.*, ecallantide or lanadelumab) or a bradykinin B2 receptor antagonist (*e.g.*, Firazyr[®]).

[0122] In other embodiments, provided herein are methods of reducing the risk of HAE attack in a human HAE patient who is in quiescent stage. Such a patient can be identified based on various factors, including history of HAE attack. An effective amount of one or more of the compounds can be given to the human patient *via* a suitable route, for example, those described herein. The compounds described herein may be used alone, or may be used in combination with other anti-HAE agents, for example, a C1 esterase inhibitor (*e.g.*, Cinryze[®] or Berinert[®]), a pKal inhibitor (*e.g.*, ecallantide or lanadelumab) or a bradykinin B2 receptor antagonist (*e.g.*, Firazyr[®]).

[0123] In yet other embodiments, provided herein are prophylactic treatment of HAE in human patients having risk to HAE attacks with one or more of the compounds described herein. Patients suitable for such prophylactic treatment may be human subjects having history of HAE attacks (*e.g.*, human subjects experiencing more than 2 attacks per month). Alternatively, patients suitable for the prophylactic treatment may be human subjects having no HAE attack history but bearing one or more risk factors for HAE (*e.g.*, family history, genetic defects in C1-

INH gene, etc.) Such prophylactic treatment may involve the compounds described herein as the sole active agent, or involve additional anti-HAE agents, such as those described herein.

[0124] In certain embodiments, provided herein are methods for preventing or reducing edema in an eye of a subject (*e.g.*, a human patient). In some examples, the human patient is a diabetic having, suspected of having, or at risk for diabetic macular edema (DME). DME is the proliferative form of diabetic retinopathy characterized by swelling of the retinal layers, neovascularization, vascular leak, and retinal thickening in diabetes mellitus due to leaking of fluid from blood vessels within the macula. To practice this method, an effective amount of one or more of the compounds described herein, or pharmaceutically acceptable salts thereof, may be delivered into the eye of the subject where treatment is needed. For example, the compound may be delivered by intraocular injection, or intravitreal injection. A subject may be treated with the compound as described herein, either as the sole active agent, or in combination with another treatment for DME. Non-limiting examples of treatment for DME include laser photocoagulation, steroids, VEGF pathway targeting agents (*e.g.*, Lucentis® (ranibizumab) or Eylea® (aflibercept)), and/or anti-PDGF agents.

[0125] In certain embodiments, the methods disclosed herein comprise administering to the subject an effective amount of a compound of Formulae (I)-(V), or a pharmaceutically acceptable salt or composition thereof. In some embodiments, the effective amount is a therapeutically effective amount. In some embodiments, the effective amount is a prophylactically effective amount.

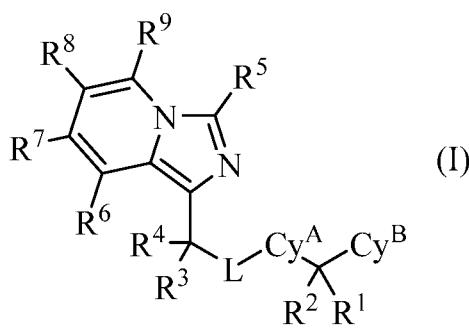
[0126] In certain embodiments, the subject being treated is an animal. The animal may be of either sex and may be at any stage of development. In certain embodiments, the subject is a mammal. In certain embodiments, the subject being treated is a human. In certain embodiments, the subject is a domesticated animal, such as a dog, cat, cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a companion animal, such as a dog or cat. In certain embodiments, the subject is a livestock animal, such as a cow, pig, horse, sheep, or goat. In certain embodiments, the subject is a zoo animal. In another embodiment, the subject is a research animal such as a rodent (*e.g.*, mouse, rat), dog, pig, or non-human primate. In certain embodiments, the animal is a genetically engineered animal. In certain embodiments, the animal is a transgenic animal.

[0127] Certain methods described herein may comprise administering one or more additional pharmaceutical agent(s) in combination with the compounds described herein. The additional pharmaceutical agent(s) may be administered at the same time as the compound of Formulae (I)-(V), or at different times than the compound of Formulae (I)-(V). For example, the compound of Formulae (I)-(V) and any additional pharmaceutical agent(s) may be on the same dosing schedule or different dosing schedules. All or some doses of the compound of Formulae (I)-(V) may be administered before all or some doses of an additional pharmaceutical agent, after all or some doses of an additional pharmaceutical agent, within a dosing schedule of an additional pharmaceutical agent, or a combination thereof. The timing of administration of the compound of Formulae (I)-(V) and additional pharmaceutical agents may be different for different additional pharmaceutical agents.

[0128] In certain embodiments, the additional pharmaceutical agent comprises an agent useful in the treatment of an edema, such as HAE or DME. Examples of such agents are provided herein.

[0129] The following numbered embodiments, while non-limiting, are exemplary of certain aspects of the present disclosure:

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof,

wherein:

Cy^A is selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclylenel having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclylene having 1-4

heteroatoms selected from oxygen, nitrogen, or sulfur, and 7- to 10-membered bicyclic heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^A is substituted with 0-4 R^A groups;

each R^A is independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

Cy^B is selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, and 7- to 10-membered bicyclic heteroaryl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^B is substituted with 0-5 R^B groups;

each R^B is independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

L is selected from -QC(R)₂-, -C(R)₂Q-, -QC(Q)-, -C(Q)Q-, -C(R)₂QC(O)-, and -C(O)QC(R)₂-, wherein each Q is independently a monovalent or divalent group as valency allows, selected from the group consisting of O, N(R), or (S);

R^1 , R^2 , R^3 , and R^4 are independently selected from hydrogen and C₁₋₆ aliphatic;

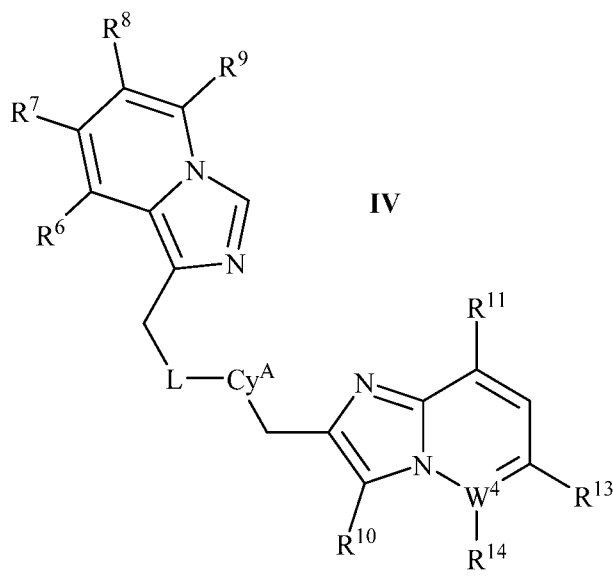
R^5 , R^6 , R^7 , R^8 , and R^9 are independently selected from hydrogen, halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

each R is independently hydrogen, -CN, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur;

with the proviso that the compound is other than N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((3-chloroquinolin-6-yl)methyl)isonicotinamide.

2. The compound of embodiment 1, wherein the compound is of Formula (IV):



or a pharmaceutically acceptable salt thereof,

wherein:

Cy^A is a 5-membered heteroaryl having 1-4 heteroatoms selected from oxygen or nitrogen, wherein Cy^A is substituted with 0-3 R^A groups;

L is selected from -NC(O)- and -C(O)N-;

R⁶, R⁸, and R⁹ are independently selected from hydrogen, halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R⁷ is -F, -Cl, or -Br;

W⁴ is carbon or nitrogen;

R¹⁰ and R¹¹ are each optionally present, and if present are independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -

$\text{S(O)}_2\text{R}$, $-\text{S(O)N(R)}_2$, $-\text{S(O)}_2\text{N(R)}_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

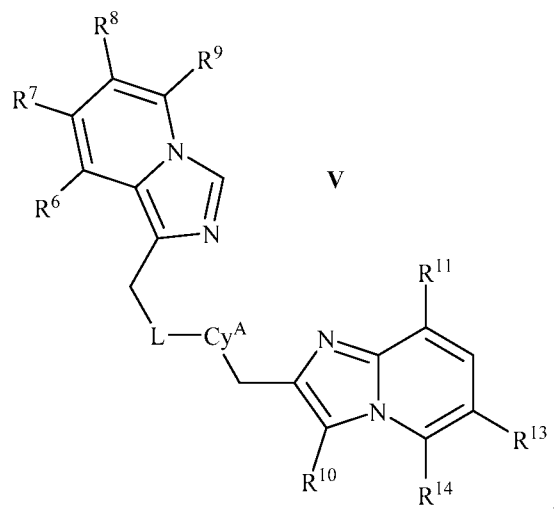
R^{13} is selected from halogen, $-\text{CN}$, $-\text{C(R)=N(R)}$, $-\text{C(O)R}$, $-\text{C(O)}_2\text{R}$, $-\text{C(O)N(R)}_2$, $-\text{NO}_2$, $-\text{N(R)-N(R)}_2$, $-\text{N(R)}_2$, $-\text{N(R)C(O)R}$, $-\text{N(R)C(O)}_2\text{R}$, $-\text{N(R)C(O)N(R)}_2$, $-\text{N(R)S(O)}_2\text{R}$, $-\text{OR}$, $-\text{OC(O)R}$, $-\text{OC(O)N(R)}_2$, $-\text{SR}$, $-\text{S(O)R}$, $-\text{S(O)}_2\text{R}$, $-\text{S(O)N(R)}_2$, $-\text{S(O)}_2\text{N(R)}_2$, or an optionally substituted group selected from C_{2-6} aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R^{14} is optionally present, and if present and is selected from halogen, $-\text{CN}$, $-\text{C(R)=N(R)}$, $-\text{C(O)R}$, $-\text{C(O)}_2\text{R}$, $-\text{C(O)N(R)}_2$, $-\text{NO}_2$, $-\text{N(R)-N(R)}_2$, $-\text{N(R)C(O)R}$, $-\text{N(R)C(O)}_2\text{R}$, $-\text{N(R)C(O)N(R)}_2$, $-\text{N(R)S(O)}_2\text{R}$, $-\text{OC(O)R}$, $-\text{OC(O)N(R)}_2$, $-\text{SR}$, $-\text{S(O)R}$, $-\text{S(O)}_2\text{R}$, $-\text{S(O)N(R)}_2$, $-\text{S(O)}_2\text{N(R)}_2$, or an optionally substituted group selected from C_{3-6} aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

each R is independently hydrogen, $-\text{CN}$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur.

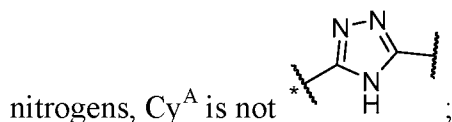
3. The compound of any one of the preceding embodiments, wherein the compound is of Formula (V):



or a pharmaceutically acceptable salt thereof,

wherein:

Cy^A is a 5-membered heteroarylene having 1-4 nitrogens, wherein when Cy^A comprises 3



L is selected from -NC(O)- and -C(O)N-;

R⁶, R⁸, and R⁹ are independently selected from hydrogen, halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R⁷ is -F, -Cl, or -Br;

R¹⁰ is optionally present, and if present is selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -

N(R)C(O)N(R)_2 , $\text{-N(R)S(O)}_2\text{R}$, -OR , -OC(O)R , -OC(O)N(R)_2 , -SR , -S(O)R , $\text{-S(O)}_2\text{R}$, -S(O)N(R)_2 , $\text{-S(O)}_2\text{N(R)}_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R^{11} is optionally present, and if present is selected from halogen, -CN , -C(R)=N(R) , -C(O)R , -C(O)N(R)_2 , -NO_2 , -N(R)-N(R)_2 , -N(R)_2 , -N(R)C(O)R , $\text{-N(R)C(O)}_2\text{R}$, -N(R)C(O)N(R)_2 , $\text{-N(R)S(O)}_2\text{R}$, -OR , -OC(O)R , -OC(O)N(R)_2 , -SR , -S(O)R , $\text{-S(O)}_2\text{R}$, -S(O)N(R)_2 , $\text{-S(O)}_2\text{N(R)}_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R^{13} is selected from -CN , -C(R)=N(R) , -C(O)R , $\text{-C(O)}_2\text{R}$, -C(O)N(R)_2 , -NO_2 , -N(R)-N(R)_2 , -N(R)_2 , -N(R)C(O)R , $\text{-N(R)C(O)}_2\text{R}$, -N(R)C(O)N(R)_2 , $\text{-N(R)S(O)}_2\text{R}$, -OR , -OC(O)R , -OC(O)N(R)_2 , -SR , -S(O)R , $\text{-S(O)}_2\text{R}$, -S(O)N(R)_2 , $\text{-S(O)}_2\text{N(R)}_2$, or an optionally substituted group selected from phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- or 5-7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R^{14} is optionally present, and if present and is selected from halogen, -CN , -C(R)=N(R) , -C(O)R , $\text{-C(O)}_2\text{R}$, -C(O)N(R)_2 , -NO_2 , -N(R)-N(R)_2 , -N(R)C(O)R , $\text{-N(R)C(O)}_2\text{R}$, -N(R)C(O)N(R)_2 , $\text{-N(R)S(O)}_2\text{R}$, -OC(O)R , -OC(O)N(R)_2 , -SR , -S(O)R , $\text{-S(O)}_2\text{R}$, -S(O)N(R)_2 , $\text{-S(O)}_2\text{N(R)}_2$, or an optionally substituted group selected from C_{3-6} aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

each R is independently hydrogen, -CN, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

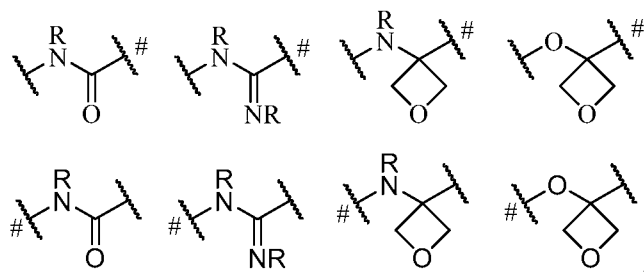
or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur.

4. The compound of any one of the preceding embodiments, wherein L is selected from -QC(R)₂-, -C(R)₂Q-, -C(Q)Q-, or -C(R)₂QC(O)-, wherein Q is independently a monovalent or divalent group as valency allows, selected from O or N(R).

5. The compound of any one of the preceding embodiments, wherein L is -N(H)C(O)-.

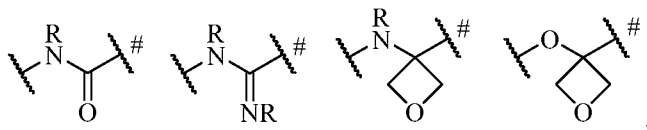
6. The compound of any one of the preceding embodiments, L is -C(O)N(H)-.

The compound of any one of the preceding embodiments, wherein L is selected from the group consisting of:



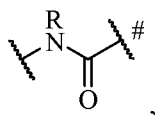
wherein # represents to point of attachment to CyA.

7. The compound of any one of the preceding embodiments, wherein L is selected from the group consisting of:



wherein # represents to point of attachment to CyA.

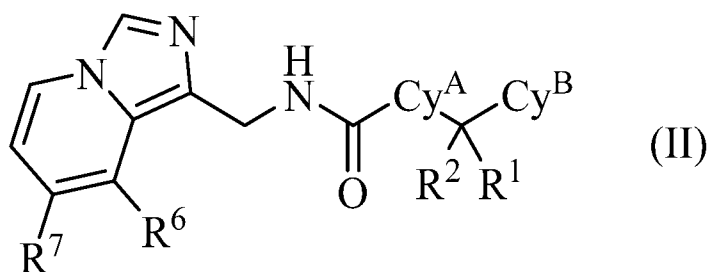
8. The compound of any one of the preceding embodiments, wherein L is:



wherein # represents to point of attachment to CyA.

9. The compound of any one of the preceding embodiments, wherein R^3 and R^4 are hydrogen.

10. The compound of any one of the preceding embodiments, wherein the compound is of Formula (II):



or a pharmaceutically acceptable salt thereof,

wherein:

Cy^A is selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclylenel having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, and 7- to 10-membered bicyclic heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^A is substituted with 0-4 R^A groups;

each R^A is independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

Cy^B is selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, and 7- to 10-membered bicyclic heteroaryl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^B is substituted with 0-5 R^B groups;

each R^B is independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R¹ and R² are independently selected from hydrogen and C₁₋₆ aliphatic;

R⁶ and R⁷ are independently selected from hydrogen, halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

each R is independently hydrogen, -CN, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur;

with the proviso that the compound is other than N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((3-chloroquinolin-6-yl)methyl)isonicotinamide.

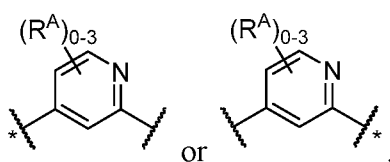
11. The compound of any one of the preceding embodiments, with the proviso that Cy^A is a group other than pyridinediyl and the compound is other than N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((3-chloroquinolin-6-yl)methyl)isonicotinamide.

12. The compound of any one of the preceding embodiments, wherein Cy^A is selected from 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, and 7- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur wherein Cy^A is substituted with 0-4 R^A groups.

13. The compound of any one of the preceding embodiments, wherein Cy^A is a 6-membered heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^A is substituted with 0-3 R^A groups.

14. The compound of any one of the preceding embodiments, wherein Cy^A is a 6-membered heteroarylene having 1 nitrogen, wherein Cy^A is substituted with 0-3 R^A groups.

15. The compound of any one of the preceding embodiments, wherein Cy^A is selected from either:



wherein * represents to point of attachment to L.

16. The compound of any one of the preceding embodiments, wherein Cy^A is a 7- to 10-membered bicyclic heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur wherein Cy^A is substituted with 0-4 R^A groups.

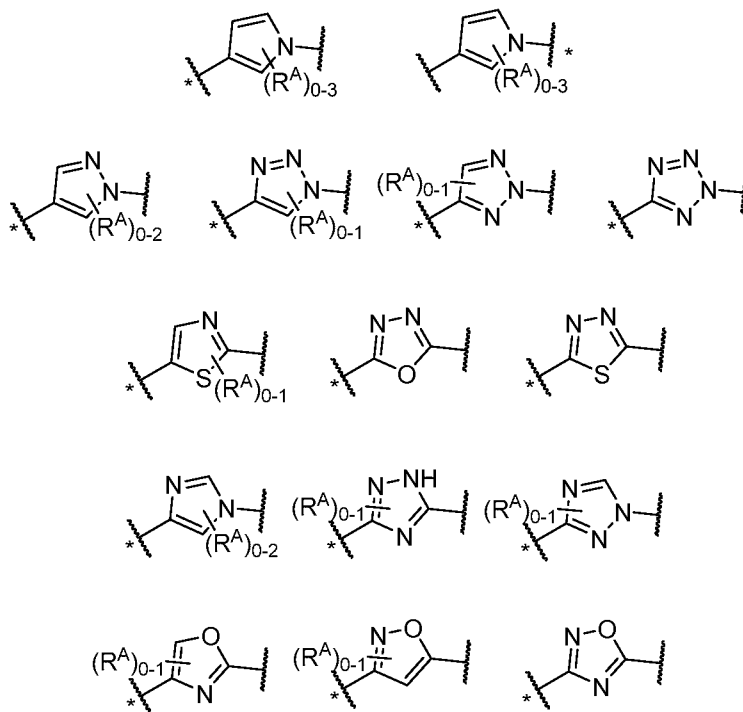
17. The compound of any one of the preceding embodiments, wherein Cy^A is a 9-membered bicyclic heteroarylene having 2 nitrogens wherein Cy^A is substituted with 0-4 R^A groups.

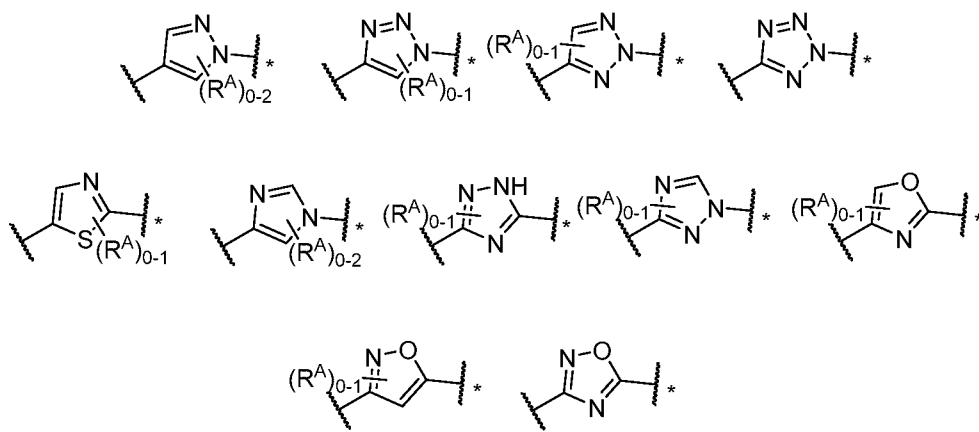
18. The compound of any one of the preceding embodiments, wherein Cy^A is a pyrrolopyridinediyl substituted with 0-4 R^A groups.

19. The compound of any one of the preceding embodiments, wherein Cy^A is a 5-membered heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^A is substituted with 0-2 R^A groups.

20. The compound of any one of the preceding embodiments, wherein Cy^A is selected from the group consisting of: pyrrolediyl substituted with 0-3 R^A groups, pyrazolediyl substituted with 0-2 R^A groups, triazolediyl substituted with 0-1 R^A groups, thiazolediyl substituted with 0-1 R^A groups, imidazolediyl substituted with 0-2 R^A groups, oxazolediyl substituted with 0-1 R^A groups, isoxazolediyl substituted with 0-1 R^A groups, unsubstituted tetrazolediyl, unsubstituted oxadiazolediyl, and unsubstituted thiadiazolediyl.

21. The compound of any one of the preceding embodiments, wherein Cy^A is selected from the group consisting of:





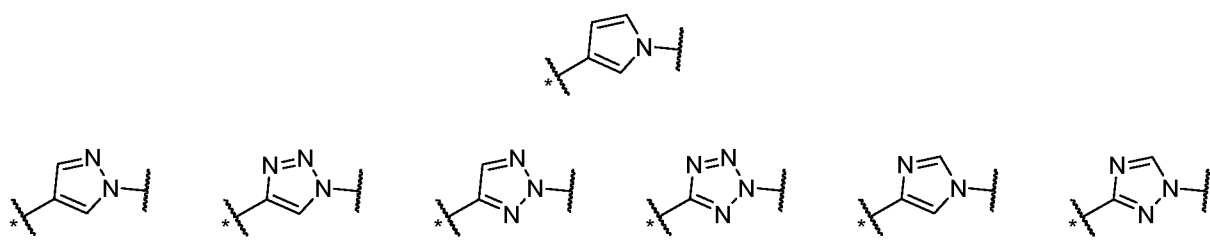
wherein * represents to point of attachment to L.

22. The compound of any one of the preceding embodiments, wherein Cy^A is a 5-membered heteroarylene having 1-4 heteroatoms selected from oxygen or nitrogen.

23. The compound of any one of the preceding embodiments, wherein Cy^A is a 5-membered heteroarylene having 1-4 nitrogens.

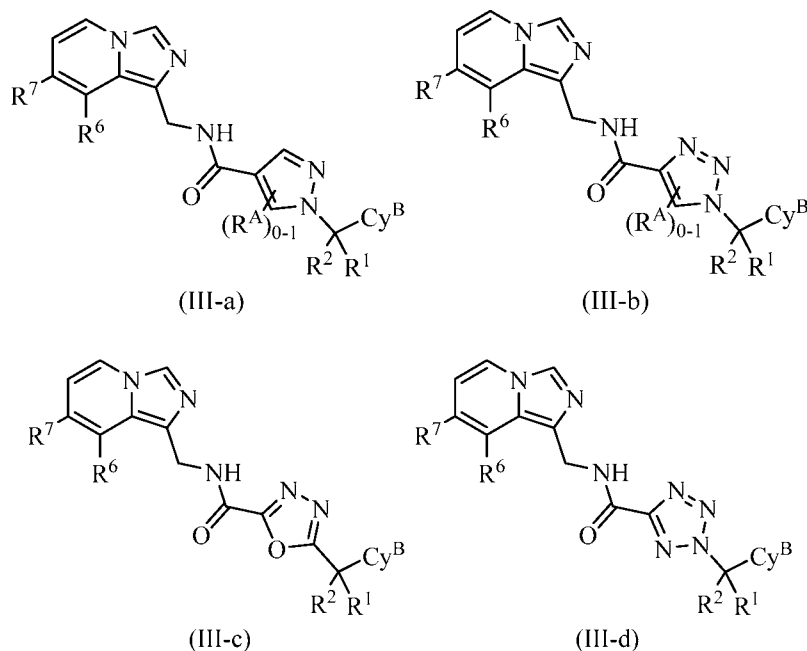
24. The compound of any one of the preceding embodiments, wherein Cy^A is a 5-membered heteroarylene having 1-4 nitrogen, wherein when Cy^A comprises 3 nitrogen, it is not a 1,2,4-triazol-5-yl.

25. The compound of any one of the preceding embodiments, wherein Cy^A is selected from the group consisting of:



wherein * represents to point of attachment to L.

26. The compound of any one of the preceding embodiments, wherein the compound is of Formula (III-a) through (III-d):



or a pharmaceutically acceptable salt thereof,

wherein:

each R^A is independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

Cy^B is selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, and 7- to 10-membered bicyclic heteroaryl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^B is substituted with 0-5 R^B groups;

each R^B is independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R¹ and R² are independently selected from hydrogen and C₁₋₆ aliphatic;

R⁶ and R⁷ are independently selected from hydrogen, halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

each R is independently hydrogen, -CN, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur.

27. The compound of any one of the preceding embodiments, wherein Cy^B is selected from phenyl, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, and 7- to 10-membered bicyclic

heteroaryl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^B is substituted with 0-5 R^B groups.

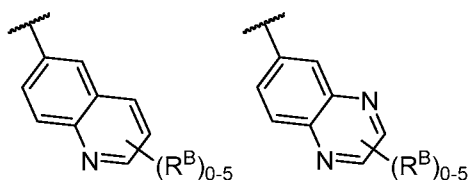
28. The compound of any one of the preceding embodiments, wherein Cy^B is a 7- to 10-membered bicyclic heteroaryl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^B is substituted with 0-5 R^B groups.

29. The compound of any one of the preceding embodiments, wherein Cy^B is a 10-membered bicyclic heteroaryl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^B is substituted with 0-5 R^B groups.

30. The compound of any one of the preceding embodiments, wherein Cy^B is a 10-membered bicyclic heteroaryl having 1 nitrogen, wherein Cy^B is substituted with 0-5 R^B groups.

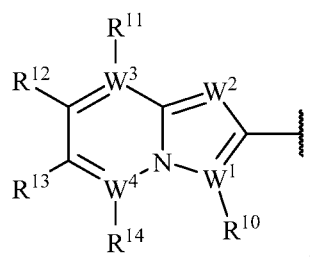
31. The compound of any one of the preceding embodiments, wherein Cy^B is selected from the group consisting of: quinolonyl group substituted with 0-5 R^B groups and quinoxalinyll group substituted with 0-5 R^B groups.

32. The compound of any one of the preceding embodiments, wherein Cy^B is selected from the group consisting of:



33. The compound of any one of the preceding embodiments, wherein Cy^B is a 9-membered bicyclic heteroaryl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^B is substituted with 0-5 R^B groups.

34. The compound of any one of the preceding embodiments, wherein Cy^B is



wherein:

W^1 , W^2 , W^3 , and W^4 are independently selected from carbon and nitrogen;

R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} are each optionally present when attached to a carbon atom, and if present correspond to an occurrence of R^B independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

each R is independently hydrogen, -CN, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur.

35. The compound of any one of the preceding embodiments, W^4 is carbon.

36. The compound of any one of the preceding embodiments, W^4 is nitrogen.

37. The compound of any one of the preceding embodiments, W^1 is nitrogen and W^2 , W^3 and W^4 are carbon.

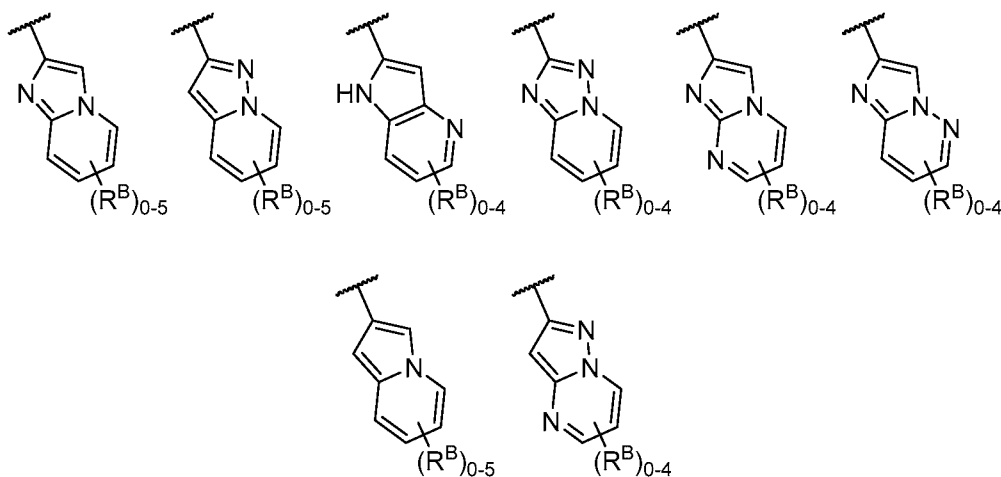
38. The compound of any one of the preceding embodiments, W^2 is nitrogen and W^1 , W^3 and W^4 are carbon.

39. The compound of any one of the preceding embodiments, nitrogen and W^1 and W^4 are carbon.

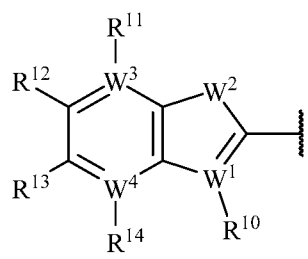
40. The compound of any one of the preceding embodiments, W^2 and W^4 are nitrogen and W^1 and W^3 are carbon.

41. The compound of any one of the preceding embodiments, wherein Cy^B is selected from the group consisting of imidazopyridinyl substituted with 0-5 R^B groups, pyrazolopyridinyl substituted with 0-5 R^B groups, pyrrolopyridinyl substituted with 0-4 R^B groups, triazolopyridinyl substituted with 0-4 R^B groups, imidazopyrimidinyl substituted with 0-4 R^B groups, imidazopyridazinyl substituted with 0-4 R^B groups, indolizinyl substituted with 0-5 R^B groups, and pyrazolopyrimidinyl substituted with 0-4 R^B groups.

42. The compound of any one of the preceding embodiments, wherein Cy^B is selected from the group consisting of:



43. The compound of any one of the preceding embodiments, wherein Cy^B is



wherein:

W^2 is selected from carbon, nitrogen, oxygen, and sulfur;

W^1 , W^3 , and W^4 are independently selected from carbon and nitrogen;

R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} are each optionally present when attached to a carbon atom, and if present correspond to an occurrence of R^B independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -

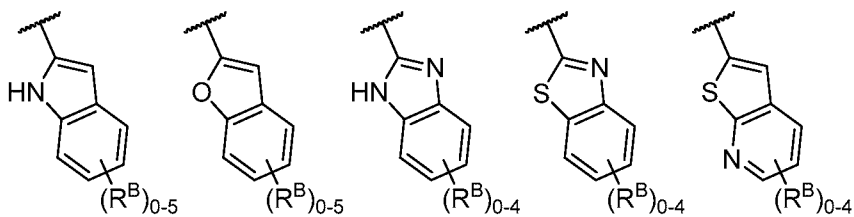
$N(R)C(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)S(O)_2R$, $-OR$, $-OC(O)R$, $-OC(O)N(R)_2$, $-SR$, $-S(O)R$, $-S(O)_2R$, $-S(O)N(R)_2$, $-S(O)_2N(R)_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

each R is independently hydrogen, $-CN$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur.

44. The compound of any one of the preceding embodiments, wherein Cy^B is selected from the group consisting of a indolyl substituted with 0-5 R^B groups, a benzofuranyl substituted with 0-5 R^B groups, a benzimidazolyl substituted with 0-4 R^B groups, and a thienopyridinyl substituted with 0-4 R^B groups.

45. The compound of any one of the preceding embodiments, wherein Cy^B is selected from the group consisting of:



46. The compound of any one of the preceding embodiments, wherein each R^A is independently selected from an optionally substituted group selected from C_{1-6} aliphatic, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered

saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur.

47. The compound of any one of the preceding embodiments, wherein substituents on an optionally substituted R^A group are independently halogen, $(CH_2)_{0-4}R^\circ$, $-(CH_2)_{0-4}OR^\circ$; and $-(CH_2)_{0-4}C(O)OR^\circ$, wherein each R° is independently hydrogen, C_{1-6} aliphatic, or a 5-6 membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

48. The compound of any one of the preceding embodiments, wherein a single instance of R^A is C_{1-6} aliphatic substituted with halogen.

49. The compound of any one of the preceding embodiments, wherein a single instance of R^A is C_{1-6} aliphatic substituted with $-(CH_2)_{0-4}OR^\circ$, wherein R° is hydrogen or C_{1-6} aliphatic.

50. The compound of any one of the preceding embodiments, wherein a single instance of R^A is C_{1-6} aliphatic substituted with $-(CH_2)_{0-4}C(O)OR^\circ$, wherein R° is hydrogen or C_{1-6} aliphatic.

51. The compound of any one of the preceding embodiments, wherein a single instance of R^A is C_{1-6} aliphatic is substituted with 5-6 membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

52. The compound of any one of the preceding embodiments, wherein a single instance of R^A is optionally substituted 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl. In some embodiments, a single instance of R^A is optionally substituted cyclopropyl. In some embodiments, a single instance of R^A is cyclopropyl substituted with $-(CH_2)_{0-4}C(O)OR^\circ$ and R° is hydrogen or C_{1-6} aliphatic.

53. The compound of any one of the preceding embodiments, wherein R^5 , R^6 , R^7 , R^8 , and R^9 are independently selected from hydrogen, halogen, $-CN$, $-N(R)_2$, $-OR$, or an optionally substituted group selected from C_{1-6} aliphatic, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, wherein each R is independently hydrogen or C_{1-6} aliphatic.

54. The compound of any one of the preceding embodiments, wherein R^5 , R^8 , and R^9 are hydrogen.

55. The compound of any one of the preceding embodiments, wherein R^6 is selected from hydrogen or halogen.
56. The compound of any one of the preceding embodiments, wherein R^6 is hydrogen.
57. The compound of any one of the preceding embodiments, wherein R^6 is halogen.
58. The compound of any one of the preceding embodiments, wherein R^6 is -F.
59. The compound of any one of the preceding embodiments, wherein R^6 is -Cl.
60. The compound of any one of the preceding embodiments, wherein R^6 is -Br.
61. The compound of any one of the preceding embodiments, wherein R^7 is selected from halogen or an optionally substituted C_{1-6} aliphatic.
62. The compound of any one of the preceding embodiments, wherein R^7 is halogen.
63. The compound of any one of the preceding embodiments, wherein R^7 is -F.
64. The compound of any one of the preceding embodiments, wherein R^7 is -Cl.
65. The compound of any one of the preceding embodiments, wherein R^7 is -Br.
66. The compound of any one of the preceding embodiments, wherein R^7 is optionally substituted C_{1-6} aliphatic.
67. The compound of any one of the preceding embodiments, wherein R^{11} is optionally present, and if present is independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur.
68. The compound of any one of the preceding embodiments, wherein R^{13} is selected from -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -

S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur.

69. The compound of any one of the preceding embodiments, wherein R¹³ is selected from halogen, optionally substituted C₁₋₆ aliphatic, and optionally substituted 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl.

70. The compound of any one of the preceding embodiments, wherein R¹³ is halogen.

71. The compound of any one of the preceding embodiments, wherein R¹³ is optionally substituted C₁₋₆ aliphatic.

72. The compound of any one of the preceding embodiments, wherein R¹³ is an optionally substituted 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl.

73. The compound of any one of the preceding embodiments, wherein R¹³ is an optionally substituted 3- or 5-7-membered saturated or partially unsaturated monocyclic carbocyclyl.

74. The compound of any one of the preceding embodiments, wherein R¹³ is an optionally substituted cyclopropyl.

75. The compound of any one of the preceding embodiments, wherein the compound is any one of compounds I-1 through I-303, or a pharmaceutically acceptable salt thereof.

76. A pharmaceutical composition comprising any one of the preceding compounds.

77. The pharmaceutical composition comprising any one of the preceding compounds further comprising a pharmaceutically acceptable excipient.

78. The pharmaceutical composition of any one of embodiments 76-77, wherein the composition is suitable for oral administration.

79. The pharmaceutical composition of any one of embodiments 76-77, wherein the composition is suitable for administration by injection.

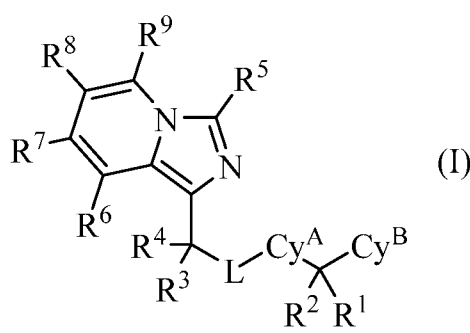
80. A method of treating a plasma kallikrein-mediated disease or disorder using a compound or composition of any one of the preceding embodiments.

81. The method of embodiment 80, wherein the disease or disorder is hereditary angioedema or diabetic macular edema.

82. A method of treating hereditary angioedema or diabetic macular edema comprising administering to a patient in need thereof a compound of any one of the preceding embodiments.

[0130] The following numbered embodiments, while non-limiting, are also exemplary of certain aspects of the present disclosure:

83. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof,

wherein:

Cy^A is selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclylenel having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, and 7- to 10-membered bicyclic heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^A is substituted with 0-4 R^A groups;

each R^A is independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-

membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

Cy^B is selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, and 7- to 10-membered bicyclic heteroaryl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^B is substituted with 0-5 R^B groups;

each R^B is independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

L is selected from -QC(R)₂-, -C(R)₂Q-, -QC(Q)-, -C(Q)Q-, -C(R)₂QC(O)-, and -C(O)QC(R)₂-, wherein each Q is independently a monovalent or divalent group as valency allows, selected from the group consisting of O, N(R), or (S);

R¹, R², R³, and R⁴ are independently selected from hydrogen and C₁₋₆ aliphatic;

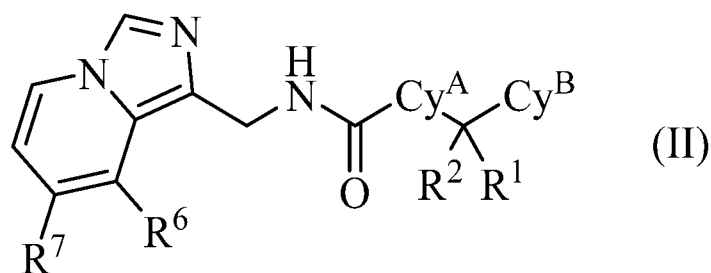
R⁵, R⁶, R⁷, R⁸, and R⁹ are independently selected from hydrogen, halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

each R is independently hydrogen, -CN, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur;

with the proviso that the compound is other than N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((3-chloroquinolin-6-yl)methyl)isonicotinamide.

84. The compound of embodiment 83, wherein the compound is of Formula (II):



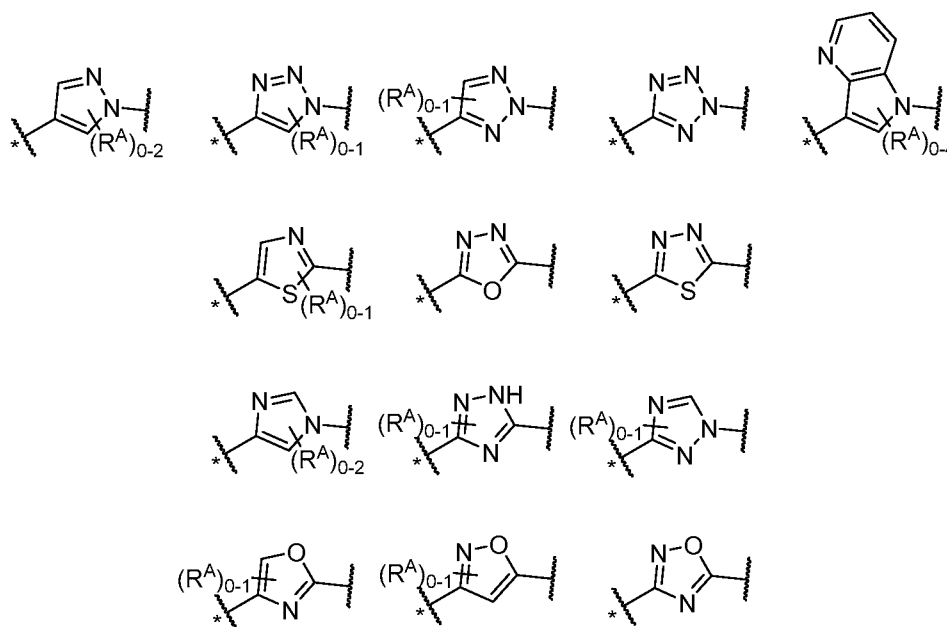
or a pharmaceutically acceptable salt thereof.

85. The compound of any one of the preceding embodiments, with the proviso that Cy^A is a group other than pyridinediyl and the compound is other than N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((3-chloroquinolin-6-yl)methyl)isonicotinamide.

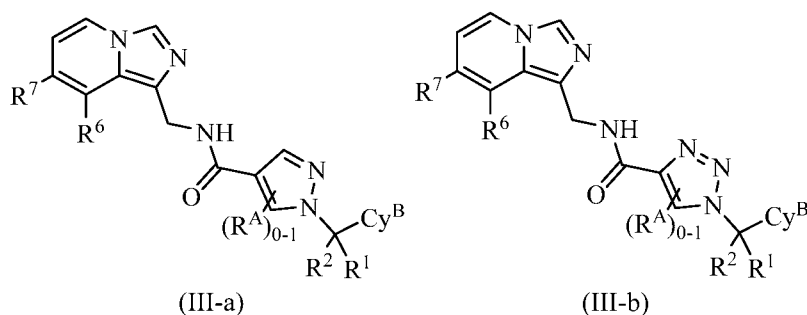
86. The compound of any one of the preceding embodiments, wherein Cy^A is selected from 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, and 7- to 10-membered bicyclic heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur wherein Cy^A is substituted with 0-4 R^A groups.

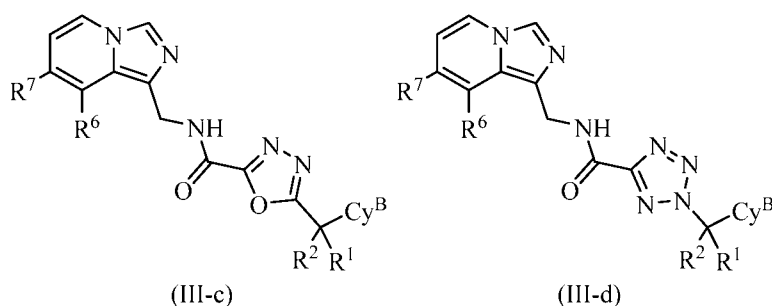
87. The compound of any one of the preceding embodiments, wherein Cy^A is selected from the group consisting of pyrrolopyridinediyl substituted with 0-4 R^A, pyrazolediyl substituted with

88. The compound of any one of the preceding embodiments, wherein Cy^A is selected from the group consisting of:



89. The compound of any one of the preceding embodiments, wherein the compound has a structure selected from the group consisting of:

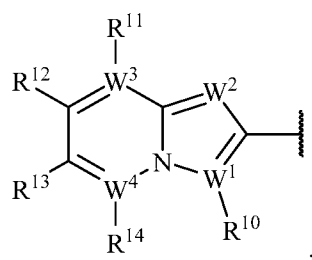




or a pharmaceutically acceptable salt thereof.

90. The compound of any one of the preceding embodiments, wherein Cy^{B} is a 7- to 10-membered bicyclic heteroaryl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^{B} is substituted with 0-5 R^{B} groups.

91. The compound of any one of the preceding embodiments, wherein Cy^{B} is



wherein:

W^1 , W^2 , W^3 , and W^4 are independently selected from carbon and nitrogen;

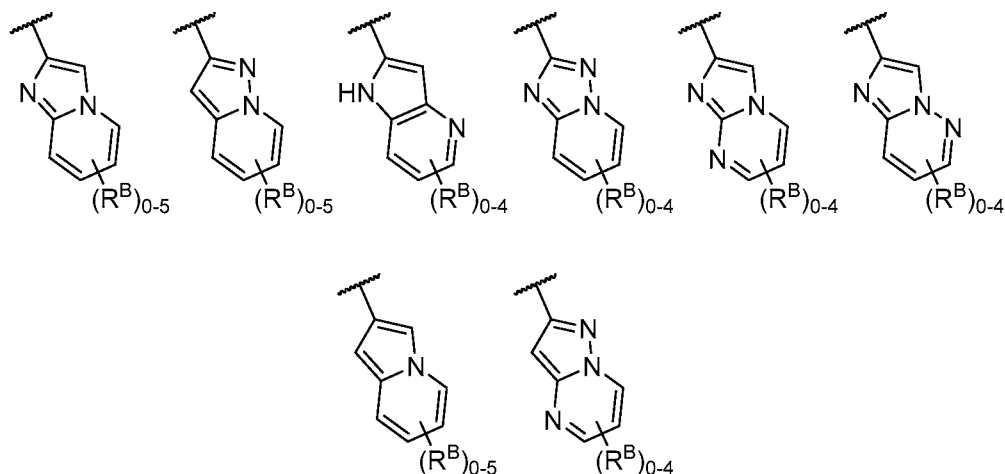
R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} are each optionally present when attached to a carbon atom, and if present correspond to an occurrence of R^{B} independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

each R is independently hydrogen, -CN, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

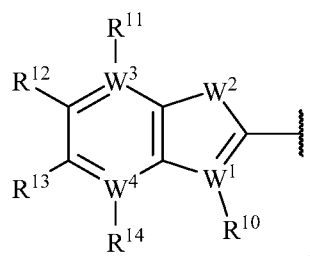
or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur.

92. The compound of any one of the preceding embodiments, wherein Cy^B is selected from the group consisting of imidazopyridinyl substituted with 0-5 R^B groups, pyrazolopyridinyl substituted with 0-5 R^B groups, pyrrolopyridinyl substituted with 0-4 R^B groups, triazolopyridinyl substituted with 0-4 R^B groups, imidazopyrimidinyl substituted with 0-4 R^B groups, imidazopyridazinyl substituted with 0-4 R^B groups, indolizinyl substituted with 0-5 R^B groups, and pyrazolopyrimidinyl substituted with 0-4 R^B groups.

93. The compound of any one of the preceding embodiments, wherein Cy^B is selected from the group consisting of:



94. The compound of any one of embodiments 83-90, wherein Cy^B is



wherein:

W^2 is selected from carbon, nitrogen, oxygen, and sulfur;

W^1 , W^3 , and W^4 are independently selected from carbon and nitrogen;

R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} are each optionally present when attached to a carbon atom, and if present correspond to an occurrence of R^B independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

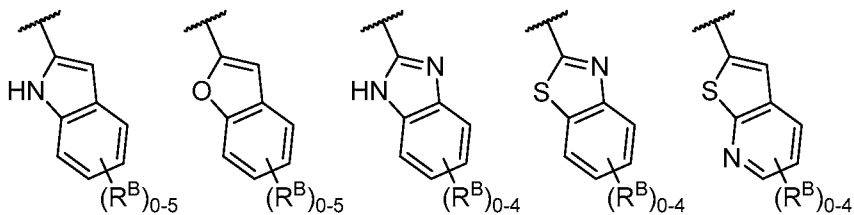
each R is independently hydrogen, -CN, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur.

95. The compound of any one of embodiments 83-90 and 94, wherein Cy^B is selected from the group consisting of a indolyl substituted with 0-5 R^B groups, a benzofuranyl substituted with

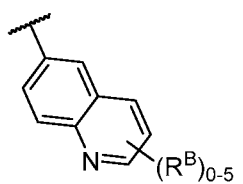
0-5 R^B groups, a pyrazolopyrimidinyl substituted with 0-4 R^B groups, a benzimidazolyl substituted with 0-4 R^B groups, and a thienopyridinyl substituted with 0-4 R^B groups.

96. The compound of any one of embodiments 83-90 and 94-95, wherein Cy^B is selected from the group consisting of:



97. The compound of any one of embodiments 83-90, wherein Cy^B is a quinolondiyyl group substituted with 0-5 R^B groups.

98. The compound of embodiment any one of embodiments 83-90 and 97, wherein Cy^B is



99. The compound of any one of the preceding embodiments, wherein L is -N(H)C(O)- or -C(O)N(H)-.

100. The compound of any one of the preceding embodiments, wherein R^6 is halogen.

101. The compound of embodiment 91 or 94, wherein R^{13} is selected from halogen, optionally substituted C_{1-6} aliphatic, and optionally substituted 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl.

102. The compound of embodiment 91 or 94, wherein R^{13} is an optionally substituted cyclopropyl.

103. A pharmaceutical composition comprising any one of the preceding compounds.

104. The pharmaceutical composition of embodiment 103 further comprising a pharmaceutically acceptable excipient.

105. The pharmaceutical composition of any one of embodiments 103-104, wherein the composition is suitable for oral administration.

106. The pharmaceutical composition of any one of embodiments 103-104, wherein the composition is suitable for administration by injection.

107. A method of treating a plasma kallikrein-mediated disease or disorder using a compound any one of embodiments 83-102 or composition according to of any one of embodiments 103-106.

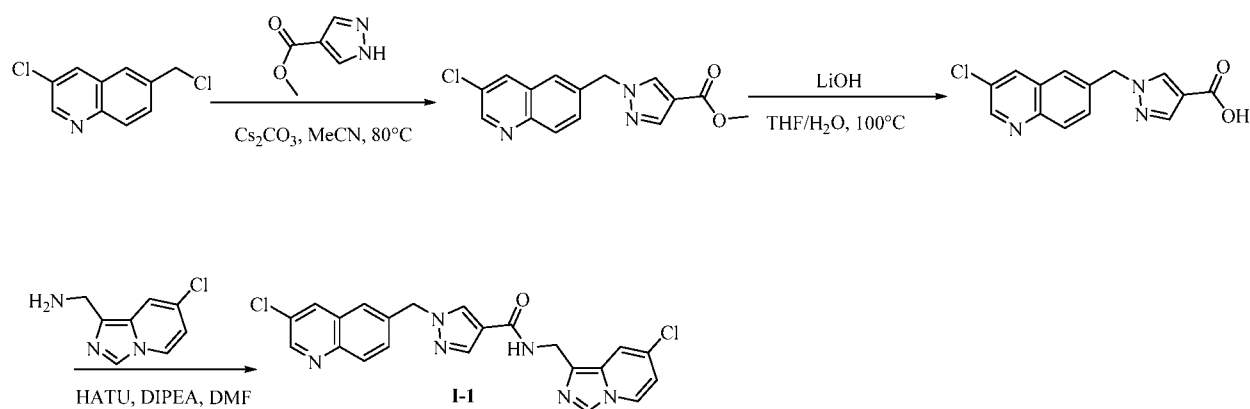
108. The method of embodiment 27, wherein the disease or disorder is hereditary angioedema or diabetic macular edema.

109. A method of treating hereditary angioedema or diabetic macular edema comprising administering to a patient in need thereof a compound of any one of embodiments 83-102 or composition according to of any one of embodiments 103-106.

IV. EXAMPLES

Example 1

Scheme 1



[0131] Synthesis of methyl 1-((3-chloroquinolin-6-yl)methyl)-1H-pyrazole-4-carboxylate. A mixture of 3-chloro-6-(chloromethyl)quinoline (200 mg, 0.95 mmol), methyl 1H-pyrazole-4-carboxylate (1.2 g, 0.95 mmol) and Cs_2CO_3 (930 mg, 2.85 mmol) in MeCN (5 mL) was stirred at 70°C for 1 h. Water was added and extracted with EtOAc, the combined

organic layers were concentrated and purified by silical gel column (EA/PE = 1/10) to give methyl 1-((3-chloroquinolin-6-yl)methyl)-1H-pyrazole-4-carboxylate (200 mg, yield: 78%) as a white solid. ESI-MS $[M+H]^+$: 302.1.

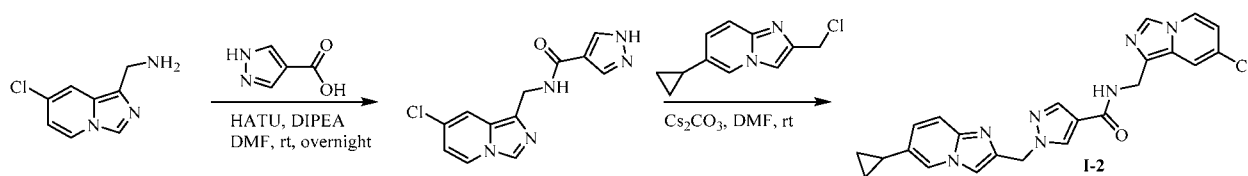
[0132] Synthesis of 1-((3-chloroquinolin-6-yl)methyl)-1H-pyrazole-4-carboxylic acid.

A mixture of methyl 1-((3-chloroquinolin-6-yl)methyl)-1H-pyrazole-4-carboxylate (200 mg, 0.66 mmol) and LiOH (158 mg, 6.6 mmol) in THF (10 mL) and H₂O (5 mL) was stirred at 100 °C for overnight. Water was added and the pH value of the mixture was adjusted to 4-5 by added 1 M HCl solution. The mixture was then extracted with EtOAc (20 mL x 3), the combined organic layers were concentrated to give 1-((3-chloroquinolin-6-yl)methyl)-1H-pyrazole-4-carboxylic acid (150 mg, yield: 72%) as a white solid, which was used into next step without further purification. ESI-MS $[M+H]^+$: 288.0.

[0133] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((3-chloroquinolin-6-yl)methyl)-1H-pyrazole-4-carboxamide (I-1). A mixture of 1-((3-chloroquinolin-6-yl)methyl)-1H-pyrazole-4-carboxylic acid (50 mg, 0.17 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine (37 mg, 0.17 mmol), and HATU (98 mg, 0.06 mmol) and DIPEA (66 mg, 0.51 mmol) in DMF (2 mL) was stirred at RT overnight. Water (10 mL) was added and extracted with EtOAc (20 mL x 3), the combined organic layers were concentrated and purified by prep-HPLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((3-chloroquinolin-6-yl)methyl)-1H-pyrazole-4-carboxamide (17.3 mg, yield: 20%) as a white solid. ESI-MS $[M+H]^+$: 451.1. Purity: 99.49%. ¹H NMR (400 MHz, DMSO): δ 8.88 (d, J = 2.2 Hz, 1H), 8.64-8.58 (m, 2H), 8.36-8.31 (m, 3H), 8.03 (d, J = 8.7 Hz, 1H), 7.94 (s, 1H), 7.80 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 8.7 Hz, 1H), 6.67 (dd, J = 7.4, 1.8 Hz, 1H), 5.56 (s, 2H), 4.57 (d, J = 5.4 Hz, 2H).

Example 2

Scheme 2

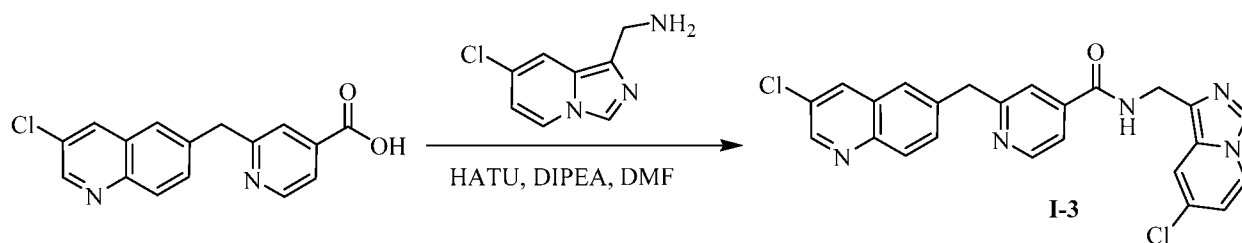


[0134] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide. To a mixture of (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (2.5 g, 11.52 mmol), 1H-pyrazole-4-carboxylic acid (920 mg, 8.23 mmol), HATU (3.9 g, 10.29 mmol) in DMF (300 mL) was added DIPEA (7.3 mL, 41.14 mmol). The resulting reaction mixture was stirred at RT for 14 h. The reaction was then concentrated to remove most of the DMF, and the residue was poured into H₂O (150 mL) and brown solid was precipitated out. The precipitate was filtered and the filtrated cake was triturated with DCM and dried to give the N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide, which was used into next step without further purification (2 g, yield: 88%). ESI-MS [M+H]⁺: 276.2.

[0135] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-2). A mixture of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (2 g, 7.27 mmol), 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (1.96 g, 9.45 mmol) and Cs₂CO₃ (7.1 g, 21.81 mmol) in DMF (50 mL) was stirred at 50 °C for 14 h. H₂O (200 mL) was added, extracted with EtOAc (300 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude, which was purified with silica gel chromatography (DCM/MeOH = 10/1) to give the N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide as a white solid (1.5 g, yield: 46%). LCMS m/z: 446.1 [M+H]⁺, t_R = 1.040 min, purity: 98.6% (214 nm), 97.4% (254 nm). ¹H NMR (400 MHz, DMSO): δ 8.58 (t, J = 5.7 Hz, 1H), 8.32-8.29 (m, 3H), 8.20 (s, 1H), 7.85 (s, 1H), 7.78 (s, 1H), 7.71 (s, 1H), 7.39 (d, J = 9.3 Hz, 1H), 7.00-6.98 (m, 1H), 6.64 (dd, J = 7.5, 2.0 Hz, 1H), 5.38 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 1.91 (ddd, J = 13.5, 8.4, 5.1 Hz, 1H), 0.99-0.87 (m, 2H), 0.77-0.61 (m, 2H).

Example 3

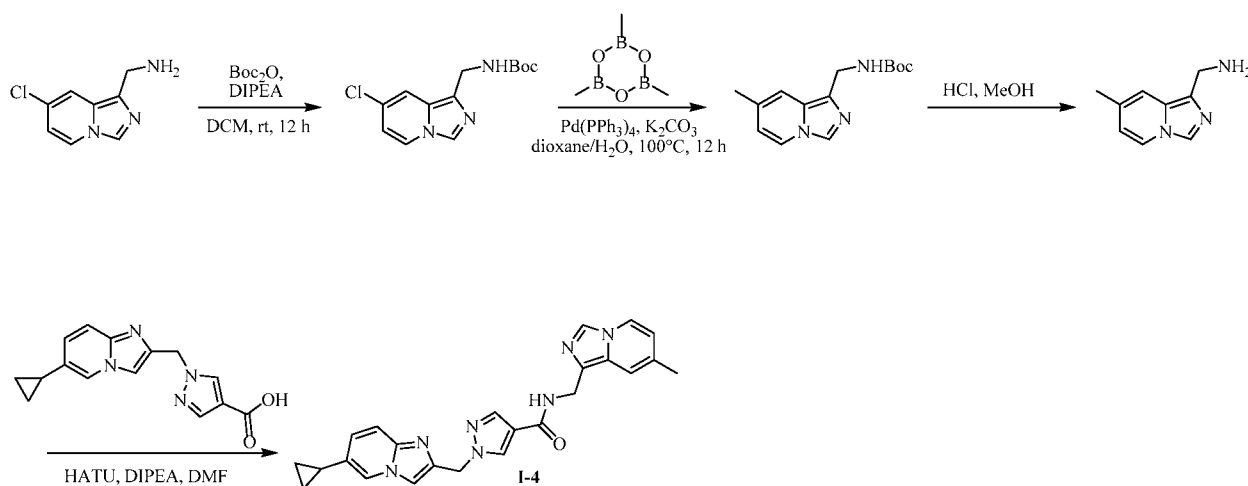
Scheme 3



[0136] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((3-chloroquinolin-6-yl)methyl)isonicotinamide (I-3). To a solution of 2-((3-chloroquinolin-6-yl)methyl)isonicotinic acid (60 mg, 0.20 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine (44 mg, 0.24 mmol) and HATU (115 mg, 0.30 mmol) in DMF (8 mL) was added DIPEA (77 mg, 0.60 mmol). The resulting reaction was stirred at RT for 12 h. H₂O (20 mL) was added, extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give the N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((3-chloroquinolin-6-yl)methyl)isonicotinamide (20 mg, yield: 22%) as a white solid. ESI-MS [M+H]⁺: 462.0. Purity: 98.3%. ¹H NMR (400 MHz, DMSO): δ 9.27-9.24 (m, 1H), 8.84-8.81 (m, 1H), 8.62 (d, J = 5.0 Hz, 1H), 8.51 (s, 1H), 8.38-8.26 (m, 2H), 7.97 (d, J = 8.6 Hz, 1H), 7.90-7.69 (m, 4H), 7.62 (d, J = 4.7 Hz, 1H), 6.66 (d, J = 7.4 Hz, 1H), 4.64 (d, J = 5.5 Hz, 2H), 4.35 (s, 2H).

Example 4

Scheme 4



[0137] Synthesis of tert-butyl ((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamate. A mixture of (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine (300 mg, 1.65 mmol), Boc₂O (537 mg, 2.4 mmol) and DIPEA (1.06 g, 8.25 mmol) in DCM (40 mL) was stirred at RT for 12 h. The reaction was quenched with H₂O (50 mL), extracted with DCM (50 mL x 2). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude, which was purified with silica gel chromatography (PE/EA = 1/1) to

give the tert-butyl ((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamate (210 mg, yield: 45%) as a yellow solid. ESI-MS $[M+H]^+$: 282.2.

[0138] Synthesis of tert-butyl ((7-methylimidazo[1,5-a]pyridin-1-yl)methyl)carbamate. A mixture of tert-butyl ((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamate (210 mg, 0.75 mmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (188 mg, 1.5 mmol), Pd(PPh₃)₄ (87 mg, 0.075 mmol) and K₂CO₃ (310 mg, 2.25 mmol) in dioxane/H₂O (10 mL/1 mL) in a sealed tube was stirred at 100 °C for 12 h. H₂O (30 mL) was added to the reaction, extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude, which was purified with silica gel chromatography (EA/PE = 1/1) to give the tert-butyl ((7-methylimidazo[1,5-a]pyridin-1-yl)methyl)carbamate (150 mg, yield: 77%) as a light yellow solid. ESI-MS $[M+H]^+$: 262.3.

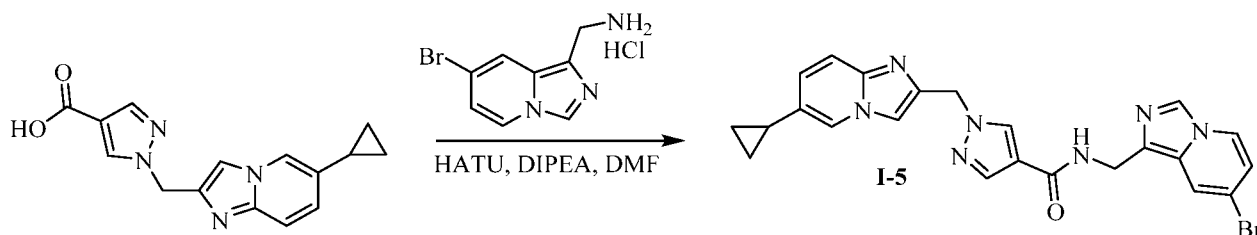
[0139] Synthesis of (7-methylimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride. To a solution of tert-butyl ((7-methylimidazo[1,5-a]pyridin-1-yl)methyl)carbamate (150 mg, 0.57 mmol) in MeOH (3 mL) was added HCl (4 M solution in MeOH, 3 mL). The resulting reaction was stirred at RT for 2 h. The reaction was concentrated in vacuo to give the (7-methylimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (95 mg, yield: 85%). ESI-MS $[M+H]^+$: 162.2.

[0140] Synthesis of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-methylimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-4). To a solution of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (136 mg, 0.48 mmol), (7-methylimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (95 mg, 0.48 mmol) and HATU (238 mg, 0.63 mmol) in DMF (15 mL) was added DIPEA (310 mg, 2.4 mmol). The resulting reaction was stirred at RT for 12 h. H₂O (25 mL) was added to the reaction, extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give the 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-methylimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (21 mg, yield: 10%) as a white solid. ESI-MS $[M+H]^+$: 426.2. Purity: 96.4%. ¹H NMR (400 MHz, DMSO): δ 8.47 (s, 1H), 8.39-8.04 (m, 5H), 7.86 (s, 1H), 7.71 (s, 1H), 7.40-7.35 (m, 2H), 6.99 (d, J = 9.1 Hz, 1H), 6.45

(d, J = 7.0 Hz, 1H), 5.38 (s, 2H), 4.54 (d, J = 4.5 Hz, 2H), 2.20 (s, 3H), 1.95-1.88 (m, 1H), 0.93-0.90 (m, 2H), 0.68-0.63 (m, 2H).

Example 5

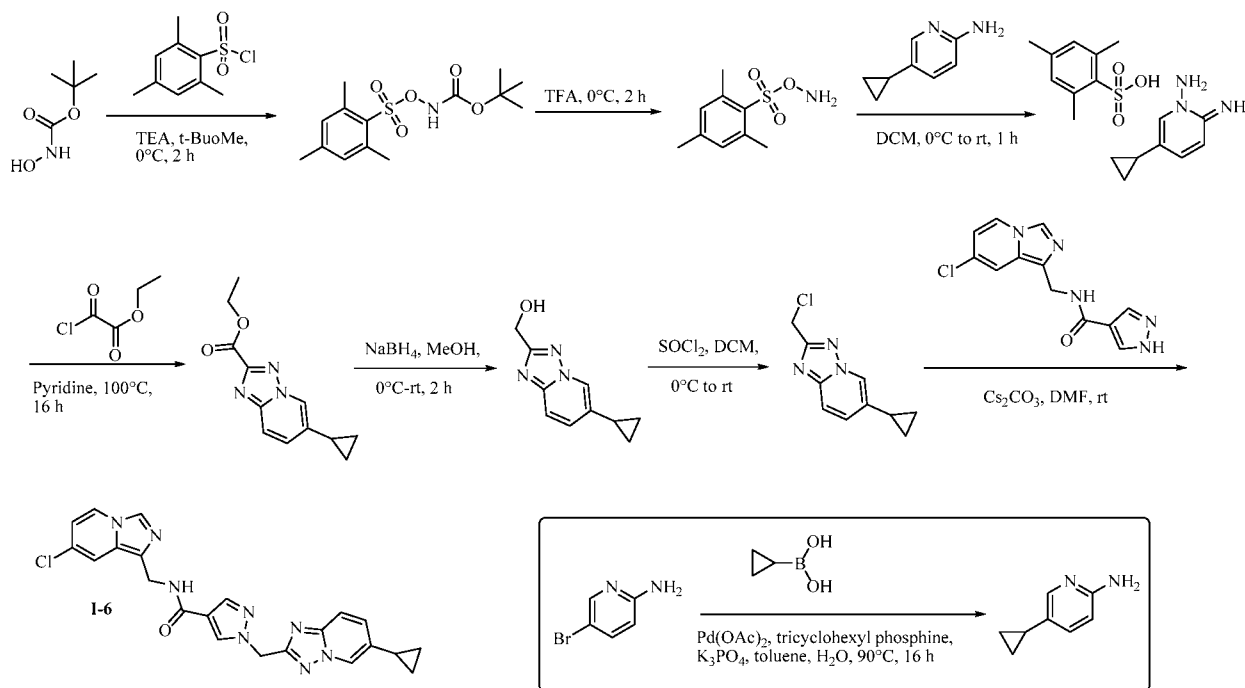
Scheme 5



[0141] Synthesis of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide. (I-5) To a solution of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (154 mg, 0.54 mmol), (7-bromoimidazo[1,5-a]pyridin-1-yl)methanamine (120 mg, 0.54 mmol) and HATU (310 mg, 0.82 mmol) in DMF (4 mL) was added DIPEA (210 mg, 1.63 mmol). The resulting reaction was stirred at RT for 12 h. H₂O (20 mL) was added, extracted with EtOAc (25 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give the N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (24 mg, yield: 9%) as a white solid. ESI-MS [M+H]⁺: 490.1. Purity: 98.24%. ¹H NMR (400 MHz, DMSO): δ 8.57 (t, J = 8.0 Hz, 1H), 8.32 (d, J = 4.2 Hz, 2H), 8.24 (d, J = 7.5 Hz, 1H), 8.20 (s, 1H), 7.95 (s, 1H), 7.85 (s, 1H), 7.71 (s, 1H), 7.39 (d, J = 9.4 Hz, 1H), 6.99 (d, J = 9.3 Hz, 1H), 6.72 (dd, J = 7.4, 1.8 Hz, 1H), 5.38 (s, 2H), 4.54 (d, J = 5.7 Hz, 2H), 1.98-1.87 (m, 1H), 1.01-0.76 (m, 2H), 0.76-0.55 (m, 2H).

Example 6

Scheme 6



[0142] Synthesis of tert-butyl ((mesitylsulfonyl)oxy)carbamate. To a mixture of tert-butyl hydroxycarbamate (3 g, 22.5 mmol) and 2,4,6-trimethylbenzenesulfonyl chloride (4.9 g, 22.5 mmol) in MTBE (100 mL) was added Et₃N (2.43 g, 24.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h. The reaction mixture was filtered and washed with MTBE. The filtrate was concentrated to give tert-butyl ((mesitylsulfonyl)oxy)carbamate (7.1 g, yield: 100%) as a light yellow solid. ESI-MS [M+Na]⁺: 338.1.

[0143] Synthesis of O-(mesitylsulfonyl)hydroxylamine. The mixture of tert-butyl ((mesitylsulfonyl)oxy)carbamate (5.9 g, 18.71 mmol) in TFA (20 mL) was stirred for at 0 °C for 2 h. The reaction mixture was poured into H₂O (150 mL) and stirred for 30 min. The precipitate was collected and dried to give O-(mesitylsulfonyl)hydroxylamine (2.2 g, yield: 55%) as a white solid which was used into next step without further purification. ESI-MS [M+H]⁺: 216.2.

[0144] Synthesis of 5-cyclopropylpyridin-2-amine. The mixture of 5-bromopyridin-2-amine (4 g, 23.12 mmol), cyclopropylboronic acid (2.98 g, 34.68 mmol), Pd(OAc)₂ (130 mg, 0.578 mmol), tricyclohexyl phosphine (324 mg, 1.16 mmol) and K₃PO₄ (17.18 g, 80.92 mmol) in

toluene (100 mL) and H₂O (10 mL) was stirred at 90 °C for 16 h. The reaction mixture was filtered and rinsed with EtOAc. The combined filtrate was washed with H₂O (150 mL x 1) and brine (150 mL x 1), dried over Na₂SO₄, concentrated and purified by silica gel chromatography (EA/PE = 1/1) to give 5-cyclopropylpyridin-2-amine (2.76 g, yield: 89%) as a yellow solid. ESI-MS [M+H]⁺: 135.2.

[0145] Synthesis of 5-cyclopropyl-2-iminopyridin-1(2H)-amine 2,4,6-trimethylbenzenesulfonate. To a stirred solution of O-(mesitylsulfonyl)hydroxylamine (2.2 g, 10.22 mmol) in DCM (40 mL) was added 5-cyclopropylpyridin-2-amine (1.37 g, 10.22 mmol) in four portions at 0 °C. The mixture was stirred at 0 °C for 10 min and warmed to RT and stirred for 1 h. The reaction mixture was concentrated and dried in vacuo to give 5-cyclopropyl-2-iminopyridin-1(2H)-amine 2,4,6-trimethylbenzenesulfonate (3.57 g, yield: 100%) as a light brown syrup. ESI-MS [M+H]⁺: 150.2.

[0146] Synthesis of ethyl 6-cyclopropyl-[1,2,4]triazolo[1,5-a]pyridine-2-carboxylate. To a stirred solution of 5-cyclopropyl-2-iminopyridin-1(2H)-amine 2,4,6-trimethylbenzenesulfonate (3.57 g, 10.22 mmol) in pyridine (30 mL) was added ethyl 2-chloro-2-oxoacetate (2.79 g, 20.44 mmol) at RT. The mixture was stirred at 100 °C for 16 h. The reaction mixture was concentrated. The residue was dissolved in EtOAc (100 mL) and washed with H₂O (100 mL x 1) brine (100 mL x 1), dried over Na₂SO₄, concentrated and purified by silica gel chromatography (EA/PE = 1/1) to give ethyl 6-cyclopropyl-[1,2,4]triazolo[1,5-a]pyridine-2-carboxylate (1.1 g, yield: 47%) as a yellow solid. ESI-MS [M+H]⁺: 232.1.

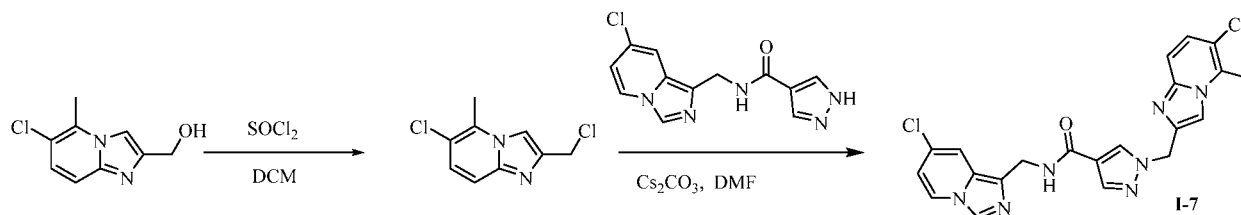
[0147] Synthesis of (6-cyclopropyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)methanol. To a stirred solution of ethyl 6-cyclopropyl-[1,2,4]triazolo[1,5-a]pyridine-2-carboxylate (300 mg, 1.30 mmol) in MeOH (10 mL) was added NaBH₄ (246 mg, 6.5 mmol) in portions at 0 °C. The mixture was stirred at RT for 2 h. The reaction mixture was then quenched with NH₄Cl aqueous. MeOH was removed and the reaction was diluted with H₂O (50 mL) and extracted with EtOAc (30 mL x 3). The combined organics was washed with brine (80 mL x 1), dried over Na₂SO₄, concentrated and purified by silica gel chromatography (EA/MeOH = 10/1) to give (6-cyclopropyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)methanol (210 mg, yield: 85%) as a yellow solid. ESI-MS [M+H]⁺: 190.2.

[0148] Synthesis of 2-(chloromethyl)-6-cyclopropyl-[1,2,4]triazolo[1,5-a]pyridine. To a stirred solution of (6-cyclopropyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)methanol (110 mg, 0.58 mmol) in DCM (5 mL) was added SOCl_2 (690 mg, 5.8 mmol) at 0 °C. The mixture was stirred at RT for 1 h. The reaction mixture was then concentrated, the residue was dissolved in EtOAc (60 mL) and washed with NaHCO_3 (50 mL x 1), brine (50 mL x 1), dried over Na_2SO_4 , concentrated to give 2-(chloromethyl)-6-cyclopropyl-[1,2,4]triazolo[1,5-a]pyridine (115 mg, yield: 96%) as a yellow solid, which was used into next step without further purification. ESI-MS $[\text{M}+\text{H}]^+$: 208.1.

[0149] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-6). The mixture of 2-(chloromethyl)-6-cyclopropyl-[1,2,4]triazolo[1,5-a]pyridine (15.8 mg, 0.0762 mmol), N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (20 mg, 0.0725 mmol) and Cs_2CO_3 (35 mg, 0.109 mmol) in DMF (3 mL) was stirred at RT for 2 h. The reaction mixture was poured into H_2O (30 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (60 mL x 3), dried over Na_2SO_4 , concentrated and purified by prep-TLC (DCM/MeOH = 5/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (15 mg, yield: 47%) as a yellow solid. ESI-MS $[\text{M}+\text{H}]^+$: 447.1. Purity: 99%. ^1H NMR (400 MHz, DMSO): δ 8.73 (s, 1H), 8.62 (t, $J = 5.7$ Hz, 1H), 8.31 (d, $J = 7.9$ Hz, 3H), 7.86 (s, 1H), 7.80 (d, $J = 0.9$ Hz, 1H), 7.66 (d, $J = 9.2$ Hz, 1H), 7.42 (dd, $J = 9.2, 1.7$ Hz, 1H), 6.65 (dd, $J = 7.5, 2.1$ Hz, 1H), 5.56 (s, 2H), 4.57 (d, $J = 5.7$ Hz, 2H), 2.03 (m, 1H), 0.97 (m, 2H), 0.78 (m, 2H).

Example 7

Scheme 7



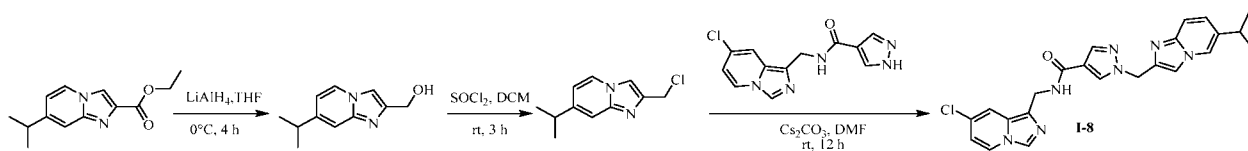
[0150] Synthesis of 6-chloro-2-(chloromethyl)-5-methylimidazo[1,2-a]pyridine. To a solution (6-chloro-5-methylimidazo[1,2-a]pyridin-2-yl)methanol (60 mg, 0.31 mmol) in DCM

(10 mL) was added SOCl_2 (1 mL) at RT. The resulting reaction was stirred at 45 °C for 2 h. The solution was evaporated to give the 6-chloro-2-(chloromethyl)-5-methylimidazo[1,2-a]pyridine (50 mg, crude) as a light yellow solid, which was used in the next step without further purification. ESI-MS $[\text{M}+\text{H}]^+$: 215.2.

[0151] Synthesis of 1-((6-chloro-5-methylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-7). To a solution 6-chloro-2-(chloromethyl)-5-methylimidazo[1,2-a]pyridine (50 mg, 0.23 mmol) in DMF (10 mL) was added N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (41 mg, 0.15 mmol) and Cs_2CO_3 (146 mg, 0.45 mmol) at RT. The resulting reaction was stirred at RT for 12 h. H_2O (30 mL) was added to the reaction and then extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give 1-((6-chloro-5-methylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (40 mg, yield: 58%) as a white solid. ESI-MS $[\text{M}+\text{H}]^+$: 454.1. Purity: 100%. ^1H NMR (400 MHz, DMSO): δ 8.59 (t, J = 5.5 Hz, 1H), 8.31-8.29 (m, 2H), 8.23 (s, 1H), 7.92 (s, 1H), 7.86 (s, 1H), 7.78 (s, 1H), 7.47 (d, J = 9.5 Hz, 1H), 7.34 (d, J = 9.5 Hz, 1H), 6.65 (d, J = 7.4 Hz, 1H), 5.44 (s, 2H), 4.55 (d, J = 5.6 Hz, 2H), 2.66 (s, 3H).

Example 8

Scheme 8



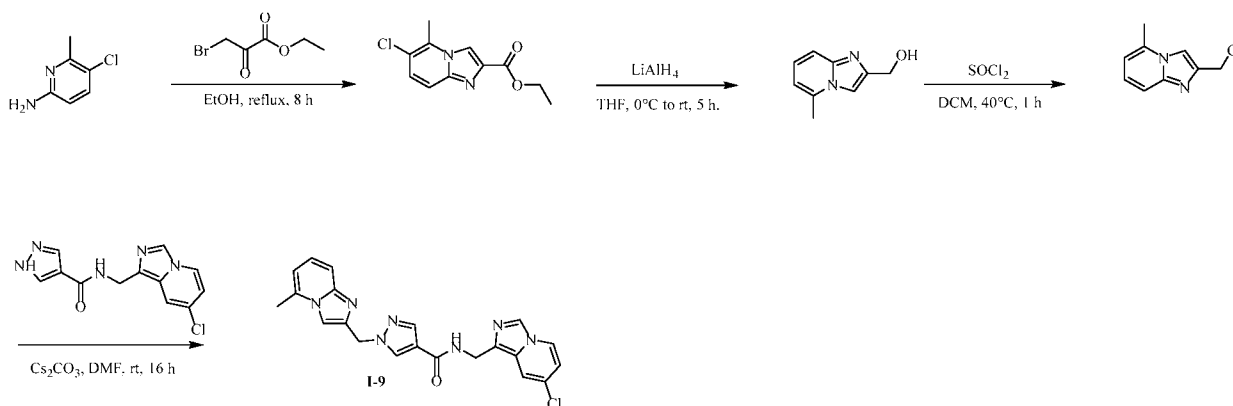
[0152] Synthesis of (7-isopropylimidazo[1,2-a]pyridin-2-yl)methanol. To a solution of ethyl 7-isopropylimidazo[1,2-a]pyridine-2-carboxylate (200 mg, 0.86 mmol) in THF (4 mL) was added LiAlH_4 (65.5 mg, 1.72 mmol). The resulting reaction was stirred at RT for 4 h. The reaction was quenched with saturated Na_2SO_4 (aq.), filtered and concentrated and purified by silica gel column (DCM/MeOH = 10/1) to give the (7-isopropylimidazo[1,2-a]pyridin-2-yl)methanol (130 mg, 80%) as a brown liquid. ESI-MS $[\text{M}+\text{H}]^+$: 191.2.

[0153] Synthesis of 2-(chloromethyl)-7-isopropylimidazo[1,2-a]pyridine. To a solution of (7-isopropylimidazo[1,2-a]pyridin-2-yl)methanol (190 mg, 1 mmol) in DCM (10 mL) was added SOCl_2 (2 mL). The resulting reaction was stirred at 50 °C for 2 h. The reaction was concentrate in vacuo to give 2-(chloromethyl)-7-isopropylimidazo[1,2-a]pyridine (220 mg crude), which was used into next step without further purification. ESI-MS $[\text{M}+\text{H}]^+$: 209.2.

[0154] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-isopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-8). A mixture of 2-(chloromethyl)-7-isopropylimidazo[1,2-a]pyridine (46 mg, 0.22 mmol), N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (38 mg, 0.14 mmol) and Cs_2CO_3 (142 mg, 0.44 mmol) in DMF (8 mL) was stirred at 80 °C for 12 h. H_2O (15 mL) was added to the reaction, extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give the N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-isopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (15 mg, 24%) as a white solid. ESI-MS $[\text{M}+\text{H}]^+$: 448.2. Purity: 100%. ^1H NMR (400 MHz, DMSO): δ 8.58 (t, J = 5.6 Hz, 1H), 8.32 (m, 3H), 8.20 (s, 1H), 7.85 (s, 1H), 7.77 (m, 2H), 7.43 (d, J = 9.3 Hz, 1H), 7.21 (d, J = 9.3 Hz, 1H), 6.64 (dd, J = 7.4, 1.9 Hz, 1H), 5.39 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 2.96-2.80 (m, 1H), 1.22 (d, J = 6.9 Hz, 6H).

Example 9

Scheme 9

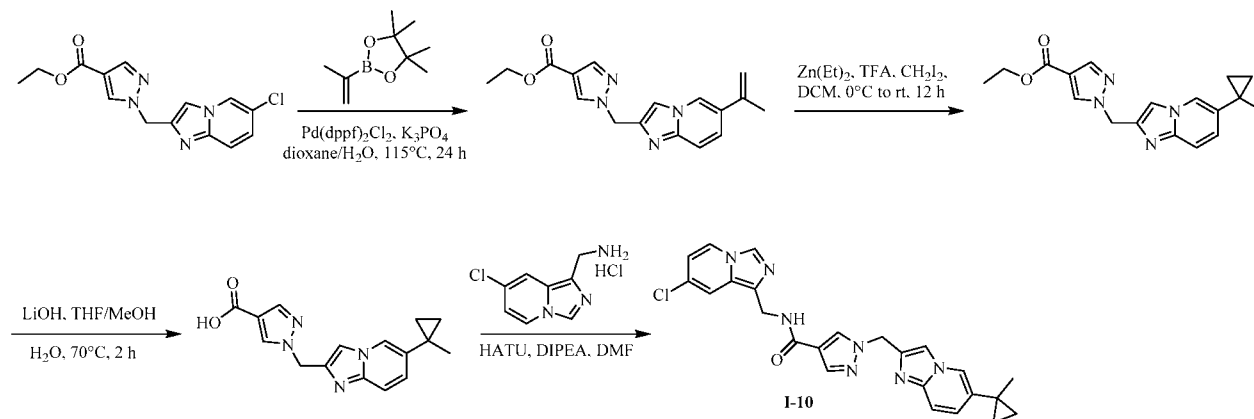


[0155] Synthesis of (5-methylimidazo[1,2-a]pyridin-2-yl)methanol. A solution of 5-chloro-6-methylpyridin-2-amine (568 mg, 4.0 mmol), ethyl 3-bromo-2-oxopropanoate (1.2 g, 6.0 mmol) in dry EtOH (10 mL) was stirred at 80 °C for 8 h. The mixture was concentrated and purified by silica gel chromatography (DCM/MeOH = 20/1) to give ethyl 6-chloro-5-methylimidazo[1,2-a]pyridine-2-carboxylate (800 mg, yield: 84.0%) as a yellow solid. ESI-MS $[M+H]^+$: 239.1.

[0156] Synthesis of (5-methylimidazo[1,2-a]pyridin-2-yl)methanol. To a solution of ethyl 6-chloro-5-methylimidazo[1,2-a]pyridine-2-carboxylate (240 mg, 1.0 mmol) in dry THF (10 mL) was added $LiAlH_4$ (115 mg, 3.0 mmol) slowly at 0 °C. The reaction mixture was stirred at RT for 5 h, then quenched with $Na_2SO_4 \cdot 10H_2O$. The mixture was filtered and the filtrate was washed with EtOAc (20 mL). The filtrate was concentrated to give (5-methylimidazo[1,2-a]pyridin-2-yl)methanol (150 mg, yield: 92%) as a yellow oil which was used in the next step without further purification. ESI-MS $[M+H]^+$: 163.1.

[0157] Synthesis of 2-(chloromethyl)-5-methylimidazo[1,2-a]pyridine. To a solution of (5-methylimidazo[1,2-a]pyridin-2-yl)methanol (150 mg, 0.925 mmol) in dry DCM (5 mL) was added $SOCl_2$ (0.5 mL) at RT. The mixture was stirred at 40 °C for 1 h. The mixture was concentrated to give crude 2-(chloromethyl)-5-methylimidazo[1,2-a]pyridine (140 mg, yield: 94.6%) as a yellow solid. ESI-MS $[M+H]^+$: 181.2.

[0158] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-9). A mixture of 2-(chloromethyl)-5-methylimidazo[1,2-a]pyridine (30 mg, 0.16 mmol), N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (30 mg, 0.11 mmol) and Cs_2CO_3 (110 mg, 0.33 mmol) in DMF (3 mL) was stirred at RT for 16 h. Water (30 mL) was added and the reaction was extracted with EtOAc (30 mL x 3). The combined organic layers were concentrated and purified by prep-TLC (DCM/MeOH = 10/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (11.5 mg, yield: 25%) as a light yellow solid. ESI-MS $[M+H]^+$: 420.1. Purity: 97.4%. ^1H NMR (400 MHz, DMSO): δ 8.58 (t, J = 5.4 Hz, 1H), 8.31-8.29 (m, 2H), 8.23 (s, 1H), 7.86 (s, 1H), 7.78 (s, 2H), 7.41 (d, J = 9.1 Hz, 1H), 7.24-7.20 (m, 1H), 6.78 (d, J = 6.8 Hz, 1H), 6.64 (dd, J = 7.5, 1.9 Hz, 1H), 5.43 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 2.56 (s, 3H).

Example 10Scheme 10

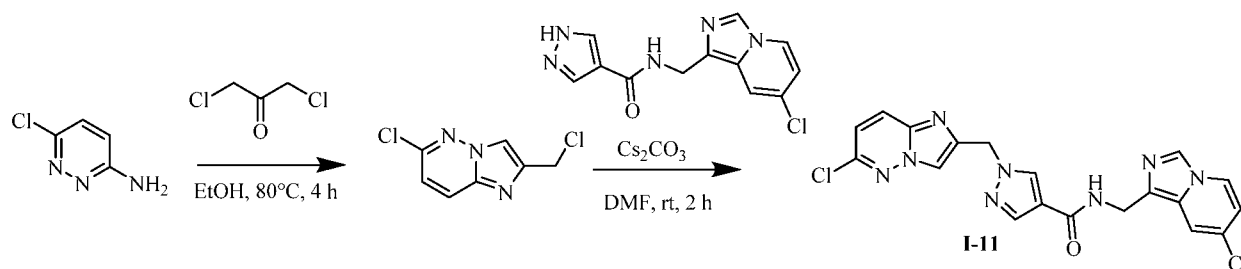
[0159] Synthesis of ethyl 1-((6-(prop-1-en-2-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A mixture of ethyl 1-((6-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (600 mg, 1.97 mmol), 4,4,5,5-tetramethyl-2-(prop-1-en-2-yl)-1,3,2-dioxaborolane (662 mg, 3.94 mmol), Pd(dppf)₂Cl₂ (160 mg, 0.2 mmol) and K₃PO₄ (1.25 g, 5.91 mmol) in dioxane/H₂O (20 mL/2 mL) was stirred at 115 °C for 24 h. H₂O (50 mL) was added to the reaction, extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give the crude, which was purified by prep-HPLC (chromatographic columns: Gemini-C18 150 x 21.2 mm, 5 μm, mobile phase: acetonitrile-H₂O (0.1%FA), gradient: 10-20) to give ethyl 1-((6-(prop-1-en-2-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (450 mg, yield: 73%) as a white solid. ESI-MS [M+H]⁺: 311.2.

[0160] Synthesis of ethyl 1-((6-(1-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. To a solution of Zn(Et)₂ (1.9 mL, 1 M solution in hexane, 1.9 mmol) in DCM (4 mL) was added TFA (220 mg, 1.9 mmol, in 1 mL DCM) dropwisely at 0 °C. The resulting reaction was stirred at 0 °C for 20 min. Then a solution of CH₂I₂ (509 mg, 1.9 mmol, in 2 mL DCM) was added at 0 °C. After stirring for another 20 min, a solution of ethyl 1-((6-(prop-1-en-2-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (50 mg, 0.16 mmol) in DCM (1 mL) was added. The resulting reaction was warmed to RT and stirred for 16 h. The reaction was quenched with H₂O (20 mL) and extracted with

DCM (25 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 15/1) to give ethyl 1-((6-(1-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (17 mg, yield: 33%) as a yellow solid. ESI-MS [M+H]⁺: 325.1.

[0161] Synthesis of 1-((6-(1-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. A mixture of ethyl 1-((6-(1-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (17 mg, 0.052 mmol) and LiOH (4 mg, 0.16 mmol) in THF/MeOH/H₂O (2 mL/2 mL/1 mL) was stirred at 70 °C for 2 h. The pH of the reaction was adjusted to 4 and H₂O (5 mL) was added and the mixture was extracted with EtOAc (20 mL x 3). The combined organic layers were then concentrated in vacuo to give the 1-((6-(1-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (15 mg, yield: 98%) as a yellow oil which was used in the next step without further purification. ESI-MS [M+H]⁺: 297.1.

[0162] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-(1-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-10). To a solution of 1-((6-(1-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (15 mg, 0.05 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (13 g, 0.06 mmol) and HATU (28 mg, 0.075 mmol) in DMF (3 mL) was added DIPEA (32 mg, 0.25 mmol). The resulting reaction was stirred at RT for 12 h. H₂O (15 mL) was added to the reaction and then extracted with EtOAc (25 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-(1-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (7.5 mg, yield: 33%) as a white solid. ESI-MS [M+H]⁺: 460.2. Purity: 93.5%. ¹H NMR (400 MHz, MeOD): δ 8.27-8.25 (m, 2H), 8.16 (d, J = 7.5 Hz, 1H), 8.12 (s, 1H), 7.91 (s, 1H), 7.73-7.72 (m, 2H), 7.40 (d, J = 9.4 Hz, 1H), 7.26 (d, J = 9.4 Hz, 1H), 6.62 (d, J = 7.3 Hz, 1H), 5.44 (s, 2H), 4.68 (s, 2H), 1.41 (s, 3H), 0.90-0.87 (m, 2H), 0.78-0.76 (m, 2H).

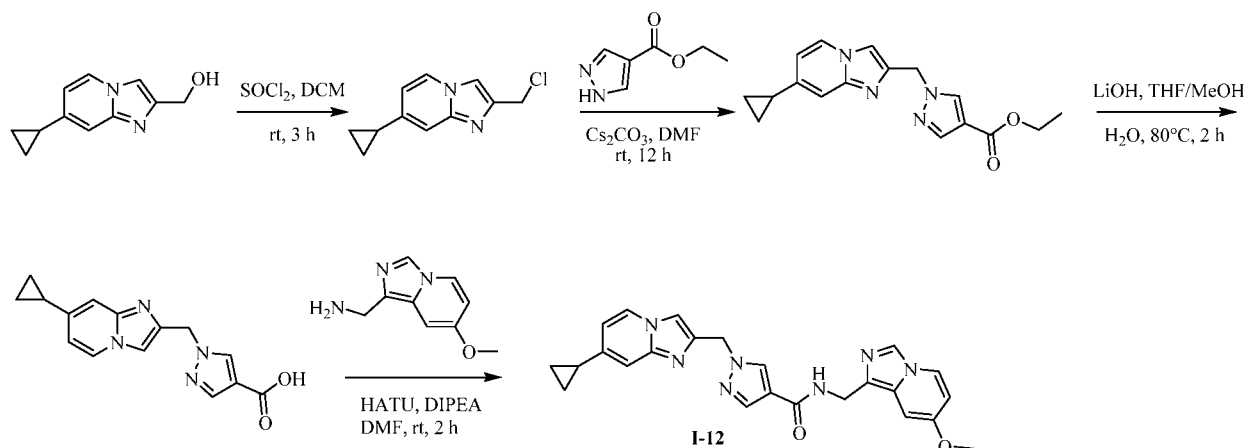
Example 11Scheme 11

[0163] Synthesis of 6-chloro-2-(chloromethyl)imidazo[1,2-b]pyridazine. A solution of 6-chloropyridazin-3-amine (5 g, 39 mmol) and 1,3-dichloropropan-2-one (20 g, 156 mmol) in EtOH (50 mL) was stirred at 90 °C for 4 h. Then the reaction mixture was diluted with H₂O (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over Na₂SO₄, concentrated and purified by column chromatography (PE/EA = 5/1) to give the desired product 6-chloro-2-(chloromethyl)imidazo[1,2-b]pyridazine (2.6 g, yield: 33%) as a yellow solid. ESI-MS [M+H]⁺: 202.2.

[0164] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-11). A solution of 6-chloro-2-(chloromethyl)imidazo[1,2-b]pyridazine (50 mg, 0.25 mmol), N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (66 mg, 0.24 mmol), Cs₂CO₃ (160 mg, 0.5 mmol) in DMF (3 mL) was stirred at RT for 2 h. Then the reaction mixture was diluted with H₂O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na₂SO₄, concentrated and purified by column chromatography (CH₂Cl₂/MeOH = 10/1) to give the desired compound N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxamide (29.5 mg, yield: 27%) as a white solid. ESI-MS [M+H]⁺: 441.1. Purity: 98%. ¹H NMR (400 MHz, DMSO): δ 8.58 (s, 1H), 8.31 (s, 3H), 8.25 (s, 1H), 8.17 (d, J = 9.3 Hz, 1H), 7.86 (s, 1H), 7.78 (s, 1H), 7.38 (d, J = 9.5 Hz, 1H), 6.65 (d, J = 7.1 Hz, 1H), 5.47 (s, 2H), 4.56 (d, J = 5.0 Hz, 2H).

Example 12

Scheme 12



[0165] Synthesis of 2-(chloromethyl)-7-cyclopropylimidazo[1,2-a]pyridine. To a solution of (7-cyclopropylimidazo[1,2-a]pyridin-2-yl)methanol (126 mg, 0.67 mmol) in DCM (10 mL) was added SOCl_2 (2 mL). The resulting reaction was stirred at 45 °C for 4 h. The reaction was concentrated in vacuo to give the 2-(chloromethyl)-7-cyclopropylimidazo[1,2-a]pyridine (150 mg crude), which was used in the next step without further purification. ESI-MS $[\text{M}+\text{H}]^+$: 207.2.

[0166] Synthesis of ethyl 1-((7-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A mixture of 2-(chloromethyl)-7-cyclopropylimidazo[1,2-a]pyridine (0.15 g crude from previous step), ethyl 1H-pyrazole-4-carboxylate (126 mg, 0.9 mmol) and Cs_2CO_3 (1.17 g, 3.6 mmol) in DMF (8 mL) was stirred at 80 °C for 12 h. H_2O (15 mL) was added to the reaction and then extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give ethyl 1-((7-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (100 mg, 36%) as a yellow solid. ESI-MS $[\text{M}+\text{H}]^+$: 311.2.

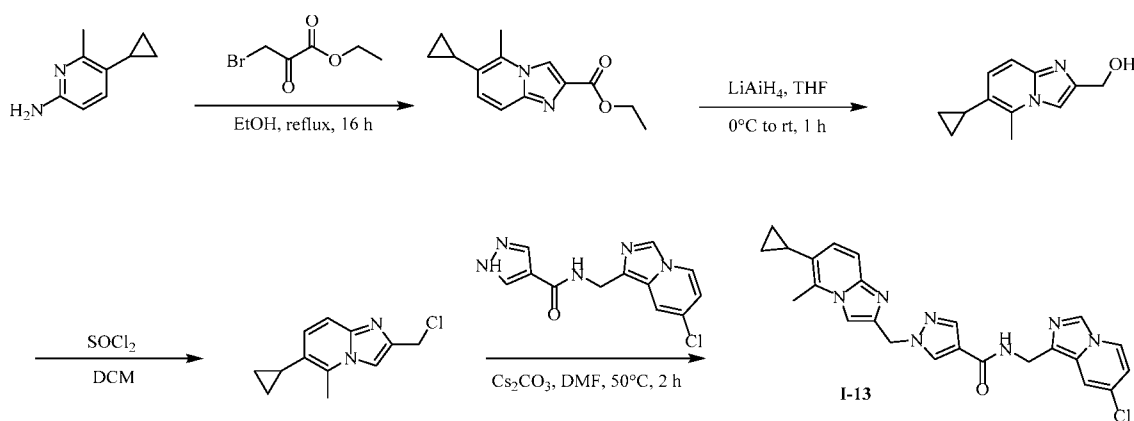
[0167] Synthesis of 1-((7-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. A mixture of ethyl 1-((7-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (600 mg, 1.94 mmol) and LiOH (270 mg, 11.6 mmol) in THF/EtOH/ H_2O (6 mL/6 mL/4 mL) was stirred at 80 °C for 2 h. The pH of reaction was adjusted

to around 5 and a yellow solid was precipitated out. The mixture was filtered and the solid was dried to give 1-((7-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (550 mg, yield: 100%) as a brown solid. ESI-MS $[M+H]^+$: 283.1.

[0168] Synthesis of 1-((7-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((6-methoxyimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-12). To a solution of 1-((7-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (23 mg, 0.08 mmol), (7-methoxyimidazo[1,5-a]pyridin-1-yl)methanamine (14 mg, 0.08 mmol) and HATU (45.6 mg, 0.12 mmol) in DMF (3 mL) was added DIPEA (30 mg, 0.24 mmol). The resulting reaction stirred at RT for overnight. H₂O (20 mL) was added to the reaction and then extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give 1-((7-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((6-methoxyimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (30 mg, yield: 85%). ESI-MS $[M+H]^+$: 442.1. Purity: 98.3%. ¹H NMR (400 MHz, MeOD): δ 8.22 (s, 1H), 8.15 (s, 1H), 8.12 (s, 1H), 8.06 (d, J = 7.6 Hz, 1H), 7.94 (s, 1H), 7.73 (s, 1H), 7.41 (d, J = 9.4 Hz, 1H), 7.14 (d, J = 9.4 Hz, 1H), 6.90 (s, 1H), 6.41 (dd, J = 7.6, 2.2 Hz, 1H), 5.46 (s, 2H), 4.69 (s, 2H), 3.81 (s, 3H), 2.05-1.83 (m, 1H), 1.07-0.92 (m, 2H), 0.86-0.63 (m, 2H).

Example 13

Scheme 13



[0169] Synthesis of ethyl 6-cyclopropyl-5-methylimidazo[1,2-a]pyridine-2-carboxylate. A mixture of 5-cyclopropyl-6-methylpyridin-2-amine (1.3 g, 8.78 mmol), ethyl 3-bromo-2-oxopropanoate (3.5 g, 17.57 mmol) in EtOH (30 mL) was stirred at 90 °C for 16 h. The mixture was concentrated and purified by silica gel chromatography (DCM/MeOH = 20/1) to give ethyl 6-cyclopropyl-5-methylimidazo[1,2-a]pyridine-2-carboxylate (150 mg, yield: 7%) as a yellow solid. ESI-MS $[M+H]^+$: 245.1.

[0170] Synthesis of (6-cyclopropyl-5-methylimidazo[1,2-a]pyridin-2-yl)methanol. To a solution of ethyl 6-cyclopropyl-5-methylimidazo[1,2-a]pyridine-2-carboxylate (110 mg, 0.45 mmol) in dry THF (5 mL) was added $LiAlH_4$ (50 mg, 1.12 mmol) slowly at 0 °C. After the mixture was stirred at RT for 1 h, it was quenched with $Na_2SO_4 \cdot 10H_2O$. The mixture was filtered and the filtrate was washed with EtOAc (20 mL). The filtrate was concentrated and purified by prep-TLC (DCM/MeOH = 15/1) to give (6-cyclopropyl-5-methylimidazo[1,2-a]pyridin-2-yl)methanol (50 mg, yield: 55%) as a yellow solid. ESI-MS $[M+H]^+$: 203.1.

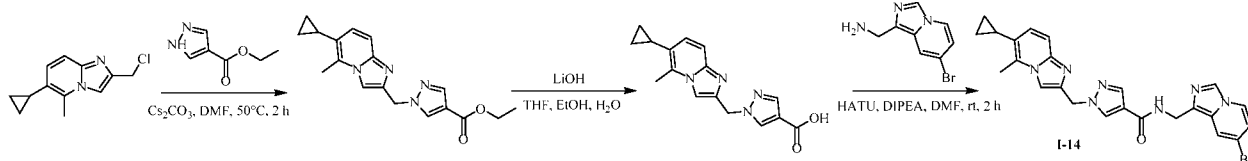
[0171] Synthesis of 2-(chloromethyl)-6-cyclopropyl-5-methylimidazo[1,2-a]pyridine. To a solution of (6-cyclopropyl-5-methylimidazo[1,2-a]pyridin-2-yl)methanol (50 mg, 0.25 mmol) in dry DCM (2.5 mL) was added $SOCl_2$ (0.5 mL) at RT. The mixture was stirred at 40 °C for 1 h. The mixture was concentrated to give 2-(chloromethyl)-6-cyclopropyl-5-methylimidazo[1,2-a]pyridine (50 mg, yield: 90.9%) as a yellow oil, which was used in the next step without further purification. ESI-MS $[M+H]^+$: 221.2.

[0172] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-13). A mixture of 2-(chloromethyl)-6-cyclopropyl-5-methylimidazo[1,2-a]pyridine (25 mg, 0.11 mmol), N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (30 mg, 0.11 mmol) and Cs_2CO_3 (110 mg, 0.33 mmol) in DMF (3 mL) was stirred at 50 °C for 2 h. Water (20 mL) was added and extracted with EtOAc (20 mL x 3). The combined organic layers were concentrated and purified by prep-TLC (DCM/MeOH = 10/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (17 mg, yield: 33.7%) as a light yellow solid. ESI-MS $[M+H]^+$: 460.2. Purity: 99.5%. ^1H NMR (400 MHz, DMSO): δ 8.57 (s, 1H), 8.30 (d, J = 7.1 Hz, 2H), 8.20 (s, 1H), 7.85 (s, 1H), 7.77 (s, 2H), 7.33 (d, J = 9.6 Hz, 1H), 6.97 (d, J = 8.6 Hz, 1H), 6.64 (d, J = 7.3

Hz, 1H), 5.40 (s, 2H), 4.54 (d, $J = 5.1$ Hz, 2H), 2.64 (s, 3H), 2.02 (s, 1H), 0.94 (d, $J = 8.2$ Hz, 2H), 0.64 (s, 2H).

Example 14

Scheme 14



[0173] Synthesis of ethyl 1-((6-cyclopropyl-5-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A mixture of 2-(chloromethyl)-6-cyclopropyl-5-methylimidazo[1,2-a]pyridine (65 mg, 0.30 mmol), ethyl 1H-pyrazole-4-carboxylate (45 mg, 0.32 mmol) and Cs_2CO_3 (245 mg, 0.75 mmol) in DMF (5 mL) was stirred at 50 °C for 2 h. Water (20 mL) was added and extracted with EtOAc (20 mL x 3). The combined organic layers were concentrated to give ethyl 1-((6-cyclopropyl-5-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (65 mg, yield: 67%) as a yellow solid. ESI-MS $[\text{M}+\text{H}]^+$: 325.1.

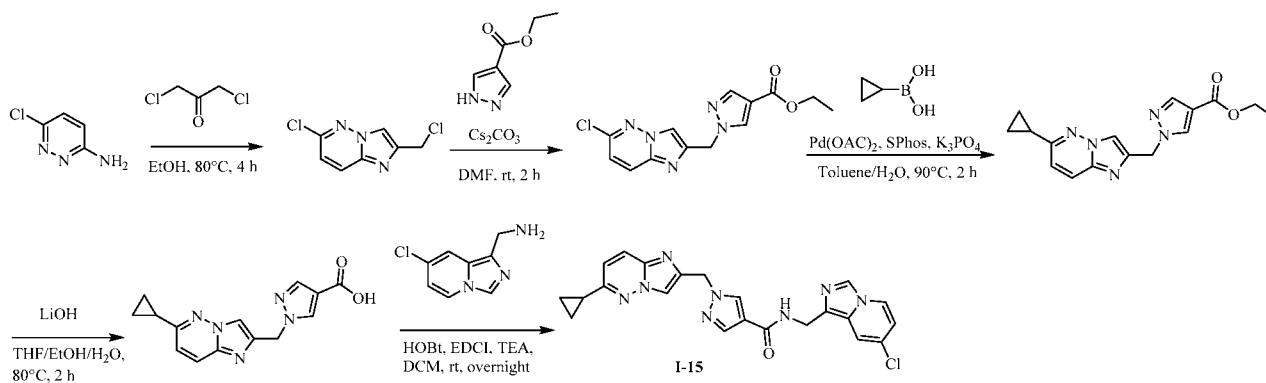
[0174] Synthesis of 1-((6-cyclopropyl-5-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. A solution of ethyl 1-((6-cyclopropyl-5-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (65 mg, 0.2 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (25 mg, 0.6 mmol) in THF/MeOH/ H_2O (1 mL/1 mL/0.5 mL) was stirred at 80 °C for 1 h. The pH of the mixture was adjusted to 4 by adding 1 M HCl solution. Water (10 mL) was added and the reaction was extracted with EtOAc (20 mL x 3). The combined organic layers were concentrated to give 1-((6-cyclopropyl-5-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (59 mg, yield: 99.7%) as a yellow oil, which was used directly in the next step without further purification. ESI-MS $[\text{M}+\text{H}]^+$: 297.1.

[0175] Synthesis of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-14). A mixture of 1-((6-cyclopropyl-5-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (59 mg, 0.2 mmol), (7-bromoimidazo[1,5-a]pyridin-1-yl)methanamine (70 mg, 0.25 mmol), HATU (120 mg, 0.3 mmol) and DIPEA (0.1 mL, 0.6 mmol) in DMF (4 mL) was

stirred at RT for 2 h. Water (20 mL) was added and the reaction was extracted with EtOAc (30 mL x 3). The organic layers were concentrated and purified by prep-TLC (DCM/MeOH = 10/1) to give N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (42.2 mg, yield: 41.9%) as a white solid. ESI-MS $[M+H]^+$: 504.1. Purity: 93.5%. ^1H NMR (400 MHz, DMSO): δ 8.57 (t, J = 5.7 Hz, 1H), 8.31 (s, 1H), 8.27-8.17 (m, 2H), 7.94 (s, 1H), 7.85 (s, 1H), 7.77 (s, 1H), 7.33 (d, J = 9.3 Hz, 1H), 6.97 (d, J = 9.3 Hz, 1H), 6.71 (dd, J = 7.4, 1.9 Hz, 1H), 5.41 (s, 2H), 4.54 (d, J = 5.7 Hz, 2H), 2.64 (s, 3H), 2.01-1.98 (m, 1H), 0.94 (dd, J = 8.4, 1.7 Hz, 2H), 0.74-0.58 (m, 2H).

Example 15

Scheme 15



[0176] Synthesis of 6-chloro-2-(chloromethyl)imidazo[1,2-b]pyridazine. A solution of 6-chloropyridazin-3-amine (20.0 g, 155.0 mmol) and 1,3-dichloropropan-2-one (49.2 g, 387.5 mmol) in EtOH (200 mL) was stirred at 80 °C for 4 h. Then the reaction mixture was concentrated and diluted with H₂O (300 mL x 3) and extracted with EtOAc (500 mL x 3). The combined organic layer were dried over Na₂SO₄, concentrated and purified by column chromatography (DCM: MeOH = 10: 1) to give the desired product 6-chloro-2-(chloromethyl)imidazo[1,2-b]pyridazine (17.0 g, yield: 54%) as a yellow solid. ESI-MS $[M+H]^+$: 202.1.

[0177] Synthesis of ethyl 1-((6-chloroimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A solution of 6-chloro-2-(chloromethyl)imidazo[1,2-b]pyridazine (10.0 g, 49.5 mmol), ethyl 1H-pyrazole-4-carboxylate (6.2 g, 44.5 mmol), Cs₂CO₃ (48.4 g, 148.5

mmol) in DMF (200 mL) was stirred at RT for 2 h. Most of the DMF was concentrated, the residue was diluted with H₂O (300 mL) and extracted with EtOAc (500 mL x 3). The combined organic layer were dried over Na₂SO₄, concentrated and purified by column chromatography (EtOAc:PE = 2:1) to give the desired compound ethyl 1-((6-chloroimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxylate (10.0 g, yield: 65%) as a yellow solid, ESI-MS [M+H]⁺: 306.1.

[0178] Synthesis of methyl 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A solution of ethyl 1-((6-chloroimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxylate (10.0 g, 32 mmol), cyclopropylboronic acid (4.2 g, 49 mmol), Pd(OAc)₂ (718.4 mg, 3.2 mmol), SPhos (1.3 g, 3.2 mmol) and K₃PO₄ (21.0 g, 96 mmol) in Tol/H₂O (100 mL/10 mL) was stirred at RT for 2 h. Then the reaction mixture was diluted with H₂O (100 mL) and extracted with EtOAc (300 mL x 3). The combined organic layer were dried over Na₂SO₄, concentrated and purified by column chromatography (EtOAc:PE = 2:1) to give the desired compound ethyl 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxylate (9.8 g, yield: 100%) as a white solid. ESI-MS [M+H]⁺: 312.2.

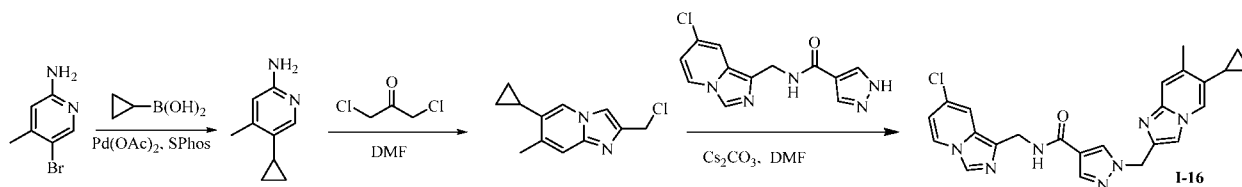
[0179] Synthesis of 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. A solution of ethyl 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxylate (9.8 g, 32.0 mmol) and LiOH (1.5 g, 64.0 mmol) in THF/EtOH/H₂O (80 mL/80 mL/80 mL) was stirred at 80 °C for 2 h. Then the reaction mixture was concentrated and diluted with H₂O (50 mL). The pH of the solution was adjusted to 5 by adding 1 M HCl solution. Solid precipitated and was filtered to give the desired compound 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (9.5 g, yield: 104.6%) as a white solid. ESI-MS [M+H]⁺: 284.1.

[0180] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-15). A solution of 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (9.5 g, 33.5 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine (9.5 g, 43.5 mmol), EDCI (7.7 g, 40.2 mmol), HOBt (5.4 g, 40.2 mmol) and TEA (10.1 g, 13.9 mL, 100.5 mmol) in dry DCM (800 mL) was stirred at RT overnight. Then the reaction mixture was diluted with H₂O (500 mL x 3) and extracted with DCM (1 L x 3). The combined organic layer were dried over

Na₂SO₄, concentrated and purified by column chromatography (DCM: MeOH = 10: 1) to give the desired compound N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxamide (6.1 g, yield: 40.9%) as a white solid. ESI-MS [M+H]⁺: 447.1. Purity: 99.05%. ¹H NMR (400 MHz, DMSO): δ 8.58-8.55 (t, J = 5.7 Hz, 1H), 8.30-8.28 (m, J = 7.5, 0.6 Hz, 2H), 8.21 (s, 1H), 8.07 (s, 1H), 7.91 (d, J = 9.5 Hz, 1H), 7.84 (s, 1H), 7.77-7.76 (m, 1H), 7.08 (d, J = 9.5 Hz, 1H), 6.63 (dd, J = 7.5, 2.1 Hz, 1H), 5.40 (s, 2H), 4.54 (d, J = 5.7 Hz, 2H), 2.50-2.14 (m, J = 9.0, 4.1 Hz, 1H), 1.07-1.03 (m, J = 6.0, 4.1 Hz, 2H), 0.97-0.93 (m, 2H).

Example 16

Scheme 16



[0181] Synthesis of 5-cyclopropyl-4-methylpyridin-2-amine. To a solution of 5-bromo-4-methylpyridin-2-amine (2 g, 10.7 mmol) in toluene/H₂O (50 mL/5 mL) was added cyclopropylboronic acid (1.36 g, 16.0 mmol), Pd(OAc)₂ (240 mg, 1.07 mmol), SPhos (439 mg, 1.07 mmol) and K₃PO₄ (6.8 g, 32.1 mmol). The reaction mixture was stirred at 95 °C for 12 h under nitrogen, then diluted with DCM (200 mL), washed with H₂O and brine, and concentrated to give the crude residue which was purified by silica gel chromatography (PE/EtOAc = 1/1) to afford 5-cyclopropyl-4-methylpyridin-2-amine as a yellow solid (4 g, yield: 90%). ESI-MS [M+H]⁺: 149.2.

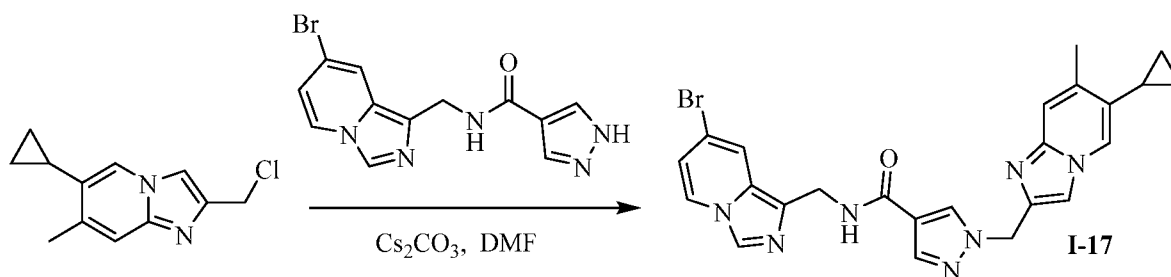
[0182] Synthesis of 2-(chloromethyl)-6-cyclopropyl-7-methylimidazo[1,2-a]pyridine. To a solution 5-cyclopropyl-4-methylpyridin-2-amine (200 mg, 1.35 mmol) in DMF (10 mL) was added 1,3-dichloropropan-2-one (514 mg, 4.05 mmol) at RT. The resulting reaction was stirred at 85 °C for 2 h. The solution was quenched with H₂O (30 mL), adjusted to pH 8 by adding saturated NaHCO₃ solution, and then extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give the crude, which was purified by prep-TLC (PE/EtOAc = 1/1) to give the 2-(chloromethyl)-6-

cyclopropyl-7-methylimidazo[1,2-a]pyridine (150 mg, yield: 51%) as a light yellow oil. ESI-MS $[M+H]^+$: 221.2.

[0183] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-7-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-17). To a solution 2-(chloromethyl)-6-cyclopropyl-7-methylimidazo[1,2-a]pyridine (55 mg, 0.25 mmol) in DMF (4 mL) was added N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (45 mg, 0.16 mmol) and Cs_2CO_3 (156 mg, 0.48 mmol) at RT. The resulting reaction was stirred at RT for 12 h. H_2O (20 mL) was added to the reaction and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , concentrated in vacuo to give the crude, which was purified by prep-TLC (DCM/MeOH = 10/1) to give the N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-7-methylimidazo[1,2-a]pyridine-2-yl)methyl)-1H-pyrazole-4-carboxamide (20 mg, yield: 27%) as a white solid. ESI-MS $[M+H]^+$: 460.1. ^1H NMR (400 MHz, DMSO): δ 8.58 (t, J = 5.7 Hz, 1H), 8.35-8.27 (m, 2H), 8.23 (s, 1H), 8.19 (s, 1H), 7.86 (s, 1H), 7.79-7.74 (m, 1H), 7.66 (s, 1H), 7.30 (s, 1H), 6.66-6.63 (m, 1H), 5.38 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 2.42 (s, 3H), 1.88-1.82 (m, 1H), 0.94-0.84 (m, 2H), 0.62-0.54 (m, 2H).

Example 17

Scheme 17

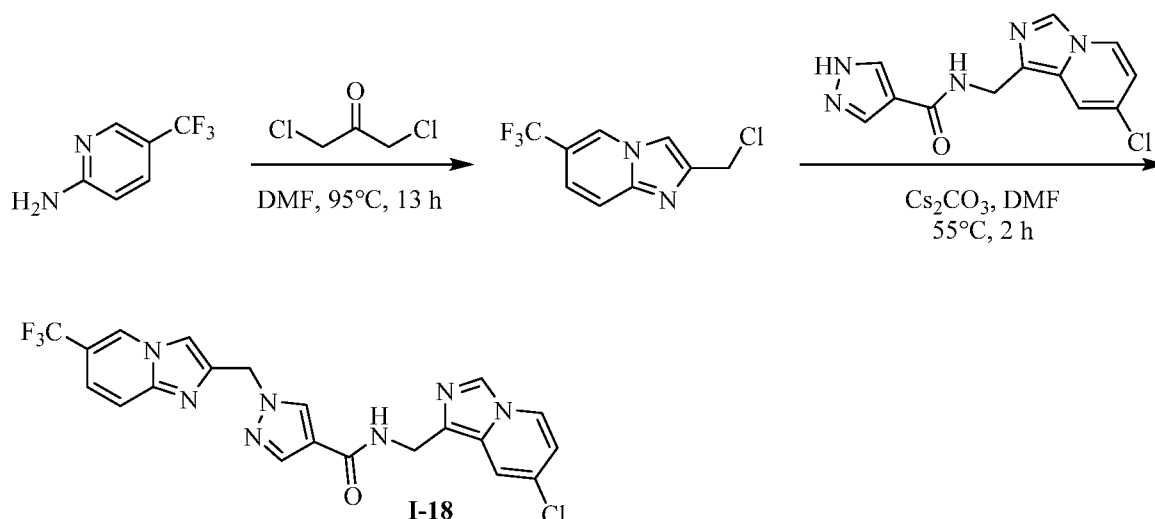


[0184] Synthesis of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-7-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-17). To a solution of 2-(chloromethyl)-6-cyclopropyl-7-methylimidazo[1,2-a]pyridine (50 mg, 0.23 mmol) in DMF (4 mL) was added N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (48 mg, 0.15 mmol) and Cs_2CO_3 (147 mg, 0.45 mmol) at RT. The

resulting reaction was stirred at RT for 12 h. the reaction was quenched with H₂O (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude, which was purified by prep-TLC (DCM/MeOH = 10/1) to give the N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-7-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (22 mg, yield: 29%) as a white solid. ESI-MS [M+H]⁺: 506.1. Purity: 91.6%. ¹H NMR (400 MHz, DMSO): δ 8.58-8.55 (m, 1H), 8.31 (s, 1H), 8.24 (d, J = 7.4 Hz, 1H), 8.19-8.17 (m, 2H), 7.95 (s, 1H), 7.84 (s, 1H), 7.62 (s, 1H), 7.26 (s, 1H), 6.73-6.70 (m, 1H), 5.35 (s, 2H), 4.54 (d, J = 5.7 Hz, 2H), 2.40 (s, 3H), 1.85-1.81 (m, 1H), 0.89-0.87 (m, 2H), 0.58-0.56 (m, 2H).

Example 18

Scheme 18

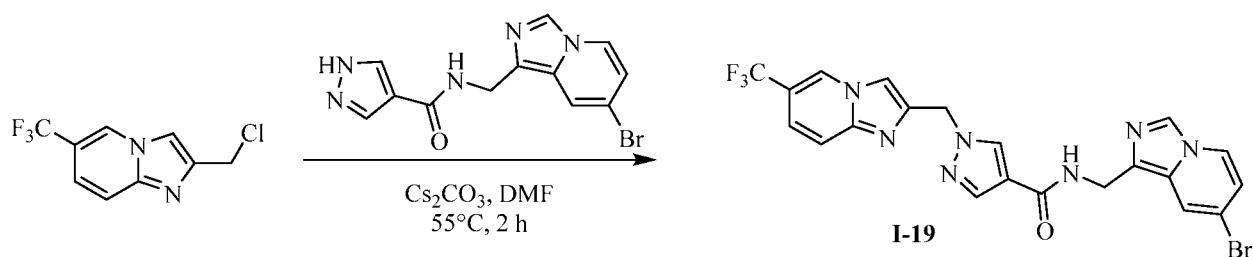


[0185] Synthesis of 2-(chloromethyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine. A solution of 5-(trifluoromethyl)pyridin-2-amine (500 mg, 3.1 mmol) and 1,3-dichloropropan-2-one (1.2 g, 9.3 mmol) in DMF (15 mL) was stirred at 95 °C for 13 h. The reaction was quenched with aqueous NaHCO₃ solution (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude, which was purified with silica gel chromatography (PE/EA = 1/2) to give the 2-(chloromethyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine (350 mg, yield: 48%) as a yellow solid. ESI-MS [M+H]⁺: 235.2.

[0186] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-18). A mixture of 2-(chloromethyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine (200 mg, 0.85 mmol), N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (234 mg, 0.85 mmol) and Cs₂CO₃ (831 mg, 2.55 mmol) in DMF (10 mL) was stirred at 55 °C for 2 h. H₂O (30 mL) was added to the reaction and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified by prep-TLC (DCM/MeOH = 10/1) to give the N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (25 mg, yield: 6.2%) as a white solid. ESI-MS [M+H]⁺: 474.2. Purity: 99.7%. ¹H NMR (400 MHz, MeOD): δ 8.99 (s, 1H), 8.27 (s, 1H), 8.19-8.17 (m, 2H), 7.93 (s, 2H), 7.75 (s, 1H), 7.66 (d, J = 9.5 Hz, 1H), 7.50 (dd, J = 9.5, 1.5 Hz, 1H), 6.63 (dd, J = 7.5, 1.9 Hz, 1H), 5.52 (s, 2H), 4.70 (s, 2H).

Example 19

Scheme 19

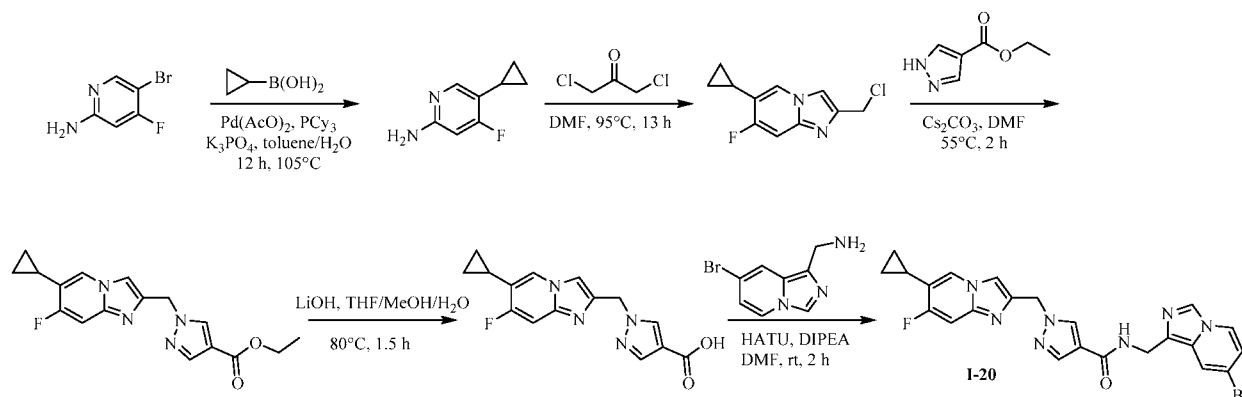


[0187] Synthesis of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-19). A mixture of 2-(chloromethyl)-6-(trifluoromethyl)imidazo[1,2-a]pyridine (200 mg, 0.85 mmol), N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (271 mg, 0.85 mmol) and Cs₂CO₃ (831 mg, 2.55 mmol) in DMF (10 mL) was stirred at 55 °C for 2 h. H₂O (30 mL) was added to the reaction and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified by prep-TLC (DCM/MeOH = 10/1) to give the N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-

carboxamide (40 mg, yield: 9%) as a white solid. ESI-MS $[M+H]^+$: 518.0. Purity: 94.14%. ^1H NMR (400 MHz, MeOD): δ 8.99 (s, 1H), 8.27 (s, 1H), 8.19 (s, 1H), 8.11 (d, $J = 7.4$ Hz, 1H), 7.94 (s, 3H), 7.66 (d, $J = 9.5$ Hz, 1H), 7.50 (d, $J = 9.5$ Hz, 1H), 6.75-6.67 (m, 1H), 5.52 (s, 2H), 4.70 (s, 2H).

Example 20

Scheme 20



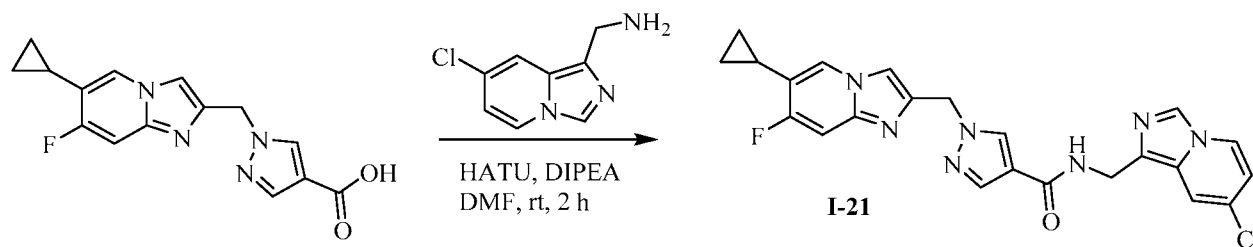
[0188] Synthesis of 5-cyclopropyl-4-fluoropyridin-2-amine. A mixture of 5-bromo-4-fluoropyridin-2-amine (1 g, 5.2 mmol), cyclopropylboronic acid (675 mg, 7.9 mmol), $\text{Pd}(\text{AcO})_2$ (116 mg, 0.52 mmol), PCy_3 (280 mg, 1 mmol) and K_3PO_4 (3.3 g, 15.6 mmol) in toluene/ H_2O (50 mL/5 mL) was stirred in a sealed tube at 105 °C under N_2 for 12 h. The reaction was concentrated to give the crude, which was purified by silica gel chromatography (PE/EA = 1/1) to give the 5-cyclopropyl-4-fluoropyridin-2-amine (500 mg, yield: 64%) as a white solid. ESI-MS $[M+H]^+$: 153.2.

[0189] Synthesis of 2-(chloromethyl)-6-cyclopropyl-7-fluoroimidazo[1,2-a]pyridine. A mixture of 5-cyclopropyl-4-fluoropyridin-2-amine (500 mg, 3.3 mmol) and 1,3-dichloropropan-2-one (1.25 g, 9.9 mmol) in DMF (30 mL) was stirred at 95 °C for 13 h. The pH of the reaction was adjusted to 9 by addition of aqueous NaHCO_3 and then extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo to give the crude, which was purified with silica gel chromatography (PE/EA = 3/1) to give the 2-(chloromethyl)-6-cyclopropyl-7-fluoroimidazo[1,2-a]pyridine (150 mg, yield: 20%) as a yellow solid. ESI-MS $[M+H]^+$: 225.1.

[0190] Synthesis of ethyl 1-((6-cyclopropyl-7-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A mixture of 2-(chloromethyl)-6-cyclopropyl-7-fluoroimidazo[1,2-a]pyridine (150 mg, 0.67 mmol), ethyl 1H-pyrazole-4-carboxylate (103 mg, 0.74 mmol) and Cs₂CO₃ (655 mg, 2.01 mmol) in DMF (10 mL) was stirred at 55 °C for 2 h. H₂O (30 mL) was added to the reaction and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give the crude, which was purified with silica gel chromatography (DCM/MeOH = 20/1) to give the ethyl 1-((6-cyclopropyl-7-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (100 mg, yield: 45%) as yellow solid. ESI-MS [M+H]⁺: 329.2.

[0191] Synthesis of 1-((6-cyclopropyl-7-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. To a solution of ethyl 1-((6-cyclopropyl-7-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (100 mg, 0.31 mmol) in THF/EtOH/H₂O (4 mL/4 mL/2 mL) was added LiOH (22 mg, 0.91 mmol). The resulting reaction was stirred at 80 °C for 1.5 h. Most of the solvent was removed. The pH of the residue was adjusted to around 5 and a yellow solid was precipitate out. The mixture was filtered and the solid was dried to give the 1-((6-cyclopropyl-7-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (75 mg, yield: 81%) as a yellow solid. ESI-MS [M+H]⁺: 301.1.

[0192] Synthesis of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-7-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-20). To a solution of 1-((6-cyclopropyl-7-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (35 mg, 0.12 mmol), (7-bromoimidazo[1,5-a]pyridin-1-yl)methanamine (35 mg, 0.15 mmol) and HATU (68 mg, 0.18 mmol) in DMF (5 mL) was added DIPEA (77 mg, 0.6 mmol). The resulting reaction was stirred at RT for 2 h. Water (30 mL) was added and extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-7-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (19 mg, yield: 32%). ESI-MS [M+H]⁺: 508.1. Purity: 90.5%. ¹H NMR (400 MHz, MeOD): δ 8.26 (s, 1H), 8.18 (d, J = 7.1 Hz, 1H), 8.13 (s, 1H), 8.10 (d, J = 7.4 Hz, 1H), 7.92 (s, 1H), 7.91 (s, 1H), 7.67 (s, 1H), 7.12 (d, J = 10.3 Hz, 1H), 6.72 (d, J = 7.4 Hz, 1H), 5.41 (s, 2H), 4.68 (s, 2H), 2.04-1.87 (m, 1H), 1.02-0.97 (m, 2H), 0.76-0.72 (m, 2H).

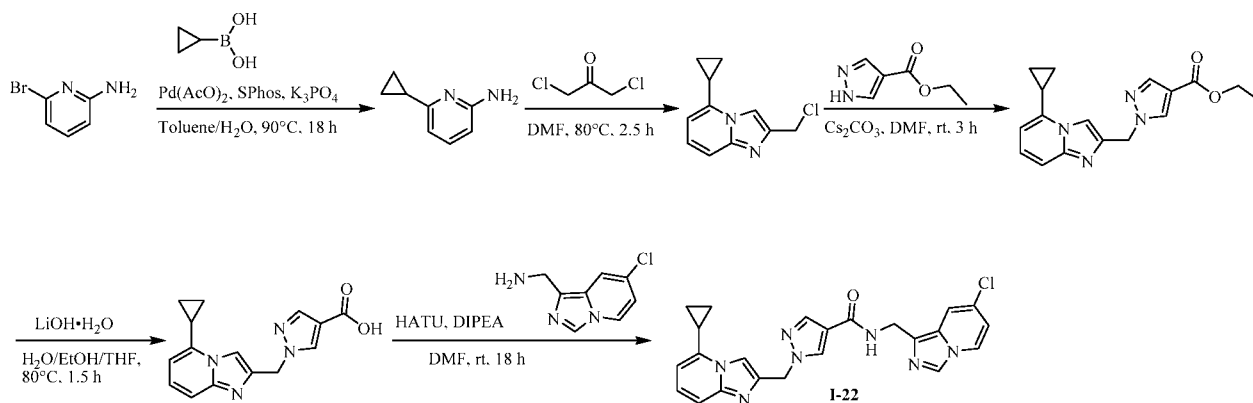
Example 21Scheme 21

[0193] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-7-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-21).

To a solution of 1-((6-cyclopropyl-7-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (35 mg, 0.12 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine (28 mg, 0.15 mmol) and HATU (68 mg, 0.18 mmol) in DMF (5 mL) was added DIPEA (77 mg, 0.6 mmol). The resulting reaction was stirred at RT for 2 h. Water (30 mL) was added and extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-7-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (20 mg, yield: 32%). ESI-MS [M+H]⁺: 464.1. Purity: 94.8%. ¹H NMR (400 MHz, MeOD): δ 8.25 (s, 1H), 8.19-8.12 (m, 3H), 7.90 (s, 1H), 7.73 (s, 1H), 7.68 (s, 1H), 7.13 (d, J = 10.3 Hz, 2H), 6.62 (dd, J = 7.5, 1.9 Hz, 1H), 5.41 (s, 2H), 4.68 (s, 2H), 1.37 (dd, J = 6.7, 3.3 Hz, 1H), 1.02-0.97 (m, 2H), 0.75-0.71 (m, 2H).

Example 22

Scheme 22



[0194] Synthesis of 6-cyclopropylpyridin-2-amine. To a solution of 2-amino-6-bromopyridine (1.0 g, 5.75 mmol) in toluene/H₂O (15 mL/3 mL) was added cyclopropylboronic acid (1.98 g, 23 mmol), Palladium diacetate (134 mg, 0.63 mmol), 2-dicyclohexylphosphino-2',6-dimethoxybiphenyl (240 mg, 0.6 mmol) and potassium phosphate (4.24 g, 20.12 mmol). The resulting mixture was stirred at 90 °C for 16 h. The reaction was diluted with H₂O (20 mL), extracted with ethyl acetate (3 × 50 mL), The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash column chromatography to give 6-cyclopropylpyridin-2-amine (621 mg, yield: 81%). ESI-MS [M+H]⁺: 135.2.

[0195] Synthesis of 2-(chloromethyl)-5-cyclopropylimidazo[1,2-a]pyridine. To a solution of 5-cyclopropylpyrimidin-2-amine (600 mg, 4.5 mmol) in N,N-dimethylformamine (2 mL) was added 1,3-dichloropropan-2-one (2.2 g, 18.0 mmol). The resulting mixture was stirred at 80 °C for 2.5 h. The reaction mixture was quenched with H₂O (50 mL) and extracted with ethyl acetate (3 × 30 mL), The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash column chromatography to give 2-(chloromethyl)-5-cyclopropylimidazo[1,2-a]pyridine (300 mg, yield: 33%). ESI-MS [M+H]⁺: 207.1.

[0196] Synthesis of ethyl 1-((5-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. To a solution of 2-(chloromethyl)-5-cyclopropylimidazo[1,2-a]pyridine (150 mg, 0.73 mmol) in N,N-dimethylformamine (2 mL) was added cesium carbonate (949 mg,

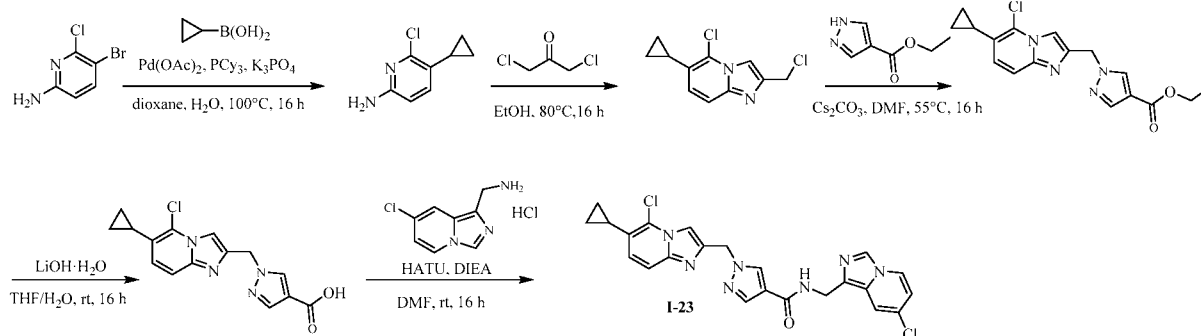
2.92 mmol) and ethyl 1H-pyrazole-4-carboxylate (102 mg, 0.73 mmol). The resulting mixture was stirred at RT for 3 h. Water (50 mL) was added and extracted with ethyl acetate (3 × 30 mL). The organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash column chromatography to give ethyl 1-((5-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (220 mg, yield: 80%). ESI-MS $[M+H]^+$: 311.2.

[0197] Synthesis of 1-((5-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. To a solution of ethyl 1-((5-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (210 mg, 0.68 mmol) in a mixture solvent of THF/EtOH/H₂O (3 mL/3 mL/1.5 mL) was added lithium hydroxide (82 mg, 3.39 mmol). The resulting mixture was stirred at 80 °C for 1.5 h. Water (50 mL) was added and the pH of the mixture was adjusted to 4-5 by adding HCl solution. The mixture was then extracted with DCM (3 × 30 mL). The organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated to give 1-((5-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (140 mg, Yield: 60%) which was used in the next step without further purification. ESI-MS $[M+H]^+$: 283.1.

[0198] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-22). To the solution of 1-((5-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (67 mg, 0.21 mmol) in dry DMF (3 mL) was added HATU (116 mg, 0.305 mmol), DIPEA (16 mg, 0.125 mmol) and (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine (44 mg, 0.24 mmol) at RT. The reaction was stirred at RT for 2 h. Water (30 mL) was added and the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by prep-HPLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (36 mg, yield: 30%) as a white solid. ESI-MS $[M+H]^+$: 446.2. Purity: 98.74. ¹H NMR (400 MHz, DMSO): δ 8.59 (t, J = 5.6 Hz, 1H), 8.34-8.26 (m, 2H), 8.25 (s, 1H), 8.02 (s, 1H), 7.86 (s, 1H), 7.78 (s, 1H), 7.41 (d, J = 9.0 Hz, 1H), 7.24-7.14 (m, 1H), 6.72-6.61 (m, 2H), 5.45 (s, 2H), 4.55 (d, J = 5.8 Hz, 2H), 2.18 (s, 1H), 1.13-1.10 (m, 2H), 0.83-0.74 (m, 2H).

Example 23

Scheme 23



[0199] Synthesis of 6-chloro-5-cyclopropylpyridin-2-amine. A mixture of 5-bromo-6-chloropyridin-2-amine (3 g, 14 mmol) and cyclopropyl boronic acid (2.4 g, 28 mmol), Pd(OAc)₂ (313.6 mg, 1.4 mmol), tricyclohexylphosphene (784 mg, 2.8 mmol) and K₃PO₄ (5.9 g, 28 mmol) in dioxane/H₂O (20 mL/20 mL) was stirred in a sealed tube at 100 °C under N₂ for 16 h. The reaction was concentrated to give the crude, which was purified by silica gel chromatography (PE/EA = 5/1) to give the 6-chloro-5-cyclopropylpyridin-2-amine (2.4 g, yield: 98%) as a white solid. ESI-MS [M+H]⁺: 169.2.

[0200] Synthesis of 5-chloro-2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine. A mixture of 6-chloro-5-cyclopropylpyridin-2-amine (2.4 g, 14.2 mmol) and 1,3-dichloropropan-2-one (7.16 g, 56.8 mmol) in ethanol (30 mL) was stirred at 78 °C for 16 h. The mixture was quenched with saturated NaHCO₃ (50 mL) and extracted with DCM (100 mL x 3). The combined organic layers were concentrated and purified by flash column silica gel chromatography (DCM/MeOH = 15/1) to give the 5-chloro-2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (1.8 g, yield: 53%) as a yellow solid. ESI-MS [M+H]⁺: 241.1.

[0201] Synthesis of ethyl 1-((5-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. To a solution of 5-chloro-2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (800 mg, 3.33 mmol) in dry DMF (10 mL) was added ethyl 1H-pyrazole-4-carboxylate (512.4 mg, 3.66 mmol) and Cs₂CO₃ (3.25 g, 10 mmol). Then the reaction mixture was stirred at 55 °C for 16 h under N₂ atmosphere. The mixture was cooled to RT, diluted with H₂O (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined

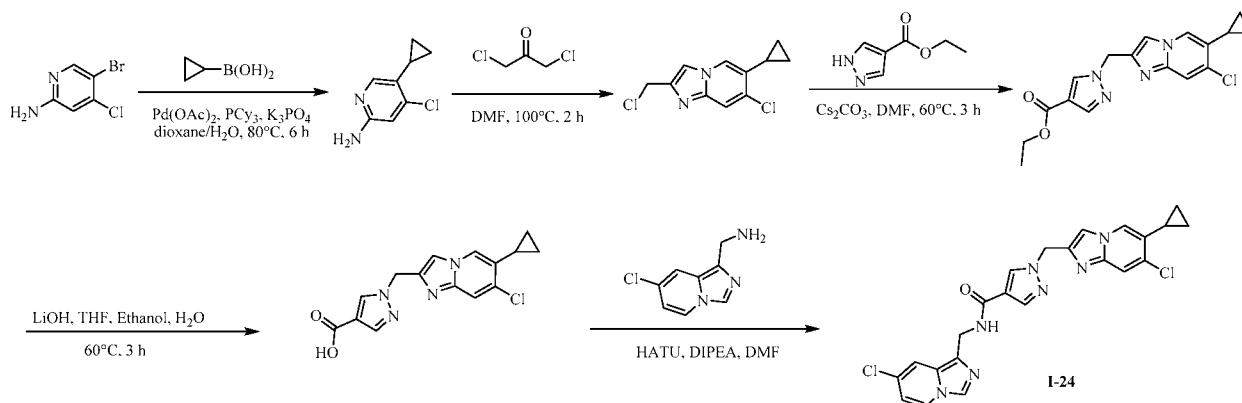
organic layers were washed with brine (20 mL x 2), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (DCM/MeOH = 10/1) to give the ethyl 1-((5-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (870 mg, yield: 76%) as a white solid. ESI-MS $[M+H]^+$: 345.2.

[0202] Synthesis of 1-((5-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. To a solution of ethyl 1-((5-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (300 mg, 0.87 mmol) in THF (5 mL) and H₂O (5 mL) was added LiOH·H₂O (110 mg, 2.62 mmol), then the reaction mixture was stirred at 50 °C for 16 h. The solvent was removed, and the pH of the residue was adjusted to around 5 by adding 1 M HCl solution allowing a yellow solid was precipitate out. The mixture was filtered and the solid was dried to give the 1-((5-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (175 mg, yield: 64%) as a white solid. ESI-MS $[M+H]^+$: 317.1.

[0203] Synthesis of 1-((5-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-23). To a solution of 1-((5-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (100 mg, 0.32 mmol) in dry DMF (3 mL) was added (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (69.4 mg, 0.32 mmol), HATU (182 mg, 0.48 mmol) and DIPEA (124 mg, 0.96 mmol), the reaction mixture was stirred at RT for 16 h. The reaction mixture diluted with H₂O (20 mL), extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by prep-TLC (DCM/MeOH = 10/1) to afford 1-((5-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (15 mg, yield: 9.8%) as a white solid. ESI-MS $[M+H]^+$: 480.1. Purity: 90.37%. ¹H NMR (400 MHz, DMSO-d₆): δ 8.58 (t, J = 5.5 Hz, 1H), 8.30 (d, J = 6.8 Hz, 2H), 8.24 (s, 1H), 7.92 (s, 1H), 7.86 (s, 1H), 7.78 (s, 1H), 7.50 (d, J = 9.3 Hz, 1H), 6.98 (d, J = 9.3 Hz, 1H), 6.64 (d, J = 7.5, 1.9 Hz, 1H), 5.46 (d, J = 9.6 Hz, 2H), 4.55 (d, J = 5.6 Hz, 2H), 2.19-2.06 (m, 1H), 1.03 (m, 2H), 0.78 (m, 2H).

Example 24

Scheme 24



[0204] Synthesis of 4-chloro-5-cyclopropylpyridin-2-amine. A mixture of 5-bromo-4-chloropyridin-2-amine (3.24 g, 15.6 mmol), cyclopropylboronic acid (2.01 g, 23.4 mmol), Pd(OAc)₂ (350 mg, 1.56 mmol), K₃PO₄ (6.62 g, 31.2 mmol) and PCy₃ (875 mg, 3.12 mmol) in toluene (40 mL) and H₂O (5 mL) was stirred at 80 °C overnight. Water (100 mL) was added and the mixture was extracted with EtOAc (100 mL x 3). The combined organics were concentrated and purified by silica gel chromatography (EA/PE = 2:3 to 10:1) to give 4-chloro-5-cyclopropylpyridin-2-amine (1.89 g, yield: 18.7%) as a yellow solid. ESI-MS [M+H]⁺: 169.1.

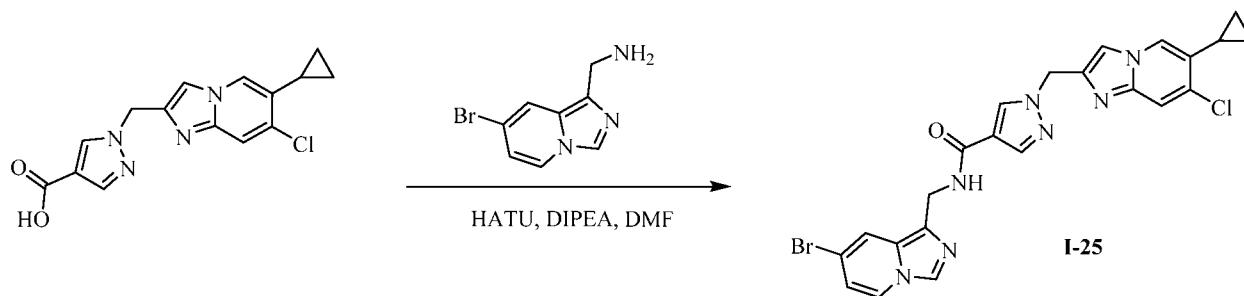
[0205] Synthesis of 7-chloro-2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine. To a solution of 4-chloro-5-cyclopropylpyridin-2-amine (1.2 g, 7.1 mmol) in DMF (20 mL) was added 1,3-dichloropropan-2-one (1.8 g, 14.2 mmol) at RT. After the mixture was stirred at 100 °C for 2 h, H₂O (50 mL) was added and extracted with EtOAc (100 mL x 3). The combined organic layers were concentrated and purified by silica gel chromatography (EA/PE = 1:10 to 3:7) to give 7-chloro-2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (674 mg, yield: 38%) as a yellow solid. ESI-MS [M+H]⁺: 241.1.

[0206] Synthesis of ethyl 1-((7-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A mixture of 7-chloro-2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (480 mg, 2.0 mmol), ethyl 1H-pyrazole-4-carboxylate (689 mg, 4.92 mmol) and Cs₂CO₃ (2.4 g, 7.38 mmol) in DMF (10 mL) was stirred at 60 °C for 3 h. Water (50 mL) was added and the mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give the crude, which was purified by silica gel chromatography (EA/PE = 7:3 to 10:1) to

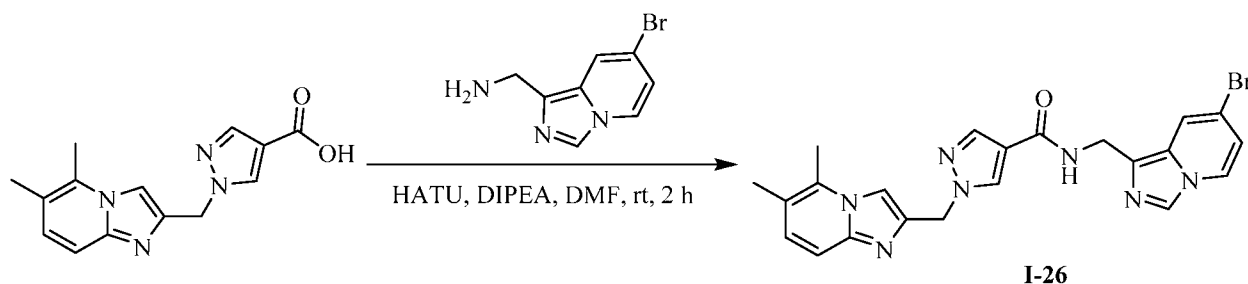
ethyl 1-((7-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (390 mg, yield: 57%) as a white solid. ESI-MS $[M+H]^+$: 345.1.

[0207] Synthesis of 1-((7-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. To a solution of ethyl 1-((7-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (200 mg, 0.58 mmol) in ethanol/THF/H₂O (3 mL/3 mL/1.5 mL) was added LiOH·H₂O (97 mg, 2.32 mmol). The reaction mixture was stirred at 65 °C for 3 h. The mixture was then concentrated and then diluted with H₂O (20 mL). The pH of the aqueous layer was adjusted to 4 by adding 1 M HCl solution and extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated to give crude 1-((7-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (230 mg) as a white solid, which was used in the next step without further purification. ESI-MS $[M+H]^+$: 317.1.

[0208] Synthesis of 1-((7-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-24). A mixture of crude 1-((7-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (230 mg, 0.73 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine (65.1 mg, 0.3 mmol), HATU (278 mg, 0.73 mmol) and DIPEA (375 mg, 2.9 mmol) in DMF (5 mL) was stirred at RT for 3 h. Water (30 mL) was added and the mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated and purified by prep-TLC (DCM:MeOH = 8:1) to give 1-((7-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (11.1 mg, yield: 7.7%) as a white solid. ESI-MS $[M+H]^+$: 480.0. Purity: 98.15%. ¹H NMR (400 MHz, DMSO): δ 8.58 (t, J = 5.3 Hz, 1H), 8.40 (s, 1H), 8.31-8.30 (m, 2H), 8.20 (s, 1H), 7.86 (s, 1H), 7.78 (s, 1H), 7.72 (s, 1H), 7.68 (s, 1H), 6.65 (dd, J = 7.4, 1.8 Hz, 1H), 5.40 (s, 2H), 4.55 (d, J = 5.6 Hz, 2H), 1.98-1.94 (m, 1H), 0.95-0.94 (m, 2H), 0.66-0.65 (m, 2H).

Example 25Scheme 25

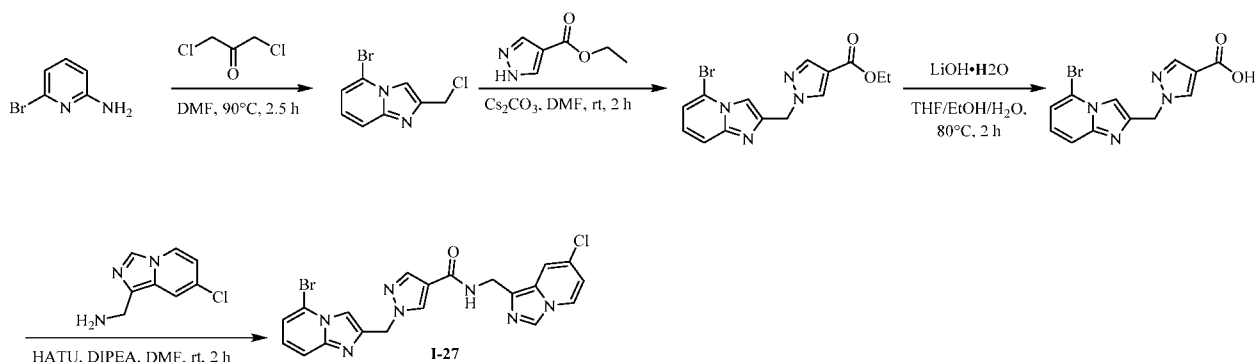
[0209] Synthesis of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((7-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-25). A mixture of crude 1-((7-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (230 mg, 0.73 mmol), (7-bromoimidazo[1,5-a]pyridin-1-yl)methanamine (67.8 mg, 0.3 mmol), HATU (278 mg, 0.73 mmol) and DIPEA (375 mg, 2.9 mmol) in DMF (5 mL) was stirred at RT for 3 h. Water (30 mL) was added and the mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated and purified by prep-TLC (DCM:MeOH = 8:1) to give N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((7-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (31.5 mg, yield: 20%) as a white solid. ESI-MS $[M+H]^+$: 524.0. Purity: 97%. ^1H NMR (400 MHz, DMSO): δ 8.58-8.57 (m, 1H), 8.39 (s, 1H), 8.31 (s, 1H), 8.23-8.20 (m, 2H), 7.94 (s, 1H), 7.85 (s, 1H), 7.69 (d, J = 13.8 Hz, 2H), 6.72-6.71 (m, 1H), 5.39 (s, 2H), 4.54 (s, 2H), 1.95-1.93 (m, 1H), 0.94-0.93 (m, 2H), 0.65-0.64 (m, 2H).

Example 26Scheme 26

[0210] Synthesis of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5,6-dimethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-26). To the solution of 1-((5,6-dimethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (54 mg, 0.2 mmol) in dry DMF (3 mL) was added HATU (114 mg, 0.3 mmol), DIPEA (129 mg, 1.0 mmol) and (7-bromoimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (52.4 mg, 0.2 mmol) at RT. The reaction was stirred at RT for 2 h. Water (30 mL) was added and the mixture was extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by prep-HPLC to give N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5,6-dimethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (9.7 mg, yield: 10.2%). ESI-MS $[M+H]^+$: 478.1. Purity: 90.33%. ^1H NMR (400 MHz, DMSO): δ 8.58 (t, J = 5.6 Hz, 1H), 8.31 (s, 1H), 8.28-8.18 (m, 2H), 7.95 (s, 1H), 7.85 (s, 1H), 7.76 (s, 1H), 7.33 (d, J = 9.1 Hz, 1H), 7.14 (d, J = 9.2 Hz, 1H), 6.76-6.67 (m, 1H), 5.40 (s, 2H), 4.54 (d, J = 5.7 Hz, 2H), 2.49 (s, 3H), 2.29 (s, 3H).

Example 27

Scheme 27



[0211] Synthesis of 5-bromo-2-(chloromethyl)imidazo[1,2-a]pyridine. To a solution of 6-bromopyridin-2-amine (800 mg, 4.6 mmol) in N,N-dimethylformamine (5 mL) was added 1,3-dichloropropan-2-one (3.05 g, 24.0 mmol). The resulting mixture was stirred at 90 °C for 2.5 h. The reaction mixture was diluted with H₂O (50 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layers were washed with brine, dried over anhydrous sodium sulfate and

concentrated. The residue was purified by flash column chromatography to give 5-bromo-2-(chloromethyl)imidazo[1,2-a]pyridine (600 mg, yield: 53%). ESI-MS $[M+H]^+$: 245.0.

[0212] Synthesis of ethyl 1-((5-bromoimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. To a solution of 5-bromo-2-(chloromethyl)imidazo[1,2-a]pyridine (200 mg, 0.82 mmol) in N,N-dimethylformamine (3 mL) was added cesium carbonate (1.1 g, 3.28 mmol) and ethyl 1H-pyrazole-4-carboxylate (115 mg, 0.82 mmol). The resulting mixture was stirred at RT for 2 h then diluted with H₂O (50 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash column chromatography to give ethyl 1-((5-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (236 mg, yield: 83%). ESI-MS $[M+H]^+$: 349.0.

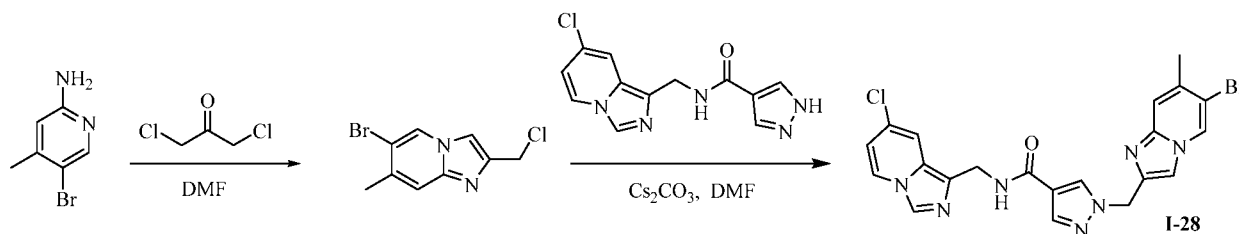
[0213] Synthesis of 1-((5-bromoimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. To a solution of ethyl 1-((5-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (236 mg, 0.68 mmol) in the mixture of THF/H₂O (3 mL/3 mL) was added lithium hydroxide (82 mg, 3.4 mmol). The resulting mixture was stirred at 80 °C for 2 h. THF was evaporated and the pH of the H₂O phase was adjusted to 5 by adding 1 M HCl solution. The resulting solid precipitate was filtered to give 1-((5-bromoimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (131 mg, Yield: 60%), which was used in the next step without further purification. ESI-MS $[M+H]^+$: 321.0.

[0214] Synthesis of 1-((5-bromoimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-27). To the solution of 1-((5-bromoimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (65 mg, 0.20 mmol) in dry DMF (3 mL) was added HATU (116 mg, 0.305 mmol), DIPEA (131 mg, 1.02 mmol) and (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (44 mg, 0.20 mmol) at RT. The reaction was stirred at RT for 2 h. Water (30 mL) was added and the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by prep-HPLC to give 1-((5-bromoimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (41 mg, yield: 37%). ESI-MS $[M+H]^+$: 484.0. Purity: 100%. ¹H NMR (400 MHz, DMSO): δ 8.60 (t, J = 5.6 Hz, 1H), 8.39 (s, 1H), 8.32

(d, J = 7.5 Hz, 1H), 8.26 (s, 1H), 7.97 (s, 1H), 7.88 (s, 1H), 7.81 (s, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.33 (d, J = 7.2 Hz, 1H), 7.31-7.21 (m, J = 8.7, 7.4 Hz, 1H), 6.72-6.63 (m, 1H), 5.48 (s, 2H), 4.57 (d, J = 5.7 Hz, 2H).

Example 28

Scheme 28



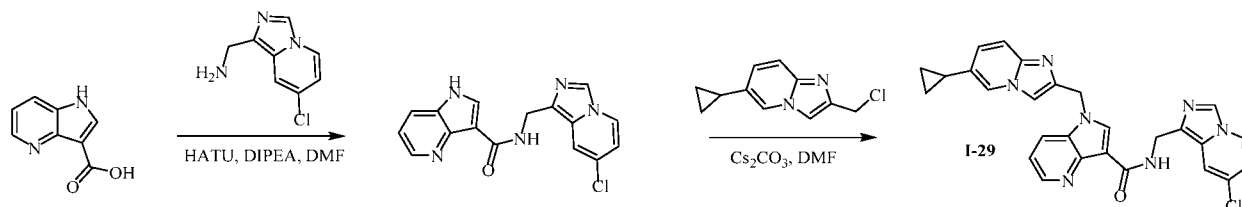
[0215] Synthesis of 6-bromo-2-(chloromethyl)-7-methylimidazo[1,2-a]pyridine. To a solution of 5-bromo-4-methylpyridin-2-amine (1000 mg, 5.37 mmol) in DMF (15 mL) was added 1,3-dichloropropan-2-one (2.04 g, 16.1 mmol) at RT. The resulting reaction was stirred at 85 °C for 2 h. The solution was quenched with H₂O (40 mL) and the pH of the mixture was adjusted to 8 by adding saturated a NaHCO₃ solution. The resulting mixture was then extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified with a silica gel column (PE/EtOAc = 1/1) to give the 6-bromo-2-(chloromethyl)-7-methylimidazo[1,2-a]pyridine (500 mg, yield:36%) as a light yellow oil. ESI-MS [M+H]⁺: 259.2.

[0216] Synthesis of 1-((6-bromo-7-methylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-28). To a solution 6-bromo-2-(chloromethyl)-7-methylimidazo[1,2-a]pyridine (56 mg, 0.22 mmol) in DMF (3 mL) was added N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole -4-carboxamide (40 mg, 0.14 mmol) and Cs₂CO₃ (140 mg, 0.43 mmol) at RT. The resulting reaction was stirred at RT for 12 h. H₂O (30 mL) was added to the reaction and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give the 1-((6-bromo-7-methylimidazo [1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (22 mg, yield: 32%) as a white solid. ESI-MS [M+H]⁺:

498.0. Purity: 98.7%. ^1H NMR (400 MHz, DMSO): δ 8.89 (s, 1H), 8.60-8.57 (m, 1H), 8.31-8.29 (m, 2H), 8.22 (s, 1H), 7.87 (s, 1H), 7.78 (s, 1H), 7.72 (s, 1H), 7.51 (s, 1H), 6.65 (d, J = 7.4 Hz, 1H), 5.40 (s, 2H), 4.55 (d, J = 5.6 Hz, 2H), 2.36 (s, 3H).

Example 29

Scheme 29



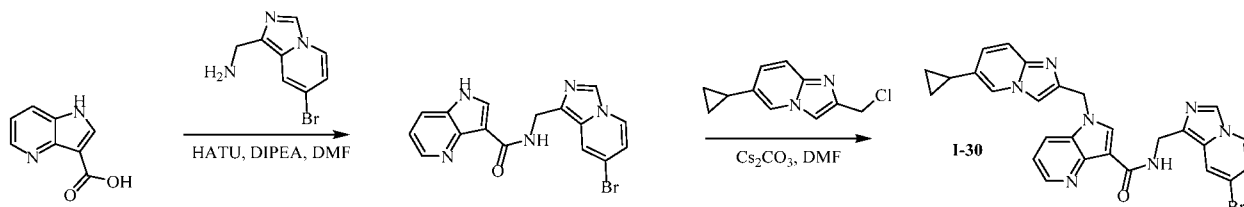
[0217] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrrolo[3,2-b]pyridine-3-carboxamide. A mixture of 1H-pyrrolo[3,2-b]pyridine-3-carboxylic acid (100 mg, 0.62 mmol), 7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (160 mg, 0.74 mmol), HATU (290 mg, 0.78 mmol) and DIPEA (0.32 mL, 1.86 mmol) in DMF (5 mL) was stirred at RT for 16 h. Water (30 mL) was added and extracted with EtOAc (30 mL x 3). The combined organic layers were concentrated and purified by prep-TLC (DCM/MeOH = 10/1) to give N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (60 mg, yield: 30%) as a yellow solid. ESI-MS $[M+H]^+$: 326.1.

[0218] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrrolo[3,2-b]pyridine-3-carboxamide (I-29). A mixture of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrrolo[3,2-b]pyridine-3-carboxamide (50 mg, 0.15 mmol), 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (40 mg, 0.19 mmol) and Cs_2CO_3 (125 mg, 0.39 mmol) in DMF (5 mL) was stirred at RT for 4 h. Water (30 mL) was added and extracted with EtOAc (30 mL x 3). The combined organic layers were concentrated and purified by prep-HPLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrrolo[3,2-b]pyridine-3-carboxamide (9.1 mg, yield: 12%) as a yellow solid. ESI-MS $[M+H]^+$: 496.1. Purity: 86.0%. ^1H NMR (400 MHz, DMSO): δ 9.06 (t, J = 5.8 Hz, 1H), 8.43 (d, J = 4.7 Hz, 1H), 8.40-8.25 (m, 4H),

8.14 (d, J = 8.3 Hz, 1H), 7.87 (s, 1H), 7.73 (s, 1H), 7.37 (d, J = 9.4 Hz, 1H), 7.26 (dd, J = 8.3, 4.7 Hz, 1H), 6.97 (d, J = 9.4 Hz, 1H), 6.66 (dd, J = 7.4, 2.0 Hz, 1H), 5.59 (s, 2H), 4.77 (d, J = 5.7 Hz, 2H), 1.96-1.81 (m, 1H), 0.96-0.83 (m, 2H), 0.73-0.56 (m, 2H).

Example 30

Scheme 30



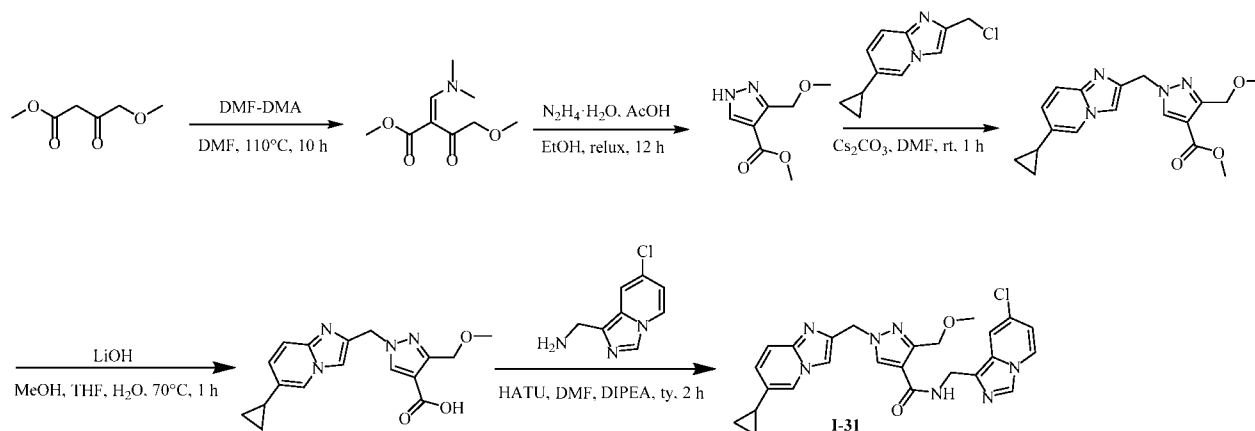
[0219] Synthesis of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrrolo[3,2-b]pyridine-3-carboxamide. A mixture of 1H-pyrrolo[3,2-b]pyridine-3-carboxylic acid (100 mg, 0.62 mmol), 7-bromoimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (190 mg, 0.74 mmol), HATU (350 mg, 0.93 mmol) and DIPEA (0.32 mL, 1.86 mmol) in DMF (5 mL) was stirred at RT for 16 h. Water (30 mL) was added and the mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were concentrated and purified by prep-TLC (DCM/MeOH = 10/1) to give N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrrolo[3,2-b]pyridine-3-carboxamide (60 mg, yield: 20%) as a yellow solid. ESI-MS $[M+H]^+$: 370.1.

[0220] Synthesis of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrrolo[3,2-b]pyridine-3-carboxamide (1-30). A mixture of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrrolo[3,2-b]pyridine-3-carboxamide (60 mg, 0.16 mmol), 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (40 mg, 0.19 mmol) and Cs_2CO_3 (125 mg, 0.39 mmol) in DMF (5 mL) was stirred at RT for 4 h. Water (30 mL) was added and the mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were concentrated and purified by prep-HPLC to give N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrrolo[3,2-b]pyridine-3-carboxamide (13.0 mg, yield: 15%) as a yellow solid. ESI-MS $[M+H]^+$: 540.1. Purity: 89.1%. ^1H NMR (400 MHz, DMSO): δ 9.06 (t, J = 6.0 Hz, 1H), 8.43 (d, J = 3.7 Hz, 1H), 8.36 (d, J = 5.4 Hz, 2H), 8.31-8.22 (m, 2H), 8.14 (d, J = 8.0 Hz, 1H), 8.04 (s,

1H), 7.73 (s, 1H), 7.37 (d, J = 9.2 Hz, 1H), 7.26 (dd, J = 8.3, 4.7 Hz, 1H), 6.97 (d, J = 9.5 Hz, 1H), 6.81-6.67 (m, 1H), 5.59 (s, 2H), 4.77 (d, J = 5.8 Hz, 2H), 1.89 (d, J = 5.1 Hz, 1H), 0.96-0.84 (m, 2H), 0.64 (d, J = 5.1 Hz, 2H).

Example 31

Scheme 31



[0221] Synthesis of methyl 2-((dimethylamino)methylene)-4-methoxy-3-oxobutanoate. A mixture of methyl 4-methoxy-3-oxobutanoate (500 mg, 3.42 mmol) and DMF-DMA (410 mg, 3.42 mmol) in dry DMF (5 mL) was stirred at 110 °C for 10 h. The mixture was concentrated to give methyl 2-((dimethylamino)methylene)-4-methoxy-3-oxobutanoate (600 mg, yield: 87%) as a yellow oil. ESI-MS $[M+H]^+$: 202.1.

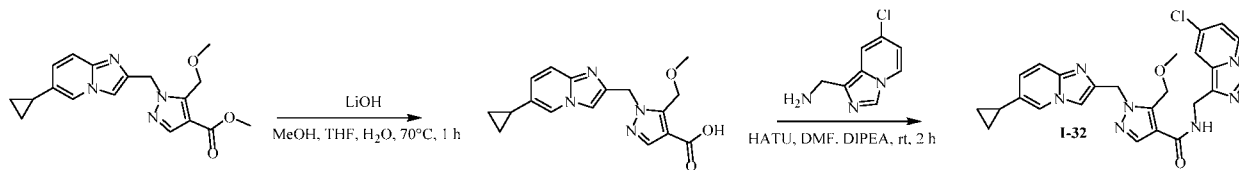
[0222] Synthesis of methyl 3-(methoxymethyl)-1H-pyrazole-4-carboxylate. A solution of methyl 2-((dimethylamino)methylene)-4-methoxy-3-oxobutanoate (600 mg, 3.0 mmol), $N_2H_4 \cdot H_2O$ (0.15 mL, 3.0 mmol) and AcOH (0.21 mL, 3.6 mmol) in dry EtOH (10 mL) was stirred at reflux for 12 h. The mixture was concentrated and purified by prep-TLC (DCM/MeOH = 30/1) to give methyl 3-(methoxymethyl)-1H-pyrazole-4-carboxylate (400 mg, yield: 78%) as a brown solid. ESI-MS $[M+H]^+$: 171.1.

[0223] Synthesis of methyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(methoxymethyl)-1H-pyrazole-4-carboxylate and methyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-5-(methoxymethyl)-1H-pyrazole-4-carboxylate. A mixture of methyl 3-(methoxymethyl)-1H-pyrazole-4-carboxylate (100 mg, 0.59 mmol), 2-(chloromethyl)-6-

cyclopropylimidazo[1,2-a]pyridine (150 mg, 0.70 mmol) and Cs_2CO_3 (480 mg, 1.48 mmol) in DMF (5 mL) was stirred at RT for 16 h. Water (50 mL) was added and the mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated and purified by prep-TLC (DCM/MeOH = 15/1) to give methyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(methoxymethyl)-1H-pyrazole-4-carboxylate (100 mg, yield: 50.0%) as a light yellow solid. ESI-MS $[\text{M}+\text{H}]^+$: 341.1 and methyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-5-(methoxymethyl)-1H-pyrazole-4-carboxylate (50 mg, yield: 25.0%) as a light yellow solid. ESI-MS $[\text{M}+\text{H}]^+$: 341.1.

[0224] Synthesis of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(methoxymethyl)-1H-pyrazole-4-carboxylic acid. A solution of methyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(methoxymethyl)-1H-pyrazole-4-carboxylate (100 mg, 0.29 mmol) and $\text{LiOH} \cdot \text{H}_2\text{O}$ (40 mg, 0.88 mmol) in THF/MeOH/ H_2O (2 mL/2 mL/1 mL) was stirred at 70 °C for 1 h. Solvent was evaporated and the pH value of the residue was adjusted to 5 by adding 1 M HCl solution. The resulting solid precipitate was filtered to give 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(methoxymethyl)-1H-pyrazole-4-carboxylic acid (90 mg, yield: 94.7%) as a yellow oil which was used in the next step without purification. ESI-MS $[\text{M}+\text{H}]^+$: 327.1.

[0225] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(methoxymethyl)-1H-pyrazole-4-carboxamide (I-31). A mixture of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(methoxymethyl)-1H-pyrazole-4-carboxylic acid (45 mg, 0.14 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine (36 mg, 0.17 mmol), HATU (105 mg, 0.28 mmol) and DIPEA (0.1 mL, 0.41 mmol) in DMF (3 mL) was stirred at RT for 2 h. Water (30 mL) was added and the mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were concentrated and purified by prep-TLC (DCM/MeOH = 10/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(methoxymethyl)-1H-pyrazole-4-carboxamide (19.6 mg, yield: 29%) as a white solid. ESI-MS $[\text{M}+\text{H}]^+$: 490.1. Purity: 97.6%. ^1H NMR (400 MHz, DMSO): δ 8.49 (s, 1H), 8.41-8.28 (m, 3H), 8.23 (s, 1H), 7.90 (s, 1H), 7.79 (s, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.29 (s, 1H), 6.66 (d, J = 6.3 Hz, 1H), 5.46 (s, 2H), 4.57 (d, J = 5.2 Hz, 2H), 4.53 (s, 2H), 3.20 (s, 3H), 1.99 (s, 1H), 0.97 (d, J = 7.5 Hz, 2H), 0.71 (d, J = 5.4 Hz, 2H).

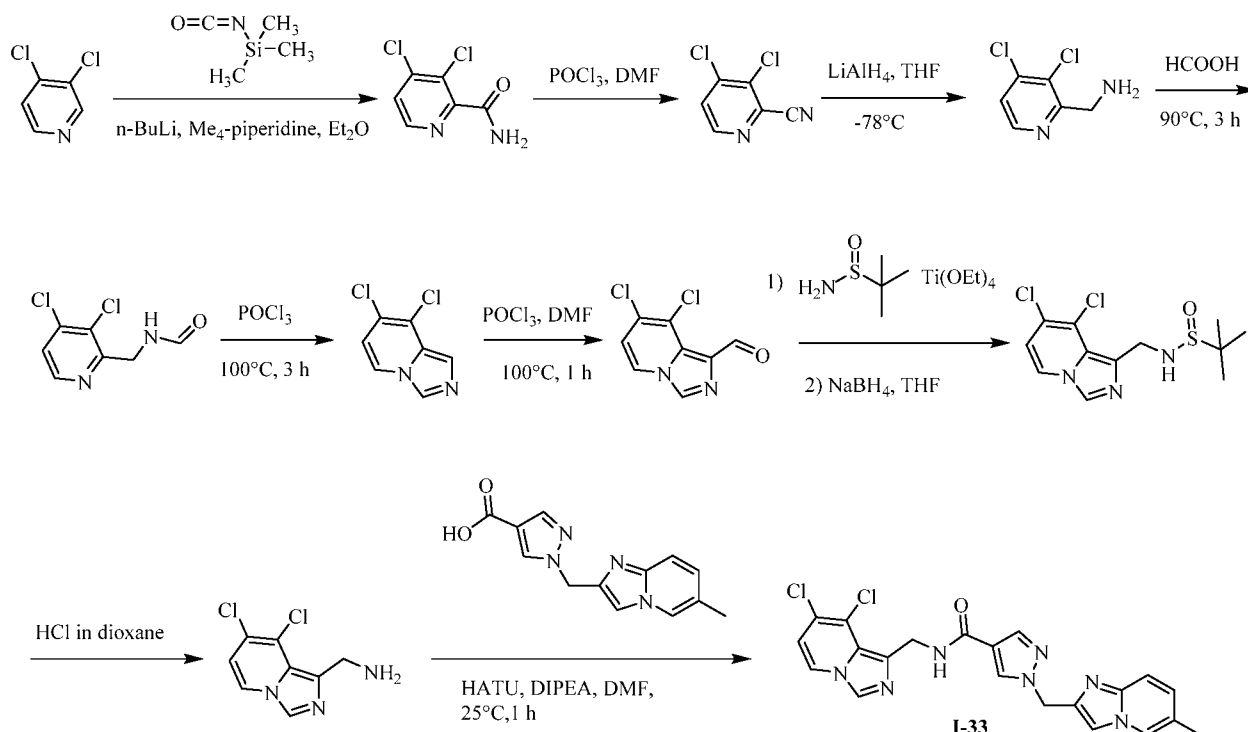
Example 32Scheme 32

[0226] Synthesis of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-5-(methoxymethyl)-1H-pyrazole-4-carboxylic acid. A solution of methyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-5-(methoxymethyl)-1H-pyrazole-4-carboxylate (50 mg, 0.15 mmol) and LiOH·H₂O (20 mg, 0.44 mmol) in THF/MeOH/H₂O (2 mL/2 mL/1 mL) was stirred at 70 °C for 1 h. Solvent was evaporated and the pH of the residue was adjusted to 5 by adding 1 M HCl solution. Solid precipitated and was filtered to give 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-5-(methoxymethyl)-1H-pyrazole-4-carboxylic acid (45 mg, yield: 94.7%) as a yellow oil. ESI-MS [M+H]⁺: 327.1.

[0227] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-5-(methoxymethyl)-1H-pyrazole-4-carboxamide (I-32). A mixture of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(methoxymethyl)-1H-pyrazole-4-carboxylic acid (45 mg, 0.14 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine (36 mg, 0.17 mmol), HATU (105 mg, 0.28 mmol) and DIPEA (0.1 mL, 0.41 mmol) in DMF (5 mL) was stirred at RT for 2 h. Water (30 mL) was added and the mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were concentrated and purified by prep-TLC (DCM/MeOH = 10/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-5-(methoxymethyl)-1H-pyrazole-4-carboxamide (40.0 mg, yield: 59%) as a white solid. ESI-MS [M+H]⁺: 490.1. Purity: 99.2%. ¹H NMR (400 MHz, DMSO): δ 8.67 (s, 1H), 8.58 (s, 1H), 8.44-8.27 (m, 2H), 8.02 (s, 1H), 7.94 (s, 1H), 7.81 (s, 1H), 7.67 (s, 1H), 7.52 (s, 1H), 6.67 (d, J = 7.2 Hz, 1H), 5.58 (s, 2H), 4.95 (s, 2H), 4.60 (d, J = 5.5 Hz, 2H), 3.25 (s, 3H), 2.05 (d, J = 16.1 Hz, 1H), 1.04 (t, J = 18.0 Hz, 2H), 0.74 (s, 2H).

Example 33

Scheme 33



[0228] Synthesis of 3,4-dichloropicolinamide. To a solution of 2,2,6,6-tetramethylpiperidine (5.2 g, 37.2 mmol) in diethyl ether (80 mL) at 0 °C was added n-BuLi (2.4 M, 15.5 mL, 37.2 mmol) dropwise. The resulting solution was stirred at 0 °C for 0.5 h and at -78 °C for 0.5 h. To this mixture was then slowly added a solution of 3,4-dichloropyridine (5 g, 33.8 mmol) in diethyl ether (10 mL) dropwise. The resulting mixture was stirred at -78 °C for 2 h before the addition of isocyanotrimethylsilane (5.83 g, 50.7 mmol). After the addition, the cooling bath was removed and the reaction mixture was allowed to warm to RT over 1 h. The reaction mixture was stirred at 25 °C for 16 h, H₂O (100 mL) was added, extracted with ethyl acetate (100 mL x 3), washed with brine (30 mL), dried over MgSO₄ and concentrated in vacuo. The residue was suspended in 20 mL of diethyl ether and sonicated. The solid was collected through filtration and washed with minimum amount of diethyl ether to give 3,4-dichloropicolinamide (2.3 g, yield: 35%) as a yellow solid. ESI-MS [M+H]⁺: 191.1.

[0229] Synthesis of 3,4-dichloropicolinonitrile. To a solution of 3,4-dichloropicolinamide (500 mg, 2.63 mmol) in DMF (20 mL) was added POCl₃ (2.4 g, 15.79

mmol) dropwise at 0 °C. The mixture was stirred at 25 °C for 16 h, then saturated NaHCO₃ (aq., 120 mL) was added and the reaction mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, concentrated to give 3,4-dichloropicolinonitrile (420 mg, yield: 93%) as a brown solid. ESI-MS [M+H]⁺: 173.0.

[0230] Synthesis of (3,4-dichloropyridin-2-yl)methanamine. To a mixture of LiAlH₄ (110 mg, 2.9 mmol) in dry THF (3 mL) was added 3,4-dichloropicolinonitrile (200 mg, 1.16 mmol) in THF at -78 °C. The mixture was stirred at -78 °C for 30 min, then stirred at -40 °C for 30 min. The mixture was quenched with H₂O (10 mL), extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated to give (3,4-dichloropyridin-2-yl)methanamine (100 mg, yield: 49%) as a yellow oil. ESI-MS [M+H]⁺: 177.0.

[0231] Synthesis of N-((3,4-dichloropyridin-2-yl)methyl)formamide. The mixture of (3,4-dichloropyridin-2-yl)methanamine (100 mg, 0.57 mmol) in HCOOH (2 mL) was stirred at 90 °C for 3 h and then concentrated to give the crude. The crude was purified by prep-TLC (DCM/MeOH = 10/1) to give N-((3,4-dichloropyridin-2-yl)methyl)formamide (70 mg, yield: 60%) as a yellow oil. ESI-MS [M+H]⁺: 205.1.

[0232] Synthesis of 7,8-dichloroimidazo[1,5-a]pyridine. The mixture of N-((3,4-dichloropyridin-2-yl)methyl)formamide (70 mg, 0.34 mmol) in POCl₃ (2 mL) was stirred at 100 °C for 3 h. Then POCl₃ was concentrated, H₂O (10 mL) was added, followed by saturated Na₂CO₃ (20 mL). The mixture was extracted with EtOAc (50 mL*3) and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated to give the crude, which was purified by prep-TLC (PE/EA = 1/2) to give 7,8-dichloroimidazo[1,5-a]pyridine (40 mg, yield: 63%) as a yellow solid. ESI-MS [M+H]⁺: 187.0.

[0233] Synthesis of 7,8-dichloroimidazo[1,5-a]pyridine-1-carbaldehyde. To a solution of 7,8-dichloroimidazo[1,5-a]pyridine (100 mg, 0.54 mmol) in dry DMF (0.2 mL) was added POCl₃ (123 mg, 0.81 mmol) at 0 °C. The mixture was stirred at 100 °C for 1 h then cooled and poured into ice H₂O. The mixture was basified with NH₄OH, extracted with DCM (50 mL x 3) and concentrated to give the crude, which was purified by prep-TLC (DCM/MeOH = 20/1) to give 7,8-dichloroimidazo[1,5-a]pyridine-1-carbaldehyde (25 mg, yield: 22%) as a yellow solid. ESI-MS [M+H]⁺: 215.0.

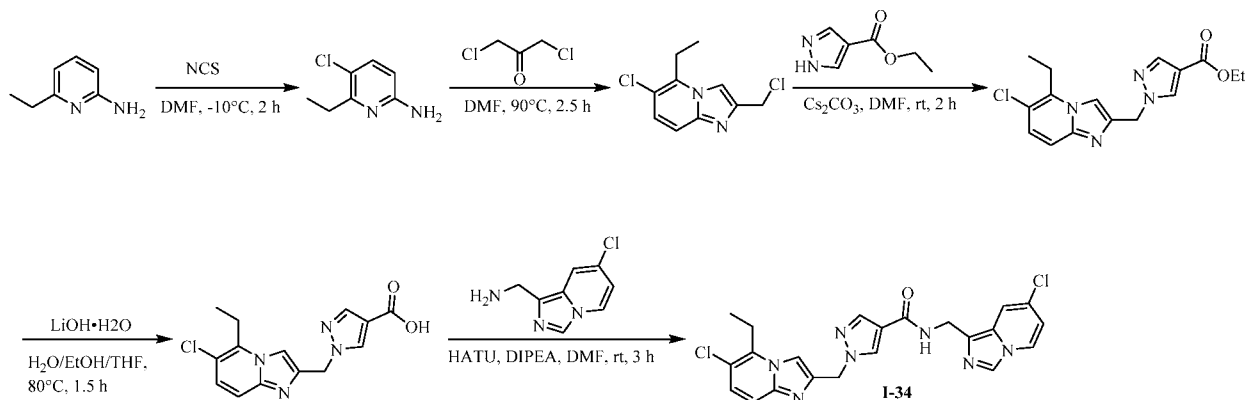
[0234] Synthesis of N-((7,8-dichloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-methylpropane-2-sulfinamide. To a mixture of 7,8-dichloroimidazo[1,5-a]pyridine-1-carbaldehyde (25 mg, 0.12 mmol) and 2-methylpropane-2-sulfinamide (17 mg, 0.14 mmol) in dry THF (2 mL) was added tetraethoxytitanium (80 mg, 0.35 mmol). The mixture was stirred at 75 °C for 16 h and then cooled to 25 °C. NaBH₄ (18 mg, 0.47 mmol) was added and stirred at 25 °C for 3 h. The reaction was quenched with H₂O (10 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated to give N-((7,8-dichloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-methylpropane-2-sulfinamide (37 mg, yield: 100%) as a yellow solid. ESI-MS [M+H]⁺: 320.0.

[0235] Synthesis of (7,8-dichloroimidazo[1,5-a]pyridin-1-yl)methanamine. The mixture of N-((7,8-dichloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-methylpropane-2-sulfinamide (37 mg, 0.12 mmol) and HCl in dioxane (1 mL, 4 M) was stirred at 25 °C for 3 h. The resulting mixture was concentrated to give (7,8-dichloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (25 mg, yield: 84%) as a yellow solid which was used in the next step without purification. ESI-MS [M-16]: 199.0.

[0236] Synthesis of N-((7,8-dichloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-33). To a mixture of (7,8-dichloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (25 mg, 0.1 mmol) and 1-((6-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (25 mg, 0.1 mmol) in dry DMF (2 mL) was added DIPEA (64 mg, 0.5 mmol) and HATU (76 mg, 0.2 mmol). The mixture was stirred at 25 °C for 1 h. Water (20 mL) was added and extracted with EtOAc (30 mL x 3). The combined organic phase was washed with brine, dried over Na₂SO₄, and concentrated to give the crude, which was purified by prep-TLC (DCM/MeOH = 10/1) to give N-((7,8-dichloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (13.3 mg, yield: 30%) as a yellow solid. ESI-MS [M+H]⁺: 454.1. Purity: 96.7%. ¹H NMR (400 MHz, DMSO): δ 8.44 (s, 1H), 8.35 (d, J = 7.4 Hz, 1H), 8.32-8.27 (m, 2H), 8.22 (s, 1H), 7.85 (s, 1H), 7.76 (s, 1H), 7.41 (d, J = 9.2 Hz, 1H), 7.11 (d, J = 9.2 Hz, 1H), 6.83 (d, J = 7.4 Hz, 1H), 5.39 (s, 2H), 4.80 (d, J = 4.9 Hz, 2H), 2.25 (s, 3H).

Example 34

Scheme 34



[0237] Synthesis of 5-chloro-6-ethylpyridin-2-amine. To a solution of 6-ethylpyridin-2-amine (1.0 g, 8.20 mmol) in dry DMF (16 mL) was added NCS (1.09 g, 8.2 mmol) at -10 °C and stirred at -10 °C for 2 h. The reaction mixture was diluted with H₂O (50 mL) and extracted with ethyl acetate (3 × 50 mL). The organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash column chromatography to give 5-chloro-6-ethylpyridin-2-amine (500 mg, yield: 39%). ESI-MS [M+H]⁺: 157.1.

[0238] Synthesis of 6-chloro-2-(chloromethyl)-5-ethylimidazo[1,2-a]pyridine. To a solution of 5-chloro-6-ethylpyridin-2-amine (500 mg, 3.2 mmol) in N,N-dimethylformamine (3 mL) was added 1,3-dichloropropan-2-one (1.62 g, 12.8 mmol). The resulting mixture was stirred at 90 °C for 2.5 h. The reaction mixture was diluted with H₂O (50 mL), adjust to approximately pH 9 by adding saturated NaHCO₃ solution, and then extracted with ethyl acetate (3 × 30 mL). The organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash column chromatography to give 6-chloro-2-(chloromethyl)-5-ethylimidazo[1,2-a]pyridine (390 mg, yield: 37%). ESI-MS [M+H]⁺: 229.1.

[0239] Synthesis of ethyl 1-((6-chloro-5-ethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. To a solution of 6-chloro-2-(chloromethyl)-5-ethylimidazo[1,2-a]pyridine (250 mg, 1.11 mmol) in N,N-dimethylformamine (3 mL) was added cesium carbonate (1.80 g, 3.33 mmol) and ethyl 1H-pyrazole-4-carboxylate (155 mg, 1.11 mmol). The resulting mixture was diluted with H₂O (30 mL) and extracted with ethyl acetate (3 × 30 mL). The organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The

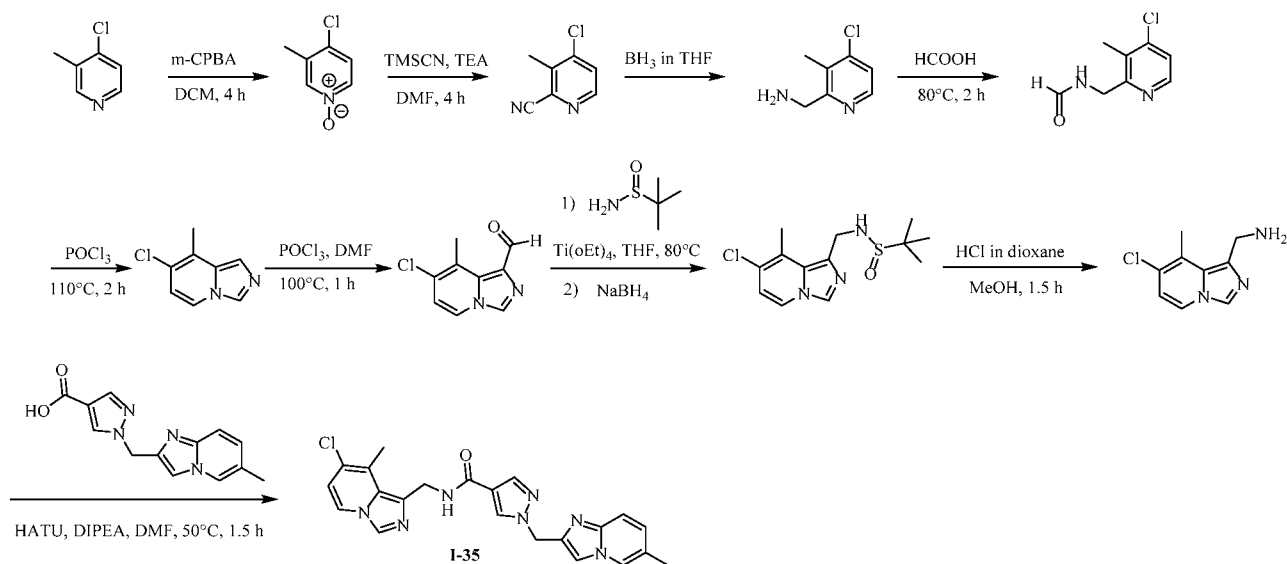
residue was purified by flash column chromatography to give ethyl 1-((6-chloro-5-ethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (360 mg, yield: 87%). ESI-MS $[M+H]^+$: 333.1.

[0240] Synthesis of 1-((6-chloro-5-ethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. To a solution of give ethyl 1-((6-chloro-5-ethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (436 mg, 1.3 mmol) in a mixed solvent of THF/EtOH/H₂O (3 mL/3 mL/1 mL) was added lithium hydroxide (126 mg, 5.3 mmol). The resulting mixture was stirred at 85 °C for 1.5 h and diluted with H₂O (15 mL). The pH of the mixture was then adjusted to 5 by adding 1 M HCl and then extracted with DCM/MeOH (5/1, 3 × 50 mL). The combined organic layers were concentrated to give 1-((6-chloro-5-ethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (200 mg, yield: 50%), which was used in the next step without further purification. ESI-MS $[M+H]^+$: 305.1.

[0241] Synthesis of 1-((6-chloro-5-ethylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-34). To the solution of 1-((6-chloro-5-ethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (65 mg, 0.21 mmol) in dry DMF (3 mL) was added HATU (120 mg, 0.32 mmol), DIPEA (135 mg, 1.05 mmol) and (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (46 mg, 0.21 mmol) at RT. The reaction was stirred at RT for 2 h. Water (30 mL) was added and the mixture was extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by prep-HPLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (41 mg, yield: 38%) as a white solid. ESI-MS $[M+H]^+$: 468.0. Purity: 100%. ¹H NMR (400 MHz, DMSO): δ 8.59 (t, J = 5.7 Hz, 1H), 8.34-8.26 (m, 2H), 8.24 (s, 1H), 8.10 (s, 1H), 7.86 (s, 1H), 7.78 (s, 1H), 7.46 (d, J = 9.5 Hz, 1H), 7.34 (d, J = 9.5 Hz, 1H), 6.69-6.60 (m, 1H), 5.43 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 3.20-3.10 (m, 2H), 1.20 (t, J = 7.5 Hz, 3H).

Example 35

Scheme 35



[0242] Synthesis of 4-chloro-3-methylpyridine 1-oxide. To a solution of 4-chloro-3-methylpyridine (5 g, 30.6 mmol) in dry DMF (100 mL) was added m-CPBA (10.8 g, 58.9 mmol). The reaction was stirred at RT for 3 h. The mixture was diluted with DCM (300 mL) and followed by saturated NaHCO_3 (300 mL). Then the mixture was extracted with DCM (300 mL x 3). The combined organic layers were concentrated and purified by silica gel chromatography (DCM/MeOH = 15/1) to give 4-chloro-3-methylpyridine 1-oxide (2.43 g, yield: 55.4%) as a white solid. ESI-MS $[\text{M}+\text{H}]^+$: 144.2.

[0243] Synthesis of 4-chloro-3-methylpicolinonitrile. To a solution of 4-chloro-3-methylpyridine 1-oxide (2.43 g, 17.0 mmol), dimethylcarbamic chloride (1.92 g, 17.9 mmol) and TMSCN (2.02 g, 20.4 mmol) in dry DMF (45 mL) was added Et_3N (4.7 mL, 34 mmol), the mixture was stirred at 100°C for 3 h. The reaction mixture was then quenched with saturated NaHCO_3 (200 mL) solution at 0°C and extracted with EtOAc (100 mL x 3). The combined organic layers were concentrated and purified by silica gel chromatography (EA/PE = 1/10) to give 4-chloro-3-methylpicolinonitrile (1.87 g, yield: 72%) as a yellow oil. ESI-MS $[\text{M}+\text{H}]^+$: 153.1.

[0244] Synthesis of (4-chloro-3-methylpyridin-2-yl)methanamine. To a solution of 4-chloro-3-methylpicolinonitrile (1.7 g, 11 mmol) in dry THF (6 mL) was added $\text{BH}_3\text{-THF}$ (1 M,

27.5 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and then stirred at RT overnight. The mixture was quenched with MeOH and stirred at RT for 1 h, then concentrated to give (4-chloro-3-methylpyridin-2-yl)methanamine (2.1 g, crude) as a yellow solid which was used in the next step without purification. ESI-MS $[M+H]^+$: 185.1.

[0245] Synthesis of N-((4-chloro-3-methylpyridin-2-yl)methyl)formamide. To a solution of 4-chloro-3-methylpicolinonitrile (2.1 g, 13.5 mmol) and formic acid (20 mL) was stirred at 80 °C for 3 h. The mixture was concentrated and purified by silica gel chromatography to give N-((4-chloro-3-methylpyridin-2-yl)methyl)formamide (1.3 g, yield: 54%) as a brown oil. ESI-MS $[M+H]^+$: 185.1.

[0246] Synthesis of 7-chloro-8-methylimidazo[1,5-a]pyridine. To a solution of N-((4-chloro-3-methylpyridin-2-yl)methyl)formamide (1.3 g, 7 mmol) and POCl₃ (22 mL) was stirred at 110 °C for 2 h. POCl₃ was removed in vacuo. Water was added and followed by saturated Na₂CO₃ (aq.). The mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give the crude, which was purified by silica gel chromatography (EA/PE = 1/1) to give 7-chloro-8-methylimidazo[1,5-a]pyridine (700 mg, yield: 60%) as a brown solid. ESI-MS $[M+H]^+$: 167.1.

[0247] Synthesis of 7-chloro-8-methylimidazo[1,5-a]pyridine-1-carbaldehyde. A mixture of 7-chloro-8-methylimidazo[1,5-a]pyridine (660 mg, 3.96 mmol), DMF (289.4 mg, 3.96 mmol) in POCl₃ (5 mL) was stirred at 100 °C for 1 h. Then the reaction mixture was poured to ice H₂O. NH₄OH solution was added to adjust pH to about 8 and then the mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated and purified by silica gel chromatography to give 7-chloro-8-methylimidazo[1,5-a]pyridine-1-carbaldehyde (165 mg, yield: 21%) as a white solid. ESI-MS $[M+H]^+$: 195.1.

[0248] Synthesis of N-((7-chloro-8-methylimidazo[1,5-a]pyridin-1-yl)methyl)-2-methylpropane-2-sulfinamide. A mixture of 7-chloro-8-methylimidazo[1,5-a]pyridine-1-carbaldehyde (154 mg, 0.8 mmol), 2-methylpropane-2-sulfinamide (116.35 mg, 0.96 mmol) and Ti(OEt)₄ (0.58 mL, 2.8 mmol) in THF (10 mL) was stirred at 80 °C overnight. After cooled to RT, NaBH₄ (151.32 mg, 4 mmol) was added. The reaction mixture was stirred at RT for 3 h. The reaction was quenched with H₂O (20 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated and purified by silica gel chromatography (DCM/CH₃OH =

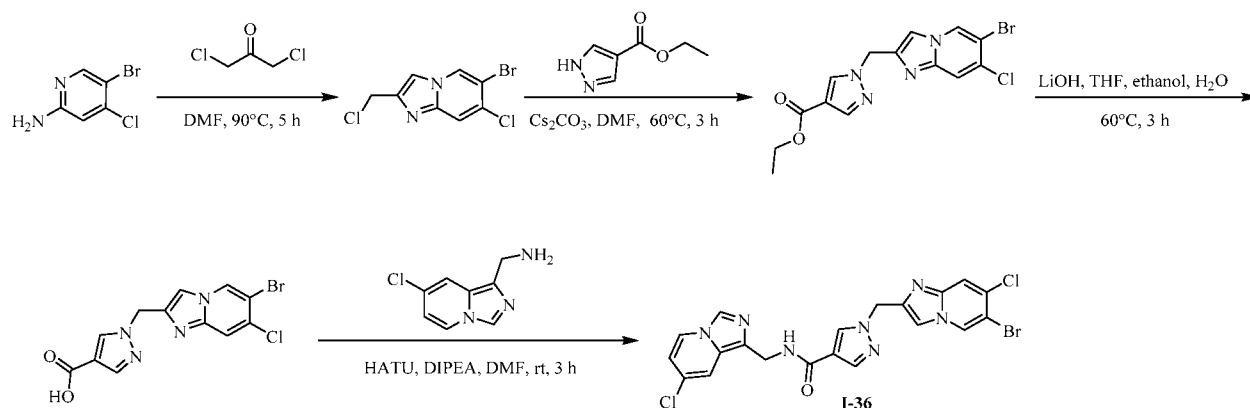
10:1) to give N-((7-chloro-8-methylimidazo[1,5-a]pyridin-1-yl)methyl)-2-methylpropane-2-sulfonamide (87 mg, yield: 36%) as a yellow solid. ESI-MS $[M+H]^+$: 300, and (131 mg, yield: 36%) as a yellow solid. ESI-MS $[M+13]^+$: 312.

[0249] Synthesis of (7-chloro-8-methylimidazo[1,5-a]pyridin-1-yl)methanamine. To a solution of N-((7-chloro-8-methylimidazo[1,5-a]pyridin-1-yl)methyl)-2-methylpropane-2-sulfonamide (187 mg, 0.62 mmol) in CH₃OH (8 mL) was added HCl (4 M in dioxane, 8 mL). The mixture was stirred at RT for 1.5 h. Then concentrated to give (7-chloro-8-methylimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (168 mg, crude) as a white solid which was used in the next step without purification. ESI-MS $[M-16]^+$: 179.1.

[0250] Synthesis of N-((7-chloro-8-methylimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-35). A mixture (7-chloro-8-methylimidazo[1,5-a]pyridin-1-yl)methanamine (44 mg, 0.22 mmol), 1-((6-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (57 mg, 0.22 mmol), HATU (167.2 mg, 0.44 mmol) and DIPEA (113.5 mg, 0.88 mmol) in DMF (5 mL) was stirred at RT for 1.5 h. Water (30 mL) was added, extracted with EtOAc (30 mL x 3), the combined organic phase were washed with brine, dried over Na₂SO₄ and concentrated to give the crude, which was purified by silica gel chromatography (DCM/MeOH = 10:1) to give N-((7-chloro-8-methylimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (27 mg, yield: 28%) as a white solid. ESI-MS $[M+H]^+$: 434.1. Purity: 99.42%. ¹H NMR (400 MHz, DMSO): δ 8.33 (t, J = 4.7 Hz, 1H), 8.26 (s, 2H), 8.17 (s, 1H), 8.13 (d, J = 7.3 Hz, 1H), 7.81 (s, 1H), 7.72 (s, 1H), 7.36 (d, J = 9.2 Hz, 1H), 7.08 (d, J = 9.2 Hz, 1H), 6.59 (d, J = 7.4 Hz, 1H), 5.33 (s, 2H), 4.62 (d, J = 4.9 Hz, 2H), 2.51 (s, 3H), 2.19 (s, 3H).

Example 36

Scheme 36



[0251] Synthesis of 6-bromo-7-chloro-2-(chloromethyl)imidazo[1,2-a]pyridine. A mixture of 5-bromo-4-chloropyridin-2-amine (1.67 g, 9.9 mmol), 1,3-dichloropropan-2-one (2.5 g, 19.8 mmol) in DMF (15 mL) was stirred at 90 °C for 5 h. The reaction mixture was diluted with H₂O (50 mL), adjusted to approximately pH 9 by adding saturated a NaHCO₃ solution, and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were concentrated and purified by silica gel chromatography (EA/PE = 7:1) to give 6-bromo-7-chloro-2-(chloromethyl)imidazo[1,2-a]pyridine (900 mg, yield: 32%) as a yellow solid. ESI-MS [M+H]⁺: 278.9.

[0252] Synthesis of ethyl 1-((6-bromo-7-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A mixture of 6-bromo-7-chloro-2-(chloromethyl)imidazo[1,2-a]pyridine (560 mg, 2.0 mmol), ethyl 1H-pyrazole-4-carboxylate (560 mg, 4.0 mmol) and Cs₂CO₃ (1.95 g, 6.0 mmol) in DMF (10 mL) was stirred at 60 °C for 3 h. The resulting mixture was diluted with H₂O (30 mL) and extracted with ethyl acetate (3 × 30 mL), The combined organic layers were concentrated and purified by silica gel chromatography (EA/PE = 10:1 to 7:13) to give ethyl 1-((6-bromo-7-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (400 mg, yield: 52%) as a white solid. ESI-MS [M+H]⁺: 383.0.

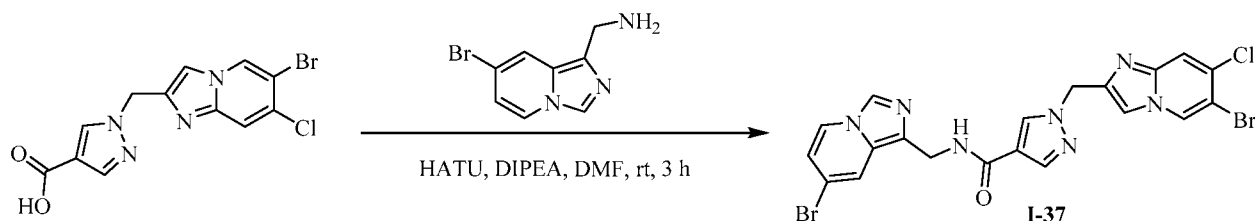
[0253] Synthesis of 1-((6-bromo-7-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. To a solution of ethyl 1-((6-bromo-7-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (216 mg, 0.56 mmol) in ethanol (3 mL), THF (3 mL)

and H₂O (1.5 mL) was added LiOH·H₂O (95 mg, 2.25 mmol). The mixture was stirred at 65 °C for 3 h. Most of the solvent was concentrated and the residue was adjusted to pH to 4 by adding 1 M HCl solution. The resulting precipitate was filtered to give 1-((6-bromo-7-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (190 mg, yield: 95%) as a white solid. ESI-MS [M+H]⁺: 355.0.

[0254] Synthesis of 1-((6-bromo-7-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-36). A mixture of 1-((6-bromo-7-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (95 mg, 0.27 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine (55 mg, 0.25 mmol), HATU (190 mg, 0.5 mmol) and DIPEA (97 mg, 0.75 mmol) in DMF (4 mL) was stirred at RT for 3 h. Water (30 mL) was added and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were concentrated and purified by prep-TLC (DCM:MeOH = 8:1) to give 1-((6-bromo-7-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (49.2 mg, yield: 38%) as a white solid. ESI-MS [M+H]⁺: 517.9. Purity: 96.34%. ¹H NMR (400 MHz, DMSO): δ 9.06 (s, 1H), 8.58 (s, 1H), 8.30-8.22 (m, 3H), 7.92-7.77 (m, 4H), 6.64 (s, 1H), 5.42 (s, 2H), 4.54 (s, 2H).

Example 37

Scheme 37

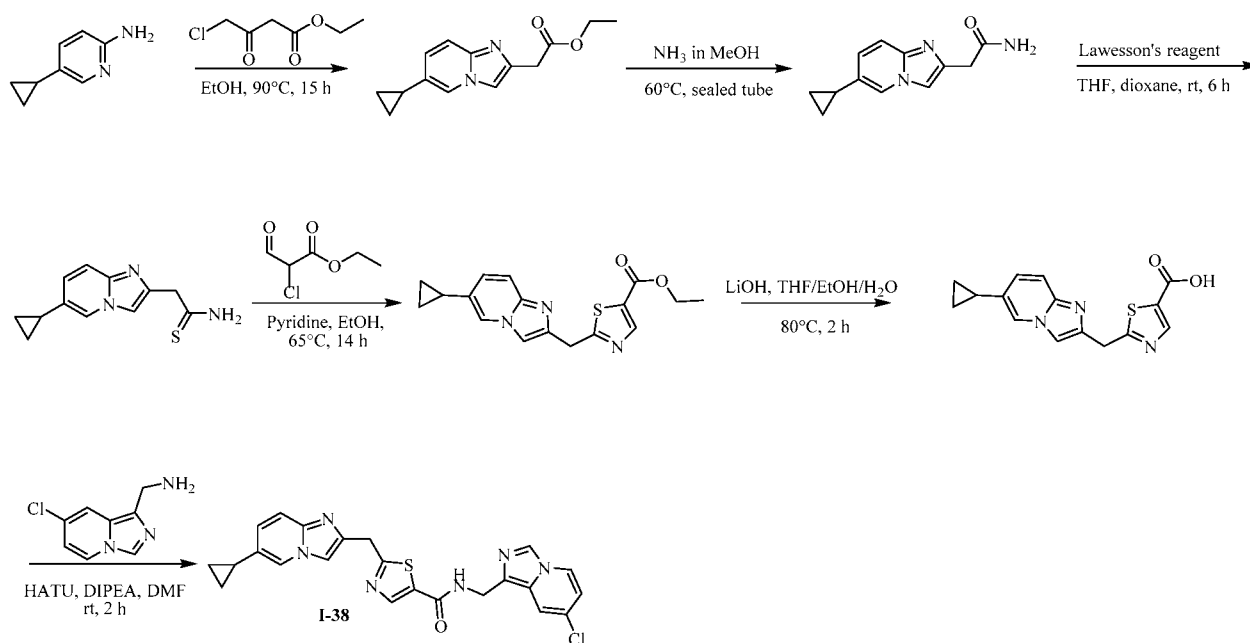


[0255] Synthesis of 1-((6-bromo-7-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-37). A mixture of 1-((6-bromo-7-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (95 mg, 0.27 mmol), (7-bromoimidazo[1,5-a]pyridin-1-yl)methanamine (56 mg, 0.25 mmol), HATU (190 mg, 0.5 mmol) and DIPEA (97 mg, 0.75 mmol) in DMF (4 mL) was stirred at RT for 3 h. Water (30 mL) was added and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined

organic layers were concentrated and purified by prep-TLC (DCM:MeOH = 8:1) to give 1-((6-bromo-7-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (43.3 mg, yield: 31%) as a white solid. ESI-MS $[M+H]^+$: 561.9. Purity: 90%. ^1H NMR (400 MHz, DMSO): δ 9.06 (s, 1H), 8.58 (t, $J = 4.9$ Hz, 1H), 8.31 (s, 1H), 8.23-8.22 (m, 2H), 7.94-7.93 (m, 2H), 7.86 (s, 1H), 7.80 (s, 1H), 6.71 (d, $J = 7.3$ Hz, 1H), 5.43 (s, 2H), 4.54 (d, $J = 5.3$ Hz, 2H).

Example 38

Scheme 38



[0256] Synthesis of ethyl 2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetate. A mixture of 5-cyclopropylpyridin-2-amine (3 g, 22.4 mmol) and ethyl 4-chloro-3-oxobutanoate (11 g, 67.2 mmol) in EtOH (150 mL) was stirred at 90 °C for 15 h. The pH of the reaction was adjusted to 8-9 with $NaHCO_3$ (4 M, 50 mL) and extracted with EtOAc (70 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give the crude, which was purified by silica gel chromatography (EA/PE = 1/1) to give ethyl 2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetate (3.6 g, yield: 72%) as a black solid. ESI-MS $[M+H]^+$: 225.2.

[0257] Synthesis of 2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetamide. A solution of ethyl 2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetate (3.6 g, 16 mmol) in NH_3 (7 M solution in MeOH, 50 mL) in sealed tube was stirred at 60 °C for 12 h. The reaction was concentrated to give the 2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetamide, which was used in the next step without further purification (3.4 g, yield: 99%) as a yellow oil. ESI-MS $[\text{M}+\text{H}]^+$: 216.2.

[0258] Synthesis of 2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)ethanethioamide. To a solution of 2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetamide (3.4 g, 15.8 mmol) in dioxane (50 mL) was added Lawesson's reagent (6.3 g, 15.8 mmol) at 0 °C. The resulting mixture was stirred at RT for 6 h. The reaction was quenched with H_2O (70 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated to give the 2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)ethanethioamide which was used in the next step without further purification. (3 g, yield: 82%) as a yellow oil. ESI-MS $[\text{M}+\text{H}]^+$: 232.2.

[0259] Synthesis of ethyl 2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)thiazole-5-carboxylate. A mixture of 2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)ethanethioamide (700 mg, 3.1 mmol), pyridine (480 mg, 6.2 mmol) and ethyl 2-chloro-3-oxopropanoate (678 mg, 4.65 mmol) in EtOH (25 mL) was stirred at 65 °C for 14 h. The reaction was concentrated to give the crude, which was purified with silica gel chromatography (EA/PE = 1/1) to give the ethyl 2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)thiazole-5-carboxylate (105 mg, yield: 10.7%) as a yellow solid. ESI-MS $[\text{M}+\text{H}]^+$: 327.1.

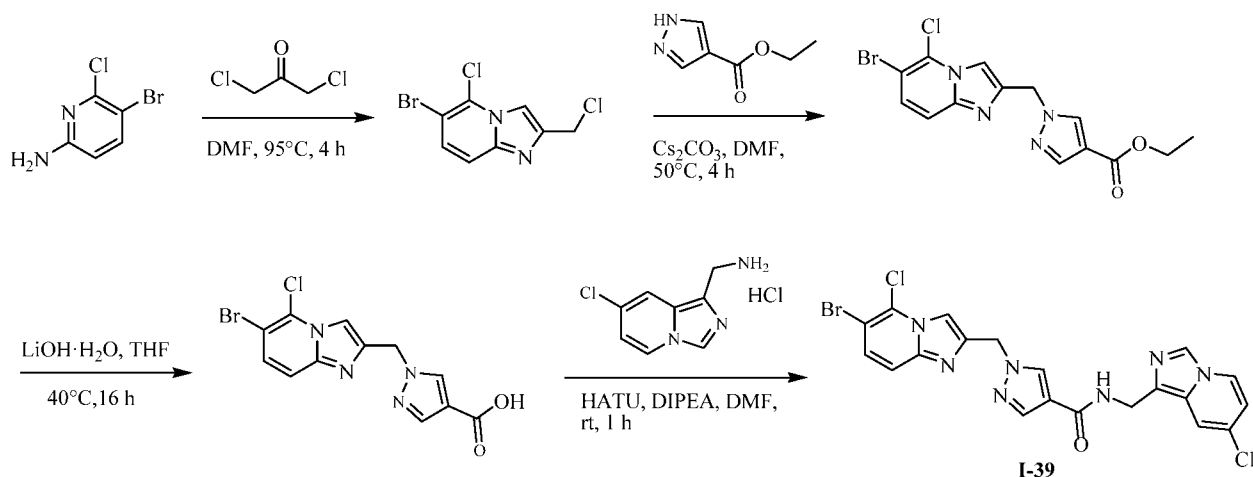
[0260] Synthesis of 2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)thiazole-5-carboxylic acid. A mixture of ethyl 2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)thiazole-5-carboxylate (105 mg, 0.32 mmol) and LiOH (23 mg, 0.96 mmol) in THF/EtOH/ H_2O (2 mL/2 mL/1 mL) was stirred at 80 °C for 2 h. The pH value of the reaction was adjusted to 4 by adding 1 M HCl solution, and then concentrated to give the crude, which was used in the next step without further purification (105 mg, crude yield: 100%). ESI-MS $[\text{M}+\text{H}]^+$: 300.2.

[0261] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)thiazole-5-carboxamide (I-38). To a solution

of 2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)thiazole-5-carboxylic acid (105 mg, crude from last step) in DMF (5 mL) was added HATU (160 mg, 0.42 mmol) and DIPEA (226 mg, 1.75 mmol). The mixture reaction was stirred for 30 min, then (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (99 mg, 0.45 mmol) was added. The resulting mixture was stirred at RT for 12 h. Water (25 mL) was added and the mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give the N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)thiazole-5-carboxamide as a white solid (15 mg, yield: 9.3%). ESI-MS [M+H]⁺: 463.1. Purity: 98.5%. ¹H NMR (400 MHz, MeOD): δ 8.30-8.27 (m, 2H), 8.19-8.16 (m, 2H), 7.81 (s, 1H), 7.73 (s, 1H), 7.49 (d, J = 9.4 Hz, 1H), 7.30 (dd, J = 9.4, 1.5 Hz, 1H), 6.63 (dd, J = 7.5, 2.0 Hz, 1H), 4.70 (s, 2H), 4.53 (s, 2H), 1.99-1.97 (m, 1H), 1.11-1.00 (m, 2H), 0.77-0.74 (m, 2H).

Example 39

Scheme 39



[0262] Synthesis of 6-bromo-5-chloro-2-(chloromethyl)imidazo[1,2-a]pyridine. The mixture of 5-bromo-6-chloropyridin-2-amine (1.38 g, 6.65 mmol) and 1,3-dichloropropan-2-one (3.35 g, 26.61 mmol) in DMF (20 mL) was stirred at 95 °C for 4 h. The reaction mixture was quenched with H₂O (150 mL) followed by adding saturated NaHCO₃ (20 mL) solution, the mixture was then extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine (150 mL x 2), dried over Na₂SO₄, concentrated and purified by trituration with EtOAc

to give 6-bromo-5-chloro-2-(chloromethyl)imidazo[1,2-a]pyridine (480 mg, 26%) as a light brown solid. ESI-MS $[M+H]^+$: 279.0.

[0263] Synthesis of ethyl 1-((6-bromo-5-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. The mixture of 6-bromo-5-chloro-2-(chloromethyl)imidazo[1,2-a]pyridine (380 mg, 1.36 mmol), ethyl 1H-pyrazole-4-carboxylate (190 mg, 1.36 mmol) and CsCO_3 (663 mg, 2.04 mmol) in DMF (10 mL) was stirred for at 50 °C for 4 h. The reaction mixture was diluted with H_2O (80 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , concentrated and purified by silica gel chromatography (EA/PE = 1/4) to give ethyl 1-((6-bromo-5-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (400 mg, yield: 77%) as a yellow solid. ESI-MS $[M+H]^+$: 383.0.

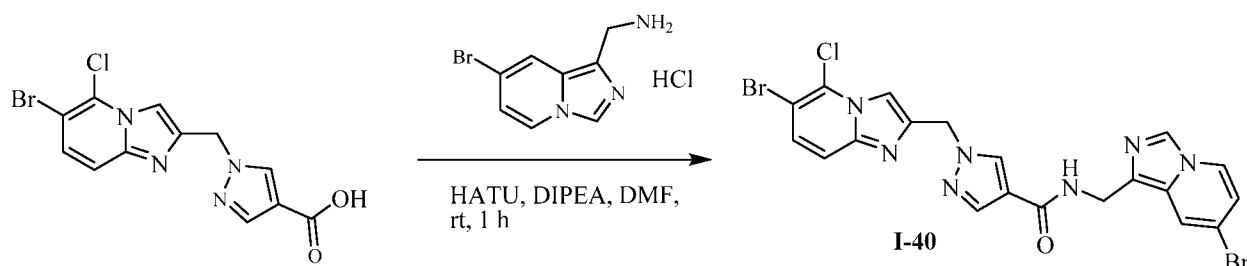
[0264] Synthesis of 1-((6-bromo-5-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. A mixture of ethyl 1-((6-bromo-5-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (350 mg, 0.912 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (307 mg, 7.30 mmol) in THF (10 mL) and H_2O (2 mL) was stirred at 40 °C for 16 h. Most of the solvent was removed and the residue was diluted with H_2O (10 mL). The pH value of mixture was adjusted to 4-5 by adding HCl (1 M). The precipitate was collected and dried to give 1-((6-bromo-5-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (285 mg, yield: 88%) as a white solid. ESI-MS $[M+H]^+$: 354.9.

[0265] Synthesis of 1-((6-bromo-5-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-39). The mixture of 1-((6-bromo-5-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (80 mg, 0.22 mmol), HATU (92 mg, 0.242 mmol) and DIPEA (85 mg, 0.66 mmol) in DMF (3 mL) was stirred at RT for 10 min. (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (48 mg, 0.22 mmol) was added and stirred at RT for 1 h. The reaction mixture was quenched with H_2O (50 mL) and extracted with EtOAc/THF (40 mL x 3, 5/1 (v/v)). The combined organic layers was washed with brine (100 mL x 3), dried over Na_2SO_4 , concentrated and purified by prep-TLC (DCM/MeOH = 7/1) to give 1-((6-bromo-5-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (50 mg, yield: 43%) as a yellow solid. ESI-MS $[M+H]^+$: 518.0. Purity: 99.23%. ^1H NMR (400 MHz,

DMSO): δ 8.59 (t, J = 5.7 Hz, 1H), 8.33-8.28 (m, 2H), 8.25 (s, 1H), 8.02 (s, 1H), 7.87 (s, 1H), 7.78-7.77 (m, 1H), 7.62-7.55 (m, 2H), 6.66-6.63 (m, 1H), 5.47 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H).

Example 40

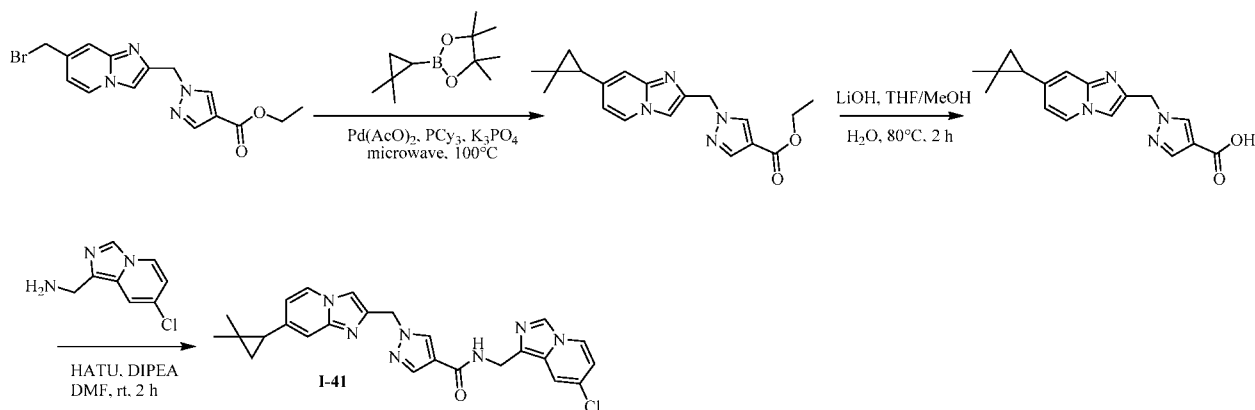
Scheme 40



[0266] Synthesis of 1-((6-bromo-5-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-40). The mixture of 1-((6-bromo-5-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (70 mg, 0.20 mmol), HATU (82 mg, 0.217 mmol) and DIPEA (76 mg, 0.591 mmol) in DMF (3 mL) was stirred at RT for 10 min. (7-bromoimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (52 mg, 0.20 mmol) was added and stirred at RT for 1 h. The reaction mixture was diluted with H₂O (50 mL) and extracted with EtOAc/THF (40 mL x 3, 5/1 (v/v)). The combined organic layers were washed with brine (100 mL x 3), dried over Na₂SO₄, concentrated and purified by prep-TLC (DCM/MeOH = 7/1) to give 1-((6-bromo-5-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (40 mg, yield: 36%) as a yellow solid. ESI-MS $[M+H]^+$: 561.9. Purity: 92.54%. ¹H NMR (400 MHz, DMSO): δ 8.58 (t, J = 5.5 Hz, 1H), 8.32 (s, 1H), 8.26-8.22 (m, 2H), 8.02 (s, 1H), 7.95 (s, 1H), 7.87 (s, 1H), 7.61-7.55 (m, 2H), 6.72 (d, J = 8.9 Hz, 1H), 5.47 (s, 2H), 4.55 (d, J = 5.6 Hz, 2H).

Example 41

Scheme 41



[0267] **Synthesis of ethyl 1-((7-(2,2-dimethylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate.** A mixture of ethyl 1-((7-bromoimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (120 mg, 0.34 mmol), 2-(2,2-dimethylcyclopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.33 g, 1.7 mmol), Pd(OAc)₂ (8 mg, 0.034), PCy₃ (10 mg, 0.034 mmol), and K₃PO₄ (220 mg, 1.3 mmol) in 1,4-dioxane (3 mL) and H₂O (1 mL) was stirred at 100 °C under microwave for 7 h. The reaction was filtered through celite and washed with DCM/MeOH (10/1, 30 mL). The filtrate was concentrated and purified by silica gel (DCM/MeOH = 10/1) to give the 1-((7-(2,2-dimethylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (60 mg, 70%) as a yellow solid. ESI-MS [M+H]⁺: 339.1.

[0268] **Synthesis of ethyl 1-((7-(2,2-dimethylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate.** A mixture of 1-((7-(2,2-dimethylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (61 mg, 0.18 mmol) and LiOH (27.6 mg, 1.2 mmol) in THF/EtOH/H₂O (3 mL/3 mL/2 mL) was stirred at 80 °C for 2 h. The pH value of the reaction was adjusted to around 5 and a yellow solid precipitated out. The solid was filtered and the filter cake was dried to give 1-((7-(2,2-dimethylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (50 mg, yield: 89%) as a yellow solid. ESI-MS [M+H]⁺: 311.1.

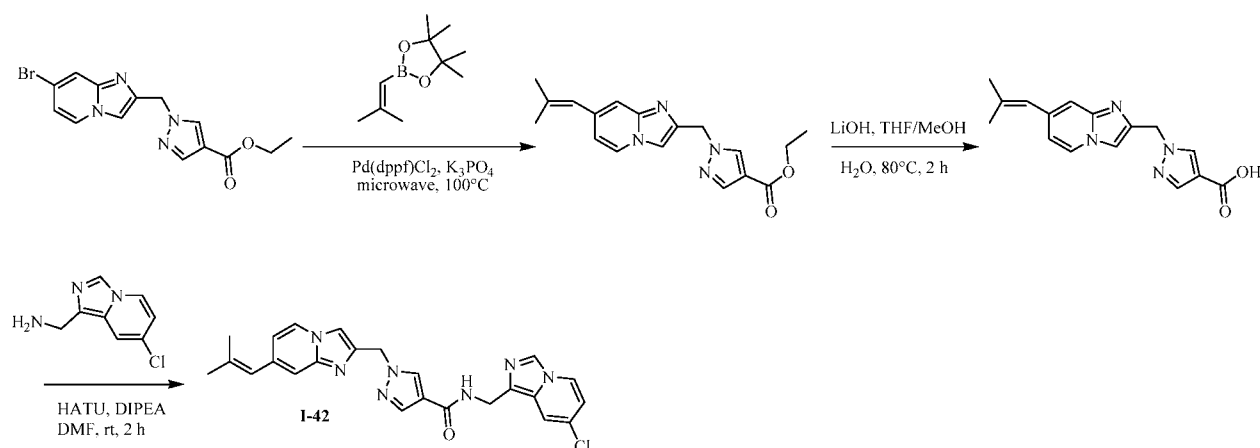
[0269] **Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((7-(2,2-dimethylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-41).** To a solution of 1-((7-(2,2-dimethylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-

pyrazole-4-carboxylate (55 mg, 0.18 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine (38 mg, 0.21 mmol) and HATU (101 mg, 0.27 mmol) in DMF (15 mL) was added DIPEA (187 mg, 1.55 mmol). The resulting reaction stirred at RT for 2 h. H₂O (30 mL) was added to the reaction and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give the N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((7-(2,2-dimethylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (12.3 mg, yield: 10%) as a white solid. ESI-MS [M+H]⁺: 474.1. Purity: 94.0%. ¹H NMR (400 MHz, MeOD): δ 8.27 (d, J = 2.7 Hz, 2H), 8.20-8.15 (m, 2H), 7.93 (s, 1H), 7.85 (s, 1H), 7.74 (m, 1H), 7.52-7.47 (m, 2H), 6.68-6.60 (m, 1H), 5.52 (s, 2H), 4.69 (s, 2H), 1.95-1.88 (m, 1H), 1.26 (s, 3H), 0.89 (s, 1H), 0.88 (d, J = 2.5 Hz, 1H), 0.83 (s, 3H).

[0270] Synthesis of 2-(2,2-dimethylcyclopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. To a solution of 4,4,5,5-tetramethyl-2-(2-methylprop-1-en-1-yl)-1,3,2-dioxaborolane (100 mg, 0.55 mmol) in toluene (5 mL) was added CH₂I₂ (0.42 g, 1.54 mmol) dropwise at 0 °C. The resulting reaction was stirred at 55 °C overnight. The reaction was filtered and washed with DCM (10 mL). The crude product was extracted with H₂O (10 mL), dried over Na₂SO₄, concentrated to give the 2-(2,2-dimethylcyclopropyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (200 mg crude) which was used in the next step without further purification. ESI-MS [M+H]⁺: 197.1.

Example 42

Scheme 42



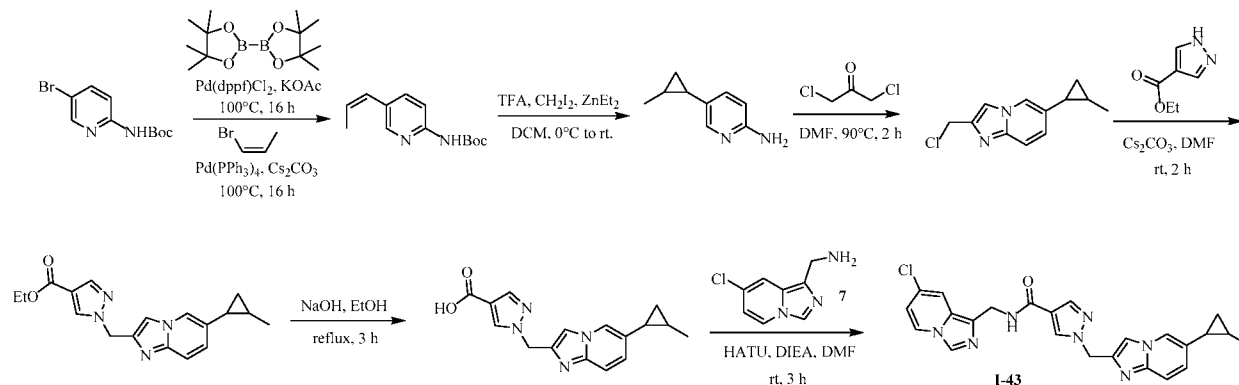
[0271] Synthesis of ethyl 1-((7-(2-methylprop-1-en-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A solution of ethyl 1-((7-bromoimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (200 mg, 0.57 mmol), 4,4,5,5-tetramethyl-2-(2-methylprop-1-en-1-yl)-1,3,2-dioxaborolane (207 mg, 1.14 mmol), Pd(dppf)Cl₂ (42, 0.057 mg), and K₃PO₄ (364 mg, 1.72 mmol) in 1,4-dioxane (10 mL) and H₂O (1 mL) in a sealed tube was stirred at 100 °C under microwave for 3 h. The reaction was filtered through celite and washed with EtOAc. The filtrate was concentrated and purified by silica gel (PE/EA = 1:2) to give the 1-((7-(2-methylprop-1-en-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (200 mg, 90%) as a brown solid. ESI-MS [M+H]⁺: 325.1.

[0272] Synthesis of 1-((7-(2-methylprop-1-en-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. A mixture of 1-((7-(2-methylprop-1-en-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (60 mg, 0.18 mmol) and LiOH (27 mg, 1.2 mmol) in THF/EtOH/H₂O (3 mL/3 mL/2 mL) was stirred at 80 °C for 2 h. The pH value of reaction was adjusted to around 5 by adding 1 M HCl solution and a solid was precipitated. The solid was filtered and the filter cake was dried to give 1-((7-(2-methylprop-1-en-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (50 mg, yield: 89%) as a brown solid. ESI-MS [M+H]⁺: 297.1.

[0273] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((7-(2-methylprop-1-en-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-42). To a solution of 1-((7-(2-methylprop-1-en-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (53 mg, 0.18 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine (38 mg, 0.21 mmol) and HATU (101 mg, 0.27 mmol) in DMF (15 mL) was added DIPEA (200 mg, 1.55 mmol). The resulting reaction stirred at RT for 2 h. H₂O (30 mL) was added and the reaction mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude, which was purified by prep-TLC (DCM/MeOH = 10/1) to give the N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((7-(2-methylprop-1-en-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (30 mg, yield: 36%) as a white solid. ESI-MS [M+H]⁺: 460.1. Purity: 95.2%. ¹H NMR (400 MHz, MeOD): δ 8.35 (s, 1H), 8.28 (s, 1H), 8.18-8.46 (m, 2H), 7.94 (s, 1H), 7.90 (s, 1H), 7.74 (s, 1H), 7.54 (d, J = 9.3 Hz, 1H), 7.49-7.38 (m, 1H), 6.63 (dd, J = 7.5, 1.9 Hz, 1H), 6.22 (s, 1H), 5.54 (s, 2H), 4.69 (s, 2H), 1.95 (s, 3H), 1.88 (s, 3H).

Example 43

Scheme 43



[0274] Synthesis of tert-butyl (Z)-(5-(prop-1-en-1-yl)pyridin-2-yl)carbamate. To a mixture of tert-butyl (5-bromopyridin-2-yl)carbamate (2.73 g, 10 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (3.81 g, 15 mmol) and KOAc (3.0 g, 30 mmol) in dioxane (30 mL) was added Pd(dppf)Cl₂ (881 mg, 1 mmol). The mixture was stirred at 100 °C for 16 h. After cooling, (Z)-1-bromoprop-1-ene (3.6 g, 30 mmol), Cs₂CO₃ (6.4 g, 20 mmol) and Pd(PPh₃)₄ (500 mg, 0.5 mmol) were added. The mixture was stirred 100 °C for another 16 h. Water (100 mL) was added and the mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were concentrated and purified by silica gel chromatography (EA/PE = 1/2) to give tert-butyl (Z)-(5-(prop-1-en-1-yl)pyridin-2-yl)carbamate (230 mg, yield: 10%) as a white solid. ESI-MS [M+H]⁺: 235.1.

[0275] Synthesis of 5-(2-methylcyclopropyl)pyridin-2-amine. To a solution of ZnEt₂ (1 M, 10mL) in DCM (20 mL) was added TFA (1.14 g, 10 mmol), followed by CH₂I₂ (2.68 g, 10 mmol). After the resulting mixture was stirred at 0 °C for 10 min, tert-butyl (Z)-(5-(prop-1-en-1-yl)pyridin-2-yl)carbamate (230 mg, 1.0 mmol) was added. The mixture was stirred at RT for 3 h. Water (50 mL) was added and extracted with EtOAc (100 mL x 3). The combined organic layers were concentrated and purified by prep-HPLC to give 5-(2-methylcyclopropyl)pyridin-2-amine (60 mg, yield: 12%) as a yellow oil. ESI-MS [M+H]⁺: 149.1.

[0276] Synthesis of 2-(chloromethyl)-6-(2-methylcyclopropyl)imidazo[1,2-a]pyridine. To a solution of 5-(2-methylcyclopropyl)pyridin-2-amine (600 mg, 0.4 mmol) in DMF (5 mL) was added 1,3-dichloropropan-2-one (206 mg, 1.6 mmol). The mixture was stirred at 90 °C for 2 h. Water (50 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give the crude, which was purified by silica gel chromatography (EA/PE = 1/1) to give 2-(chloromethyl)-6-(2-methylcyclopropyl)imidazo[1,2-a]pyridine (40 mg, yield: 79%) as a yellow oil. ESI-MS [M+H]⁺: 221.1.

[0277] Synthesis of ethyl 1-((6-(2-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. To a solution of 2-(chloromethyl)-6-(2-methylcyclopropyl)imidazo[1,2-a]pyridine (40 mg, 0.18 mmol) and ethyl 1H-pyrazole-4-carboxylate (30 mg, 0.22 mmol) in DMF (3 mL) was added CsCO₃ (118 mg, 0.36 mmol) at RT. The mixture was stirred at RT for 2 h. The reaction was diluted with H₂O (30 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate, concentrated and purified by prep-TLC (MeOH/DCM = 1/10) to give ethyl 1-((6-(2-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (30 mg, yield: 50%) as a yellow oil. ESI-MS [M+H]⁺: 325.1.

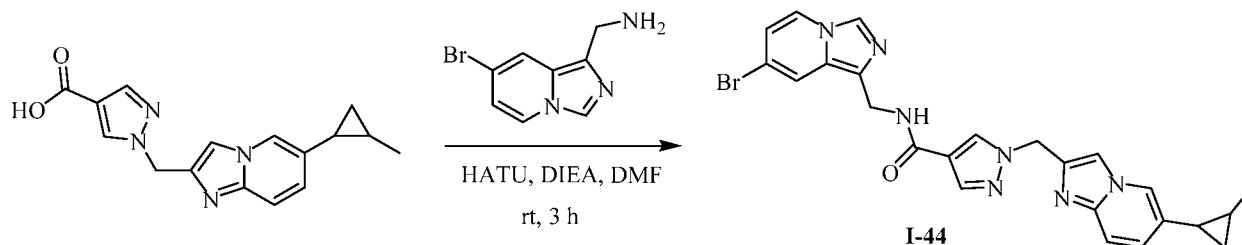
[0278] Synthesis of 1-((6-(2-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. To a solution of ethyl 1-((6-((1S,2R)-2-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (30 mg, 0.1 mmol) in a mixed solvent of THF/EtOH/H₂O (2 mL/2 mL/1 mL) was added NaOH (4 M, 0.1 mL, 0.4 mmol). The mixture was stirred at refluxed for 3 h. Most of the solvent was removed and the residue was diluted with H₂O (3 mL) and the pH value of mixture was adjusted to 4-5 by adding HCl aqueous (1 M). The mixture was freeze-dried to give 1-((6-(2-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (crude, 40 mg) as a yellow solid which was used in the next step without purification. ESI-MS [M+H]⁺: 297.1.

[0279] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-(2-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-43). To a solution of 1-((6-(2-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-

carboxylic acid (40 mg, crude from last step) and (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (44 mg, 0.2 mmol) in dry DMF (1 mL) was added HATU (106 mg, 0.28 mmol) and DIPEA (90 mg, 0.7 mmol) at RT. The reaction was stirred at RT for 3 h. Water (20 mL) was added and the mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, concentrated and purified by prep-TLC (DCM/MeOH = 10/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-(2-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-3-carboxamide (25 mg, yield: 54% for two steps) as a yellow solid. ESI-MS $[M+H]^+$: 460.1. Purity: 91%. ^1H NMR (400 MHz, DMSO): δ 8.58 (t, J = 5.3 Hz, 1H), 8.31-8.29 (m, 3H), 8.23 (s, 1H), 7.86 (s, 1H), 7.78 (s, 1H), 7.73 (s, 1H), 7.40 (d, J = 9.0 Hz, 1H), 7.14 (d, J = 8.9 Hz, 1H), 6.64 (dd, J = 7.5, 1.9 Hz, 1H), 5.39 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 2.02 (dd, J = 14.3, 8.6 Hz, 1H), 1.18-1.07 (m, 1H), 1.04-0.88 (m, 1H), 0.75 (d, J = 6.2 Hz, 3H), 0.60 (dd, J = 10.5, 5.2 Hz, 1H).

Example 44

Scheme 44



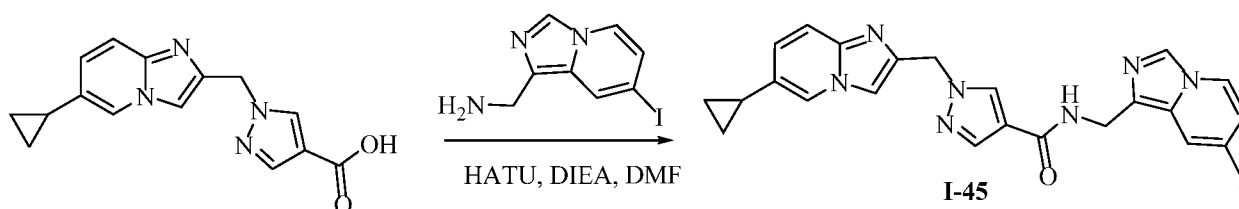
[0280] Synthesis of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-(2-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-44).

To a solution of 1-((6-(2-methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (40 mg, 0.1 mmol) and (7-bromoimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (52 mg, 0.2 mmol) in dry DMF (3 mL) was added HATU (106 mg, 0.28 mmol) and DIPEA (90 mg, 0.7 mmol) at RT. The reaction was stirred at RT for 3 h. Water (20 mL) was added and the mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate, concentrated and purified by prep-TLC (DCM/MeOH = 10/1) to give N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-(2-

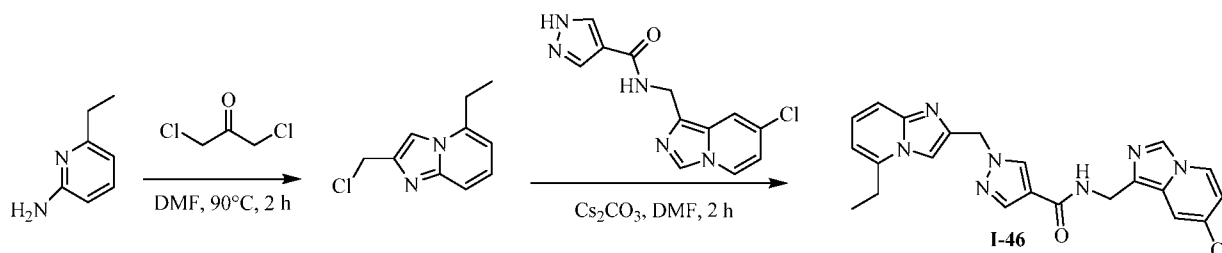
methylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (25.5 mg, yield: 37%) as a yellow solid. ESI-MS $[M+H]^+$: 504.1. Purity: 91.53%. ^1H NMR (400 MHz, DMSO): δ 8.59 (t, J = 5.7 Hz, 1H), 8.31 (s, 2H), 8.26-8.19 (m, 2H), 8.00-7.92 (m, 1H), 7.86 (s, 1H), 7.73 (s, 1H), 7.40 (d, J = 9.3 Hz, 1H), 7.15 (dd, J = 9.3, 1.6 Hz, 1H), 6.72 (dd, J = 7.4, 1.9 Hz, 1H), 5.39 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 2.02 (dd, J = 14.4, 8.4 Hz, 1H), 1.18-1.11 (m, 1H), 0.99-0.93 (m, 1H), 0.75 (d, J = 6.2 Hz, 3H), 0.60 (dd, J = 10.7, 5.5 Hz, 1H).

Example 45

Scheme 45



[0281] Synthesis of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-iodoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-45). To a solution of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (60 mg, 0.21 mmol), (7-iodoimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (99 mg, 0.32 mmol) and HATU (120 mg, 0.31 mmol) in DMF (5 mL) was added DIPEA (81 mg, 0.63 mmol). The resulting reaction was stirred at RT for 12 h. H_2O (25 mL) was added to the reaction, extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give the 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-iodoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (20 mg, yield: 18%) as a white solid. ESI-MS $[M+H]^+$: 538.0. Purity: 97.4%. ^1H NMR (400 MHz, DMSO): δ 8.56 (t, J = 5.7 Hz, 1H), 8.32 (s, 1H), 8.29 (s, 1H), 8.20 (s, 1H), 8.13 (s, 1H), 8.12-8.08 (m, 1H), 7.85 (s, 1H), 7.71 (s, 1H), 7.39 (d, J = 9.3 Hz, 1H), 6.99 (dd, J = 9.3, 1.7 Hz, 1H), 6.78 (dd, J = 7.3, 1.6 Hz, 1H), 5.39 (s, 2H), 4.54 (d, J = 5.7 Hz, 2H), 1.94-1.88 (m, 1H), 0.96-0.85 (m, 2H), 0.71-0.58 (m, 2H).

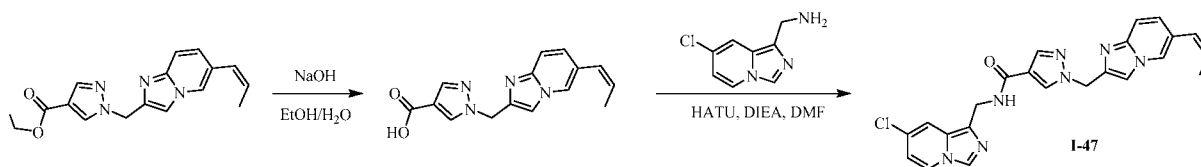
Example 46Scheme 46

[0282] Synthesis of 2-(chloromethyl)-5-ethylimidazo[1,2-a]pyridine. A solution of 6-ethylpyridin-2-amine (1 g, 8.2 mmol) and 1, 3-dichloropropan-2-one (4.7 g, 36.9 mmol) in DMF (10 mL) was stirred at 90 °C for 3 h. Then the reaction mixture was diluted with H₂O (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over Na₂SO₄, concentrated and purified by column chromatography (CH₂Cl₂: MeOH = 20:1) to give the desired product 2-(chloromethyl)-5-ethylimidazo[1,2-a]pyridine (450 mg, yield: 28%) as a white solid. ESI-MS [M+H]⁺: 195.1.

[0283] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-ethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-46). A solution of 2-(chloromethyl)-5-ethylimidazo[1,2-a]pyridine (60 mg, 0.31 mmol), N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide and Cs₂CO₃ (303 mg, 0.93 mmol) in DMF (3 mL) was stirred at RT for 2 h. Then the reaction mixture was diluted with H₂O (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were dried over Na₂SO₄, concentrated and purified by column chromatography (CH₂Cl₂/MeOH = 20/1) to give the desired compound N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-ethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (16 mg, yield: 12%) as a white solid. ESI-MS [M+H]⁺: 434.1. Purity: 98.90%. ¹H NMR (400 MHz, DMSO): δ 8.58 (t, J = 5.8 Hz, 2H), 8.33-8.27 (m, 2H), 8.23 (s, 1H), 7.86 (d, J = 6.8 Hz, 2H), 7.80-7.75 (m, 1H), 7.42 (d, J = 9.0 Hz, 1H), 7.29-7.21 (m, 1H), 6.78-6.73 (m, 1H), 6.67-6.61 (m, 1H), 5.42 (s, 2H), 4.55 (d, J = 5.8 Hz, 2H), 2.95-2.86 (m, 2H), 1.36-1.27 (m, 3H).

Example 47

Scheme 47

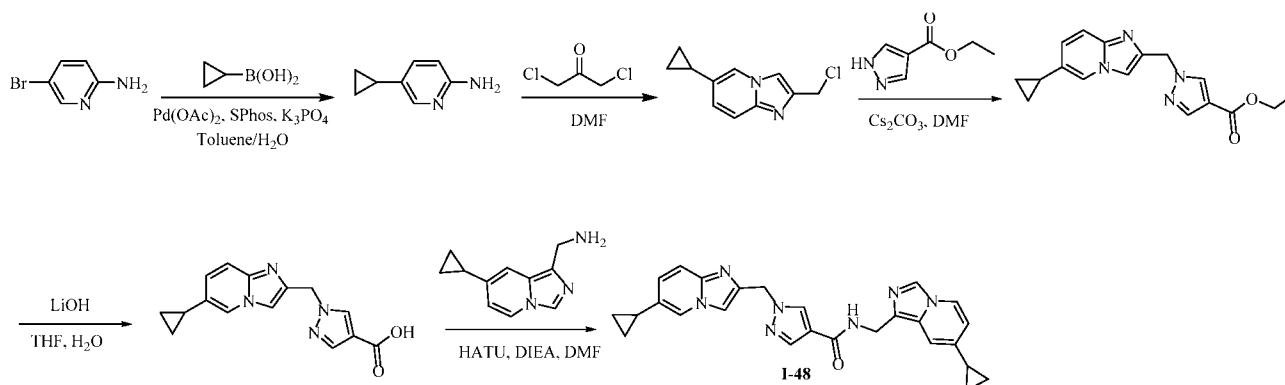


[0284] Synthesis of (Z)-1-((6-(prop-1-en-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. A mixture of ethyl (Z)-1-((6-(prop-1-en-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (150 mg, 0.48 mmol) and NaOH (40 mg, 1.6 mmol) in EtOH/H₂O (2 mL/1 mL) was stirred at 50 °C for 3 h. The reaction was monitored by LCMS until the starting material consumed. The pH value of mixture was adjusted to 2-3 by adding 1 M aqueous HCl solution and extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated to give (Z)-1-((6-(prop-1-en-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (65 mg, 48% yield) as a white solid. ESI-MS [M+H]⁺: 283.0.

[0285] Synthesis of (Z)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-(prop-1-en-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-47). A mixture of 1-((6-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (65 mg, 0.23 mmol) in DMF (3 mL) was added (5-chloro-2H-indazol-3-yl)methanamine hydrochloride (100 mg, 0.46 mmol), DIPEA (150 mg, 1.15 mmol) and HATU (133 mg, 0.35 mmol). The resulting mixture was stirred at RT for 3 h. The reaction was quenched with H₂O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude, which was purified with prep-TLC (EA/PE = 1/5) to give the (Z)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-(prop-1-en-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (9.3 mg, yield: 6.2%) as a white solid. ESI-MS [M+H]⁺: 446.1. Purity: 95.3%. ¹H NMR (400 MHz, DMSO): δ 8.60 (t, J = 5.6 Hz, 1H), 8.50 (s, 1H), 8.38-8.26 (m, 2H), 8.24 (s, 1H), 7.87 (s, 1H), 7.80 (d, J = 14.2 Hz, 2H), 7.48 (d, J = 9.3 Hz, 1H), 7.22 (d, J = 9.3 Hz, 1H), 6.65 (dd, J = 7.4, 2.0 Hz, 1H), 6.35 (d, J = 11.5 Hz, 1H), 5.84 (td, J = 14.4, 7.1 Hz, 1H), 5.42 (s, 2H), 4.56 (d, J = 5.7 Hz, 2H), 1.87 (dd, J = 7.2, 1.6 Hz, 3H).

Example 48

Scheme 48



[0286] Synthesis of 5-cyclopropylpyridin-2-amine. A solution of 5-bromopyridin-2-amine (5 g, 29.1 mmol), cyclopropylboronic acid (3.75 g, 43.6 mmol), Pd(OAc)₂ (651 mg, 2.91 mmol), SPhos (1.19 g, 2.91 mmol) and K₃PO₄ (18.5 g, 87.3 mmol) in toluene/H₂O (100 mL/10 mL) was stirred at 95 °C for 12 h under nitrogen. Then the reaction mixture was quenched with H₂O (50 mL) and extracted with DCM (200 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to give the crude residue which was purified by silica gel chromatography (PE/EtOAc = 1/1) to give the 5-cyclopropylpyridin-2-amine as yellow solid (3.8 g, 97.4% yield). ESI-MS [M+H]⁺: 135.2.

[0287] Synthesis of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine. To a solution 5-cyclopropyl-4-methylpyridin-2-amine (500 mg, 3.70 mmol) in DMF (10 mL) was added 1,3-dichloropropan-2-one (1409 mg, 11.1 mmol) at RT. The resulting reaction was stirred at 85 °C for 2 h. The solution was quenched with H₂O (60 mL), adjusted to pH 8 by adding saturated NaHCO₃ solution, and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give the crude, which was purified with prep-TLC (PE/EtOAc = 1/1) to give the 2-(chloromethyl)-6-cyclopropyl-7-methylimidazo[1,2-a]pyridine (300 mg, yield:39%) as a light yellow oil. ESI-MS [M+H]⁺: 207.2.

[0288] Synthesis of ethyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. To a solution 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (2 g, 9.70 mmol) in DMF (20 mL) was added ethyl 1H-pyrazole-4-carboxylate (906 mg, 6.46

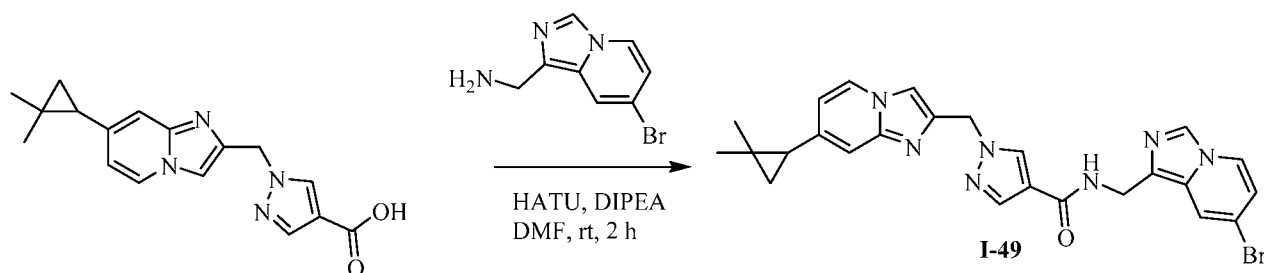
mmol) and Cs_2CO_3 (6.32 g, 19.38 mmol) at RT. The resulting reaction was stirred at RT for 12 h. H_2O (150 mL) was added to the reaction and then the mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , concentrated in vacuo to give the crude, which was purified with silica gel chromatography (DCM/MeOH = 20/1) to give the ethyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (1.5 g, yield: 75%) as a white solid. ESI-MS $[\text{M}+\text{H}]^+$: 311.2.

[0289] Synthesis of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. To a solution of ethyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (1.2 g, 3.87 mmol) in THF (20 mL) and H_2O (10 mL) was added LiOH (464 mg, 19.35 mmol). The mixture was stirred at RT for 16 h. Most of the THF was removed and the pH was adjusted to 4~5 by adding HCl (1 M). The resulting precipitate was collected and dried to give the 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid as a white solid (1.0 g, yield: 91%). ESI-MS $[\text{M}+\text{H}]^+$: 283.2.

[0290] Synthesis of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-cyclopropylimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-48). To a solution of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (60 mg, 0.21 mmol), (7-cyclopropylimidazo[1,5-a]pyridin-1-yl)methanamine (59 mg, 0.32 mmol) and HATU (120 mg, 0.31 mmol) in DMF (5 mL) was added DIPEA (81 mg, 0.63 mmol). The resulting reaction was stirred at RT for 12 h. H_2O (30 mL) was added to the reaction, extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give the 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-cyclopropylimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (20 mg, yield: 21%) as a white solid. ESI-MS $[\text{M}+\text{H}]^+$: 452.2. Purity: 99.8%. ^1H NMR (400 MHz, DMSO): δ 8.47 (t, J = 5.6 Hz, 1H), 8.32 (s, 1H), 8.21 (s, 1H), 8.16-8.14 (m, 2H), 7.86 (s, 1H), 7.71 (s, 1H), 7.40-7.38 (m, 1H), 7.32 (s, 1H), 7.00-6.97 (m, 1H), 6.32-6.30 (m, 1H), 5.38 (s, 2H), 4.55 (d, J = 5.6 Hz, 2H), 1.95-1.78 (m, 2H), 0.95-0.83 (m, 4H), 0.70-0.60 (m, 4H).

Example 49

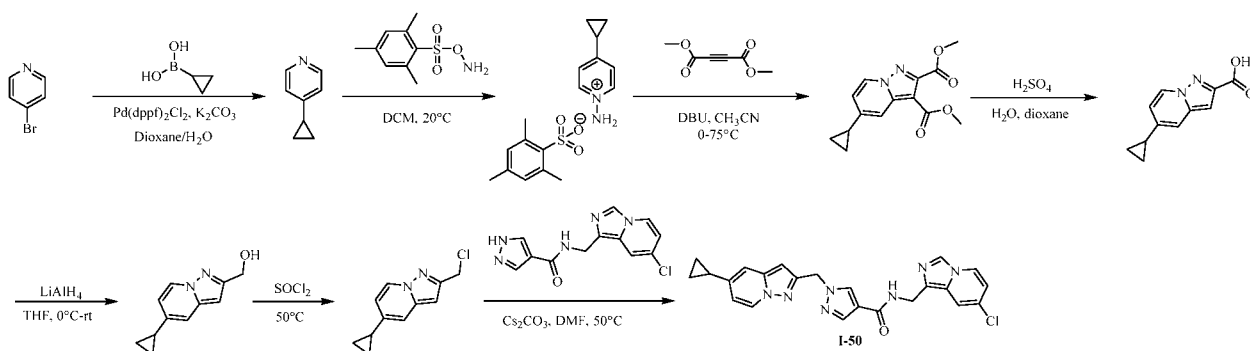
Scheme 49



[0291] Synthesis of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((7-(2,2-dimethylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-49). To a solution of 1-((7-(2,2-dimethylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (56 mg, 0.18 mmol), (7-bromoimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (55 mg, 0.21 mmol) and HATU (102 mg, 0.27 mmol) in DMF (10 mL) was added DIPEA (199 mg, 1.55 mmol). The resulting reaction stirred at RT for 2 h. H₂O (30 mL) was added to the reaction and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give the N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((7-(2,2-dimethylcyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (17.5 mg, yield: 18.8%) as a white solid. ESI-MS [M+H]⁺: 518.1. Purity: 91.25%. ¹H NMR (400 MHz, MeOD): δ 8.85 (s, 1H), 8.53 (s, 1H), 8.30 (s, 1H), 8.24 (d, J = 7.5 Hz, 1H), 8.11 (s, 2H), 7.98 (s, 1H), 7.87 (dd, J = 9.3, 1.4 Hz, 1H), 7.75 (d, J = 9.3 Hz, 1H), 6.98 (dd, J = 7.5, 1.4 Hz, 1H), 5.68 (s, 2H), 4.77 (s, 2H), 2.03-1.98 (m, 1H), 1.29 (s, 3H), 1.00-0.93 (m, 2H), 0.85 (s, 3H).

Example 50

Scheme 50



[0292] Synthesis of 4-cyclopropylpyridine. A mixture of 4-bromopyridine (5 g, 25.71 mmol), cyclopropylboronic acid (2.5 g, 28.28 mmol), K_2CO_3 (10.6 g, 77.13 mmol) and $Pd(dppf)_2Cl_2$ (2.1 g, 2.57 mmol) in dioxane (80 mL) and H_2O (16 mL) was refluxed under N_2 for 16 h. The reaction mixture was filtered through celite and washed with EtOAc (20 mL). The solvent was evaporated, the residue was diluted with H_2O (30 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated to give a yellow oil, which was purified by silica gel chromatography to give 4-cyclopropylpyridine (2.774 g, yield: 91.5%) as a yellow oil. ESI-MS $[M+H]^+$: 120.1.

[0293] Synthesis of 1-amino-4-cyclopropylpyridin-1-ium 2,4,6-trimethylbenzenesulfonate. To a solution of 4-cyclopropylpyridine (1.5 g, 12.61 mmol) in DCM (5 mL) was added O-(mesitylsulfonyl)hydroxylamine (2.7 g, 12.61 mmol) at 0 °C, then the reaction mixture was stirred at RT for 2 h. The reaction mixture was concentrated to give the 1-amino-4-cyclopropylpyridin-1-ium 2,4,6-trimethylbenzenesulfonate (4.2 g, yield: 100%) as a yellow oil, which was used in the next step without further purification. ESI-MS $[M+H]^+$: 135.1.

[0294] Synthesis of dimethyl 5-cyclopropylpyrazolo[1,5-a]pyridine-2,3-dicarboxylate. To a solution of 1-amino-4-cyclopropylpyridin-1-ium 2, 6-dimethylbenzenesulfonate (4.2 g, 12.6 mmol) and dimethyl but-2-ynedioate (3.6 g, 25.22 mmol) in CH_3CN (60 mL) was added DBU (3.8 g, 25.22 mmol) at 0 °C for 30 min. Then the resulting mixture was stirred at RT for 16 h. The reaction mixture was concentrated to give the crude, which was purified with silica gel chromatography (PE/EA = 2/1) to give dimethyl 5-

cyclopropylpyrazolo[1,5-a]pyridine-2, 3-dicarboxylate (2.5 g, yield: 72.4%) as a yellow oil. ESI-MS $[M+H]^+$: 275.1.

[0295] Synthesis of 5-cyclopropylpyrazolo[1,5-a]pyridine-2-carboxylic acid. A mixture of dimethyl 5-cyclopropylpyrazolo [1, 5-a] pyridine-2, 3-dicarboxylate (1.5 g, 5.47 mmol) and 50% H_2SO_4 in dioxane (8 mL) was heated at 85 °C for 5 h. Water (20 mL) was added and the mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give the crude, which was purified by silica gel chromatography (PE/EA = 1/1) to give 5-cyclopropylpyrazolo [1,5-a] pyridine-2-carboxylic acid (600 mg, yield: 54.0%) as a white solid. ESI-MS $[M+H]^+$: 203.1.

[0296] Synthesis of (5-cyclopropylpyrazolo[1,5-a]pyridin-2-yl)methanol. To a solution of 5-cyclopropylpyrazolo[1,5-a]pyridine-2-carboxylic acid (202 mg, 1.0 mmol) in THF (10 mL) was added $LiAlH_4$ (1.5 mL, 1 M) at 0 °C, the reaction mixture was stirred at 0 °C for 30 min. then warmed to RT and stirred for 4 h. The reaction was quenched by H_2O (10 mL) resulting in a precipitate. The filtrate was concentrated to give (5-cyclopropylpyrazolo[1,5-a]pyridin-2-yl)methanol (140 mg, yield: 74.5%) as a yellow oil which was used in the next step without further purification. ESI-MS $[M+H]^+$: 189.1.

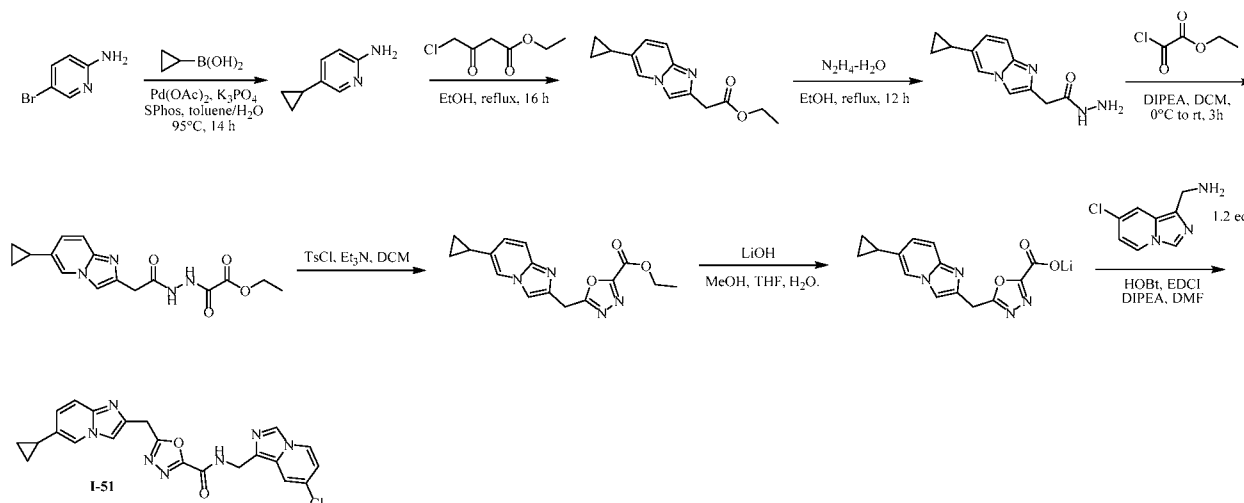
[0297] Synthesis of 2-(chloromethyl)-5-cyclopropylpyrazolo[1,5-a]pyridine. A mixture of (5-cyclopropylpyrazolo [1,5-a]pyridin-2-yl) methanol (140 mg, 0.74 mmol) and $SOCl_2$ (3 mL) was stirred at 50 °C for 1 h. The reaction mixture was concentrated to give the crude product 2-(chloromethyl)-5-cyclopropylpyrazolo[1,5-a]pyridine (200 mg, crude) as a black oil which was used in the next step without purification. ESI-MS $[M+H]^+$: 207.1.

[0298] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyclopropylpyrazolo[1,5-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-50). A mixture of 2-(chloromethyl)-5-cyclopropylpyrazolo[1,5-a]pyridine (30 mg, 0.15 mmol), N-((7-chloroimidazo [1, 5-a] pyridin-1-yl) methyl)-1H-pyrazole-4-carboxamide (42 mg, 0.15 mmol), Cs_2CO_3 (200 mg, 0.61 mmol) in DMF (3 mL) was stirred at 50 °C for 16 h. Water (30 mL) was added and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, concentrated and purified by prep-HPLC to obtain product as a white solid (2.2 mg, yield: 3.3%). ESI-MS $[M+H]^+$: 446.7. Purity: 100%. ^1H NMR (400 MHz, DMSO): δ 8.62-8.50 (m, 2H), 8.47 (d, J = 8.0 Hz, 1H), 8.32 (s, 2H), 8.30 (s, 1H), 8.23 (s,

1H), 7.87 (s, 1H), 7.78 (s, 1H), 7.32 (s, 1H), 6.65 (d, J = 8.0 Hz, 1H), 6.57 (dd, J = 8.0, 2.0 Hz, 1H), 6.27 (s, 1H), 5.45 (s, 2H), 4.55 (d, J = 4.0 Hz, 2H), 1.99-1.93 (m, 1H), 1.02-0.95 (m, 2H), 0.78-0.70 (m, 2H).

Example 51

Scheme 51



[0299] Synthesis of 5-cyclopropylpyridin-2-amine. To a solution of 5-bromopyridin-2-amine (50 g, 290 mmol) in toluene/H₂O (700 mL/70 mL) was added cyclopropylboronic acid (37.4 g, 435 mmol), Pd(OAc)₂ (6.49 g, 29.0 mmol), SPhos (12.8 g, 29.0 mmol) and K₃PO₄ (184.4 g, 870 mmol). The reaction mixture was stirred at 95 °C for 14 h under nitrogen. Then the mixture was concentrated in vacuo. Water (400 mL) was added and the mixture was extracted with DCM (500 mL x 2). The combined organic layers were concentrated to give the crude product, which was purified by silica gel chromatography (PE/EtOAc = 1/1) to give the 5-cyclopropylpyridin-2-amine as a yellow solid (38 g, yield: 97%). ESI-MS [M+H]⁺: 135.2.

[0300] Synthesis of ethyl 2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetate. To a solution 5-cyclopropyl-4-methylpyridin-2-amine (30 g, 223.9 mmol) in EtOH (400 mL) was added ethyl 4-chloro-3-oxobutanoate (110 g, 671.7 mmol) at RT. The resulting mixture was stirred at 90 °C for 16 h and then concentrated in vacuo. H₂O (500 mL) was added, the pH value of the mixture was adjusted to 8 by adding saturated NaHCO₃ solution, and then the mixture was extracted with EtOAc (400 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated to give the crude product, which was purified by silica gel

chromatography (DCM/MeOH = 10/1) to give ethyl 2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetate (40 g, impure) as a black solid. ESI-MS $[M+H]^+$: 245.2.

[0301] Synthesis of 2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetohydrazide. A mixture of ethyl 2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetate (40 g, impure) and $N_2H_4 \cdot H_2O$ (50 mL) in EtOH (300 mL) was stirred at 85 °C for 12 h. The mixture was then concentrated and purified by silica gel chromatography (DCM/MeOH = 10/1) to give 2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetohydrazide (17.1 g, yield: 31.5% in 2 steps) as a yellow solid. ESI-MS $[M+H]^+$: 231.1.

[0302] Synthesis of ethyl 2-(2-(2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetyl)hydrazinyl)-2-oxoacetate. To a solution of 2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetohydrazide (17 g, 73.9 mmol) and DIPEA (38 mL, 222 mmol) in DCM (300 mL) was added ethyl 2-chloro-2-oxoacetate (15 g, 111 mmol) slowly at 0 °C. The reaction mixture was stirred at RT for 2 h. Water (200 mL) was added and the mixture was extracted with DCM (200 mL x 2). The combined organic layers were concentrated to give the crude product, which was purified by silica gel chromatography (DCM/MeOH = 10/1) to give (ethyl 2-(2-(2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetyl)hydrazinyl)-2-oxoacetate (17 g, yield: 70%) as a yellow solid. ESI-MS $[M+H]^+$: 331.1.

[0303] Synthesis of ethyl 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate. To a solution of ethyl 2-(2-(2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetyl)hydrazinyl)-2-oxoacetate (17 g, 51.5 mmol) and Et_3N (14 mL, 2 mmol) in DCM (300 mL) was added a solution of TsCl (11.8 g, 61.8 mmol) in DCM (50 mL) at RT. The reaction mixture was stirred at this temperature for 16 h. Water (200 mL) was added and the mixture was extracted with DCM (200 mL x 2). The combined organic layers were concentrated and purified by silica gel chromatography (DCM/MeOH = 10/1) to give 2-(chloromethyl)-5-methylimidazo[1,2-a]pyridine (8.2 g, yield: 51%) as a yellow oil. ESI-MS $[M+H]^+$: 313.2.

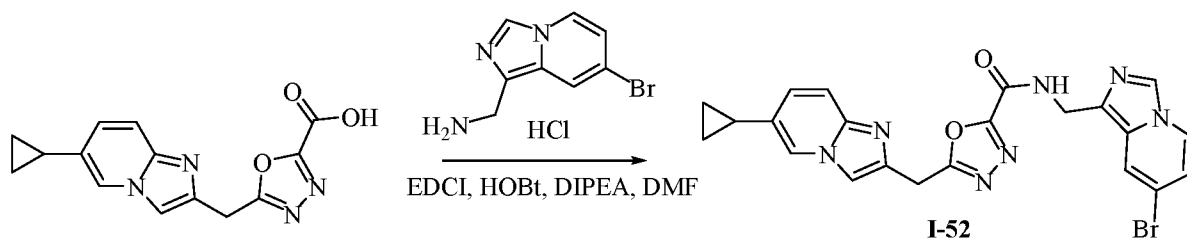
[0304] Synthesis of lithium 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate. A solution of ethyl 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate (8.0 g, 25.6 mmol) and $LiOH \cdot H_2O$ (2.1 g, 51.2 mmol) in a mixed solvent of THF/MeOH/ H_2O (50 mL/50 mL/50 mL) was stirred at RT for 2 h. THF and methanol were removed in vacuo at 20 °C and the remaining H_2O phase was

lyophilized to give lithium 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate (7.4 g, yield: 100%) as a yellow solid. This material was used directly in the next step without further purification. ESI-MS $[M+H]^+$: 285.1.

[0305] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide (I-51). A mixture of lithium 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate (7 g, 24 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine (6.28 g, 28.8 mmol), EDCI (9.2 g, 48 mmol), HOBt (6.48 g, 48 mmol) and DIPEA (12 mL, 72 mmol) in DMF (100 mL) was stirred at 20 °C for 48 h. The mixture was concentrated to remove DMF, diluted with DCM/MeOH (300 mL, 10/1 (v/v)) and washed with H₂O (100 mL x 2). The organic layer was separated, dried over Na₂SO₄, and concentrated in vacuo to give the crude product, which was purified by silica gel chromatography (DCM/MeOH = 10/1) and then triturated with methanol to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide (3.1 g, yield: 28.7%) as a light yellow solid. ESI-MS $[M+H]^+$: 448.2. Purity: 99%. ¹H NMR (400 MHz, DMSO): δ 9.73 (t, J = 5.8 Hz, 1H), 8.32-8.29 (m, 3H), 7.83 (d, J = 1.0 Hz, 1H), 7.79 (s, 1H), 7.37 (d, J = 9.3 Hz, 1H), 6.98 (dd, J = 9.4, 1.7 Hz, 1H), 6.67 (dd, J = 7.4, 2.1 Hz, 1H), 4.62 (d, J = 5.9 Hz, 2H), 4.42 (s, 2H), 1.98-1.85 (m, 1H), 0.97-0.85 (m, 2H), 0.75-0.59 (m, 2H).

Example 52

Scheme 52

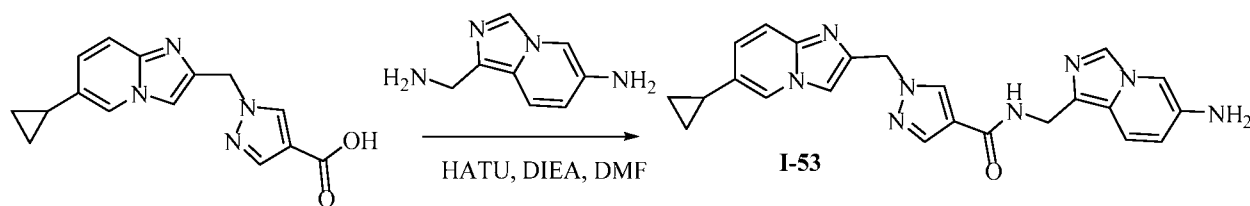


[0306] Synthesis of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide (I-52). A mixture of 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylic acid (50 mg, 0.18 mmol), (7-bromoimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (55

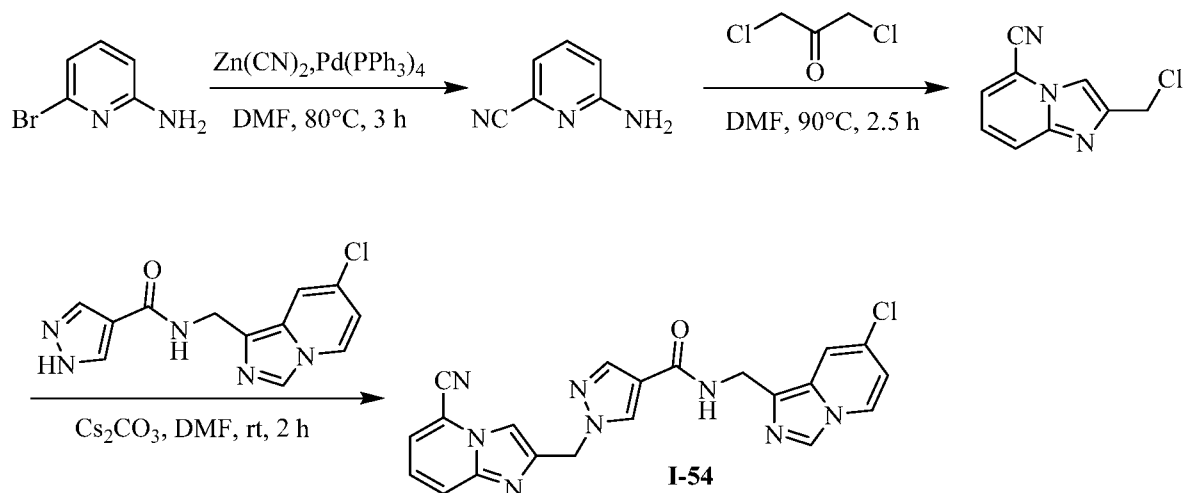
mg, 0.21 mmol), EDCI (70 mg, 0.35 mmol), HOBT (50 mg, 0.35 mmol) and DIPEA (0.1 mL, 0.53 mmol) in DMF (3 mL) was stirred at 50 °C for 16 h. Water (30 mL) was added and extracted with EtOAc (30 mL x 3). The combined organic layers concentrated and purified by prep-HPLC to give N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide (3.0 mg, yield: 3.5%) as a light yellow solid. ESI-MS $[M+H]^+$: 492.1. Purity: 96.8%. ^1H NMR (400 MHz, DMSO): δ 9.73 (t, J = 5.9 Hz, 1H), 8.32 (s, 2H), 8.25 (d, J = 7.4 Hz, 1H), 8.00 (s, 1H), 7.79 (s, 1H), 7.37 (d, J = 9.4 Hz, 1H), 6.98 (dd, J = 9.3, 1.7 Hz, 1H), 6.74 (dd, J = 7.4, 1.9 Hz, 1H), 4.62 (d, J = 5.9 Hz, 2H), 4.42 (s, 2H), 1.95-1.89 (m, 1H), 0.99-0.82 (m, 2H), 0.68-0.66 (m, 2H).

Example 53

Scheme 53



[0307] Synthesis of N-((6-aminoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-53). To a solution of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (60 mg, 0.21 mmol), 1-((6-aminoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (51 mg, 0.32 mmol) and HATU (120 mg, 0.31 mmol) in DMF (5 mL) was added DIPEA (81 mg, 0.63 mmol). The resulting reaction was stirred at RT for 12 h. H₂O (25 mL) was added and the reaction was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give the N-((6-aminoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (10 mg, yield: 11%) as a white solid. ESI-MS $[M+H]^+$: 427.2. Purity: 92.3%. ^1H NMR (400 MHz, DMSO): δ 8.47 (t, J = 5.6 Hz, 1H), 8.32 (s, 1H), 8.21 (s, 1H), 8.16-8.14 (m, 2H), 7.86 (s, 1H), 7.71 (s, 1H), 7.40-7.38 (m, 1H), 7.32 (s, 1H), 7.00-6.97 (m, 1H), 6.32-6.30 (m, 1H), 5.38 (s, 2H), 4.55 (d, J = 5.6 Hz, 2H), 1.95-1.78 (m, 2H), 0.95-0.83 (m, 4H), 0.70-0.60 (m, 4H).

Example 54Scheme 54

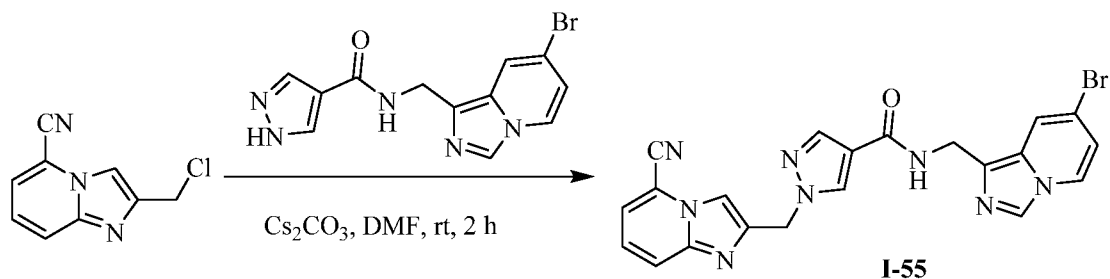
[0308] Synthesis of 6-aminopyridin-2-amine. To a solution of 6-bromopyridin-2-amine (500 mg, 2.9 mmol) in DMF (10 mL) was added $\text{Zn}(\text{CN})_2$ (480 mg, 4.1 mmol) and tetrakis(triphenylphosphine)palladium(0) (335 mg, 0.29 mmol). The resulting mixture was stirred at 80 °C under nitrogen for 3 h. The reaction mixture was filtered through celite and the filtrate was diluted with H_2O (100 mL) and extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash column chromatography to give 6-aminopyridin-2-amine (250 mg, yield: 72%). ESI-MS $[\text{M}+\text{H}]^+$: 120.1.

[0309] Synthesis of 2-(chloromethyl)imidazo[1,2-a]pyridine-5-carbonitrile. To a solution of 6-aminopyridin-2-amine (200 mg, 1.67 mmol) in DMF (3 mL) was added 1,3-dichloropropan-2-one (1.0 g, 8.33 mmol). The resulting mixture was stirred at 90 °C for 2.5 h. The reaction mixture was diluted with H_2O (50 mL), extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash column chromatography to give 2-(chloromethyl)imidazo[1,2-a]pyridine-5-carbonitrile (150 mg, yield: 47%). ESI-MS $[\text{M}+\text{H}]^+$: 192.0.

[0310] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyanoimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-54). To a solution of 2-(chloromethyl)imidazo[1,2-a]pyridine-5-carbonitrile (44 mg, 0.23 mmol) in DMF (3 mL) was added cesium carbonate (224 mg, 0.69 mmol) and N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (63 mg, 0.23 mmol). The resulting mixture was diluted with H₂O (30 mL), extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by prep-HPLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyanoimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (12.7 mg, yield: 12.8%). ESI-MS [M+H]⁺: 431.1. Purity: 99.08%. ¹H NMR (400 MHz, DMSO): δ 8.59 (t, J = 5.8 Hz, 1H), 8.34-8.26 (m, 2H), 8.26 (s, 1H), 8.14 (s, 1H), 7.94 (d, J = 9.1 Hz, 1H), 7.87 (s, 1H), 7.84-7.79 (m, 1H), 7.79-7.77 (m, 1H), 7.41-7.35 (m, 1H), 6.67-6.62 (m, 1H), 5.50 (s, 2H), 4.56 (d, J = 5.7 Hz, 2H).

Example 55

Scheme 55

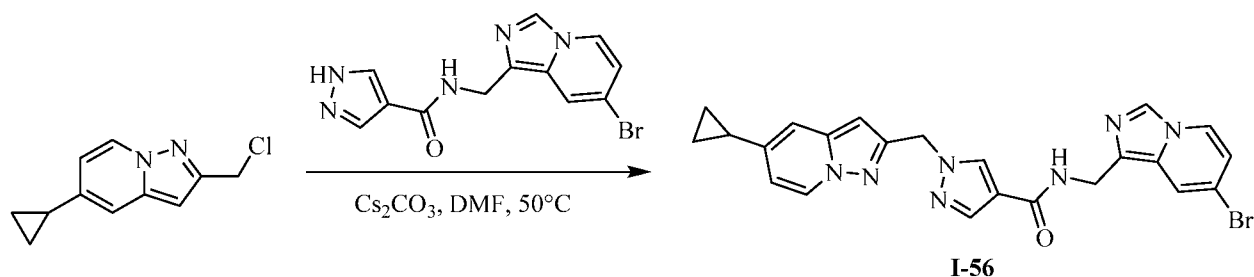


[0311] Synthesis of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyanoimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-75). To a solution of 2-(chloromethyl)imidazo[1,2-a]pyridine-5-carbonitrile (49 mg, 0.26 mmol) in DMF (3 mL) was added cesium carbonate (250 mg, 0.77 mmol) and N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (83 mg, 0.26 mmol). The resulting mixture was diluted with H₂O (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layer were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by prep-HPLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-

cyanoimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (21 mg, yield: 17%). ESI-MS $[M+H]^+$: 475.1. Purity: 97.73%. ^1H NMR (400 MHz, DMSO): δ 8.59 (t, $J = 5.6$ Hz, 1H), 8.32 (s, 1H), 8.26 (s, 1H), 8.26-8.22 (m, 1H), 8.14 (s, 1H), 7.97-7.92 (m, 2H), 7.87 (s, 1H), 7.83-7.79 (m, 1H), 7.41-7.35 (m, 1H), 6.74-6.70 (m, 1H), 5.50 (s, 2H), 4.55 (d, $J = 5.7$ Hz, 2H).

Example 56

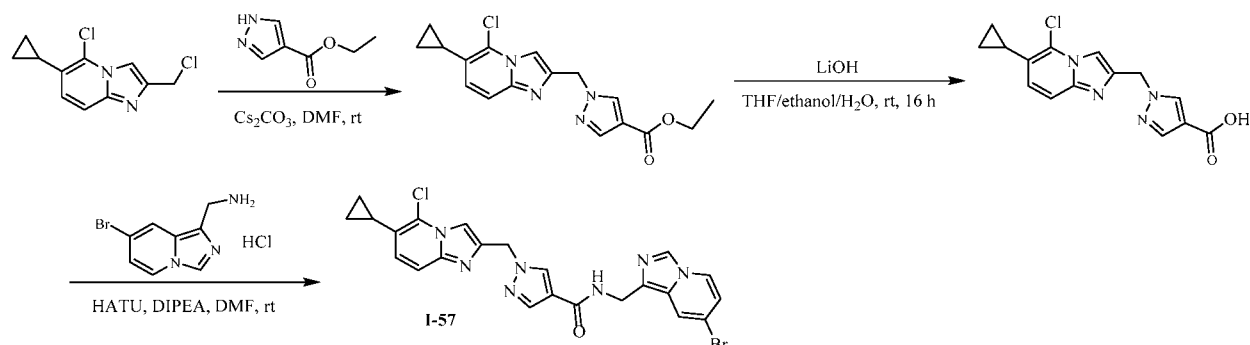
Scheme 56



[0312] Synthesis of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyclopropylpyrazolo[1,5-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-56). A mixture of 2-(chloromethyl)-5-cyclopropylpyrazolo[1,5-a]pyridine (30 mg, 0.15 mmol), N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (48 mg, 0.15 mmol) and Cs_2CO_3 (200 mg, 0.61 mmol) in DMF (3 mL) was stirred at 50 °C for 16 h. Water (30 mL) was added and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, concentrated and purified by prep-HPLC to give N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-cyclopropylpyrazolo[1,5-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (10 mg, yield: 13%) as a white solid. ESI-MS $[M+H]^+$: 490.0. Purity: 86.77%. ^1H NMR (400 MHz, DMSO): δ 8.62-8.55 (m, 1H), 8.47 (d, $J = 8.0$ Hz, 1H), 8.32 (s, 1H), 8.25 (d, $J = 0.8$ Hz, 1H), 8.23 (s, 1H), 7.95 (d, $J = 1.2$ Hz, 1H), 7.87 (s, 1H), 7.32 (s, 1H), 6.72 (dd, $J = 8.0, 2.0$ Hz, 1H), 6.57 (dd, $J = 8.0, 2.0$ Hz, 1H), 6.27 (s, 1H), 5.45 (s, 2H), 4.55 (d, $J = 4.0$ Hz, 2H), 2.00-1.90 (m, 1H), 1.03-0.92 (m, 2H), 0.78-0.70 (m, 2H).

Example 57

Scheme 57



[0313] Synthesis of ethyl 1-((5-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A mixture of 5-chloro-2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (190 mg, 0.79 mmol), ethyl 1H-pyrazole-4-carboxylate (221 mg, 1.58 mmol) and Cs_2CO_3 (769 mg, 2.36 mmol) in DMF (6 mL) was stirred at 60 °C for 3 h. Water (50 mL) was added and the mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were concentrated and purified by silica gel chromatography (EA/PE = 2:3 to 10:1) to give ethyl 1-((5-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (220 mg, yield: 64%) as a white solid. ESI-MS $[\text{M}+\text{H}]^+$: 345.2.

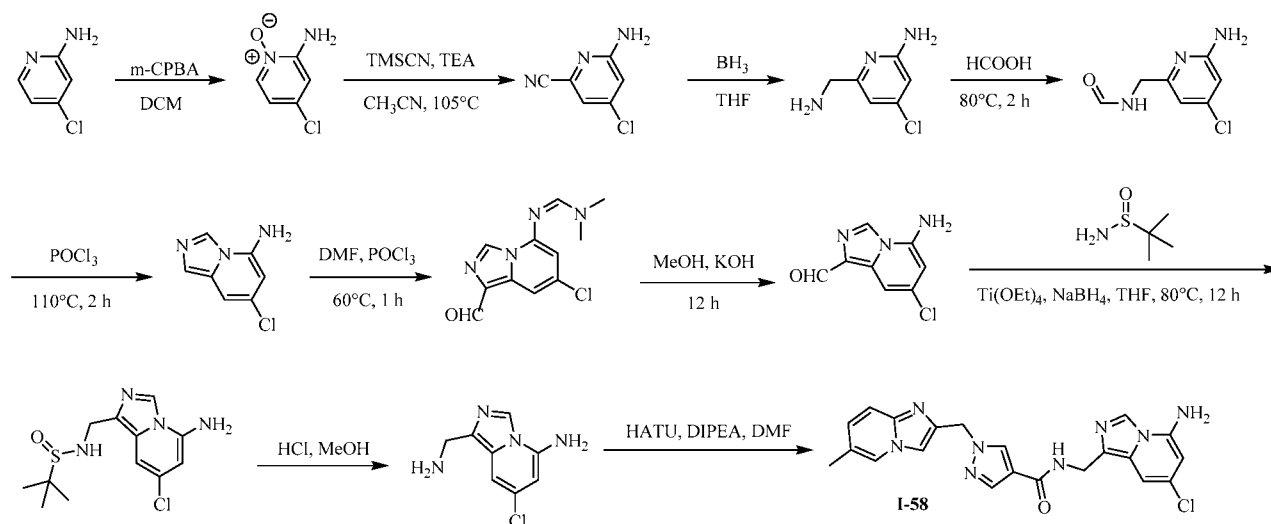
[0314] Synthesis of 1-((5-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. To a solution of 1-((5-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (220 mg, 0.64 mmol) in a mixed solvent of ethanol/THF/ H_2O (3 mL/3 mL/1.5 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (107 mg, 2.55 mmol). The mixture was stirred at 60 °C for 3 h. Most of the solvent was removed and the residue was diluted with H_2O (10 mL), the pH value of mixture was adjusted to 4-5 by adding aqueous HCl (1 M). The solution was extracted with EtOAc (50 mL x 4). The combined organic layers were concentrated to give 1-((5-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (160 mg, yield: 80%) as a white solid. ESI-MS $[\text{M}+\text{H}]^+$: 317.2.

[0315] Synthesis of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-57). A mixture of 1-((5-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (63.2 mg, 0.2 mmol), (7-bromoimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (52.4 mg, 0.2 mmol), HATU (190 mg, 0.5 mmol) and DIPEA (77.5 mg, 0.6

mmol) in DMF (3 mL) was stirred at RT for 3 h. Water (30 mL) was added and the mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated and purified by prep-TLC (DCM: MeOH = 8:1) to give N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-chloro-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (19.9 mg, yield: 19%) as a white solid. ESI-MS $[M+H]^+$: 524.1. Purity: 92.44%. ^1H NMR (400 MHz, DMSO): δ 8.58 (t, $J = 5.6$ Hz, 1H), 8.31 (s, 1H), 8.24-8.22 (m, 2H), 7.94-7.86 (m, 3H), 7.49 (d, $J = 9.3$ Hz, 1H), 6.97 (d, $J = 9.3$ Hz, 1H), 6.71 (dd, $J = 7.4, 1.8$ Hz, 1H), 5.45 (s, 2H), 4.54 (d, $J = 5.7$ Hz, 2H), 2.14-2.09 (m 1H), 1.03-1.0 (m, 2H), 0.78-0.74 (m, 2H).

Example 58

Scheme 58



[0316] Synthesis of 2-amino-4-chloropyridine 1-oxide. To a solution of 4-chloropyridin-2-amine (5.14 g, 40 mmol) in DCM (200 mL) at 0 °C was added m-CPBA slowly. The reaction mixture was stirred at RT for 4 h. Water (100 mL) was added and the pH of the mixture was adjusted to 8 by adding saturated NaHCO_3 solution. Then the H_2O layer was extracted with DCM/ CH_3OH (10:1, 100 mL x 5). The combined organic layers were concentrated to give 2-amino-4-chloropyridine 1-oxide (3.4 g, yield: 61%) as a yellow solid, which was used in the next step without further purification. ESI-MS $[M+H]^+$: 145.1.

[0317] Synthesis of 6-amino-4-chloropicolinonitrile. A mixture of 2-amino-4-chloropyridine 1-oxide (1.74 g, 12 mmol), TMSCN (24 mL, 192 mmol) and TEA (26 mL, 192

mmol) in CH₃CN (20 mL) was stirred at 105 °C overnight in a sealed tube. Saturated aqueous NaHCO₃ was added to adjust the pH to 8, and then extracted with DCM (100 mL x 2). The combined organic layers were concentrated and purified by silica gel chromatography (EA/PE = 1/4) to give 6-amino-4-chloropicolinonitrile (1.16 g, yield: 63%) as a yellow solid. ESI-MS [M+H]⁺: 154.1.

[0318] Synthesis of 6-(aminomethyl)-4-chloropyridin-2-amine. To a solution of 6-amino-4-chloropicolinonitrile (1.16 g, 7.6 mmol) in dry THF (10 mL) was added BH₃ (1 M in THF, 19 mL) dropwise. The mixture was stirred at RT overnight. Then the mixture was quenched with CH₃OH and stirred at RT for 1 h. the resulting mixture was then concentrated to give 6-(aminomethyl)-4-chloropyridin-2-amine (1.18 g, yield: 99%) as a yellow solid, which was used in the next step without further purification. ESI-MS [M+H]⁺: 158.1.

[0319] Synthesis of N-((6-amino-4-chloropyridin-2-yl)methyl)formamide. A solution of 6-(aminomethyl)-4-chloropyridin-2-amine (1.18 g, 7.5 mmol), HCOOH (20 mL) and EtOH (20 mL) was stirred at 80 °C for 2 h. Solvent was concentrated, H₂O (20 mL) was added, and the pH of the mixture was adjusted to 8 by adding saturated aqueous NaHCO₃ solution. The mixture was then extracted with EtOAc (50 mL x 5). The combined organic layers were concentrated to give N-((6-amino-4-chloropyridin-2-yl)methyl)formamide (1.05 g, yield: 75%) as a white solid. ESI-MS [M+H]⁺: 186.1.

[0320] Synthesis of 7-chloroimidazo[1,5-a]pyridin-5-amine. A solution of N-((6-amino-4-chloropyridin-2-yl)methyl)formamide (1.6 g, 8.6 mmol) in POCl₃ (15 mL) was stirred at 120 °C for 2 h. Solvent was concentrated and the residue was diluted with H₂O (20 mL). The pH of the mixture was adjusted to 8 by adding saturated NaHCO₃ solution and then extracted with EtOAc (100 mL x 3). The combined organics were concentrated and purified by silica gel chromatography (CH₂Cl₂/CH₃OH = 10/1) to give 7-chloroimidazo[1,5-a]pyridin-5-amine (3.4 g, yield: 61%) as a gray solid. ESI-MS [M+H]⁺: 168.1

[0321] Synthesis of N'-(7-chloro-1-formylimidazo[1,5-a]pyridin-5-yl)-N,N-dimethylformimide. A mixture of 7-chloroimidazo[1,5-a]pyridin-5-amine (155 mg, 0.92 mmol), DMF (203 mg, 2.76 mmol) and POCl₃ (3 mL) was stirred at 60 °C for 1 h. Then the reaction mixture was poured in to ice H₂O and NH₄OH was added to adjust pH to about 8. The resulting mixture was extracted with EtOAc (30 mL x 5). The combined organic layers were

concentrated to give N'-(7-chloro-1-formylimidazo[1,5-a]pyridin-5-yl)-N,N-dimethylformimidamide (220 mg, yield: 96%) as a yellow solid. ESI-MS $[M+H]^+$: 251.1.

[0322] Synthesis of 5-amino-7-chloroimidazo[1,5-a]pyridine-1-carbaldehyde. A mixture of N'-(7-chloro-1-formylimidazo[1,5-a]pyridin-5-yl)-N,N-dimethylformimidamide (220 mg, 0.88 mmol), CH₃OH (5 mL) and aqueous KOH (5 M, 1 mL) was stirred at RT overnight. Water (20 mL) was added and the mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated and purified by silica gel chromatography (CH₂Cl₂/CH₃OH = 9/1) to give 5-amino-7-chloroimidazo[1,5-a]pyridine-1-carbaldehyde (50 mg, yield: 29%) as an orange solid. ESI-MS $[M+H]^+$: 196.1.

[0323] Synthesis of N-((5-amino-7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-methylpropane-2-sulfinamide. A mixture of 5-amino-7-chloroimidazo[1,5-a]pyridine-1-carbaldehyde (22 mg, 0.11 mmol), 2-methylpropane-2-sulfinamide (15.7 mg, 0.13 mmol) and Ti(OEt)₄ (0.12 mL, 0.55 mmol) in THF (0.2 mL) was stirred at 80 °C overnight. After cooled to RT, NaBH₄ (20.8 mg, 0.55 mmol) was added. The reaction mixture was stirred at RT for 3 h. Water (10 mL) and EtOAc (10 mL) was added and the mixture was filtered. The filtration was extracted with EtOAc (30 mL x 3). The combined organic layers were concentrated and purified by silica gel chromatography (CH₂Cl₂/CH₃OH = 10/1) to give N-((5-amino-7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-methylpropane-2-sulfinamide (10 mg, yield: 30%) as a yellow solid. ESI-MS $[M+H]^+$: 313.1.

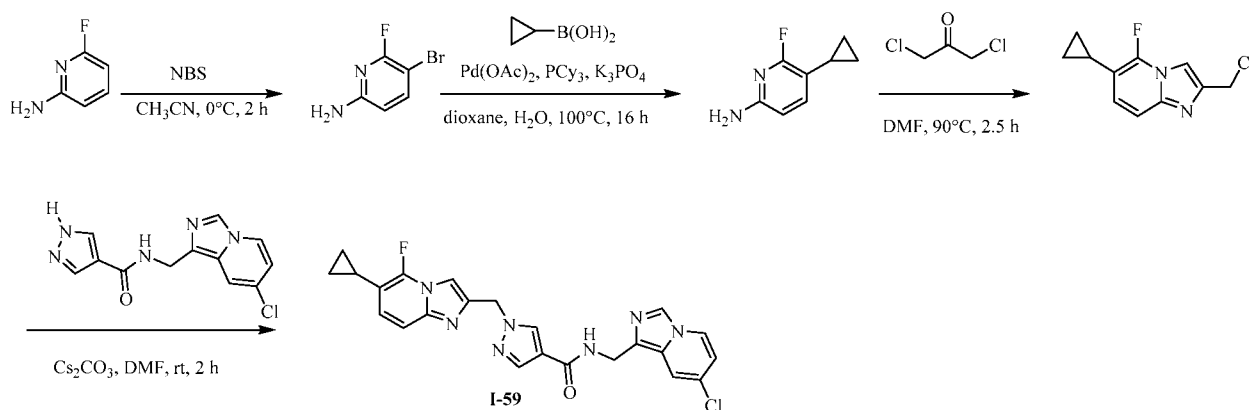
[0324] Synthesis of 1-(aminomethyl)-7-chloroimidazo[1,5-a]pyridin-5-amine. To a solution of N-((5-amino-7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-methylpropane-2-sulfinamide (48 mg, 0.16 mmol) in CH₃OH (2 mL) was added HCl (4 M in dioxane, 0.25 mL). The mixture was stirred at RT for 1 h, then concentrated to give 1-(aminomethyl)-7-chloroimidazo[1,5-a]pyridin-5-amine (31 mg, yield: 99%) as a yellow solid which was used in the next step without purification. ESI-MS $[M-16]^+$: 180.1.

[0325] Synthesis of N-((5-amino-7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-58). A mixture of 1-(aminomethyl)-7-chloroimidazo[1,5-a]pyridin-5-amine (22 mg, 0.11 mmol), 1-((6-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (28 mg, 0.11 mmol), HATU (84 mg, 0.22 mmol), and DIPEA (43 mg, 0.33 mmol) in DMF (2 mL) was stirred at RT

for 2 h. Water (10 mL) was added and extracted with DCM/MeOH (30 mL x 3, 10/1, (v/v)). The combined organic layers were concentrated and purified by silica gel chromatography (DCM/CH₃OH = 6/1) to give N-((5-amino-7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (9 mg, yield: 9%) as a white solid. ESI-MS [M+H]⁺: 435.2. Purity: 100%. ¹H NMR (400 MHz, DMSO): δ 8.50 (t, J = 5.6 Hz, 1H), 8.31 (s, 1H), 8.27 (s, 1H), 8.21 (s, 1H), 7.86 (s, 1H), 7.75 (s, 1H), 7.41 (d, J = 9.2 Hz, 1H), 7.10 (dd, J = 9.2, 1.3 Hz, 1H), 7.03 (d, J = 1.3 Hz, 1H), 6.84 (s, 2H), 5.64 (d, J = 1.8 Hz, 1H), 5.39 (s, 2H), 4.53 (d, J = 5.7 Hz, 2H), 2.24 (s, 3H).

Example 59

Scheme 59



[0326] Synthesis of 6-fluoropyridin-2-amine. A mixture of 6-fluoropyridin-2-amine (3 g, 26.8 mmol) and N-bromosuccinimide (5.25 g, 29.5 mmol) in dry CH₃CN (20 mL) was stirred at 0 °C for 2 h. Water (100 mL) was added and the mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were concentrated and purified by silica gel chromatography (EA/PE = 1/5) to give 5-bromo-6-fluoropyridin-2-amine (4.31 g, yield: 84.2%) as a white solid. ESI-MS [M+H]⁺: 191.0.

[0327] Synthesis of 5-cyclopropyl-6-fluoropyridin-2-amine. A solution of 5-bromo-6-fluoropyridin-2-amine (3.0 g, 15.8 mmol), cyclopropylboronic acid (2.04 mg, 23.7 mmol), Pd(OAc)₂ (354 mg, 1.58 mmol), PCy₃ (886.2 mg, 3.16 mmol) and K₃PO₄ (6.7 g, 31.6 mmol) in dioxane/H₂O (30 mL/3 mL) was stirred at 100 °C for 16 h. Then the reaction mixture was diluted with H₂O (50 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were

dried over Na_2SO_4 and concentrated to give the desired compound 5-cyclopropyl-6-fluoropyridin-2-amine (yellow oil, 2.2 g). ESI-MS $[\text{M}+\text{H}]^+$: 153.2.

[0328] Synthesis of 2-(chloromethyl)-6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridine.

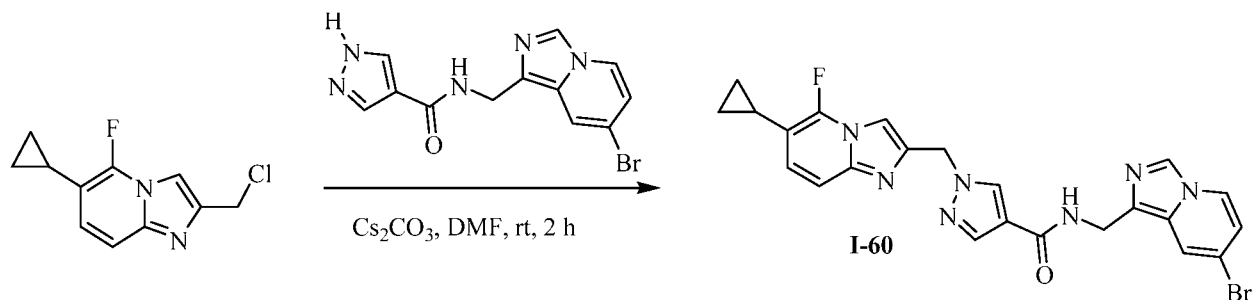
A solution of 5-cyclopropyl-6-fluoropyridin-2-amine (1.5 g, 10 mmol) and 1,3-dichloropropan-2-one (3.8 g, 30 mmol) in dry DMF (15 mL) was stirred at 90 °C for 2.5 h. Then the reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over Na_2SO_4 , concentrated and purified by column chromatography (PE:EA = 5:1) to give the desired product 2-(chloromethyl)-6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridine (325 mg, yield: 15%) as a yellow solid. ESI-MS $[\text{M}+\text{H}]^+$: 225.1.

[0329] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-59).

A solution of 2-(chloromethyl)-6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridine (22 mg, 0.1 mmol), N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (28 mg, 0.1 mmol), and Cs_2CO_3 (98 mg, 0.3 mmol) in dry DMF (2 mL) was stirred at RT for 2 h. Then the reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na_2SO_4 , concentrated and purified by column chromatography (DCM/MeOH = 15/1) to give the desired compound N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (17 mg, yield: 33%) as a yellow solid, ESI-MS $[\text{M}+\text{H}]^+$: 446.2; $[\text{M}/2+\text{H}]^+$: 232.7. Purity: 97.80%. ^1H NMR (400 MHz, DMSO): δ 8.57 (t, J = 5.7 Hz, 1H), 8.30-8.28 (m, 2H), 8.21 (s, 1H), 7.85 (d, J = 3.3 Hz, 2H), 7.76-7.76 (m, 1H), 7.33 (d, J = 9.3 Hz, 1H), 7.04-7.00 (m, 1H), 6.63 (dd, J = 7.5, 2.1 Hz, 1H), 5.41 (s, 2H), 4.54 (d, J = 5.8 Hz, 2H), 2.04-2.00 (m, 1H), 0.97-0.94 (m, 2H), 0.76-0.72 (m, 2H).

Example 60

Scheme 60

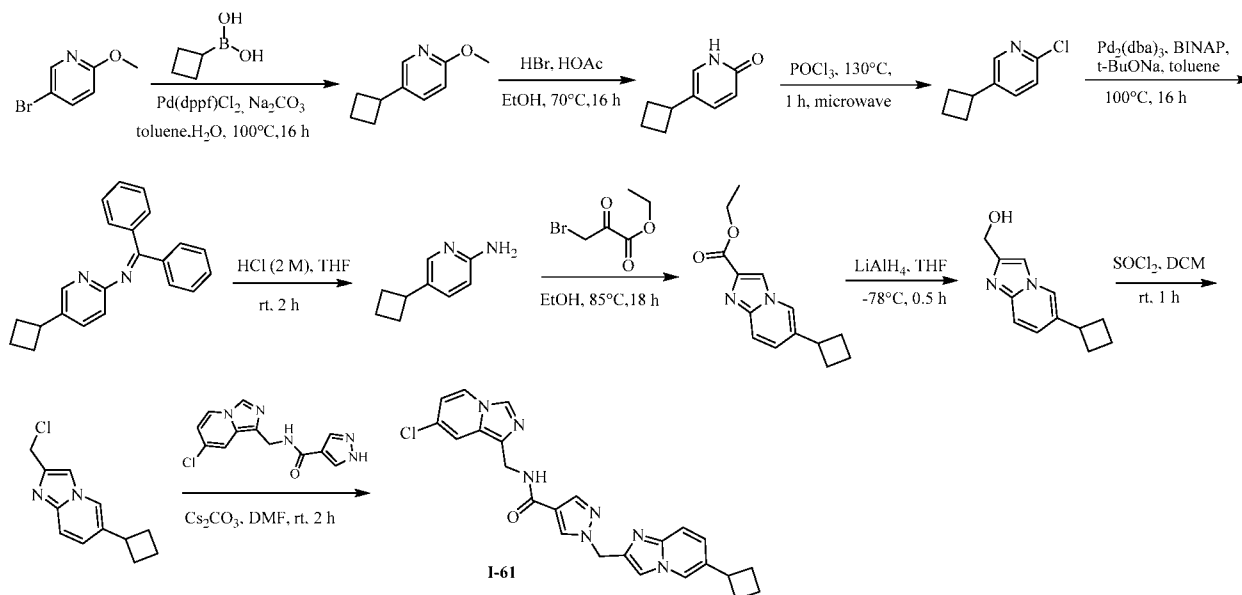


[0330] Synthesis of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-60).

A solution of 2-(chloromethyl)-6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridine (22 mg, 0.1 mmol), N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (32 mg, 0.1 mmol), and Cs_2CO_3 (98 mg, 0.3 mmol) in dry DMF (2 mL) was stirred at RT for 2 h. Then the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na_2SO_4 , concentrated and purified by column chromatography (DCM/MeOH = 15/1) to give the desired compound N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (11 mg, yield: 22%) as a yellow solid. ESI-MS $[\text{M}+\text{H}]^+$: 508.1; $[\text{M}/2+\text{H}]^+$: 254.7. Purity: 91.63%. ^1H NMR (400 MHz, DMSO): δ 8.58 (t, J = 5.7 Hz, 1H), 8.31 (s, 1H), 8.25-8.22 (m, 2H), 7.95 (s, 1H), 7.86 (d, J = 3.8 Hz, 2H), 7.34 (d, J = 9.3 Hz, 1H), 7.03 (t, J = 8.8 Hz, 1H), 6.72 (dd, J = 7.4, 1.9 Hz, 1H), 5.43 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 2.05-2.01 (m, 1H), 0.98-0.95 (m, 2H), 0.82-0.65 (m, 2H).

Example 61

Scheme 61



[0331] Synthesis of 5-cyclobutyl-2-methoxypyridine. A mixture of 5-bromo-2-methoxypyridine (4.0 g, 21.27 mmol), cyclobutylboronic acid (2.34 g, 23.40 mmol), Pd(dppf)Cl₂ (1.55 g, 2.13 mmol) and Na₂CO₃ (2.93 g, 27.65 mmol) in toluene (100 mL) and H₂O (20 mL) was stirred at 100 °C for 16 h. The reaction mixture was concentrated, diluted with EtOAc (100 mL) and filtered. The filtrate was washed with H₂O (100 mL x 1) and brine (100 mL x 1), dried over Na₂SO₄, concentrated and purified by silica gel chromatography (EA/PE = 1/60) to give 5-cyclobutyl-2-methoxypyridine (1.5 g, yield: 43%) as yellow oil. ESI-MS [M+H]⁺: 164.2.

[0332] Synthesis of 5-cyclobutylpyridin-2(1H)-one. A mixture of 5-cyclobutyl-2-methoxypyridine (1.5 g, 9.19 mmol) and HBr (15 mL, 40% (v/v) in H₂O) in EtOH (6 mL) was stirred for at 80 °C for 48 h. The reaction mixture was cooled to RT, concentrated, neutralized with NaHCO₃ aqueous to adjust the pH to 7 and extracted with DCM/MeOH (60 mL x 3, 10/1 (v/v)). The combined organics was washed with brine (150 mL x 1), dried over Na₂SO₄, concentrated and purified by silica gel chromatography (EA) to give 5-cyclobutylpyridin-2(1H)-one (260 mg, yield: 19%) as a yellow syrup. ESI-MS [M+H]⁺: 150.2.

[0333] Synthesis of 2-chloro-5-cyclobutylpyridine. A solution of 5-cyclobutylpyridin-2(1H)-one (260 mg, 1.74 mmol) in POCl₃ (3 mL) was stirred at 130 °C for 1 h under microwave. The reaction mixture was concentrated and the residue was dissolved in EtOAc (100 mL),

washed with NaHCO_3 aqueous (50 mL x 1) and brine (50 mL x 1), dried over Na_2SO_4 , concentrated and then purified by silica gel chromatography (EA/PE = 1/50) to give 2-chloro-5-cyclobutylpyridine (250 mg, yield: 86%) as yellow oil. ESI-MS $[\text{M}+\text{H}]^+$: 168.1.

[0334] Synthesis of N-(5-cyclobutylpyridin-2-yl)-1,1-diphenylmethanimine. A mixture of 2-chloro-5-cyclobutylpyridine (220 mg, 1.31 mmol), diphenylmethanimine (357 mg, 1.97 mmol), $\text{Pd}_2(\text{dba})_3$ (120 mg, 0.131 mmol), BINAP (163 mg, 0.262 mmol) and t-BuONa (315 mg, 3.28 mmol) in toluene (8 mL) was stirred at 100 °C for 16 h. The reaction mixture was then diluted in EtOAc (100 mL) and filtered. The filtrate was washed with H_2O (50 mL x 1), dried over Na_2SO_4 , concentrated and purified by silica gel chromatography (EA/PE = 1/8) to give N-(5-cyclobutylpyridin-2-yl)-1,1-diphenylmethanimine (130 mg, yield: 32%) as a yellow solid. ESI-MS $[\text{M}+\text{H}]^+$: 313.2.

[0335] Synthesis of 5-cyclobutylpyridin-2-amine. A mixture of N-(5-cyclobutylpyridin-2-yl)-1,1-diphenylmethanimine (130 mg, 0.41 mmol) and HCl (2 mL, 2 M) in THF (4 mL) was stirred at RT for 2 h. The reaction mixture was concentrated. Water (20 mL) was added and the pH of the mixture was adjusted to 9 by adding saturated aqueous NaHCO_3 solution. This resulting mixture was extracted with DCM/MeOH (50 mL x 3, 10/1 (v/v)). The combined organics was washed with brine (100 mL x 1), dried over Na_2SO_4 , concentrated and purified by prep-TLC (EA) to give 5-cyclobutylpyridin-2-amine (35 mg, yield: 57%) as a yellow syrup. ESI-MS $[\text{M}+\text{H}]^+$: 149.2.

[0336] Synthesis of ethyl 6-cyclobutylimidazo[1,2-a]pyridine-2-carboxylate. The mixture of 5-cyclobutylpyridin-2-amine (28 mg, 0.19 mmol) and ethyl 3-bromo-2-oxopropanoate (41 mg, 0.20 mmol) in EtOH (5 mL) was heated to reflux and stirred for 18 h. The reaction mixture was concentrated and the residue was dissolved in EtOAc (20 mL), washed with NaHCO_3 aqueous (20 mL x 1) and brine (20 mL x 1), dried over Na_2SO_4 , concentrated and purified by silica gel chromatography (EA) to give ethyl 6-cyclobutylimidazo[1,2-a]pyridine-2-carboxylate (15 mg, yield: 33%) as a yellow solid. ESI-MS $[\text{M}+\text{H}]^+$: 245.2.

[0337] Synthesis of (6-cyclobutylimidazo[1,2-a]pyridin-2-yl)methanol. To a stirred solution of LiAlH_4 (19 mg, 0.49 mmol) in THF (2 mL) was added dropwise the solution of 6-cyclobutylimidazo[1,2-a]pyridine-2-carboxylate (15 mg, 0.061 mmol) in THF (1 mL) at -78 °C. The mixture was stirred at -78 °C for 30 min. The reaction mixture was then quenched with

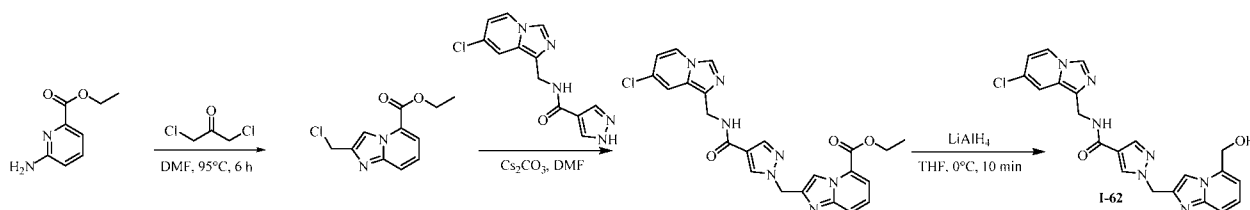
Na₂SO₄·10 H₂O and filtered. The filtrate was washed with THF (10 mL) and concentrated to give (6-cyclobutylimidazo[1,2-a]pyridin-2-yl)methanol (8 mg, yield: 64%) as a yellow solid which was used in the next step without purification. ESI-MS [M+H]⁺: 203.2.

[0338] Synthesis of 2-(chloromethyl)-6-cyclobutylimidazo[1,2-a]pyridine. To a stirred solution of (6-cyclobutylimidazo[1,2-a]pyridin-2-yl)methanol (8 mg, 0.039 mmol) in DCM (1 mL) was added SOCl₂ (47 mg, 0.39 mmol) in DCM (0.5 mL). The mixture was stirred at RT for 1 h. The reaction mixture was concentrated to give 2-(chloromethyl)-6-cyclobutylimidazo[1,2-a]pyridine (10 mg, yield: 100%) as a yellow solid. ESI-MS [M+H]⁺: 221.1.

[0339] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclobutylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-61). The mixture of 2-(chloromethyl)-6-cyclobutylimidazo[1,2-a]pyridine (10 mg, 0.045 mmol), N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (12 mg, 0.045 mmol) and Cs₂CO₃ (30 mg, 0.09 mmol) in DMF (2 mL) was stirred at RT for 2 h. Water (10 mL) was added and the mixture was extracted with EtOAc/THF (15 mL x 3, 5/1 (v/v)). The combined organic layers were washed with brine (40 mL x 3), dried over Na₂SO₄, concentrated and purified by prep-TLC (DCM/MeOH = 10/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclobutylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (8 mg, yield: 38%) as a white solid. ESI-MS [M+H]⁺: 460.2. Purity: 95.58%. ¹H NMR (400 MHz, DMSO): δ 8.57 (t, J = 5.7 Hz, 1H), 8.34 (s, 1H), 8.30 (m, 2H), 8.20 (s, 1H), 7.86 (s, 1H), 7.77 (m, 2H), 7.44 (d, J = 9.3 Hz, 1H), 7.18 (dd, J = 9.3, 1.7 Hz, 1H), 6.64 (dd, J = 7.4, 2.1 Hz, 1H), 5.39 (s, 2H), 4.55 (d, J = 5.8 Hz, 2H), 3.50 (m, 1H), 2.28 (m, 2H), 2.04 (m, 3H), 1.83 (m, 1H).

Example 62

Scheme 62



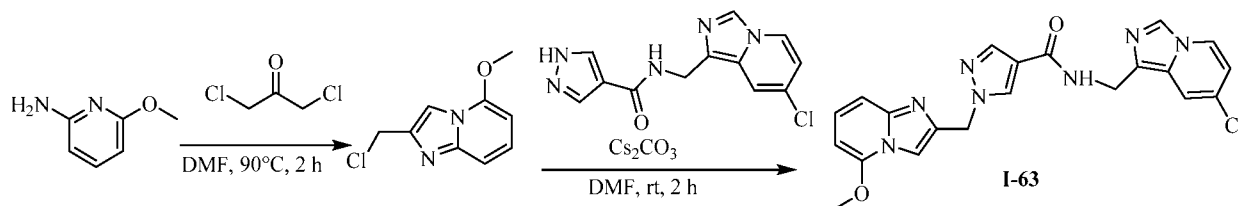
[0340] Synthesis of ethyl 2-(chloromethyl)imidazo[1,2-a]pyridine-5-carboxylate. A mixture of ethyl 6-aminopicolinate (166 mg, 1.0 mmol) and 1, 3-dichloropropan-2-one (630 mg, 5.0 mmol) in dry DMF (10 mL) was stirred at 95 °C for 6 h. Water (100 mL) was added and the mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated and purified by silica gel chromatography (EA/PE = 1/1) to give ethyl 2-(chloromethyl)imidazo[1,2-a]pyridine-5-carboxylate (70 mg, yield: 29%) as a yellow oil. ESI-MS $[M+H]^+$: 239.1.

[0341] Synthesis of ethyl 2-((4-((7-chloroimidazo[1,5-a]pyridin-1-yl)methylcarbamoyl)-1H-pyrazol-1-yl)methyl)imidazo[1,2-a]pyridine-5-carboxylate. A mixture of ethyl 2-(chloromethyl)imidazo[1,2-a]pyridine-5-carboxylate (70 mg, 0.29 mmol), N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (80 mg, 0.29 mmol) and Cs_2CO_3 (270 mg, 0.87 mmol) in DMF (5 mL) was stirred at RT for 4 h. Water (30 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated and purified by prep-TLC (DCM/MeOH = 10/1) to give ethyl 2-((4-((7-chloroimidazo[1,5-a]pyridin-1-yl)methylcarbamoyl)-1H-pyrazol-1-yl)methyl)imidazo[1,2-a]pyridine-5-carboxylate (90 mg, yield: 65%) as a yellow solid. ESI-MS $[M+H]^+$: 478.1.

[0342] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-62). To a solution of ethyl 2-((4-((7-chloroimidazo[1,5-a]pyridin-1-yl)methylcarbamoyl)-1H-pyrazol-1-yl)methyl)imidazo[1,2-a]pyridine-5-carboxylate (30 mg, 0.06 mmol) in dry THF (5 mL) was added LiAlH_4 (7 mg, 0.18 mmol) at 0 °C and the mixture was stirred at 0 °C for 10 min. Water (10 mL) was added to quench the reaction and extracted with EtOAc (30 mL x 3). The combined organic layers were concentrated and purified by prep-TLC (DCM/MeOH = 10/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (16.5 mg, yield: 63.5%) as a light yellow solid. ESI-MS $[M+H]^+$: 436.1. Purity: 95.3%. ^1H NMR (400 MHz, DMSO): δ 8.59 (s, 1H), 8.30 (d, J = 6.7 Hz, 2H), 8.23 (s, 1H), 7.84 (d, J = 9.7 Hz, 2H), 7.78 (s, 1H), 7.47 (d, J = 9.1 Hz, 1H), 7.33-7.20 (m, 1H), 6.91 (d, J = 6.6 Hz, 1H), 6.64 (dd, J = 7.5, 2.1 Hz, 1H), 5.67 (t, J = 5.7 Hz, 1H), 5.44 (s, 2H), 4.71 (d, J = 5.5 Hz, 2H), 4.55 (d, J = 5.8 Hz, 2H).

Example 63

Scheme 63

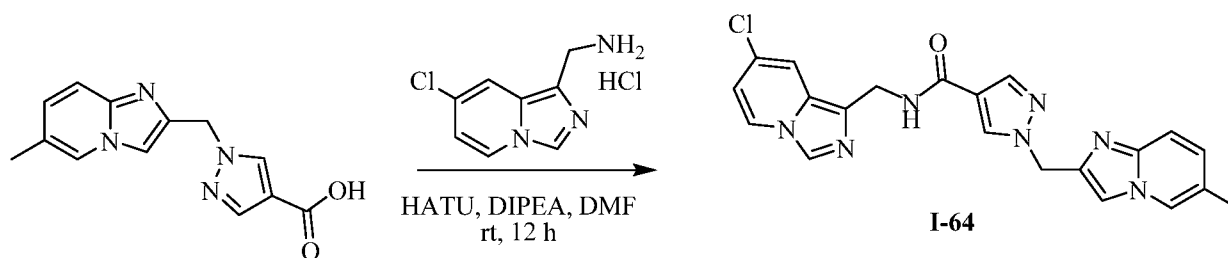


[0343] Synthesis of 2-(chloromethyl)-5-methoxyimidazo[1,2-a]pyridine. A solution of 6-methoxypyridin-2-amine (500 mg, 4.1 mmol) and 1,3-dichloropropan-2-one (2.58 g, 20.5 mmol) in DMF (10 mL) was stirred at 90 °C for 2 h. Then the reaction mixture was diluted with H₂O (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over Na₂SO₄, concentrated and purified by column chromatography (CH₂Cl₂/MeOH = 3/1) to give the desired product 2-(chloromethyl)-5-methoxyimidazo[1,2-a]pyridine (200 mg, yield: 25%) as brown oil. ESI-MS [M+H]⁺: 197.1.

[0344] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-methoxyimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-63). A solution of 2-(chloromethyl)-5-methoxyimidazo[1,2-a]pyridine (36 mg, 0.18 mmol), N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (50 mg, 0.18 mmol) and Cs₂CO₃ (235 mg, 0.72 mmol) in DMF (3 mL) was stirred at RT for 2 h. Water (30 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were dried over Na₂SO₄, concentrated and purified by column chromatography (CH₂Cl₂/MeOH = 10/1) to give the desired compound N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-methoxyimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (20 mg, yield: 28%) as a white solid. ESI-MS [M+H]⁺: 436.1. Purity: 96.0%. ¹H NMR (400 MHz, DMSO): δ 8.58 (t, J = 5.7 Hz, 1H), 8.32-8.27 (m, 2H), 8.22 (s, 1H), 7.85 (s, 1H), 7.78 (s, 1H), 7.66 (s, 1H), 7.33-7.27 (m, 1H), 7.14 (d, J = 9.0 Hz, 1H), 6.66-6.62 (m, 1H), 6.35 (d, J = 7.4 Hz, 1H), 5.41 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 4.07 (s, 3H).

Example 64

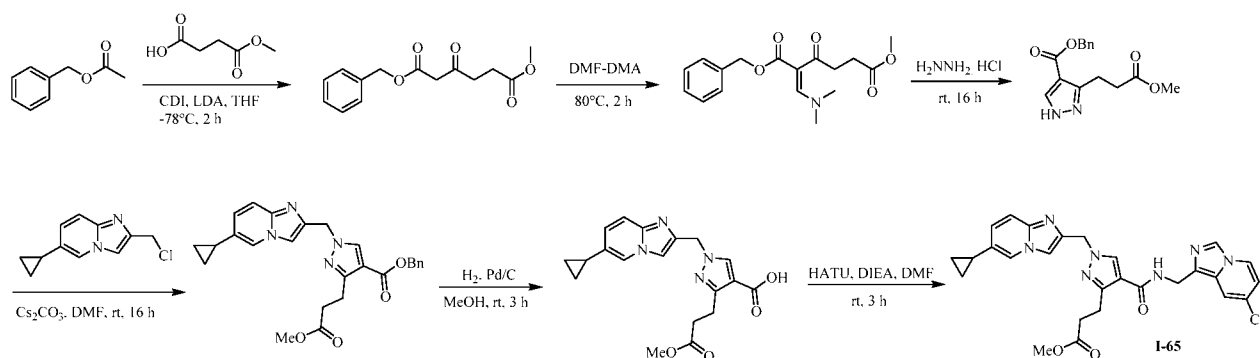
Scheme 64



[0345] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-64). To a solution of 1-((6-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (128 mg, 0.5 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (141 mg, 0.65 mmol) and HATU (285 mg, 0.75 mmol) in DMF (10 mL) was added DIPEA (323 mg, 2.5 mmol). The resulting reaction was stirred at RT for 12 h. H₂O (25 mL) was added to the reaction and extracted with EtOAc (25 mL x 4). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give the N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-methylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (55 mg, yield: 26%) as a white solid. ESI-MS [M+H]⁺: 420.1. Purity: 96.6%. ¹H NMR (400 MHz, DMSO): δ 8.59 (s, 1H), 8.35-8.30 (m, 4H), 8.22 (s, 1H), 7.89 (s, 1H), 7.78-7.76 (m, 2H), 7.41 (d, J = 9.0 Hz, 1H), 7.11 (d, J = 9.0 Hz, 1H), 6.65 (d, J = 6.8 Hz, 1H), 5.39 (s, 2H), 4.55 (d, J = 5.2 Hz, 2H), 2.25 (s, 3H).

Example 65

Scheme 65



[0346] Synthesis of 1-benzyl 6-methyl 3-oxohexanedioate. To a solution of benzyl acetate (1.5 g, 10 mmol) in THF (10 mL) was added LDA (1 M, 15 mmol) at -78 °C and stirred for 1 h (solution A). To a solution of 4-methoxy-4-oxobutanoic acid (1.58 g, 12 mmol) in THF (10 mL) was added CDI (1.94 g, 12 mmol) and stirred at RT for 30 min (solution B). Solution B was added to solution A at -78 °C and stirred for another 2 h. Saturated NH_4Cl (100 mL) was added to quench the reaction and the reaction mixture was extracted with EtOAc (100 mL x 3). The combined organics were concentrated and purified by silica gel chromatography (EA/PE = 1/10) to give 1-benzyl 6-methyl 3-oxohexanedioate (500 mg, yield: 19%) as a colorless oil. ESI-MS $[\text{M}+\text{H}]^+$: 265.1.

[0347] Synthesis of 1-benzyl 6-methyl (E)-2-((dimethylamino)methylene)-3-oxohexanedioate. A solution of 1-benzyl 6-methyl 3-oxohexanedioate (490 mg, 1.86 mmol) in DMFDMA (443 mg, 3.72 mmol) was heated to 80 °C for 2 h. The resulting mixture was concentrated to give 1-benzyl 6-methyl (E)-2-((dimethylamino)methylene)-3-oxohexanedioate (600 mg, crude) as a yellow oil which was used in the next step without purification. ESI-MS $[\text{M}+\text{H}]^+$: 320.1.

[0348] Synthesis of benzyl 3-(3-methoxy-3-oxopropyl)-1H-pyrazole-4-carboxylate. To a solution of 1-benzyl 6-methyl (E)-2-((dimethylamino)methylene)-3-oxohexanedioate (600 mg, 1.86 mmol) in MeOH (6 mL) was added hydrazine hydrochloride (255 mg, 3.72 mmol). The mixture was stirred at RT for 16 h. The reaction was concentrated to give the crude, which was purified by silica gel chromatography (EA/PE = 1/1) to give benzyl 3-(3-methoxy-3-oxopropyl)-

1H-pyrazole-4-carboxylate (384 mg, yield: 64% for two steps) as a yellow oil. ESI-MS $[M+H]^+$: 289.1.

[0349] Synthesis of benzyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(3-methoxy-3-oxopropyl)-1H-pyrazole-4-carboxylate. To a solution of benzyl 3-(3-methoxy-3-oxopropyl)-1H-pyrazole-4-carboxylate (90 mg, 0.31 mmol) and 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (78 mg, 0.38 mmol) in DMF (5 mL) was added CsCO_3 (302 mg, 0.93 mmol) at RT. The mixture was stirred at RT for 16 h. The reaction was diluted with H_2O (30 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over sodium sulfate and concentrated. The residue was purified by prep-TLC (MeOH/DCM = 1/15) to give benzyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(3-methoxy-3-oxopropyl)-1H-pyrazole-4-carboxylate (70 mg, yield: 50%) as a yellow oil. ESI-MS $[M+H]^+$: 459.1.

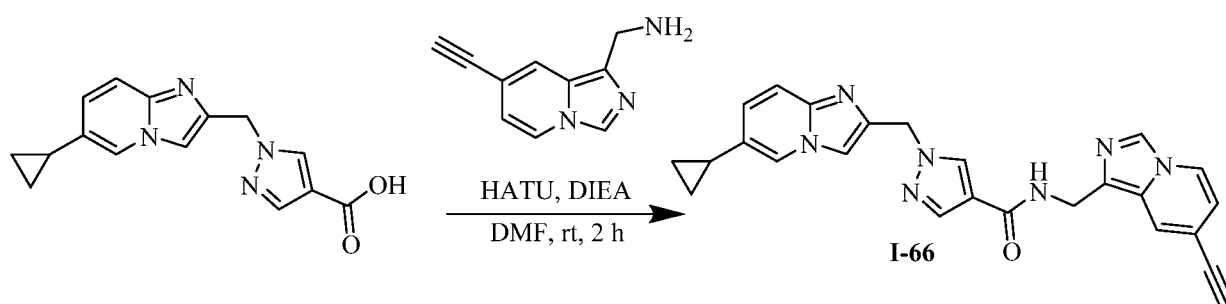
[0350] Synthesis of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(3-methoxy-3-oxopropyl)-1H-pyrazole-4-carboxylic acid. To a solution of benzyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(3-methoxy-3-oxopropyl)-1H-pyrazole-4-carboxylate (100 mg, 0.22 mmol) in MeOH (10 mL) was added Pd/C (10%, 30 mg). The mixture was stirred at RT for 3 h under H_2 . The mixture was filtered and concentrated to give 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(3-methoxy-3-oxopropyl)-1H-pyrazole-4-carboxylic acid (67 mg, 83%) as a white solid. ESI-MS $[M+H]^+$: 369.1.

[0351] Synthesis of methyl 3-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-3-yl)propanoate (I-65). To a solution of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(3-methoxy-3-oxopropyl)-1H-pyrazole-4-carboxylic acid (80 mg, 0.22 mmol) and (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (56 mg, 0.26 mmol) in dry DMF (4 mL) was added HATU (125 mg, 0.33 mmol) and DIPEA (114 mg, 0.88 mmol) at RT. The reaction was stirred at RT for 3 h. Water (20 mL) was added and the mixture was extracted with EtOAc (30 mL x 3). The organic layers were washed with brine (50 mL), dried over sodium sulfate, and concentrated. The crude residue was purified by prep-TLC (DCM/MeOH = 10/1) to give methyl 3-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-3-yl)propanoate (70 mg, yield: 61%)

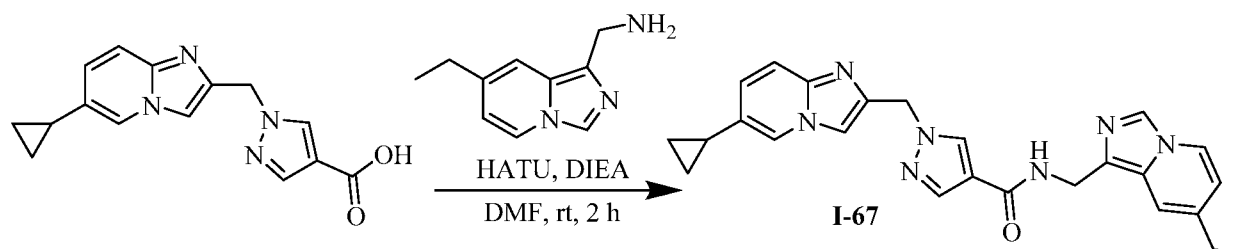
as a yellow solid. ESI-MS $[M+H]^+$: 532.2. Purity: 95.2%. ^1H NMR (400 MHz, DMSO): δ 8.53 (t, $J = 5.7$ Hz, 0.3H), 8.43-8.38 (m, 0.7H), 8.36-8.27 (m, 3H), 8.15 (s, 0.7H), 7.92 (s, 0.3H), 7.84-7.67 (m, 1.75H), 7.58 (s, 0.3H), 7.40-7.35 (m, 1H), 7.03-6.93 (m, 1H), 6.66-6.63 (m, 1H), 5.42 (s, 0.6H), 5.28 (s, 1.4H), 4.64-4.47 (m, 2H), 3.57-3.56 (m, 3H), 3.29-3.19 (m, 0.6H), 3.17-2.99 (m, 1.4H), 2.74-2.55 (m, 2H), 1.97-1.84 (m, 1H), 0.94-0.89 (m, 2H), 0.68-0.64 (m, 2H).

Example 66

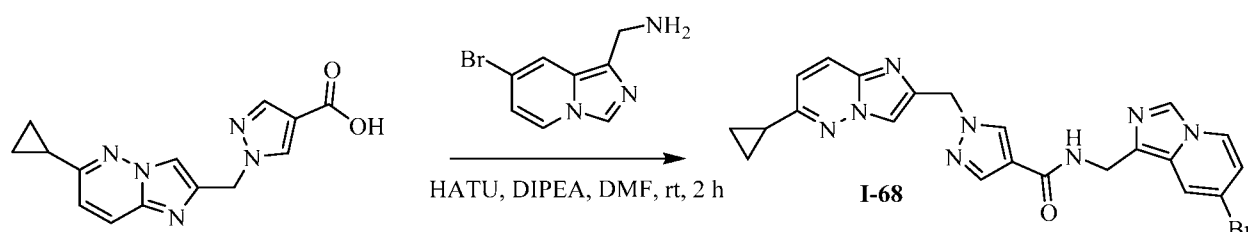
Scheme 66



[0352] Synthesis of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-ethynylimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-66). A solution of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (68 mg, 0.24 mmol), (7-ethynylimidazo[1,5-a]pyridin-1-yl)methanamine (50 mg, 0.24 mmol), HATU (183 mg, 0.48 mmol) and DIPEA (93 mg, 0.72 mmol) in DMF (3 mL) was stirred at RT for 2 h. Then the reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were dried over Na_2SO_4 , concentrated and purified by column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 10/1$) to give the desired compound 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-ethynylimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (40 mg, yield: 38%) as a white solid. ESI-MS $[M+H]^+$: 436.2. Purity: 100%. ^1H NMR (400 MHz, DMSO): δ 8.59 (t, $J = 5.7$ Hz, 1H), 8.34-8.31 (m, 2H), 8.26-8.22 (m, 1H), 8.20 (s, 1H), 7.88 (s, 1H), 7.86 (s, 1H), 7.71 (s, 1H), 7.39 (d, $J = 9.4$ Hz, 1H), 7.01-6.97 (m, 1H), 6.59-6.55 (m, 1H), 5.38 (s, 2H), 4.58 (d, $J = 5.8$ Hz, 2H), 4.26 (s, 1H), 1.95-1.88 (m, 1H), 0.93-0.88 (m, 2H), 0.68-0.64 (m, 2H).

Example 67Scheme 67

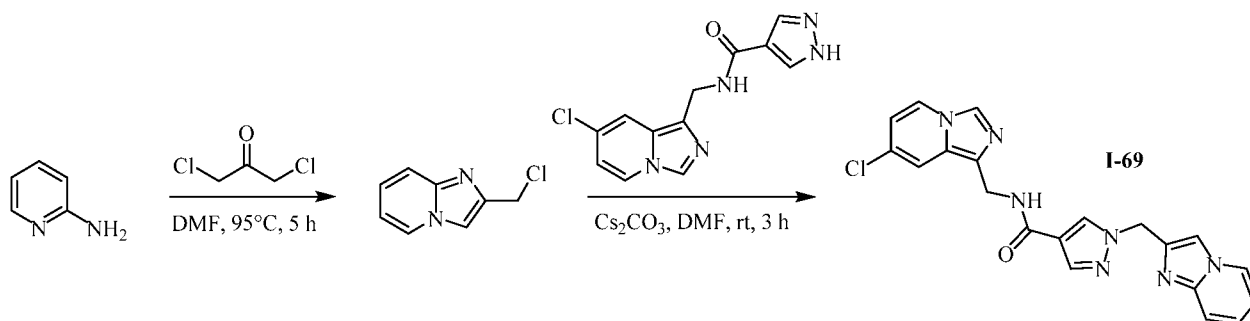
[0353] Synthesis of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-ethylimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-67). A solution of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (64 mg, 0.23 mmol), (7-ethylimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (49 mg, 0.23 mmol), HATU (175 mg, 0.46 mmol) and DIPEA (90 mg, 0.69 mmol) in DMF (3 mL) was stirred at RT for 2 h. Then the reaction mixture was diluted with H₂O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na₂SO₄, concentrated and purified by column chromatography (CH₂Cl₂/MeOH = 10/1) to give the desired compound 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-ethylimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (50 mg, yield: 49%) as a white solid. ESI-MS [M+H]⁺: 440.2. Purity: 97%. ¹H NMR (400 MHz, DMSO): δ 8.47 (t, J = 5.5 Hz, 1H), 8.32 (s, 1H), 8.22-8.16 (m, 3H), 7.86 (s, 1H), 7.71 (s, 1H), 7.42-7.32 (m, 2H), 7.01-6.96 (m, 1H), 6.52-6.48 (m, 1H), 5.38 (s, 2H), 4.56 (d, J = 5.6 Hz, 2H), 3.33-3.29 (m, 2H), 1.94-1.88 (m, 1H), 1.14 (t, J = 7.5 Hz, 3H), 0.93-0.88 (m, 2H), 0.69-0.63 (m, 2H).

Example 68Scheme 68

[0354] Synthesis of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-68). A solution of 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (48 mg, 0.17 mmol), (7-bromoimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (45 mg, 0.17 mmol), HATU (134 mg, 0.35 mmol) and DIPEA (65 mg, 0.53 mmol) in DMF (3 mL) was stirred at RT for 2 h. Then the reaction mixture was diluted with H₂O (30 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were dried over Na₂SO₄, concentrated and purified by column chromatography (CH₂Cl₂/MeOH = 8/1) to give the desired compound N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxamide (20 mg, yield: 24%) as a white solid. ESI-MS [M+H]⁺: 491.1. Purity: 93%. ¹H NMR (400 MHz, DMSO): δ 8.56 (t, J = 5.7 Hz, 1H), 8.31 (s, 1H), 8.26-8.19 (m, 2H), 8.08 (s, 1H), 7.96-7.90 (m, 2H), 7.85 (s, 1H), 7.09 (d, J = 9.5 Hz, 1H), 6.74-6.69 (m, 1H), 5.41 (s, 2H), 4.54 (d, J = 5.7 Hz, 2H), 2.20-2.14 (m, 1H), 1.09-1.03 (m, 2H), 0.99-0.93 (m, 2H).

Example 69

Scheme 69

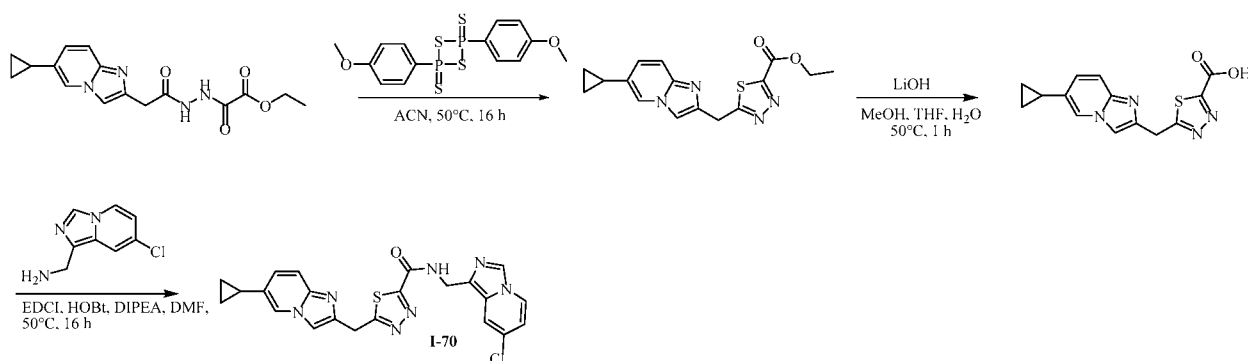


[0355] Synthesis of 2-(chloromethyl)imidazo[1,2-a]pyridine. A mixture of pyridin-2-amine (600 mg, 6.4 mmol) and 1, 3-dichloropropan-2-one (4.0 g, 32.0 mmol) in dry DMF (10 mL) was stirred at 95 °C for 6 h. Water (100 mL) was added and the mixture was extracted with EtOAc (80 mL x 3). The combined organic layers were concentrated and purified by silica gel chromatography (EA/PE = 1/1) to give 2-(chloromethyl)imidazo[1,2-a]pyridine (80 mg, yield: 7.5%) as a yellow oil. ESI-MS [M+H]⁺: 167.1.

[0356] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-(imidazo[1,2-a]pyridin-2-ylmethyl)-1H-pyrazole-4-carboxamide (I-69). A mixture of 2-(chloromethyl)imidazo[1,2-a]pyridine (80 mg, 0.48 mmol), N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (130 mg, 0.48 mmol) and Cs₂CO₃ (469 mg, 1.44 mmol) in DMF (5 mL) was stirred at RT for 3 h. Water (50 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layer were concentrated and purified by prep-TLC (DCM/MeOH = 10/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-(imidazo[1,2-a]pyridin-2-ylmethyl)-1H-pyrazole-4-carboxamide (27 mg, yield: 14%) as a white solid. ESI-MS [M+H]⁺: 406.2. Purity: 99.6%. ¹H NMR (400 MHz, DMSO): δ 8.59 (t, J = 5.7 Hz, 1H), 8.51 (d, J = 6.8 Hz, 1H), 8.30 (d, J = 7.1 Hz, 2H), 8.23 (s, 1H), 7.85 (d, J = 14.5 Hz, 2H), 7.78 (s, 1H), 7.49 (d, J = 9.1 Hz, 1H), 7.27-7.18 (m, 1H), 6.87 (t, J = 6.7 Hz, 1H), 6.65 (dd, J = 7.4, 2.0 Hz, 1H), 5.42 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H).

Example 70

Scheme 70



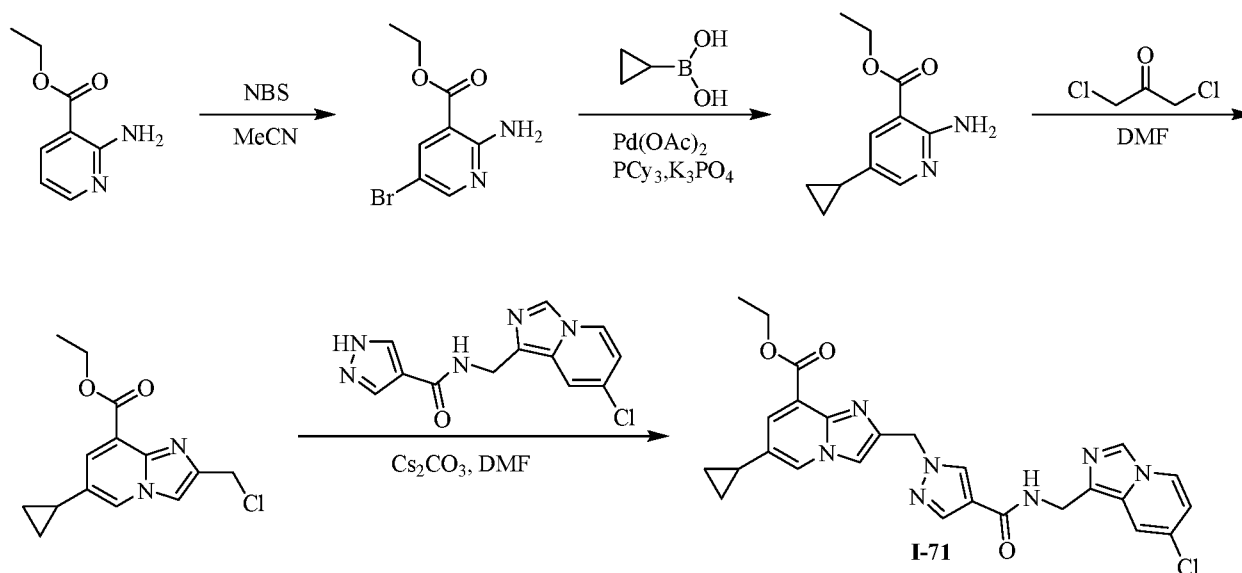
[0357] Synthesis of ethyl 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-thiadiazole-2-carboxylate. A mixture of ethyl 2-(2-(2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetyl)hydrazinyl)-2-oxoacetate (330 mg, 1.0 mmol) and Lawesson's Reagent (600 mg, 1.5 mmol) in CH₃CN (20 mL) was stirred at 50 °C for 16 h under N₂. The mixture was concentrated and purified by silica gel chromatography (DCM/MeOH = 10/1) to give ethyl 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-thiadiazole-2-carboxylate (280 mg, yield: 85.4%) as a yellow oil. ESI-MS [M+H]⁺: 329.1

[0358] Synthesis of lithium 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-thiadiazole-2-carboxylate. A solution of ethyl 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-thiadiazole-2-carboxylate (280 mg, 0.85 mmol) and LiOH·H₂O (70 mg, 1.70 mmol) in THF/MeOH/H₂O (2 mL/2 mL/2 mL) was stirred at 50 °C for 2 h. The mixture was concentrated to give lithium 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-thiadiazole-2-carboxylate (320 mg, crude) as a yellow solid. ESI-MS [M+H]⁺: 301.1.

[0359] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-thiadiazole-2-carboxamide (I-70). A mixture of 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-thiadiazole-2-carboxylic acid (100 mg, crude), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (72 mg, 0.33 mmol), EDCI (130 mg, 0.66 mmol), HOBT (90 mg, 0.66 mmol) and DIPEA (0.2 mL, 0.99 mmol) in DMF (4 mL) was stirred at 50 °C for 16 h. Water (30 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated and purified by prep-HPLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-thiadiazole-2-carboxamide (12.1 mg, yield: 7.9%) as a light yellow solid. ESI-MS [M+H]⁺: 464.1. Purity: 95.4%. ¹H NMR (400 MHz, DMSO): δ 9.62 (t, J = 5.9 Hz, 1H), 8.40 (s, 1H), 8.35-8.26 (m, 2H), 7.91-7.80 (m, 2H), 7.49 (d, J = 9.3 Hz, 1H), 7.13 (d, J = 9.4 Hz, 1H), 6.67 (dd, J = 7.5, 2.1 Hz, 1H), 4.74-4.48 (m, 4H), 1.99-1.93 (m, 1H), 1.00-0.88 (m, 2H), 0.71-0.69 (m, 2H).

Example 71

Scheme 71

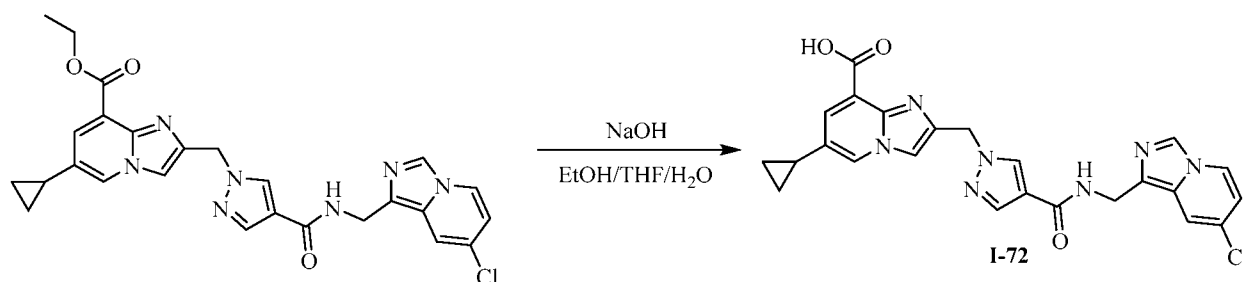


[0360] Synthesis of ethyl 2-amino-5-bromonicotinate. To a solution of ethyl 2-aminonicotinate (500 mg, 3.00 mmol) in dry MeCN (20 mL) was added NBS (643 mg, 3.6 mmol) slowly at RT. The resulting mixture was stirred at RT for 1 h. The reaction was then quenched with H₂O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give the crude product of ethyl 2-amino-5-bromonicotinate (700 mg, yield: 95.2%) as a white solid, which was used in the next step without purification. ESI-MS [M+H]⁺: 245.0.

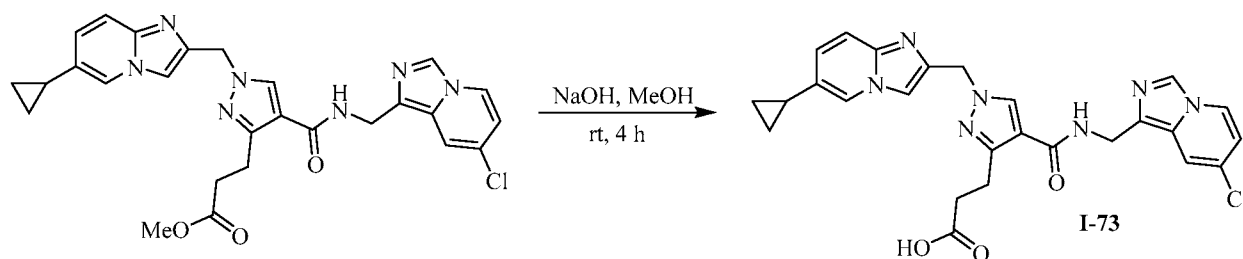
[0361] Synthesis of ethyl 2-amino-5-cyclopropylnicotinate. A mixture ethyl 2-amino-5-bromonicotinate (700 mg, 2.85 mmol), cyclopropylboronic acid (728 mg, 8.5 mmol), Pd(OAc)₂ (140 mg, 0.05 mmol), K₃PO₄ (3 g, 14.2 mmol) and PCy₃ (0.3 g, 1.14 mmol) in dioxane/H₂O (50 mL/5 mL) was stirred at 95 °C for 12 h in N₂. The resulting mixture was quenched with H₂O (40 mL), extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried with Na₂SO₄ and concentrated in vacuo to give the crude, which was purified with silica gel chromatography with PE/EA (1/1) to give ethyl 2-amino-5-cyclopropylnicotinate (500 mg, 86% yield) as a white solid. ESI-MS [M+H]⁺: 207.1. Purity: 95%.

[0362] Synthesis of ethyl 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carboxylate. To a solution of ethyl 2-amino-5-cyclopropylnicotinate (500 mg, 1.94 mmol) in DMF (10 mL) was added 1,3-dichloropropan-2-one (986 mg, 77.7 mmol) at 95 °C for 3 h. Water (50 mL) was added and the pH of the reaction was adjusted to 8 with NaHCO₃ and then extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified with silica gel chromatography (EtOAc/PE = 1/2) to give ethyl 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carboxylate (550 mg, yield: 65.3%) as a white solid. ESI-MS [M+H]⁺: 278.7. Purity: 90%.

[0363] Synthesis of ethyl 2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carboxylate (I-71). A mixture of ethyl 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carboxylate (173 mg, 0.6 mmol) in DMF (3 mL) was added N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (138 mg, 0.5 mmol) and Cs₂CO₃ (406 mg, 1.25 mmol). The resulting mixture was stirred at RT for 3 h. The reaction was quenched with H₂O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give the ethyl 2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carboxylate (10 mg, yield: 3.2%) as a white solid. ESI-MS [M+H]⁺: 518.2. Purity: 91.3%. ¹H NMR (400 MHz, DMSO): δ 8.63-8.49 (m, 2H), 8.31-8.29 (m, 2H), 8.21 (s, 1H), 7.89 (s, 1H), 7.78 (d, J = 1.9 Hz, 1H), 7.75 (s, 1H), 7.60 (d, J = 1.7 Hz, 1H), 6.64 (dd, J = 7.5, 2.1 Hz, 1H), 5.45 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 4.33 (q, J = 7.1 Hz, 2H), 2.03-1.96 (m, 1H), 1.31 (t, J = 7.1 Hz, 3H), 1.00-0.86 (m, 2H), 0.75-0.59 (m, 2H).

Example 72Scheme 72

[0364] Synthesis of 2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carboxylic acid (I-72). To a solution of ethyl 2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carboxylate (40 mg, 0.077 mmol) in EtOH/THF/H₂O (2 mL/2 mL/1 mL) was added NaOH (0.5 mL, 1 M), then the reaction was stirred at RT for 1 h. Most of the solvent was removed and the residue was diluted with H₂O (3 mL). The pH of mixture was adjusted to 4-5 by adding HCl aqueous (1 M). The resulting mixture was concentrated to give the crude, which was purified by prep-HPLC to give 2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carboxylate (9.7 mg, 26% yield) as a white solid. ESI-MS [M+H]⁺: 490.1. Purity: 97.9%. ¹H NMR (400 MHz, DMSO): δ 8.66-8.54 (m, 2H), 8.34-8.27 (m, 2H), 8.25 (s, 1H), 7.90 (s, 1H), 7.84 (s, 1H), 7.79-7.74 (m, 1H), 7.70 (d, J = 1.7 Hz, 1H), 6.64 (dd, J = 7.5, 2.1 Hz, 1H), 5.49 (s, 2H), 4.56 (d, J = 5.7 Hz, 2H), 2.08-2.00 (m, 1H), 0.99-0.94 (m, 2H), 0.74-0.70 (m, 2H).

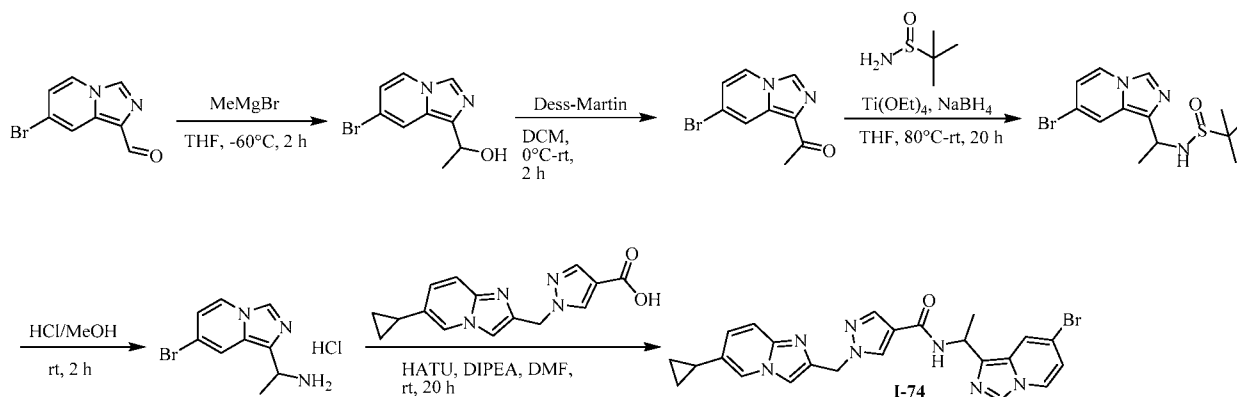
Example 73Scheme 73

[0365] Synthesis of 3-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-3-yl)propanoic acid (I-73).

To a solution of methyl 3-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-3-yl)propanoate (53 mg, 0.1 mmol) in MeOH/H₂O (2 mL/0.5 mL) was added aqueous NaOH (4 M, 0.1 mL). The reaction was stirred at RT for 4 h. The pH of mixture was adjusted to 4 by adding HCl (1 M). After concentrating the mixture, the crude product was purified by prep-HPLC to give 3-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-3-yl)propanoic acid (40 mg, yield: 77%) as a white solid. ESI-MS [M+H]⁺: 518.1. Purity: 97.7%. ¹H NMR (400 MHz, DMSO): δ 9.31 (s, 2H), 8.37-8.24 (m, 3H), 8.03 (s, 1H), 7.80 (d, J = 1.0 Hz, 1H), 7.71 (s, 1H), 7.39 (d, J = 9.3 Hz, 1H), 6.99 (dd, J = 9.4, 1.7 Hz, 1H), 6.63 (dd, J = 7.5, 2.1 Hz, 1H), 5.28 (s, 2H), 4.53 (d, J = 5.7 Hz, 2H), 2.89 (t, J = 7.3 Hz, 2H), 2.43 (t, J = 7.3 Hz, 2H), 1.95-1.88 (s, 1H), 0.96-0.85 (m, 2H), 0.68-0.64 (m, 2H).

Example 74

Scheme 74



[0366] Synthesis of 1-(7-bromoimidazo[1,5-a]pyridin-1-yl)ethan-1-ol. To a solution of 7-bromoimidazo[1,5-a]pyridine-1-carbaldehyde (550 mg, 2.46 mmol) in THF (10 mL) was added methylmagnesium bromide (4.1 mL, 12.3 mmol) at -60 °C. The mixture was stirred at -60 °C for 2 h. LCMS confirmed the starting material consumed completely. Saturated ammonium chloride solution (30 mL) was added and the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated salt H₂O and concentrated. The

residue was purified by flash column chromatography (ethyl acetate/petroleum ether from 0 to 20%) to give 1-(7-bromoimidazo[1,5-a]pyridin-1-yl)ethan-1-ol (300 mg, yield: 51%) as a brown oil. ESI-MS $[M+H]^+$: 241.0.

[0367] Synthesis of 1-(7-bromoimidazo[1,5-a]pyridin-1-yl)ethan-1-one. To the solution of 1-(7-bromoimidazo[1,5-a]pyridin-1-yl)ethan-1-ol (290 mg, 1.2 mL) in DCM (10 mL) was added Dess-Martin (1.0 g, 2.4 mmol) at 0 °C, Then the reaction mixture was warmed to RT and stirred for 2 h. Saturated sodium bicarbonate solution (40 mL) was added and the mixture was extracted with DCM (30 mL x 3). The combined organic layers were washed with saturated salt H₂O and concentrated. The residue was purified by flash column chromatography (ethyl acetate/petroleum ether from 0 to 15%) to give 1-(7-bromoimidazo[1,5-a]pyridin-1-yl)ethan-1-one (150 mg, yield: 52%) as a brown solid. ESI-MS $[M+H]^+$: 239.0.

[0368] Synthesis of N-(1-(7-bromoimidazo[1,5-a]pyridin-1-yl)ethyl)-2-methylpropane-2-sulfonamide. To the mixture of 1-(7-bromoimidazo[1,5-a]pyridin-1-yl)ethan-1-one (150 mg, 0.63 mmol) and 2-methylpropane-2-sulfonamide (92 mg, 0.76 mmol) in THF (5 mL) was added tetraethyl titanate (429 mg, 1.90 mmol). The mixture was stirred at 80 °C for 18 h and cooled to RT. Sodium borohydride (120 mg, 3.15 mmol) was added and the mixture was stirred at RT for 2 h. Saturated ammonium chloride solution (30 mL) was added and the mixture was extracted with ethyl acetate (30 mL x 3). The combined organic layers were concentrated and purified by flash column chromatography (ethyl acetate/petroleum ether from 0 to 15%) to give N-(1-(7-bromoimidazo[1,5-a]pyridin-1-yl)ethyl)-2-methylpropane-2-sulfonamide (40 mg, yield: 18.5%) as a brown oil. ESI-MS $[M+H]^+$: 344.0.

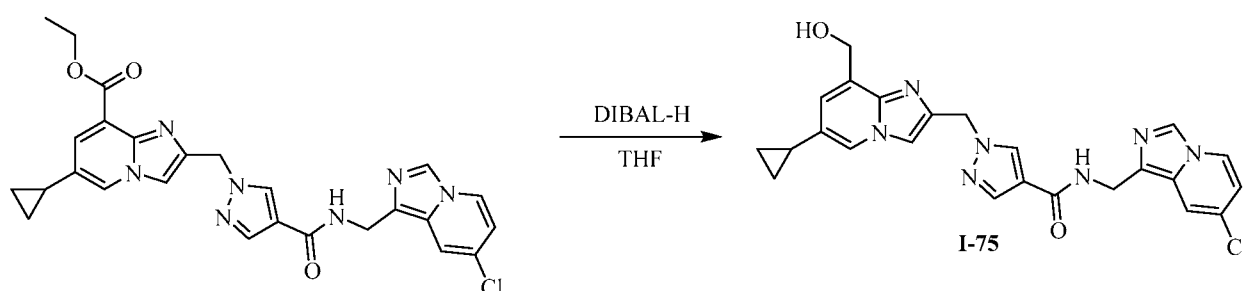
[0369] Synthesis of 1-(7-bromoimidazo[1,5-a]pyridin-1-yl)ethan-1-amine hydrochloride. A mixture of N-(1-(7-bromoimidazo[1,5-a]pyridin-1-yl)ethyl)-2-methylpropane-2-sulfonamide (40 mg, 0.12 mmol) in HCl/MeOH (5 mL, 4 M) was stirred at RT for 2 h and concentrated to give 1-(7-bromoimidazo[1,5-a]pyridin-1-yl)ethan-1-amine hydrochloride (30 mg, yield: 94%) which was used in the next step directly. ESI-MS $[M+H]^+$: 240.0

[0370] Synthesis of N-(1-(7-bromoimidazo[1,5-a]pyridin-1-yl)ethyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-74). To the solution of 1-(7-bromoimidazo[1,5-a]pyridin-1-yl)ethan-1-amine hydrochloride (30 mg, crude) and 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (20 mg,

0.042 mmol) in dry DMF (3 mL) was added HATU (24 mg, 0.63 mmol) and DIPEA (16 mg, 0.125 mmol) at RT. The reaction was stirred at RT for 18 h. Water (30 mL) was added and the mixture was extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by prep-HPLC to give N-(1-(7-bromoimidazo[1,5-a]pyridin-1-yl)ethyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (4.4 mg, yield: 21%) as a white solid. ESI-MS $[M+H]^+$: 504.1. Purity: 98.49%. ^1H NMR (400 MHz, DMSO): δ 8.41 (d, J = 8.0 Hz, 1H), 8.33 (s, 1H), 8.31 (s, 1H), 8.27-8.19 (m, 2H), 7.89-7.85 (m, 2H), 7.72 (s, 1H), 7.39 (d, J = 9.3 Hz, 1H), 7.02-6.97 (m, 1H), 6.72-6.67 (m, 1H), 5.49-5.40 (m, 1H), 5.38 (s, 2H), 1.96-1.87 m, 1H), 1.54 (d, J = 7.0 Hz, 3H), 0.94-0.88 (m, 2H), 0.69-0.63 (m, 2H).

Example 75

Scheme 75

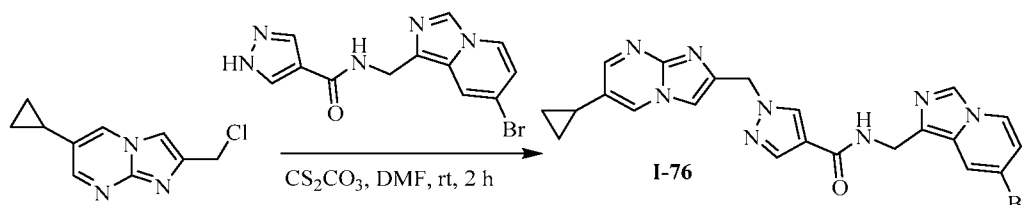


[0371] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-75). A solution of ethyl 2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carboxylate (40 mg, 0.074 mmol) in THF (3 mL) was added DIBAL-H (0.5 mL, 1 M) and the mixture was stirred at RT for 1 h. The reaction was quenched with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were concentrated to give the crude, which was purified by prep-HPLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (26.4 mg, 75% yield) as a white solid. ESI-MS $[M+H]^+$: 476.2. Purity: 100%. ^1H NMR (400 MHz, DMSO): δ 8.58 (t, J = 5.6 Hz, 1H), 8.31-8.29 (m, 2H), 8.21-8.19 (m, 2H), 7.87 (s, 1H), 7.78 (s, 1H), 7.69 (s, 1H), 7.00 (s, 1H), 6.64 (dd, J = 7.4, 2.0 Hz, 1H), 5.38 (s,

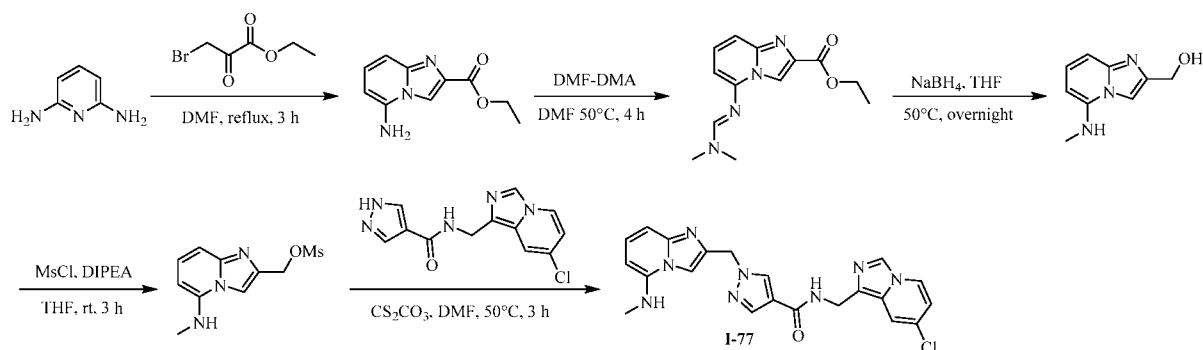
2H), 5.32 (t, $J = 3.8$ Hz, 1H), 4.74 (d, $J = 3.8$ Hz, 2H), 4.55 (d, $J = 5.7$ Hz, 2H), 1.97-1.90 (m, 1H), 0.97-0.86 (m, 2H), 0.70-0.60 (m, 2H).

Example 76

Scheme 76



[0372] **Synthesis of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyrimidin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-76).** A mixture of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyrimidine (40 mg, 0.19 mmol), N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (61 mg, 0.19 mmol), Cs_2CO_3 (248 mg, 0.76 mmol) in DMF (2 mL) was stirred at RT for 2 h. Then the reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na_2SO_4 , concentrated and purified by column chromatography (PE/EA = 10/1) to give the desired compound N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyrimidin-2-yl)methyl)-1H-pyrazole-4-carboxamide (25 mg, yield: 27%) as a white solid. ESI-MS $[\text{M}+\text{H}]^+$: 491.1. Purity: 96.39%. ^1H NMR (400 MHz, DMSO): δ 8.69 (d, $J = 2.4$ Hz, 1H), 8.59 (t, $J = 5.7$ Hz, 1H), 8.41 (d, $J = 2.5$ Hz, 1H), 8.32 (s, 1H), 8.27-8.20 (m 2H), 7.95 (d, $J = 0.9$ Hz, 1H), 7.87 (s, 1H), 7.63 (s, 1H), 6.75-6.69 (m, 1H), 5.43 (s, 2H), 4.55 (d, $J = 5.7$ Hz, 2H), 2.02-1.93 (m, 1H), 1.02-0.92 (m, 2H), 0.79-0.70 (m, 2H).

Example 77Scheme 77

[0373] Synthesis of ethyl 5-aminoimidazo[1,2-a]pyridine-2-carboxylate. A mixture of pyridine-2,6-diamine (1.09 g, 10 mmol), ethyl 3-bromo-2-oxopropanoate (1.62 g, 8.3 mmol) in DMF (10 mL) was stirred at 90 °C for 3 h. The mixture was concentrated to give crude ethyl 5-aminoimidazo[1,2-a]pyridine-2-carboxylate (2.7 g, yield: 100%) as a black solid, which was used in the next step without further purification. ESI-MS $[M+H]^+$: 206.2.

[0374] Synthesis of ethyl (E)-5-(((dimethylamino)methylene)amino)imidazo[1,2-a]pyridine-2-carboxylate. A mixture of ethyl 5-aminoimidazo[1,2-a]pyridine-2-carboxylate (1.7 g, crude) and DMF-DMA (5 mL) in DMF (5 mL) was stirred at 50 °C for 3 h. The mixture was diluted with H₂O (50 mL), extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified by silica gel chromatography (MeOH/DCM = 1/10) to give ethyl (E)-5-(((dimethylamino)methylene)amino)imidazo[1,2-a]pyridine-2-carboxylate (307 mg, yield: 14%) as a white solid. ESI-MS $[M+H]^+$: 261.2.

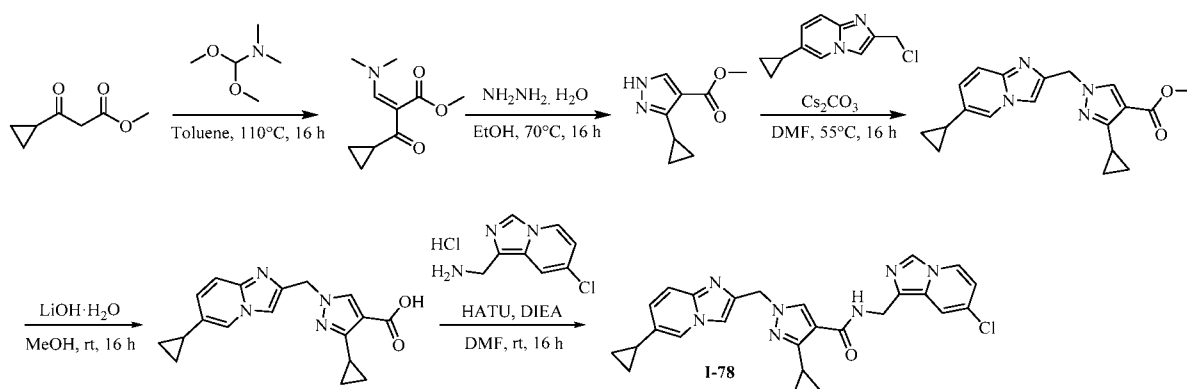
[0375] Synthesis of (5-(methylamino)imidazo[1,2-a]pyridin-2-yl)methanol. A mixture of ethyl (E)-5-(((dimethylamino)methylene)amino)imidazo[1,2-a]pyridine-2-carboxylate (217 mg, 0.83 mmol) and NaBH₄ (314 mg, 8.3 mmol) in THF (10 mL) was stirred at 60 °C overnight. The mixture was then quenched with 1 M HCl solution and filtered. The filtrate was concentrated to get a crude, which was purified by prep-TLC (MeOH/DCM = 1/3) to give (5-(methylamino)imidazo[1,2-a]pyridin-2-yl)methanol (52 mg, yield: 35%) as a white solid. ESI-MS $[M+H]^+$: 178.2.

[0376] Synthesis of (5-(methylamino)imidazo[1,2-a]pyridin-2-yl)methyl

methanesulfonate. To a solution of (5-(methylamino)imidazo[1,2-a]pyridin-2-yl)methanol (32 mg, 0.18 mmol) and DIPEA (70 mg, 0.54 mmol) in THF (10 mL) was added methanesulfonyl chloride (50.4 mg, 2.4 mmol). The mixture was stirred at RT for 3 h. Water (50 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated to give the (5-(methylamino)imidazo[1,2-a]pyridin-2-yl)methyl methanesulfonate, which was used into the next step without further purification. ESI-MS $[M+H]^+$: 256.2.

[0377] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-

(methylamino)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-77). A mixture of (5-(methylamino)imidazo[1,2-a]pyridin-2-yl)methyl methanesulfonate (45.9 mg, crude), N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (50 mg, 0.18 mmol), and Cs_2CO_3 (596 mg, 1.8 mmol) in DMF (5 mL) was stirred at 50 °C for 3 h. Water (30 mL) was added to the reaction and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give the crude, which was purified by prep-HPLC (DCM/MeOH = 10/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((5-(methylamino)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (5.2 mg, yield: 6.6%) as a white solid. ESI-MS $[M+H]^+$: 435.2. Purity: 96.21%. ^1H NMR (400 MHz, DMSO): δ 8.59 (t, J = 5.6 Hz, 1H), 8.31-8.29 (m, 2H), 8.22 (s, 1H), 7.87 (s, 1H), 7.79-7.78 (m, 1H), 7.70 (s, 1H), 7.20-7.16 (m, 1H), 6.80-6.77 (m, 2H), 6.64 (dd, J = 7.4, 2.1 Hz, 1H), 5.80 (d, J = 7.4 Hz, 1H), 5.40 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 2.86 (d, J = 4.6 Hz, 3H).

Example 78**Scheme 78**

[0378] Synthesis of methyl (Z)-2-(cyclopropanecarbonyl)-3-

(dimethylamino)acrylate. To a mixture of 3-cyclopropyl-3-oxo-propionic acid methyl ester (5 g, 35 mmol) in toluene (20 mL) was added DMF-DMA (8 mL, 36.75 mmol). The resulting reaction was heated at 110 °C for 16 h. After cooled to RT, the mixture was concentrated to give crude 2-cyclopropanecarbonyl-3-dimethylamino-acrylic acid methyl ester (5.3 g, yield: 77%) as a white solid, which was used in the next step without further purification. ESI-MS $[M+H]^+$: 198.1.

[0379] Synthesis of methyl 3-cyclopropyl-1H-pyrazole-4-carboxylate. To a solution of methyl (Z)-2-(cyclopropanecarbonyl)-3-(dimethylamino)acrylate (5.3 g, 27 mmol) in EtOH (20 mL) was added hydrazine hydrate (4 mL) dropwise. The reaction mixture was stirred at 70 °C for 16 h under N₂ atmosphere. The reaction mixture was concentrated to give the residue, which was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5/1) to give methyl 3-cyclopropyl-1H-pyrazole-4-carboxylate (2.9 g, yield 65%) as a white solid. ESI-MS $[M+H]^+$: 167.1.

[0380] Synthesis of methyl 3-cyclopropyl-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. To a solution of methyl 3-cyclopropyl-1H-pyrazole-4-carboxylate (200 mg, 1.20 mmol) in dry DMF (5 mL) was added 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (248 mg, 1.20 mmol) and Cs₂CO₃ (1.17 g, 3.6 mmol). Then the reaction mixture was stirred at 55 °C for 16 h under N₂ atmosphere. After cooling to RT, the reaction was diluted with H₂O (50 mL), extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo to give the residue, which was purified by silica gel column chromatography (DCM/methanol = 10/1) to give methyl 3-cyclopropyl-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (390 mg, yield 96%) as a white solid. ESI-MS $[M+H]^+$: 337.4.

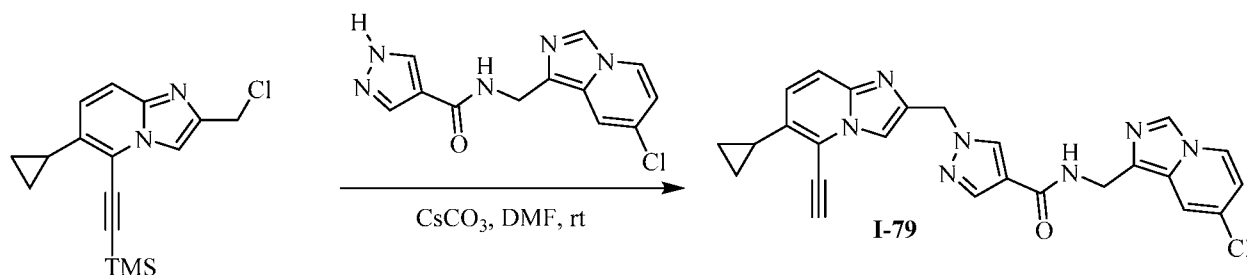
[0381] Synthesis of 3-cyclopropyl-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. To a solution of methyl 3-cyclopropyl-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (300 mg, 0.89 mmol) in methanol (5 mL) and H₂O (5 mL) was added LiOH·H₂O (187 mg, 4.45 mmol). The resulting

reaction was stirred at 50 °C for 16 h. Most of the solvent was removed and the residue was diluted with H₂O (10 mL), the pH value of mixture was adjusted to 4-5 by adding HCl (1 M). The precipitate was collected and dried to give 3-cyclopropyl-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (230 mg yield 80%) as a white solid. ESI-MS [M+H]⁺: 323.1.

[0382] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-3-cyclopropyl-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-78). To a solution of 3-cyclopropyl-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (110 mg, 0.34 mmol) in dry DMF (3 mL) was added (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (148 mg, 0.68 mmol), HATU (194 mg, 0.51 mmol) and DIPEA (132 mg, 1.02 mmol). The reaction mixture was stirred at RT for 16 h. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried over anhydrous Na₂SO₄ and concentrated in vacuo to give a residue, which was purified by prep-TLC (DCM/MeOH = 10/1) to afford N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-3-cyclopropyl-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (47 mg, yield: 29%) as a white solid. ESI-MS [M+H]⁺: 486.2. Purity: 100%. ¹H NMR (400 MHz, DMSO-d₆): δ 8.34-8.29 (m, 4H), 8.07 (s, 1H), 7.83-7.72 (m, 1H), 7.70 (s, 1H), 7.39 (d, J = 9.3 Hz, 1H), 6.99 (dd, J = 9.4, 1.7 Hz, 1H), 6.64 (dd, J = 7.5, 2.1 Hz, 1H), 5.24 (s, 2H), 4.53 (d, J = 5.7 Hz, 2H), 2.71-2.60 (m, 1H), 1.97-1.86 (m, 1H), 0.95-0.88 (m, 2H), 0.85-0.79 (m, 2H), 0.76-0.72 (m, 2H), 0.68-0.64 (m, 2H).

Example 79

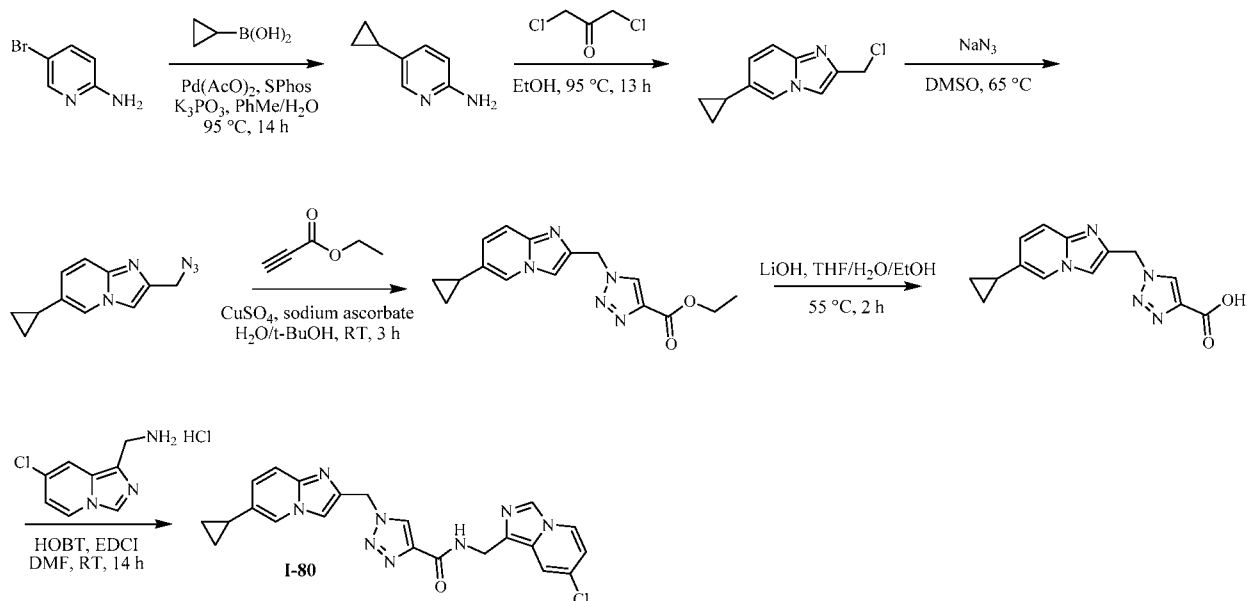
Scheme 79



[0383] N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-ethynylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-79). To a solution of 2-(chloromethyl)-6-cyclopropyl-5-((trimethylsilyl)ethynyl)imidazo[1,2-a]pyridine (30 mg, 0.1 mmol) and N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (27.5 mg, 0.1 mmol) in DMF (4 mL) was added Cs₂CO₃ (174 mg, 0.8 mmol). The reaction was stirred at RT for 4 h. The reaction mixture was concentrated to give the crude which was purified by prep-HPLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-ethynylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (7.7 mg, yield: 16.7%) as a pale solid. ESI-MS [M+H]⁺: 470.1. Purity: 100%. ¹H NMR (400 MHz, DMSO) 8.58 (t, J = 5.7 Hz, 1H), 8.33-8.27 (m, 2H), 8.22 (s, 1H), 7.90 (s, 1H), 7.86 (s, 1H), 7.80-7.74 (m, 1H), 7.54 (d, J = 9.4 Hz, 1H), 6.81 (d, J = 9.5 Hz, 1H), 6.67-6.62 (m, 1H), 5.46-5.42 (m, 3H), 4.55 (d, J = 5.7 Hz, 2H), 2.30-2.22 (m, 1H), 1.12-1.01 (m, 2H), 0.85-0.75 (m, 2H).

Example 80

Scheme 80



[0384] Synthesis of 5-cyclopropylpyridin-2-amine. A mixture of 5-bromopyridin-2-amine (100 g, 585 mmol), cyclopropylboronic acid (60 g, 701 mmol), Pd(AcO)₂ (6.5 g, 29 mmol), SPhos (24 g, 58.5 mmol) and K₃PO₄ (372 g, 1.755 mol) in toluene/H₂O (1.2 L/0.12 L)

was stirred at 90 °C for 14 h under N₂. The reaction was concentrated in vacuo to give the crude, which was purified with silica gel chromatography (PE/EA = 1/2) to give the 5-cyclopropylpyridin-2-amine (61 g, yield: 78%) as a yellow solid. ESI-MS [M+H]⁺: 135.1.

[0385] Synthesis of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine. A mixture of 5-cyclopropylpyridin-2-amine (61 g, 455 mmol) and 1,3-dichloropropan-2-one (172 g, 1365 mmol) in EtOH (1 L) was stirred at 95 °C for 13 h. The reaction was concentrated to remove the EtOH. The pH of the residue was adjusted to 9 by addition of aqueous NaHCO₃ and extracted with EtOAc (1 L x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified with silica gel chromatography (EA) to give the 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (40 g, yield: 42%) as a yellow solid. ESI-MS [M+H]⁺: 207.1.

[0386] Synthesis of 2-(azidomethyl)-6-cyclopropylimidazo[1,2-a]pyridine. To a solution of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (40 g, 193 mmol) in DMF (600 mL) was added NaN₃ (18.8 g, 290 mmol). The resulting reaction was stirred at RT for 2 h. The reaction was diluted with H₂O (500 mL) and extracted with EtOAc (500 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified with silica gel chromatography (PE/EA = 2/1) to give the 2-(azidomethyl)-6-cyclopropylimidazo[1,2-a]pyridine (35 g, yield: 85%) as a yellow solid. ESI-MS [M+H]⁺: 214.1.

[0387] Synthesis of ethyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate. A mixture of 2-(azidomethyl)-6-cyclopropylimidazo[1,2-a]pyridine (35 g, 163.5 mmol), ethyl propiolate (17.6 g, 180 mmol), CuSO₄ (2.6 g, 16.35 mmol) and sodium ascorbate (3.3 g, 16.35 mmol) in H₂O/t-BuOH (150 mL/150 mL) was stirred at RT for 3 h. Yellow solid was precipitated after 3 h and the mixture was filtered. The cake was dried to give the ethyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (29 g, yield: 57%) as a yellow solid, which was used in the next step without further purification. ESI-MS [M+H]⁺: 312.1.

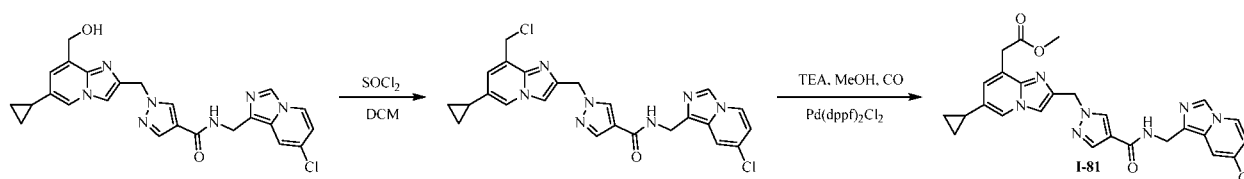
[0388] Synthesis of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid. A mixture of ethyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (29 g, 93.2 mmol) and LiOH (6.7 g, 279.6 mmol,

solution in 50 mL H₂O) in THF/EtOH (150 mL/150 mL) was stirred at 50 °C for 2 h. The reaction was concentrated to remove most of the solvent. The pH of the residue was adjusted to 4 by 2 N HCl and a pink solid was precipitated out. The mixture was filtered and the filter cake was dried to give 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (20 g, 77%) as a pink solid. ESI-MS [M+H]⁺: 284.1.

[0389] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (I-80). To a solution of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (10 g, 35.3 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (9.2 g, 42.4 mmol), HOBT (6.67 g, 49.42 mmol) and EDCI (9.5 g, 49.42 mmol) in DMF (500 mL) was added DIPEA (31.3 mL, 176.5 mmol). The resulting mixture was stirred at RT for 14 h. The reaction was poured into H₂O (1 L) and yellow solid was precipitated out. The mixture was filtered and the cake was dried to give the crude, which was purified with silica gel chromatography (DCM/MeOH = 10/1) to give the N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (7.2 g, yield: 45.9%) as a white solid. HPLC Purity: 99.09% (214 nm), 99.18% (254nm). LCMS m/z: 447.1 [M+H]⁺, t_R = 1.098 (min). ¹H NMR (400 MHz, DMSO): δ 8.91 (t, J = 5.8 Hz, 1H), 8.56 (s, 1H), 8.34 (s, 1H), 8.31-8.29 (m, 2H), 7.84-7.82 (m, 2H), 7.40 (d, J = 9.3 Hz, 1H), 7.01 (dd, J = 9.4, 1.7 Hz, 1H), 6.64 (dd, J = 7.5, 2.1 Hz, 1H), 5.72 (s, 2H), 4.62 (d, J = 5.9 Hz, 2H), 1.95-1.89 (m, 1H), 0.94-0.89 (m, 2H), 0.69-0.65 (m, 2H).

Example 81

Scheme 81



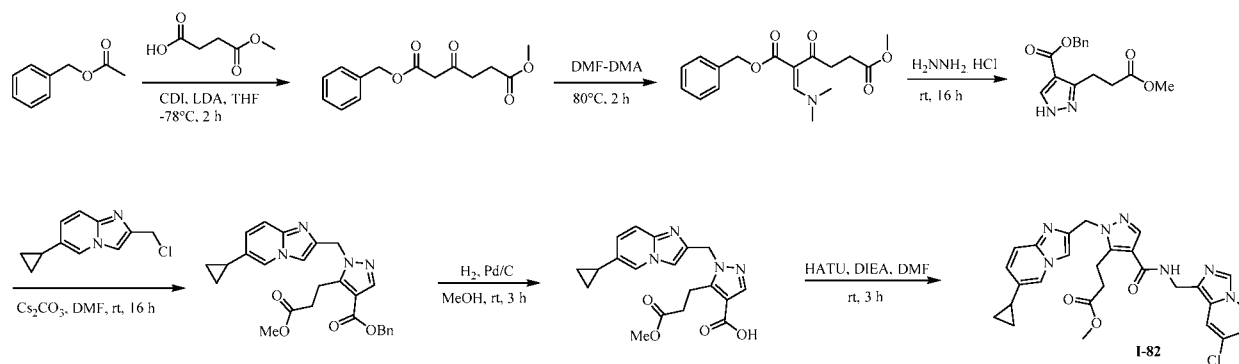
[0390] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide. To a solution of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-

cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (80 mg, 0.17 mmol) in DCM (5 mL) was added SOCl₂ (0.5 mL, 1.7 mmol) slowly at 0 °C. The resulting mixture was stirred at RT for 2 h. The reaction was concentrated in vacuo to give the crude, which was purified by silica gel chromatography (EtOAc/PE = 2/1) to give methyl 2-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetate (20 mg, yield: 24%) as a white solid. ESI-MS [M+H]⁺: 494.2.

[0391] Synthesis of methyl 2-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetate (I-81). A mixture methyl 2-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetate (40 mg, 0.08 mmol), Pd(dppf)₂Cl₂ (20 mg, 0.016 mmol), TEA (0.5 mL, 0.4 mmol) in MeOH (15 mL) was stirred at 55 °C for 3 h under CO atmosphere. The reaction was monitored by LCMS until the starting material consumed. The reaction was concentrated in vacuo to give the crude, which was purified by prep-HPLC to give methyl 2-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetate (22.7 mg, 55% yield) as a white solid. ESI-MS [M+H]⁺: 518.1. Purity: 95.6%. ¹H NMR (400 MHz, DMSO): δ 8.58 (t, J = 5.7 Hz, 1H), 8.34-8.28 (m, 2H), 8.25 (d, J = 1.3 Hz, 1H), 8.18 (s, 1H), 7.87 (s, 1H), 7.80-7.74 (m, 1H), 7.66 (s, 1H), 6.94 (d, J = 1.2 Hz, 1H), 6.64 (dd, J = 7.4, 2.1 Hz, 1H), 5.38 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 3.89 (s, 2H), 3.57 (s, 3H), 1.94-1.87 (m, 1H), 0.94-0.89 (m, 2H), 0.69-0.60 (m, 2H).

Example 82

Scheme 82



[0392] Synthesis of 1-benzyl 6-methyl 3-oxohexanedioate. To a solution of benzyl acetate (1.5 g, 10 mmol) in THF (10 mL) was added LDA (1 M, 15 mmol) at -78 °C and stirred for 1 h (solution A). To a solution of 4-methoxy-4-oxobutanoic acid (1.58 g, 12 mmol) in THF (10 mL) was added CDI (1.94 g, 12 mmol) and stirred at RT for 30 min (solution B). Solution B was added to solution A at -78 °C and stirred for another 2 h. Saturated NH₄Cl (100 mL) was added to quench the reaction and the reaction mixture was extracted with EtOAc (100 mL x 3). The combined organics were concentrated and purified by silica gel chromatography (EA/PE = 1/10) to give 1-benzyl 6-methyl 3-oxohexanedioate (500 mg, yield: 19%) as a colorless oil. ESI-MS [M+H]⁺: 265.1.

[0393] Synthesis of 1-benzyl 6-methyl (E)-2-((dimethylamino)methylene)-3-oxohexanedioate. A solution of 1-benzyl 6-methyl 3-oxohexanedioate (490 mg, 1.86 mmol) in DMF-DMA (443 mg, 3.72 mmol) was heated to 80 °C for 2 h and then concentrated to give 1-benzyl 6-methyl (E)-2-((dimethylamino)methylene)-3-oxohexanedioate (600 mg, crude) as a yellow oil which was used in the next step without purification. ESI-MS [M+H]⁺: 320.1.

[0394] Synthesis of benzyl 3-(3-methoxy-3-oxopropyl)-1H-pyrazole-4-carboxylate. To a solution of 1-benzyl 6-methyl (E)-2-((dimethylamino)methylene)-3-oxohexanedioate (600 mg, 1.86 mmol) in MeOH (6 mL) was added hydrazine hydrochloride (255 mg, 3.72 mmol). The mixture was stirred at RT for 16 h. The reaction was concentrated to give the crude, which was purified by silica gel chromatography (EA/PE = 1/1) to give benzyl 3-(3-methoxy-3-oxopropyl)-1H-pyrazole-4-carboxylate (384 mg, yield: 64% for two steps) as a yellow oil. ESI-MS [M+H]⁺: 289.1.

[0395] Synthesis of benzyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-5-(3-methoxy-3-oxopropyl)-1H-pyrazole-4-carboxylate. To a solution of benzyl 3-(3-methoxy-3-oxopropyl)-1H-pyrazole-4-carboxylate (90 mg, 0.31 mmol) and 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (78 mg, 0.38 mmol) in DMF (5 mL) was added Cs₂CO₃ (302 mg, 0.93 mmol) at RT. The mixture was stirred at RT for 16 h. The reaction was quenched with H₂O (10 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layers were washed with brine, dried over Na₂SO₄, and the solvent is evaporated under reduced pressure to give a residue which was purified by prep-TLC (MeOH/DCM = 1/15) to give benzyl 1-((6-

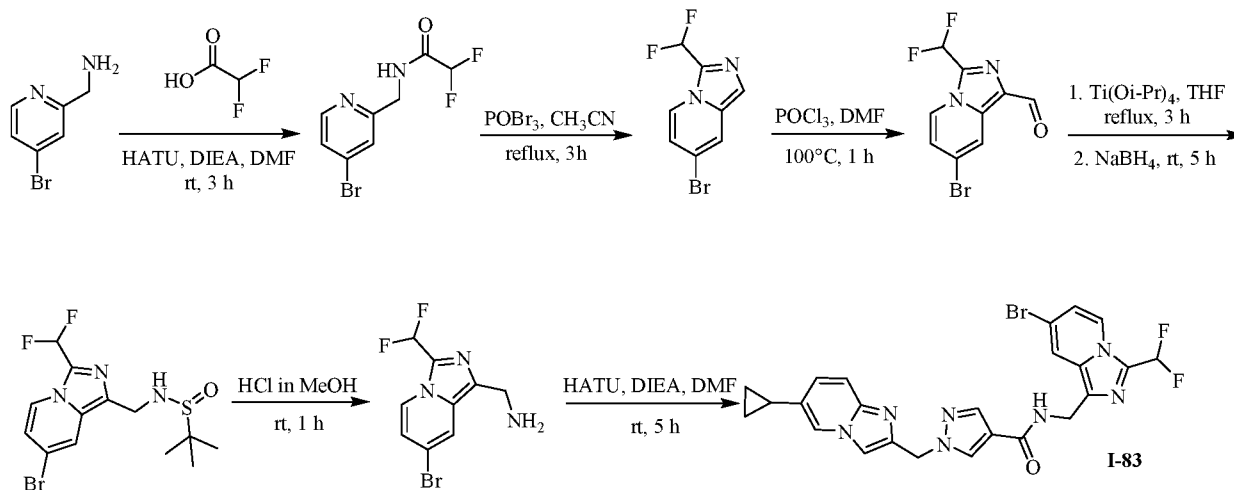
cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-5-(3-methoxy-3-oxopropyl)-1H-pyrazole-4-carboxylate (30 mg, yield: 20%) as yellow oil. ESI-MS $[M+H]^+$: 459.1.

[0396] Synthesis of 1-(((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-5-(3-methoxy-3-oxopropyl)-1H-pyrazole-4-carboxylic acid. To a solution of benzyl 1-(((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-5-(3-methoxy-3-oxopropyl)-1H-pyrazole-4-carboxylate (100 mg, 0.22 mmol) in MeOH (10 mL) was added Pd/C (10%, 30 mg). The mixture was stirred at RT for 3 h under H₂. The reaction was filtrated and concentrated to give 1-(((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-5-(3-methoxy-3-oxopropyl)-1H-pyrazole-4-carboxylic acid (67 mg, 83%) as a white solid. ESI-MS $[M+H]^+$: 369.1.

[0397] Synthesis of methyl 3-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-(((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-5-yl)propanoate (I-82). To a solution of 1-(((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-5-(3-methoxy-3-oxopropyl)-1H-pyrazole-4-carboxylic acid (80 mg, 0.22 mmol) and (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (48 mg, 0.26 mmol) in dry DMF (4 mL) was added HATU (125 mg, 0.33 mmol) and DIPEA (114 mg, 0.88 mmol) at RT. The reaction was stirred for 3 h. Water (30 mL) was added and the mixture was extracted with EtOAc (50 mL x 3). The organic layers were washed with brine (80 mL), dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified by prep-HPLC (DCM/MeOH = 10/1) to give methyl 3-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-(((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-5-yl)propanoate (15.4 mg, yield: 13%) as a yellow solid. ESI-MS $[M+H]^+$: 532.2. Purity: 98.7%. ¹H NMR (400 MHz, DMSO): δ 8.70-8.54 (m, 2H), 8.48 (s, 1H), 8.34 (dd, J = 7.5, 0.8 Hz, 1H), 8.04-8.01 (m, 2H), 7.87-7.79 (m, 1H), 7.74 (d, J = 9.3 Hz, 1H), 7.62 (d, J = 9.0 Hz, 1H), 6.72 (dd, J = 7.5, 2.1 Hz, 1H), 5.66 (s, 2H), 4.61 (d, J = 5.7 Hz, 2H), 3.58 (s, 3H), 3.33-3.24 (m, 2H), 2.69-2.59 (m, 2H), 2.13-1.97 (m, 1H), 1.09-0.97 (m, 2H), 0.81-0.69 (m, 2H).

Example 83

Scheme 83



[0398] Synthesis of N-((4-bromopyridin-2-yl)methyl)-2,2-difluoroacetamide. To a mixture of (4-bromopyridin-2-yl)methanamine (500 mg, 2.67 mmol), DIPEA (1.7 g, 13.4 mmol) and 2, 2-difluoroacetic acid (256 mg, 2.67 mmol) in DMF (10 mL) was added HATU (2.0 g, 5.34 mmol). The mixture was stirred at RT for 3 h. Water (100 mL) was added and the mixture was extracted with EtOAc (100 mL x 3). The combined organics were washed with brine, dried over Na₂SO₄ and concentrated to give the crude, which was purified by silica gel chromatography (EA/PE = 1/2) to give N-((4-bromopyridin-2-yl)methyl)-2, 2-difluoroacetamide (400 mg, yield: 56%) as a yellow oil. ESI-MS [M+H]⁺: 265.0

[0399] Synthesis of 7-bromo-3-(difluoromethyl)imidazo[1,5-a]pyridine. To a solution of N-((4-bromopyridin-2-yl)methyl)-2, 2-difluoroacetamide (400 mg, 1.5 mmol) in CH₃CN (10 mL) was added POBr₃ (2.2 g, 7.5 mmol). The mixture was heated to reflux for 3 h. After cooled to RT, H₂O (50 mL) was added and extracted with EtOAc (50 mL x 4). The organic layers were dried over Na₂SO₄ and concentrated to give the crude, which was purified by silica gel chromatography (EA/PE = 1/2) to give 7-bromo-3-(difluoromethyl)imidazo[1,5-a]pyridine (180 mg, yield: 49%) as a yellow oil. ESI-MS [M+H]⁺: 247.0.

[0400] Synthesis of 7-bromo-3-(difluoromethyl)imidazo[1,5-a]pyridine-1-carbaldehyde. To a solution of 7-bromo-3-(difluoromethyl)imidazo[1,5-a]pyridine (180 mg, 0.73 mmol) in DMF (3 mL) was added POCl₃ (223 mg, 1.46 mmol). The mixture was stirred at

100 °C for 1 h. After cooled to RT, H₂O (30 mL) was added and extracted with EtOAc (50 mL x 3). The organic phase was dried over Na₂SO₄, concentrated and purified by silica gel chromatography (EA/PE = 1/2) to give 7-bromo-3-(difluoromethyl)imidazo[1,5-a]pyridine-1-carbaldehyde (100 mg, yield: 50%) as a yellow oil. ESI-MS [M+H]⁺: 275.0.

[0401] Synthesis of N-((7-bromo-3-(difluoromethyl)imidazo[1,5-a]pyridin-1-yl)methyl)-2-methylpropane-2-sulfinamide. To a solution of 7-bromo-3-(difluoromethyl)imidazo[1,5-a]pyridine-1-carbaldehyde (100 mg, 0.36 mmol) and 2-methylpropane-2-sulfinamide (65 mg, 0.54 mmol) in THF (5 mL) was added Ti(Oi-Pi)₄ (305 mg, 1.08 mmol). The mixture was refluxed for 3 h. After cooled to RT, NaBH₄ (69 mg, 1.8 mmol) was added. The mixture was stirred at RT for 5 h. The reaction was then quenched with H₂O (20 mL) and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the residue, which was purified by prep-TLC (MeOH/DCM = 1/25) to give N-((7-bromo-3-(difluoromethyl)imidazo[1,5-a]pyridin-1-yl)methyl)-2-methylpropane-2-sulfinamide (100 mg, yield: 73%) as a yellow oil. ESI-MS [M+H]⁺: 380.0.

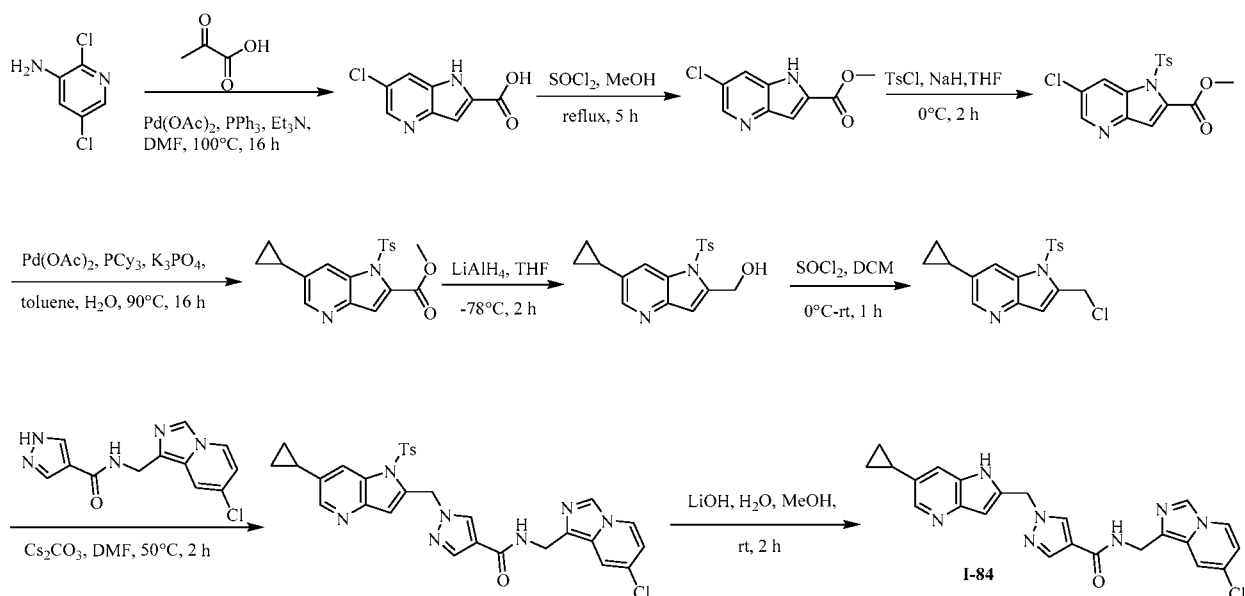
[0402] Synthesis of (7-bromo-3-(difluoromethyl)imidazo[1,5-a]pyridin-1-yl)methanamine. A mixture of N-((7-bromo-3-(difluoromethyl)imidazo[1,5-a]pyridin-1-yl)methyl)-2-methylpropane-2-sulfinamide (100 mg, 0.26 mmol) in HCl (4 M solution in MeOH, 5 mL) was stirred at RT for 1 h. The reaction was concentrated to give (7-bromo-3-(difluoromethyl)imidazo[1,5-a]pyridin-1-yl)methanamine (60 mg, 83%) as a white solid, which was used in the next step without further purification. ESI-MS [M+H]⁺: 276.0.

[0403] Synthesis of N-((7-bromo-3-(difluoromethyl)imidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-83). To a solution of (7-bromo-3-(difluoromethyl)imidazo[1,5-a]pyridin-1-yl)methanamine (40 mg, 0.15 mmol) and 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (49 mg, 0.17 mmol) in dry DMF (3 mL) was added HATU (83 mg, 0.22 mmol) and DIPEA (75 mg, 0.58 mmol) at RT. The reaction was stirred at RT for 5 h. Water (20 mL) was added and the mixture was extracted with EtOAc (25 mL x 3). The organic layers were washed with brine (50 mL), dried over Na₂SO₄ and concentrated under reduced pressure to give the crude product, which was purified by prep-HPLC (DCM/MeOH = 10/1) to

give N-((7-bromo-3-(difluoromethyl)imidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (6 mg, yield: 8%) as a yellow solid. ESI-MS $[M+H]^+$: 540.1. Purity: 71.3%. ^1H NMR (400 MHz, DMSO): δ 8.68 (t, $J = 5.5$ Hz, 1H), 8.46 (s, 1H), 8.33 (d, $J = 7.4$ Hz, 1H), 8.25 (s, 1H), 8.18 (s, 1H), 7.90-7.87 (m, 2H), 7.61-7.48 (m, 2H), 7.25 (d, $J = 8.7$ Hz, 1H), 7.00 (dd, $J = 7.5, 1.8$ Hz, 1H), 5.49 (s, 2H), 4.59 (d, $J = 5.6$ Hz, 2H), 1.99-1.94 (m, 1H), 1.06-0.86 (m, 2H), 0.72-0.69 (m, 2H).

Example 84

Scheme 84



[0404] Synthesis of 6-chloro-1H-pyrrolo[3,2-b]pyridine-2-carboxylic acid. A mixture of 2,5-dichloropyridin-3-amine (2.0 g, 12.27 mmol), 2-oxopropanoic acid (3.24 g, 36.81 mmol), Pd(OAc)₂ (551 mg, 2.45 mmol), PPh₃ (2.57 g, 9.82 mmol) and Et₃N (4.97 g, 49.08 mmol) in DMF (30 mL) was stirred at 100 °C for 16 h. The reaction mixture was concentrated to give a crude which was purified by silica gel chromatography (DCM/MeOH = 5/1) to give 6-chloro-1H-pyrrolo[3,2-b]pyridine-2-carboxylic acid (2.41 g, yield: 100%) as a yellow solid. ESI-MS $[M+H]^+$: 197.0.

[0405] Synthesis of methyl 6-chloro-1H-pyrrolo[3,2-b]pyridine-2-carboxylate. To a stirred solution of 6-chloro-1H-pyrrolo[3,2-b]pyridine-2-carboxylic acid (2.41 g, 12.27 mmol) in

MeOH (80 mL) was added SOCl₂ (4.38 g, 36.81 mmol) at RT. The mixture was stirred at 80 °C for 5 h. The reaction mixture was concentrated to give the residue, which was dissolved in EtOAc (100 mL) and washed with NaHCO₃ (100 mL) and brine (100 mL), dried over Na₂SO₄, concentrated and purified by silica gel chromatography (EA/PE = 1/5) to give methyl 6-chloro-1H-pyrrolo[3,2-b]pyridine-2-carboxylate (1.0 g, yield: 39%) as a yellow solid. ESI-MS [M+H]⁺: 211.1.

[0406] Synthesis of methyl 6-chloro-1-tosyl-1H-pyrrolo[3,2-b]pyridine-2-carboxylate. To a stirred solution of NaH (42 mg, 1.04 mmol) in THF (4 mL) was added the solution of 6-chloro-1H-pyrrolo[3,2-b]pyridine-2-carboxylate (200 mg, 0.95 mmol) in THF (1 mL) at 0 °C. After stirring for 20 min, a solution of TsCl (199 mg, 1.04 mmol) in THF (1 mL) was added thereto at 0 °C. The resulting mixture was stirred at 0 °C for another 2 h. The reaction mixture was quenched with 1 M HCl, diluted with H₂O (20 mL) and extracted with EtOAc (25 mL x 3). The combined organics were washed with NaHCO₃ (20 mL), brine (80 mL), dried over Na₂SO₄, concentrated and purified by silica gel chromatography (EA/PE = 1/5) to give methyl 6-chloro-1-tosyl-1H-pyrrolo[3,2-b]pyridine-2-carboxylate (240 mg, yield: 69%) as a yellow solid. ESI-MS [M+H]⁺: 365.1.

[0407] Synthesis of methyl 6-cyclopropyl-1-tosyl-1H-pyrrolo[3,2-b]pyridine-2-carboxylate. A mixture of methyl 6-chloro-1-tosyl-1H-pyrrolo[3,2-b]pyridine-2-carboxylate (240 mg, 0.658 mmol), cyclopropylboronic acid (170 mg, 1.97 mmol), Pd(OAc)₂ (15 mg, 0.0658 mmol), tricyclohexyl phosphine (37 mg, 0.132 mmol) and K₃PO₄ (489 mg, 2.30 mmol) in toluene (10 mL) and H₂O (2 mL) was stirred at 100 °C for 16 h. The reaction mixture was filtered and washed with EtOAc (50 mL). The combined filtrate was washed with H₂O (50 mL x 1) and brine (50 mL x 1), dried over Na₂SO₄, concentrated and purified by silica gel chromatography (EA/PE = 1/3) to give methyl 6-cyclopropyl-1-tosyl-1H-pyrrolo[3,2-b]pyridine-2-carboxylate (180 mg, yield: 74%) as a yellow solid. ESI-MS [M+H]⁺: 371.1.

[0408] Synthesis of (6-cyclopropyl-1-tosyl-1H-pyrrolo[3,2-b]pyridin-2-yl)methanol. To a stirred solution of LiAlH₄ (74 mg, 1.94 mmol) in THF (5 mL) was added the solution of methyl 6-cyclopropyl-1-tosyl-1H-pyrrolo[3,2-b]pyridine-2-carboxylate (180 mg, 0.486 mmol) in THF (1 mL) at -78 °C dropwise. The mixture was stirred at -78 °C for 2 h. The reaction mixture was quenched with Na₂SO₄·10H₂O and filtered. The filtrate was concentrated and dried to give

(6-cyclopropyl-1-tosyl-1H-pyrrolo[3,2-b]pyridin-2-yl)methanol (105 mg, yield: 63%) as a yellow solid. ESI-MS $[M+H]^+$: 343.1.

[0409] Synthesis of 2-(chloromethyl)-6-cyclopropyl-1-tosyl-1H-pyrrolo[3,2-b]pyridine. To a stirred solution of (6-cyclopropyl-1-tosyl-1H-pyrrolo[3,2-b]pyridin-2-yl)methanol (105 mg, 0.307 mmol) in DCM (10 mL) was added the solution of SOCl_2 (182 mg, 1.53 mmol) in DCM (1 mL) at 0 °C dropwise. The mixture was stirred at RT for 1 h. The reaction mixture was concentrated to give the residue, which was dissolved in EtOAc (40 mL) and washed with NaHCO_3 (40 mL) and brine (40 mL), dried over Na_2SO_4 , concentrated and dried in vacuo to give 2-(chloromethyl)-6-cyclopropyl-1-tosyl-1H-pyrrolo[3,2-b]pyridine (110 mg, yield: 99%) as a yellow syrup. ESI-MS $[M+H]^+$: 361.1.

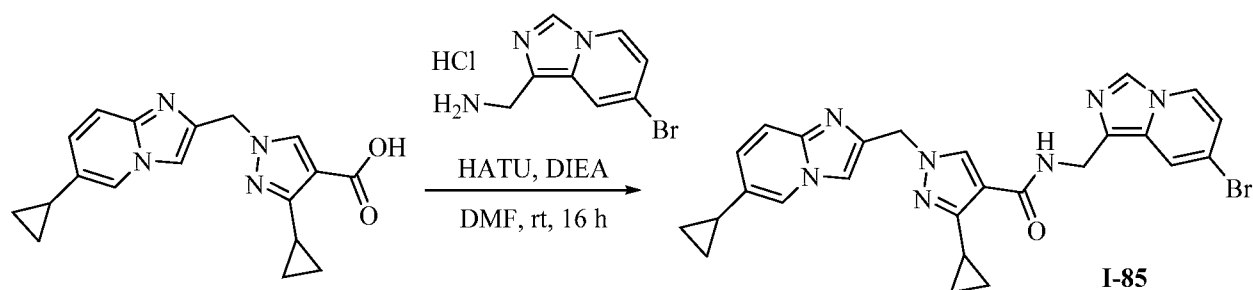
[0410] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-1-tosyl-1H-pyrrolo[3,2-b]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide. A mixture of 2-(chloromethyl)-6-cyclopropyl-1-tosyl-1H-pyrrolo[3,2-b]pyridine (110 mg, 0.305 mmol), N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (70 mg, 0.254 mmol) and Cs_2CO_3 (248 mg, 0.762 mmol) in DMF (5 mL) was stirred at 50 °C for 2 h. The reaction mixture was poured into H_2O (40 mL) and extracted with EtOAc/THF (50 mL x 3, 5/1 (v/v)). The combined organic layers were washed with brine, dried over Na_2SO_4 , concentrated and purified by prep-TLC (DCM/MeOH = 10/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-1-tosyl-1H-pyrrolo[3,2-b]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (38 mg, yield: 25%) as a yellow solid. ESI-MS $[M+H]^+$: 600.1.

[0411] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-1H-pyrrolo[3,2-b]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-84). A mixture of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-1-tosyl-1H-pyrrolo[3,2-b]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (35 mg, 0.0583 mmol) and $\text{LiOH}\cdot\text{H}_2\text{O}$ (307 mg, 7.30 mmol) in MeOH/ H_2O (2 mL/0.5 mL) was stirred at RT for 2 h. The reaction was concentrated in vacuo to remove the MeOH. And the residue was diluted in H_2O (15 mL) and extracted with EtOAc (30 mL x 3). The combined organics were washed with brine (90 mL), dried over Na_2SO_4 , concentrated and purified by prep-TLC (DCM/MeOH = 7/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-1H-pyrrolo[3,2-b]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (12 mg, yield: 46%) as a white solid. ESI-

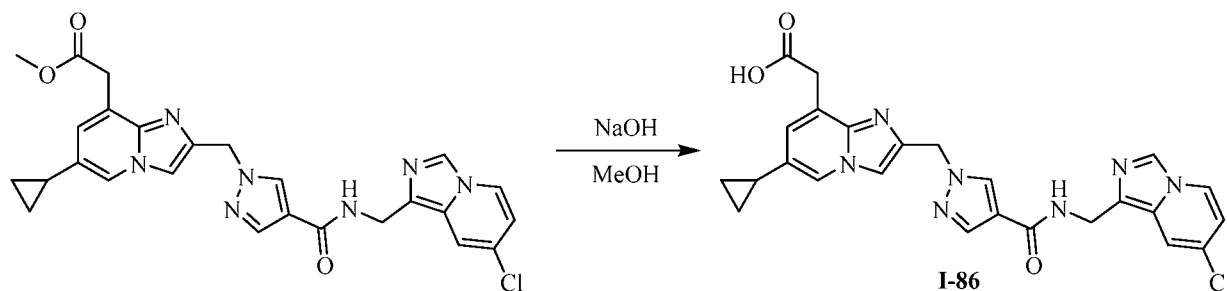
MS $[M+H]^+$: 446.0. Purity: 97.56%. ^1H NMR (400 MHz, DMSO): δ 11.22 (s, 1H), 8.59 (t, J = 5.4 Hz, 1H), 8.30 (m, 2H), 8.18 (d, J = 20.8 Hz, 2H), 7.90 (s, 1H), 7.77 (s, 1H), 7.28 (s, 1H), 6.64 (d, J = 7.3 Hz, 1H), 6.45 (s, 1H), 5.47 (s, 2H), 4.55 (d, J = 5.5 Hz, 2H), 2.01 (m, 1H), 0.96 (m, 2H), 0.68 (m, 2H).

Example 85

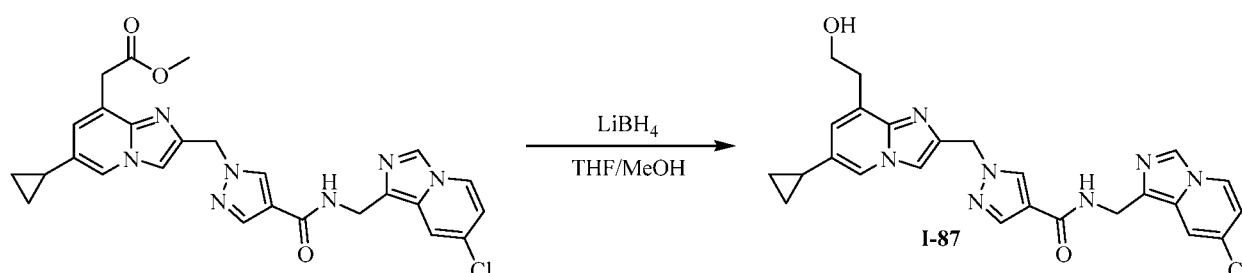
Scheme 85



[0412] Synthesis of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-3-cyclopropyl-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-85). To a solution of 3-cyclopropyl-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (50 mg, 0.16 mmol), in dry DMF (5 mL), was added (7-bromoimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (54 mg, 0.21 mmol), HATU (91 mg, 0.24 mmol) and DIPEA (62 mg, 0.48 mmol). The reaction mixture was stirred at RT for 16 h. The reaction mixture diluted with H_2O (20 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by prep-TLC (DCM/MeOH = 10:1) to afford N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-3-cyclopropyl-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (30 mg, yield: 36%) as a white solid. ESI-MS $[M+H]^+$: 532.2. Purity: 99.12%. ^1H NMR (400 MHz, DMSO- d_6): δ 8.33 (m, 3H), 8.24 (d, J = 7.4 Hz, 1H), 8.07 (s, 1H), 7.94 (d, J = 0.8 Hz, 1H), 7.70 (s, 1H), 7.39 (d, J = 9.3 Hz, 1H), 6.99 (dd, J = 9.4, 1.6 Hz, 1H), 6.71 (dd, J = 7.4, 1.9 Hz, 1H), 5.24 (s, 2H), 4.53 (d, J = 5.7 Hz, 2H), 2.67-2.61 (m, 1H), 1.93-1.88 (m, 1H), 0.94-0.89 (m, 2H), 0.85-0.80 (m, 2H), 0.75-0.73 (m, 2H), 0.69-0.64 (m, 2H).

Example 86Scheme 86

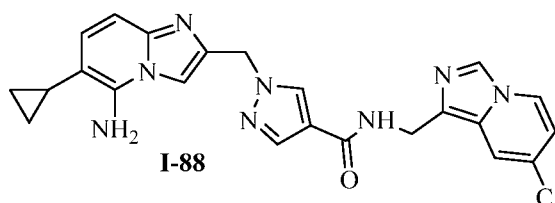
[0413] **Synthesis of 2-(2-(((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetic acid (I-86).** To a solution of methyl 2-(2-(((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetate (50 mg, 0.096 mmol) in EtOH (3 mL) was added NaOH (3 mL, 1 M solution in H₂O). The resulting reaction was stirred at RT for 1 h. HCl (1 M, 3 mL) was added and the reaction was concentrated to give a crude product, which was purified by prep-HPLC to give 2-(2-(((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetic acid (16.6 mg, 35% yield) as a white solid. ESI-MS [M+H]⁺: 504.1. Purity: 97.1%. ¹H NMR (400 MHz, DMSO): δ 8.64 (t, J = 5.6 Hz, 1H), 8.30-8.28 (m, 2H), 8.23 (s, 1H), 8.10 (s, 1H), 7.87 (s, 1H), 7.78 (s, 1H), 7.61 (s, 1H), 6.84 (s, 1H), 6.63 (dd, J = 7.4, 2.0 Hz, 1H), 5.38 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 3.51 (s, 2H), 1.87-1.81 (m, 1H), 0.89-0.83 (m, 2H), 0.62-0.56 (m, 2H).

Example 87Scheme 87

[0414] **Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxyethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-87).** To the solution of methyl 2-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetate (20 mg, 0.039 mmol) in THF/MeOH (3 mL/1 mL) was added LiBH₄ (4.25 mg, 0.195 mmol). The resulting reaction was stirred at RT for 1 h. The reaction was quenched with H₂O (3 mL) and concentrated in vacuo to give the crude, which was purified with prep-HPLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxyethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (7.1 mg, 37% yield) as a white solid. ESI-MS [M+H]⁺: 490.2. Purity: 99.6%. ¹H NMR (400 MHz, DMSO): δ 8.58 (t, J = 5.7 Hz, 1H), 8.34-8.28 (m, 2H), 8.20-8.12 (m, 2H), 7.87 (s, 1H), 7.79-7.73 (m, 1H), 7.65 (s, 1H), 6.84 (s, 1H), 6.65 (dd, J = 7.5, 2.1 Hz, 1H), 5.39 (s, 2H), 4.78 (t, J = 5.8 Hz, 1H), 4.55 (d, J = 5.8 Hz, 2H), 3.74-3.70 (m, 2H), 2.96 (t, J = 6.7 Hz, 2H), 1.91-1.85 (m, 1H), 0.92-0.79 (m, 2H), 0.67-0.63 (m, 2H).

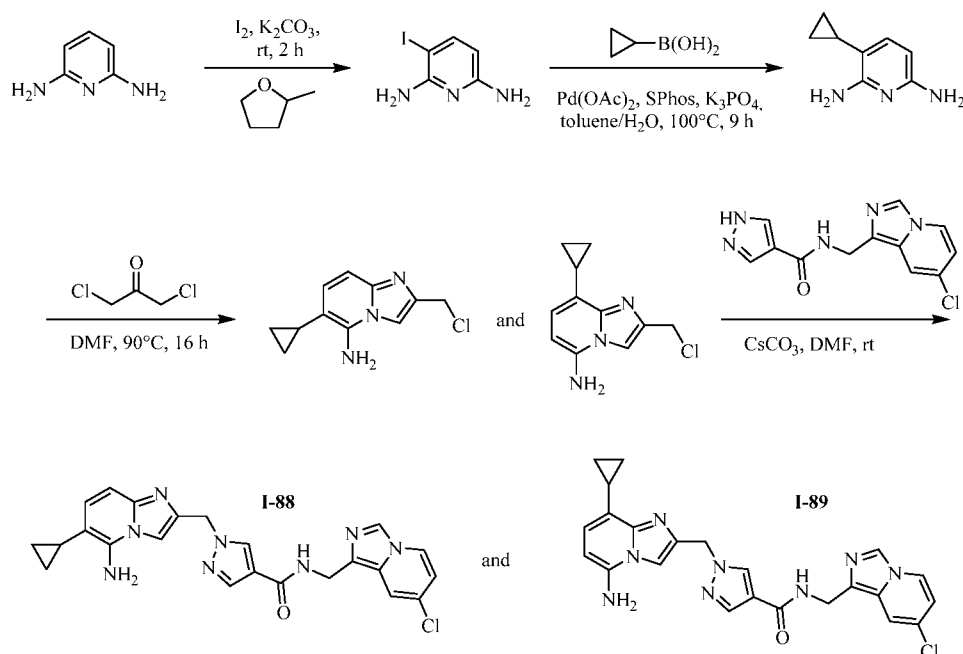
Example 88

[0415] **See Example 89 for Synthesis of 1-((5-amino-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-88).**



Example 89

Scheme 88



[0416] Synthesis of 3-iodopyridine-2,6-diamine. To a solution of 3-iodopyridine-2,6-diamine (5.0 g, 45.9 mmol) in 2-methyltetrahydrofuran (35 mL) was added K_2CO_3 (6.7 g, 48.2 mmol) followed by addition of a solution of I_2 (12.2 g, 48.2 mmol) in 2-methyltetrahydrofuran (20 mL) dropwise over 0.5 h. The resulting reaction was stirred at RT for 5 h. Water (100 mL) was added to the reaction and extracted with EtOAc (150 mL x 2). The combined organic layers were concentrated in vacuo to give the crude, which was purified by silica gel chromatography (DCM/MeOH = 20/1) to give 3-iodopyridine-2,6-diamine (8.5 g, yield: 78.7%) as a yellow solid. ESI-MS $[M+H]^+$: 236.0.

[0417] Synthesis of 3-cyclopropylpyridine-2,6-diamine. To a solution of 3-iodopyridine-2,6-diamine (2.0 g, 8.5 mmol) and cyclopropylboronic acid (2.2 g, 25.5 mmol) in toluene/ H_2O (30 mL/3 mL) was added K_3PO_4 (6.3 g, 29.8 mmol), SPhos (1.0 g, 2.6 mmol) and $Pd(OAc)_2$ (0.3 g, 1.3 mmol). The resulting mixture was stirred at 90 °C for 16 h under N_2 atmosphere. Water (100 mL) was added to the reaction and extracted with EtOAc (100 mL x 3). The combined organic layers were concentrated and purified by silica gel chromatography

(DCM/MeOH = 20/1) to give 3-cyclopropylpyridine-2,6-diamine (0.78 g, yield: 61.9%) as a yellow solid. ESI-MS $[M+H]^+$: 150.3.

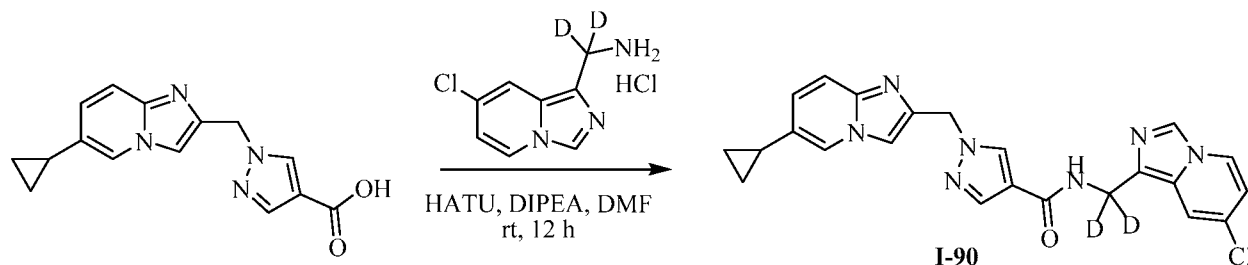
[0418] Synthesis of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-5-amine and 2-(chloromethyl)-8-cyclopropylimidazo[1,2-a]pyridin-5-amine. To a solution of 3-cyclopropylpyridine-2,6-diamine (0.48 g, 3.22 mmol) in DMF (10 mL) was added 1, 3-dichloropropan-2-one (2.04 g, 16.1 mmol). The mixture was stirred at 90 °C for 16 h. Water (50 mL) was added to the reaction and extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated and purified by silica gel chromatography (DCM/MeOH = 20/1) to give mixture of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-5-amine and 2-(chloromethyl)-8-cyclopropylimidazo[1,2-a]pyridin-5-amine (0.18 g, yield: 16.4%) as a yellow solid. ESI-MS $[M+H]^+$: 222.3.

[0419] Synthesis of 1-((5-amino-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-88) and 1-((5-amino-8-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-89). To a mixture of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-5-amine and 2-(chloromethyl)-8-cyclopropylimidazo[1,2-a]pyridin-5-amine (80 mg, 0.36 mmol) and N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (99 mg, 0.36 mmol) in DMF (4 mL) was added Cs_2CO_3 (234 mg, 0.72 mmol). The mixture was stirred at RT for 8 h. Water (50 mL) was added to the reaction and extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated and purified by prep-HPLC to give 1-((5-amino-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (16.4 mg, yield: 10.0%) as a white solid. ESI-MS $[M+H]^+$: 461.2. Purity: 99.5% and 1-((5-amino-8-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (4.1 mg, yield: 2.5%) as a white solid. ESI-MS $[M+H]^+$: 461.1. Purity: 95.3%. 1-((5-amino-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide ^1H NMR (400 MHz, DMSO): δ 8.58 (t, J = 5.6 Hz, 1H), 8.37-8.13 (m, 3H), 7.82 (d, J = 31.9 Hz, 3H), 6.92 (d, J = 9.0 Hz, 1H), 6.74-6.58 (m, 2H), 6.41 (s, 2H), 5.36 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 1.76 (m, 1H), 0.88 (m, 2H), 0.51 (t, J = 4.7 Hz, 2H). 1-((5-amino-8-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide. ^1H

NMR (400 MHz, DMSO): δ 8.60 (t, J = 5.7 Hz, 1H), 8.30 (d, J = 7.1 Hz, 1H), 8.22 (s, 1H), 7.89 (s, 1H), 7.79 (s, 1H), 7.65 (s, 1H), 6.84-6.59 (m, 2H), 6.28 (s, 2H), 5.85 (d, J = 7.6 Hz, 1H), 5.42 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 2.23 (m, 1H), 0.92-0.79 (m, 2H), 0.72 (m, 1H).

Example 90

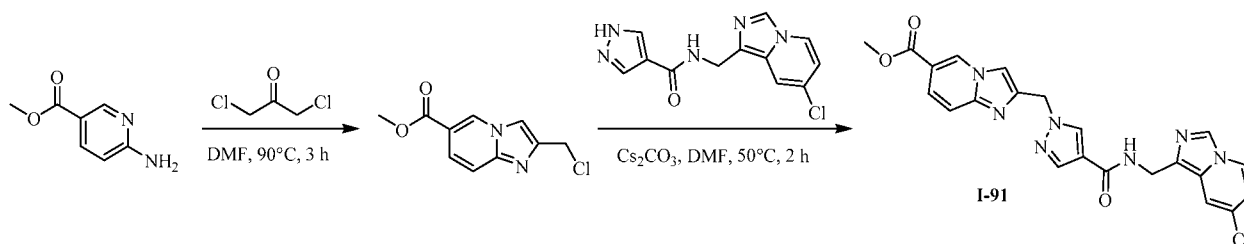
Scheme 89



[0420] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl-d₂)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-90). To a solution of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (65 mg, 0.23 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methan-d₂-amine hydrochloride (50 mg, 0.23 mmol) and HATU (114 mg, 0.3 mmol) in DMF (15 mL) was added DIPEA (148 mg, 1.15 mmol). The resulting reaction was stirred at RT for 12 h. H₂O (25 mL) was added to the reaction and extracted with EtOAc (25 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give the N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl-d₂)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (20 mg, yield: 19%). ESI-MS $[M+H]^+$: 448.2. Purity: 95.1%. ¹H NMR (400 MHz, DMSO): δ 8.56 (s, 1H), 8.32-8.29 (m, 3H), 8.20 (s, 1H), 7.85 (s, 1H), 7.78 (s, 1H), 7.71 (s, 1H), 7.39 (d, J = 9.3 Hz, 1H), 6.99 (d, J = 9.3 Hz, 1H), 6.71-6.58 (m, 1H), 5.38 (s, 2H), 1.91 (ddd, J = 13.3, 8.6, 5.1 Hz, 1H), 0.91 (q, J = 5.7 Hz, 2H), 0.66 (q, J = 5.0 Hz, 2H).

Example 91

Scheme 90

**[0421] Synthesis of methyl 2-(chloromethyl)imidazo[1,2-a]pyridine-6-carboxylate.**

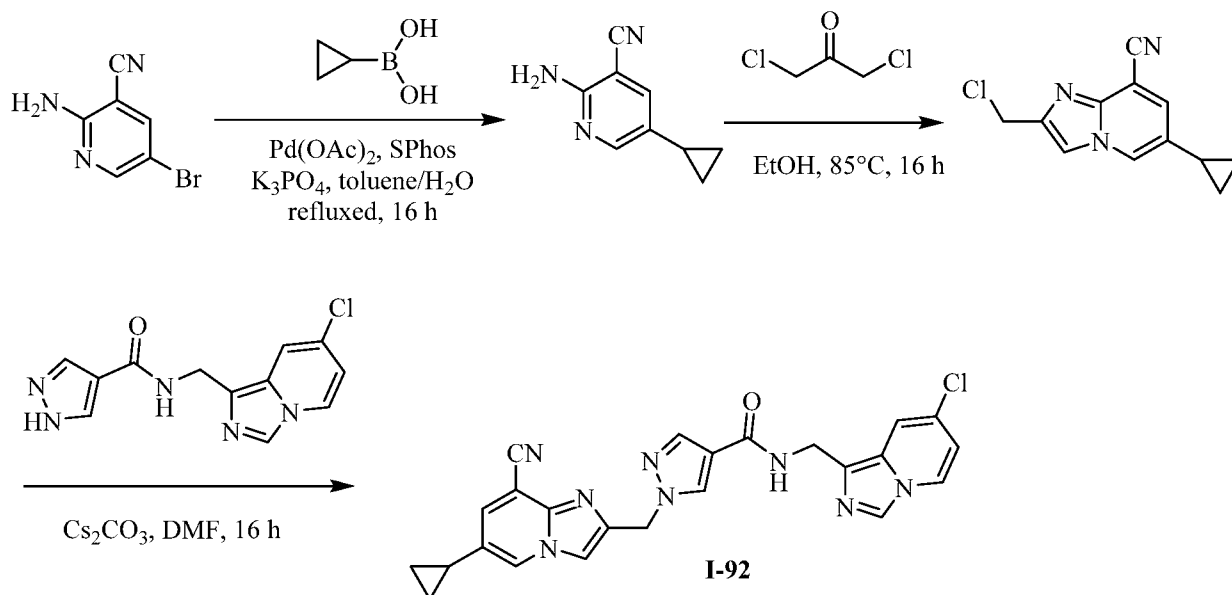
The mixture of methyl 6-aminonicotinate (1.20 g, 7.88 mmol) and 1,3-dichloropropan-2-one (2.0 g, 15.77 mmol) in DMF (10 mL) was heated to 90 °C and stirred for 3 h. The reaction mixture was poured into H₂O (60 mL), adjusted pH to 9 by addition of aqueous NaHCO₃ and extracted with EtOAc (60 mL x 3). The combined organics were washed with brine (100 mL), dried over anhydrous Na₂SO₄, concentrated and purified by column chromatography (EtOAc/PE = 1:1) to afford methyl 2-(chloromethyl)imidazo[1,2-a]pyridine-6-carboxylate (570 mg, 32%) as a yellow solid. ESI-MS [M+H]⁺: 225.1.

[0422] Synthesis of methyl 2-(((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)imidazo[1,2-a]pyridine-6-carboxylate (I-91).

A mixture of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (100 mg, 0.36 mmol), methyl 2-(chloromethyl)imidazo[1,2-a]pyridine-6-carboxylate (90 mg, 0.40 mmol) and Cs₂CO₃ (235 mg, 0.72 mmol) in DMF (5 mL) was stirred for 2 h at 50 °C. The reaction mixture was poured into H₂O (50 mL), solid was precipitated and filtered to give the crude product, which was purified by column chromatography (DCM:MeOH = 10:1) to afford methyl 2-(((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)imidazo[1,2-a]pyridine-6-carboxylate (70 mg, 42%) as a yellow solid. ESI-MS [M+H]⁺: 464.1. Purity: 99.39%. ¹H NMR (400 MHz, DMSO): δ 9.32 (s, 1H), 8.59 (t, J = 5.5 Hz, 1H), 8.29 (m, 3H), 8.01 (s, 1H), 7.88 (s, 1H), 7.79 (s, 1H), 7.60 (dd, J = 25.5, 9.5 Hz, 2H), 6.65 (dd, J = 7.5, 1.8 Hz, 1H), 5.46 (s, 2H), 4.56 (d, J = 5.6 Hz, 2H), 3.87 (s, 3H).

Example 92

Scheme 91



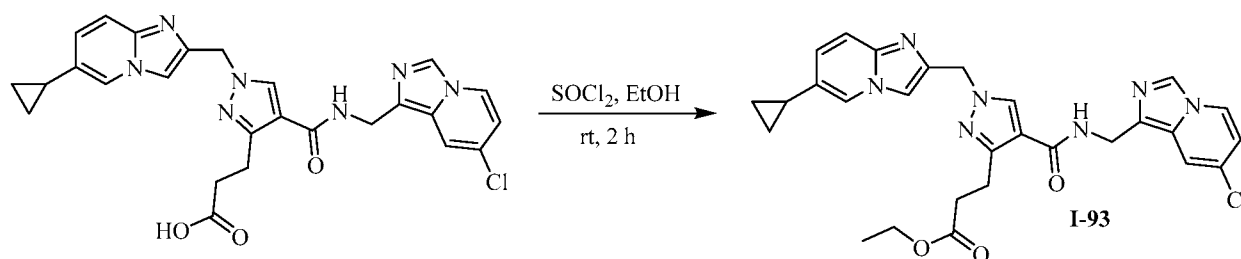
[0423] Synthesis of 2-amino-5-cyclopropylnicotinonitrile. To a mixture of 2-amino-5-bromonicotinonitrile (1 g, 5.1 mmol), cyclopropylboronic acid (647 mg, 7.6 mmol) and K_3PO_4 (3.78 g, 17.85 mmol) in toluene/ H_2O (20 mL/2 mL) was added Pd(OAc)_2 (114 mg, 0.51 mmol) and SPhos (209 mg, 0.51 mmol). The mixture was stirred at 95 °C for 16 h. The reaction was cooled to RT and the reaction residue was filtered. The filtrate was concentrated to give the crude product which was purified by silica gel chromatography (EA/PE = 4/1) to give 2-amino-5-cyclopropylnicotinonitrile (570 mg, yield: 71%) as a yellow solid. ESI-MS $[\text{M}+\text{H}]^+$: 160.1.

[0424] Synthesis of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carbonitrile. To a solution of 2-amino-5-cyclopropylnicotinonitrile (570 mg, 3.58 mmol) in EtOH (20 mL) was added 1, 3-dichloropropan-2-one (1.37 g, 10.75 mmol). The reaction mixture was stirred at 85 °C for 16 h. The reaction was concentrated and the residue was diluted with NaHCO_3 (aq, 20 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated to give the crude which was purified by silica gel chromatography (EA/PE = 2/1) to give 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carbonitrile (500 mg, yield: 58%) as a yellow solid. ESI-MS $[\text{M}+\text{H}]^+$: 232.1.

[0425] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-92). To a mixture of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carbonitrile (80 mg, 0.35 mmol) in dry DMF (5 mL) was added N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (95 mg, 0.35 mmol) and Cs₂CO₃ (338 mg, 1.04 mmol). The mixture was stirred at RT for 16 h. Then H₂O (30 mL) was added to the reaction and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give the crude, which was purified by prep-TLC (DCM/MeOH = 10/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (34.5 mg, yield: 21%) as a white solid. ESI-MS [M+H]⁺: 471.1. Purity: 98.67%. ¹H NMR (400 MHz, DMSO): δ 8.67 (d, J = 1.5 Hz, 1H), 8.60 (t, J = 5.7 Hz, 1H), 8.31-8.29 (m, 2H), 8.24 (s, 1H), 7.87 (d, J = 13.6 Hz, 2H), 7.78 (t, J = 1.9 Hz, 2H), 6.65 (dd, J = 7.4, 2.1 Hz, 1H), 5.47 (s, 2H), 4.56 (d, J = 5.7 Hz, 2H), 1.99-1.95 (m, 1H), 0.97-0.93 (m, 2H), 0.77-0.73 (m, 2H).

Example 93

Scheme 92

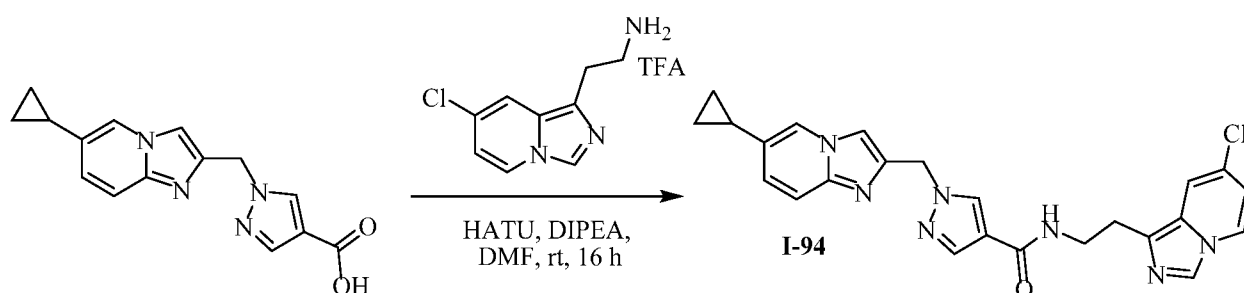


[0426] Synthesis of ethyl 3-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-3-yl)propanoate (I-93). To a solution of 3-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-3-yl)propanoic acid (20 mg, 0.04 mmol) in EtOH (4 mL) was added SOCl₂ (0.5 mL). The reaction was stirred at RT for 2 h. After concentration, the crude product was purification by prep-TLC (DCM/MeOH = 10/1) to give ethyl 3-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-3-yl)propanoate (13 mg, yield: 57%) as a white solid. ESI-MS [M+H]⁺: 546.2. Purity: 89.6%. ¹H

NMR (400 MHz, MeOD): δ 8.23 (s, 1H), 8.17-8.11 (m, 2H), 8.01 (d, J = 3.3 Hz, 1H), 7.71 (d, J = 0.8 Hz, 1H), 7.66 (s, 1H), 7.35 (d, J = 9.4 Hz, 1H), 7.07 (dd, J = 9.4, 1.7 Hz, 1H), 6.60 (dd, J = 7.5, 2.0 Hz, 1H), 5.33 (s, 2H), 4.65 (s, 2H), 4.03 (q, J = 7.1 Hz, 2H), 3.15 (t, J = 7.6 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 1.95-1.89 (m, 1H), 1.14 (t, J = 7.1 Hz, 3H), 1.01-0.90 (m, 2H), 0.72-0.66 (m, 2H).

Example 94

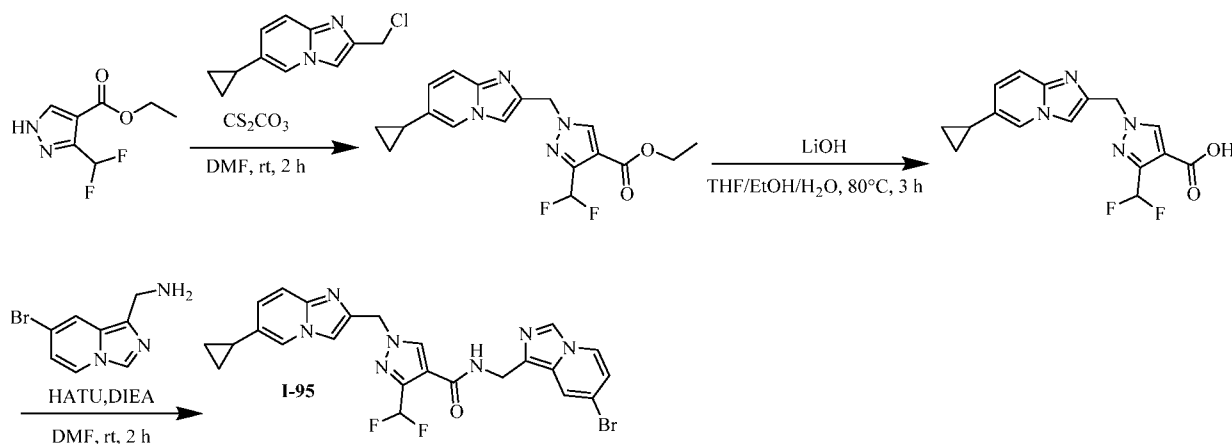
Scheme 93



[0427] **Synthesis of N-(2-(7-chloroimidazo[1,5-a]pyridin-1-yl)ethyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-94).** A mixture of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (60 mg, 0.2 mmol), 2-(7-chloroimidazo[1,5-a]pyridin-1-yl)ethanamine (60 mg, 0.2 mmol), HATU (90 mg, 0.24 mmol) and DIPEA (0.1 mL, 0.5 mmol) in DMF (10 mL) was stirred at RT for 16 h. H₂O (20 mL) was added to reaction and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified by prep-HPLC to give N-(2-(7-chloroimidazo[1,5-a]pyridin-1-yl)ethyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (31 mg, yield: 33.8%) as a yellow solid. ESI-MS $[M+H]^+$: 460.1. Purity: 100.0%. ¹H NMR (400 MHz, DMSO): δ 8.34 (s, 1H), 8.29 (s, 1H), 8.26 (d, J = 7.4 Hz, 1H), 8.14 (s, 2H), 7.76 (d, J = 22.4 Hz, 2H), 7.60 (d, J = 0.9 Hz, 1H), 7.40 (d, J = 9.4 Hz, 1H), 7.00 (dd, J = 9.4, 1.7 Hz, 1H), 6.57 (dd, J = 7.5, 2.0 Hz, 1H), 5.39 (s, 2H), 3.44 (dd, J = 13.2, 6.9 Hz, 3H), 2.95 (t, J = 7.2 Hz, 2H), 2.01-1.77 (m, 1H), 1.00-0.76 (m, 2H), 0.75-0.54 (m, 2H).

Example 95

Scheme 94



[0428] Synthesis of ethyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(difluoromethyl)-1H-pyrazole-4-carboxylate. A solution of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyrimidine (40 mg, 0.19 mmol), N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (60 mg, 0.19 mmol), and Cs_2CO_3 (248 mg, 0.76 mmol) in DMF (3 mL) was stirred at RT for 2 h. Then the reaction mixture was diluted with H_2O (40 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated to give the desired compound ethyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(difluoromethyl)-1H-pyrazole-4-carboxylate (400 mg, yield: 67%) as brown oil, which was used in the next step without purification. ESI-MS $[\text{M}+\text{H}]^+$: 361.1.

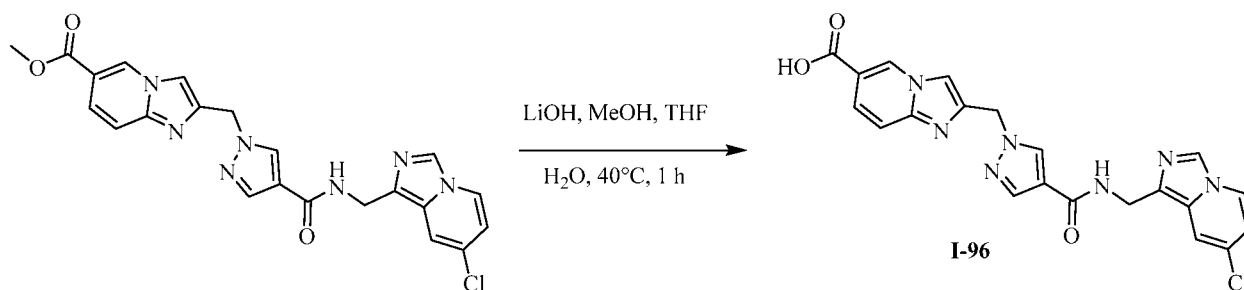
[0429] Synthesis of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(difluoromethyl)-1H-pyrazole-4-carboxylic. A solution of ethyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(difluoromethyl)-1H-pyrazole-4-carboxylate (400 mg, 1.11 mmol) and LiOH (233 mg, 5.55 mmol) in THF/EtOH/ H_2O (10 mL/10 mL/5 mL) was stirred at RT for 3 h. Most of the solvent was concentrated and the pH of the residue was adjusted to 4 by adding 1 M HCl solution. Solid was precipitated and filtered to give 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(difluoromethyl)-1H-pyrazole-4-carboxylic acid (300 mg, yield: 81%) as a brown solid, which was used in the next step without purification. ESI-MS $[\text{M}+\text{H}]^+$: 333.1.

[0430] Synthesis of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(difluoromethyl)-1H-pyrazole-4-

carboxamide (I-95). A solution of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(difluoromethyl)-1H-pyrazole-4-carboxylic acid (65 mg, 0.19 mmol), (7-bromoimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (50 mg, 0.19 mmol), HATU (149 mg, 0.39 mmol) and DIPEA (76 mg, 0.58 mmol) in DMF (5 mL) was stirred at RT for 2 h. Then the reaction mixture was diluted with H₂O (25 mL) and extracted with EtOAc (25 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified by column chromatography (PE/EA = 10/1) to give the desired compound N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamide (18 mg, yield: 18%) as a white solid. ESI-MS [M+H]⁺: 540.1. Purity: 98.48%. ¹H NMR (400 MHz, DMSO): δ 8.77 (s, 1H), 8.66 (s, 1H), 8.48 (s, 1H), 8.39 (s, 1H), 8.26 (d, J = 7.4 Hz, 1H), 8.14 (s, 1H), 7.97 (s, 1H), 7.73 (d, J = 9.3 Hz, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.38 (t, J = 53.8 Hz, 2H), 6.83-6.76 (m, 1H), 5.69 (s, 2H), 4.59 (s, 2H), 2.11-2.02 (m, 1H), 1.07-0.98 (m, 2H), 0.82-0.72 (m, 2H).

Example 96

Scheme 95

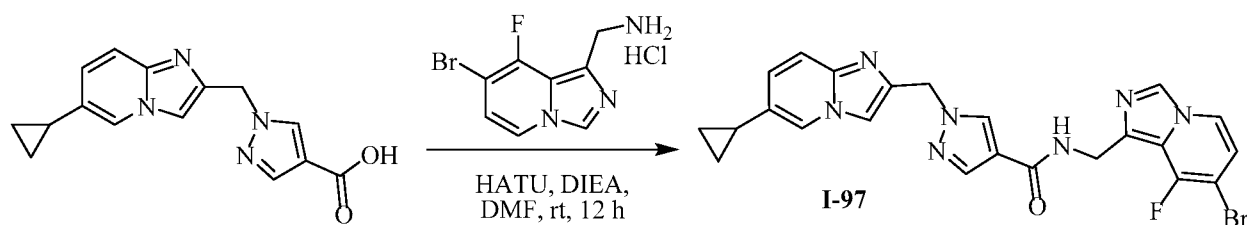


[0431] Synthesis of 2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)imidazo[1,2-a]pyridine-6-carboxylic acid (I-96). To a solution of methyl 2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)imidazo[1,2-a]pyridine-6-carboxylate (35 mg, 0.075 mmol) in methanol (2 mL), THF (2 mL) and H₂O (1 mL) was added lithium hydroxide monohydrate (44 mg, 1.05 mmol). The mixture was stirred for 1 h at 40 °C. The pH value of the residue was adjusted to 4 by adding 1 M HCl solution. The resulting mixture was concentrated and purified by prep-HPLC to give 2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-

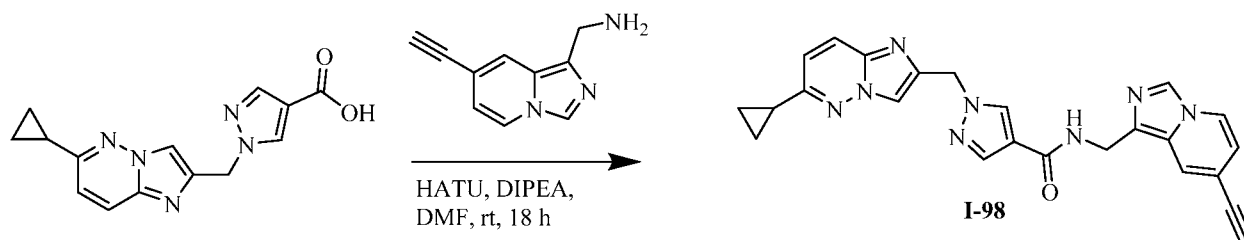
1-yl)methyl)imidazo[1,2-a]pyridine-6-carboxylic acid (25 mg, 74%) as a white solid. ESI-MS $[M+H]^+$: 225.1. Purity: 93.06%. ^1H NMR (400 MHz, DMSO): δ 13.15 (s, 1H), 9.25 (s, 1H), 8.59 (t, $J = 5.8$ Hz, 1H), 8.31 (m, 2H), 8.25 (s, 1H), 7.98 (s, 1H), 7.87 (s, 1H), 7.79 (s, 1H), 7.59 (m, 2H), 6.65 (dd, $J = 7.5, 2.0$ Hz, 1H), 5.45 (s, 2H), 4.56 (d, $J = 5.7$ Hz, 2H).

Example 97

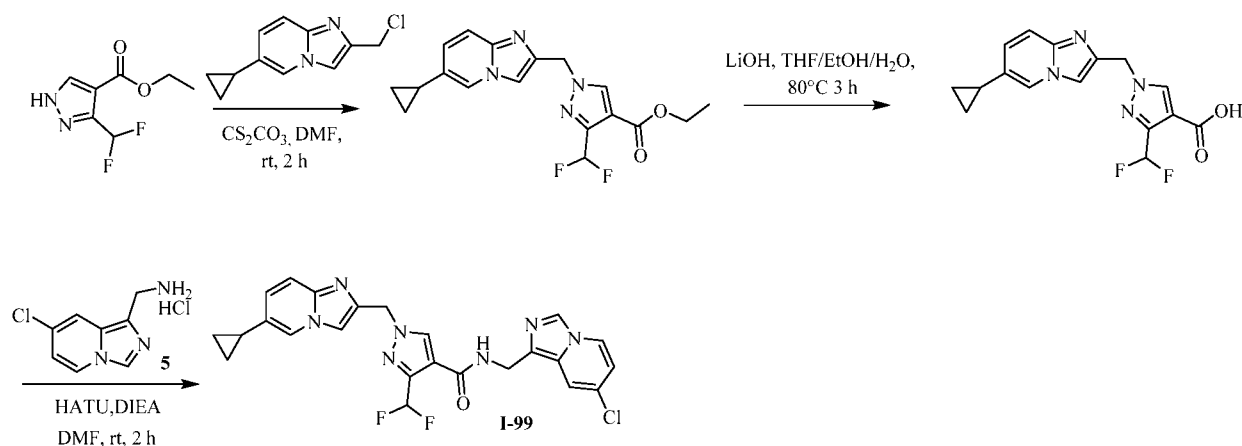
Scheme 96



[0432] Synthesis of N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-97). To a solution of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (60 mg, 0.21 mmol), (7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (84 mg, 0.32 mmol) and HATU (120 mg, 0.31 mmol) in DMF (5 mL) was added DIPEA (81 mg, 0.63 mmol). The resulting reaction was stirred at RT for 12 h. H_2O (25 mL) was added to the reaction, extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to the N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (20 mg, yield: 19%) as a white solid. ESI-MS $[M+H]^+$: 508.1. Purity: 98.9%. ^1H NMR (400 MHz, DMSO): δ 8.46 (d, $J = 2.2$ Hz, 1H), 8.42 (t, $J = 4.8$ Hz, 1H), 8.33 (s, 1H), 8.20 (s, 1H), 8.14 (d, $J = 7.3$ Hz, 1H), 7.84 (s, 1H), 7.72 (s, 1H), 7.39 (d, $J = 9.3$ Hz, 1H), 6.99 (d, $J = 9.3$ Hz, 1H), 6.82 (t, $J = 6.6$ Hz, 1H), 5.39 (s, 2H), 4.62 (d, $J = 5.2$ Hz, 2H), 1.94-1.88 (m, 1H), 0.95-0.87 (m, 2H), 0.71-0.61 (m, 2H).

Example 98Scheme 97

[0433] Synthesis of 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-N-((7-ethynylimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-98). A solution of 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (66 mg, 0.23 mmol), (7-ethynylimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (47 mg, 0.23 mmol), HATU (175 mg, 0.46 mmol) and DIPEA (89 mg, 0.69 mmol) in DMF (5 mL) was stirred at RT for 2 h. Then the reaction mixture was diluted with H₂O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to give the crude, which was purified by prep-HPLC to give 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-N-((7-ethynylimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (10 mg, yield: 10%) as a white solid. ESI-MS [M+H]⁺: 437.2. Purity: 97.51%. ¹H NMR (400 MHz, DMSO): δ 8.61 (t, J = 5.6 Hz, 1H), 8.48 (s, 1H), 8.27 (d, J = 7.1 Hz, 1H), 8.22 (s, 1H), 8.10 (s, 1H), 7.96-7.91 (m, 2H), 7.85 (s, 1H), 7.11 (t, J = 7.7 Hz, 1H), 6.63 (d, J = 7.3 Hz, 1H), 5.42 (s, 2H), 4.60 (d, J = 5.7 Hz, 2H), 4.30 (s, 1H), 2.22-2.13 (m, 1H), 1.10-1.03 (m, 2H), 1.00-0.94 (m, 2H).

Example 99Scheme 98

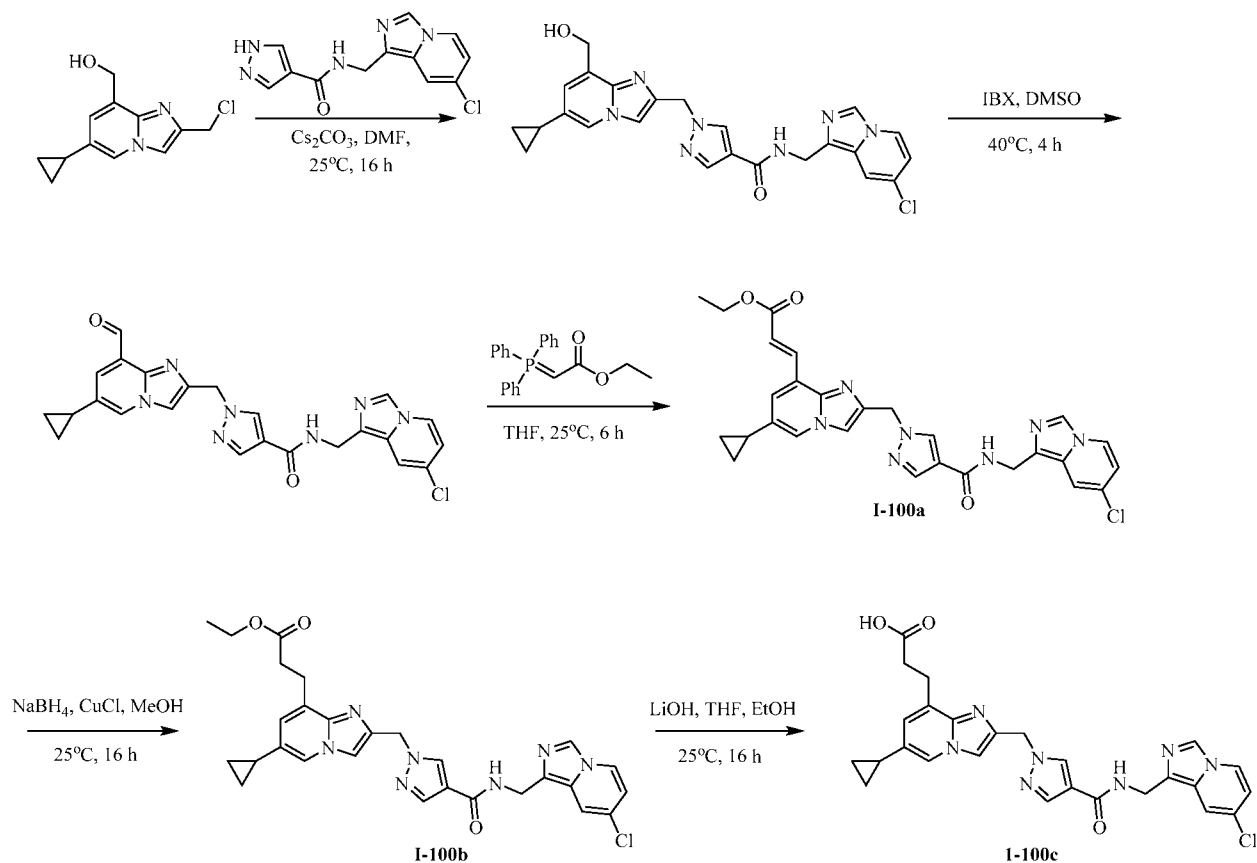
[0434] Synthesis of ethyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(difluoromethyl)-1H-pyrazole-4-carboxylate. A mixture of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (40 mg, 0.19 mmol), N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (60 mg, 0.19 mmol) and Cs_2CO_3 (248 mg, 0.76 mmol) in DMF (2 mL) was stirred at RT for 2 h. Then the reaction mixture was diluted with H_2O (40 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give the desired compound ethyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(difluoromethyl)-1H-pyrazole-4-carboxylate (400 mg, yield: 67%) as brown oil, which was used in the next step without purification. ESI-MS $[\text{M}+\text{H}]^+$: 361.1.

[0435] Synthesis of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(difluoromethyl)-1H-pyrazole-4-carboxylic. A solution of ethyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(difluoromethyl)-1H-pyrazole-4-carboxylate (400 mg, 1.11 mmol) and LiOH (233 mg, 5.55 mmol) in THF/EtOH/ H_2O (10 mL/10 mL/5 mL) was stirred at RT for 3 h. Most of the solvent was concentrated and the pH of the residue was adjusted to 4 by adding 1 M HCl solution. Solid was precipitated and filtered to give the desired compound 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(difluoromethyl)-1H-pyrazole-4-carboxylic acid (300 mg, yield: 81%) as a brown solid, which was used in the next step without purification. ESI-MS $[\text{M}+\text{H}]^+$: 333.2.

[0436] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamide (I-99). A solution of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(difluoromethyl)-1H-pyrazole-4-carboxylic acid (65 mg, 0.19 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (41 mg, 0.19 mmol), HATU (149 mg, 0.39 mmol) and DIPEA (76 mg, 0.58 mmol) in DMF (5 mL) was stirred at RT for 2 h. Then the reaction mixture was diluted with H₂O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to give the crude, which was purified by column chromatography (DCM/MeOH = 10/1) to give the desired compound N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(difluoromethyl)-1H-pyrazole-4-carboxamide (18 mg, yield: 18%) as a white solid. ESI-MS [M+H]⁺: 496.2. Purity: 91.43%. ¹H NMR (400 MHz, DMSO): δ 8.61 (t, J = 5.6 Hz, 1H), 8.48 (s, 1H), 8.27 (d, J = 7.1 Hz, 1H), 8.22 (s, 1H), 8.10 (s, 1H), 7.96-7.91 (m, 2H), 7.85 (s, 1H), 7.11 (t, J = 7.7 Hz, 1H), 6.63 (d, J = 7.3 Hz, 1H), 5.42 (s, 2H), 4.60 (d, J = 5.7 Hz, 2H), 4.30 (s, 1H), 2.22-2.13 (m, 1H), 1.10-1.03 (m, 2H), 1.00-0.94 (m, 2H).

Example 100

Scheme 99



[0437] **Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide.** To a mixture of (2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methanol (370 mg, 1.56 mmol) in dry DMF (10 mL) was added N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (430 mg, 1.56 mmol) and Cs_2CO_3 (1.53 g, 4.68 mmol). The mixture was stirred at 25 °C for 16 h. Then H_2O (50 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated to give the crude, which was purified by silica gel chromatography (DCM/MeOH = 10/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (400 mg, yield: 53.8%) as a yellow solid. ESI-MS $[\text{M}+\text{H}]^+$: 476.2.

[0438] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-formylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide. To a mixture of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (400 mg, 0.84 mmol) in DMSO (10 mL) was added 2-iodoxybenzoic acid (472 mg, 1.68 mmol). The mixture was stirred at 40 °C for 4 h. Then H₂O (80 mL) was added, and the precipitate was filtered and dried to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-formylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (200 mg, yield: 50%) as a white solid, which was used in the next step without purification. ESI-MS [M+H]⁺: 474.1.

[0439] Synthesis of ethyl 3-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acrylate (I-100a). To a mixture of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-formylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (200 mg, 0.4 mmol) in dry THF (8 mL) was added Ethyl (triphenylphosphoranylidene)acetate (152 mg, 0.44 mmol) at 0 °C. The mixture was stirred at 25 °C for 6 h, concentrated to give the crude, which was purified by Pre-TLC (DCM/MeOH = 10/1) to give ethyl 3-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acrylate (120 mg, yield: 52%) as a yellow solid. ESI-MS [M+H]⁺: 544.2. purity: 93.12%.

¹H NMR (400 MHz, DMSO) δ 8.59 (t, J = 5.7 Hz, 1H), 8.43-8.42 (m, 1H), 8.31-8.29 (m, 2H), 8.22 (s, 1H), 7.90 (s, 1H), 7.79-7.75 (m, 3H), 7.64-7.60 (m, 1H), 7.44-7.43 (m, 1H), 6.64 (dd, J = 7.4, 2.1 Hz, 1H), 5.47 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H), 1.95-1.91 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 0.94-0.91 (m, 2H), 0.76-0.72 (m, 2H).

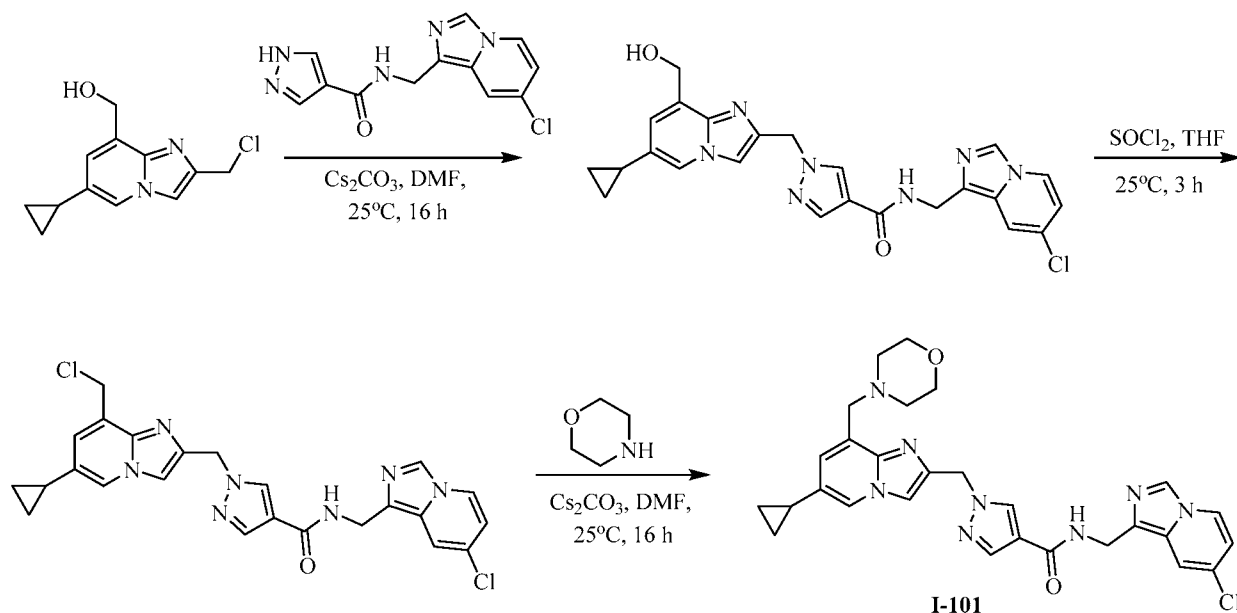
[0440] Synthesis of ethyl 3-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)propanoate (I-100b). To a mixture of ethyl 3-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acrylate (120 mg, 0.22 mmol) in MeOH (5 mL) was CuCl (43 mg, 0.44 mmol) and NaBH₄ (25 mg, 0.66 mmol). The mixture was stirred at 25 °C for 16 h. Water (30 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried

over Na₂SO₄, filtered and concentrated to give the crude, which was purified by prep-TLC (DCM/MeOH = 10/1) to give ethyl 3-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)propanoate (110 mg, yield: 91%) as a yellow solid. ESI-MS [M+H]⁺: 546.2. Purity: 99.11%. ¹H NMR (400 MHz, DMSO): δ 8.59 (t, J = 5.5 Hz, 1H), 8.31-8.29 (m, 2H), 8.20-8.19 (m, 2H), 7.88 (s, 1H), 7.78 (s, 1H), 7.66 (s, 1H), 6.82 (s, 1H), 6.64 (dd, J = 7.4, 2.0 Hz, 1H), 5.40 (s, 2H), 4.55 (d, J = 5.6 Hz, 2H), 4.04 (q, J = 7.1 Hz, 2H), 3.07 (t, J = 7.6 Hz, 2H), 2.77 (t, J = 7.6 Hz, 2H), 1.90-1.84 (m, 1H), 1.14 (t, J = 7.1 Hz, 3H), 0.92-0.87 (m, 2H), 0.66-0.62 (m, 2H).

[0441] Synthesis of 3-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)propanoic acid (I-100c). To a mixture of ethyl 3-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)propanoate (40 mg, 0.07 mmol) in THF/EtOH/H₂O (1 mL/1 mL/1 mL) was added LiOH (5.3 mg, 0.22 mmol). The mixture was stirred at 25 °C for 6 h. The pH of the residue was adjusted to 4 by adding 1 M HCl solution. The mixture was concentrated and purified by prep-HPLC to give 3-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)propanoic acid (14 mg, yield: 37%) as a yellow solid. ESI-MS [M+H]⁺: 518.2. Purity: 99.18%. ¹H NMR (400 MHz, DMSO) δ 12.18 (s, 1H), 8.59 (t, J = 5.6 Hz, 1H), 8.31-8.29 (m, 2H), 8.20-8.18 (m, 2H), 7.88 (s, 1H), 7.78 (s, 1H), 7.65 (s, 1H), 6.82 (s, 1H), 6.66-6.63 (m, 1H), 5.40 (s, 2H), 4.55 (d, J = 5.6 Hz, 2H), 3.04 (t, J = 7.5 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 1.89-1.85 (m, 1H), 0.90-0.88 (m, 2H), 0.66-0.64 (m, 2H).

Example 101

Scheme 100



[0442] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide. To a mixture of (2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methanol (370 mg, 1.56 mmol) in dry DMF (10 mL) was added N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (430 mg, 1.56 mmol) and Cs_2CO_3 (1.53 g, 4.68 mmol). The mixture was stirred at 25 °C for 16 h. Then H_2O (100 mL) was added to the reaction and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated to give the crude, which was purified by prep-TLC (DCM/MeOH = 10/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (400 mg, yield: 53.9%) as a yellow solid. ESI-MS $[\text{M}+\text{H}]^+$: 476.1.

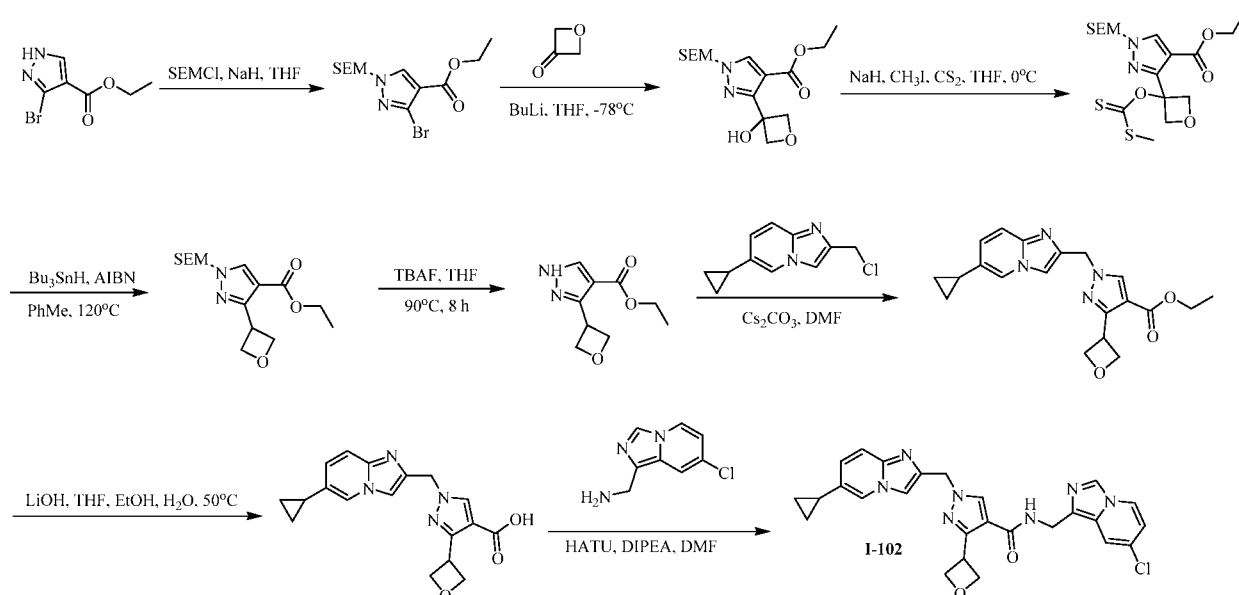
[0443] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide. To a mixture of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide

(50 mg, 0.1 mmol) in THF (2 mL) was added SOCl₂ (0.5 mL). The mixture was stirred at 25 °C for 3 h. Then the reaction mixture was concentrated to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (50 mg, yield: 96%) as a yellow solid, which was used into the next step without purification. ESI-MS [M+H]⁺: 494.1.

[0444] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(morpholinomethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-101). To a mixture of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (50 mg, 0.1 mmol) in dry DMF (3 mL) was added morpholine (17.6 mg, 0.2 mmol) and Cs₂CO₃ (163 mg, 0.5 mmol). The mixture was stirred at 25 °C for 16 h. Water (30 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give the crude, which was purified by prep-TLC (DCM/MeOH = 8/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(morpholinomethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (11.6 mg, yield: 21%) as a white solid. ESI-MS [M+H]⁺: 545.2. Purity: 99.15%. ¹H NMR (400 MHz, DMSO): δ 8.58 (t, J = 5.7 Hz, 1H), 8.31-8.29 (m, 2H), 8.22-8.19 (m, 2H), 7.87 (s, 1H), 7.77 (m, 1H), 7.68 (s, 1H), 6.99 (s, 1H), 6.64 (dd, J = 7.5, 2.1 Hz, 1H), 5.39 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 3.75 (s, 2H), 3.60-3.58 (m, 4H), 2.44 (s, 4H), 1.96-1.89 (m, 1H), 0.94-0.89 (m, 2H), 0.66-0.62 (m, 2H).

Example 102

Scheme 101



[0445] Synthesis of ethyl 3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxylate. To a solution of ethyl 3-bromo-1H-pyrazole-4-carboxylate (547 mg, 2.5 mmol) and NaH (150 mg, 3.75 mmol, 60% oil) in THF (5 mL) and under N₂ was added SEMCl (458 mg, 2.75 mmol) at 0 °C. The reaction mixture was stirred at RT for 2 h. The reaction was quenched with H₂O (30 mL) and extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to afford ethyl 3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxylate as a yellow oil (873 mg, yield: 99%) and a mixture of N1 and N2 regioisomers. ESI-MS [M+H]⁺: 350.1.

[0446] Synthesis of ethyl 3-(3-hydroxyoxetan-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxylate. To a solution of ethyl 3-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxylate (615 mg, 1.76 mmol) in THF (8 mL) under N₂ was added BuLi (0.9 mL, 2.11 mmol, 2.4 M solution in hexane) at -78 °C. Then oxetan-3-one (2.1 mL, 35.2 mmol) was added. The reaction was allowed to warm to RT and stirred for 2 h. The reaction mixture was quenched with saturated NH₄Cl solution (20 mL) and extracted with EtOAc (50 mL x3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give crude, which was purified by a column flash

(PE:EA = 2:1) to get ethyl 3-(3-hydroxyoxetan-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxylate (169 mg, yield: 28%) as a yellow oil. ESI-MS $[M+H]^+$: 343.2.

[0447] Synthesis of ethyl 3-(3-(((methylthio)carbonothioyl)oxy)oxetan-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxylate. To a mixture of NaH (54 mg, 1.34 mmol, 60% oil) in THF (1 mL) was added a solution of ethyl 3-(3-hydroxyoxetan-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxylate (306 mg, 0.89 mmol) in THF (0.5 mL) at 0 °C dropwise. The resulting solution was stirred at 0 °C for 30 min. Then a solution of CS₂ (102 mg, 1.34 mmol) in THF (0.5 mL) was added to the reaction at 0 °C dropwise. The resulting solution was stirred at 0 °C for another 1 h. To the mixture above was added a solution of iodomethane (190 mg, 1.34 mmol) in THF (0.5 mL) dropwise at 0 °C. The resulting solution was stirred at 0 °C for 1 h, then quenched with aqueous NH₄Cl (10 mL), and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to afford ethyl 3-(3-(((methylthio)carbonothioyl)oxy)oxetan-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxylate (385 mg crude) as yellow oil, which was used into next step without further purification. ESI-MS $[M+H]^+$: 433.1.

[0448] Synthesis of ethyl 3-(oxetan-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxylate. To a solution of ethyl 3-(3-(((methylthio)carbonothioyl)oxy)oxetan-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxylate (385 crude from previous step) in toluene (10 mL) were added Bu₃SnH (311 mg, 1.07 mmol) and AIBN (29 mg, 0.18 mmol). The resulting mixture was stirred at 120 °C for 3 h. The reaction was cooled to RT and concentrate in vacuo to give the crude, which was purified by silica gel column (PE/EA = 5/1) to isolate ethyl 3-(oxetan-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxylate (204 mg, yield: 70%) as yellow oil. ESI-MS $[M+H]^+$: 327.2.

[0449] Synthesis of ethyl 3-(oxetan-3-yl)-1H-pyrazole-4-carboxylate. To a solution of TBAF (3.2 mL, 3.13 mmol, 1 M solution in THF) was added ethyl 3-(oxetan-3-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazole-4-carboxylate (204 mg, 0.63 mmol). The mixture was stirred at 90 °C for 8 h. H₂O (25 mL) was added to the reaction and extracted with EtOAc (35 mL x 3). The combined organic layer were washed with brine, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by silica gel column (PE/EA = 1/2) to isolate

ethyl 3-(oxetan-3-yl)-1H-pyrazole-4-carboxylate (81 mg, yield: 66%) as a white solid. ESI-MS $[M+H]^+$: 197.2.

[0450] Synthesis of ethyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(oxetan-3-yl)-1H-pyrazole-4-carboxylate. To a solution of ethyl 3-(oxetan-3-yl)-1H-pyrazole-4-carboxylate (50 mg, 0.25 mmol) in DMF (5 mL) was added 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (63 mg, 0.31 mmol) and Cs_2CO_3 (245 mg, 0.75 mmol). The mixture was stirred at RT for 3 h. Water (20 mL) was added and extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give a residue, which was purified by silica gel column (DCM/MeOH = 20/1) to give ethyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(oxetan-3-yl)-1H-pyrazole-4-carboxylate (90 mg, yield: 98%) as a white solid. ESI-MS $[M+H]^+$: 367.2.

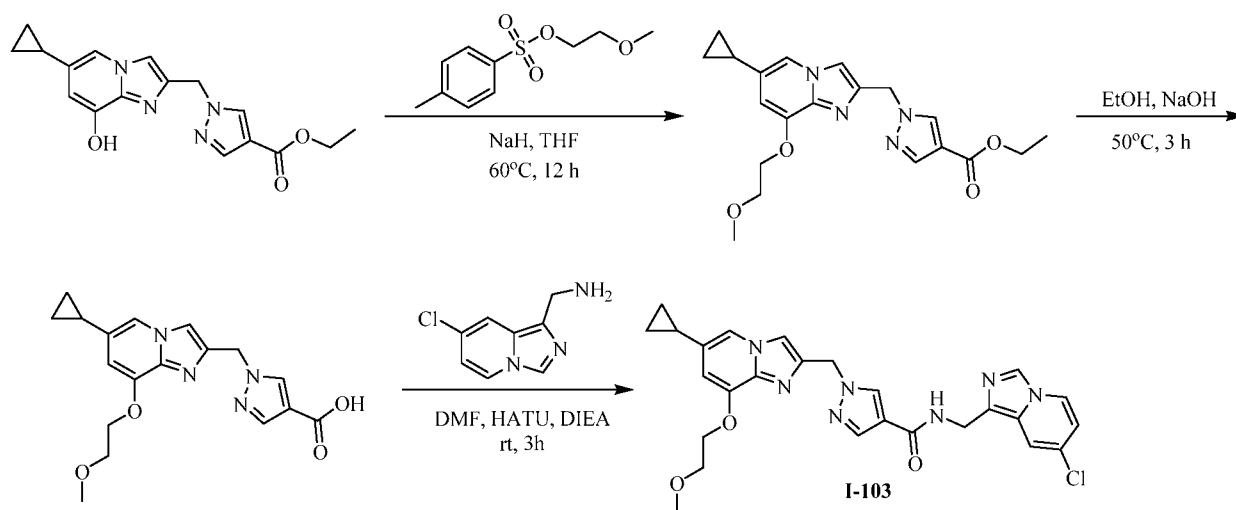
[0451] Synthesis of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(oxetan-3-yl)-1H-pyrazole-4-carboxylic acid. To a solution of ethyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(oxetan-3-yl)-1H-pyrazole-4-carboxylate (45 mg, 0.12 mmol) in THF/EtOH/ H_2O (2 mL/2 mL/1 mL) was added LiOH (10 mg, 0.24 mmol). The resulting mixture was stirred at 50 °C for 3 h. The mixture was freeze-dried to give 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(oxetan-3-yl)-1H-pyrazole-4-carboxylic acid as a lithium salt (50 mg crude), which was used in the next step without purification. ESI-MS $[M+H]^+$: 339.2.

[0452] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(oxetan-3-yl)-1H-pyrazole-4-carboxamide (I-102). To a solution of ethyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(oxetan-3-yl)-1H-pyrazole-4-carboxylic acid (50 mg crude from previous step) in DMF (3 mL) was added (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine (22 mg, 0.12 mmol), HATU (91 mg, 0.24 mmol) and DIPEA (47 mg, 0.36 mmol). The mixture was stirred at RT for 14 h. H_2O (20 mL) was added to the reaction and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give a residue. The residue was purified by flash silica gel column (DCM/MeOH = 8/1) to isolate N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-3-(oxetan-3-yl)-1H-pyrazole-4-carboxamide (34.8 mg, yield: 58%) as a white solid. ESI-MS $[M+H]^+$: 502.1. Purity: 97.10%. ^1H NMR (400 MHz, DMSO): δ 8.43 (t, J = 5.8 Hz, 1H), 8.34 (s,

1H), 8.30-8.29 (m, 2H), 8.21 (s, 1H), 7.77 (s, 1H), 7.74 (d, J = 1.9 Hz, 1H), 7.39 (d, J = 9.3 Hz, 1H), 7.00 (dd, J = 9.4, 1.7 Hz, 1H), 6.64 (dd, J = 7.5, 2.1 Hz, 1H), 5.36 (s, 2H), 4.83-4.82 (m, J = 8.4, 2H), 4.71-4.68 (m, 2H), 4.60-4.54 (m, 1H), 4.50 (d, J = 5.7 Hz, 2H), 1.95-1.88 (m, 1H), 0.94-0.89 (m, 2H), 0.68-0.64 (m, 2H).

Example 103

Scheme 102



[0453] Synthesis of ethyl 1-((8-((2-methoxyethoxy)methyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. To a mixture of ethyl 1-((8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (200 mg, 0.59 mmol) in THF (10 mL) was added 2-methoxyethyl 4-methylbenzenesulfonate (1.4 g, 5.9 mmol) and NaH (25 mg, 0.88 mmol). The resulting mixture was stirred at 60 °C for 12 h. Then reaction was quenched with H₂O (10 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude. The crude was purified with prep-TLC (PE/EA = 3/1) to give the ethyl 1-((8-((2-methoxyethoxy)methyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (158 mg, yield: 70%) as a white solid. ESI-MS [M+H]⁺: 385.1.

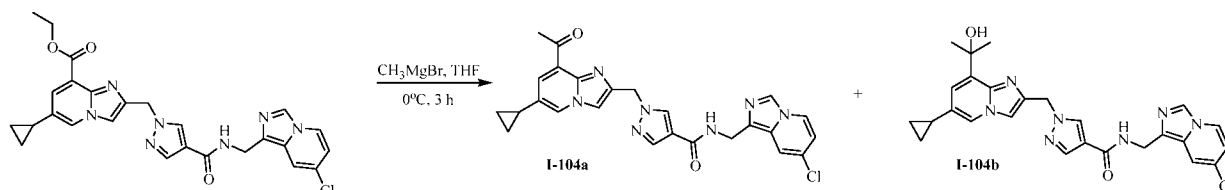
[0454] Synthesis of 1-((6-cyclopropyl-8-(2-methoxyethoxy)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. To a mixture of ethyl 1-((6-cyclopropyl-8-(2-

methoxyethoxy)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (158 mg, 0.41 mmol) in EtOH (5 mL) was added NaOH (64 mg, 1.6 mmol) in H₂O (2 mL). The mixture was stirred at 50 °C for 3 h. The pH value of the reaction was adjusted to 2-3. The resulting mixture was concentrated to give 1-((6-cyclopropyl-8-(2-methoxyethoxy)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (210 mg, crude) as a white solid which was used in the next step without purification. ESI-MS [M+H]⁺: 357.1.

[0455] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2-methoxyethoxy)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-103). To a mixture of 1-((6-cyclopropyl-8-(2-methoxyethoxy)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (210 mg, crude from last step) in DMF (5 mL) was added (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (126 mg, 0.58 mmol), DIPEA (146 mg, 1.45 mmol) and HATU (1.67 g, 0.44 mmol). The mixture was stirred at RT for 3 h. The reaction was quenched with H₂O (30 mL) and was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give the N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2-methoxyethoxy)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (28.7 mg, yield: 13% in 2 steps) as a white solid. ESI-MS [M+H]⁺: 534.2. Purity: 98.1%. ¹H NMR (400 MHz, DMSO): δ 8.69 (t, J = 5.6 Hz, 1H), 8.62 (s, 1H), 8.57 (s, 1H), 8.36 (d, J = 7.5 Hz, 1H), 8.32 (s, 1H), 8.11 (s, 1H), 7.97 (s, 1H), 7.87 (s, 1H), 7.64 (s, 1H), 6.77 (d, J = 7.3 Hz, 1H), 5.63 (s, 2H), 4.78 (s, 2H), 4.61 (d, J = 5.6 Hz, 2H), 3.63-3.56 (m, 2H), 3.53-3.37 (m, 2H), 3.20 (s, 3H), 2.10-2.04 (m, 1H), 1.06-1.02 (m, 2H), 0.79-0.75 (m, 2H).

Example 104

Scheme 103



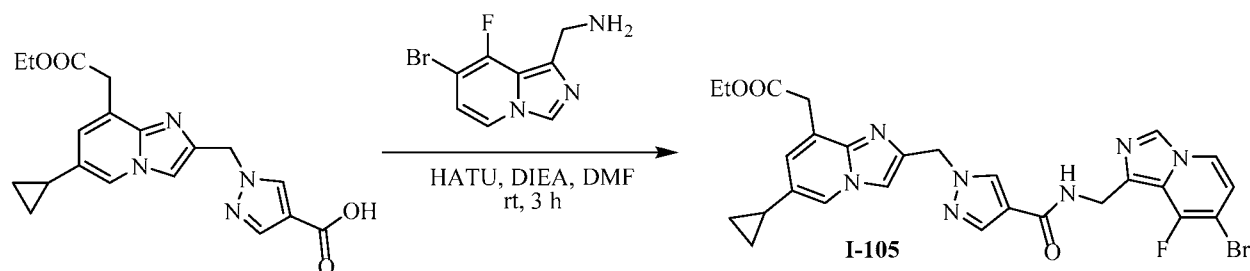
[0456] Synthesis of 1-((8-acetyl-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-104a).

A mixture of ethyl 2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carboxylate (150 mg, 0.29 mmol) in THF (5 mL) was added CH_3MgBr (1 M in THF, 1.45 mL, 1.45 mmol) at 0 °C. The mixture was stirred at 0 °C for 3 h under N_2 . The reaction was quenched with saturated NH_4Cl (aq., 3 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give the crude, which was purified with prep-HPLC to give 1-((8-acetyl-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (1.5 mg, yield: 1.05%) as a white solid. ESI-MS $[\text{M}+\text{H}]^+$: 488.2. Purity: 95.1%. ^1H NMR (400 MHz, MeOD): δ 8.85 (s, 1H), 8.72 (d, $J = 1.0$ Hz, 1H), 8.45 (d, $J = 1.4$ Hz, 1H), 8.34-8.30 (m, 2H), 8.06 (s, 1H), 7.98 (s, 1H), 7.92 (s, 1H), 6.89 (dd, $J = 7.5, 1.8$ Hz, 1H), 5.71 (s, 2H), 4.77 (s, 2H), 2.78 (s, 3H), 2.22-2.17 (m, 1H), 1.20-1.12 (m, 2H), 1.01-0.87 (m, 2H).

[0457] From the above reaction, N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2-hydroxypropan-2-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (**I-104b**) was also isolated (3.8 mg, yield: 2.6%) as a white solid. ESI-MS $[\text{M}+\text{H}]^+$: 504.2. Purity: 98.1%. ^1H NMR (400 MHz, MeOD): δ 8.15 (s, 1H), 8.06-8.05 (m, 2H), 7.98 (s, 1H), 7.82 (s, 1H), 7.63 (s, 1H), 7.55 (s, 1H), 7.06 (s, 1H), 6.55-6.49 (m, 1H), 5.38 (s, 2H), 4.58 (s, 2H), 1.87-1.79 (m, 1H), 1.58 (s, 6H), 0.91-0.83 (m, 2H), 0.65-0.58 (m, 2H).

Example 105

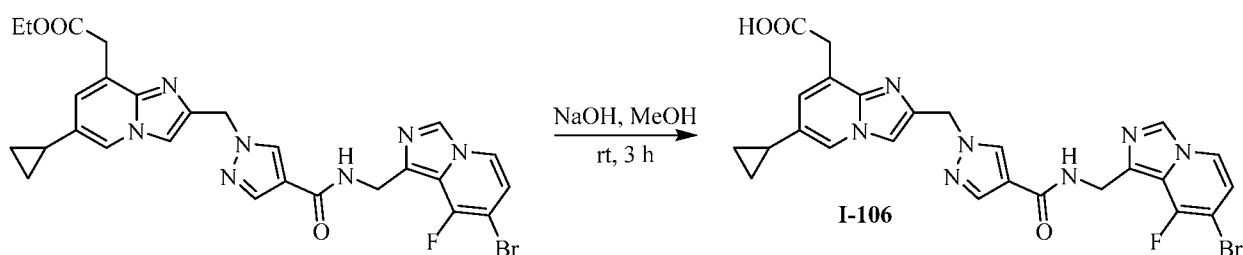
Scheme 104



[0458] Synthesis of ethyl 2-(2-((4-(((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetate (I-105). To a mixture of 1-((6-cyclopropyl-8-(2-ethoxy-2-oxoethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (150 mg, 0.42 mmol) in DMF (5 mL) was added (7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (235 mg, 0.84 mmol), DIPEA (150 mg, 1.15 mmol) and HATU (240 mg, 0.63 mmol). The mixture was stirred at RT for 3 h. H₂O (30 mL) was added and the reaction was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified with prep-HPLC to give the 2-(2-((4-(((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetate (21.6 mg, yield: 10.2%) as a white solid. ESI-MS [M+H]⁺: 494.1. Purity: 97.7%. ¹H NMR (400 MHz, DMSO): δ 8.61 (s, 1H), 8.49-8.47 (m, 2H), 8.30 (s, 1H), 8.15 (d, J = 7.4 Hz, 1H), 8.08 (s, 1H), 7.96 (s, 1H), 7.56 (s, 1H), 6.84 (dd, J = 7.2, 6.2 Hz, 1H), 5.62 (s, 2H), 4.64 (d, J = 5.2 Hz, 2H), 4.11-4.06 (m, 4H), 2.07-2.00 (m, 1H), 1.16 (t, J = 7.1 Hz, 3H), 1.06-1.01 (m, 2H), 0.77-0.73 (m, 2H).

Example 106

Scheme 105

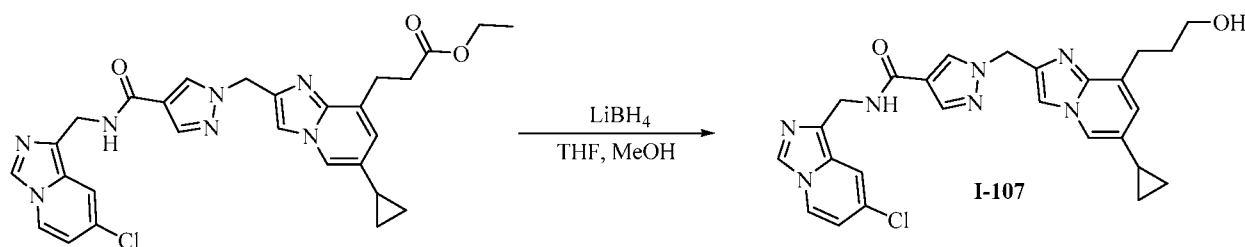


[0459] Synthesis of 2-(2-((4-(((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetic acid (I-106). To a solution of ethyl 2-(2-((4-(((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetate (20 mg, 0.034 mmol) in EtOH (2 mL) was added NaOH (4 mg, 0.16 mmol) in H₂O (1

mL). The mixture was stirred at RT for 3 h. The pH of the mixture was adjusted to 2-3. The resulting mixture was concentrated to give the crude, which was purified by prep-HPLC to give 2-(2-((4-(((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetic acid (7.1 mg, yield: 37%) as a white solid. ESI-MS $[M+H]^+$: 566.1. Purity: 92.9%. ^1H NMR (400 MHz, DMSO): δ 8.48-8.38 (m, 2H), 8.36 (s, 1H), 8.20-8.18 (m, 2H), 8.14 (d, $J = 7.3$ Hz, 1H), 7.86 (s, 1H), 7.65 (s, 1H), 6.91 (s, 1H), 6.82 (t, $J = 6.6$ Hz, 1H), 5.38 (s, 2H), 4.62 (d, $J = 4.9$ Hz, 2H), 3.72 (s, 2H), 1.90-1.86 (m, 1H), 0.93-0.85 (m, 2H), 0.66-0.61 (m, 2H).

Example 107

Scheme 106

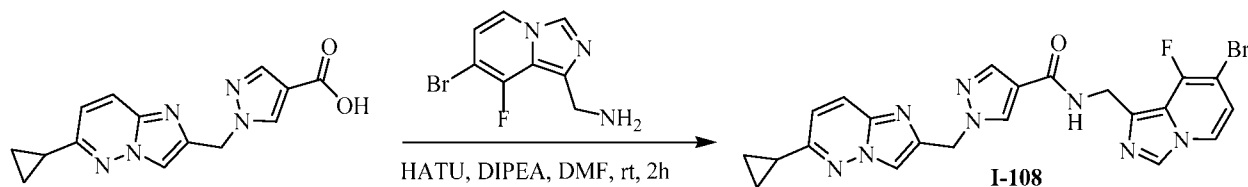


[0460] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(3-hydroxypropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-107). To a solution of ethyl 3-(2-((4-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)propanoate (35 mg, 0.064 mmol) in THF/MeOH (5 mL/0.5 mL) was added LiBH_4 (7 mg, 0.321 mmol) at 0 °C. The resulting reaction was stirred at RT for 4 h. H_2O (15 mL) was added to the reaction and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(3-hydroxypropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (10 mg, yield: 31%) as a white solid. ESI-MS $[M+H]^+$: 504.2. Purity: 97.9%. ^1H NMR (400 MHz, DMSO): δ 8.58 (t, $J = 5.7$ Hz, 1H), 8.32-8.28 (m, 2H), 8.22-8.15 (m, 2H), 7.88 (s, 1H), 7.78 (s, 1H), 7.64 (s, 1H), 6.80 (s, 1H), 6.66-6.62 (m, 1H), 5.39 (s, 2H), 4.57-4.52 (m,

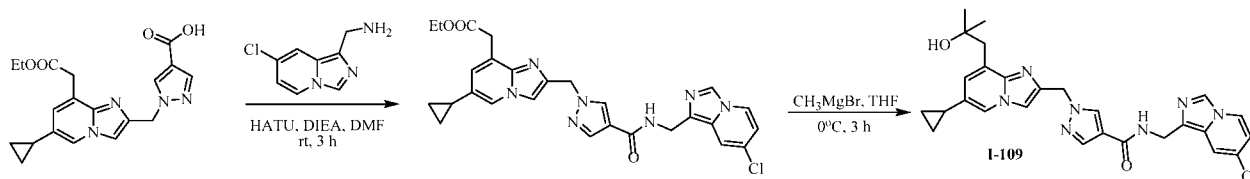
3H), 3.44-3.92 (m, 2H), 2.88-2.78 (m, 2H), 1.94-1.77 (m, 3H), 0.92-0.87 (m, 2H), 0.69-0.59 (m, 2H).

Example 108

Scheme 107



[0461] Synthesis of N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-108). A mixture of 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (46 mg, 0.16 mmol), HATU (76 mg, 0.20 mmol) and DIPEA (103 mg, 0.80 mmol) in dry DMF (4 mL) was stirred at RT for 1 h. Then (7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine (40 mg, 0.16 mmol) was added. The resulting mixture was stirred at RT for another 1 h. Water (30 mL) was added and the mixture was extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄ and concentrated to give a residue, which was purified by prep-HPLC to give N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxamide (8 mg, yield: 9.7%) as a white solid. ESI-MS [M+H]⁺: 509.1. Purity: 98.27%. ¹H NMR (400 MHz, DMSO): δ 8.46 (d, J = 2.4 Hz, 1H), 8.40 (t, J = 5.2 Hz, 1H), 8.20 (s, 1H), 8.14 (d, J = 7.4 Hz, 1H), 8.10 (s, 1H), 7.93 (d, J = 9.5 Hz, 1H), 7.83 (s, 1H), 7.11 (d, J = 9.5 Hz, 1H), 6.85-6.79 (m, 1H), 5.42 (s, 2H), 4.62 (d, J = 5.2 Hz, 2H), 2.22-2.13 (m, 1H), 1.12-1.03 (m, 2H), 1.00-0.94 (m, 2H).

Example 109Scheme 108

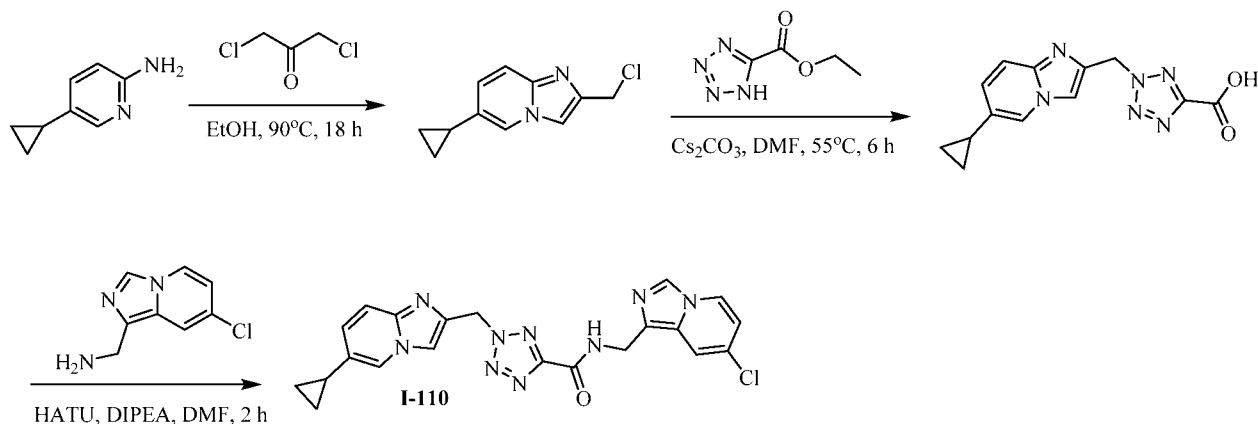
[0462] Synthesis of ethyl 2-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetate. To a mixture of 1-((6-cyclopropyl-8-(2-ethoxy-2-oxoethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (150 mg, 0.41 mmol) in DMF (3 mL) was added (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (107 mg, 0.49 mmol), DIPEA (0.49 mL, 3 mmol) and HATU (234 mg, 0.62 mmol). The mixture was stirred at RT for 3 h. The reaction was diluted with H₂O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give the crude which was purified by prep-TLC (DCM/MeOH = 10/1) to give ethyl 2-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetate (70 mg, yield: 32%) as a white solid. ESI-MS [M+H]⁺: 532.1.

[0463] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2-hydroxy-2-methylpropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-109). To a mixture of ethyl 2-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetate (70 mg, 0.13 mmol) in THF (5 mL) was added CH₃MgBr (1 M in THF, 0.65 mL, 0.65 mmol) at 0 °C. The mixture was stirred at 0 °C for 3 h under N₂. The reaction was quenched with NH₄Cl (10 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified by prep-HPLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2-hydroxy-2-methylpropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (5.4 mg, yield: 8%) as a white solid. ESI-MS [M+H]⁺: 518.2. Purity: 99.1%. ¹H NMR (400 MHz, DMSO): δ 8.58 (s, 1H), 8.32-8.30 (m, 2H), 8.18 (d, J = 8.3 Hz, 2H), 7.88 (s, 1H), 7.78 (s, 1H),

7.65 (s, 1H), 6.90 (s, 1H), 6.65 (d, J = 7.3 Hz, 1H), 5.39 (s, 2H), 5.24 (s, 1H), 4.56 (d, J = 5.2 Hz, 2H), 2.98 (s, 2H), 1.92-1.85 (m, 1H), 1.06 (s, 6H), 0.94-0.88 (m, 2H), 0.67-0.62 (m, 2H).

Example 110

Scheme 109



[0464] Synthesis of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine. A mixture of 5-cyclopropylpyridin-2-amine (320 mg, 2.38 mmol), 1,3-dichloropropan-2-one (906 mg, 7.14 mmol) in EtOH (5 mL) was stirred at 90 °C for 18 h. Saturated aqueous NaHCO₃ (20 mL) was added and the mixture was extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to give the crude product which was purified by silica gel chromatography (EA/PE = 2/1) to give 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (200 mg, yield: 41%) as a brown solid. ESI-MS [M+H]⁺: 207.1.

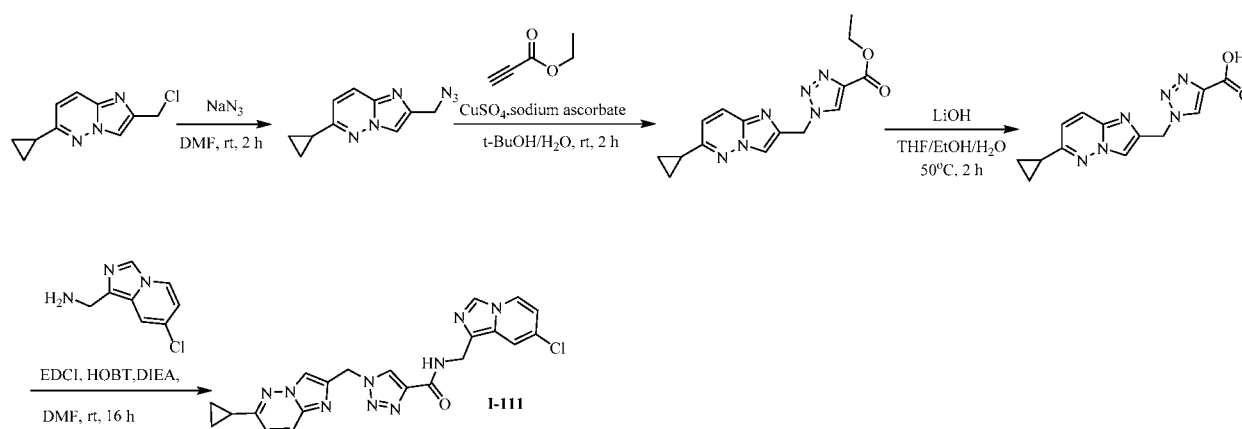
[0465] Synthesis of 2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-tetrazole-5-carboxylic acid. A mixture of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (104 mg, 0.5 mmol), ethyl 1H-tetrazole-5-carboxylate (71 mg, 0.5 mmol) and Cs₂CO₃ (978 mg, 3 mmol) in DMF (5 mL) was stirred at 55 °C for 6 h. After cooled to RT, H₂O (30 mL) was added and the mixture was extracted with EtOAc (30 mL x 3). The pH value of the H₂O layer was adjusted to 5-6 by adding 1 M aqueous HCl solution, then freeze-dried to give 2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-tetrazole-5-carboxylic acid (71 mg, yield:

50%) as a yellow solid. This was used into next step without purification. ESI-MS $[M+H]^+$: 285.1.

[0466] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-tetrazole-5-carboxamide (I-109). A mixture of 2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-tetrazole-5-carboxylic acid (71 mg, 0.25 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine (36 mg, 0.2 mmol), HATU (190 mg, 0.5 mmol) and DIPEA (97 mg, 0.75 mmol) in DMF (3 mL) was stirred at RT for 2 h. Water (20 mL) was added and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give the crude product, which was purified by silica gel column chromatography ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH} = 10/1$) to provide N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-tetrazole-5-carboxamide (20.2 mg, yield: 23%) as a white solid. ESI-MS $[M+H]^+$: 448.1. Purity: 98.48%. ^1H NMR (400 MHz, DMSO): δ 9.44 (t, $J = 5.8$ Hz, 1H), 8.36 (s, 1H), 8.31-8.30 (m, 2H), 7.94 (s, 1H), 7.83 (s, 1H), 7.38 (d, $J = 9.3$ Hz, 1H), 7.01 (dd, $J = 9.4, 1.6$ Hz, 1H), 6.65 (dd, $J = 7.4, 2.0$ Hz, 1H), 6.06 (s, 2H), 4.64 (d, $J = 5.9$ Hz, 2H), 1.96-1.89 (m, 1H), 1.02-0.84 (m, 2H), 0.83-0.57 (m, 2H).

Example 111

Scheme 110



[0467] Synthesis of 2-(azidomethyl)-6-cyclopropylimidazo[1,2-b]pyridazine. To a solution of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-b]pyridazine (900 mg, 4.33 mmol) in dry DMF (5 mL) was added NaN₃ (631 mg, 9.71 mmol). The reaction mixture was stirred at RT for 2 h. Water (30 mL) was added and the mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to give the crude product, which was purified by flash chromatography with silica gel (EtOAc/PE = 40%) to give 2-(azidomethyl)-6-cyclopropylimidazo[1,2-b]pyridazine (735 mg, yield: 79%) as dark-red oil. ESI-MS [M+H]⁺: 215.2.

[0468] Synthesis of ethyl 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate. To a solution of 2-(azidomethyl)-6-cyclopropylimidazo[1,2-b]pyridazine (730 mg, 3.41 mmol) and ethyl propiolate (501.42 mg, 5.11 mmol) in a mixture of t-BuOH/H₂O (5 mL/5 mL) was added CuSO₄ (543.85 mg, 3.41 mmol) and sodium ascorbate (675.05 mg, 3.41 mmol). Then the mixture was stirred at RT for 2 h. The mixture was concentrated and purified by flash silica gel chromatography (EtOAc/PE = 10%) to give ethyl 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (600 mg, yield: 56.44%) as a red solid. ESI-MS [M+H]⁺: 313.2.

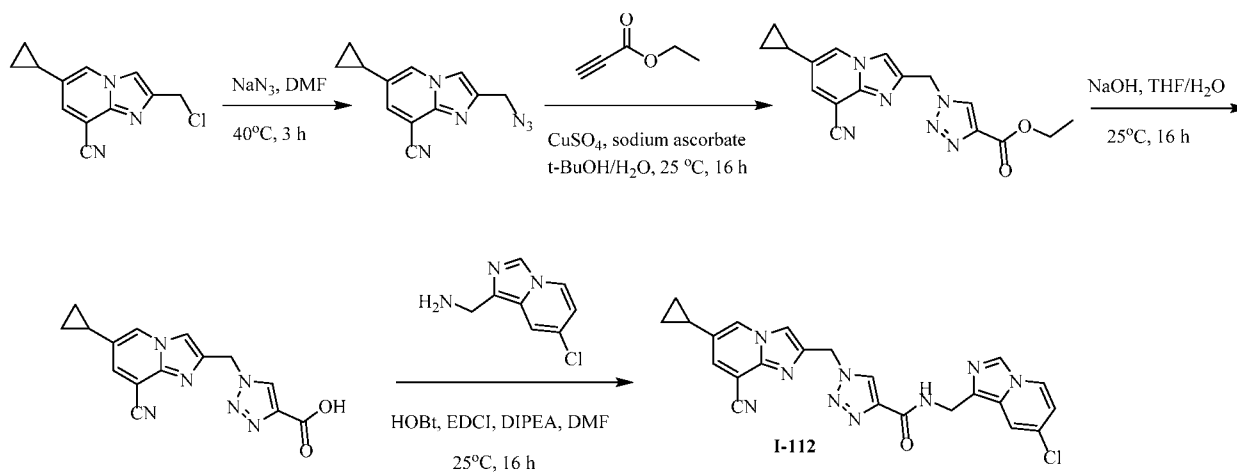
[0469] Synthesis of 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid. To a solution of ethyl 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (100 mg, 0.32 mmol) in a mixture of THF/EtOH/H₂O (2 mL/2 mL/1 mL) was added LiOH (15.33 mg, 0.64 mmol). The mixture was heated to 50 °C for 2 h. Then the mixture was freeze-dried to give 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (110 mg, crude) as a white solid which was used into next step without purification. ESI-MS [M+H]⁺: 285.1.

[0470] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (I-111). To a solution of 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (30 mg, crude from last step) in DMF (2 mL) was added EDCI (30.35 mg, 0.158 mmol), HOBT (21.39 mg, 0.158 mmol), DIPEA (68.20 mg, 0.528 mmol) and (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine (19.17 mg, 0.106 mmol). Then the mixture was stirred at RT for 16 h. Water (15 mL) was added and the mixture was extracted with ethyl acetate

(25 mL x 4). The combined organic layers were concentrated to give the crude product, which was purified by prep-TLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (28 mg, yield: 59.09%) as a white solid. ESI-MS $[M+H]^+$: 448.2. Purity: 96%. ^1H NMR (400 MHz, DMSO): δ 8.91 (t, J = 5.8 Hz, 1H), 8.57 (s, 1H), 8.33-8.27 (m, 2H), 8.19 (s, 1H), 7.93 (d, J = 9.4 Hz, 1H), 7.83 (s, 1H), 7.10 (d, J = 9.4 Hz, 1H), 6.67-6.62 (m, 1H), 5.75 (s, 2H), 4.61 (d, J = 5.9 Hz, 2H), 2.22-2.13 (m, 1H), 1.12-1.02 (m, 2H), 1.00-0.94 (m, 2H).

Example 112

Scheme 111



[0471] Synthesis of 2-(azidomethyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carbonitrile. To a mixture of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carbonitrile (100 mg, 0.43 mmol) in dry DMF (2 mL) was added NaN_3 (39 mg, 0.65 mmol). The mixture was stirred at 25 °C for 3 h. Then H_2O (20 mL) was added and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to give the crude, which was purified by prep-TLC (EA/PE = 3/2) to give 2-(azidomethyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carbonitrile (70 mg, yield: 68%) as a yellow solid. ESI-MS $[M+H]^+$: 239.2.

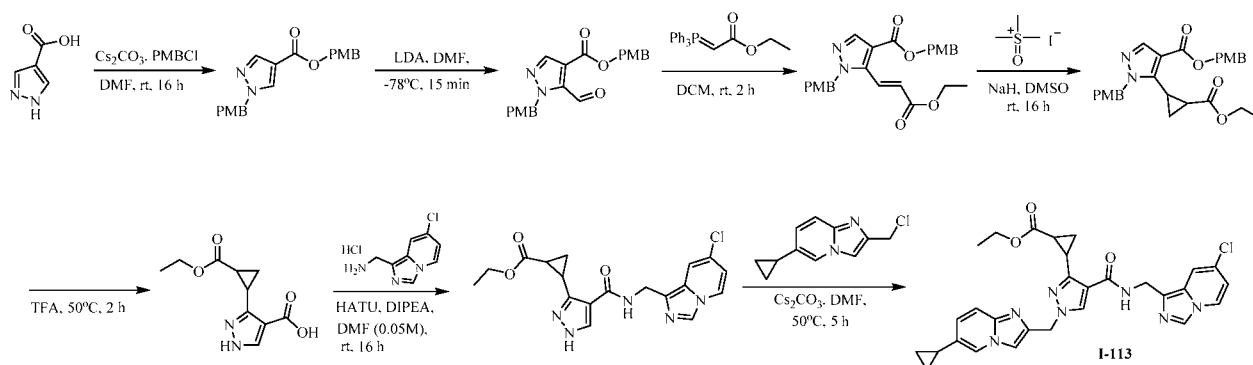
[0472] Synthesis of ethyl 1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate. To a mixture of 2-(azidomethyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carbonitrile (70 mg, 0.29 mmol), CuSO₄ (24 mg, 0.15 mmol), sodium ascorbate (30 mg, 0.15 mmol) in t-BuOH/H₂O (3/3 mL) was added ethyl propiolate (43 mg, 0.44 mmol). The mixture was stirred at 25 °C for 16 h and then concentrated to give the crude product. PE/EA (10 mL/1 mL) was added, stirred at 25 °C for 5 min, and a solid was filtered and washed with PE to give ethyl 1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (95 mg, yield: 96%) as a yellow solid, which was used into next step without purification. ESI-MS [M+H]⁺: 337.2.

[0473] Synthesis of 1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid. To a mixture of ethyl 1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (95 mg, 0.28 mmol) in THF/H₂O (4 mL/2 mL) was added NaOH (34 mg, 0.85 mmol). The mixture was stirred at 25 °C for 16 h. The pH of the mixture was adjusted to 5 with 1 M HCl, then extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to give 1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (70 mg, yield: 80%) as a grey solid. ESI-MS [M+H]⁺: 309.2.

[0474] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (I-112). To a mixture of 1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (60 mg, 0.19 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine (42 mg, 0.23 mmol), HOBt (54 mg, 0.4 mmol), EDCI (75 mg, 0.4 mmol) in DMF (3 mL) was added DIPEA (126 mg, 0.98 mmol). The mixture was stirred at 25 °C for 16 h. Water (20 mL) was added, extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give the crude product, which was purified by prep-HPLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (53.7 mg, yield: 58%) as a yellow solid. ESI-MS [M+H]⁺: 472.1. Purity: 99.54%. ¹H NMR (400 MHz, DMSO): δ 8.94 (s, 1H), 8.69-8.60 (m, 2H), 8.31-8.30 (m, 2H), 7.99 (s, 1H), 7.84-7.80 (m, 2H), 6.65 (s, 1H), 5.81 (s, 2H), 4.63 (s, 2H), 1.98-1.97 (m, 1H), 0.96-0.95 (m, 2H), 0.76-0.75 (m, 2H).

Example 113

Scheme 112



[0475] Synthesis of 4-methoxybenzyl 1-(4-methoxybenzyl)-1H-pyrazole-4-carboxylate. A solution of 1H-pyrazole-4-carboxylic acid (6 g, 53.53 mmol), PMBCl (18.4 g, 117.76 mmol) and Cs₂CO₃ (52.3 mg, 160.59 mmol) in DMF (100 mL) was stirred at RT for 16 h. The reaction mixture was poured into H₂O (600 mL) and extracted with EtOAc (500 mL x 3). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄ and concentrated. The crude product was purified by silica gel chromatography (EA/PE = 1/5) to give 4-methoxybenzyl 1-(4-methoxybenzyl)-1H-pyrazole-4-carboxylate (9.8 g, yield: 52%) as a white solid. ESI-MS [M+H]⁺: 353.2.

[0476] Synthesis of 4-methoxybenzyl 5-formyl-1-(4-methoxybenzyl)-1H-pyrazole-4-carboxylate. To a solution of 4-methoxybenzyl 1-(4-methoxybenzyl)-1H-pyrazole-4-carboxylate (9.8 g, 27.81 mmol) in THF (100 mL) was added dropwise of LDA (41.7 mL, 41.7 mmol) at -78 °C over 10 min. After stirring for 5 min, DMF (12.2 g, 167.86 mmol) was added. The resulting mixture was stirred at -78 °C for another 10 min. The reaction was quenched with saturated NH₄Cl aqueous (100 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated and purified by silica gel chromatography (EA/PE = 1/3) to give 4-methoxybenzyl 5-formyl-1-(4-methoxybenzyl)-1H-pyrazole-4-carboxylate (4.9 g, yield: 44%) as a white solid. ESI-MS [M+H]⁺: 403.1.

[0477] Synthesis of 4-methoxybenzyl (E)-5-(3-ethoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxybenzyl)-1H-pyrazole-4-carboxylate. To a solution of 4-methoxybenzyl 5-formyl-1-(4-

methoxybenzyl)-1H-pyrazole-4-carboxylate (4.9 g, 12.88 mmol) in DCM (100 mL) was added ethyl 2-(triphenyl-15-phosphanylidene)acetate (5.83 g, 16.74 mmol) in portions at 0 °C. The mixture was stirred at RT for 16 h. Water (200 mL) was added and the mixture was extracted with DCM (200 mL x 3). The combined organic layers were concentrated to give the crude product, which was purified by silica gel chromatography (EA/PE = 1/3) to give 4-methoxybenzyl (E)-5-(3-ethoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxybenzyl)-1H-pyrazole-4-carboxylate (5.7 g, 98%) as a yellow solid. ESI-MS $[M+H]^+$: 451.2.

[0478] Synthesis of 4-methoxybenzyl 5-(2-(ethoxycarbonyl)cyclopropyl)-1-(4-methoxybenzyl)-1H-pyrazole-4-carboxylate. To a suspension of NaH (102 mg, 2.68 mmol) in DMSO (10 mL) was added trimethylsulfoxonium iodide (967 mg, 4.39 mmol) at RT. The mixture was stirred at RT for 10 mins. Then a solution of 4-methoxybenzyl (E)-5-(3-ethoxy-3-oxoprop-1-en-1-yl)-1-(4-methoxybenzyl)-1H-pyrazole-4-carboxylate (1.1 g, 2.44 mmol) in DMSO/THF (6 mL, 1/1 (v/v)) was added. The resulting mixture was stirred at RT for 16 h. The reaction mixture was quenched with NH₄Cl aqueous (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated and purified by silica gel chromatography (EA/PE = 1/2) to give 4-methoxybenzyl 5-(2-(ethoxycarbonyl)cyclopropyl)-1-(4-methoxybenzyl)-1H-pyrazole-4-carboxylate (1.1 g, yield: 97%) as a yellow solid. ESI-MS $[M+H]^+$: 465.2.

[0479] Synthesis of 3-(2-(ethoxycarbonyl)cyclopropyl)-1H-pyrazole-4-carboxylic acid. A solution of 4-methoxybenzyl 5-(2-(ethoxycarbonyl)cyclopropyl)-1-(4-methoxybenzyl)-1H-pyrazole-4-carboxylate (1.1 g, 2.37 mmol) in TFA (10 mL) was stirred at 50 °C for 16 h. The reaction mixture was concentrated and diluted in H₂O (50 mL) and the pH was adjusted to 6-7 by adding saturated NaHCO₃ and then extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated and purified by silica gel chromatography (EA/PE = 1/3) to give 3-(2-(ethoxycarbonyl)cyclopropyl)-1H-pyrazole-4-carboxylic acid (230 mg, yield: 43%) as a yellow solid. ESI-MS $[M+H]^+$: 225.1.

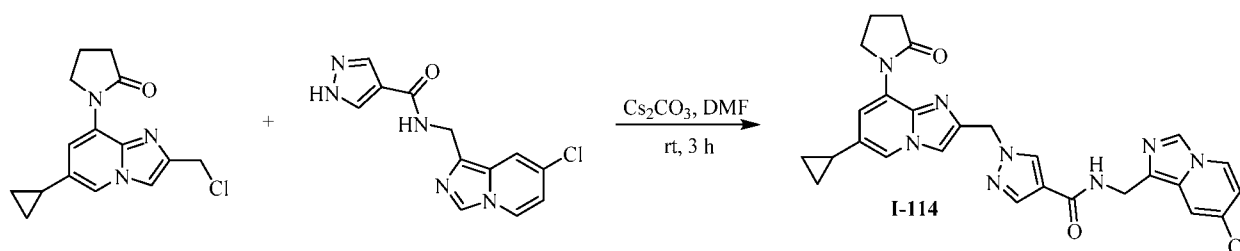
[0480] Synthesis of ethyl 2-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-3-yl)cyclopropane-1-carboxylate. A mixture of 3-(2-(ethoxycarbonyl)cyclopropyl)-1H-pyrazole-4-carboxylic acid (230 mg, 1.03 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (337 mg, 1.545 mmol), HATU

(431 mg, 1.133 mmol) and DIPEA (399 mg, 3.09 mmol) in DMF (10 mL) was stirred at RT for 16 h. The reaction mixture was poured into H₂O (120 mL) and extracted with EtOAc/THF (80 mL x 3, 5/1 (v/v)). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated and purified by silica gel chromatography (DCM/MeOH = 20/1) to give ethyl 2-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-3-yl)cyclopropane-1-carboxylate (150 mg, yield: 38%) as a yellow solid. ESI-MS [M+H]⁺: 388.1.

[0481] Synthesis of ethyl 2-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-(((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-3-yl)cyclopropane-1-carboxylate (I-113). A mixture of ethyl 2-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-3-yl)cyclopropane-1-carboxylate (150 mg, 0.387 mmol), 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (96 mg, 0.464 mmol) and Cs₂CO₃ (189 mg, 0.581 mmol) in DMF (6 mL) was stirred at 50 °C for 5 h. Water (50 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated and purified by silica gel chromatography (DCM/MeOH = 8/1) to give ethyl 2-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-(((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-3-yl)cyclopropane-1-carboxylate (110 mg, yield: 51%) as a yellow solid. ESI-MS [M+H]⁺: 558.2. Purity: 95.76%. ¹H NMR (400 MHz, DMSO): δ 8.45 (t, J = 5.6 Hz, 1H), 8.35-8.28 (m, 3H), 8.14 (s, 1H), 7.75 (m, 2H), 7.39 (d, J = 9.3 Hz, 1H), 6.99 (dd, J = 9.4, 1.7 Hz, 1H), 6.64 (dd, J = 7.4, 2.1 Hz, 1H), 5.27 (s, 2H), 4.53 (d, J = 5.7 Hz, 2H), 4.08 (q, J = 7.0 Hz, 2H), 3.22-3.16 (m, 1H), 2.01-1.95 (m, 1H), 1.91 (m, 1H), 1.41-1.32 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H), 0.94-0.88 (m, 2H), 0.69-0.63 (m, 2H).

Example 114

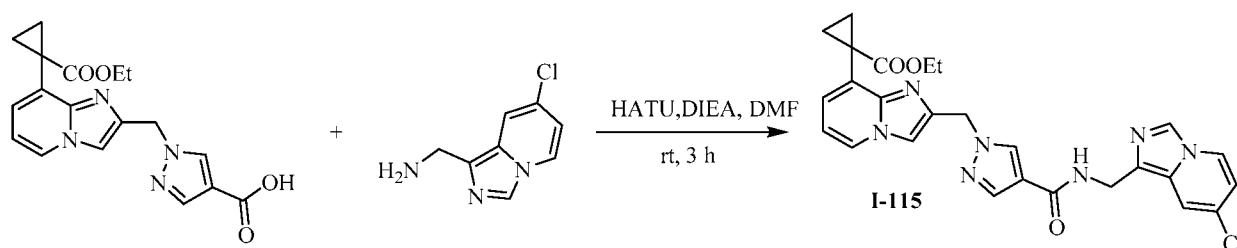
Scheme 113



[0482] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2-oxopyrrolidin-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-114). A mixture of 1-(2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)pyrrolidin-2-one (25 mg, 0.087 mmol), N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (26 mg, 0.095 mmol) and Cs₂CO₃ (70 mg, 0.216 mmol) in DMF (3 mL) was stirred at RT for 3 h. The reaction was quenched with H₂O (30 mL) was added and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified by prep-HPLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2-oxopyrrolidin-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (16.2 mg, yield: 35%) as a white solid. ESI-MS [M+H]⁺: 529.2. Purity: 99.4%. ¹H NMR (400 MHz, DMSO): δ 8.58 (t, J = 5.7 Hz, 1H), 8.31-8.30 (m, 2H), 8.26 (d, J = 1.2 Hz, 1H), 8.19 (s, 1H), 7.89 (s, 1H), 7.78 (d, J = 1.2 Hz, 1H), 7.71 (s, 1H), 7.16 (d, J = 1.5 Hz, 1H), 6.65 (dd, J = 7.5, 2.1 Hz, 1H), 5.41 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 4.10 (t, J = 7.1 Hz, 2H), 2.45 (t, J = 8.2 Hz, 2H), 2.14-2.03 (m, 2H), 1.95-1.88 (m, 1H), 0.98-0.89 (m, 2H), 0.68-0.59 (m, 2H).

Example 115

Scheme 114

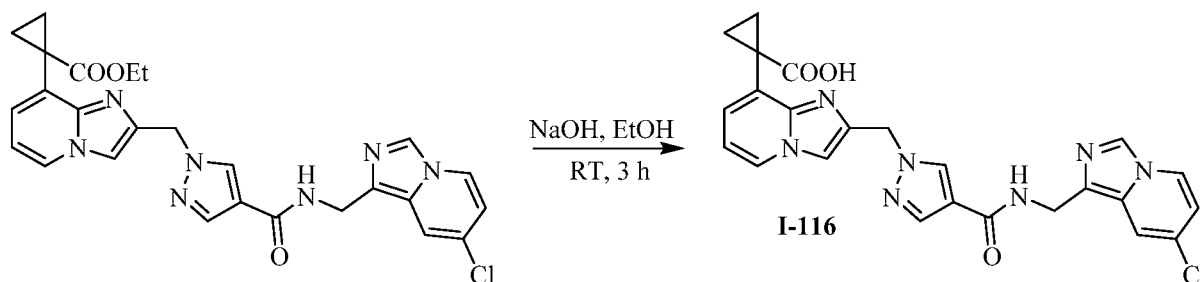


[0483] Synthesis of ethyl 1-(2-((4-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)imidazo[1,2-a]pyridin-8-yl)cyclopropane-1-carboxylate (I-115). A mixture of 1-((8-(1-(ethoxycarbonyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (108 mg, 0.27 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (89 mg, 0.41 mmol), DIPEA (174 mg, 1.35 mmol) and HATU (205 mg, 0.54 mmol) in DMF (3 mL) was stirred at RT for 3 h. The reaction was diluted

with H₂O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified by prep-HPLC to give ethyl 1-(2-(((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)imidazo[1,2-a]pyridin-8-yl)cyclopropane-1-carboxylate (13.4 mg, yield: 8.9%) as a white solid. ESI-MS [M+H]⁺: 558.2. Purity: 98.1%. ¹H NMR (400 MHz, MeOD): δ 8.25 (s, 1H), 8.15 (d, J = 7.5 Hz, 1H), 8.09 (d, J = 2.1 Hz, 2H), 7.91 (s, 1H), 7.73 (s, 1H), 7.67 (s, 1H), 7.02 (d, J = 1.3 Hz, 1H), 6.61 (dd, J = 7.4, 1.6 Hz, 1H), 5.44 (s, 2H), 4.67 (s, 2H), 3.97 (q, J = 7.1 Hz, 2H), 1.91 (ddd, J = 13.5, 8.5, 5.2 Hz, 1H), 1.68 (dd, J = 7.2, 4.2 Hz, 2H), 1.25 (dd, J = 7.2, 4.2 Hz, 2H), 1.05-0.86 (m, 5H), 0.75-0.62 (m, 2H).

Example 116

Scheme 115

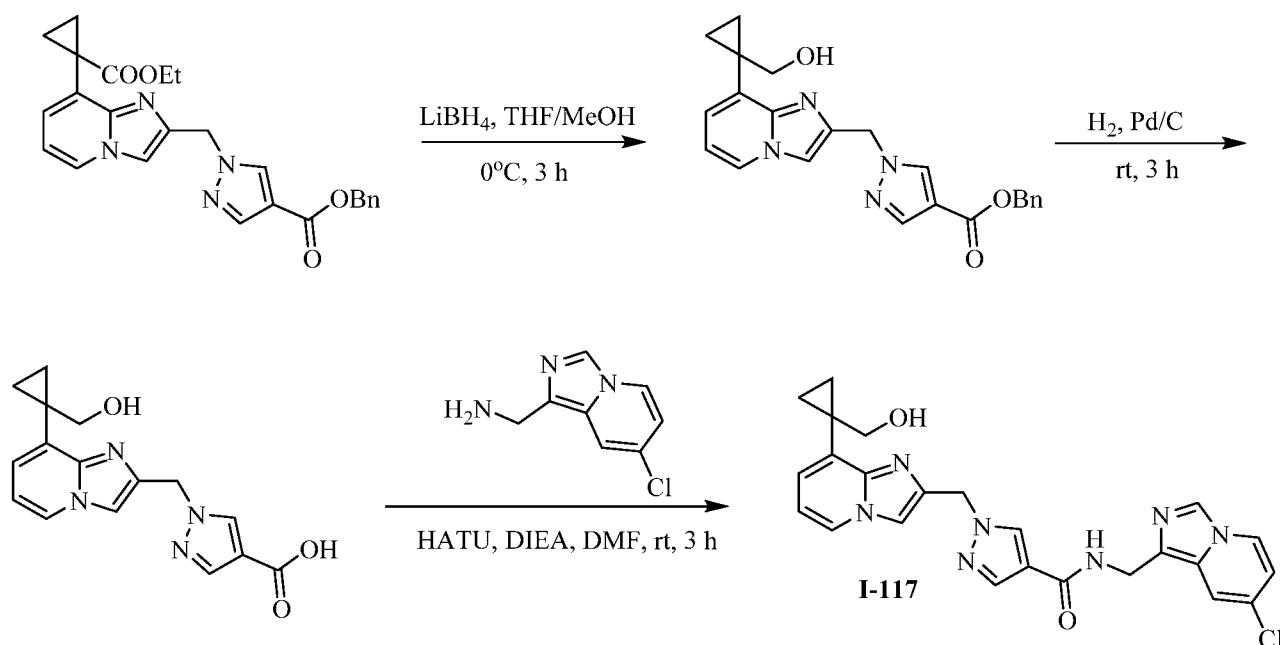


[0484] Synthesis of 1-(2-(((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)imidazo[1,2-a]pyridin-8-yl)cyclopropane-1-carboxylic acid (I-116). To a mixture of ethyl 1-(2-(((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)imidazo[1,2-a]pyridin-8-yl)cyclopropane-1-carboxylate (50 mg, 0.09 mmol) in EtOH (2 mL) was added NaOH (6.4 mg, 0.16 mmol) in H₂O (1 mL). The mixture was stirred at RT for 3 h. The pH of the residue was adjusted to 4 by adding 1 M HCl solution. The mixture was then concentrated and purified by prep-HPLC to give the 1-(2-(((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)imidazo[1,2-a]pyridin-8-yl)cyclopropane-1-carboxylic acid (21.6 mg, yield: 45%) as a white solid. ESI-MS [M+H]⁺: 530.2. Purity: 96.5%. ¹H NMR (400 MHz, MeOD): δ 8.25 (s, 1H), 8.16 (d, J = 7.5 Hz, 1H), 8.11 (s, 2H), 7.91 (s, 1H), 7.73 (s, 1H), 7.67 (s, 1H), 7.09 (d, J = 1.5 Hz,

1H), 6.62 (dd, $J = 7.5, 2.0$ Hz, 1H), 5.46 (s, 2H), 4.67 (s, 2H), 1.93 (ddd, $J = 13.5, 8.4, 5.1$ Hz, 1H), 1.72 (dd, $J = 7.1, 4.1$ Hz, 2H), 1.25 (dd, $J = 7.2, 4.2$ Hz, 2H), 1.01-0.91 (m, 2H), 0.78-0.66 (m, 2H).

Example 117

Scheme 116



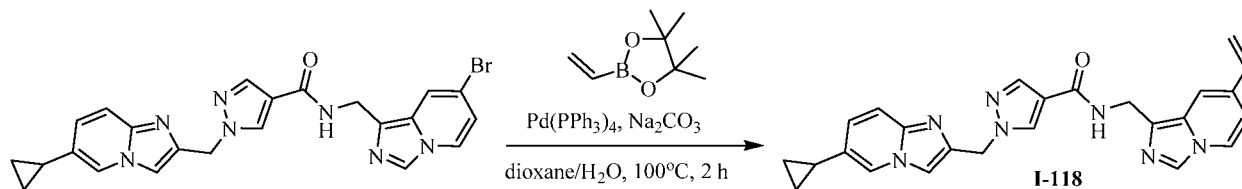
[0485] Synthesis of benzyl 1-((8-(1-(hydroxymethyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. To a mixture of benzyl 1-((8-(1-(ethoxycarbonyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (266 mg, 0.6 mmol) in THF/MeOH (5 mL/0.5 mL) was added LiBH_4 (136 mg, 6 mmol) at 0 °C. The mixture was stirred at 0 °C for 3 h. The reaction was quenched with H_2O (20 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated in vacuo to give the crude which was purified by prep-TLC (DCM/MeOH: 10/1) to give benzyl 1-((8-(1-(hydroxymethyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (94 mg, yield: 38%) as a white solid. ESI-MS $[\text{M}+\text{H}]^+$: 403.1.

[0486] Synthesis of 1-((8-(1-(hydroxymethyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. To a mixture of benzyl 1-((8-(1-(hydroxymethyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (94 mg, 0.23 mmol) in MeOH (3 mL) was added Pd/C (30 mg, 0.3 mmol). The mixture was stirred at RT for 3 h under H₂. The reaction was filtered and concentrated in vacuo to give 1-((8-(1-(hydroxymethyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (70 mg, yield: 97%) as a white solid, which was used into the next step without purification. ESI-MS [M+H]⁺: 313.1.

[0487] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-(1-(hydroxymethyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-117). A mixture of 1-((8-(1-(hydroxymethyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (70 mg, 0.2 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (87.2 mg, 0.4 mmol), DIPEA (129 mg, 1 mmol) and HATU (152 mg, 0.4 mmol) in DMF (3 mL) was stirred at RT for 3 h. The reaction was diluted with H₂O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified with prep-HPLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-(1-(hydroxymethyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (26 mg, yield: 23%) as a white solid. ESI-MS [M+H]⁺: 516.2. Purity: 97.0%. ¹H NMR (400 MHz, MeOD): δ 8.24 (s, 1H), 8.17-8.09 (m, 2H), 8.04 (s, 1H), 7.90 (d, J = 9.6 Hz, 1H), 7.72 (s, 1H), 7.65 (s, 1H), 6.99 (d, J = 1.3 Hz, 1H), 6.60 (dd, J = 7.5, 1.9 Hz, 1H), 5.46 (s, 2H), 4.67 (s, 2H), 3.71 (s, 2H), 1.89 (ddd, J = 13.4, 8.5, 5.1 Hz, 1H), 0.98-0.84 (m, 6H), 0.72-0.64 (m, 2H).

Example 118

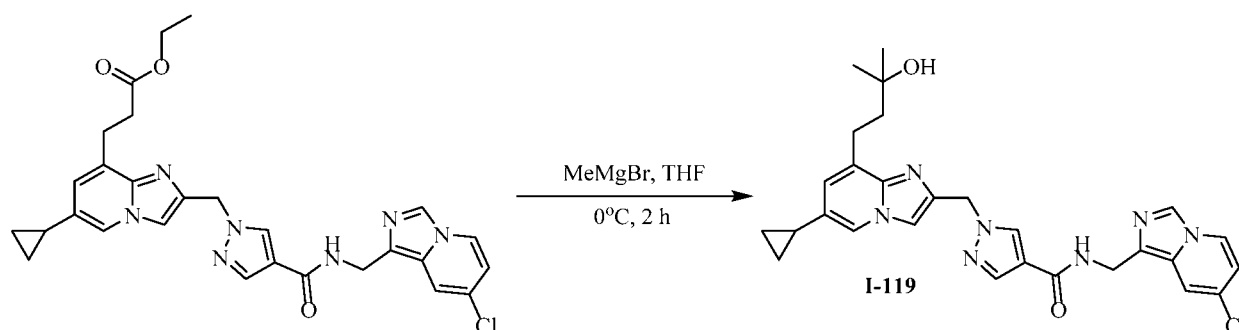
Scheme 117



[0488] Synthesis of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-vinylimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-118). A mixture of N-((7-bromoimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (50 mg, 0.16 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (17 mg, 0.11 mmol), tetrakis(triphenylphosphine)palladium(0) (23 mg, 0.02 mmol) in dioxane/H₂O (2 mL/0.5 mL) was stirred at 100 °C for 2 h. Water (20 mL) was added and extracted with ethyl acetate (30 mL*3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by Prep-HPLC to give 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-vinylimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (34 mg, yield: 75%) as a white solid. ESI-MS [M+H]⁺: 438.2. Purity: 93.19%. ¹H NMR (400 MHz, DMSO) δ 8.52 (t, J = 5.5 Hz, 1H), 8.32 (s, 1H), 8.27 (s, 1H), 8.25-8.17 (m, 2H), 7.86 (s, 1H), 7.71 (s, 1H), 7.55 (s, 1H), 7.39 (d, J = 9.3 Hz, 1H), 7.02-6.96 (m, 1H), 6.94-6.88 (m, 1H), 6.68-6.57 (m, 1H), 5.77 (d, J = 17.5 Hz, 1H), 5.38 (s, 2H), 5.26 (d, J = 11.0 Hz, 1H), 4.57 (d, J = 5.6 Hz, 2H), 1.96-1.87 (m, 1H), 0.94-0.88 (m, 2H), 0.69-0.63 (m, 2H).

Example 119

Scheme 118

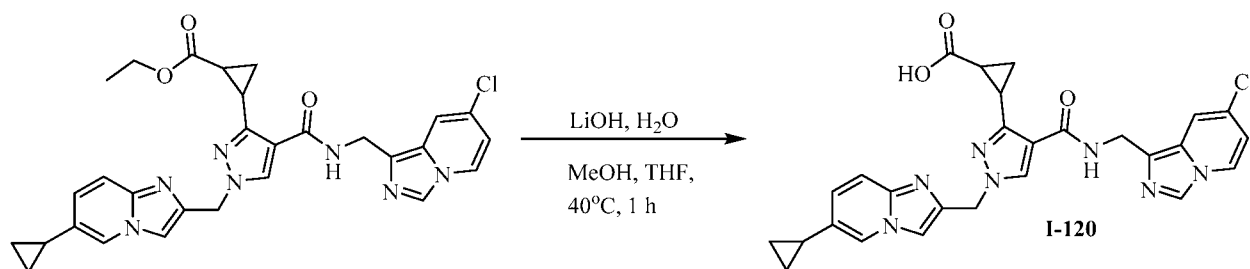


[0489] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(3-hydroxy-3-methylbutyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-119). To a solution of ethyl 3-(2-((4-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)propanoate (35 mg, 0.064 mmol) in THF (3 mL) was added MeMgBr (0.32 mL, 1.0 M

solution in THF, 0.32 mmol) slowly 0 °C. The reaction was stirred at 0 °C for 2 h., quenched with aqueous NH₄Cl (15 mL), and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give the crude product, which was purified by prep-TLC (DCM/MeOH = 10/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(3-hydroxy-3-methylbutyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (20 mg, yield: 58.8%) as a white solid. ESI-MS [M+H]⁺: 532.2. Purity: 95.7%. ¹H NMR (400 MHz, DMSO): δ 8.60 (s, 1H), 8.32-8.30 (m, 2H), 8.18 (d, J = 18.5 Hz, 2H), 7.89 (s, 1H), 7.79 (s, 1H), 7.63 (s, 1H), 6.80 (s, 1H), 6.65 (d, J = 5.5 Hz, 1H), 5.41 (s, 2H), 4.56 (s, 2H), 4.31 (s, 1H), 2.87 (s, 2H), 2.00-1.85 (m, 1H), 1.75 (s, 2H), 1.16 (s, 6H), 1.00-0.85 (m, 2H), 0.72-0.63 (m, 2H).

Example 120

Scheme 119

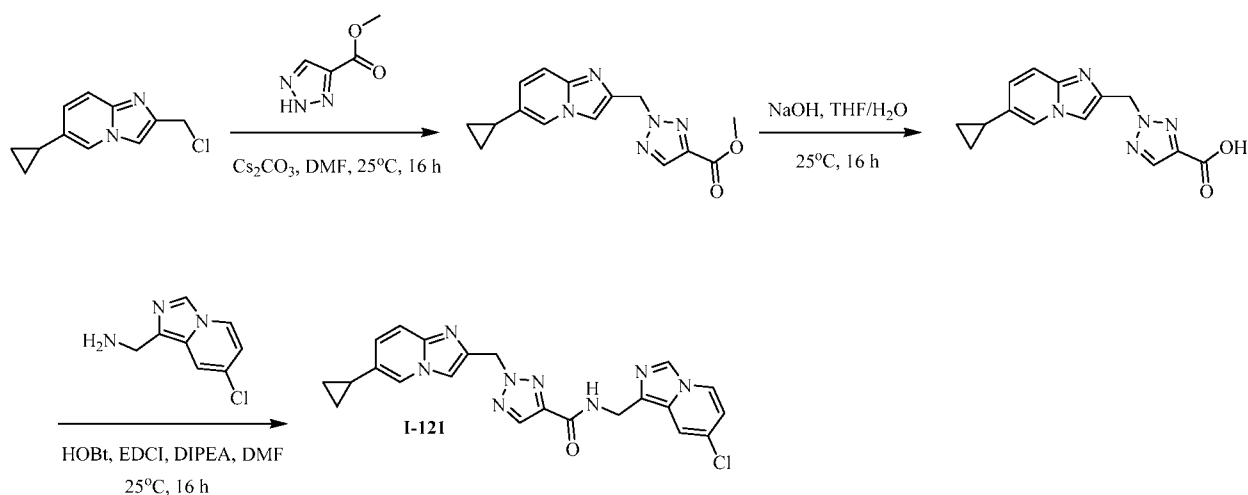


Synthesis of 2-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-3-yl)cyclopropane-1-carboxylic acid (I-120). To a solution of ethyl 2-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-3-yl)cyclopropane-1-carboxylate (80 mg, 0.143 mmol) in MeOH/THF/H₂O (3 mL/3 mL/2 mL) was added lithium hydroxide monohydrate (30 mg, 0.717 mmol). The mixture was stirred at 40 °C for 1 h. Most of the solvent was removed and the residue was diluted with H₂O (10 mL). The pH of the mixture was adjusted to 4-5 by adding HCl aqueous (1 M) and extracted with DCM/MeOH (30 mL x 3, 10/1). The combined organic layers were washed with brine, dried

over Na₂SO₄, concentrated and purified by prep-TLC (DCM/MeOH = 10/1) to give 2-(4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1-(((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazol-3-yl)cyclopropane-1-carboxylic acid (6 mg, yield: 8%) as a yellow solid. ESI-MS [M+H]⁺: 530.2. Purity: 95.64%. ¹H NMR (400 MHz, DMSO): δ 12.16 (s, 1H), 8.43 (t, J = 5.6 Hz, 1H), 8.39-8.26 (m, 3H), 8.13 (s, 1H), 7.75 (m, 2H), 7.39 (d, J = 9.3 Hz, 1H), 7.00 (dd, J = 9.4, 1.7 Hz, 1H), 6.64 (dd, J = 7.5, 2.1 Hz, 1H), 5.27 (s, 2H), 4.60-4.48 (m, 2H), 3.21-3.13 (m, 1H), 1.96-1.85 (m, 2H), 1.36-1.29 (m, 2H), 0.91 (m, 2H), 0.72-0.63 (m, 2H).

Example 121

Scheme 120



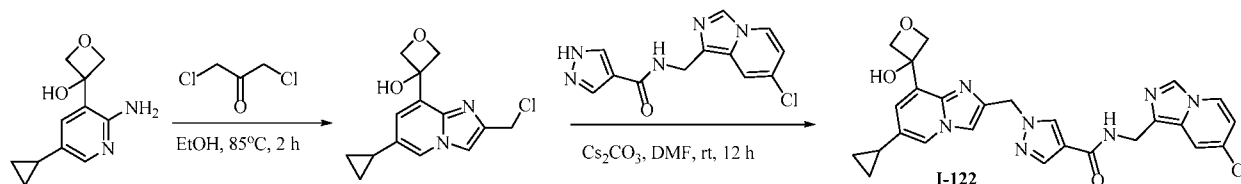
[0490] Synthesis of methyl 2-(((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-1,2,3-triazole-4-carboxylate. To the mixture of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (200 mg, 0.97 mmol) in dry DMF (5 mL) was added methyl 2H-1,2,3-triazole-4-carboxylate (135 mg, 1.06 mmol) and Cs₂CO₃ (949 mg, 2.91 mmol). The mixture was stirred at 25 °C for 16 h. Then H₂O (30 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give the crude product, which was purified by prep-TLC (DCM/MeOH = 10/1) to give methyl 2-(((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-1,2,3-triazole-4-carboxylate (90 mg, yield: 31%) as a yellow solid. ESI-MS [M+H]⁺: 298.1.

[0491] Synthesis of 2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-1,2,3-triazole-4-carboxylic acid. To a mixture of methyl 2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-1,2,3-triazole-4-carboxylate (90 mg, 0.3 mmol) in THF/H₂O (3 mL/2 mL) was added NaOH (36 mg, 0.9 mmol). The mixture was stirred at 25 °C for 16 h and the pH of the mixture was adjusted to 5 by adding 1 M HCl. The mixture was then extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to give 2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-1,2,3-triazole-4-carboxylic acid (80 mg, yield: 93%) as a yellow solid. ESI-MS [M+H]⁺: 284.0.

[0492] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-1,2,3-triazole-4-carboxamide (I-121). To a mixture of 2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-1,2,3-triazole-4-carboxylic acid (60 mg, 0.21 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (54 mg, 0.25 mmol), HOBT (57 mg, 0.42 mmol), EDCI (81 mg, 0.42 mmol) in DMF (5 mL) was added DIPEA (135 mg, 1.04 mmol). The mixture was stirred at 25 °C for 16 h. Water (30 mL) was added and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give the crude product, which was purified by prep-TLC (DCM/MeOH = 10/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-1,2,3-triazole-4-carboxamide (39.1 mg, yield: 41%) as a white solid. ESI-MS [M+H]⁺: 447.1. Purity: 99.57%. ¹H NMR (400 MHz, DMSO): δ 8.90 (t, J = 5.8 Hz, 1H), 8.31-8.30 (m, 3H), 8.15 (s, 1H), 7.83-7.82 (m, 1H), 7.77 (s, 1H), 7.39 = 7.36 (m, 1H), 7.00-6.98 (m, 1H), 6.66-6.64 (m, 1H), 5.74 (s, 2H), 4.60 (d, J = 5.9 Hz, 2H), 1.95-1.88 (m, 1H), 0.94-0.89 (m, 2H), 0.68-0.64 (m, 2H).

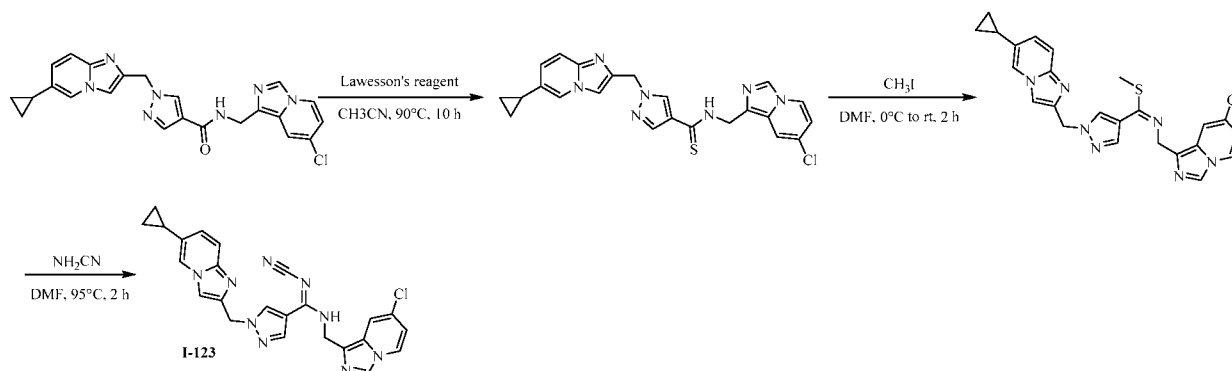
Example 122

Scheme 121



Synthesis of 3-(2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)oxetan-3-ol. To a solution of 3-(2-amino-5-cyclopropylpyridin-3-yl)oxetan-3-ol (800 mg, 3.88 mmol) in EtOH (10 mL) was added 1,3-dichloropropan-2-one (1.48 g, 11.6 mmol) at RT. The resulting reaction mixture was stirred at 85 °C for 2 h. Water (30 mL) was added and the pH was adjusted to 8 by adding saturated NaHCO₃ solution. The mixture was then extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude product, which was purified by silica gel chromatography (PE/EtOAc = 1/1) to give the 3-(2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)oxetan-3-ol (900 mg, yield: 83%) as a light yellow oil. ESI-MS [M+H]⁺: 279.2.

Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-122). To a solution 3-(2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)oxetan-3-ol (90 mg, 0.33 mmol) in DMF (5 mL) was added N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (60 mg, 0.22 mmol) and Cs₂CO₃ (215 mg, 0.66 mmol) at RT. The resulting reaction mixture was stirred at RT for 12 h. Water (30 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude product, which was purified with prep-TLC (DCM/MeOH = 10/1) to give the N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (20 mg, yield: 12%) as a white solid. ESI-MS [M+H]⁺: 518.1. Purity: 97.8%. ¹H NMR (400 MHz, DMSO): δ 8.59 (s, 1H), 8.33-8.26 (m, 3H), 8.20 (s, 1H), 7.90 (s, 1H), 7.81-7.75 (m, 1H), 7.66 (s, 1H), 7.06 (d, J = 1.6 Hz, 1H), 6.67-6.62 (m, 1H), 6.44 (s, 1H), 5.43 (s, 2H), 5.23 (d, J = 6.5 Hz, 2H), 4.63 (d, J = 6.5 Hz, 2H), 4.55 (d, J = 5.7 Hz, 2H), 1.98-1.91 (m, 1H), 0.95-0.88 (m, 2H), 0.70-0.64 (m, 2H).

Example 123Scheme 122

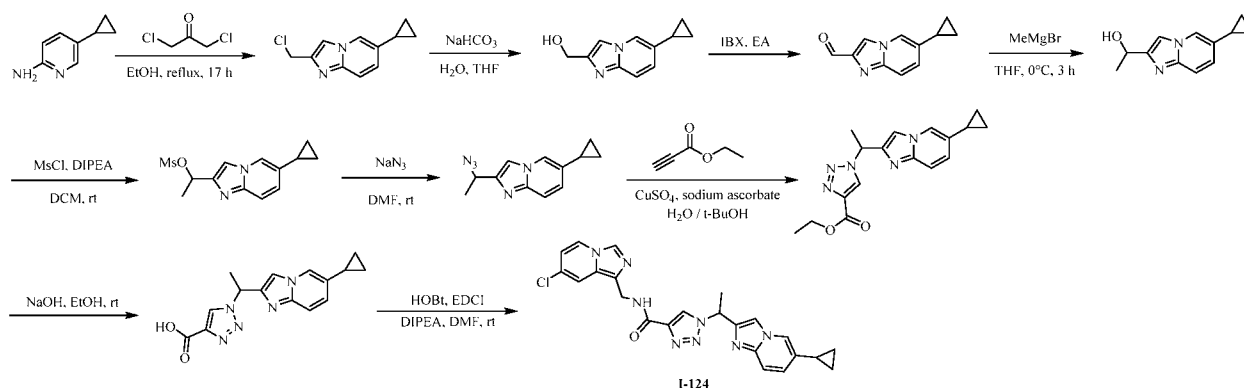
[0493] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carbothioamide. A mixture of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (400 mg, 0.9 mmol) and Lawesson's reagent (544 mg, 1.35 mmol) in CH₃CN (10 mL) was stirred at 90 °C for 16 h. The reaction mixture was cooled to RT and then filtered to provide the crude product (400 mg, yield: 96.6%) as a white solid which was used in the next step without purification. ESI-MS [M+H]⁺: 462.1.

[0494] Synthesis of methyl N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carbimidothioate. To a solution of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carbothioamide (440 mg, 0.95 mmol) in DMF (5 mL) was added NaH (76 mg, 1.9 mmol) and the reaction was stirred at 0 °C for 30 min. Then MeI (203 mg, 1.43 mmol) was added. The resulting reaction mixture was stirred at RT for 2 h. Water (30 mL) was added and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated to give methyl N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carbimidothioate (250 mg, crude), which was used in the next step without further purification. ESI-MS [M+H]⁺: 476.2.

[0495] Synthesis of N'-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-N-cyano-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboximidamide (I-123). A mixture of methyl N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carbimidothioate (250 mg, 0.53 mmol) and NH_2CN (88 mg, 2.1 mmol) in DMF (3 mL) was stirred at 90 °C for 2 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated. The crude product was purified by prep-TLC (DCM/MeOH = 10/1) to provide N'-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-N-cyano-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboximidamide (5 mg, yield: 2%). ESI-MS $[\text{M}+\text{H}]^+$: 470.2. Purity: 90.02%. ^1H NMR (400 MHz, DMSO): δ 8.45 (s, 1H), 8.30 (s, 1H), 8.21-8.18 (m, 2H), 8.12 (s, 1H), 7.77-7.74 (m, 2H), 7.45 (d, J = 8 Hz, 1H), 7.14 (t, J = 12.0 Hz, 1H), 6.67 (m, 1H), 5.52 (s, 2H), 4.76 (s, 2H), 1.96-1.92 (m, 1H), 0.99-0.96 (m, 2H), 0.73-0.70 (s, 2H).

Example 124

Scheme 123



[0496] Synthesis of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine. A mixture of 5-cyclopropylpyridin-2-amine (3.3 g, 25 mmol, 1.0 equiv) and 1,3-dichloropropan-2-one (12.4 g, 99 mmol, 4.0 equiv) in EtOH (60 mL) was stirred at 85 °C for 16 h. The solvent was removed in vacuo. Water (100 mL) was added and extracted with EtOAc (200 mL x 3). The combined organic layers were concentrated and purified by silica gel chromatography (PE:EA = 5:3) to

provide 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (1.8 g, yield: 34.9%). ESI-MS $[M+H]^+$: 207.1.

[0497] Synthesis of (6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methanol. A solution of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (1.8 g, 8.7 mmol) and NaHCO_3 (5 mL, aq., sat.) in THF (10 mL) was stirred at 100 °C for 16 h. Then Water (50 mL) was added and the mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated to provide (6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methanol (1.45 g, crude) which was used in the next step without further purification. ESI-MS $[M+H]^+$: 189.1.

[0498] Synthesis of 6-cyclopropylimidazo[1,2-a]pyridine-2-carbaldehyde. A mixture of (6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methanol (1.45 g, crude from last step) and IBX (4.3 g, 15.4 mmol, 2.0 equiv.) in EtOAc (50 mL) was refluxed at 80 °C for 16 h. Then H_2O (50 mL) was added and extracted by EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated to give the crude product, which was purified by silica gel chromatography (PE:EA = 2:1) to provide 6-cyclopropylimidazo[1,2-a]pyridine-2-carbaldehyde (780 mg, yield : 48% in 2 steps). ESI-MS $[M+H]^+$: 187.1

[0499] Synthesis of 1-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)ethan-1-ol. To a solution of 6-cyclopropylimidazo[1,2-a]pyridine-2-carbaldehyde (750 mg, 4.0 mmol) in THF (10 mL) was added MeMgBr (2 mL, 6.0 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 3 h. Then reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and extracted by EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated to give the crude product, which was purified by silica gel chromatography (DCM:MeOH = 10:1) to give 1-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)ethan-1-ol (725 mg, yield: 89.7%). ESI-MS $[M+H]^+$: 203.2.

[0500] Synthesis of 1-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)ethyl methanesulfonate. A mixture of 1-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)ethan-1-ol (725 mg, 3.5 mmol), DIPEA (1.35 g, 10.5 mmol) and MsCl (519 mg, 4.55 mmol) in DCM (20 mL) was stirred at RT for 2 h. Water (20 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated to give the crude compound (980 mg, crude), which was used into the next step directly.

[0501] Synthesis of 2-(1-azidoethyl)-6-cyclopropylimidazo[1,2-a]pyridine. A mixture of 1-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)ethyl methanesulfonate (980 mg, crude form last step) and NaN₃ (680 mg, 10.5 mmol) in DMF (5 mL) was stirred at RT for 2 h. Water (30 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated to give the crude product which was purified by prep-TLC (PE:EA = 2:1) to give 2-(1-azidoethyl)-6-cyclopropylimidazo[1,2-a]pyridine (225 mg, yield: 28% in 2 steps) as a yellow solid. ESI-MS [M+H]⁺: 228.2.

[0502] Synthesis of ethyl 1-(1-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)ethyl)-1H-1,2,3-triazole-4-carboxylate. A mixture of 2-(1-azidoethyl)-6-cyclopropylimidazo[1,2-a]pyridine (225 mg, 0.99 mmol), ethyl propiolate (107.0 mg, 1.09 mmol), CuSO₄ (173 mg, 1.09 mmol) and sodium ascorbate (200 mg, 0.99 mmol) in a mixture of t-BuOH (10 mL) and H₂O (10 mL) was stirred at RT for 16 h. Solid precipitated and filtered to give ethyl 1-(1-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)ethyl)-1H-1,2,3-triazole-4-carboxylate (250 mg, yield: 77%) as a yellow solid. ESI-MS [M+H]⁺: 326.2.

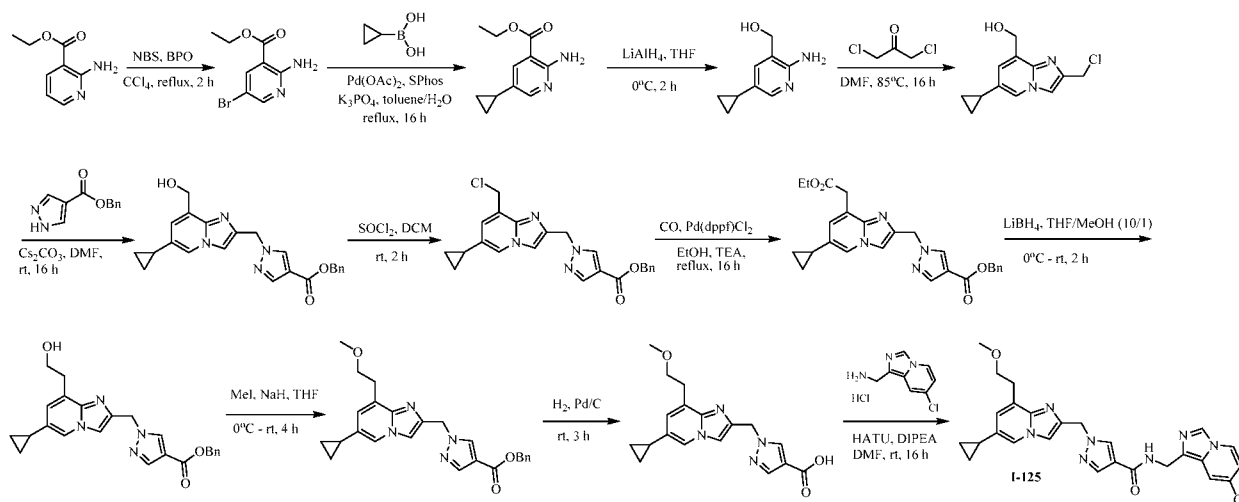
[0503] Synthesis of 1-(1-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)ethyl)-1H-1,2,3-triazole-4-carboxylic acid. A mixture of ethyl 1-(1-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)ethyl)-1H-1,2,3-triazole-4-carboxylate (250 mg, 0.77 mmol) and NaOH (111 mg, 2.77 mmol) in THF (10 mL) and H₂O (5 mL) was stirred at 50 °C for 3 h. Most of the solvent was removed and the residue was diluted with H₂O (5 mL). The pH of mixture was adjusted to 4-5 by adding HCl aqueous (1 M). The precipitate was collected and dried to give the 1-(1-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)ethyl)-1H-1,2,3-triazole-4-carboxylic acid (150 mg, 65%) as a yellow solid. ESI-MS [M+H]⁺: 298.1.

[0504] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-(1-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)ethyl)-1H-1,2,3-triazole-4-carboxamide (I-124). A mixture of 1-(1-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)ethyl)-1H-1,2,3-triazole-4-carboxylic acid (150 mg, 0.51 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (132 mg, 0.61 mmol), HOBt (138 mg, 1.02 mmol), EDCI (196 mg, 1.02 mmol) and DIPEA (329 mg, 2.55 mmol) in DMF (5 mL) was stirred at RT for 16 h. Water (50 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine and dried over Na₂SO₄, and concentrated. The residue was purified by prep-TLC (DCM:MeOH =

10:1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-(1-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)ethyl)-1H-1,2,3-triazole-4-carboxamide (10 mg, yield: 4%). ESI-MS $[M+H]^+$: 461.2. Purity: 100%. ^1H NMR (400 MHz, MeOD): δ 8.35 (s, 1H), 8.30 (s, 1H), 8.18-8.15 (m, 2H), 7.76 (s, 2H), 7.37 (d, $J = 8.0$ Hz, 1H), 7.10 (d, $J = 8$ Hz, 1H), 6.61 (d, $J = 8.0$ Hz, 1H), 6.12-6.07 (m, 1H), 4.75 (s, 2H), 2.02 (d, $J = 8.0$ Hz, 3H), 1.96-1.90 (m, 1H), 0.99-0.95 (m, 2H), 0.72-0.69 (s, 2H).

Example 125

Scheme 124



[0505] Synthesis of ethyl 2-amino-5-bromonicotinate. To a solution of ethyl 2-aminonicotinate (25 g, 150.44 mmol) in CH_3CN (500 mL) was added NBS (32.1 g, 180.5 mmol) in portions over 30 min at 0°C . The mixture was warmed to RT and stirred for 2 h. The reaction mixture was concentrated. The residue was washed with NaHCO_3 aqueous (300 mL) and extracted with EtOAc (300 mL x 3), the combined organic layers were concentrated to give ethyl 2-amino-5-bromonicotinate (36.9 g, yield: 100%) as a yellow solid, which was used in the next step without further purification. ESI-MS $[M+H]^+$: 245.1.

[0506] Synthesis of ethyl 2-amino-5-cyclopropylnicotinate. The mixture of ethyl 2-amino-5-bromonicotinate (14.7 g, 60.18 mmol), cyclopropylboronic acid (7.75 g, 90.27 mmol), $\text{Pd}(\text{OAc})_2$ (1.35 g, 6.018 mmol), SPhos (4.94 g, 12.04 mmol) and K_3PO_4 (44.7 g, 210.58 mmol) in a mixture of toluene (200 mL) and H_2O (40 mL) was stirred at 100°C for 16 h. The reaction

mixture was filtered through celite and the filtrate was washed with EA (100 mL) and concentrated. The crude product was purified by silica gel chromatography (EA/PE = 1/5) to give ethyl 2-amino-5-cyclopropylnicotinate (6.0 g, yield: 48%) as a yellow solid. ESI-MS $[M+H]^+$: 207.1.

[0507] Synthesis of (2-amino-5-cyclopropylpyridin-3-yl)methanol. To a stirred suspension of $LiAlH_4$ (2.21 g, 58.2 mmol) in THF (120 mL) was added dropwise a solution of ethyl 2-amino-5-cyclopropylnicotinate (6.0 g, 29.1 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with H_2O (2.2 mL), 15% (v/v) NaOH aqueous (2.2 mL) and H_2O (6.6 mL). The mixture was stirred for 30 min at 0 °C and for 2 h at RT. Filtered and washed with EtOAc (100 mL). The filtrate was dried, concentrated and purified by silica gel chromatography (EtOAc) to give (2-amino-5-cyclopropylpyridin-3-yl)methanol (4.4 g, yield: 92%) as a yellow solid. ESI-MS $[M+H]^+$: 165.2.

[0508] Synthesis of (2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methanol. A mixture of (2-amino-5-cyclopropylpyridin-3-yl)methanol (2 g, 12.18 mmol) and 1,3-dichloropropan-2-one (4.6 g, 36.54 mmol) in DMF (20 mL) was stirred at 85 °C for 16 h. The reaction mixture was poured into H_2O (150 mL) and adjusted to pH 8 with a $NaHCO_3$ aqueous solution and then extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , concentrated and purified by silica gel chromatography (EA/PE = 1/2) to give (2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methanol (913 mg, 32%) as a yellow solid. ESI-MS $[M+H]^+$: 237.1.

[0509] Synthesis of benzyl 1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A mixture of (2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methanol (730 mg, 3.08 mmol), benzyl 1H-pyrazole-4-carboxylate (624 mg, 3.08 mmol) and Cs_2CO_3 (1.5 g, 4.62 mmol) in DMF (10 mL) was stirred at RT for 16 h. The reaction mixture was poured into H_2O (100 mL) and extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine, dried over Na_2SO_4 , concentrated and purified by silica gel chromatography (EA/PE = 1/1) to give benzyl 1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (1.1 g, yield: 89%) as a yellow solid. ESI-MS $[M+H]^+$: 403.2.

[0510] Synthesis of benzyl 1-((8-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. To a solution of benzyl 1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (1.1 g, 2.73 mmol) in DCM (10 mL) was added dropwise SOCl₂ (1.63 mg, 13.67 mmol) at 0 °C. The mixture was stirred at for RT 1 h. The reaction mixture was concentrated. The residue was dissolved in EtOAc (100 mL) and washed with NaHCO₃ (100 mL) and brine (100 mL), dried over Na₂SO₄, concentrated and dried in vacuo to give benzyl 1-((8-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (1.15 g, yield: 100%) as a yellow solid. ESI-MS [M+H]⁺: 421.1.

[0511] Synthesis of benzyl 1-((6-cyclopropyl-8-(2-ethoxy-2-oxoethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. The mixture of benzyl 1-((8-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (1.15 g, 2.73 mmol), Pd(dppf)Cl₂ (200 mg, 0.273 mmol) and Et₃N (829 mg, 8.19 mmol) in EtOH (20 mL) was stirred at reflux for 16 h under CO. The reaction mixture was concentrated and dissolved in EtOAc (100 mL), filtered and the filtrate was washed with H₂O (50 mL) and brine (50 mL), dried over Na₂SO₄, concentrated and purified by silica gel chromatography (EA/PE = 1/3) to give benzyl 1-((6-cyclopropyl-8-(2-ethoxy-2-oxoethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (800 mg, yield: 64%) as a yellow solid. ESI-MS [M+H]⁺: 459.2.

[0512] Synthesis of benzyl 1-((6-cyclopropyl-8-(2-hydroxyethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. To a solution of benzyl 1-((6-cyclopropyl-8-(2-ethoxy-2-oxoethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (500 mg, 1.09 mmol) in THF (10 mL) and MeOH (1 mL) was added LiBH₄ (119 mg, 5.45 mmol) in portions at 0 °C. The mixture was stirred at RT for 2 h. The reaction mixture was quenched with saturated NH₄Cl aqueous solution (10 mL) and diluted with H₂O (50 mL). the mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated and purified by silica gel chromatography (EtOAc) to give benzyl 1-((6-cyclopropyl-8-(2-hydroxyethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (270 mg, yield: 59%) as a yellow solid. ESI-MS [M+H]⁺: 417.2.

[0513] Synthesis of benzyl 1-((6-cyclopropyl-8-(2-methoxyethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. To a solution of benzyl 1-((6-cyclopropyl-8-(2-hydroxyethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (250 mg, 0.60 mmol) in THF (6 mL) was added NaH (48 mg, 1.2 mmol) at 0 °C. After stirring for 30 min, MeI (170 mg, 1.2 mmol) in THF (1 mL) was added. The mixture was stirred at RT for 3.5 h. The reaction mixture was quenched with H₂O (50 mL) and extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated and purified by silica gel chromatography (EA/PE = 1/2) to give benzyl 1-((6-cyclopropyl-8-(2-methoxyethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (70 mg, yield: 27%) as a yellow solid. ESI-MS [M+H]⁺: 417.2.

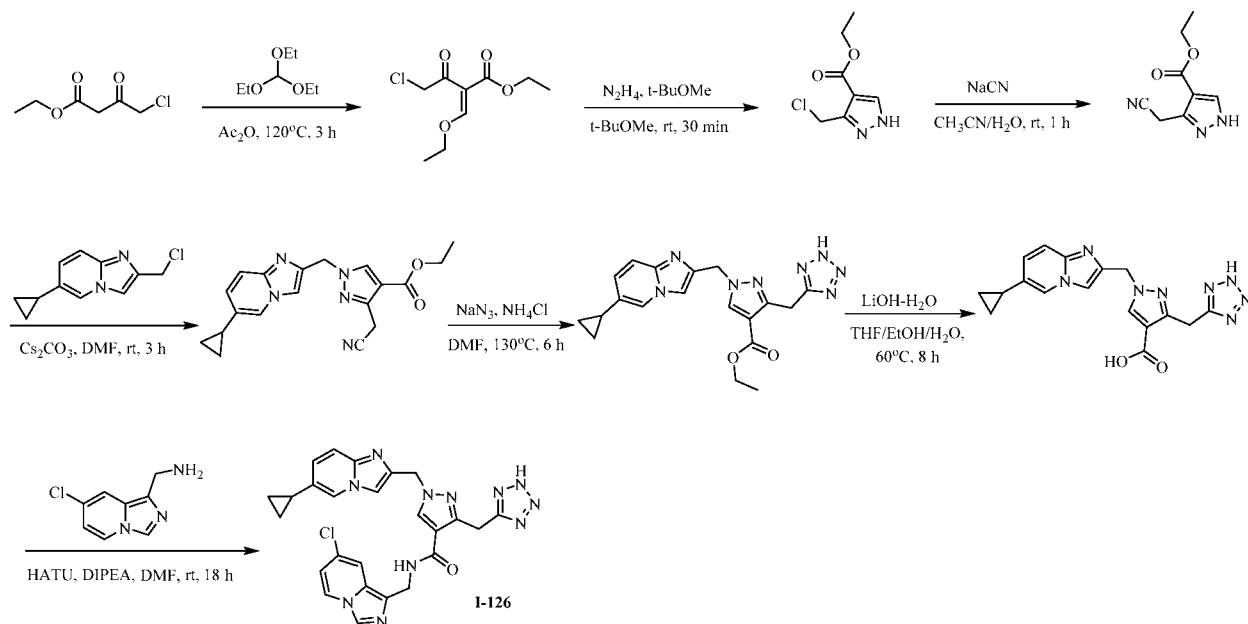
[0514] Synthesis of 1-((6-cyclopropyl-8-(2-methoxyethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. A mixture of benzyl 1-((6-cyclopropyl-8-(2-methoxyethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (70 mg, 0.163 mmol) and Pd/C (30 mg) in MeOH (5 mL) was stirred at RT for 2 h under H₂ (balloon). The reaction mixture was filtered and the filtrate was concentrated to give 1-((6-cyclopropyl-8-(2-methoxyethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (55 mg, yield: 100%) as a yellow solid, which was used into the next step without further purification. ESI-MS [M+H]⁺: 341.2.

[0515] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2-methoxyethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-125). A mixture of 1-((6-cyclopropyl-8-(2-methoxyethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (90 mg, 0.264 mmol), HATU (110 mg, 0.29 mmol) and DIPEA (102 mg, 0.792 mmol) in DMF (4 mL) was stirred at RT for 10 min. (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride hydrochloride (58 mg, 0.264 mmol) was added and stirred at RT for 16 h. Water (30 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated and purified by prep-HPLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(2-methoxyethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (30 mg, yield: 23%) as a white solid. ESI-MS [M+H]⁺: 504.2. Purity: 97.98%. ¹H NMR (400 MHz, DMSO): δ 8.58 (t, J = 5.7 Hz, 1H), 8.34-8.27 (m, 2H), 8.22-8.15 (m, 2H), 7.87 (s, 1H), 7.79-7.75 (m, 1H), 7.65 (s, 1H), 6.86 (s, 1H), 6.64 (dd, J = 7.5, 2.1 Hz,

1H), 5.39 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 3.67 (t, J = 6.8 Hz, 2H), 3.21 (s, 3H), 3.04 (t, J = 6.8 Hz, 2H), 1.88 (m, 1H), 0.90 (m, 2H), 0.67-0.62 (m, 2H).

Example 126

Scheme 125



[0516] Synthesis of ethyl-4-chloro-2-(ethoxymethylene)-3-oxobutanoate. A solution of ethyl 4-chloro-3-oxobutanoate (8 mL, 59 mmol), triethoxymethane (59 mL) and Ac₂O (25 mL) was stirred at 120 °C for 3 h. The reaction mixture was concentrated and n-heptane was added to the residue. Solid precipitated and was filtered to give ethyl-4-chloro-2-(ethoxymethylene)-3-oxobutanoate (6 g, yield: 46%) as a yellow solid, which was used into next step without purification. ESI-MS [M+H]⁺: 221.2.

[0517] Synthesis of ethyl 3-(chloromethyl)-1H-pyrazole-4-carboxylate. To a solution of ethyl-4-chloro-2-(ethoxymethylene)-3-oxobutanoate (3 g, 13.6 mmol) in t-BuOMe (20 mL) was added N₂H₄ (3 mL). The reaction mixture was stirred at RT for 30 min. H₂O (50 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated to give the crude product, which was purified by silica gel (PE/EA = 10/1) to obtain ethyl 3-(chloromethyl)-1H-pyrazole-4-carboxylate (1.7 g, yield: 66.5%) as a yellow solid. ESI-MS [M+H]⁺: 189.1.

[0518] Synthesis of ethyl 3-(cyanomethyl)-1H-pyrazole-4-carboxylate. To a solution of NaCN (390 mg, 8.0 mmol) in a mixture of CH₃CN (20 mL) and H₂O (3 mL) was added ethyl 3-(chloromethyl)-1H-pyrazole-4-carboxylate (507 mg, 2.7 mmol). The reaction mixture was stirred at RT for 1 h. Water (50 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated to give the crude product, which was purified by C-18 reverse phase chromatography to afford ethyl 3-(cyanomethyl)-1H-pyrazole-4-carboxylate (200 mg, yield: 41%) as a white solid. ESI-MS [M+H]⁺: 180.2.

[0519] Synthesis of ethyl 3-(cyanomethyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A mixture of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (103 mg, 0.5 mmol), ethyl 3-(cyanomethyl)-1H-pyrazole-4-carboxylate (90 mg, 0.5 mmol) and Cs₂CO₃ (489 mg, 3 mmol) in DMF (3 mL) was stirred at RT for 3 h. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated to give the crude product, which was purified by silica gel chromatography (CH₂Cl₂:CH₃OH = 10:1) to give ethyl 3-(cyanomethyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (55 mg, yield: 31%) as a brown solid. ESI-MS [M+H]⁺: 350.2.

[0520] Synthesis of ethyl 3-((2H-tetrazol-5-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A mixture of ethyl 3-(cyanomethyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (460 mg, 1.32 mmol), NaN₃ (428 mg, 6.58 mmol), NH₄Cl (352 mg, 6.58 mmol) in DMF (5 mL) was stirred in a sealed tube at 130 °C for 6 h. Water (50 mL) was added and extracted with EtOAc (50 mL x 4). The combined organic layers were concentrated to give ethyl 3-((2H-tetrazol-5-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (121 mg, yield: 23%) as a brown solid which was used into next step without purification. ESI-MS [M+H]⁺: 393.2.

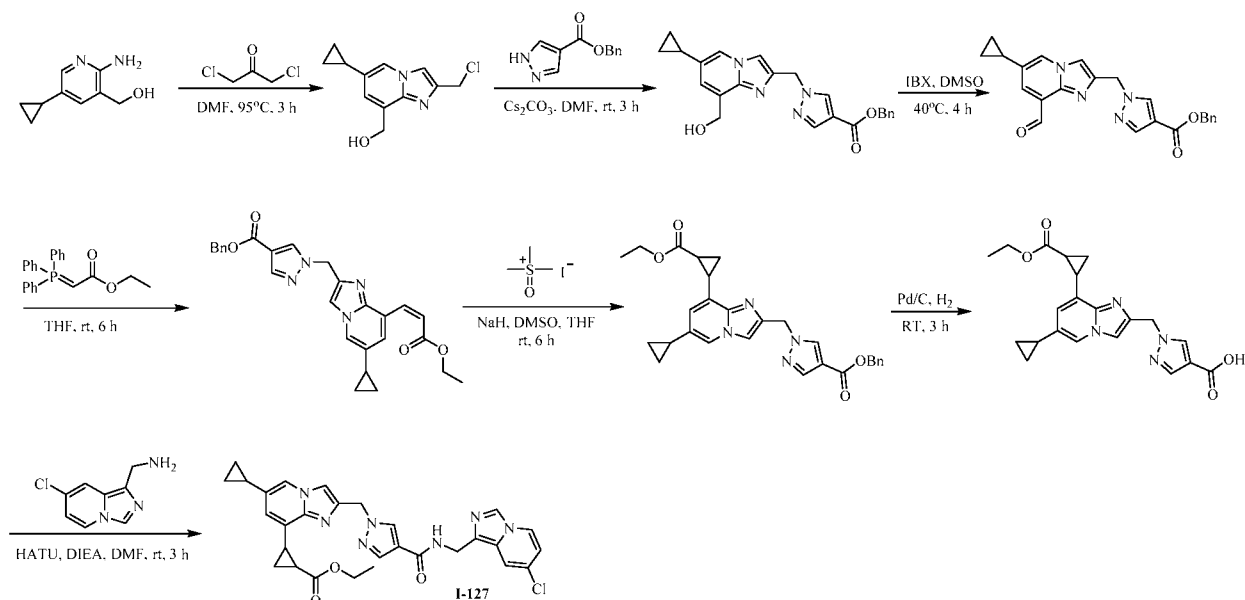
[0521] Synthesis of 3-((2H-tetrazol-5-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. To a solution of ethyl 3-((2H-tetrazol-5-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (121 mg, 0.31 mmol) in a mixture of THF/EtOH/H₂O (2 mL/2 mL/1 mL) was added LiOH·H₂O (26 mg, 0.62 mmol). The mixture was stirred at 60 °C for 8 h. The pH of the mixture was

adjusted to 6 by adding 2 M aqueous HCl solution, and was filtered to give 3-((2H-tetrazol-5-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (96 mg, yield: 85%) as a brown solid. ESI-MS $[M+H]^+$: 365.1.

[0522] Synthesis of 3-((2H-tetrazol-5-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-126). A mixture of 3-((2H-tetrazol-5-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (40 mg, 0.11 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (24 mg, 0.11 mmol), HOBT (28 mg, 0.22 mmol), EDCI (40 mg, 0.22 mmol) and DIPEA (72 mg, 0.55 mmol) in DMF (2 mL) was stirred at RT for 18 h. Water (15 mL) was added and extracted with EtOAc (20 mL x 3). The H₂O layer was concentrated to give the crude product, which was purified by prep-HPLC to give 3-((2H-tetrazol-5-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (9.9 mg, yield: 17%) as a white solid. ESI-MS $[M+H]^+$: 528.1. Purity: 98.16%. ¹H NMR (400 MHz, DMSO): δ 9.08 (s, 1H), 8.32-8.28 (m, 3H), 8.17 (s, 1H), 7.76-7.75 (m, 2H), 7.39 (d, J = 9.3 Hz, 1H), 6.99 (dd, J = 9.4, 1.7 Hz, 1H), 6.63 (dd, J = 7.4, 2.0 Hz, 1H), 5.30 (s, 2H), 4.54 (d, J = 5.6 Hz, 2H), 4.36 (s, 2H), 1.95-1.88 (m, 1H), 0.93-0.88 (m, 2H), 0.68-0.64 (m, 2H).

Example 127

Scheme 126



[0523] Synthesis of (2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methanol. To a solution of (2-amino-5-cyclopropylpyridin-3-yl)methanol (4.8 g, 29 mmol) in DMF (30 mL) was added 1,3-dichloropropan-2-one (14.8 g, 117 mmol). The mixture was stirred at 95 °C for 3 h. The reaction was quenched with NaHCO₃ aqueous (150 mL), and extracted with EtOAc (150 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude, which was purified with silica gel chromatography (EtOAc/PE = 1/2) to give the (2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methanol (3.5 g, yield: 51%) as a white solid. ESI-MS [M+H]⁺: 237.1.

[0524] Synthesis of benzyl 1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. The mixture of (2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methanol (3.5 g, 14.65 mmol), benzyl 1H-pyrazole-4-carboxylate (2.8 g, 14.7 mmol) and Cs₂CO₃ (11.9 g, 36.6 mmol) in DMF (15 mL) was stirred at RT for 3 h. The reaction was quenched with H₂O (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified with silica gel chromatography (DCM/MeOH = 10/1) to give benzyl 1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (3.16 g, yield: 54%) as a white solid. ESI-MS [M+H]⁺: 403.1.

[0525] Synthesis of benzyl 1-((6-cyclopropyl-8-formylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. The mixture of benzyl 1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (3.16 g, 7.9 mmol) and IBX (4.4 g, 15.7 mmol) in DMSO (15 mL) was stirred at 40 °C for 4 h. The reaction was quenched with H₂O (60 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified with silica gel chromatography (DCM/MeOH = 10/1) to give 1-((6-cyclopropyl-8-formylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (1.48 g, yield: 47%) as a yellow solid. ESI-MS [M+H]⁺: 401.1.

[0526] Synthesis of benzyl (Z)-1-((6-cyclopropyl-8-(3-ethoxy-3-oxoprop-1-en-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. To a solution of the benzyl 1-((6-cyclopropyl-8-formylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (1.48 g, 3.7 mmol) in THF (30 mL) was added ethyl 2-(triphenyl-15-phosphanylidene)acetate (1.42 g, 41 mmol), the mixture was stirred at RT for 6 h. The reaction was concentrated in vacuo to give the crude, which was purified with silica gel chromatography (DCM/MeOH = 15/1) to give benzyl 1-((6-cyclopropyl-8-(2-(ethoxycarbonyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (890 mg, yield: 51%) as a white solid. ESI-MS [M+H]⁺: 471.1.

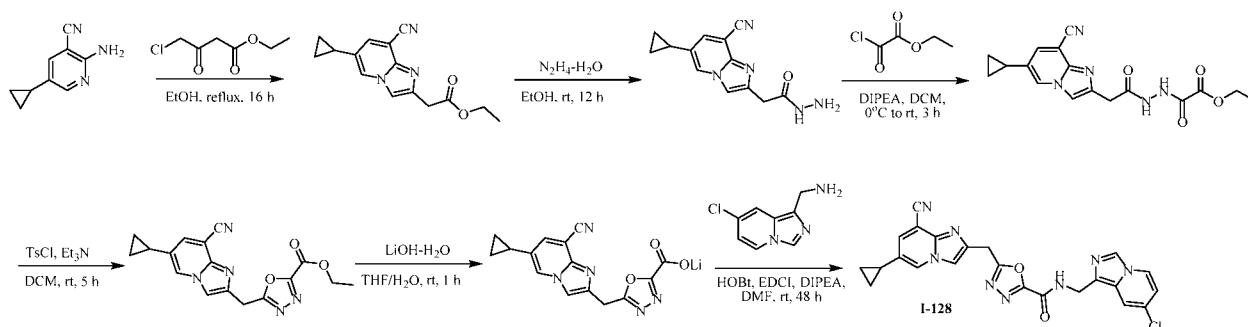
[0527] Synthesis of benzyl 1-((6-cyclopropyl-8-(2-(ethoxycarbonyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. To a suspension of NaH (68.4 mg, 2.85 mmol) in DMSO (10 mL) was added trimethylsulfoxonium iodide (967 mg, 4.39 mmol) at RT. The mixture was stirred at RT for 10 min. Then a solution of 1-((6-cyclopropyl-8-(2-(ethoxycarbonyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (890 mg, 1.9 mmol) in DMSO (3 mL) was added. The mixture was stirred at RT for 6 h. H₂O (50 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified using a silica gel column (DCM/MeOH: 10/1) to give the benzyl 1-((6-cyclopropyl-8-(2-(ethoxycarbonyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (545 mg, yield: 59%) as a yellow solid. ESI-MS [M+H]⁺: 485.1.

[0528] Synthesis of 1-((6-cyclopropyl-8-(2-(ethoxycarbonyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. To a mixture of 1-((6-cyclopropyl-8-(2-(ethoxycarbonyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (545 mg, 1.13 mmol) in MeOH (10 mL) was added Pd/C (100 mg). The mixture was stirred at RT for 3 h. The reaction was filtered and concentrated in vacuo to give 1-((6-cyclopropyl-8-(2-(ethoxycarbonyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (354 mg, yield: 80%) as a yellow solid, which was used into next step without purification. ESI-MS $[M+H]^+$: 495.1.

[0529] Synthesis ethyl 2-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)cyclopropane-1-carboxylate (I-127). A mixture of 1-((6-cyclopropyl-8-(2-(ethoxycarbonyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (354 mg, 0.72 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (188 mg, 0.86 mmol), DIPEA (1 mL, 7.5 mmol) and HATU (410 mg, 1.08 mmol) in DMF (5 mL) was stirred at RT for 3 h. The reaction was diluted with H₂O (30 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated in vacuo to give the crude, which was purified with prep-TLC (DCM/MeOH = 10/1) to give ethyl 2-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)cyclopropane-1-carboxylate (17.5 mg, yield: 4.4%) as a white solid. ESI-MS $[M+H]^+$: 558.2. ¹H NMR (400 MHz, DMSO): δ 8.59 (t, J = 5.7 Hz, 1H), 8.35-8.26 (m, 2H), 8.23-8.14 (m, 2H), 7.88 (s, 1H), 7.81-7.74 (m, 1H), 7.66 (s, 1H), 6.73 (d, J = 1.4 Hz, 1H), 6.65 (dd, J = 7.5, 2.1 Hz, 1H), 5.40 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 4.09 (q, J = 7.1 Hz, 2H), 2.84-2.79 (m, 1H), 2.44-2.37 (m, 1H), 1.89-1.82 (m, 1H), 1.76-1.73 (m, 1H), 1.49-1.41 (m, 1H), 1.19 (t, J = 7.1 Hz, 3H), 0.90-0.85 (m, 2H), 0.72-0.62 (m, 2H).

Example 128

Scheme 127



[0530] Synthesis of ethyl 2-(8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetate. To a solution of 2-amino-5-cyclopropylnicotinonitrile (1.5 g, 9.4 mmol) in EtOH (30 mL) was added ethyl 4-chloro-3-oxobutanoate (4.0 g, 28.2 mmol) at RT and the resulting mixture was stirred at reflux for 16 h. Water (100 mL) was added to the mixture adjusted to approximately pH 8 by adding a saturated NaHCO₃ solution. Then the mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to give the crude product, which was purified by silica gel chromatography (DCM/MeOH = 10/1) to give ethyl 2-(8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetate (1.4 g, yield: 55%) as a yellow oil. ESI-MS [M+H]⁺: 270.1.

[0531] Synthesis of 2-(8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetohydrazide. A mixture of ethyl 2-(8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetate (1.4 g, 5.2 mmol) and N₂H₄·H₂O (2 mL) in EtOH (10 mL) was stirred at RT for 12 h. The mixture was then concentrated and purified by silica gel chromatography (DCM/MeOH = 10/1) to give 2-(8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetohydrazide (1.3 g, yield: 98%) as a yellow solid, which was used in the next step without purification. ESI-MS [M+H]⁺: 256.1.

[0532] Synthesis of ethyl 2-(2-(2-(8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetyl)hydrazinyl)-2-oxoacetate. To a solution of 2-(8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetohydrazide (700 mg, 2.7 mmol) and DIPEA (1.05 g, 8.1 mmol) in DCM (20 mL) was added ethyl 2-chloro-2-oxoacetate (561 mg, 4.1 mmol) slowly at 0 °C. The reaction mixture was stirred at RT for 2 h. Water (30 mL) was added and the mixture was extracted with

DCM (50 mL x 3). The combined organic layers were concentrated to give the crude product, which was purified by silica gel chromatography (DCM/MeOH = 10/1) to give ethyl 2-(2-(2-(8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetyl)hydrazinyl)-2-oxoacetate (500 mg, yield: 50%) as a yellow oil. ESI-MS $[M+H]^+$: 356.1.

[0533] Synthesis of ethyl 5-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate. To a solution of ethyl 2-(2-(2-(8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetyl)hydrazinyl)-2-oxoacetate (500 mg, 1.4 mmol) and Et₃N (426 mg, 4.2 mmol) in DCM (10 mL) was added a solution of TsCl (400 mg, 2.1 mmol) in DCM (5 mL) at RT, the mixture was stirred at this temperature for 16 h. Water (30 mL) was added and the mixture was extracted with DCM (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated to give the crude product which was purified by silica gel chromatography (DCM/MeOH = 10/1) to give ethyl 5-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate (200 mg, yield: 42%) as a yellow oil. ESI-MS $[M+H]^+$: 338.1.

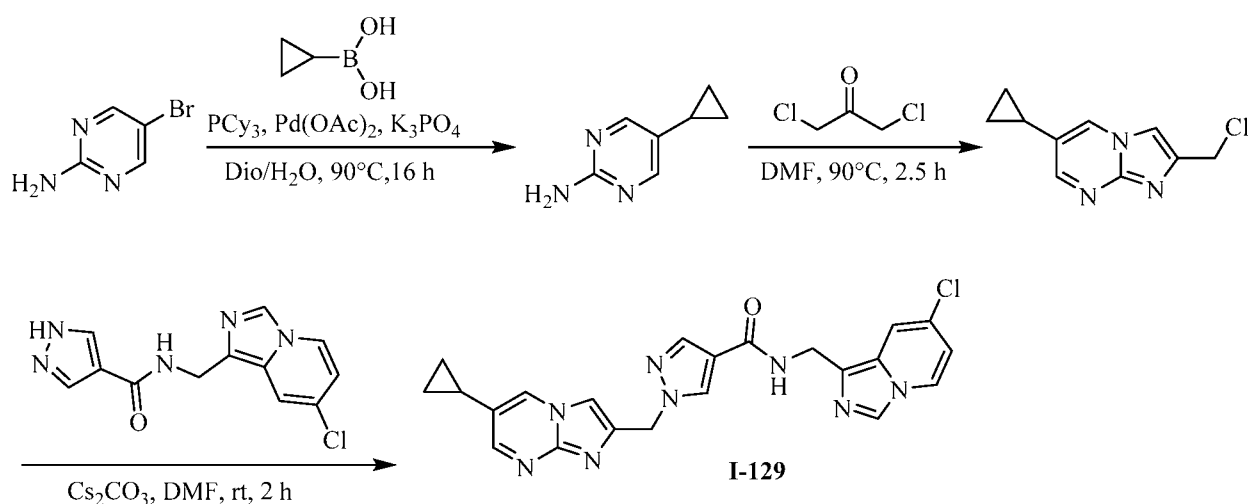
[0534] Synthesis of lithium 5-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate. A solution of ethyl 5-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate (200 mg, 0.59 mmol) and LiOH (43 mg, 1.8 mmol) in a mixture of THF/H₂O (4 mL/2 mL) was stirred at RT for 1 h. THF were concentrated and the remaining H₂O phase was lyophilized to give lithium 5-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate (220 mg, crude) as a red solid, which was used directly in the next step without further purification. ESI-MS $[M+H]^+$: 310.1.

[0535] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide (I-128). A mixture of lithium 5-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate (100 mg, 0.31 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (82 mg, 0.38 mmol), EDCI (123 mg, 0.64 mmol), HOBT (86 mg, 0.64 mmol) and DIPEA (206 mg, 1.6 mmol) in DMF (5 mL) was stirred at RT for 48 h. The mixture was diluted with DCM/MeOH (30 mL, 10/1 (v/v)) and washed with H₂O (20 mL). The organic layer was separated, dried over Na₂SO₄ and concentrated in vacuo to give the crude

product, which was purified by silica gel chromatography (DCM/MeOH = 10/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide (25 mg, yield: 17%) as a yellow solid. ESI-MS $[M+H]^+$: 473.1. Purity: 96.2%. ^1H NMR (400 MHz, DMSO): δ 9.77 (t, J = 5.7 Hz, 1H), 8.69 (d, J = 1.4 Hz, 1H), 8.48 (s, 1H), 8.37-8.26 (m, 2H), 8.00 (s, 1H), 7.83 (d, J = 1.9 Hz, 1H), 7.77 (d, J = 1.6 Hz, 1H), 6.67 (dd, J = 7.4, 2.1 Hz, 1H), 4.63 (d, J = 5.8 Hz, 2H), 4.52 (s, 2H), 2.01-1.95 (m, 1H), 0.99-0.91 (m, 2H), 0.80-0.72 (m, 2H).

Example 129

Scheme 128

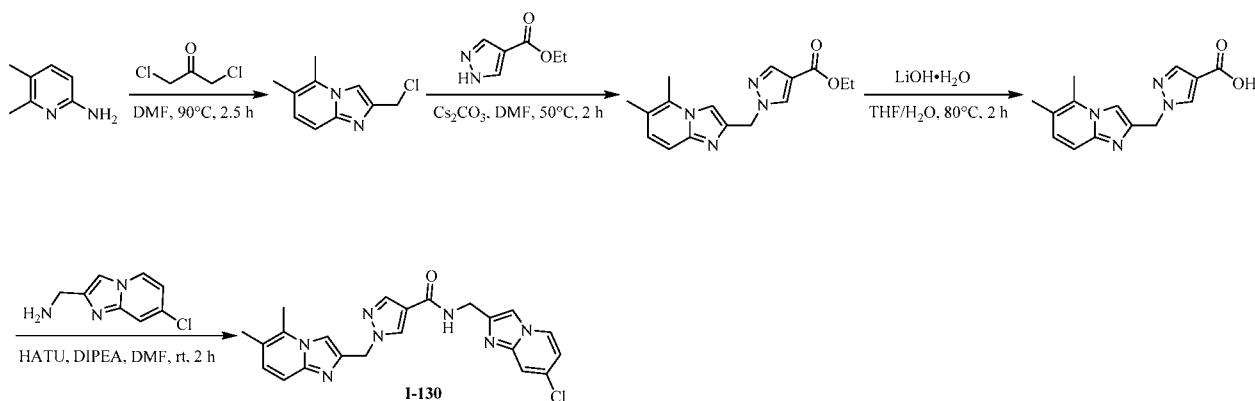


[0536] Synthesis of 5-cyclopropylpyrimidin-2-amine. To a solution of 5-bromopyrimidin-2-amine (1.0 g, 5.75 mmol) in dioxane/H₂O (20 mL/3 mL) was added cyclopropylboronic acid (1.98 g, 23 mmol), palladium diacetate (134 mg, 0.63 mmol), tricyclohexyl phosphine (322 mg, 1.15 mmol) and potassium phosphate (4.24 g, 20.12 mmol). The resulting mixture was stirred at 90 °C for 16 h. The reaction was diluted with H₂O (20 mL), extracted with ethyl acetate (3 × 50 mL), The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash column chromatography to give 5-cyclopropylpyrimidin-2-amine (807 mg, yield: 95%). ESI-MS $[M+H]^+$: 136.2.

[0537] Synthesis of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyrimidine. To a solution of 5-cyclopropylpyrimidin-2-amine (600 mg, 4.44 mmol) in DMF (5 mL) was added

1,3-dichloropropan-2-one (2.73 g, 22.2 mmol). The resulting mixture was stirred at 80 °C for 2.5 h. The reaction mixture was diluted with H₂O (50 mL), extracted with ethyl acetate (3 × 30 mL), The organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash column chromatography to give 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyrimidine (80 mg, Yield: 9%). ESI-MS [M+H]⁺: 208.1.

[0538] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyrimidin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-129). To a solution of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyrimidine (75 mg, 0.36 mmol) in DMF (2 mL) was added cesium carbonate (234 mg, 0.72 mmol), N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (97 mg, 0.36 mmol). The resulting mixture was diluted with H₂O (50 mL), extracted with ethyl acetate (3 × 30 mL), The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by prep-HPLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyrimidin-2-yl)methyl)-1H-pyrazole-4-carboxamide (15 mg, Yield: 12%) as a white solid. ESI-MS [M+H]⁺: 447.1. Purity: 98.61%. ¹H NMR (400 MHz, DMSO): δ 8.69 (d, J = 2.0 Hz, 1H), 8.60 (t, J = 5.8 Hz, 1H), 8.41 (d, J = 2.3 Hz, 1H), 8.30 (d, J = 7.2 Hz, 2H), 8.24 (s, 1H), 7.88 (s, 1H), 7.78 (s, 1H), 7.63 (s, 1H), 6.64 (dd, J = 7.4, 1.8 Hz, 1H), 5.43 (s, 2H), 4.55 (d, J = 5.6 Hz, 2H), 1.97 (dd, J = 8.9, 4.2 Hz, 1H), 0.97 (d, J = 6.7 Hz, 2H), 0.74 (d, J = 5.9 Hz, 2H).

Example 130Scheme 129

[0539] Synthesis of 5,6-dimethylpyridin-2-amine. To a solution of 5,6-dimethylpyridin-2-amine (1.0 g, 8.2 mmol) in DMF (10 mL) was added 1,3-dichloropropan-2-one (4.2 g, 32.8 mmol). The resulting mixture was stirred at 90 °C for 2 h. The reaction mixture was diluted with H₂O (150 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash column chromatography to give 2-(chloromethyl)-5,6-dimethylimidazo[1,2-a]pyridine (1.0 g, yield: 63%). ESI-MS [M+H]⁺: 195.1.

[0540] Synthesis of ethyl 1-((5,6-dimethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. To a solution of 2-(chloromethyl)-5,6-dimethylimidazo[1,2-a]pyridine (150 mg, 0.77 mmol) in DMF (5 mL) was added cesium carbonate (500 mg, 1.54 mmol), ethyl 1H-pyrazole-4-carboxylate (119 mg, 0.85 mmol). The resulting mixture was stirred at 50 °C for 2 h, then diluted with H₂O (50 mL), and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by flash column chromatography to give ethyl 1-((5,6-dimethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (200 mg, yield: 87%). ESI-MS [M+H]⁺: 299.2.

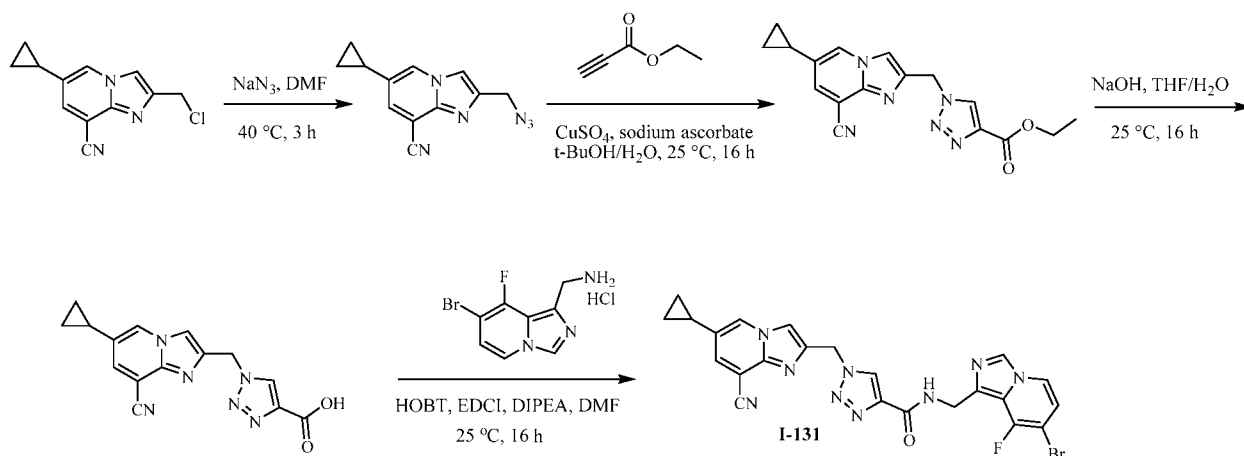
[0541] Synthesis of 1-((5,6-dimethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (I-131). To a solution of ethyl 1-((5,6-dimethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (194 mg, 0.65 mmol) in a mixed solvent of THF/H₂O (3 mL/3 mL) was added Lithium hydroxide (78 mg, 3.3 mmol). The resulting mixture was stirred

at 80 °C for 2 h. THF was evaporated and the pH of the H₂O phase was adjusted to 5 by adding 1 M HCl solution. The resulting solid precipitate was filtered to give 1-((5,6-dimethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (160 mg, yield: 90%) which was used in the next step without further purification. ESI-MS [M+H]⁺: 270.1.

[0542] Synthesis of N-((7-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-1-((5,6-dimethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-130). To the solution of 1-((5,6-dimethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (100 mg, 0.37 mmol) in dry DMF (5 mL) was added HATU (184 mg, 0.49 mmol), DIPEA (125 mg, 0.97 mmol) and (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (58 mg, 0.37 mmol) at RT. The reaction was stirred at RT for 2 h. Water (30 mL) was added and the mixture was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by prep-HPLC to give N-((7-chloroimidazo[1,2-a]pyridin-2-yl)methyl)-1-((5,6-dimethylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (33.7 mg, yield: 21%). ESI-MS [M+H]⁺: 434.1. Purity: 99.2%. ¹H NMR (400 MHz, DMSO): δ 8.80 (s, 1H), 8.72 (t, J = 5.5 Hz, 1H), 8.40 (d, J = 7.5 Hz, 1H), 8.38-8.32 (m, 2H), 7.98 (s, 1H), 7.95 (s, 1H), 7.84 (d, J = 9.2 Hz, 1H), 7.71 (d, J = 9.2 Hz, 1H), 6.87 (d, J = 7.4 Hz, 1H), 5.67 (s, 2H), 4.64 (d, J = 5.6 Hz, 2H), 2.67 (s, 3H), 2.42 (s, 3H).

Example 131

Scheme 130



[0543] Synthesis of 2-(azidomethyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carbonitrile. To a mixture of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carbonitrile (100 mg, 0.43 mmol) in dry DMF (2 mL) was added NaN₃ (39 mg, 0.65 mmol) and stirred at 25 °C for 3 h. Then H₂O (20 mL) was added and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give the crude product, which was purified by Prep-TLC (EtOAc/PE = 3/2) to give 2-(azidomethyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carbonitrile (70 mg, yield: 68%) as a yellow solid. ESI-MS [M+H]⁺: 239.2.

[0544] Synthesis of ethyl 1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate. To a mixture of 2-(azidomethyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carbonitrile (70 mg, 0.29 mmol), CuSO₄ (24 mg, 0.15 mmol), sodium ascorbate (30 mg, 0.15 mmol) in t-BuOH/H₂O (3/3 mL) was added ethyl propiolate (43 mg, 0.44 mmol). The mixture was stirred at 25 °C for 16 h. Then H₂O (20 mL) was added, extracted with EtOAc (30 mL x 3). The combined organic layers were concentrated to give ethyl 1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (95 mg, crude) as a yellow solid. ESI-MS [M+H]⁺: 337.2.

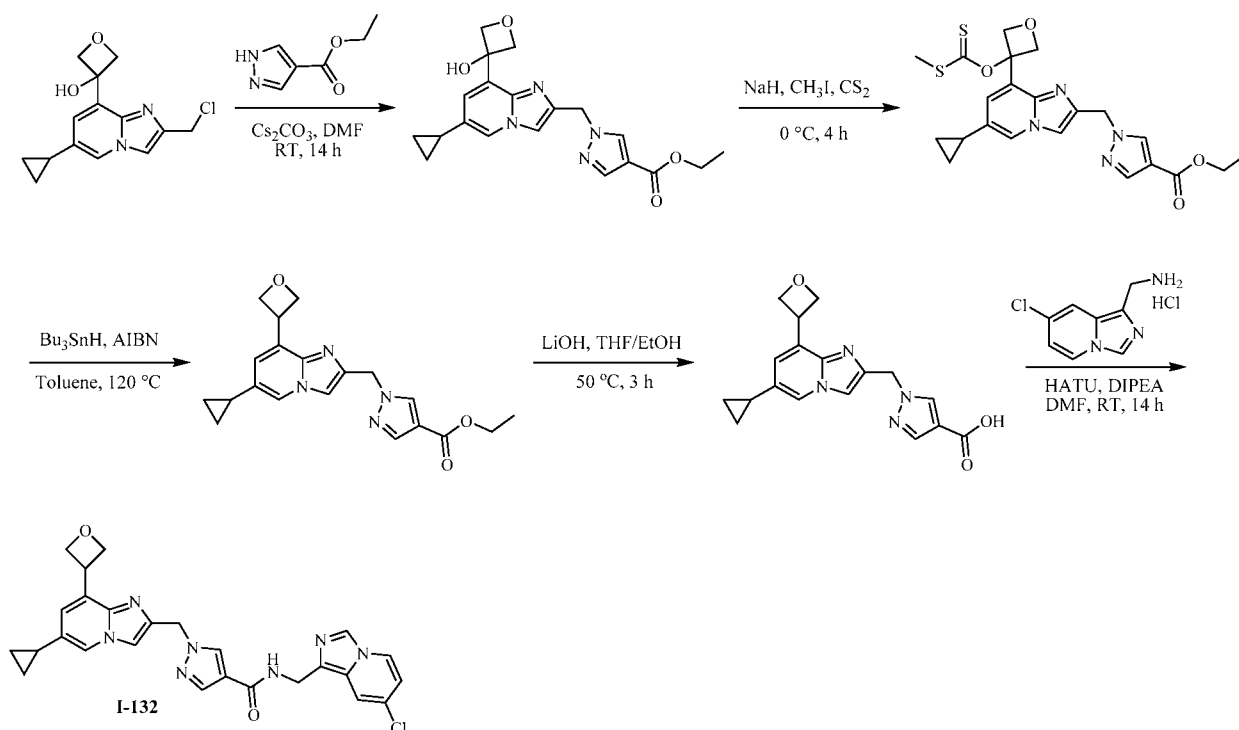
[0545] Synthesis of 1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid. To a mixture of ethyl 1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (95 mg, crude from last step) in THF/H₂O (2/2 mL) was added NaOH (34 mg, 0.85 mmol). The mixture was stirred at 25 °C for 16 h, 1 M HCl was added to adjust pH about 5, extracted with EtOAc/MeOH (10:1, 20 mL x 3), the combined organic layers were concentrated to give 1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (70 mg, crude) as a grey solid. ESI-MS [M+H]⁺: 309.2.

[0546] Synthesis of N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (I-131). To a mixture of 1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (70 mg, crude from last step), (7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (55 mg, 0.23 mmol), HOBt (54 mg, 0.4 mmol), EDCI (75 mg, 0.4 mmol) in DMF (3 mL) was added DIPEA (126 mg, 0.98 mmol). The mixture

was stirred at 25 °C for 16 h. Then the reaction was poured into H₂O (20 mL), the precipitate was filtered and washed with DCM (10 mL) to give N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (60 mg, yield: 38%) as a white solid. ESI-MS [M+H]⁺: 534.1. Purity: 96.81(214nm), 98.17 (254nm). ¹H NMR (400 MHz, DMSO-d₆) δ 8.73-8.69 (m, 2H), 8.59-8.50 (m, 2H), 8.14 (d, J = 6.8 Hz, 1H), 7.99 (s, 1H), 7.80 (s, 1H), 6.82 (s, 1H), 5.81 (s, 2H), 4.70 (s, 2H), 1.99-1.98 (m, 1H), 0.97-0.96 (m, 2H), 0.76-0.75 (m, 2H).

Example 132

Scheme 131



[0547] Synthesis of ethyl 1-((6-cyclopropyl-8-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A mixture of 3-(2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)oxetan-3-ol (1.2 g, 4.3 mmol), ethyl 1H-pyrazole-4-carboxylate (725 mg, 5.2 mmol) and Cs₂CO₃ (2.1 g, 6.45 mmol) in DMF (30 mL) was stirred at RT for 14h. Water (150 mL) was added to the reaction, extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to

give the crude product which was purified with silica gel chromatography (DCM/MeOH = 20/1) to give the ethyl 1-((6-cyclopropyl-8-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (1.1 g, yield: 67%) as a yellow solid. ESI-MS $[M+H]^+$: 383.2.

[0548] Synthesis of ethyl 1-((6-cyclopropyl-8-(3-(((methylthio)carbonothioyl)oxy)oxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. To a solution of ethyl 1-((6-cyclopropyl-8-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (600 mg, 1.57 mmol) in THF (15 mL) was added NaH (127 mg, 3.14 mmol, 60% in oil) at 0 °C slowly. The resulting mixture was stirred at 0 °C for 30 min. Then CS₂ (239 mg, 3.14 mmol) was added thereto at 0 °C. After stirring for 30 min, CH₃I (446 mg, 3.14 mmol) was added and stirred at RT for 1 h. The reaction was quenched with aqueous NH₄Cl, extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the ethyl 1-((6-cyclopropyl-8-(3-(((methylthio)carbonothioyl)oxy)oxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (650 mg crude), which was used into next step without further purification. ESI-MS $[M+H]^+$: 473.1

[0549] Synthesis of ethyl 1-((8-(oxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A solution of ethyl 1-((6-cyclopropyl-8-(3-(((methylthio)carbonothioyl)oxy)oxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (650 mg crude from previous step) and Bu₃SnH (917 mg, 3.14 mmol) and AIBN (515 mg, 3.14 mmol) in toluene (20 mL) was stirred at 120 °C for 12 h. The reaction was concentrated in vacuo to give the residue, which was diluted with H₂O (50 mL), extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude product, which was purified with silica gel chromatography (EA/PE = 2/1) to give the ethyl 1-((8-(oxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (100 mg, yield: 17% over 2 steps) as a white solid. ESI-MS $[M+H]^+$: 367.2.

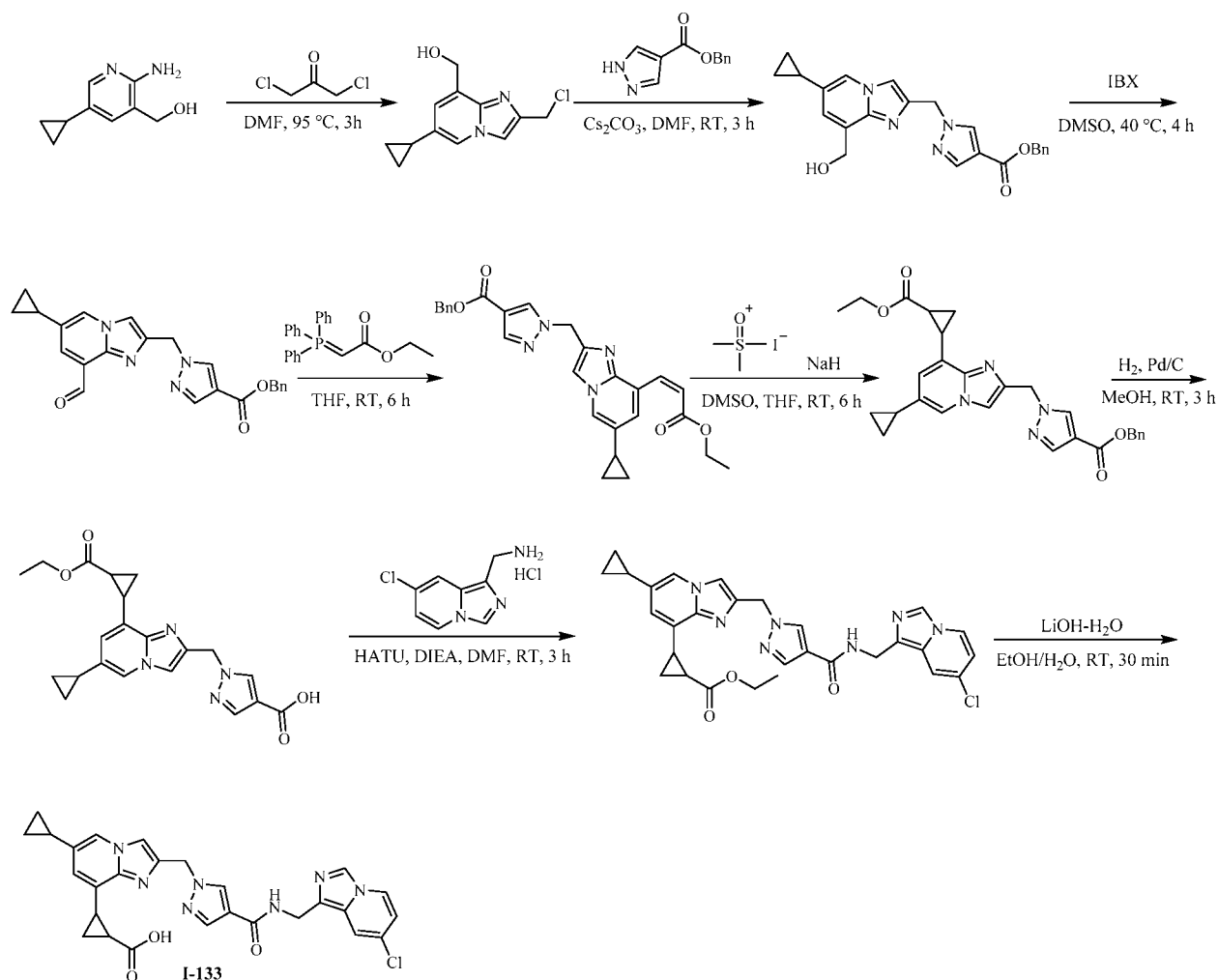
[0550] Synthesis of 1-((8-(oxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. A mixture of ethyl 1-((8-(oxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (100 mg, 0.27 mmol) and LiOH (37 mg, 1.53 mmol) in THF/H₂O (10 mL/5 mL) was stirred at 50 °C for 3 h. The reaction was concentrate in vacuo to give the 1-((8-

(oxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid sodium salt (150 mg crude), which was used into next step without further purification. ESI-MS $[M+H]^+$: 339.1.

[0551] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(oxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-132). To a solution of 1-((8-(oxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (150 mg, crude from previous step), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (87 mg, 0.4 mmol), HATU (177 mg, 0.47 mmol) in DMF (10 mL) was added DIPEA (200 mg, 1.55 mmol). The resulting mixture was stirred at RT for 14 h. H₂O (30 mL) was added into the reaction, extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude product which was purified with Prep-TLC (DCM/MeOH = 10/1) to give the N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(oxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (25 mg, yield: 18% over 2 steps) as a white solid. ESI-MS $[M+H]^+$: 502.2. Purity: 99.2(214nm), 99.0(254nm). ¹H NMR (400 MHz, DMSO-d₆) δ 8.58 (t, J = 5.7 Hz, 1H), 8.33-8.27 (m, 2H), 8.23 (s, 1H), 8.17 (m, 1H), 7.88 (s, 1H), 7.82-7.78 (m, 1H), 7.66 (s, 1H), 7.02 (s, 1H), 6.67-6.62 (m, 1H), 5.39 (s, 2H), 4.94-4.91 (m, 2H), 4.85-4.75 (m, 2H), 4.69-4.63 (m, 1H), 4.55 (d, J = 5.7 Hz, 2H), 1.96-1.88 (m, 1H), 0.94-0.88 (m, 2H), 0.72-0.67 (m, 2H).

Example 133

Scheme 132

**[0552] Synthesis of (2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methanol.**

To a solution of (2-amino-5-cyclopropylpyridin-3-yl)methanol (4.8 g, 29 mmol) in DMF (30 mL) was added 1,3-dichloropropan-2-one (14.8 g, 117 mmol) at RT and then heated at 95 °C. The reaction was monitored by LCMS until the starting material consumed (~3 h). The reaction was cooled to RT, then quenched with NaHCO₃ until pH = 8 and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude product, which was purified with flash silica gel column (eluent: EtOAc/PE:

1/2) to give the (2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methanol (3.5 g, purity: 93%, yield: 51%) as a white solid. ESI-MS $[M+H]^+$: 236.1.

[0553] Synthesis of benzyl 1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A mixture of (2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methanol (3.5 g, 14.65 mmol), benzyl 1H-pyrazole-4-carboxylate (2.8 g, 14.65 mmol) and Cs_2CO_3 (11.9 g, 36.6 mmol) in DMF (15 mL) was stirred at RT for 3 h. The reaction was quenched with H_2O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , concentrated in vacuo to give the crude product which was purified with prep-TLC (eluent: DCM/MeOH: 10/1) to give the benzyl 1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (3.16 g, yield: 54%) as a white solid. ESI-MS $[M+H]^+$: 402.1.

[0554] Synthesis of benzyl 1-((6-cyclopropyl-8-formylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A solution of benzyl 1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (3.16 g, 7.9 mmol) in DMSO (15 mL) was added IBX (4.4 g, 15.7 mmol) at RT and then warmed to 40 °C and stirred for 4 h. The reaction was quenched with H_2O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , concentrated in vacuo to give the crude product, which was purified with silica gel column (eluent: DCM/MeOH: 10/1) to give the 1-((6-cyclopropyl-8-formylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (1.48 g, yield: 54%) as a yellow solid. ESI-MS $[M+H]^+$: 401.1.

[0555] Synthesis of benzyl (Z)-1-((6-cyclopropyl-8-(3-ethoxy-3-oxoprop-1-en-1-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A solution of the benzyl 1-((6-cyclopropyl-8-formylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (1.48 g, 3.7 mmol) in THF (30 mL) was added ethyl 2-(triphenyl-15-phosphanylidene)acetate (1.42 g, 41 mmol) at RT and stirred for 6 h. The reaction was concentrated in vacuo to give the crude mixture, which was purified with flash silica gel column (eluent: DCM/MeOH: 15/1) to give the benzyl 1-((6-cyclopropyl-8-(2-(ethoxycarbonyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (890 mg, purity: 91.5%, yield: 51%) as a white solid. ESI-MS $[M+H]^+$: 470.1.

[0556] Synthesis of benzyl 1-((6-cyclopropyl-8-(2-(ethoxycarbonyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A mixture of 1-((6-cyclopropyl-8-(2-(ethoxycarbonyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (890 mg, 1.9 mmol) and trimethyl sulfoxonium iodide (627 mg, 2.85 mmol) in THF/DMSO (30/3 mL) was added NaH (190 mg, 2.85 mmol) was stirred at RT for 6 h. The reaction was quenched with H₂O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude product, which was purified with flash silica gel column (eluent: DCM/MeOH: 10/1) to give the benzyl 1-((6-cyclopropyl-8-(2-(ethoxycarbonyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (545 mg, yield: 59%) as a yellow solid. ESI-MS [M+H]⁺: 485.2.

[0557] Synthesis of 1-((6-cyclopropyl-8-(2-(ethoxycarbonyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. A solution of 1-((6-cyclopropyl-8-(2-(ethoxycarbonyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (545 mg, 1.13 mmol) in MeOH (10 mL) was added Pd/C (50 mg) and stirred at RT under hydrogen for 3 h. The reaction was filtered through a pad of Celite, washed with MeOH and concentrated in vacuo to give crude 1-((6-cyclopropyl-8-(2-(ethoxycarbonyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (354 mg, yield: 80%) as a yellow solid. ESI-MS [M+H]⁺: 394.1.

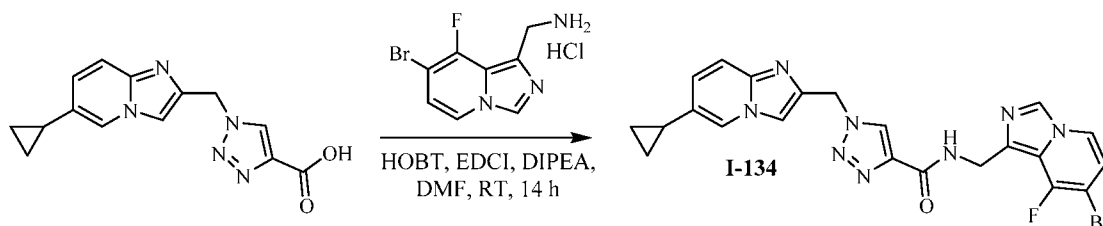
[0558] Synthesis ethyl 2-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)cyclopropane-1-carboxylate. A mixture of 1-((6-cyclopropyl-8-(2-(ethoxycarbonyl)cyclopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (35.4 mg, 0.09 mmol) in DMF (3 mL) was added (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (31 mg, 0.14 mmol), DIPEA (0.1 mL, 0.75 mmol), HATU (45 mg, 0.12 mmol) and stirred at RT for 3 h. The reaction was quenched with H₂O (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo to give the crude product, which was purified by prep-TLC (eluent: DCM/MeOH: 10/1) to give ethyl 2-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)cyclopropane-1-carboxylate (17.5 mg, yield: 35%) as a white solid. ESI-MS [M+H]⁺: 558.2. Purity: 96.0 (214nm), 95.8 (254nm). ¹H NMR (400 MHz, DMSO-d₆) δ 8.59 (t, J = 5.7 Hz, 1H), 8.35-8.26 (m, 2H), 8.23-8.14 (m, 2H), 7.88 (s, 1H), 7.81-

7.74 (m, 1H), 7.66 (s, 1H), 6.73 (d, J = 1.4 Hz, 1H), 6.65 (dd, J = 7.5, 2.1 Hz, 1H), 5.40 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 4.09 (q, J = 7.1 Hz, 2H), 2.84-2.79 (m, 1H), 2.44-2.37 (m, 1H), 1.89-1.82 (m, 1H), 1.76-1.73 (m, 1H), 1.49-1.41 (m, 1H), 1.19 (t, J = 7.1 Hz, 3H), 0.90-0.85 (m, 2H), 0.72-0.62 (m, 2H).

[0559] Synthesis of 2-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)cyclopropane-1-carboxylic acid (I-133). To a mixture of ethyl 2-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)cyclopropane-1-carboxylate (56 mg, 0.1 mmol) in EtOH/H₂O (3 mL/1 mL) was added LiOH·H₂O (24 mg, 0.56 mmol). The mixture was stirred at RT for 30 min. After adjusting to pH = 6 with HCl(aq), the reaction mixture was extracted with EtOAc(30 mL x3), the combined organic layers were concentrated and the crude residue was purified by Prep-HPLC to give 2-(2-((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)cyclopropane-1-carboxylic acid (30 mg, yield: 57%) as a white solid. ESI-MS [M-H]⁻: 529.8. Purity: 97.1 (214nm), 98.0 (254nm). ¹H NMR (400 MHz, DMSO-d₆) δ 11.95 (s, 1H), 8.59 (t, J = 5.5 Hz, 1H), 8.31-8.29 (m, 2H), 8.20 (s, 1H), 8.17 (s, 1H), 7.88 (s, 1H), 7.78 (s, 1H), 7.65 (s, 1H), 6.70 (s, 1H), 6.65 (dd, J = 7.4, 1.9 Hz, 1H), 5.41 (s, 2H), 4.56 (d, J = 5.6 Hz, 2H), 2.84-2.75 (m, 1H), 2.26-2.16 (m, 1H), 1.90-1.82 (m, 1H), 1.76-1.68 (m, 1H), 1.49-1.35 (m, 1H), 0.92-1.84 (m, 2H), 0.75-0.58 (m, 2H).

Example 134

Scheme 133

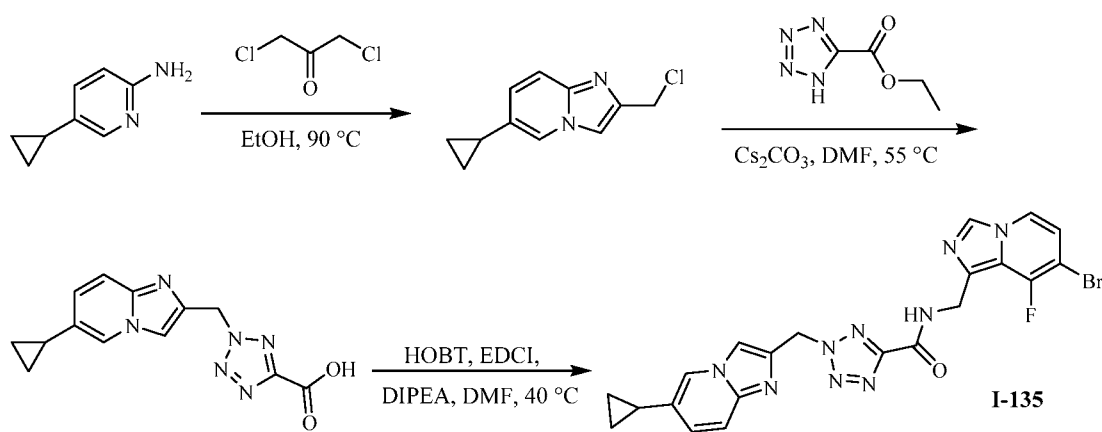


[0560] Synthesis of N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (I-134). To a solution of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-

carboxylic acid (100 mg, 0.35 mmol), (7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (114 mg, 0.41 mmol), HOBT (67 mg, 0.49 mmol) and EDCI (94 mg, 0.49 mmol) in DMF (5 mL) was added DIPEA (226 mg, 1.75 mmol). The resulting mixture was stirred at RT for 14 h. The reaction was poured into H₂O (40 mL), and yellow solid was precipitate out. The mixture was filtered and the cake was dried to give the crude product, which was triturated with DCM (25 mL) to give the N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (65 mg, yield: 36%) as a white solid. ESI-MS [M+H]⁺: 509.0, purity : 98.79 (214nm), 98.38 (254nm). ¹H NMR (400 MHz, DMSO-d₆) δ 8.69 (t, J = 5.2 Hz, 1H), 8.55 (s, 1H), 8.45 (s, 1H), 8.35 (s, 1H), 8.14 (d, J = 7.3 Hz, 1H), 7.83 (s, 1H), 7.41 (d, J = 9.3 Hz, 1H), 7.01 (dd, J = 9.3, 1.5 Hz, 1H), 6.83-6.80 (m, 1H), 5.73 (s, 2H), 4.69 (d, J = 5.4 Hz, 2H), 1.96-1.89 (m, 1H), 0.94-0.89 (m, 2H), 0.69-0.65 (m, 2H).

Example 135

Scheme 134



[0561] Synthesis of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine. A mixture of 5-cyclopropylpyridin-2-amine (320 mg, 2.38 mmol), 1,3-dichloropropan-2-one (906 mg, 7.14 mmol) in EtOH (5 mL) was stirred at 90 °C overnight. The reaction mixture was concentrated and a saturated aqueous NaHCO₃ was added until pH to about 8, and then extracted with EtOAc (50 mL x 2). The combined organic layers were concentrated and purified by silica gel

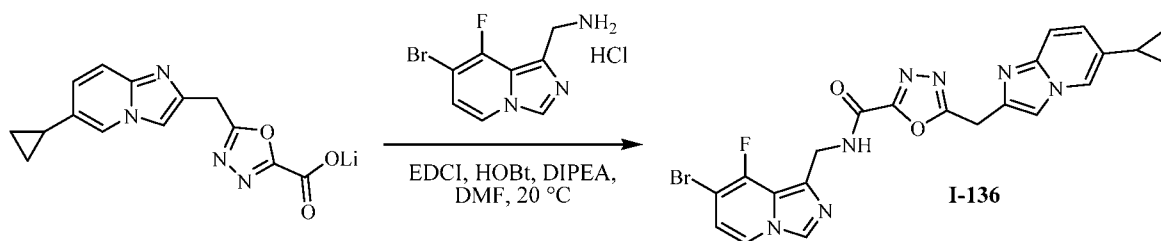
chromatography (EA/PE = 2/1) to give 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (200 mg, yield: 41%) as a brown solid. ESI-MS $[M+H]^+$: 207.1.

[0562] Synthesis of 2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-tetrazole-5-carboxylic acid. A mixture of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (104 mg, 0.5 mmol), ethyl 1H-tetrazole-5-carboxylate (71 mg, 0.5 mmol) and Cs_2CO_3 (323 mg, 1 mmol) in DMF (3 mL) was stirred at 55 °C for 6 h. Then H_2O was added (10 mL), pH of the mixture was adjusted to 5 by adding HCl (2 N), then lyophilized to give 2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-tetrazole-5-carboxylic acid (500 mg, crude) as a yellow solid, which was used into next step without purification. ESI-MS $[M+H]^+$: 285.1.

[0563] Synthesis of N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-tetrazole-5-carboxamide (I-135). A mixture of 2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-tetrazole-5-carboxylic acid (250 mg, crude from last step), (7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (45 mg, 0.16 mmol), HOBt (73 mg, 0.54 mmol), EDCI (103 mg, 0.54 mmol) and DIPEA (174 mg, 1.35 mmol) in DMF (2 mL) was stirred at 40 °C for 26 h. Water (20 mL) was added and extracted with EtOAc (30 mL x 3), the combined organic layers were washed by H_2O (10 mL), then by brine, and then concentrated, the crude was purified by prep-HPLC to give N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-2H-tetrazole-5-carboxamide (3.3 mg, yield: 4.03%) as a white solid. ESI-MS $[M+H]^+$: 510.0. Purity: 97.65% (214 nm), 99.08% (254 nm). ^1H NMR (400 MHz, DMSO-d_6) δ 9.29 (t, $J = 5.4$ Hz, 1H), 8.45 (d, $J = 2.4$ Hz, 1H), 8.36 (s, 1H), 8.14 (d, $J = 7.3$ Hz, 1H), 7.94 (s, 1H), 7.39 (d, $J = 9.3$ Hz, 1H), 7.01 (dd, $J = 9.4, 1.7$ Hz, 1H), 6.82 (t, $J = 8$ Hz, 1H), 6.06 (s, 2H), 4.71 (d, $J = 5.5$ Hz, 2H), 1.96-1.89 (m, 1H), 0.93-0.91 (m, 2H), 0.69-0.65 (m, 2H).

Example 136

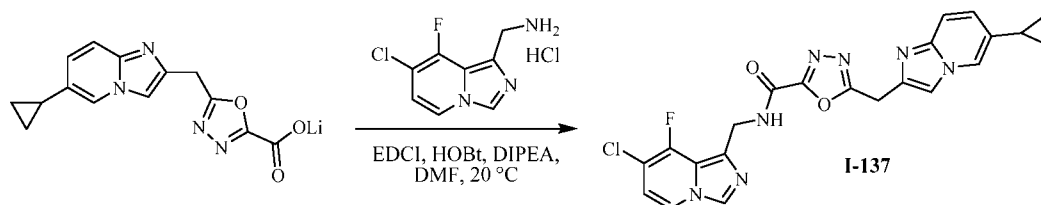
Scheme 135



[0564] Synthesis of N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide (I-136). A mixture of lithium 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate (100.0 mg, 0.35 mmol), (7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)-methanamine hydrochloride (98.6 mg, 0.35 mmol), EDCI (134.4 mg, 0.70 mmol), HOBT (94.5 mg, 0.70 mmol) and DIPEA (0.18 mL, 1.05 mmol) in DMF (5 mL) was stirred at 20 °C for 48 h. The mixture was concentrated to remove DMF, diluted with DCM/MeOH (300 mL, 10/1 (v/v)) and washed with H₂O (100 mL x 2). The organic layer was separated, dried over Na₂SO₄, and concentrated in vacuo to give the crude product, which was purified by Prep-HPLC to give N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide (25.5 mg, yield: 14.3%) as a light yellow solid. ESI-MS [M+H]⁺: 509.9. Purity: 95.1 (214nm), 96.6 (254nm). ¹H NMR (400 MHz, DMSO-d₆) δ 9.63 (t, J = 5.5 Hz, 1H), 8.46 (d, J = 2.4 Hz, 1H), 8.33 (s, 1H), 8.15 (d, J = 7.3 Hz, 1H), 7.79 (s, 1H), 7.38 (d, J = 9.3 Hz, 1H), 6.98 (dd, J = 9.3, 1.8 Hz, 1H), 6.83 (dd, J = 7.3, 6.1 Hz, 1H), 4.69 (d, J = 5.5 Hz, 2H), 4.43 (s, 2H), 1.98-1.85 (m, 1H), 1.00-0.84 (m, 2H), 0.74-0.61 (m, 2H).

Example 137

Scheme 136

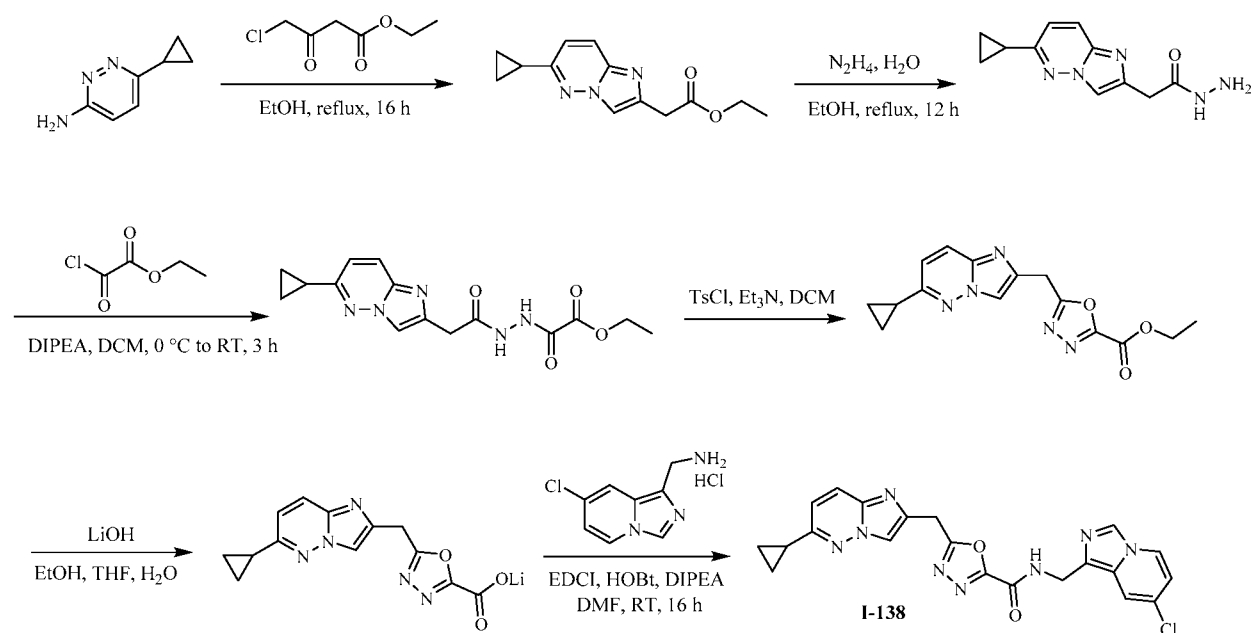


[0565] Synthesis of N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide (I-137). A mixture of lithium 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate (100.0 mg, 0.35 mmol), (7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (82.3 mg, 0.35 mmol), EDCI (134.4 mg, 0.70 mmol), HOBT (94.5 mg, 0.70 mmol) and DIPEA (0.18 mL, 1.05 mmol) in DMF (5 mL) was stirred at 20 °C for 48 h. The

mixture was concentrated to remove DMF, diluted with DCM/MeOH (300 mL, 10/1 (v/v)) and washed with H₂O (100 mL). The organic layer was separated, dried over Na₂SO₄, and concentrated in vacuo to give the crude product, which was purified by Prep-HPLC to give N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide (30.0 mg, yield: 18.4%) as a white solid. ESI-MS [M+H]⁺: 466.2. Purity: 97.6 (214nm), 99.1 (254nm). ¹H NMR (400 MHz, DMSO-d₆) δ 9.63 (t, J = 5.4 Hz, 1H), 8.45 (d, J = 2.4 Hz, 1H), 8.33 (s, 1H), 8.22 (d, J = 7.4 Hz, 1H), 8.15 (s, 1H), 7.80 (s, 1H), 7.38 (d, J = 9.3 Hz, 1H), 6.98 (dd, J = 9.3, 1.7 Hz, 1H), 6.84-6.70 (m, 1H), 4.69 (d, J = 5.5 Hz, 2H), 4.43 (s, 2H), 1.93-1.87 (m, 1H), 1.01-0.85 (m, 2H), 0.75-0.55 (m, 2H).

Example 138

Scheme 137



[0566] Synthesis of ethyl 2-(6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)acetate. A mixture of 6-cyclopropylpyridazin-3-amine (1.00 g, 7.40 mmol) in EtOH (10 mL) was added ethyl 4-chloro-3-oxobutanoate (3.65 g, 22.19 mmol) at RT. Then the mixture was heated to 80 °C and stirred for 16 h. The mixture was concentrated and purified by flash silica gel chromatography (0 ~ 10% MeOH in DCM) to give ethyl 2-(6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)acetate (1.1 g, crude) as dark-red oil. ESI-MS [M+H]⁺: 246.2.

[0567] Synthesis of 2-(6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)acetohydrazide. To a solution of ethyl 2-(6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)acetate (1.00 g, crude from last step) in EtOH (10 mL) was added hydrazine hydrate (1 mL) at RT. The mixture was heated to 80 °C and stirred for 12 h. The mixture were concentrated and purified by flash silica gel chromatography (0~100% EtOAc in PE) to give 2-(6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)acetohydrazide (480 mg, 29% over 2 steps) as a red solid. ESI-MS $[M+H]^+$: 232.1.

[0568] Synthesis of ethyl 2-(2-(2-(6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)acetyl)hydrazinyl)-2-oxoacetate. To a solution of 2-(6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)acetohydrazide (477 mg, 2.06 mmol) in DCM (10 mL) was added DIPEA (533.18 mg, 4.13 mmol) and ethyl 2-chloro-2-oxoacetate (422.4 mg, 3.09 mmol) at 0 °C. The mixture was stirred at 0 °C for 3 h. The mixture were concentrated and purified by flash silica gel chromatography (0~10% MeOH in DCM) to give ethyl 2-(2-(2-(6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)acetyl)hydrazinyl)-2-oxoacetate (450 mg, yield: 65%) as a yellow solid. ESI-MS $[M+H]^+$: 332.2.

[0569] Synthesis of ethyl 5-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate. To a solution of ethyl 2-(2-(2-(6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)acetyl)hydrazinyl)-2-oxoacetate (450 mg, 1.36 mmol) in DCM (10 mL) was added TsCl (258 mg, 1.36 mmol), Et₃N (274 mg, 2.72 mmol) at RT. The mixture was stirred for 2 h. Water (20 mL) was added and extracted with EtOAc (30 mL x 3). The combined organic layers were concentrated and purified by flash silica gel chromatography (0~100% EtOAc in PE) to give ethyl 5-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate (240 mg, yield: 56%) as a white solid. ESI-MS $[M+H]^+$: 314.2.

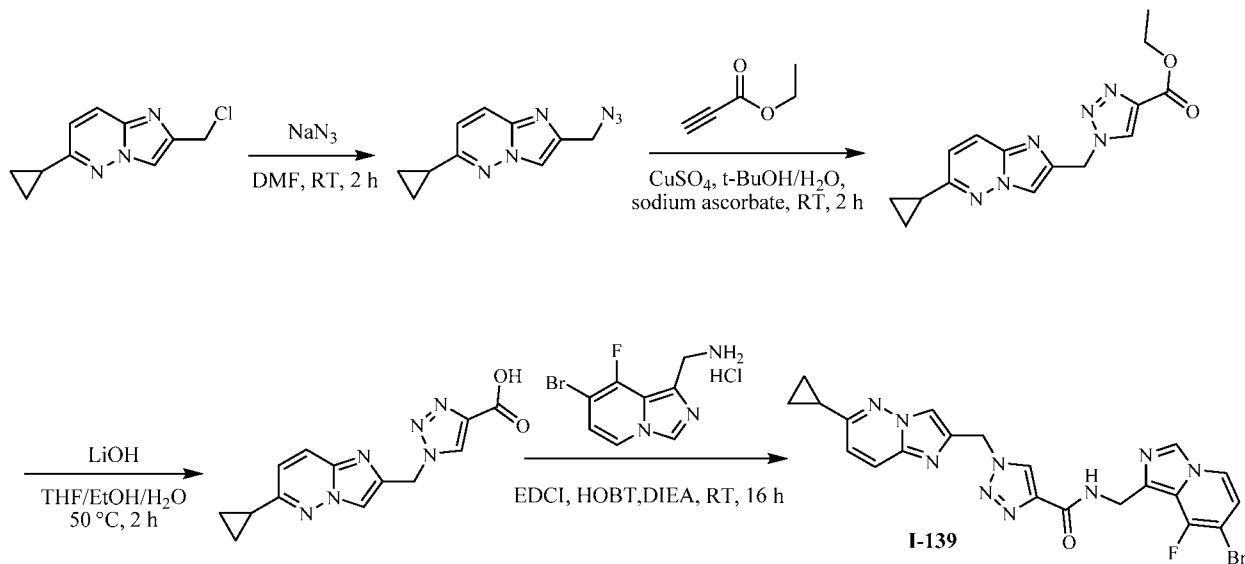
[0570] Synthesis of lithium 5-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate. To a solution of ethyl 5-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate (40 mg, 0.128 mmol) in EtOH/THF/H₂O (1 mL/1 mL/1 mL) was added LiOH·H₂O (10 mg, 0.255 mmol) at RT. The mixture was heated to 40 °C stirred for 0.5 h. The mixture was freeze-dried to give lithium 5-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate (50 mg, crude) as a pink solid. ESI-MS $[M+H]^+$: 286.1.

[0571] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide (I-138).

To a solution of lithium 5-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate (50 mg, crude from last step) in DMF (3 mL) was added EDCI (58 mg, 0.3 mmol), HOBT (40 mg, 0.2 mmol), DIPEA (65 mg, 0.5 mmol) and (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (54 mg, 0.25 mmol) at RT. The mixture was stirred for 16 h. The mixture was concentrated and purified by Prep-HPLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide (3 mg, yield:5%) as a white solid. ESI-MS $[M+H]^+$: 449.0. Purity: 98.12(214nm), 97.17(254nm). ^1H NMR (400 MHz, DMSO- d_6) δ 9.73 (t, J = 5.8 Hz, 1H), 8.31-8.33 (m, 2H), 8.14 (s, 1H), 7.91 (d, J = 9.6 Hz, 1H), 7.84-7.82 (m, 1H), 7.08 (d, J = 9.4 Hz, 1H), 6.69-6.65 (m, 1H), 4.62 (d, J = 5.9 Hz, 2H), 4.47 (s, 2H), 2.13-2.23 (m, 1H), 1.09-1.03 (m, 2H), 0.99-0.93 (m, 2H).

Example 139

Scheme 138



[0572] Synthesis of 2-(azidomethyl)-6-cyclopropylimidazo[1,2-b]pyridazine. A mixture of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-b]pyridazine (900 mg, 4.33 mmol) in dry DMF (5 mL) was added NaN_3 (631 mg, 9.71 mmol) at RT. After the mixture was stirred for 2 h, H_2O (50 mL)

was added and the mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated and purified by flash silica gel chromatography (0 ~ 40% EtOAc in PE) to give 2-(azidomethyl)-6-cyclopropylimidazo[1,2-b]pyridazine (735 mg, yield: 79.16%) as dark-red oil. ESI-MS $[M+H]^+$: 215.2

[0573] Synthesis of ethyl 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate. To a solution of 2-(azidomethyl)-6-cyclopropylimidazo[1,2-b]pyridazine (730 mg, 3.4 mmol) and ethyl propiolate (501.42 mg, 5.11 mmol) in t-BuOH/H₂O (5 mL/5 mL) was added CuSO₄ (543 mg, 3.4 mmol) and sodium ascorbate (675 mg, 3.41 mmol) at RT. After the mixture was stirred for 2 h, it was concentrated and purified by flash silica gel chromatography (0~10% EtOAc in PE) to give ethyl 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (600 mg, yield: 56%) as a red solid. ESI-MS $[M+H]^+$: 313.2.

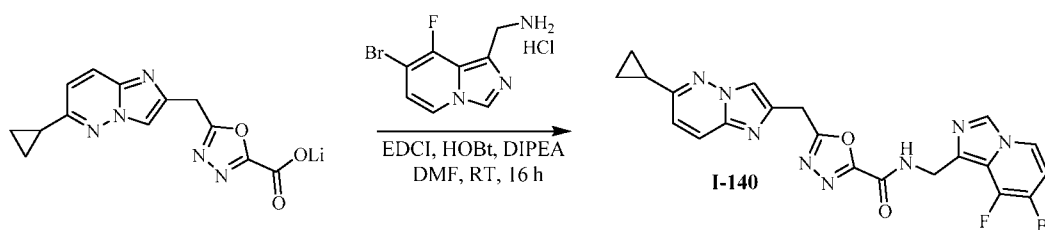
[0574] Synthesis of 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid. To a solution of ethyl 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (100 mg, 0.32 mmol) in THF/EtOH/H₂O (0.2 mL/0.2 mL/0.2 mL) was added LiOH (15.33 mg, 0.64 mL). The mixture was heated to 50 °C for 2 h. pH of the mixture was adjust to 5 by adding HCl (2 M), and then the mixture was freeze-dried to give 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (110 mg, crude) as a white solid. ESI-MS $[M+H]^+$: 285.1.

[0575] Synthesis of N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (I-139). To a solution of 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (110 mg, crude from last step) in DMF (5 mL) was added EDCI (101 mg, 0.53 mmol), HOBt (71 mg, 0.53 mmol), DIPEA (227 mg, 1.76 mmol) and (7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (99 mg, 0.35 mmol) at RT. After the mixture was stirred for 16 h, the reaction was poured into H₂O, the precipitate was filtered and washed by MeOH to give N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (25.8 mg, yield:15%) as a white solid. ESI-MS $[M+H]^+$: 510.0. Purity: 97.38(214nm), 93.35(254nm). ¹H NMR (400 MHz, DMSO-d₆) δ 8.69 (t, J = 5.3 Hz, 1H), 8.56 (s, 1H), 8.45 (d, J = 2.2 Hz, 1H),

8.20 (s, 1H), 8.14 (d, J = 7.3 Hz, 1H), 7.94 (d, J = 9.5 Hz, 1H), 7.11 (d, J = 9.5 Hz, 1H), 6.85-6.77 (m, 1H), 5.75 (s, 2H), 4.69 (d, J = 5.5 Hz, 2H), 2.23-2.13 (m, 1H), 1.10-1.02 (m, 2H), 1.00-0.93 (m, 2H).

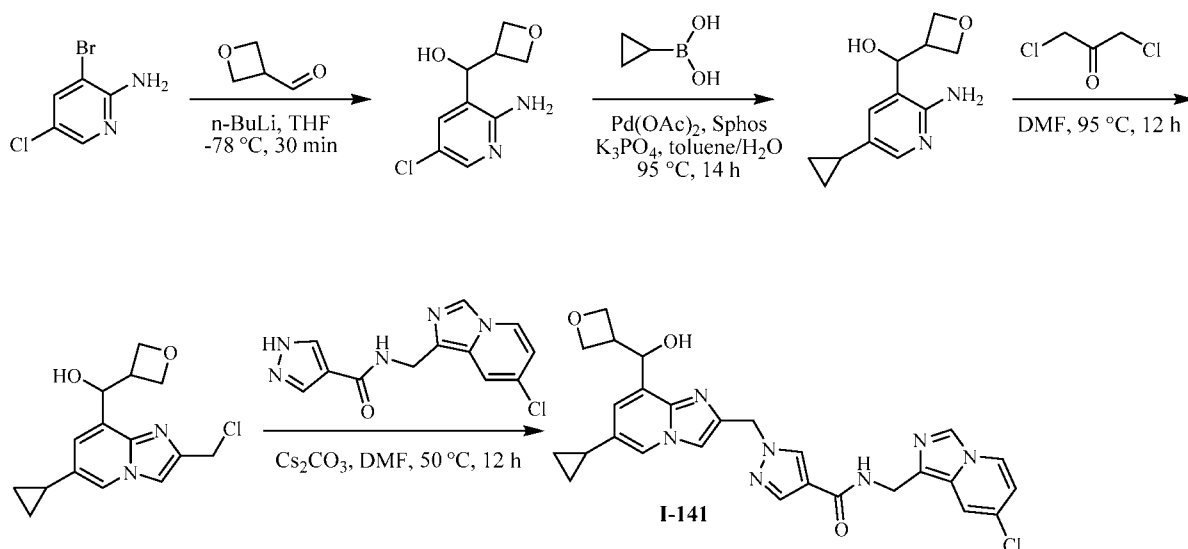
Example 140

Scheme 139



[0576] Synthesis of N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide (I-140).

To a solution of lithium 5-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate (50 mg, crude) in DMF (3 mL) was added EDCI (58 mg, 0.3 mmol), HOBT (40 mg, 0.3 mmol), DIPEA (65 mg, 0.5 mmol) and (7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (70 mg, 0.25 mmol) at RT. The mixture was stirred for 16 h. The mixture was concentrated and purified by Prep-HPLC to give N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide (5 mg) as a yellow solid. ESI-MS $[M+H]^+$: 511.0. Purity: 95.73(214nm), 96.89(254nm). ^1H NMR (400 MHz, DMSO- d_6) δ 9.63 (t, J = 5.4 Hz, 1H), 8.46 (d, J = 2.4 Hz, 1H), 8.15 (d, J = 7.4 Hz, 2H), 7.91 (d, J = 9.4 Hz, 1H), 7.09 (d, J = 9.4 Hz, 1H), 6.83 (dd, J = 7.3, 6.1 Hz, 1H), 4.69 (d, J = 5.5 Hz, 2H), 4.47 (s, 2H), 2.21-2.14 (m, 1H), 1.12-1.02 (m, 2H), 1.01-0.92 (m, 2H).

Example 141Scheme 140

[0577] Synthesis of (2-amino-5-chloropyridin-3-yl)(oxetan-3-yl)methanol. To a solution of 3-bromo-5-chloropyridin-2-amine (800 mg, 3.86 mmol) in THF (20 mL) was added n-BuLi (6.4 mL, 15.5 mmol, 2.4 M solution in hexane) at -78 °C and stirred for 10 min. Then a solution of oxetane-3-carbaldehyde (1.3 g, 15.4 mmol) in 5 mL THF was added. The resulting reaction was stirred at -78 °C for 5 min. The reaction was quenched with aqueous NH₄Cl (20 mL), extracted with EtOAc (50 mL x3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude product, which was purified with silica gel chromatography (DCM/MeOH = 10/1) to give the (2-amino-5-chloropyridin-3-yl)(oxetan-3-yl)methanol (400 mg, yield: 48%) as a yellow solid. ESI-MS [M+H]⁺: 215.2.

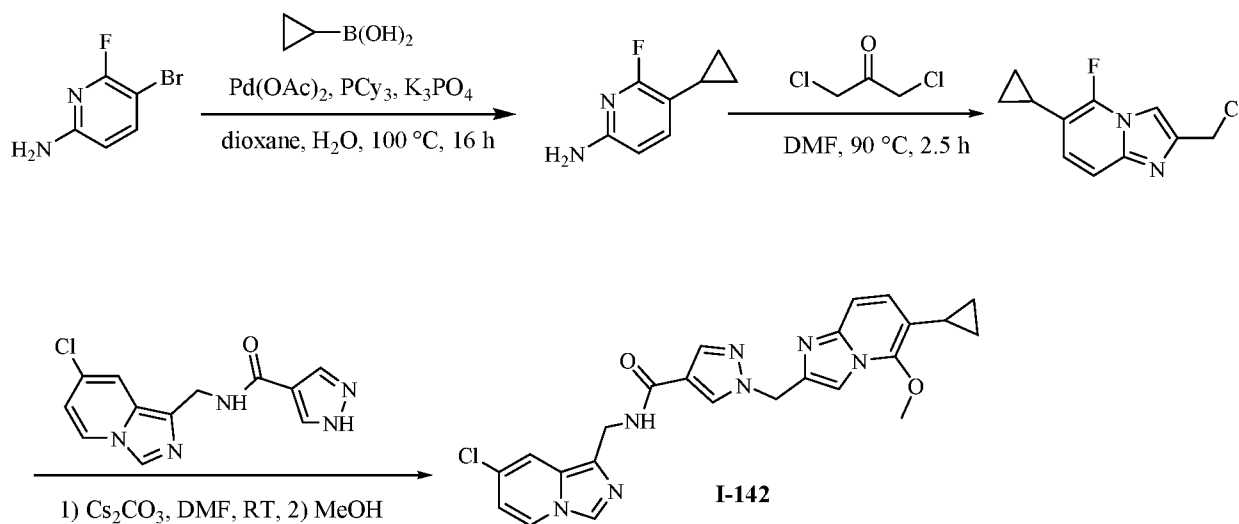
[0578] Synthesis of (2-amino-5-cyclopropylpyridin-3-yl)(oxetan-3-yl)methanol. A mixture of (2-amino-5-chloropyridin-3-yl)(oxetan-3-yl)methanol (400 mg, 1.87 mmol), cyclopropylboronic acid (209 mg, 2.43 mmol), Pd(OAc)₂ (42 mg, 0.187 mmol), SPhos (165 mg, 0.374 mmol) and K₃PO₄ (1.2 g, 5.61 mmol) in toluene/H₂O (25 mL/2.5 mL) was stirred at 95 °C for 14 h. The reaction mixture was filtered, and the filtrate was concentrated in vacuo to give the crude product, which was purified with silica gel chromatography (DCM/MeOH = 10/1) to give the (2-amino-5-cyclopropylpyridin-3-yl)(oxetan-3-yl)methanol (250 mg, yield: 60.8%) as a yellow solid. ESI-MS [M+H]⁺: 221.2.

[0579] Synthesis of (2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)(oxetan-3-yl)methanol. A mixture of (2-amino-5-cyclopropylpyridin-3-yl)(oxetan-3-yl)methanol (250 mg, 1.13 mmol) and 1,3-dichloropropan-2-one (572 mg, 4.5 mmol) in DMF (10 mL) was stirred at 95 °C for 12 h. H₂O (30 mL) was added to the reaction, extracted with EtOAc (30 mL x 2). The aqueous layer was free-dried to give the (2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)(oxetan-3-yl)methanol (200 mg crude), which was used into next step without further purification. ESI-MS [M+H]⁺: 293.2

[0580] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxy(oxetan-3-yl)methyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-141). A mixture of (2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)(oxetan-3-yl)methanol (100 mg, crude from last step), N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (94 mg, 0.34 mmol) and Cs₂CO₃ (332 mg, 1.02 mmol) in DMF (10 mL) was stirred at 50 °C for 12 h. H₂O (30 mL) was added to the reaction, extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude product, which was purified with Prep-HPLC to give the N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxy(oxetan-3-yl)methyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (22 mg, yield: 12%) as a white solid. ESI-MS [M+H]⁺: 531.9. Purity: 97.2(214nm), 95.9(254nm). ¹H NMR (400 MHz, DMSO-d₆) δ 8.75-8.68 (m, 1H), 8.64-8.59 (m, 1H), 8.53-8.30 (m, 3H), 8.22-8.18 (m, 1H), 7.99 (s, 1H), 7.79 (s, 1H), 7.63 (d, J = 6.3 Hz, 1H), 6.67-6.63 (m, 1H), 5.83-5.76 (m, 2H), 5.02-4.98 (m, 0.5H), 4.88-4.86 (m, 0.5H), 4.61-4.46 (m, 3H), 4.13-4.07 (m, 1H), 3.91-3.82 (m, 1H), 3.76-3.69 (m, 1H), 3.64-3.58 (m, 1H), 3.54-3.44 (m, 1H), 2.14-2.08 (m, 1H), 1.08-1.04 (m, 2H), 0.78-0.75 (m, 2H).

Example 142

Scheme 141



[0581] Synthesis of 5-cyclopropyl-6-fluoropyridin-2-amine. To a solution of 5-bromo-6-fluoropyridin-2-amine (40 g, 209 mmol) in dioxane/H₂O (400 mL/40 mL) was added cyclopropylboronic acid (36 g, 418 mmol), Pd(OAc)₂ (4.7 g, 21 mmol), PCy₃ (11.75 g, 42 mmol) and K₃PO₄ (133 g, 628 mmol), then the mixture was stirred at 100 °C for 16 h. The mixture was treated with H₂O (100 mL) and extracted with EtOAc (300 mL x 3). The organic layers were concentrated to give the crude product, which was purified by flash silica gel chromatography (PE/EA = 2/1) to give 5-cyclopropyl-6-fluoropyridin-2-amine (26 g, yield: 81%) as a white solid. ESI-MS [M+H]⁺: 153.1.

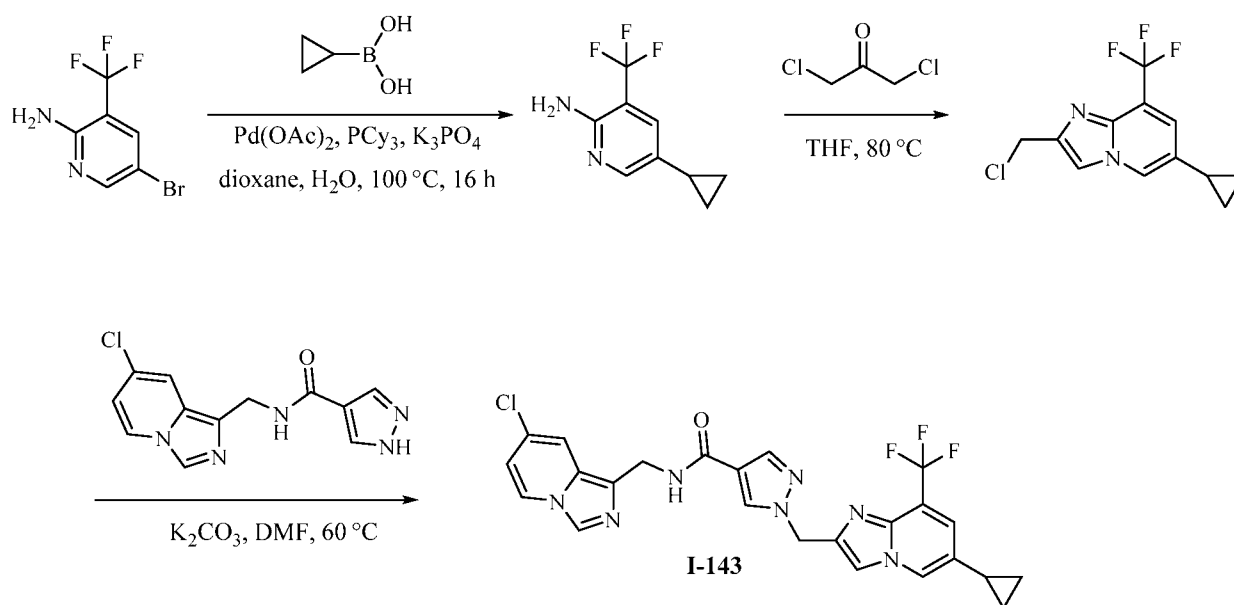
[0582] Synthesis of 2-(chloromethyl)-6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridine. To a solution of 5-cyclopropyl-6-fluoropyridin-2-amine (30 g, 197 mmol) in EtOAc (50 mL) was added 1,3-dichloropropan-2-one (32.54 g, 256 mmol), then the mixture was stirred at 60 °C for 16 h. The mixture was treated with NaHCO₃ (aqueous) to adjust pH to 8 and then extracted with Ethyl Acetate. The organic layer was concentrated to give the crude product which was purified by flash silica gel chromatography (PE/EA = 3:1) to give 2-(chloromethyl)-6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridine (12.5 g, yield: 28%) as a white solid. ESI-MS [M+H]⁺: 224.9.

[0583] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-methoxyimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide. To a solution of 2-

(chloromethyl)-6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridine (1.94 g, 8.64 mmol) in DMF (200 mL) at RT was added N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (2.38 g, 8.64 mmol) and Cs₂CO₃ (8.44 g, 25.9 mmol). The reaction mixture was stirred at RT for 16 h. The mixture was concentrated to remove DMF, diluted with MeOH (200 mL) and stirred at 60 °C for 4 h and then removed MeOH, diluted with EtOAc (200 mL), washed with H₂O (200 mL). The organic layer was separated, dried over Na₂SO₄, and concentrated in vacuo to give the crude product, which was purified by silica gel chromatography (DCM/MeOH = 20:1 to 10:1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-methoxyimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (3.5 g, yield: 85%) as a gray solid. ESI-MS [M+H]⁺: 476.1. Purity: 97.35 (214nm), 93.50 (254nm). ¹H NMR (400 MHz, CDCl₃) δ = 8.0 (s, 2H), 7.82 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.66 (s, 1H), 7.52 (s, 1H), 7.26 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.63 (t, J = 4.0 Hz, 1H), 6.50 (dd, J = 7.2, 2.0 Hz, 1H), 5.45 (s, 2H), 4.74 (d, J = 5.6, 2H), 4.08 (s, 3H), 2.10-2.02 (m, 1H), 1.04-0.98 (m, 2H), 0.74-0.69 (m, 2H).

Example 143

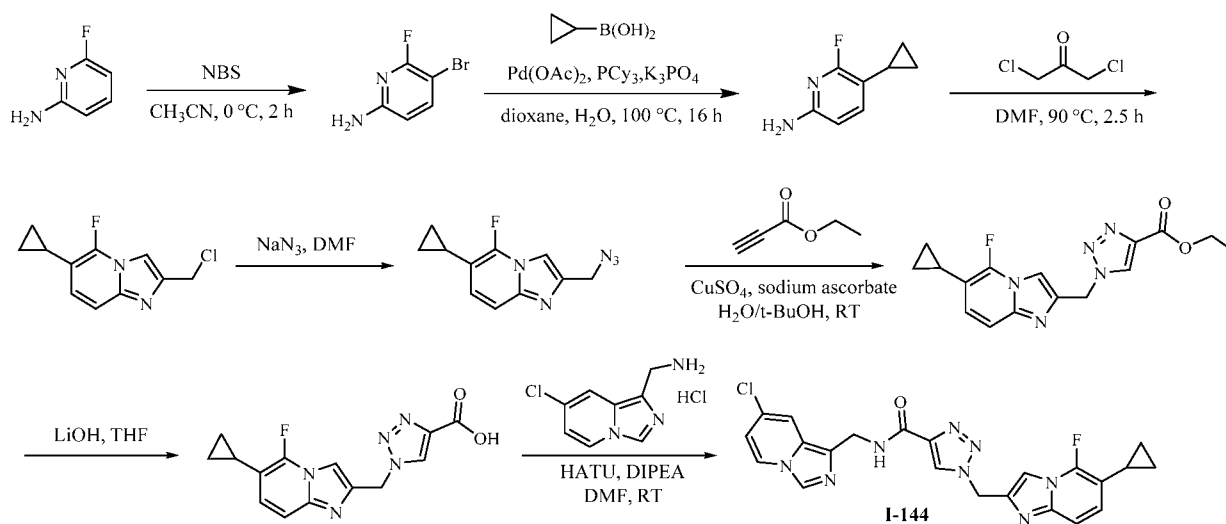
Scheme 142



[0584] Synthesis of 5-cyclopropyl-3-(trifluoromethyl)pyridin-2-amine. To a solution of 5-bromo-3-(trifluoromethyl)pyridin-2-amine (2 g, 7.2 mmol) in dioxane/H₂O (100 mL/10 mL) was added cyclopropylboronic acid (1.425 g, 16.6 mmol), Pd(OAc)₂ (186 mg, 0.83 mmol), PCy₃ (465 mg, 1.66 mmol) and K₃PO₄ (3.523 g, 16.6 mmol). The reaction mixture was stirred at 100 °C for 14 h under nitrogen. Then the mixture was concentrated in vacuo. Water (100 mL) was added and the mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were concentrated to give the crude product, which was purified by silica gel chromatography (PE/EtOAc = 10/1) to give the 5-cyclopropyl-3-(trifluoromethyl)pyridin-2-amine as a yellow solid (708 mg, yield: 48%). ESI-MS [M+H]⁺: 203.1.

[0585] Synthesis of 2-(chloromethyl)-6-cyclopropyl-8-(trifluoromethyl)imidazo[1,2-a]pyridine. To a solution of 5-cyclopropyl-3-(trifluoromethyl)pyridin-2-amine (634 mg, 3.14 mmol) and 1,3-dichloropropan-2-one (1.194 g, 9.41 mmol) in THF (30 mL) the reaction mixture was stirred at 80 °C overnight. Then H₂O (50 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated to give the crude product, which was purified by silica gel chromatography (PE/EtOAc = 10/1) to give 2-(chloromethyl)-6-cyclopropyl-8-(trifluoromethyl)imidazo[1,2-a]pyridine (232 mg, yield: 27%) as a white solid. ESI-MS [M+H]⁺: 275.0.

[0586] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-143). To a solution of 2-(chloromethyl)-6-cyclopropyl-8-(trifluoromethyl)imidazo[1,2-a]pyridine (126 mg, 0.45 mmol), N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (126 mg, 0.45 mmol) and K₂CO₃ (127 mg, 0.917 mmol) in DMF (10 mL). The resulting mixture was stirred overnight at 60 °C. The mixture was concentrated to give the crude product, which was purified by silica gel chromatography (DCM/MeOH = 20/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(trifluoromethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (58 mg, yield: 25%) as a white solid. ESI-MS [M+H]⁺: 514.1. Purity: 95.44 (214nm), 95.85 (254nm). ¹H NMR (400 MHz, MeOD) δ 8.42 (s, 1H), 8.28 (s, 1H), 8.19 (s, 1H), 8.18 (d, J = 0.9 Hz, 1H), 7.95 (s, 1H), 7.78 (s, 1H), 7.76 (s, 1H), 7.51 (s, 1H), 6.65 (dd, J = 7.5, 2.0 Hz, 1H), 5.51 (s, 2H), 4.71 (s, 2H), 2.07-1.98 (m, 1H), 1.01-0.97 (m, 2H), 0.75-0.72 (m, 2H).

Example 144Scheme 143

[0587] Synthesis of 5-cyclopropyl-6-fluoropyridin-2-amine. To a solution of 5-bromo-6-fluoropyridin-2-amine (40 g, 209 mmol) in dioxane/H₂O (400 mL/40 mL) was added cyclopropylboronic acid (36 g, 418 mmol), Pd(OAc)₂ (4.7 g, 21 mmol), PCy₃ (11.75 g, 42 mmol) and K₃PO₄ (133 g, 628 mmol), then the mixture was stirred at 100 °C for 16 h. The mixture was treated with H₂O (100 mL) and extracted with EtOAc (300 mL x 3). The organic layers were concentrated to give the crude product, which was purified by flash silica gel chromatography (PE/EA = 2/1) to give 5-cyclopropyl-6-fluoropyridin-2-amine (26 g, yield: 81%) as a white solid. ESI-MS [M+H]⁺: 153.1.

[0588] Synthesis of 2-(chloromethyl)-6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridine. To a solution of 5-cyclopropyl-6-fluoropyridin-2-amine (30 g, 197 mmol) in EtOAc (50 mL) was added 1,3-dichloropropan-2-one (32.54 g, 256 mmol), then the mixture was stirred at 60 °C for 16 h. The mixture was treated with NaHCO₃ (aqueous) to adjust pH to 8 and then extracted with Ethyl Acetate. The organic layer was concentrated to give the crude product which was purified by flash silica gel chromatography (PE/EA = 3:1) to give 2-(chloromethyl)-6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridine (12.5 g, yield: 28%) as a white solid. ESI-MS [M+H]⁺: 224.9.

[0589] Synthesis of 2-(azidomethyl)-6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridine.

To a solution of 2-(chloromethyl)-6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridine (200 mg, 0.89 mmol) in DMF (3 mL) was added NaN₃ (58 mg, 0.89 mmol), then the mixture was stirred at RT for 5 h. Water (30 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give 2-(azidomethyl)-6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridine (220 mg, crude) as a white solid that was used directly in the next step. ESI-MS [M+H]⁺: 232.1.

[0590] Synthesis of ethyl 1-((6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate.

To a solution of 2-(azidomethyl)-6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridine (220 mg, crude) in t-BuOH/H₂O (5 mL/5 mL) was added ethyl propiolate (186 mg, 1.9 mmol), CuSO₄ (30 mg, 0.19 mmol) and sodium ascorbate (56 mg, 0.28 mmol), then the mixture was stirred at RT for 0.5 h. The reaction mixture showed product precipitated which was filtered and washed with H₂O (10 mL) and methanol (10 mL) to give ethyl 1-((6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (250 mg, yield: 85%) as a white solid. ESI-MS [M+H]⁺: 330.1.

[0591] Synthesis of 1-((6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid.

To a solution of ethyl 1-((6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (250 mg, 0.75 mmol) in THF/H₂O (6 mL/3 mL) was added LiOH (42.03 mg, 1.76 mmol), then the mixture was stirred at RT overnight. The mixture was treated with HCl (aq) to adjust the pH to 4, the precipitate was filtered and washed with H₂O (10 mL) to give 1-((6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (120 mg, yield: 52%) as a white solid which was used into next step without further purification. ESI-MS [M+H]⁺: 302.1.

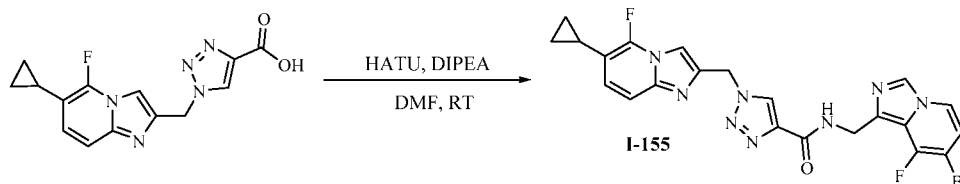
[0592] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (I-144).

To a solution of 1-((6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (60 mg, 0.2 mmol) in DMF (2 mL) was added (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (87 mg, 0.4 mmol), HATU (151 mg, 0.4 mmol) and DIPEA (154 mg, 1.19 mmol), then the mixture was stirred at RT for 0.5 h. The reaction mixture was poured into H₂O (15 mL), the solid formed, filtered and washed with

H₂O and methanol to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (53 mg, yield: 57%) as a white solid. ESI-MS [M+H]⁺: 465.1. Purity: 98.44 (214nm), 97.99 (254nm). ¹H NMR (400 MHz, DMSO-d₆) δ 8.93 (t, J = 4.0 Hz, 1H), 8.58 (s, 1H), 8.30 (brs, 2H), 7.98 (s, 1H), 7.84 (s, 1H), 7.36 (t, J = 4.0 Hz, 1H), 7.03 (t, J = 4.0 Hz, 1H), 6.65 (q, J = 4.0 Hz, 1H), 5.77 (s, 2H), 4.62 (d, J = 8.0 Hz, 2H), 2.06-2.03 (m, 1H), 0.99-0.96 (m, 2H), 0.77-0.74 (m, 2H).

Example 145

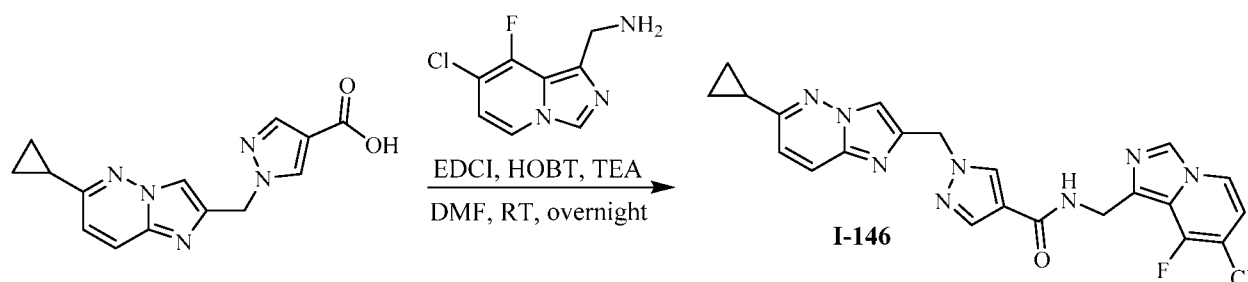
Scheme 144



[0593] Synthesis of N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (I-145). To a solution of 1-((6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (60 mg, 0.2 mmol) in DMF (2 mL) was added (7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine (97 mg, 0.4 mmol), HATU (151 mg, 0.4 mmol) and DIPEA (154 mg, 1.19 mmol), then the mixture was stirred at RT for 0.5 h. The mixture was filtrated to give N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-5-fluoroimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (62 mg, yield: 59%) as a white solid. ESI-MS [M+H]⁺: 527.0. Purity: 99.01 (214nm), 98.76 (254nm). ¹H NMR (400 MHz, DMSO-d₆) δ 8.70 (t, J = 4.0 Hz, 1H), 8.57 (s, 1H), 8.45 (d, J = 4.0 Hz, 1H), 8.13 (d, J = 4.0 Hz, 1H), 8.00 (s, 1H), 7.36 (d, J = 4.0 Hz, 1H), 7.03 (t, J = 4.0 Hz, 1H), 6.82 (t, J = 8.0 Hz, 1H), 5.77 (s, 2H), 4.70 (d, J = 4.0 Hz, 2H), 2.06-2.01 (m, 1H), 1.00-0.96 (m, 2H), 0.77-0.74 (m, 2H).

Example 146

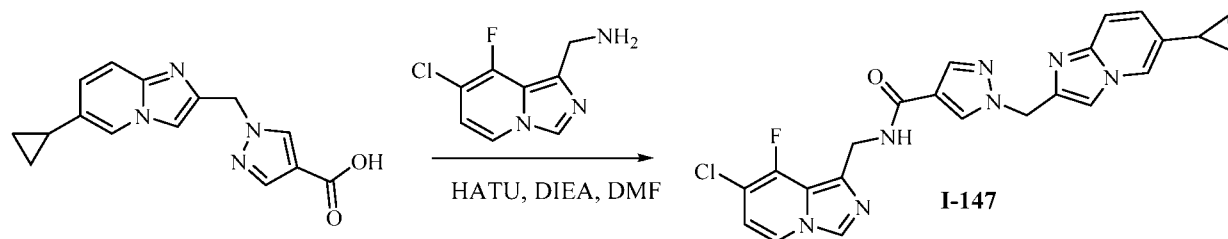
Scheme 145



[0594] Synthesis of N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-146). A solution of 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (105 mg, 0.37 mmol), (7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (113 mg, 0.48 mmol), EDCI (86 mg, 0.45 mmol), HOBT (60 mg, 0.45 mmol) and TEA (112 mg, 1.1 mL, 0.15 mmol) in dry DMF (5 mL) was stirred at RT overnight. Then the reaction mixture was diluted with H₂O (30 mL) and extracted with EtOAc 50 mL x 3). The combined organic layers were dried over Na₂SO₄, concentrated and purified by flash column chromatography (DCM: MeOH = 10: 1) to give the desired compound N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo [1,2-b]pyridazin-2-yl)methyl)-1H-pyrazole-4-carboxamide (53.8 mg, yield: 31%) as a white solid. ESI-MS [M+H]⁺: 465.1. Purity: 99.88 (214nm), 100.00 (254nm). ¹H NMR (400 MHz, DMSO-d₆) δ 8.44 (d, J = 2.2 Hz, 1H), 8.41 (t, J = 5.0 Hz, 1H), 8.21-8.20 (m, 2H), 8.09 (s, 1H), 7.92 (d, J = 9.4 Hz, 1H), 7.83 (s, 1H), 7.09 (d, J = 9.5 Hz, 1H), 6.76 (t, J = 6.9 Hz, 1H), 5.41 (s, 2H), 4.62 (d, J = 5.2 Hz, 2H), 2.19-2.15 (m, 1H), 1.08-1.04 (m, 2H), 0.98-0.94 (m, 2H).

Example 147

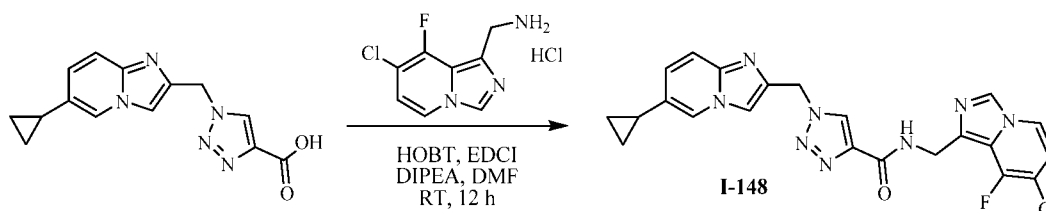
Scheme 146



[0595] Synthesis of N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-147). To a solution of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (60 mg, 0.21 mmol), (7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (75 mg, 0.32 mmol) and HATU (120 mg, 0.31 mmol) in DMF (3 mL) was added DIPEA (81 mg, 0.63 mmol). The resulting reaction was stirred at RT for 12 h. H₂O (25 mL) was added to the reaction, extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude product, which was purified with Prep-TLC (DMC/MeOH = 10/1) to give the N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (20 mg, yield: 21%) as a white solid. ESI-MS [M+H]⁺: 464.1. Purity: 99.3(214nm), 99.2(254nm). ¹H NMR (400 MHz, DMSO-d₆) δ 8.49-8.38 (m, 2H), 8.33 (s, 1H), 8.24-8.29 (m, 2H), 7.84 (s, 1H), 7.72 (s, 1H), 7.39 (d, J = 9.3 Hz, 1H), 7.01-6.96 (m, 1H), 6.80-6.72 (m, 1H), 5.38 (s, 2H), 4.62 (d, J = 5.2 Hz, 2H), 1.95-1.86 (m, 1H), 0.96-0.85 (m, 2H), 0.70-0.61 (m, 2H).

Example 148

Scheme 147

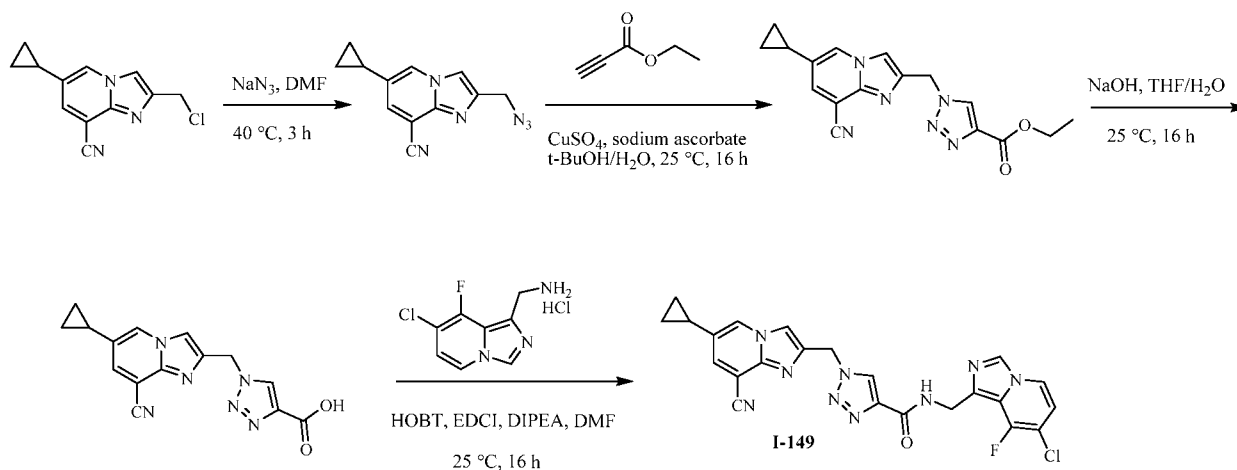


[0596] Synthesis of N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (I-148). To a suspension of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (37 mg, 0.13 mmol) and (7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (35 mg, 0.15 mmol) in DMF (3 mL) was added HOBT (40 mg, 0.3 mmol) and EDCI (57 mg, 0.3 mmol), followed by DIPEA (65 mg, 0.5 mmol). The resulting mixture was stirred at RT for 12 h. The reaction mixture was poured into H₂O (15 mL) slowly.

The suspension mixture was stirred for 1 h, and filtered. The filtered cake was washed with H₂O (20 mL) and MeOH (20 mL) then dried under vacuum pump to give the N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide as pale solid (30 mg, yield: 50%). ESI-MS [M+H]⁺: 465.0. Purity: 98.4% (214 nm), 98.5% (254 nm). ¹H NMR (400 MHz, DMSO-d₆): 8.70 (t, J = 5.4 Hz, 1H), 8.55 (s, 1H), 8.44 (d, J = 2.4 Hz, 1H), 8.35 (s, 1H), 8.21 (d, J = 7.4 Hz, 1H), 7.83 (s, 1H), 7.41 (d, J = 9.3 Hz, 1H), 7.01 (dd, J = 9.4, 1.8 Hz, 1H), 6.76 (dd, J = 7.3, 6.6 Hz, 1H), 5.73 (s, 2H), 4.70 (d, J = 5.5 Hz, 2H), 1.94-1.90 (m, 1H), 0.94-0.89 (m, 2H), 0.69-0.65 (m, 2H).

Example 149

Scheme 148



[0597] Synthesis of 2-(azidomethyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carbonitrile. To a mixture of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carbonitrile (200 mg, 0.86 mmol) in DMF (5 mL) was added NaN₃ (91 mg, 1.4 mmol). The mixture was stirred at 25 °C for 3 h. Then H₂O (30 mL) was added, extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give the crude product, which was purified by Prep-TLC (EA/PE = 3/2) to give 2-(azidomethyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carbonitrile (140 mg, yield: 68%) as a yellow solid. ESI-MS [M+H]⁺: 239.2.

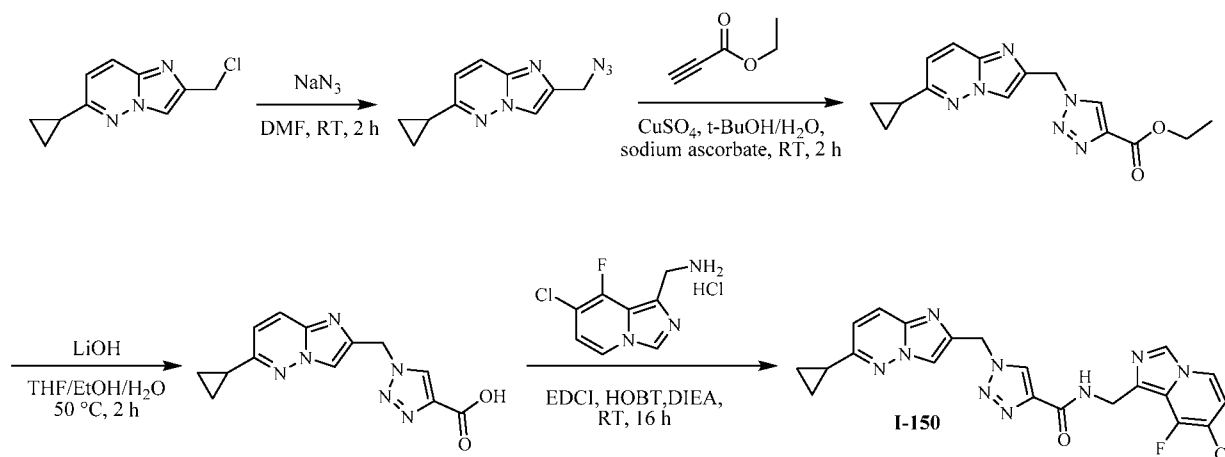
[0598] Synthesis of ethyl 1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate. To a mixture of 2-(azidomethyl)-6-cyclopropylimidazo[1,2-a]pyridine-8-carbonitrile (140 mg, 0.58 mmol), CuSO₄ (24 mg, 0.15 mmol), sodium ascorbate (30 mg, 0.15 mmol) in t-BuOH/H₂O (3/3 mL) was added ethyl propiolate (88 mg, 0.9 mmol). The mixture was stirred at 25 °C for 16 h. Water (30 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give ethyl 1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (95 mg, yield: 48%) as a yellow solid. ESI-MS [M+H]⁺: 337.2.

[0599] Synthesis of 1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid. To a mixture of ethyl 1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (95 mg, 0.28 mmol) in THF/H₂O (4/2 mL) was added NaOH (34 mg, 0.85 mmol). The mixture was stirred at 25 °C for 16 h. The pH of reaction was adjusted to 4 by 1 M HCl, then concentrated to give 1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (130 mg, crude) as a grey solid. ESI-MS [M+H]⁺: 309.2.

[0600] Synthesis of N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (I-149). To a mixture of 1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (130 mg, crude from last step), (7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (58 mg, 0.25 mmol), HOBt (44 mg, 0.32 mmol), EDCI (62 mg, 0.32 mmol) in DMF (3 mL) was added DIPEA (103 mg, 0.8 mmol). The mixture was stirred at 25 °C for 16 h. The reaction was quenched by H₂O (20 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give the crude product, which was purified by Prep-HPLC to give N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (15.6 mg, yield: 13%) as a yellow solid. ESI-MS [M+H]⁺: 489.9. Purity: 98.83(214nm), 99.11 (254nm). ¹H NMR (400 MHz, DMSO-d₆) δ 8.64-8.63 (m, 3H), 8.45 (s, 1H), 8.21 (s, 1H), 7.99-7.98 (m, 1H), 7.80 (s, 1H), 6.76 (s, 1H), 5.81 (s, 2H), 4.70 (s, 2H), 1.98-1.97 (m, 1H), 0.96-0.95 (m, 2H), 0.76-0.75 (m, 2H).

Example 150

Scheme 149

**[0601] Synthesis of 2-(azidomethyl)-6-cyclopropylimidazo[1,2-b]pyridazine. A**

mixture of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-b]pyridazine (900 mg, 4.33 mmol) in dry DMF (5 mL) was added NaN_3 (631 mg, 9.71 mmol) at RT. After the mixture was stirred for 2 h. Water (30 mL) was added and the mixture was extracted with EtOAc (50 mL x 3). The combined organics were concentrated and purified by flash silica gel chromatography (0 ~ 40% EtOAc in PE) to give 2-(azidomethyl)-6-cyclopropylimidazo[1,2-b]pyridazine (735 mg, yield: 79%) as dark-red oil. ESI-MS $[\text{M}+\text{H}]^+$: 215.2

[0602] Synthesis of ethyl 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate.

To a solution of 2-(azidomethyl)-6-cyclopropylimidazo[1,2-b]pyridazine (730 mg, 3.41 mmol) and ethyl propiolate (501 mg, 5.11 mmol) in t-BuOH/ H_2O (5 mL/5 mL) was added CuSO_4 (543 mg, 3.41 mmol) and sodium ascorbate (675 mg, 3.41 mmol) at RT. After the mixture was stirred for 2 h. The mixture were concentrated and purified by flash silica gel chromatography (0~10% EtOAc in PE) to give ethyl 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (600 mg, yield: 56%) as a red solid. ESI-MS $[\text{M}+\text{H}]^+$: 313.2.

[0603] Synthesis of 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid.

To a solution of ethyl 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (100 mg, 0.32 mmol) in THF/EtOH/ H_2O (2 mL/2

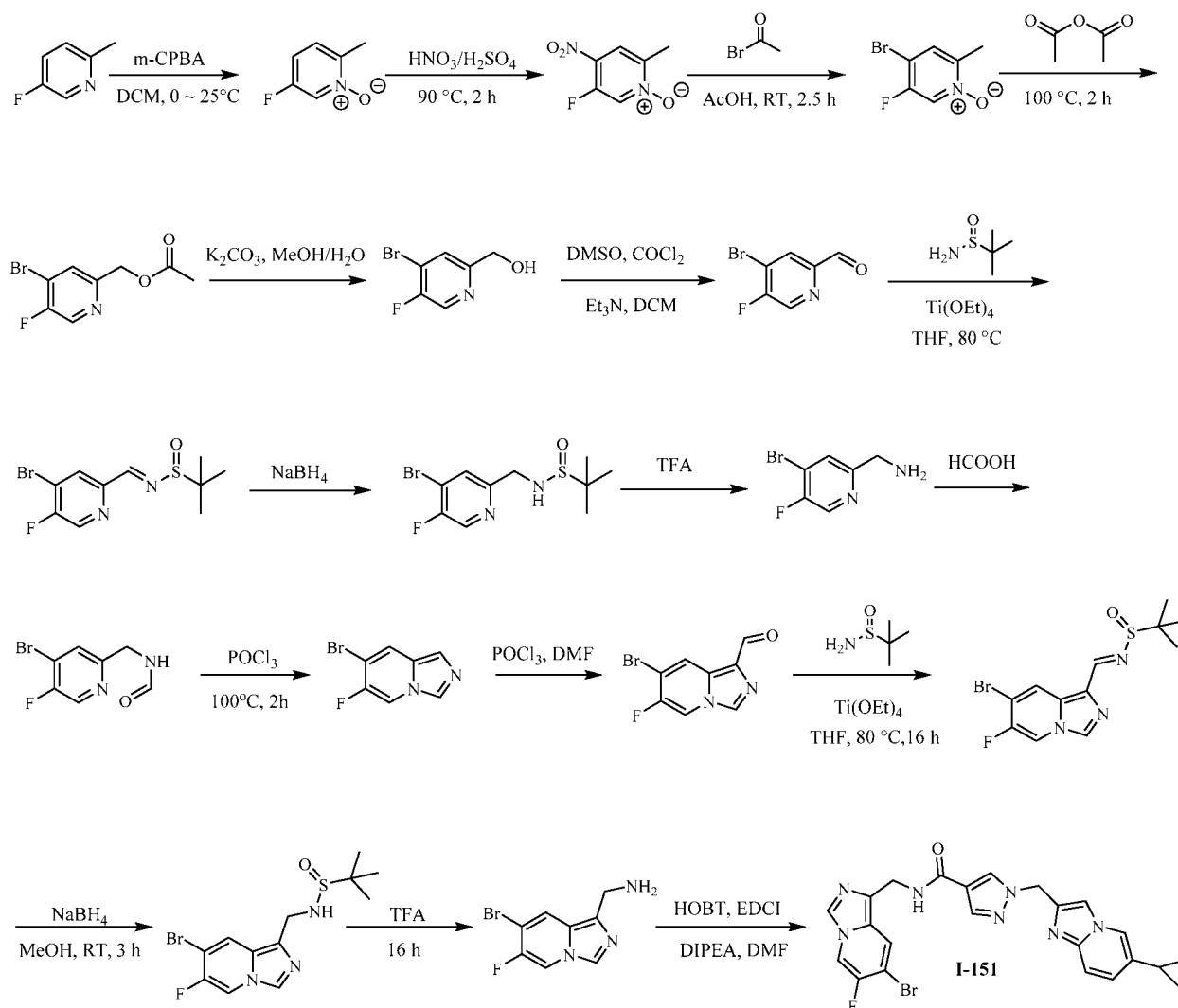
mL/2 mL) was added LiOH (15.33 mg, 0.64 mL). The mixture was heated to 50 °C and refluxed for 2 h. HCl (2 M) was added to adjust the pH to 4 and the mixture was freeze-dried to give 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (120 mg, crude) as a white solid. ESI-MS $[M+H]^+$: 285.1.

[0604] Synthesis of N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (I-150).

To a solution of 1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (120 mg, crude from last step) in DMF (3 mL) was added EDCI (111 mg, 0.58 mmol), HOBT (78 mg, 0.58 mmol), DIPEA (250.06 mg, 1.93 mmol) and (7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (90 mg, 0.38 mmol) at RT. After the mixture was stirred for 16 h. The mixture was poured into H₂O, precipitate was filtered and washed with H₂O and methanol to give N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (26.1 mg, yield: 17%) as a white solid. ESI-MS $[M+H]^+$: 466.1. Purity: 98.56(214nm), 95.15(254nm). ¹H NMR (400 MHz, DMSO-d₆) δ 8.70 (t, J = 5.4 Hz, 1H), 8.56 (s, 1H), 8.44 (d, J = 2.3 Hz, 1H), 8.23-8.17 (m, 2H), 7.94 (d, J = 9.5 Hz, 1H), 7.11 (d, J = 9.5 Hz, 1H), 6.80-6.72 (m, 1H), 5.75 (s, 2H), 4.69 (d, J = 5.5 Hz, 2H), 2.22-2.14 (m, 1H), 1.10-1.03 (m, 2H), 1.01-0.93 (m, 2H).

Example 151

Scheme 150



[0605] Synthesis of 5-fluoro-2-methylpyridine 1-oxide. To a stirred solution of 5-fluoro-2-methylpyridine (5 g, 45 mmol) in DCM (100 mL) was added m-CPBA (11.6 g, 67.5 mmol) at 0 °C and the mixture was stirred at 25 °C for 16 h. The mixture was quenched with saturated aqueous Na₂S₂O₃, stirred vigorously for 15 min, and then poured into saturated aqueous NaHCO₃. The layers were separated, and the aqueous layer was extracted twice more with DCM. The combined organic layers were dried over MgSO₄, filtered and concentrated to give 5-fluoro-2-methylpyridine 1-oxide (4.7 g, 82 %) as a yellow solid which was used into next step without further purification. ESI-MS [M+H]⁺: 128.2.

[0606] Synthesis of 5-fluoro-2-methyl-4-nitropyridine 1-oxide. Concentrated H_2SO_4 (15 mL) was slowly added to 5-fluoro-2-methylpyridine 1-oxide (4.7 g, 37 mmol) at 0 °C. A mixture of fuming HNO_3 (10 mL) and concentrated H_2SO_4 (15 mL) was then added dropwise to the mixture at 0 °C. Then the mixture was heated to 90 °C for 16 h. The mixture was slowly poured into 400 g of ice and then neutralized with solid NH_4HCO_3 . The mixture was extracted three times with DCM, and the combined organic layers were dried over MgSO_4 , filtered and concentrated to give 5-fluoro-2-methyl-4-nitropyridine 1-oxide (4.7 g, 74 %) as a yellow solid which was used without further purification. ESI-MS $[\text{M}+\text{H}]^+$: 173.1.

[0607] Synthesis of 4-bromo-5-fluoro-2-methylpyridine 1-oxide. To a solution of 5-fluoro-2-methyl-4-nitropyridine 1-oxide (4.7 g, 27.3 mmol) in acetic acid (40 mL) was added acetyl bromide (15 mL) dropwise over 5 mins. After addition, the mixture was stirred at 80 °C for 16 h. The reaction mixture was poured into ice and the solution basified to pH 8 with cold 2 M sodium hydroxide. The aqueous layer was extracted with DCM (100 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated to give 4-bromo-5-fluoro-2-methylpyridine 1-oxide (5.5 g, 98 %) as a yellow solid. ESI-MS $[\text{M}+\text{H}]^+$: 206.0.

[0608] Synthesis of (4-bromo-5-fluoropyridin-2-yl)methyl acetate. A mixture of 4-bromo-5-fluoro-2-methylpyridine 1-oxide (5.5 g, 26.8 mmol) in acetic anhydride (30 mL) was stirred at 100 °C for 2 h, then cooled to 25 °C, concentrated to give the crude product, NaHCO_3 (aq) was added to adjust pH about 9, extracted with DCM (100 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated to give the crude product which was purified by column chromatography (PE:EA = 20:1 to 10:1) to give (4-bromo-5-fluoropyridin-2-yl)methyl acetate (3.2 g, yield: 48%) as a yellow oil . ESI-MS $[\text{M}+\text{H}]^+$: 248.1.

[0609] Synthesis of (4-bromo-5-fluoropyridin-2-yl)methanol. To a mixture of (4-bromo-5-fluoropyridin-2-yl)methyl acetate (2.5 g, 10 mmol) in MeOH/ H_2O (20/2 mL) was added K_2CO_3 (7 g, 50 mmol). The mixture was stirred at 25 °C for 16 h. Then MeOH was remove. Water (20 mL) was added, extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated to give (4-bromo-5-

fluoropyridin-2-yl)methanol (2 g, yield: 96%) as a yellow oil which was used into next step without further purification.. ESI-MS $[M+H]^+$: 206.0.

[0610] Synthesis of 4-bromo-5-fluoropicolinaldehyde. To a solution of oxalyl chloride (1.86 g, 14.6 mmol) in DCM (50 mL) under nitrogen was added dropwise a solution of DMSO (1.52 g, 19.5 mmol) in DCM (20 mL) at -78 °C. Stirring was continued for 10 minutes. A solution of (4-bromo-5-fluoropyridin-2-yl)methanol (2 g, 9.76 mmol) in DCM (20 mL) was then added dropwise over 20 minutes. The reaction was stirred for 1 h. Triethylamine (4.93 g, 48.8 mmol) was added dropwise and the reaction was allowed to warm to RT over 1.5 h. The reaction was then quenched by addition of H₂O (50 mL). The organics were separated and H₂O phase was extracted with DCM (50 mL x 2). Concentrated in vacuo to give 4-bromo-5-fluoropicolinaldehyde (1.2 g, yield: 59%) as a brown oil which was used into next step without further purification. ESI-MS $[M+H]^+$: 204.2

[0611] Synthesis of (E)-N-((4-bromo-5-fluoropyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide. To a mixture of 4-bromo-5-fluoropicolinaldehyde (1.2 g, 5.9 mmol), 2-methylpropane-2-sulfinamide (857 mg, 7.08 mmol) in dry THF (20 mL) was added Ti(OEt)₄ (4.03 g, 17.7 mmol). The mixture was stirred at 75 °C for 16 h. Water (100 mL) was added and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give (E)-N-((4-bromo-5-fluoropyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (1.8 g, crude). ESI-MS $[M+H]^+$: 307.1

[0612] Synthesis of N-((4-bromo-5-fluoropyridin-2-yl)methyl)-2-methylpropane-2-sulfinamide. To a mixture of (E)-N-((4-bromo-5-fluoropyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (1.8 g, crude from last step) in dry THF (30 mL) was added NaBH₄ (897 mg, 23.6 mmol). The mixture was stirred at 25 °C for 3 h. Then H₂O (20 mL) was added, extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give the crude product, which was purified by Prep-TLC (DCM/MeOH = 10/1) to give N-((4-bromo-5-fluoropyridin-2-yl)methyl)-2-methylpropane-2-sulfinamide (900 mg, yield: 50% over 2 steps) as a yellow oil. ESI-MS $[M+H]^+$: 309.0.

[0613] Synthesis of (4-bromo-5-fluoropyridin-2-yl)methanamine. A mixture of N-((4-bromo-5-fluoropyridin-2-yl)methyl)-2-methylpropane-2-sulfinamide (900 mg, 2.92 mmol) in

TFA (10 mL) was stirred at 40 °C for 16 h. Then concentrated to give (4-bromo-5-fluoropyridin-2-yl)methanamine (590 mg, yield: 99%) as a yellow oil which was used in the next step without further purification.. ESI-MS $[M+H]^+$: 205.1.

[0614] Synthesis of N-((4-bromo-5-fluoropyridin-2-yl)methyl)formamide. A mixture of (4-bromo-5-fluoropyridin-2-yl)methanamine (590 mg, 2.89 mmol) in HCOOH (10 mL) was stirred at 90 °C for 3 h. Then concentrated to give the crude product, which was purified by Prep-TLC (DCM/MeOH = 10/1) to give N-((4-bromo-5-fluoropyridin-2-yl)methyl)formamide (400 mg, yield: 60%) as a yellow solid. ESI-MS $[M+H]^+$: 233.1.

[0615] Synthesis of 7-bromo-6-fluoroimidazo[1,5-a]pyridine. A mixture of N-((4-bromo-5-fluoropyridin-2-yl)methyl)formamide (400 mg, 1.72 mmol) in POCl₃ (10 mL) was stirred at 100 °C for 1 h. Then POCl₃ was concentrated, H₂O (20 mL) was added, followed by Na₂CO₃ (aq) to adjust pH about 8, extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. The crude product was purified by Prep-TLC (EA/PE = 2/1) to give 7-bromo-6-fluoroimidazo[1,5-a]pyridine (300 mg, yield: 81%) as a yellow solid. ESI-MS $[M+H]^+$: 215.0.

[0616] Synthesis of 7-bromo-6-fluoroimidazo[1,5-a]pyridine-1-carbaldehyde. To a mixture of 7-bromo-6-fluoroimidazo[1,5-a]pyridine (300 mg, 1.4 mmol) in dry DMF (1 mL) was added POCl₃ (321 mg, 2.1 mmol). The mixture was stirred at 100 °C for 1 h. Then cooled to 25 °C and poured into ice H₂O (10 mL), the solution was basified with NH₃·H₂O and extracted with DCM (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give the crude product, which was purified by Prep-TLC (DCM/MeOH = 25/1) to give 7-bromo-6-fluoroimidazo[1,5-a]pyridine-1-carbaldehyde (80 mg, yield: 23.6%) as a yellow solid. ESI-MS $[M+H]^+$: 243.0.

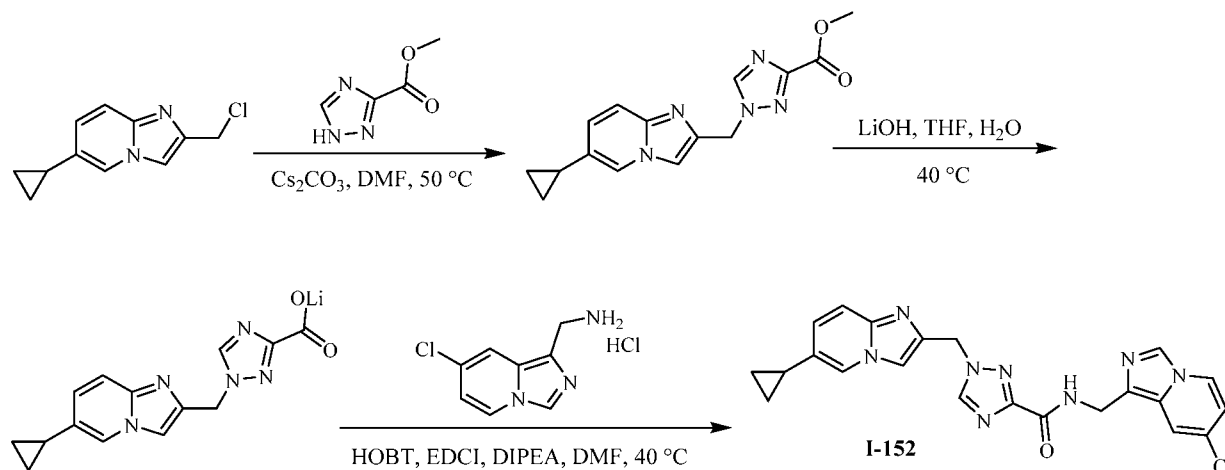
[0617] Synthesis of N-((7-bromo-6-fluoroimidazo[1,5-a]pyridin-1-yl)methylene)-2-methylpropane-2-sulfinamide. To a mixture of 7-bromo-6-fluoroimidazo[1,5-a]pyridine-1-carbaldehyde (50 mg, 0.2 mmol), 2-methylpropane-2-sulfinamide (30 mg, 0.24 mmol) in dry THF (3 mL) was added Ti(OEt)₄ (137 mg, 0.6 mmol). The mixture was stirred at 80 °C for 16 h. Water (20 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated to give N-((7-bromo-6-

fluoroimidazo[1,5-a]pyridin-1-yl)methylene)-2-methylpropane-2-sulfinamide, which was used in the next step without further purification. (71.4 mg, crude). ESI-MS $[M+H]^+$: 346.2

[0618] Synthesis of N-((7-bromo-6-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-2-methylpropane-2-sulfinamide. To a mixture of N-((7-bromo-6-fluoroimidazo[1,5-a]pyridin-1-yl)methylene)-2-methylpropane-2-sulfinamide (71.4 mg, crude from last step) in dry THF (3 mL) was added NaBH_4 (30 mg, 0.8 mmol). The mixture was stirred at 25 °C for 3 h. Then H_2O (10 mL) was added, extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated to give the crude product which was purified by Prep-TLC (DCM/MeOH = 10/1) to give N-((7-bromo-6-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-2-methylpropane-2-sulfinamide (60 mg, yield: 85% over 2 steps) as a yellow oli. ESI-MS $[M+H]^+$: 348.1

[0619] Synthesis of (7-bromo-6-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine. A mixture of N-((7-bromo-6-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-2-methylpropane-2-sulfinamide (60 mg, 0.17 mmol) in TFA (2 mL) was stirred at RT for 16 h. Then concentrated to give (7-bromo-6-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine (39 mg, crude) as a yellow solid which was used in the next step without further purification. ESI-MS $[M+H]^+$: 227.0.

[0620] Synthesis of N-((7-bromo-6-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-151). To a mixture of 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (20 mg, 0.071 mmol), (7-bromo-6-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine (17.2 mg, 0.071 mmol), HOBt (19 mg, 0.14 mmol), EDCI (27 mg, 0.14 mmol) in DMF (3 mL) was added DIPEA (46 mg, 0.36 mmol). The mixture was stirred at 25 °C for 3 h. Water (20 mL) was added and the mixture was extracted with EtOAc (30 mL x 3). The combined organic layers was concentrated and purified by Prep-TLC (DCM/MeOH = 10/1) to give N-((7-bromo-6-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (18.9 mg, yield: 53%) as a yellow solid. ESI-MS $[M+H]^+$: 507.9. Purity: 94.07(214nm), 96.76 (254nm). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.65-8.59(m, 2H), 8.33-8.29 (m, 2H), 8.20-8.16 (m, 2H), 7.85 (s, 1H), 7.72 (s, 1H), 7.39 (d, J = 9.3 Hz, 1H), 6.99 (dd, J = 9.3, 1.4 Hz, 1H), 5.38 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 1.95-1.88 (m, 1H), 0.92-0.89 (m, 2H), 0.68-0.65 (m, 2H).

Example 152Scheme 151

[0621] Synthesis of methyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,4-triazole-3-carboxylate. A mixture of 2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridine (207 mg, 1.0 mmol), methyl 1H-1,2,4-triazole-3-carboxylate (190 mg, 1.5 mmol) and Cs_2CO_3 (1.6 g, 5 mmol) in DMF (8 mL) was stirred at 50 for 2 h. H_2O (50 mL) was added to the reaction, then extracted with EtOAc (50 mL x 2). The combined organic layers were concentrated, and purified by flash silica gel column ($\text{CH}_2\text{Cl}_2/\text{MeOH} = 15/1$) to give methyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,4-triazole-3-carboxylate (130 mg, yield: 44%) as a white solid. ESI-MS $[\text{M}+\text{H}]^+$: 298.1.

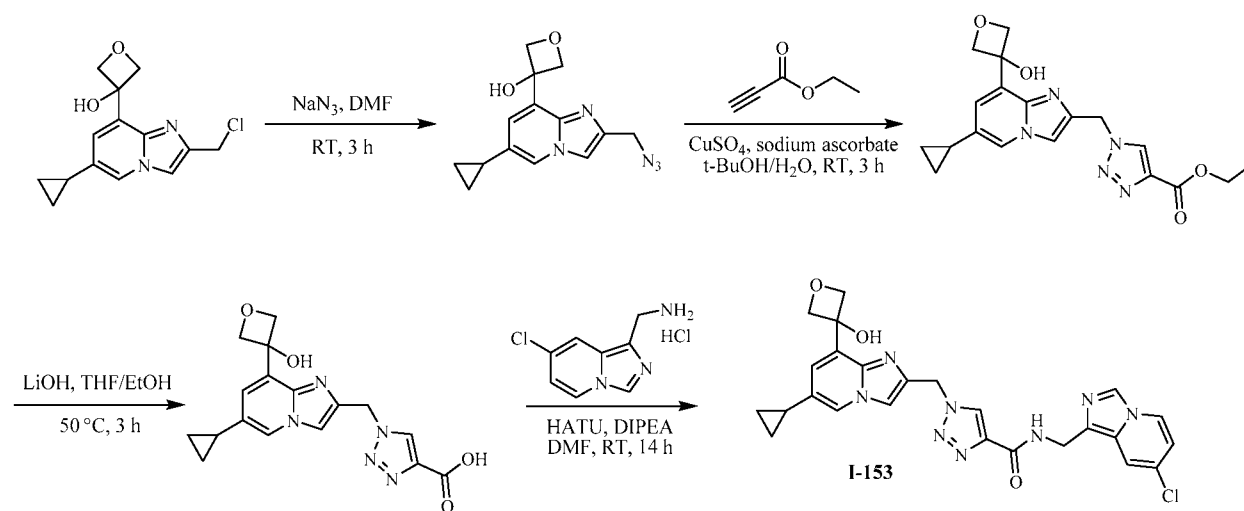
[0622] Synthesis of lithium 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,4-triazole-3-carboxylate. To a solution of methyl 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,4-triazole-3-carboxylate (57 mg, 0.19 mmol) in THF/EtOH/ H_2O (1 mL/1 mL/0.5 mL) was added LiOH (16 mg, 0.38 mmol). The mixture was stirred at 40 °C for 1 h. Then concentrated and lyophilized to give lithium 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,4-triazole-3-carboxylate (75 mg, crude) as a yellow solid. ESI-MS $[\text{M}+\text{H}]^+$: 284.1.

[0623] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,4-triazole-3-carboxamide (I-152). A

mixture of lithium 1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,4-triazole-3-carboxylate (75 mg, crude), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (41 mg, 0.19 mmol), HOBT (52 mg, 0.38 mmol), EDCI (73 mg, 0.38 mmol) and DIPEA (123 mg, 0.95 mmol) in DMF (2.5 mL) was stirred at 40 °C for 26 h. Water (10 mL) was added and extracted with EtOAc (30 mL x 2), the combined organic layers were washed with brine, concentrated, the crude was purified by flash silica gel column (CH₂Cl₂/MeOH = 5/1) to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,4-triazole-3-carboxamide (27.9 mg, yield: 32%) as a yellow solid. ESI-MS [M+H]⁺: 447.1. Purity: 99.48% (214 nm), 100% (254 nm). ¹H NMR (400 MHz, DMSO-d₆) δ 8.83 (t, J = 5.1 Hz, 1H), 8.72 (s, 1H), 8.34-8.29 (m, 3H), 7.83-7.79 (m, 2H), 7.38 (d, J = 9.3 Hz, 1H), 7.00 (d, J = 9.1 Hz, 1H), 6.64 (d, J = 6.8 Hz, 1H), 5.54 (s, 2H), 4.60 (d, J = 5.6 Hz, 2H), 1.95-1.88 (m, 1H), 0.96-0.85 (m, 2H), 0.70-0.61 (m, 2H).

Example 153

Scheme 152



[0624] Synthesis of ethyl 1-((6-cyclopropyl-8-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A mixture of 3-(2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)oxetan-3-ol (500 mg, 1.8 mmol) and NaN₃ (176 mg, 2.7 mmol) in DMF (15 mL) was stirred at RT for 3 h. H₂O (30 mL) was added to the reaction, extracted with EtOAc (50 mL x 3). The combined organic layers were washed brine, dried over Na₂SO₄, concentrate in vacuo to give the crude product, which was purified with silica gel

chromatography (EA/PE = 1/1) to give the 3-(2-(azidomethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)oxetan-3-ol (420 mg, yield: 82%) as a yellow solid. ESI-MS $[M+H]^+$: 286.1

[0625] Synthesis of ethyl 1-((8-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate. To a solution of 3-(2-(azidomethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)oxetan-3-ol (420 mg, 1.47 mmol) in t-BuOH/H₂O (10 mL/10 mL) was added ethyl propiolate (158 mg, 1.6 mmol), CuSO₄ (70 mg, 0.44 mmol) and sodium ascorbate (87 mg, 0.44 mmol). The resulting reaction was stirred at RT for 3 h. The reaction was concentrated in vacuo to give the residue, which was purified with silica gel chromatography (EA/PE = 1/1) to give the ethyl 1-((8-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (400 mg, yield: 71%) as a yellow solid. ESI-MS $[M+H]^+$: 383.2

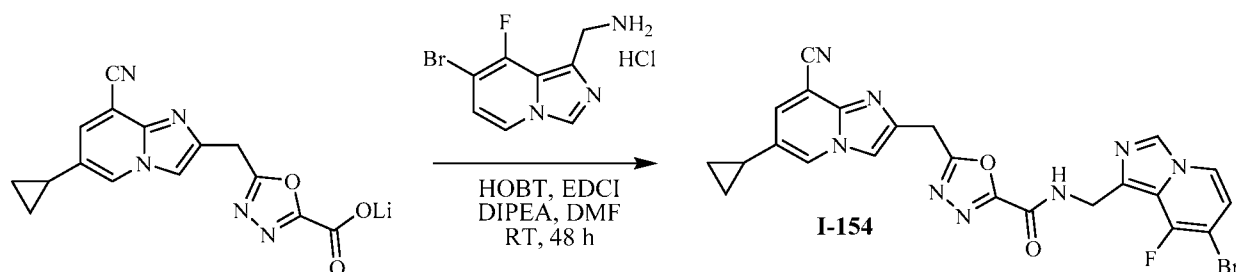
[0626] Synthesis of 1-((8-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid. A mixture of ethyl 1-((8-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (400 mg, 1.05 mmol) and LiOH (140 mg, 5.8 mmol) in THF/H₂O (15 mL/5 mL) was stirred at 50 °C for 3 h. The reaction was concentrate in vacuo to give crude product, which was purified with Prep-HPLC to give 1-((8-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (220 mg, yield: 58%) as a yellow solid. ESI-MS $[M+H]^+$: 356.2

[0627] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (I-153). To a solution of 1-((8-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (100 mg, 0.28 mmol), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (87 mg, 0.4 mmol), HATU (177 mg, 0.47 mmol) in DMF (5 mL) was added DIPEA (200 mg, 1.55 mmol). The resulting mixture was stirred at RT for 14 h. H₂O (30 mL) was added into the reaction, extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude product, which was purified with Prep-TLC (DCM/MeOH = 10/1) to give the N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(3-hydroxyoxetan-3-yl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide (30 mg, yield: 20%) as off white solid. ESI-MS $[M+H]^+$: 518.9. Purity: 94.5(214nm), 93.5(254nm). ¹H NMR (400 MHz,

DMSO- d_6) δ 8.92 (t, J = 5.9 Hz, 1H), 8.56 (s, 1H), 8.34-8.28 (m, 3H), 7.85-7.82 (m, 1H), 7.79 (s, 1H), 7.07 (d, J = 1.4 Hz, 1H), 6.66-6.62 (m, 1H), 6.42 (s, 1H), 5.76 (s, 2H), 5.22 (d, J = 6.5 Hz, 2H), 4.62 (t, J = 6.8 Hz, 4H), 1.98-1.91 (m, 1H), 0.95-0.90 (m, 2H), 0.70-0.66 (m, 2H).

Example 154

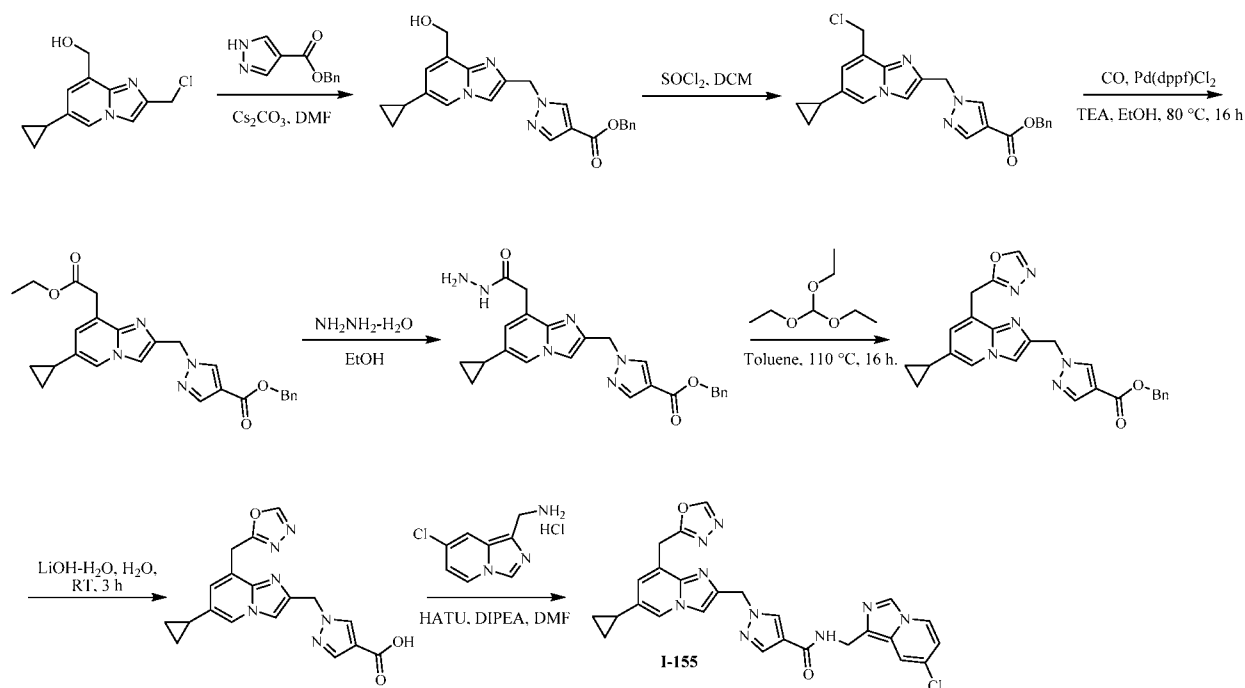
Scheme 153



[0628] Synthesis of N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide (I-154). A mixture of lithium 5-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate (100 mg, 0.32 mmol), (7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (106 mg, 0.38 mmol), EDCI (123 mg, 0.64 mmol), HOBT (86 mg, 0.64 mmol) and DIPEA (206 mg, 1.6 mmol) in DMF (3 mL) was stirred at RT for 48 h. The mixture was concentrated to remove DMF, diluted with DCM/MeOH (30 mL, 10/1 (v/v)) and washed with H₂O (10 mL x 2). The organic layer was separated, dried over Na₂SO₄, and concentrated in vacuo to give the crude product, which was purified by silica gel chromatography (DCM/MeOH = 10/1) to give N-((7-bromo-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide (25.4 mg, yield: 15%) as a yellow solid. ESI-MS $[M+H]^+$: 535.0. Purity: 96.4 (214nm), 96.4 (254nm). ¹H NMR (400 MHz, DMSO- d_6) δ 9.64 (t, J = 5.4 Hz, 1H), 8.69 (s, 1H), 8.46 (d, J = 2.2 Hz, 1H), 8.15 (d, J = 7.3 Hz, 1H), 8.00 (s, 1H), 7.77 (s, 1H), 6.89-6.78 (m, 1H), 4.69 (d, J = 5.4 Hz, 2H), 4.53 (s, 2H), 2.00-1.95 (m, 1H), 1.02-0.91 (m, 2H), 0.82-0.70 (m, 2H).

Example 155

Scheme 154



[0629] Synthesis of benzyl 1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A mixture of (2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methanol (550 mg, 2.33 mmol), benzyl 1H-pyrazole-4-carboxylate (520 mg, 2.56 mmol) and Cs_2CO_3 (1.90 g, 5.83 mmol) in DMF (10 mL) was stirred at RT for 16 h. The mixture was concentrated and purified by flash silica gel chromatography (DCM/MeOH = 15/1) to give benzyl 1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (710 mg, yield: 75%) as a white solid. ESI-MS $[\text{M}+\text{H}]^+$: 403.1

[0630] Synthesis of benzyl 1-((8-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. To a solution of benzyl 1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (200 mg, 0.50 mmol) in DCM (5 mL) was added SOCl_2 (0.5 mL) at 0 °C and the mixture was stirred for 2 h. The mixture was concentrated to give benzyl 1-((8-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (200 mg, crude) as a yellow solid. ESI-MS $[\text{M}+\text{H}]^+$: 421.1.

[0631] Synthesis of benzyl 1-((6-cyclopropyl-8-(2-ethoxy-2-oxoethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A mixture of benzyl 1-((8-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (200 mg, 0.48 mmol), Pd(dppf)Cl₂ (40 mg, 0.048 mmol) and TEA (1.0 mL) in EtOH (6.0 mL) was stirred at 80 °C under CO for 16 h. The mixture was concentrated and purified by Prep-TLC (DCM/MeOH = 20/1) to give benzyl 1-((6-cyclopropyl-8-(2-ethoxy-2-oxoethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (170 mg, yield:77%) as a light yellow oil. ESI-MS [M+H]⁺: 458.9.

[0632] Synthesis of benzyl 1-((6-cyclopropyl-8-(2-hydrazinyl-2-oxoethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A mixture of benzyl 1-((6-cyclopropyl-8-(2-ethoxy-2-oxoethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (100 mg, 0.22 mmol) and NH₂NH₂·H₂O (0.5 mL) in EtOH (6.0 mL) was stirred at RT for 16 h. The mixture was concentrated to give benzyl 1-((6-cyclopropyl-8-(2-hydrazinyl-2-oxoethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (100 mg, crude) as a white solid. ESI-MS [M+H]⁺: 445.1.

[0633] Synthesis of benzyl 1-((8-((1,3,4-oxadiazol-2-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate. A mixture of benzyl 1-((6-cyclopropyl-8-(2-hydrazinyl-2-oxoethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (50 mg, crude from last step), AcOH (0.15 mL) and triethoxymethane (0.15 mL) in toluene (3.0 mL) was stirred at 110 °C for 16 h. The mixture was concentrated and purified by Prep-TLC (DCM/MeOH = 10/1) to give benzyl 1-((8-((1,3,4-oxadiazol-2-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (40 mg, yield:80%) as a yellow oil. ESI-MS [M+H]⁺: 455.1.

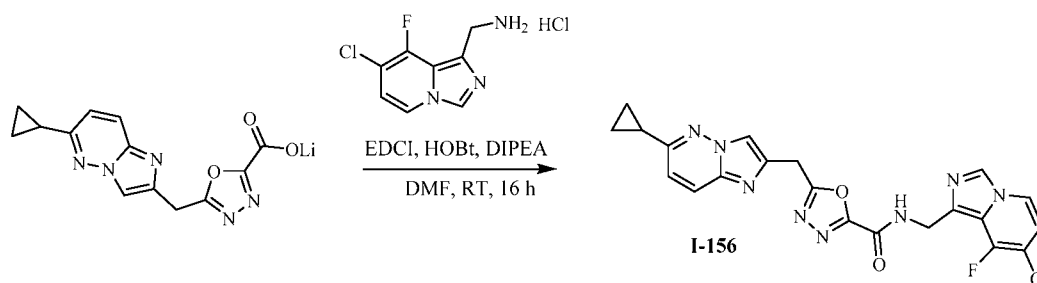
[0634] Synthesis of 1-((8-((1,3,4-oxadiazol-2-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. A solution of benzyl 1-((8-((1,3,4-oxadiazol-2-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (20.0 mg, 0.044 mmol) and LiOH·H₂O (9.3 mg, 0.22 mmol) in a mixed solvent of THF/MeOH/H₂O (1 mL/1 mL/1 mL) was stirred at RT for 3 h. The pH value was adjusted to 3 by 1 M HCl solution and the mixture was extracted with i-PrOH/DCM = 1/3 (30 mL x 3). The combined organic layers were concentrated to give 1-((8-((1,3,4-oxadiazol-2-yl)methyl)-6-

cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (10.0 mg, crude) as a yellow oil. This material was used directly in the next step without further purification. ESI-MS $[M+H]^+$: 365.1.

[0635] Synthesis of 1-((8-((1,3,4-oxadiazol-2-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (I-157). A mixture of 1-((8-((1,3,4-oxadiazol-2-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (10.0 mg, crude from last step), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (7.5 mg, 0.034 mmol), HATU (15.4 mg, 0.041 mmol) and DIPEA (10.5 mg, 0.081 mmol) in DMF (2 mL) was stirred at 20 °C for 4 h. The mixture was concentrated and purified by Prep-HPLC to give 1-((8-((1,3,4-oxadiazol-2-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (2.5 mg, yield: 11 %) as a light yellow solid. ESI-MS $[M+H]^+$: 528.1. Purity: 98.5 (214nm), 93.9 (254nm). ^1H NMR (400 MHz, DMSO- d_6) δ 9.10 (s, 1H), 8.58 (t, J = 5.6 Hz, 1H), 8.30 (d, J = 8.4 Hz, 3H), 8.17 (s, 1H), 7.87 (s, 1H), 7.78 (s, 1H), 7.69 (s, 1H), 7.00 (s, 1H), 6.65 (dd, J = 7.4, 2.0 Hz, 1H), 5.38 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 4.50 (s, 2H), 1.98-1.84 (m, 1H), 0.93-0.89 (m, 2H), 0.66-0.63 (m, 2H).

Example 156

Scheme 155

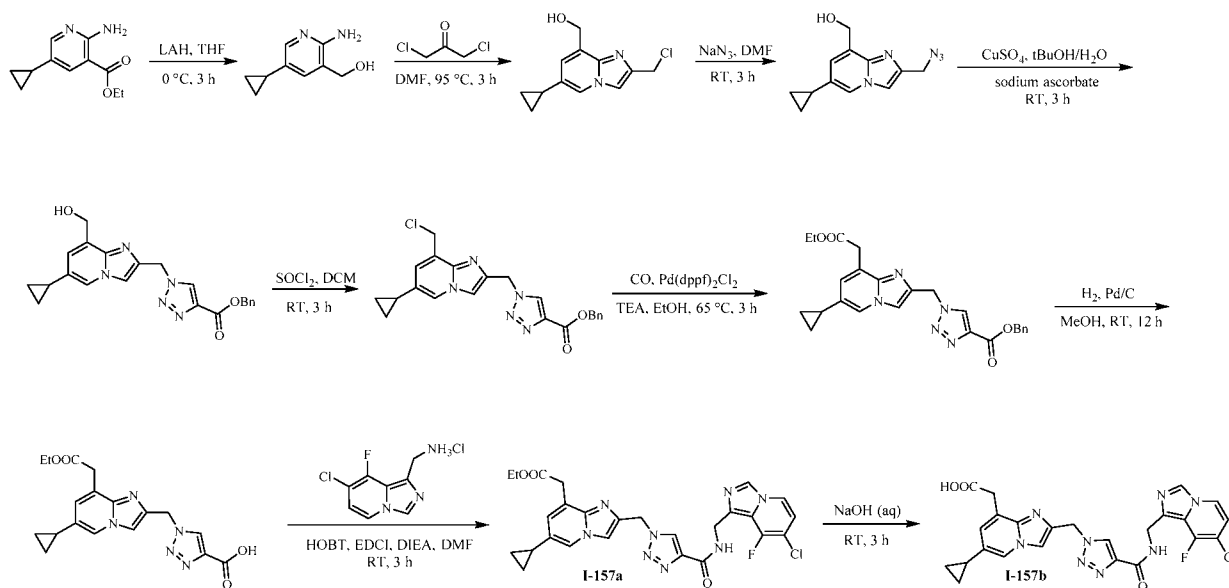


[0636] Synthesis of N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide (I-156). To a solution of lithium 5-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate (50 mg, 0.13 mmol, crude) in DMF (5 mL) was added EDCI (58 mg, 0.3 mmol), HOBT (40 mg, 0.3 mmol), DIPEA (65 mg, 0.5 mmol) and (7-chloro-8-

fluoroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (59 mg, 0.25 mmol). The reaction was stirred at RT for 16 h. The mixture was poured into H₂O, the solid formed, filtered and washed with H₂O and MeOH to give N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-b]pyridazin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide (15 mg, yield: 25%) as a yellow solid. ESI-MS [M+H]⁺: 467.1. Purity: 96.71%(214nm), 96.91%(254nm). ¹H NMR (400 MHz, DMSO-d₆) δ 9.63 (t, J = 5.4 Hz, 1H), 8.45 (d, J = 2.2 Hz, 1H), 8.22 (d, J = 7.4 Hz, 1H), 8.14 (s, 1H), 7.91 (d, J = 9.4 Hz, 1H), 7.09 (d, J = 9.4 Hz, 1H), 6.78 (t, J = 6.9 Hz, 1H), 4.70 (d, J = 5.5 Hz, 2H), 4.47 (s, 2H), 2.21-2.13 (m, 1H), 1.10-1.03 (m, 2H), 1.00-0.93 (m, 2H).

Example 157

Scheme 156



[0637] Synthesis of (2-amino-5-cyclopropylpyridin-3-yl)methanol. To a mixture of ethyl 2-amino-5-cyclopropylpyridine-3-carboxylate (7.4 g, 36 mmol) in THF (70 mL) was added LAH (2.3 g, 61 mmol) was stirred at 0 °C. The mixture was stirred at 0 °C for 3 h under N₂ atmosphere. The reaction was monitored by LCMS until the starting material consumed. The reaction was quenched with H₂O (5 mL), NaOH (15% aq., 5 mL), H₂O (15 mL), after the mixture was stirred for 10 min, the mixture was filtered through celite and concentrated to give a residue. Which was

diluted with H₂O (100 mL) and extracted with EtOAc (100 mL x 5). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude product, which was purified with silica gel (eluent: EtOAc/PE: 1/2 to 1/0) to give the (2-amino-5-cyclopropylpyridin-3-yl)methanol (5 g, yield: 84%) as a white solid. ESI-MS [M+H]⁺: 165.2.

[0638] Synthesis of (2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methanol. To a solution of (2-amino-5-cyclopropylpyridin-3-yl)methanol (5 g, 30 mmol) in DMF (30 mL) was added 1,3-dichloropropan-2-one (14.8 g, 117 mmol). The mixture was stirred at 95 °C for 3 h. The reaction was monitored by LCMS until the starting material consumed. The reaction was quenched with saturated aqueous NaHCO₃ until pH = 8 and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude product, which was purified with silica gel (eluent: DCM/MeOH: 50/1 to 10/1) to give (2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methanol (4.7 g, yield: 66%) as a yellow solid. ESI-MS [M+H]⁺: 237.1.

[0639] Synthesis of (2-(azidomethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methanol. To a solution of (2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methanol (4.7 g, 20 mmol) in DMF (30 mL) was added sodium azide (1.82 g, 28 mmol). The mixture was stirred at RT for 3 h. The reaction was monitored by LCMS until the starting material consumed. The reaction was quenched with H₂O (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude product, which was purified with silica gel (eluent: DCM/MeOH: 50/1 to 10/1) to give (2-(azidomethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methanol (2.1 g, yield: 43%) as a white solid. ESI-MS [M+H]⁺: 244.2.

[0640] Synthesis of benzyl 1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate. A mixture of (2-(azidomethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)methanol (2.1 g, 8.6 mmol) benzyl propiolate (2.1 g, 13 mmol), sodium ascorbate (1.7 g, 8.6 mmol), CuSO₄ (1.4 g, 8.6 mmol) in tBuOH/H₂O (20 mL/20 mL) was stirred at RT for 3 h. The reaction was quenched with H₂O (50 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude product, which was purified with silica gel (eluent: DCM/MeOH: 50/1 to 10/1) to give benzyl 1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-

a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (1.4 g, yield: 40%) as a white solid. ESI-MS $[M+H]^+$: 404.2.

[0641] Synthesis of benzyl 1-((8-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate. To a mixture of benzyl 1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (1.4 g, 3.5 mmol) in DCM (15 mL) was added SOCl_2 (5 mL). The mixture was stirred at RT for 3 h. The reaction was concentrated in vacuo to give the crude of benzyl 1-((8-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (1.43 g, crude) as a yellow solid. ESI-MS $[M+H]^+$: 422.1.

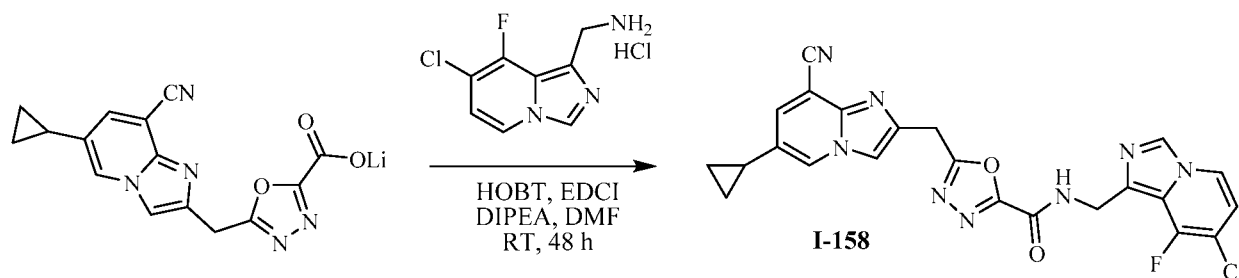
[0642] Synthesis of benzyl 1-((6-cyclopropyl-8-(2-ethoxy-2-oxoethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate. To a mixture of benzyl 1-((8-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (1.4 g, 3.4 mmol) in EtOH (15 mL) was added $\text{Pd}(\text{dppf})_2\text{Cl}_2$ (38 mg, 0.34 mmol) and TEA (1.7 g, 17 mmol), the mixture was stirred at 65 °C for 3 h under CO atmosphere. The reaction was concentrated in vacuo to give the crude product, which was purified with silica gel (eluent: DCM/MeOH: 50/1 to 10/1) to give benzyl 1-((6-cyclopropyl-8-(2-ethoxy-2-oxoethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (1.1 g, yield: 70%) as a white solid. ESI-MS $[M+H]^+$: 460.1.

[0643] Synthesis of 1-((6-cyclopropyl-8-(2-ethoxy-2-oxoethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid. To a mixture of benzyl 1-((6-cyclopropyl-8-(2-ethoxy-2-oxoethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate (1.1 g, 2.4 mmol) in MeOH (20 mL) was added Pd/C (10%, 200 mg). The mixture was stirred at RT under H_2 atmosphere for 12 h. The reaction was filtered and washed with methanol, the filtrate was concentrated in vacuo to give the 1-((6-cyclopropyl-8-(2-ethoxy-2-oxoethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (600 mg, yield: 67%) as a yellow solid. ESI-MS $[M+H]^+$: 370.2.

[0644] Synthesis of ethyl 2-(2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetate (I-157a). To a mixture of 1-((6-cyclopropyl-8-(2-ethoxy-2-oxoethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylic acid (300 mg, 0.81 mmol) in DMF (5 mL)

was added (7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine HCl salt (228 mg, 0.97 mmol), HOBT (147 mg, 1.1 mmol), EDCI (211 mg, 1.1 mmol) and DIPEA (502 mg, 4 mmol). The mixture was stirred at RT for 3 h. The reaction was quenched with H₂O (30 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, concentrated in vacuo to give the crude product, which was purified with silica gel (eluent: DCM/MeOH: 50/1 to 10/1) to give the ethyl 2-(2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetate (200 mg, yield: 45%) as a white solid. ESI-MS [M+H]⁺: 551.2. Purity: 96.2 (214nm), 95.9 (254nm). ¹H NMR (400 MHz, DMSO-d₆) δ 8.69 (t, J = 5.2 Hz, 1H), 8.51 (s, 1H), 8.45 (s, 1H), 8.28 (s, 1H), 8.21 (d, J = 7.2 Hz, 1H), 7.81 (s, 1H), 6.96 (s, 1H), 6.76 (t, J = 6.7 Hz, 1H), 5.72 (s, 2H), 4.70 (d, J = 5.2 Hz, 2H), 4.04 (q, J = 7.1 Hz, 2H), 3.87 (s, 2H), 1.97-1.87 (m, 1H), 1.12 (t, J = 7.1 Hz, 3H), 0.98-0.88 (m, 2H), 0.70-0.62 (m, 2H).

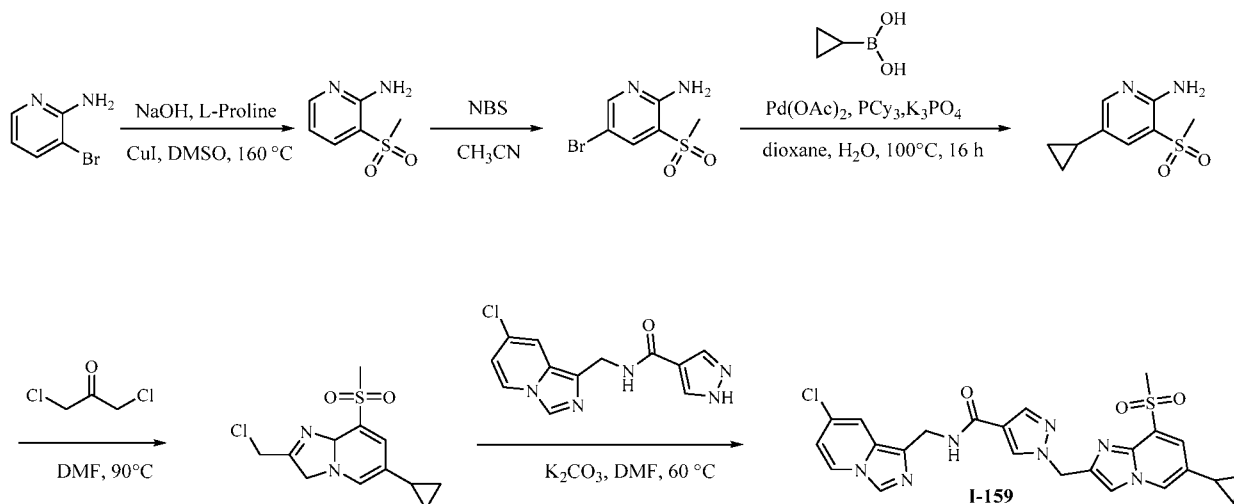
[0645] Synthesis of 2-(2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetic acid (I-157b). A mixture of ethyl 2-(2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetate (100 mg, 0.18 mmol) and NaOH (20 mg in 1 mL H₂O) in EtOH (20 mL) was stirred at RT for 3 h. The reaction was quenched with HCl (1N, 1 mL). The resulting mixture was concentrated to give the crude which was purified by Prep-HPLC to give 2-(2-((4-(((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-1,2,3-triazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)acetic acid (18 mg, 19% yield) as a white solid. ESI-MS [M+H]⁺: 523.0. Purity: 91.0 (214nm), 94.5 (254nm). ¹H NMR (400 MHz, DMSO-d₆) δ 8.72 (t, J = 4.8 Hz, 1H), 8.53 (s, 1H), 8.45 (s, 1H), 8.31-8.17 (m, 2H), 7.78 (s, 1H), 6.94 (s, 1H), 6.76 (t, J = 6.9 Hz, 1H), 5.72 (s, 2H), 4.70 (d, J = 5.3 Hz, 2H), 3.75 (s, 2H), 1.95-1.86 (m, 1H), 0.95-0.85 (m, 2H), 0.67-0.62 (m, 2H).

Example 158Scheme 157

[0646] Synthesis of N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide. A mixture of lithium 5-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxylate (100 mg, 0.32 mmol), (7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methanamine (113 mg, 0.48 mmol), EDCI (123 mg, 0.64 mmol), HOBT (86 mg, 0.64 mmol) and DIPEA (206 mg, 1.6 mmol) in DMF (3 mL) was stirred at RT for 48 h. The mixture was concentrated to remove DMF, diluted with DCM/MeOH (30 mL, 10/1 (v/v)) and washed with H₂O (20 mL x 2). The organic layers were separated, dried over Na₂SO₄, and concentrated in vacuo to give the crude product, which was purified by silica gel chromatography (DCM/MeOH = 10/1) to give N-((7-chloro-8-fluoroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((8-cyano-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1,3,4-oxadiazole-2-carboxamide (20 mg, yield: 13%) as a yellow solid. ESI-MS [M+H]⁺: 490.9. Purity: 99.0 (214nm), 98.6 (254nm). ¹H NMR (400 MHz, DMSO-d₆) δ 9.65 (t, J = 5.4 Hz, 1H), 8.69 (d, J = 1.3 Hz, 1H), 8.45 (d, J = 2.4 Hz, 1H), 8.22 (d, J = 7.4 Hz, 1H), 8.00 (s, 1H), 7.78 (d, J = 1.6 Hz, 1H), 6.83-6.73 (m, 1H), 4.70 (d, J = 5.5 Hz, 2H), 4.53 (s, 2H), 2.02-1.95 (m, 1H), 1.02-0.89 (m, 2H), 0.78-0.74 (m, 2H).

Example 159

Scheme 158



[0647] Synthesis of 3-(methylsulfonyl)pyridin-2-amine. To a solution of 3-bromopyridin-2-amine (2 g, 11.5 mmol) in DMSO (20 mL) was added sodium methanesulfonate (1.534 g, 15 mmol), L-Proline (266 mg, 2.31 mmol), CuI (220 mg, 1.16 mmol) and NaOH (92 mg, 2.31 mmol). The reaction mixture was degassed with nitrogen for 2 min and irradiated in microwave at 160 °C for 40 min, and subsequently quenched with H₂O (30 mL), extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated to give the crude product, which was purified by silica gel chromatography (PE/EtOAc = 2/1) to give the 3-(methylsulfonyl)pyridin-2-amine as a yellow solid (843 mg, yield: 42%). ESI-MS [M+H]⁺: 173.1.

[0648] Synthesis of ethyl 5-bromo-3-(methylsulfonyl)pyridin-2-amine. To a solution 3-(methylsulfonyl)pyridin-2-amine (843 mg, 4.9 mmol) in CH₃CN (20 mL) was added NBS (915 mg, 5.14 mmol) at RT. The resulting mixture was stirred at RT for 0.5 h and subsequently concentrated to give the residue, which was diluted with H₂O (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated to give the crude product, which was purified by silica gel chromatography (PE/EtOAc = 1/1) to give 5-bromo-3-(methylsulfonyl)pyridin-2-amine (1.161 g, yield: 94%) as a yellow solid. ESI-MS [M+H]⁺: 250.9

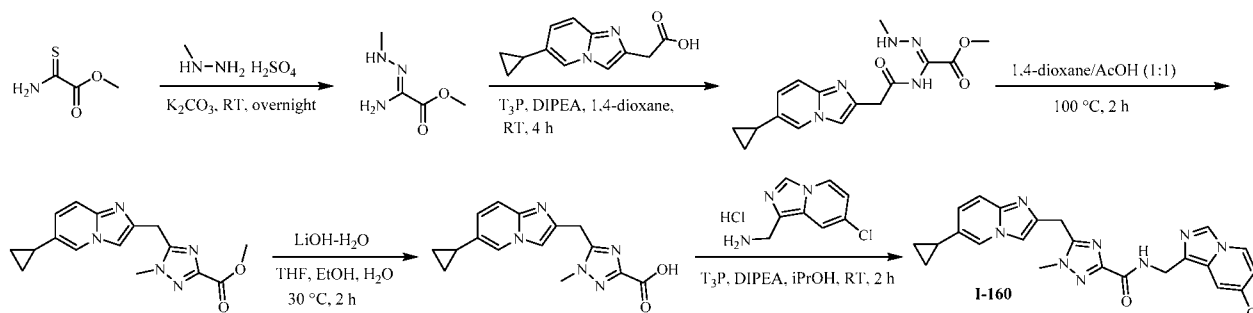
[0649] Synthesis of 5-cyclopropyl-3-(methylsulfonyl)pyridin-2-amine. To a solution of 5-bromo-3-(methylsulfonyl)pyridin-2-amine (1.16 g, 4.62 mmol) in dioxane/H₂O (50 mL/50 mL) was added cyclopropylboronic acid (794 mg, 9.25 mmol), Pd(OAc)₂ (104 mg, 0.46 mmol), PCy₃ (259 mg, 0.925 mmol) and K₃PO₄ (1.963 g, 9.25 mmol). The reaction mixture was stirred at 100 °C for 14 h under nitrogen. Then the mixture was concentrated in vacuo. Water (100 mL) was added and the mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were concentrated to give the crude product, which was purified by silica gel chromatography (PE/EtOAc = 1/1) to give the 5-cyclopropyl-3-(methylsulfonyl)pyridin-2-amine as a yellow solid (619 mg, yield: 63%). ESI-MS [M+H]⁺: 213.1.

[0650] Synthesis of 2-(chloromethyl)-6-cyclopropyl-8-(methylsulfonyl)-3,8a-dihydroimidazo[1,2-a]pyridine. To a solution of 5-cyclopropyl-3-(methylsulfonyl)pyridin-2-amine (102 mg, 0.45 mmol) and 1,3-dichloropropan-2-one (183 mg, 1.44 mmol) in EtOAc (10 mL). The reaction mixture was stirred at 90 °C for 20 h. Then H₂O (30 mL) was added and extracted with EtOAc (50 mL x 3). The combined organic layers were concentrated to give the crude product, which was purified by silica gel chromatography (PE/EtOAc = 2/1) to give 2-(chloromethyl)-6-cyclopropyl-8-(methylsulfonyl)-3,8a-dihydroimidazo[1,2-a]pyridine (97 mg, yield: 75%) as a yellow solid. ESI-MS [M+H]⁺: 285.0.

[0651] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(methylsulfonyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (I-159). To a solution of 2-(chloromethyl)-6-cyclopropyl-8-(methylsulfonyl)imidazo[1,2-a]pyridine (97 mg, 0.34 mmol), N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1H-pyrazole-4-carboxamide (94 mg, 0.68 mmol) and K₂CO₃ (94 mg, 0.68 mmol) in DMF (10 mL). The resulting mixture was stirred for overnight at 60 °C. The mixture was concentrated to remove solvent to give the crude product, which was purified by prep-HPLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(methylsulfonyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (40 mg, yield: 23%) as a light yellow solid. ESI-MS [M+H]⁺: 523.9. Purity: 96.55% (214 nm), 95.34% (254 nm). ¹H NMR (400 MHz, MeOD) δ 9.07 (s, 1H), 8.54 (s, 1H), 8.36 (d, J = 7.6 Hz, 1H), 8.24 (s, 1H), 7.98 (s, 1H), 7.92 (s, 2H), 7.81 (s, 1H), 7.00 (d, J = 2.0 Hz, 1H), 5.56 (s, 2H), 4.80 (s, 2H), 3.40 (s, 3H), 2.11-2.03 (m, 1H), 1.11-1.03 (m, 2H), 0.81-0.76 (m, 2H).

Example 160

Scheme 159



[0652] Synthesis of methyl 2-amino-2-(2-methylhydrazono)acetate. A mixture of methylhydrazine sulfate (360 mg, 2.5 mmol) and K_2CO_3 (690 mg, 5.0 mmol) in ethanol (10 mL) was stirred at RT for 10 minutes, and then ethyl 2-amino-2-thioacetate (333 mg, 2.5 mmol) was added at 0 °C. The mixture was stirred at RT overnight and filtered. The filtrate was concentrated and purified by Prep-TLC (DCM/MeOH = 15:1) to give methyl 2-amino-2-(2-methylhydrazono)acetate (180 mg, yield: 55%) as a yellow solid. ESI-MS $[M+H]^+$: 132.2

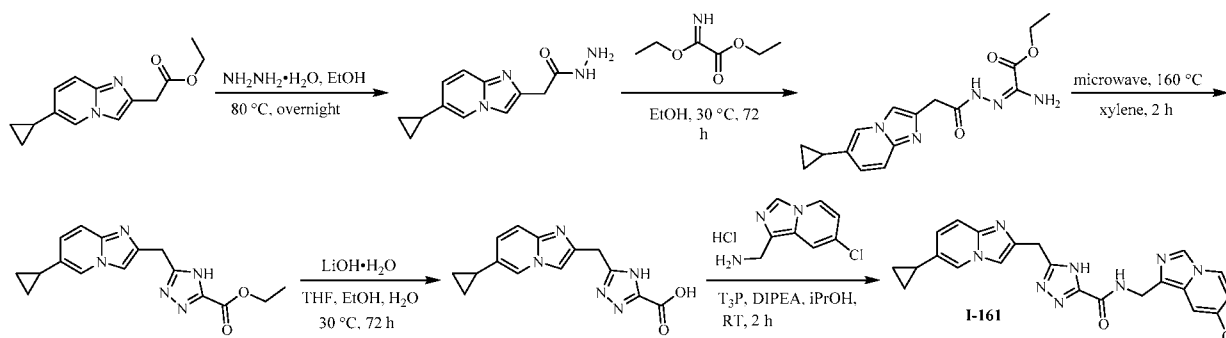
[0653] Synthesis of methyl 2-(2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetamido)-2-(2-methylhydrazono)acetate. A solution of methyl 2-amino-2-(2-methylhydrazono)acetate (52 mg, 0.4 mmol), 2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetic acid (86.4 mg, 0.4 mmol) in 1,4-dioxane (6 mL) was stirred at RT for 10 minutes, and then T_3P (50 wt.% in EA, 524 mg, 0.8 mmol) and DIPEA (100 mg, 0.8 mmol) were added. After the mixture was stirred at RT for 1.5 h, solvent was concentrated and the crude product was used into the next step without further purification. ESI-MS $[M+H]^+$: 330.2.

[0654] Synthesis of methyl 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1-methyl-1H-1,2,4-triazole-3-carboxylate. A solution of methyl 2-(2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetamido)-2-(2-methylhydrazono)acetate (crude from last step) in AcOH/1,4-dioxane (1:1, 5 mL) was stirred at 100 °C for 2 h. Water (20 mL) was added and the mixture was extracted with EtOAc (50 mL*3). The combined organic layers were concentrated and purified by Prep-TLC (DCM:MeOH = 15:1) to give methyl 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-

yl)methyl)-1-methyl-1H-1,2,4-triazole-3-carboxylate (60 mg, yield: 48% over 2 steps) as a white solid. ESI-MS $[M+H]^+$: 312.2.

[0655] Synthesis of 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1-methyl-1H-1,2,4-triazole-3-carboxylic acid. To a solution of methyl 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1-methyl-1H-1,2,4-triazole-3-carboxylate (50 mg, 0.16 mmol) in ethanol (3 mL)/THF (3 mL)/H₂O (1.5 mL) was added LiOH·H₂O (16 mg, 0.39 mmol). The mixture was stirred at 30 °C for 2 h. The mixture was concentrated and the crude product (60 mg, crude) was used into the next step without further purification. ESI-MS $[M+H]^+$: 298.2.

[0656] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1-methyl-1H-1,2,4-triazole-3-carboxamide. A mixture of 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1-methyl-1H-1,2,4-triazole-3-carboxylic acid (60 mg, crude from last step), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (41 mg, 0.19 mmol), and DIPEA (101 mg, 0.785 mmol) in isopropanol (6 mL) was stirred at RT for 10 minutes. T₃P (50 wt.% in EA, 250 mg, 0.39 mmol) was added. The mixture was stirred at RT overnight. Water (10 mL) was added and extracted with EtOAc (30 mL*3). The combined organic layers were concentrated and purified by Prep-HPLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1-methyl-1H-1,2,4-triazole-3-carboxamide (7.3 mg, yield: 10% over 2 steps) as a yellow solid. ESI-MS $[M+H]^+$: 461.1. Purity: 98.14 (214 nm), 98.24 (254 nm). ¹H NMR (400 MHz, DMSO-d₆) δ 8.70 (t, J = 5.9 Hz, 1H), 8.28-8.25 (m, 3H), 7.81 (s, 1H), 7.64 (s, 1H), 7.32 (d, J = 9.3 Hz, 1H), 6.92 (d, J = 9.2 Hz, 1H), 6.61 (dd, J = 7.4, 1.8 Hz, 1H), 4.56 (d, J = 5.9 Hz, 2H), 4.25 (s, 2H), 3.86 (s, 3H), 1.91-1.85 (m, 1H), 0.90-0.85 (m, 2H), 0.64-0.61 (m, 2H).

Example 161Scheme 160

[0657] Synthesis of 2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetohydrazide. A mixture of ethyl 2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetate (650 mg, 2.66 mmol) and hydrazine hydrate (2.0 mL) in ethanol (8 mL) was stirred at 80 °C overnight. The mixture was concentrated and purified by silica gel chromatography (DCM/MeOH = 5:1) to give 2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetohydrazide (240 mg, yield: 39%) as a white solid. ESI-MS $[M+H]^+$: 231.1

[0658] Synthesis of ethyl 2-amino-2-(2-(2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetyl)hydrazono)acetate. A solution of 2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetohydrazide (115 mg, 0.5 mmol) and ethyl 2-ethoxy-2-iminoacetate (145 mg, 1.0 mmol) in ethanol (2.0 mL) was stirred at RT for 3 days. The mixture was concentrated to get a yellow solid (165 mg, crude) which was used into the next step without further purification. ESI-MS $[M+H]^+$: 330.1.

[0659] Synthesis of ethyl 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-4H-1,2,4-triazole-3-carboxylate. A solution of ethyl 2-amino-2-(2-(2-(6-cyclopropylimidazo[1,2-a]pyridin-2-yl)acetyl)hydrazono)acetate (165 mg, crude from last step) in xylene (4.0 mL) was stirred at 160 °C under microwave irradiation for 3 h. The mixture was concentrated and purified by Prep-TLC (DCM/MeOH = 5:1) to give ethyl 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-4H-1,2,4-triazole-3-carboxylate (100 mg, yield: 64% over 2 steps) as a yellow solid. ESI-MS $[M+H]^+$: 312.1.

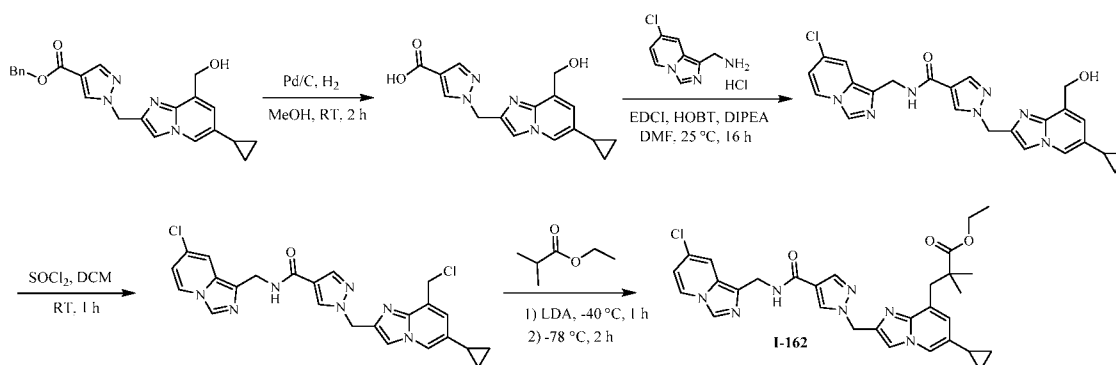
[0660] Synthesis of 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-4H-1,2,4-triazole-3-carboxylic acid. To a solution of ethyl 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-

yl)methyl)-4H-1,2,4-triazole-3-carboxylate (50 mg, 0.16 mmol) in ethanol (3 mL)/THF (3 mL)/H₂O (0.5 mL) was added LiOH·H₂O (13.5 mg, 0.32 mmol). After the mixture was stirred at RT overnight, solvent was concentrated and the crude (60 mg) was used into the next step without further purification. ESI-MS [M+H]⁺: 284.2.

[0661] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-4H-1,2,4-triazole-3-carboxamide (I-161). A solution of crude 5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-4H-1,2,4-triazole-3-carboxylic acid (60 mg, crude from last step), (7-chloroimidazo[1,5-a]pyridin-1-yl)methanamine hydrochloride (35 mg, 0.16 mmol), and DIPEA (83 mg, 0.64 mmol) in isopropanol (6 mL) was stirred at RT for 10 minutes. And then T₃P (50 wt.% in EA, 204 mg, 0.32 mmol) was added. The mixture was stirred at RT overnight, H₂O (15 mL) was added and extracted with DCM and MeOH (10:1, 50 mL*3). The combined organic layers were concentrated and purified by Prep-HPLC to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-5-((6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-4H-1,2,4-triazole-3-carboxamide (13.1 mg, yield: 18% over 2 steps) as a white solid. ESI-MS [M+H]⁺: 447.2. Purity: 95.13 (214 nm), 96.02 (254 nm). ¹H NMR (400 MHz, DMSO-d₆) δ 8.83 (s, 1H), 8.24-8.22 (m, 3H), 7.79 (s, 1H), 7.55 (s, 1H), 7.27 (d, J = 9.3 Hz, 1H), 6.88 (d, J = 9.3 Hz, 1H), 6.58 (dd, J = 7.4, 1.8 Hz, 1H), 4.54 (d, J = 5.9 Hz, 2H), 4.09 (s, 2H), 1.87-1.81 (m, 1H), 0.85-0.82 (m, 2H), 0.61-0.57 (m, 2H).

Example 162

Scheme 161



[0662] Synthesis of 1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid. The mixture of benzyl 1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylate (260 mg, 0.646 mmol) and Pd/C (100 mg) in MeOH (6 mL) and THF (3 mL) was stirred at RT for 2 h under H₂ (balloon). The reaction mixture was filtered and the filtrate was concentrated and dried in vacuo to give 1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (180 mg, yield: 89%) as a yellow solid. ESI-MS [M+H]⁺: 313.0.

[0663] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide. The mixture of 1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxylic acid (180 mg, 0.576 mmol), (5-chloro-2-(1H-tetrazol-5-yl)phenyl)methanamine (188 mg, 0.864 mmol), EDCI (133 mg, 0.691 mmol), HOBT (93 mg, 0.691 mmol) and DIPEA (223 mg, 1.728 mmol) in DMF (6 mL) was stirred at 25 °C for 16 h. The reaction mixture was poured into H₂O (60 mL) and the precipitate was collected, dried in vacuo to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (200 mg, yield: 73%) as a pale white solid. ESI-MS [M+H]⁺: 475.9.

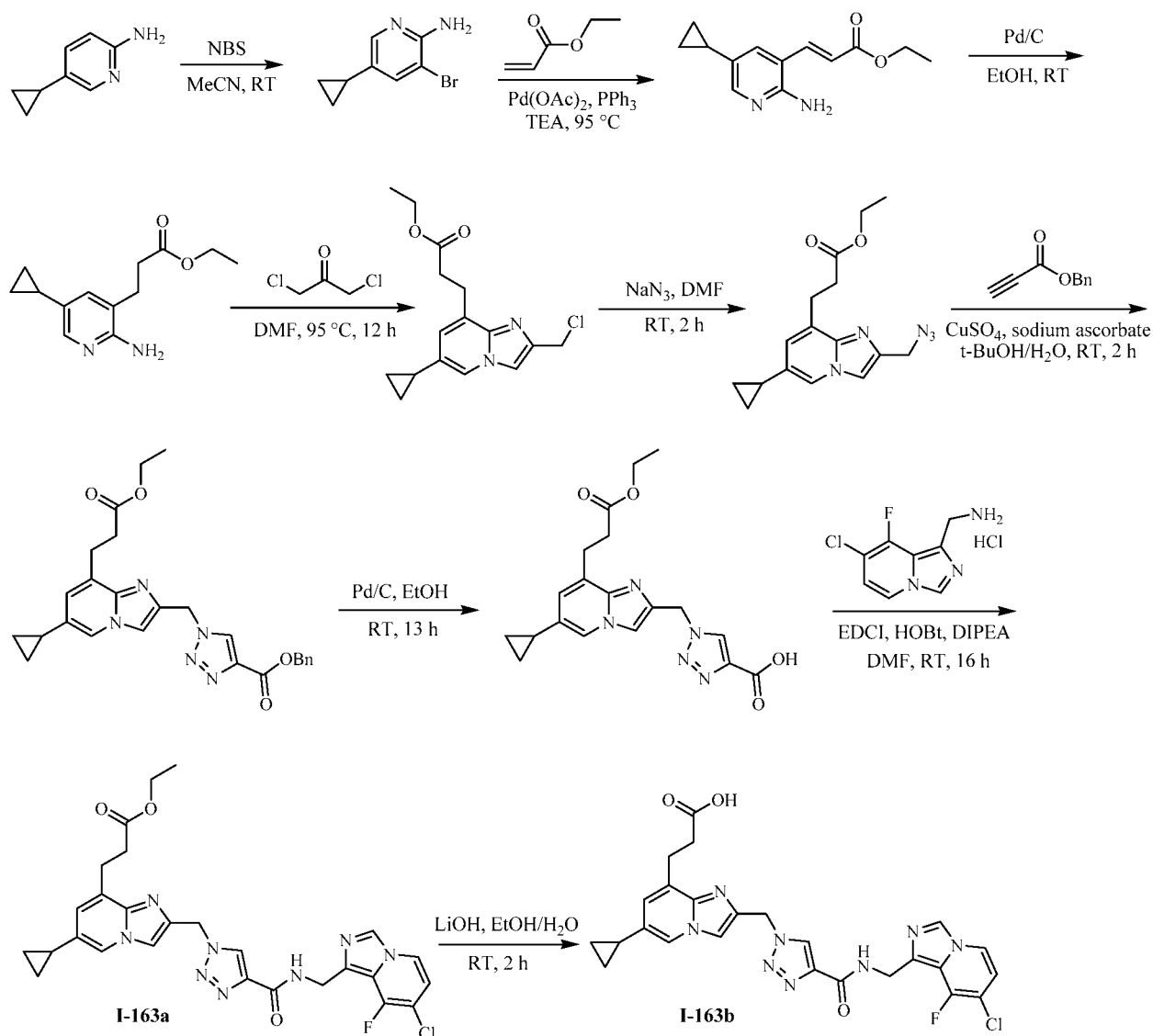
[0664] Synthesis of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide. To a stirred solution of N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((6-cyclopropyl-8-(hydroxymethyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (180 mg, 0.378 mmol) in DCM (10 mL) and THF (4 mL) was added dropwise of SOCl₂ (450 mg, 3.78 mmol) at 0 °C. The mixture was stirred at RT for 1 h. The reaction mixture was concentrated. The residue was dissolved in EtOAc (30 mL) and washed with NaHCO₃ (30 mL) and brine (30 mL), dried over Na₂SO₄, concentrated and dried in vacuo to give N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (150 mg, crude) as a yellow solid. ESI-MS [M+H]⁺: 494.0.

[0665] Synthesis of ethyl 3-(2-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbonyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)-

2,2-dimethylpropanoate (I-162). To a stirred solution of ethyl isobutyrate (0.53 g, 4.5 mmol) in THF (6 mL) was added LDA (2.4 mL, 2 M in THF) at -40 °C under N₂. After 1 h, the solution above was added dropwise to the suspension of N-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-1-((8-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-2-yl)methyl)-1H-pyrazole-4-carboxamide (150 mg, crude from last step) in THF (10 mL) at -78 °C. The resulting mixture was stirred for 2 h at -78 °C. The reaction mixture was quenched with saturated aqueous NH₄Cl (30 mL), then adjusted the pH to 9~10 by NaHCO₃ aqueous, extracted with EtOAc/THF (50 mL x 3). The combined organics were washed with brine, dried over Na₂SO₄, concentrated and purified by Prep-TLC (DCM/MeOH = 8/1) to give ethyl 3-(2-(((4-(((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)carbamoyl)-1H-pyrazol-1-yl)methyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)-2,2-dimethylpropanoate (10 mg, yield: 5%) as a white solid. ESI-MS [M+H]⁺: 574.1. Purity: 96.55 (214nm), 95.05 (254nm). ¹H NMR (400 MHz, DMSO-d₆) δ 8.55 (t, J = 5.5 Hz, 1H), 8.33-8.28 (m, 2H), 8.20 (s, 1H), 8.15 (s, 1H), 7.87 (s, 1H), 7.77 (s, 1H), 7.65 (s, 1H), 6.70-6.62 (m, 2H), 5.37 (s, 2H), 4.55 (d, J = 5.7 Hz, 2H), 3.95 (q, J = 7.1 Hz, 2H), 3.09 (s, 2H), 1.91-1.83 (m, 1H), 1.24-1.07 (m, 9H), 0.93-0.86 (m, 2H), 0.62 -0.57 (m, 2H).

Example 163

Scheme 162



[0666] Synthesis of 3-bromo-5-cyclopropylpyridin-2-amine. A mixture of 5-cyclopropylpyridin-2-amine (10 g, 74.5 mmol) in MeCN (130 mL) was added 1-Bromo-2, 5-pyrrolidinedione (16 g, 89.4 mmol) at RT. The mixture was stirred for 3 h. The mixture was concentrated, diluted with H₂O (200 mL) and exacted by EtOAc (200 mL x 3) and H₂O (250 mL). The combined organic phases were concentrated to give 3-bromo-5-cyclopropylpyridin-2-amine (15.0 g, crude) as a yellow solid. ESI-MS [M+H]⁺: 213.0

[0667] Synthesis of ethyl 3-(2-amino-5-cyclopropylpyridin-3-yl)acrylate. To a solution of 3-bromo-5-cyclopropylpyridin-2-amine (7.00 g, 33 mmol) in DMF (60 mL) was added TEA (15 mL), PPh_3 (1.74 g, 16.43 mmol), $\text{Pd}(\text{OAc})_2$ (0.75 g 3.3 mmol) and ethyl acrylate (6 mL, 65.7 mmol) at RT. The mixture was heated to 95 °C and stirred for 16 h. Water (70 mL) was added and the mixture were extracted by EtOAc (100 mL x 3). The organic phases were concentrated to give ethyl 3-(2-amino-5-cyclopropylpyridin-3-yl)acrylate (4 g, yield: crude) as a yellow solid. ESI-MS $[\text{M}+\text{H}]^+$: 233.1.

[0668] Synthesis of ethyl 3-(2-amino-5-cyclopropylpyridin-3-yl)propanoate. To a solution of ethyl (E)-3-(2-amino-5-cyclopropylpyridin-3-yl)acrylate (4 g, crude from last step) in EtOH(50 mL)/EtOAc() (10 mL) was added Pd/C (400 mg) at RT. The mixture was stirred for 16 h. The mixture were filtered and concentrated to give ethyl 3-(2-amino-5-cyclopropylpyridin-3-yl)propanoate (4 g, crude) as a yellow oil. ESI-MS $[\text{M}+\text{H}]^+$: 235.1.

[0669] Synthesis of ethyl 3-(2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)propanoate. To a solution of 3-(2-amino-5-cyclopropylpyridin-3-yl)propanoate (4 g, crude) in DMF (30 mL) was added 1,3-dichloropropan-2-one (11.7 g, 92 mmol) at RT. The mixture was heated to 95 °C and stirred for 16 h. H_2O (100 mL) was added to reaction, extracted by EtOAc (100 mL x 3). The organic phases were concentrated and purified by flash silica gel chromatography (0~60% EtOAc in PE) to give ethyl 3-(2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)propanoate (2.2 g, yield: 22 % over 3 steps) as a red oil. ESI-MS $[\text{M}+\text{H}]^+$: 307.1.

[0670] Synthesis of ethyl 3-(2-(azidomethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)propanoate. To a solution of ethyl 3-(2-(chloromethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)propanoate (2.2 g, 7.17 mmol) in DMF (30 mL) was added NaN_3 (416 mg, 6.40 mmol) at RT. The mixture was stirred for 2 h. H_2O (100 mL) was added to reaction, extracted by EtOAc (100 mL x 3). The combined organic phases were washed with brine, dried over Na_2SO_4 , concentrated to give ethyl 3-(2-(azidomethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)propanoate (1.6 g, crude) as a red oil. ESI-MS $[\text{M}+\text{H}]^+$: 314.1.

[0671] Synthesis of benzyl 1-((6-cyclopropyl-8-(3-ethoxy-3-oxopropyl)imidazo[1,2-a]pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxylate. To a solution of ethyl 3-(2-(azidomethyl)-6-cyclopropylimidazo[1,2-a]pyridin-8-yl)propanoate (1.6 g, crude) in t-

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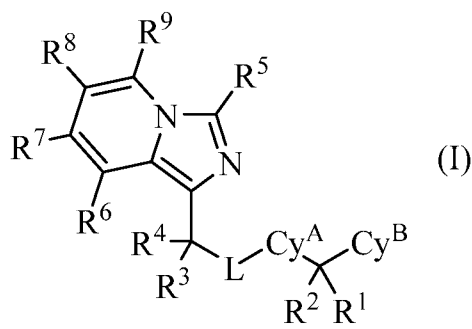
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CLAIMS

What is claimed is:

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof,

wherein:

Cy^A is selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclylenel having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, and 7- to 10-membered bicyclic heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^A is substituted with 0-4 R^A groups;

each R^A is independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

Cy^B is selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-

membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, and 7- to 10-membered bicyclic heteroaryl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^B is substituted with 0-5 R^B groups;

each R^B is independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

L is selected from -QC(R)₂-, -C(R)₂Q-, -QC(Q)-, -C(Q)Q-, -C(R)₂QC(O)-, and -C(O)QC(R)₂-, wherein each Q is independently a monovalent or divalent group as valency allows, selected from the group consisting of O, N(R), or (S);

R¹, R², R³, and R⁴ are independently selected from hydrogen and C₁₋₆ aliphatic;

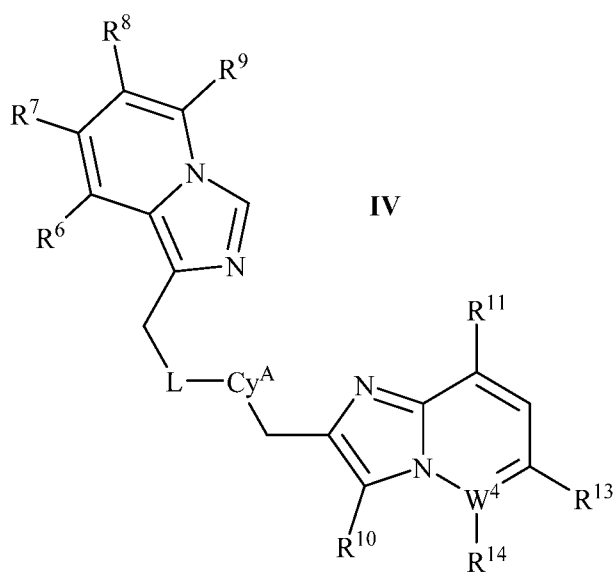
R⁵, R⁶, R⁷, R⁸, and R⁹ are independently selected from hydrogen, halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

each R is independently hydrogen, -CN, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur;

with the proviso that the compound is other than N-((7-chloroimidazo[1,5-a]pyridin-1-yl)methyl)-2-((3-chloroquinolin-6-yl)methyl)isonicotinamide.

2. The compound of claim 1, wherein the compound is of Formula (IV):



or a pharmaceutically acceptable salt thereof,

wherein:

Cy^A is a 5-membered heteroarylene having 1-4 heteroatoms selected from oxygen or nitrogen, wherein Cy^A is substituted with 0-3 R^A groups;

L is selected from -NC(O)- and -C(O)N-;

R⁶, R⁸, and R⁹ are independently selected from hydrogen, halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen,

or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R⁷ is -F, -Cl, or -Br;

W⁴ is carbon or nitrogen;

R¹⁰ and R¹¹ are each optionally present, and if present are independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

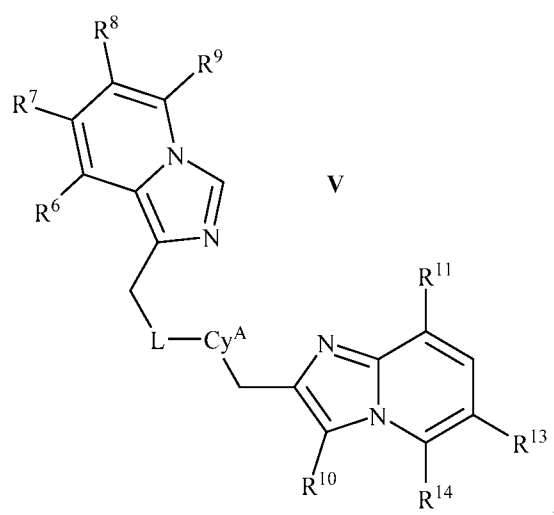
R¹³ is selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₂₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R¹⁴ is optionally present, and if present and is selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₃₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

each R is independently hydrogen, -CN, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur.

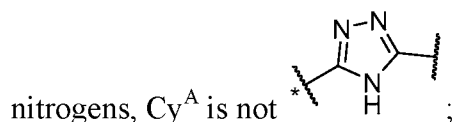
3. The compound of any one of the preceding claims, wherein the compound is of Formula (V):



or a pharmaceutically acceptable salt thereof,

wherein:

Cy^A is a 5-membered heteroarylene having 1-4 nitrogens, wherein when Cy^A comprises 3



L is selected from -NC(O)- and -C(O)N-;

R^6 , R^8 , and R^9 are independently selected from hydrogen, halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R^7 is -F, -Cl, or -Br;

R^{10} is optionally present, and if present is selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R^{11} is optionally present, and if present is selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R^{13} is selected from -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- or 5-7-membered saturated or partially unsaturated

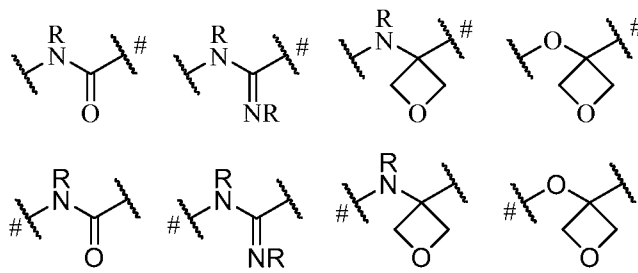
monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R¹⁴ is optionally present, and if present and is selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₃₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

each R is independently hydrogen, -CN, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

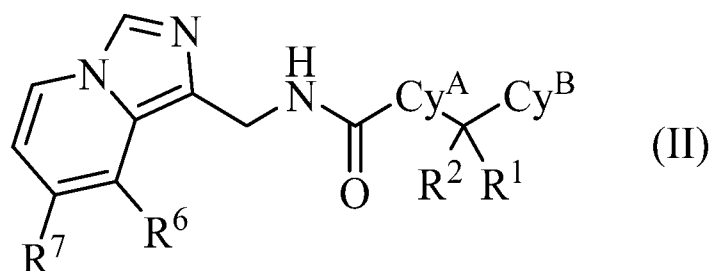
or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur.

4. The compound of any one of the preceding claims, wherein L is selected from the group consisting of:



wherein # represents to point of attachment to CyA.

5. The compound of any one of the preceding claims, wherein the compound is of Formula (II):



or a pharmaceutically acceptable salt thereof,

wherein:

Cy^A is selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclylenel having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, and 7- to 10-membered bicyclic heteroarylene having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^A is substituted with 0-4 R^A groups;

each R^A is independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

Cy^B is selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-5 heteroatoms

selected from oxygen, nitrogen, or sulfur, and 7- to 10-membered bicyclic heteroaryl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^B is substituted with 0-5 R^B groups;

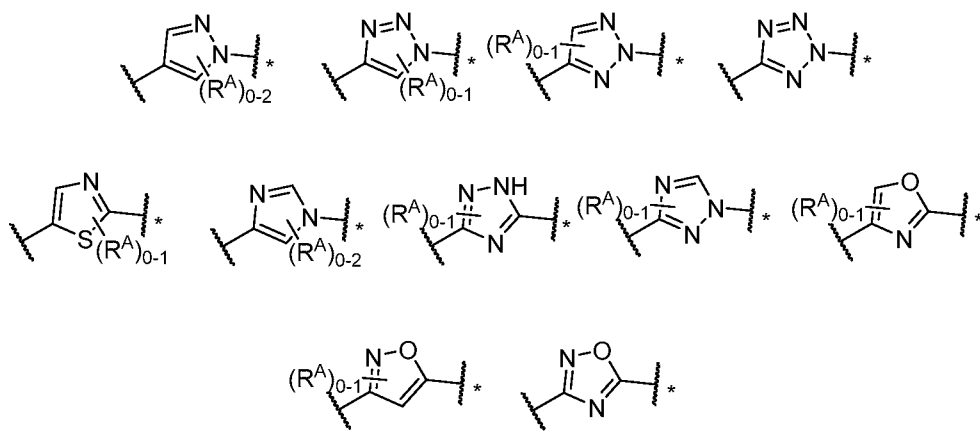
each R^B is independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R¹ and R² are independently selected from hydrogen and C₁₋₆ aliphatic;

R⁶ and R⁷ are independently selected from hydrogen, halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

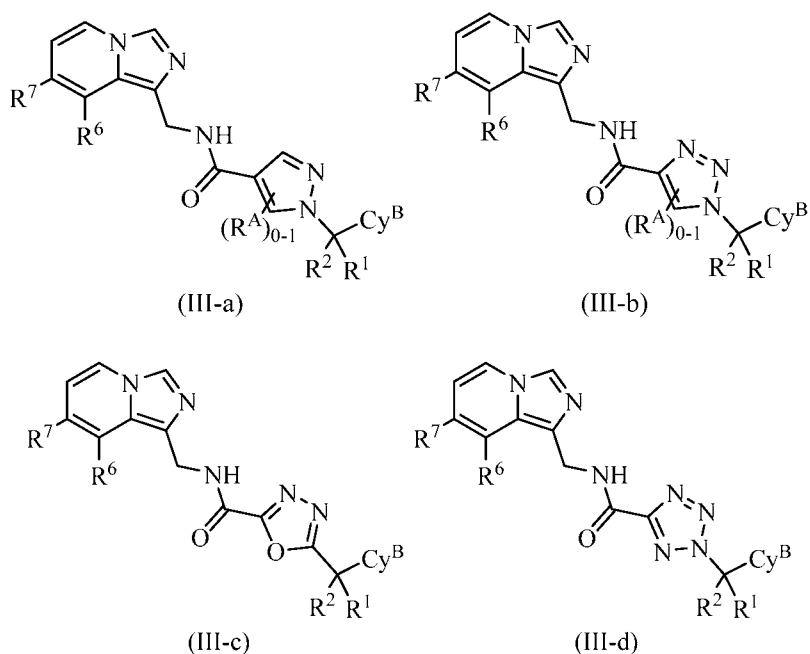
each R is independently hydrogen, -CN, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur;



wherein * represents to point of attachment to L.

9. The compound of any one of the preceding claims, wherein the compound is of Formula (III-a) through (III-d):



or a pharmaceutically acceptable salt thereof,

wherein:

each R^A is independently selected from halogen, $-CN$, $-C(R)=N(R)$, $-C(O)R$, $-C(O)_2R$, $-C(O)N(R)_2$, $-NO_2$, $-N(R)-N(R)_2$, $-N(R)_2$, $-N(R)C(O)R$, $-N(R)C(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)S(O)_2R$, $-OR$, $-OC(O)R$, $-OC(O)N(R)_2$, $-SR$, $-S(O)R$, $-S(O)_2R$, $-S(O)N(R)_2$, -

$S(O)_2N(R)_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

Cy^B is selected from 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 7- to 10-membered saturated or partially unsaturated bicyclic heterocyclyl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, and 7- to 10-membered bicyclic heteroaryl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^B is substituted with 0-5 R^B groups;

each R^B is independently selected from halogen, $-CN$, $-C(R)=N(R)$, $-C(O)R$, $-C(O)_2R$, $-C(O)N(R)_2$, $-NO_2$, $-N(R)-N(R)_2$, $-N(R)_2$, $-N(R)C(O)R$, $-N(R)C(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)S(O)_2R$, $-OR$, $-OC(O)R$, $-OC(O)N(R)_2$, $-SR$, $-S(O)R$, $-S(O)_2R$, $-S(O)N(R)_2$, $-S(O)_2N(R)_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

R^1 and R^2 are independently selected from hydrogen and C_{1-6} aliphatic;

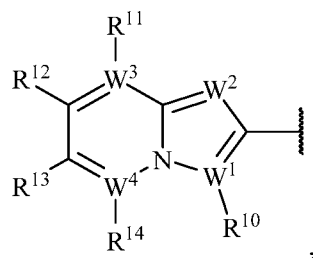
R^6 and R^7 are independently selected from hydrogen, halogen, $-CN$, $-C(R)=N(R)$, $-C(O)R$, $-C(O)_2R$, $-C(O)N(R)_2$, $-NO_2$, $-N(R)-N(R)_2$, $-N(R)_2$, $-N(R)C(O)R$, $-N(R)C(O)_2R$, $-N(R)C(O)N(R)_2$, $-N(R)S(O)_2R$, $-OR$, $-OC(O)R$, $-OC(O)N(R)_2$, $-SR$, $-S(O)R$, $-S(O)_2R$, $-S(O)N(R)_2$, $-S(O)_2N(R)_2$, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

each R is independently hydrogen, -CN, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur.

10. The compound of any one of the preceding claims, wherein Cy^B is a 7- to 10-membered bicyclic heteroaryl having 1-5 heteroatoms selected from oxygen, nitrogen, or sulfur, wherein Cy^B is substituted with 0-5 R^B groups.

11. The compound of any one of the preceding claims, wherein Cy^B is



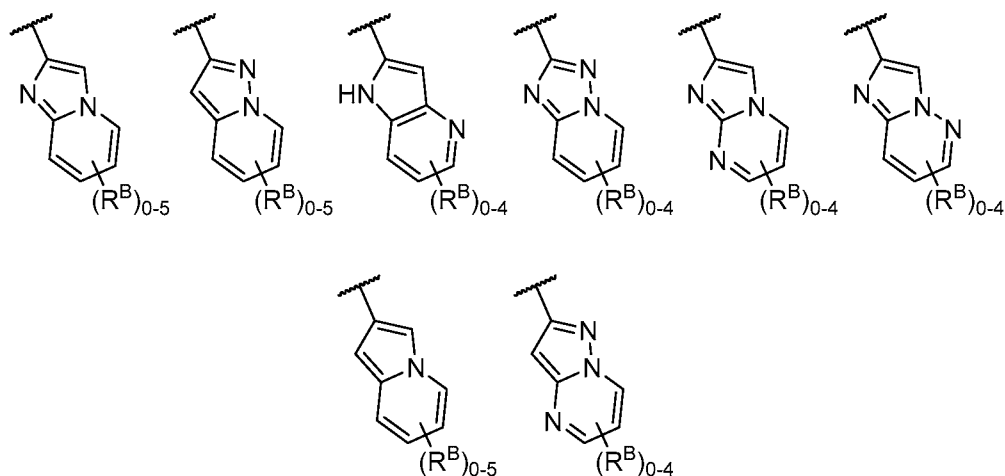
wherein:

W¹, W², W³, and W⁴ are independently selected from carbon and nitrogen;

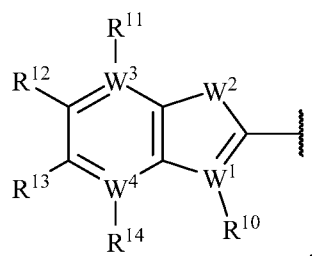
R¹⁰, R¹¹, R¹², R¹³, and R¹⁴ are each optionally present when attached to a carbon atom, and if present correspond to an occurrence of R^B independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic

carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and each R is independently hydrogen, -CN, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur.

12. The compound of any one of the preceding claims, wherein Cy^B is selected from the group consisting of:



13. The compound of any one of the preceding claims, wherein Cy^B is



wherein:

W^2 is selected from carbon, nitrogen, oxygen, and sulfur;

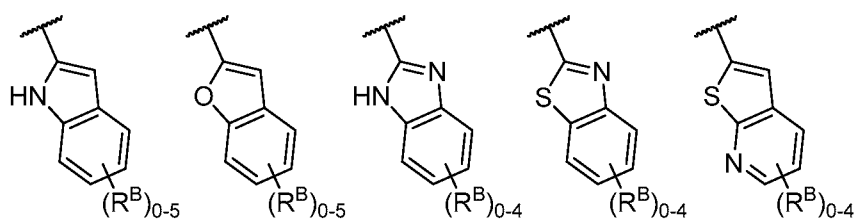
W^1 , W^3 , and W^4 are independently selected from carbon and nitrogen;

R^{10} , R^{11} , R^{12} , R^{13} , and R^{14} are each optionally present when attached to a carbon atom, and if present correspond to an occurrence of R^B independently selected from halogen, -CN, -C(R)=N(R), -C(O)R, -C(O)₂R, -C(O)N(R)₂, -NO₂, -N(R)-N(R)₂, -N(R)₂, -N(R)C(O)R, -N(R)C(O)₂R, -N(R)C(O)N(R)₂, -N(R)S(O)₂R, -OR, -OC(O)R, -OC(O)N(R)₂, -SR, -S(O)R, -S(O)₂R, -S(O)N(R)₂, -S(O)₂N(R)₂, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur; and

each R is independently hydrogen, -CN, or an optionally substituted group selected from C₁₋₆ aliphatic, phenyl, 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, and 3- to 7-membered saturated or partially unsaturated monocyclic heterocyclyl having 1-2 heteroatoms selected from oxygen, nitrogen, or sulfur;

or two R groups on the same carbon or nitrogen are taken together with their intervening atoms to form a ring selected from 3- to 7-membered saturated or partially unsaturated monocyclic ring having 0-2 heteroatoms selected from oxygen, nitrogen, or sulfur, and 5- to 6-membered heteroaryl having 1-4 heteroatoms selected from oxygen, nitrogen, or sulfur.

14. The compound of any one of the preceding claims, wherein Cy^B is selected from the group consisting of:



15. The compound of any one of the preceding claims, wherein R^5 , R^6 , R^7 , R^8 , and R^9 are independently selected from hydrogen, halogen, -CN, -N(R)₂, -OR, or an optionally substituted group selected from C₁₋₆ aliphatic, 3- to 7-membered saturated or partially unsaturated monocyclic carbocyclyl, wherein each R is independently hydrogen or C₁₋₆ aliphatic.

16. The compound of any one of the preceding claims, wherein R^6 is selected from hydrogen or halogen.

17. The compound of any one of the preceding claims, wherein the compound is any one of compounds I-1 through I-303 as shown in Table 1, or a pharmaceutically acceptable salt thereof.

18. A pharmaceutical composition comprising any one of the preceding compounds further comprising a pharmaceutically acceptable excipient.

19. A method of treating a plasma kallikrein-mediated disease or disorder using a compound or composition of any one of the preceding claims.

20. A method of treating hereditary angioedema or diabetic macular edema comprising administering to a patient in need thereof a compound of any one of the preceding claims.

