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(71) Applicant: **LYSOSOMAL THERAPEUTICS INC.** [US/US]; 19 Blackstone Street, Cambridge, MA 02139 (US).

(72) Inventors: **SKERLJ, Renato,** T.; 12 Crocker Circle, West Newton, MA 02465 (US). **BOURQUE, Elyse Marie Josee;** 162 Ch Bouffard, L'etang-du-nord, QC G4T 3G6 (CA). **LANSBURY, Peter,** T.; 24 Elm Street, Brookline, MA 02445 (US). **GREENLEE, William, J.;** 115 Herrick Avenue, Teaneck, NJ 07666 (US). **GOOD, Andrew, C ;** 52 High Hill Road, Wallingford, CT 06492 (US).

(74) Agents: **DAVIS, Chad, E.** et al; Goodwin Procter Lip, 100 Northern Avenue, Boston, MA 02210 (US).

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(54) Title: IMIDAZO [1,5-A]PYRIMIDINYL CARBOXAMIDE COMPOUNDS AND THEIR USE IN THE TREATMENT OF MEDICAL DISORDERS

(57) Abstract: The invention provides substituted imidazo[l,5-a]pyrimidinyl carboxamide and related organic compounds, compos - itions containing such compounds, medical kits, and methods for using such compounds and compositions to treat medical dis - orders, e.g., Gaucher disease, Parkinson's disease, Lewy body disease, dementia, or multiple system atrophy, in a patient. Exemplary substituted imidazo[l,5-a]pyrimidinyl carboxamide compounds described herein include substituted 2-heterocyclyl-4-alkyl-imidazo[l,5-a]pyrirnidine-8-carboxamide compounds and variants thereof.

IMIDAZO[l,5-a]PYRIMIDINYL CARBOXAMIDE COMPOUNDS AND THEIR USE IN THE TREATMENT OF MEDICAL DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to United States Provisional Patent Application serial number 62/318,936, filed April 6, 2016, the contents of which are hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The invention provides substituted imidazo[l,5-a]pyrirnidinyl carboxamide and related organic compounds, compositions containing such compounds, medical kits, and methods for using such compounds and compositions to treat medical disorders in a patient.

BACKGROUND

[0003] Gaucher disease is a genetic disorder associated with a deficiency of the lysosomal enzyme, glucocerebrosidase. Gaucher disease has been reported to have an incidence of approximately 1 in 20,000 live births in the general population, and it is a common lysosomal storage disorder. Current treatments for patients suffering from this disease include enzyme replacement therapy, which tends to be expensive, analgesics for bone pain relief, and medical procedures such as blood and platelet transfusions, splenectomy, and joint replacement for patients who experience bone erosion. However, new treatment options are needed having improved efficacy across a broader range of patients and/or reduced adverse side effects.

[0004] Mutations in the gene encoding glucocerebrosidase are also a risk factor for Parkinson's disease and diffuse Lewy Body Disease. Parkinson's disease is a degenerative disorder of the central nervous system associated with death of dopamine-containing cells in a region of the midbrain. Parkinson's disease afflicts millions of people, and the incidence of the disease increases with age. Treatment of Parkinson's disease frequently involves use of levodopa and dopamine agonists. However, these drugs can produce significant side effects such as hallucinations, insomnia, nausea, and constipation. Further, patients often develop tolerance to these drugs such that the drugs become ineffective at treating the symptoms of the

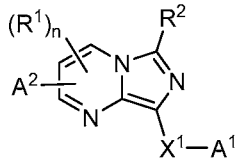
disease, while sometimes also producing a movement disorder side effect called dyskinesia. Diffuse Lewy Body disease is a dementia that is sometimes confused with Alzheimer's disease.

[0005] Accordingly, the need exists for new therapeutic agents for treating Gaucher disease, Parkinson's disease, and related medical disorders. The present invention addresses this need and provides other related advantages.

SUMMARY

[0006] The invention provides substituted imidazo[l,5-a]pyrimidinyl carboxamide and related organic compounds, compositions containing such compounds, medical kits, and methods for using such compounds and compositions to treat medical disorders, *e.g.,* Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma, multiple sclerosis, endometriosis, and multiple myeloma, in a patient. Various aspects and embodiments of the invention are described in further detail below.

[0007] Accordingly, one aspect of the invention provides a family of substituted imidazo[l,5-a]pyrimidinyl carboxamide and related organic compounds embraced by Formula I that may be used in the methods, compositions and kits described herein, wherein Formula I is represented by:

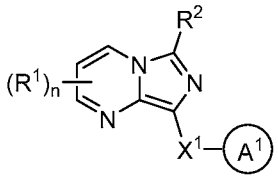


(I)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in the detailed description. Further description of additional collections of substituted imidazo[l,5-a]pyrimidinyl carboxamide and related organic compounds embraced by Formula I are described in the detailed description.

[0008] Another aspect of the invention provides a family of substituted imidazo[l,5-a]pyrimidinyl carboxamide and related organic compounds embraced by Formula II that may

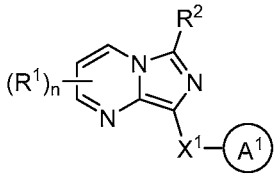
be used in the methods, compositions, and kits described herein, wherein Formula II is represented by:



(II)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in the detailed description. Further description of additional collections of substituted irnidazo[l,5-a]pyrimidinyl carboxamide and related organic compounds embraced by Formula II are described in the detailed description

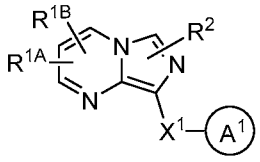
[0009] Another aspect of the invention provides a family of substituted imidazo[l,5-a]pyrimidinyl carboxamide and related organic compounds embraced by Formula III that may be used in the methods, compositions, and kits described herein, wherein Formula III is represented by:



(III)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in the detailed description. Further description of additional collections of substituted imidazo[l,5-a]pyrimidinyl carboxamide and related organic compounds embraced by Formula III are described in the detailed description.

[0010] Another aspect of the invention provides a family of substituted imidazo[l,5-a]pyrimidinyl carboxamide and related organic compounds embraced by Formula IV that may be used in the methods, compositions, and kits described herein, wherein Formula IV is represented by:



(IV)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in the detailed description. Further description of additional collections of substituted imidazo[l,5-ajpyrimidinyl carboxamide and related organic compounds embraced by Formula IV are described in the detailed description.

[0011] Another aspect of the invention provides a pharmaceutical composition, comprising a pharmaceutically acceptable carrier and a substituted imidazo[l,5-a]pyrimidinyl carboxamide or related organic compound described herein, such as a compound of Formula I, II, III, or IV.

[0012] Another aspect of the invention provides a method of treating a disorder, e.g., Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma, multiple sclerosis, endometriosis, and multiple myeloma, in a patient. The method comprises administering to a patient in need thereof a therapeutically effective amount of a substituted imidazo[l,5-a]pyrimidinyl carboxamide or related organic compound described herein, such as a compound of Formula I, II, III, or IV, to treat the disorder, e.g., Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma, multiple sclerosis, or multiple myeloma.

DETAILED DESCRIPTION

[0013] The invention provides substituted imidazo[l,5-a]pyrimidinyl carboxamide and related organic compounds, compositions containing such compounds, medical kits, and methods for using such compounds and compositions to treat medical disorders in a patient. The practice of the present invention employs, unless otherwise indicated, conventional techniques of organic chemistry, pharmacology, cell biology, and biochemistry. Such techniques are explained in the literature, such as in "Comprehensive Organic Synthesis" (B.M. Trost & I. Fleming, eds., 1991-1992); "Current protocols in molecular biology" (F.M. Ausubel

etal, eds., 1987, and periodic updates); and "Current protocols in immunology" (J.E. Coligan *et al*, eds., 1991), each of which is herein incorporated by reference in its entirety. Various aspects of the invention are set forth below in sections; however, aspects of the invention described in one particular section are not to be limited to any particular section.

I. DEFINITIONS

[0014] To facilitate an understanding of the present invention, a number of terms and phrases are defined below.

[0015] The terms "a" and "an" as used herein mean "one or more" and include the plural unless the context is inappropriate.

[0016] The term "alkyl" as used herein refers to a saturated straight or branched hydrocarbon, such as a straight or branched group of 1-12, 1-10, or 1-6 carbon atoms, referred to herein as Ci-Ci$_2$alkyl, Ci-Cioalkyl, and Ci-Cealkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methy$_{1-1}$-propyl, 2-methyl-2-propyl, 2-methy$_{1-1}$-butyl, 3-methyl- 1-butyl, 2-methy$_{1-3}$-butyl, 2,2-dimethy$_{1-1}$-propyl, 2-methyl- 1-pentyl, 3-methyl-l-pentyl, 4-methyl-l-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethy$_{1-1}$-butyl, 3,3-dimethyl-l-butyl, 2-ethy$_{1-1}$-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, etc.

[0017] The term "alkylene" refers to a diradical of an alkyl group. An exemplary alkylene group is -CH$_2$CH$_2$-.

[0018] The term "haloalkyl" refers to an alkyl group that is substituted with at least one halogen. For example, -CH_2F, -CHF_2, -CF_3, -CH_2CF_3, -CF_2CF_3, and the like.

[0019] The term "hydroxyalkyl" refers to an alkyl group that is substituted with at least one hydroxyl group. For example, exemplary hydroxyalkyl groups include -CH_2OH, -C(H)(OH)CH$_3$, and the like. In certain embodiments, the hydroxyalkyl is an alkyl group that is substituted with just one hydroxyl group.

[0020] The term "cyanoalkyl" refers to an alkyl group that is substituted with one cyano group.

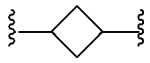
[0021] The term "heteroalkyl" as used herein refers to an "alkyl" group in which at least one carbon atom has been replaced with a heteroatom (e.g., an O, N, or S atom). The

heteroalkyl may be, for example, an -O-Ci-Cioalkyl group, an -Ci-Cealkylene-O-Ci-Cealkyl group, or a C1-C6 alkylene-OH group. In certain embodiments, the "heteroalkyl" may be 2-8 membered heteroalkyl, indicating that the heteroalkyl contains from 2 to 8 atoms selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. In yet other embodiments, the heteroalkyl may be a 2-6 membered, 4-8 membered, or a 5-8 membered heteroalkyl group (which may contain for example 1 or 2 heteroatoms selected from the group oxygen and nitrogen). One type of heteroalkyl group is an "alkoxyl" group.

[0022] The term "alkenyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond, such as a straight or branched group of 2-12, 2-10, or 2-6 carbon atoms, referred to herein as C2-Ci2alkenyl, C2-Cioalkenyl, and $C2\text{-}C_6$alkenyl, respectively. Exemplary alkenyl groups include vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl, and the like.

[0023] The term "alkynyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond, such as a straight or branched group of 2-12, 2-10, or 2-6 carbon atoms, referred to herein as C2-Ci2alkynyl, C2-Cioalkynyl, and C2-Cealkynyl, respectively. Exemplary alkynyl groups include ethynyl, prop-l-yn-l-yl, and but-1-yn-l-yl.

[0024] The term "cycloalkyl" refers to a monovalent saturated cyclic, bicyclic, bridged cyclic (e.g., adamantyl), or spirocyclic hydrocarbon group of 3-12, 3-8, 4-8, or 4-6 carbons, referred to herein, e.g., as "C_{4-8}cycloalkyl," derived from a cycloalkane. Exemplary cycloalkyl groups include, but are not limited to, cyclohexanes, cyclopentanes, cyclobutanes and cyclopropanes. Unless specified otherwise, cycloalkyl groups are optionally substituted at one or more ring positions with, for example, alkanoyl, alkoxy, alkyl, haloalkyl, alkenyl, alkynyl, amido, amidino, amino, aryl, arylalkyl, azido, carbamate, carbonate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, imino, ketone, nitro, phosphate, phosphonato, phosphinato, sulfate, sulfide, sulfonamido, sulfonyl or thiocarbonyl. In certain embodiments, the cycloalkyl group is not substituted, i.e., it is unsubstituted.

[0025] The term "cycloalkylene" refers to a diradical of an cycloalkyl group. An exemplary cycloalkylene group is  .

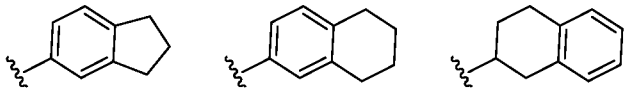
[0026] The term "cycloalkenyl" as used herein refers to a monovalent unsaturated cyclic, bicyclic, or bridged cyclic (e.g., adamantyl) hydrocarbon group of 3-12, 3-8, 4-8, or 4-6 carbons containing one carbon-carbon double bond, referred to herein, e.g., as "C4-gcycloalkenyl," derived from a cycloalkane. Exemplary cycloalkenyl groups include, but are not limited to, cyclohexenes, cyclopentenes, and cyclobutenes. Unless specified otherwise, cycloalkenyl groups are optionally substituted at one or more ring positions with, for example, alkanoyl, alkoxy, alkyl, alkenyl, alkynyl, amido, amidino, amino, aryl, arylalkyl, azido, carbamate, carbonate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, imino, ketone, nitro, phosphate, phosphonato, phosphinato, sulfate, sulfide, sulfonamido, sulfonyl or thiocarbonyl. In certain embodiments, the cycloalkenyl group is not substituted, i.e., it is unsubstituted.

[0027] The term "aryl" is art-recognized and refers to a carbocyclic aromatic group. Representative aryl groups include phenyl, naphthyl, anthracenyl, and the like. The term "aryl" includes polycyclic ring systems having two or more carbocyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic and, e.g., the other ring(s) may be cycloalkyls, cycloalkenyls, cycloalkynyls, and/or aryls. Unless specified otherwise, the aromatic ring may be substituted at one or more ring positions with, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, carboxylic acid, -C(0)alkyl, -CC^alkyl, carbonyl, carboxyl, alkylthio, sulfonyl, sulfonamido, sulfonamide, ketone, aldehyde, ester, heterocyclyl, aryl or heteroaryl moieties, $-CF_3$, -CN, or the like. In certain embodiments, the aromatic ring is substituted at one or more ring positions with halogen, alkyl, hydroxyl, or alkoxyl. In certain other embodiments, the aromatic ring is not substituted, i.e., it is unsubstituted. In certain embodiments, the aryl group is a 6-10 membered ring structure.

[0028] The term "aralkyl" refers to an alkyl group substituted with an aryl group.

[0029] The term "bicyclic carbocyclyl that is partially unsaturated" refers to a bicyclic carbocyclic group containing at least one double bond between ring atoms and at least one ring

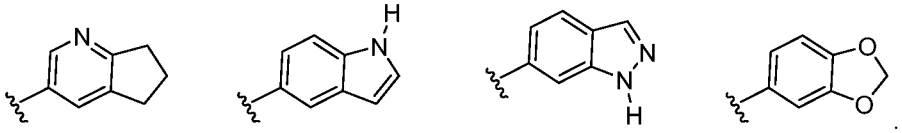
in the bicyclic carbocyclic group is not aromatic. Representative examples of a bicyclic carbocyclyl that is partially unsaturated include, for example:



[0030] The terms ortho, meta and para are art-recognized and refer to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and ortho-dimethylbenzene are synonymous.

[0031] The terms "heterocyclyl" and "heterocyclic group" are art-recognized and refer to saturated, partially unsaturated, or aromatic 3- to 10-membered ring structures, alternatively 3- to 7-membered rings, whose ring structures include one to four heteroatoms, such as nitrogen, oxygen, and sulfur. The number of ring atoms in the heterocyclyl group can be specified using C_x-C_x nomenclature where x is an integer specifying the number of ring atoms. For example, a $_{C\ 3}$-Cvheterocyclyl group refers to a saturated or partially unsaturated 3- to 7-membered ring structure containing one to four heteroatoms, such as nitrogen, oxygen, and sulfur. The designation "C3-C7" indicates that the heterocyclic ring contains a total of from 3 to 7 ring atoms, inclusive of any heteroatoms that occupy a ring atom position. One example of a Csheterocyclyl is aziridinyl. Heterocycles may be, for example, mono-, bi-, or other multi-cyclic ring systems. A heterocycle may be fused to one or more aryl, partially unsaturated, or saturated rings. Heterocyclyl groups include, for example, biotinyl, chromenyl, dihydrofuryl, dihydroindolyl, dihydropyranyl, dihydrothienyl, dithiazolyl, homopiperidinyl, imidazolidinyl, isoquinolyl, isothiazolidinyl, isooxazolidinyl, morpholinyl, oxolanyl, oxazolidinyl, phenoxanthenyl, piperazinyl, piperidinyl, pyranyl, pyrazolidinyl, pyrazolinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolidin-2-onyl, pyrrolinyl, tetrahydrofuryl, tetrahydroisoquinolyl, tetrahydropyranyl, tetrahydroquinolyl, thiazolidinyl, thiolanyl, thiomorpholinyl, thiopyranyl, xanthenyl, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. Unless specified otherwise, the heterocyclic ring is optionally substituted at one or more positions with substituents such as alkanoyl, alkoxy, alkyl, alkenyl, alkynyl, amido, amidino, amino, aryl, arylalkyl, azido, carbamate, carbonate, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, imino, ketone, nitro, oxo, phosphate, phosphonato, phosphinato, sulfate, sulfide, sulfonamido, sulfonyl and thiocarbonyl. In certain embodiments, the heterocyclyl group is not substituted, i.e., it is unsubstituted.

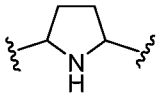
[0032] The term "tricyclic heterocyclyl" refers to a heterocyclyl group that contains two rings that are fused together. Representative examples of a bicyclic heterocyclyl include, for example:



In certain embodiments, the bicyclic heterocyclyl is an carbocyclic ring fused to partially unsaturated heterocyclic ring, that together form a bicyclic ring structure having 8-10 ring atoms (e.g., where there are 1, 2, 3, or 4 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur).

[0033] The term "oxoheterocyclyl" refers to a heterocyclyl group that is substituted with at least one oxo group (i.e., **=0).** In certain embodimetns, the oxoheterocyclyl is substituted with 1 or 2 oxo groups. In certain embodimetns, the oxoheterocyclyl is a 5-6 membered saturated heterocyclyl substituted with 1 or 2 oxo groups.

[0034] The term "heterocycloalkyl" is art-recognized and refers to a saturated heterocyclyl group as defined above. In certain embodiments, the "heterocycloalkyl" is a 3- to 10-membered ring structures, alternatively a 3- to 7-membered rings, whose ring structures include one to four heteroatoms, such as nitrogen, oxygen, and sulfur.

[0035] The term "heterocycloalkylene" refers to a diradical of a heterocycloalkyl group. An exemplary heterocycloalkylene group is  . The heterocycloalkylene may contain, for example, 3-6 ring atom (i.e., a 3-6 membered heterocycloalkylene). In certain embodiments, the heterocycloalkylene is a 3-6 membered heterocycloalkylene containing 1, 2, or 3 three heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur.

[0036] The term "heteroaryl" is art-recognized and refers to aromatic groups that include at least one ring heteroatom. In certain instances, a heteroaryl group contains 1, 2, 3, or 4 ring heteroatoms. Representative examples of heteroaryl groups include pyrrolyl, furanyl, thiophenyl, imidazolyl, oxazolyl, thiazolyl, triazolyl, pyrazolyl, pyridinyl, pyrazinyl, pyridazinyl and pyrimidinyl, and the like. Unless specified otherwise, the heteroaryl ring may be substituted at one or more ring positions with, for example, halogen, azide, alkyl, aralkyl,

alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, carboxylic acid, -C(0)alkyl, -C02alkyl, carbonyl, carboxyl, alkylthio, sulfonyl, sulfonamido, sulfonamide, ketone, aldehyde, ester, heterocyclyl, aryl or heteroaryl moieties, $-CF_3$, -CN, or the like. The term "heteroaryl" also includes polycyclic ring systems having two or more rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is heteroaromatic, e.g., the other cyclic rings may be cycloalkyls, cycloalkenyls, cycloalkynyls, and/or aryls. In certain embodiments, the heteroaryl ring is substituted at one or more ring positions with halogen, alkyl, hydroxyl, or alkoxyl. In certain other embodiments, the heteroaryl ring is not substituted, i.e., it is unsubstituted. In certain embodiments, the heteroaryl group is a 5- to 10-membered ring structure, alternatively a 5- to 6-membered ring structure, whose ring structure includes 1, 2, 3, or 4 heteroatoms, such as nitrogen, oxygen, and sulfur.

[0037] The term "heteroaralkyl" refers to an alkyl group substituted with a heteroaryl group.

[0038] The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines, e.g., a moiety represented by the general formula $-N(R^{50})(R^{51})$, wherein R^{50} and R^{51} each independently represent hydrogen, alkyl, cycloalkyl, heterocyclyl, alkenyl, aryl, aralkyl, or $-(CH_2)_m-R^{61}$; or R^{50} and R^{51}, taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R^{61} represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle or a polycycle; and m is zero or an integer in the range of 1 to 8. In certain embodiments, R^{50} and R^{51} each independently represent hydrogen, alkyl, alkenyl, or $-(CH_2)_m-R^{61}$.

[0039] The terms "alkoxyl" or "alkoxy" are art-recognized and refer to an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxyl, such as may be represented by one of -O-alkyl, -O-alkenyl, -O-alkynyl, $-0-(CH_2)_m$-R6i, where m and R6i are described above. The term "haloalkoxyl" refers to an alkoxyl group that is substituted with at least one halogen. For example, $-0-CH_2F$, $-0-CHF_2$, $-O-CF_3$, and the like. In certain embodimetns, the haloalkoxyl is an alkoxyl group

that is substituted with at least one fluoro group. In certain embodimetns, the haloalkoxyl is an alkoxyl group that is substituted with from 1-6, 1-5, 1-4, 2-4, or 3 fluoro groups.

[0040] The term "carbamate" as used herein refers to a radical of the form **-RgOC(0)N(¾)-, -RgOC(0)N(Rh)Ri_,** or **-OC(0)NRhRi,** wherein $\mathbf{R_g}$, $\mathbf{R_h}$ and R_i are each independently alkoxy, aryloxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carboxy, cyano, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, nitro, sulfide, sulfonyl, or sulfonamide. Exemplary carbamates include arylcarbamates and heteroaryl carbamates, e.g., wherein at least one of $\mathbf{Rg}$, $\mathbf{R_h}$ and R_i are independently aryl or heteroaryl, such as phenyl and pyridinyl.

[0041] The term "carbonyl" as used herein refers to the radical -C(O)-.

[0042] The term "carboxamido" as used herein refers to the radical **-C(0)NRR',** where **R** and **R'** may be the same or different. **R** and **R'** may be independently alkyl, aryl, arylalkyl, cycloalkyl, formyl, haloalkyl, heteroaryl, or heterocyclyl.

[0043] The term "carboxy" as used herein refers to the radical -COOH or its corresponding salts, e.g. -COONa, etc.

[0044] The term "amide" or "amido" as used herein refers to a radical of the form **-$\mathbf{R_a}$C(0)N(Rb)-, -$\mathbf{R_a}$C(0)N(Rb)$\mathbf{R_c}$-, -C(0)NR $_b\mathbf{R_c}$,** or -C**(0**)NH_2, wherein $\mathbf{R_a}$, $\mathbf{R_b}$ and $\mathbf{R_c}$ are each independently alkoxy, alkyl, alkenyl, alkynyl, amide, amino, aryl, arylalkyl, carbamate, cycloalkyl, ester, ether, formyl, halogen, haloalkyl, heteroaryl, heterocyclyl, hydrogen, hydroxyl, ketone, or nitro. The amide can be attached to another group through the carbon, the nitrogen, $\mathbf{R_b}$, $\mathbf{R_c}$, or $\mathbf{R_a}$. The amide also may be cyclic, for example $\mathbf{R_b}$ and $\mathbf{R_c}$, $\mathbf{R_a}$ and $\mathbf{R_b}$, or $\mathbf{R_a}$ and $\mathbf{R_c}$ may be joined to form a 3- to 12-membered ring, such as a 3- to 10-membered ring or a 5- to 6-membered ring.

[0045] The term "amidino" as used herein refers to a radical of the form **-C(=NR)NR'R''** where **R, R',** and **R"** are each independently alkyl, alkenyl, alkynyl, amide, aryl, arylalkyl, cyano, cycloalkyl, haloalkyl, heteroaryl, heterocyclyl, hydroxyl, ketone, or nitro.

[0046] The term "alkanoyl" as used herein refers to a radical -O-CO-alkyl.

[0047] The term "oxo" is art-recognized and refers to a **"=0"** substituent. For example, a cyclopentane susbsituted with an oxo group is cyclopentanone.

[0048] The term "sulfonamide" or "sulfonamido" as used herein refers to a radical having the structure $-N(R_r)-S(0)2-R_s-$ or $-S(0)2-N(R_r)R_s$, where R_r, and R_s can be, for example, hydrogen, alkyl, aryl, cycloalkyl, and heterocyclyl. Exemplary sulfonamides include alkylsulfonamides (e.g., where R_s is alkyl), arylsulfonamides (e.g., where R_s is aryl), cycloalkyl sulfonamides (e.g., where R_s is cycloalkyl), and heterocyclyl sulfonamides (e.g., where R_s is heterocyclyl), etc.

[0049] The term "sulfonyl" as used herein refers to a radical having the structure $R_USC>2-$, where R_u can be alkyl, aryl, cycloalkyl, and heterocyclyl, e.g., alkylsulfonyl. The term "alkylsulfonyl" as used herein refers to an alkyl group attached to a sulfonyl group.

[0050] The symbol "〰" indicates a point of attachment.

[0051] The compounds of the disclosure may contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as geometric isomers, enantiomers or diastereomers. The term "stereoisomers" when used herein consist of all geometric isomers, enantiomers or diastereomers. These compounds may be designated by the symbols "R" or "S," depending on the configuration of substituents around the stereogenic carbon atom. The present invention encompasses various stereoisomers of these compounds and mixtures thereof. Stereoisomers include enantiomers and diastereomers. Mixtures of enantiomers or diastereomers may be designated "(±)" in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly. It is understood that graphical depictions of chemical structures, e.g., generic chemical structures, encompass all stereoisomeric forms of the specified compounds, unless indicated otherwise.

[0052] Individual stereoisomers of compounds of the present invention can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, or (3) direct separation of the mixture of optical enantiomers on chiral chromatographic columns. Stereoisomeric mixtures can also be resolved into their component stereoisomers by well-

known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Further, enantiomers can be separated using supercritical fluid chromatographic (SFC) techniques described in the literature. Still further, stereoisomers can be obtained from stereomerically-pure intermediates, reagents, and catalysts by well-known asymmetric synthetic methods.

[0053] Geometric isomers can also exist in the compounds of the present invention. The symbol ⎓ denotes a bond that may be a single, double or triple bond as described herein. The present invention encompasses the various geometric isomers and mixtures thereof resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a carbocyclic ring. Substituents around a carbon-carbon double bond are designated as being in the "Z" or "*E*" configuration wherein the terms "Z" and "*E*" are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the *"E"* and "Z" isomers.

[0054] Substituents around a carbon-carbon double bond alternatively can be referred to as "cis" or "trans," where "cis" represents substituents on the same side of the double bond and "trans" represents substituents on opposite sides of the double bond. The arrangement of substituents around a carbocyclic ring are designated as "cis" or "trans." The term "cis" represents substituents on the same side of the plane of the ring and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated "cis/trans."

[0055] The invention also embraces isotopically labeled compounds of the invention which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, $^{18}0$, $^{17}0$, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and $^{36}C1$, respectively.

[0056] Certain isotopically-labeled disclosed compounds *(e.g.,* those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated *(i.e.,* ^{3}H) and carbon-14 *(i.e.,* ^{14}C) isotopes are particularly preferred for their ease of preparation and

detectability. Further, substitution with heavier isotopes such as deuterium *(i.e.,* ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability *(e.g.,* increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the invention can generally be prepared by following procedures analogous to those disclosed in, e.g., the Examples herein by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[0057] As used herein, the terms "subject" and "patient" refer to organisms to be treated by the methods of the present invention. Such organisms are preferably mammals *(e.g.,* murines, simians, equines, bovines, porcines, canines, felines, and the like), and more preferably humans.

[0058] As used herein, the term "effective amount" refers to the amount of a compound *(e.g.,* a compound of the present invention) sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route. As used herein, the term "treating" includes any effect, *e.g.,* lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof.

[0059] As used herein, the term "pharmaceutical composition" refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo* or *ex vivo.*

[0060] As used herein, the term "pharmaceutically acceptable carrier" refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions *(e.g.,* such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, see Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, PA [1975].

[0061] As used herein, the term "pharmaceutically acceptable salt" refers to any pharmaceutically acceptable salt *(e.g.,* acid or base) of a compound of the present invention which, upon administration to a subject, is capable of providing a compound of this invention or an active metabolite or residue thereof. As is known to those of skill in the art, "salts" of the compounds of the present invention may be derived from inorganic or organic acids and bases.

Examples of acids include, but are not limited to, hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, benzenesulfonic acid, and the like. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

[0062] Examples of bases include, but are not limited to, alkali metal (e.g., sodium) hydroxides, alkaline earth metal (e.g., magnesium) hydroxides, ammonia, and compounds of formula NW_4^+, wherein W is C_{1-4} alkyl, and the like.

[0063] Examples of salts include, but are not limited to: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, flucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, undecanoate, and the like. Other examples of salts include anions of the compounds of the present invention compounded with a suitable cation such as Na^+, NH_4^+, and NW_4^+ (wherein W is a C_{1-4} alkyl group), and the like.

[0064] For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

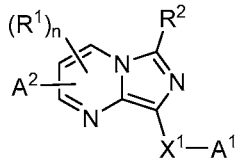
[0065] Abbreviations as used herein include 0-(7-azabenzotriazol-l-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HATU); diisopropylethylamine (DIPEA); dimethylformamide (DMF); methylene chloride (DCM); tert-butoxycarbonyl (Boc); tetrahydrofuran (THF); trifluoroacetic acid (TFA); N-methylmorpholine (NMM); triethylamine (TEA); Boc anhydride ($(Boc)_20$); dimethylsulfoxide (DMSO); diisopropylethylamine (DIEA); flash column chromatography (FCC); and supercritical fluid chromatography (SFC).

[0066] Throughout the description, where compositions and kits are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions and kits of the present invention that consist essentially of, or consist of, the recited components, and that there are processes and methods according to the present invention that consist essentially of, or consist of, the recited processing steps.

[0067] As a general matter, compositions specifying a percentage are by weight unless otherwise specified. Further, if a variable is not accompanied by a definition, then the previous definition of the variable controls.

II. SUBSTITUTED lMiDAzo[l,5-a]PYRiMiDiNYL CARBOXAMIDE AND RELATED ORGANIC COMPOUNDS

[0068] One aspect of the invention provides substituted imidazo[l,5-a]pyrimidinyl carboxamide and related organic compounds. The substituted imidazo[l,5-a]pyrimidinyl carboxamide and related organic compounds are contemplated to be useful in the methods, compositions, and kits described herein. In certain embodiments, the substituted imidazo[l,5-a]pyrimidinyl carboxamide or related organic compound is a compound embraced by Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxy alkyl, C_{1-4} cyanoalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, cyclopropyl, cyano, halogen, hydroxyl, $-N(R^4)_2$, -0-(C_{1-4} alkylene)-C_{1-6} alkoxyl, or -(Ci_4alkylene)-(2 -6 membered heteroalkyl optionally substituted by one or more halogen);

R^3 represents independently for each occurrence hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl;

R^4 represents independently for each occurrence hydrogen, C_{1-4} alkyl, cyclopropyl, or $-C(0)R^3$;

R^5 represents independently for each occurrence C_{1-4} alkyl or C_{3-6} cycloalkyl;

R^6 represents independently for each occurrence C_{1-4} alkyl, Ci^ haloalkyl, C1-4 alkoxyl, cyano, halogen, hydroxyl, or $-N(R^4)_2$;

X^1 is a carbonyl-containing linker selected from -C(O)N(H)-ψ, -C(O)N(H)(Ci_6 alkylene optionally substituted with C_{1-4} alkoxyl or C_{3-6} cycloalkyl)-ψ, -C(0)N(H)(Ci_6 haloalkylene)-ψ, -C(O)N(H)(C_{3-6} cycloalkylene)-ψ, -C(0)N(H)(3-6 membered heterocycloalkylene)-ψ, -C(0)-(3-6 membered heterocycloalkylene containing at least one ring -N(H)- group)-ψ, -C(O)N(H)C(O)-ψ, and -C(0)N(H)C(0)(Ci_6 alkylene)-ψ; where ψ is a bond to A^1;

A^1 is one of the following:

- a cyclic group selected from a 3-14 membered saturated carbocyclyl, a 5-14 membered partially unsaturated carbocyclyl, a 3-16 membered heterocyclyl, or phenyl; each of which is substituted by 0, 1, or 2 occurrences of Y^1 and 0, 1, 2, or 3 occurrences of Y^2; or
- Ci-8 alkyl or *C2-6* alkynyl;

A^2 is one of the following:

- a cyclic group selected from a 3-12 membered heterocyclyl, 4-12 membered oxoheterocyclyl, 4-10 membered cycloalkyl, or phenyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, cyano, C_{1-4} alkyl, Ci^ haloalkyl, C_{1-4} alkoxyl, Ci^ haloalkoxyl, C_{3-6} cycloalkyl, -0-(C_{3-6} cycloalkyl), -0-(Ci_6 alkylene)-Ci-6 alkoxyl, -(Ci_6 alkylene)-CN, $-N(R^4)_2$, $-C(0)N(R^4)_2$, and heteroaryl;
- $-N(R^4)$(3-10 membered heterocyclyl, C_{3-10} cycloalkyl, or phenyl, each optionally substituted by 1, 2, or 3 R^6 groups) or -0(3-10 membered heterocyclyl, C_{3-10} cycloalkyl, or phenyl, each optionally substituted by 1, 2, or 3 R^6 groups); or
- $-C(0)N(R^4)$(aryl or heteroaryl);

Y^1 represents, independently for each occurrence, one of the following:

- 2-8 membered heteroalkyl optionally substituted by a 6-10 membered aryl, a 3-10 membered heterocyclyl, or C_{3-6} halocycloalkyl;

- 3-10 membered heterocyclyl, 6-10 membered aryl, C3-7 cycloalkyl, -O-C3-6 cycloalkyl, -0-(3-6 membered heterocyclyl), -O-(6-10 membered aryl), or -O-(C_{2-6} alkynyl); or
- C2-6 alkynyl, -C≡C-(Ci-6 alkylene)-OR 4, -C≡C-(Ci-6 alkylene)-N(R 3)2, -(C2-4 alkynylene)-(5-6 membered heteroaryl), or C2-6 alkenyl;

Y^2 represents, independently for each occurrence, Ci-6 alkyl, C 3-6 cycloalkyl, halogen, Ci-6 haloalkyl, C1-6 hydroxy alkyl, hydroxyl, Ci-6 alkoxyl, -0-(Ci-8 haloalkyl), cyano, azido, -N(R^3)2, -(Ci-6 alkylene)-(5-6 membered heterocyclyl), -(Ci-6 alkylene)-C0 2R3, -CO2R3, -C(0)R^5, -S(0)2R^5, -C(0)N(R^5)2, -C(0)N(R^3)2, or Ci-6 haloalkyl-substituted C 3-6 cycloalkyl; and

n is 1, 2, or 3;

wherein R^1 is other than hydrogen, when X^A 1 is -C(0)N(H)-(5-6 membered heteroaryl containing at least 1 nitrogen atom, wherein the heteroaryl is substituted by 0, 1, or 2 occurrences of Y^1 and 0, 1, 2, or 3 occurrences of Y^2).

[0069] Definitions of the variables in Formula I above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii), ***e.g.***, such as where X^1 is -C(O)N(H)-ψ, R^1 and R^2 each represent independently for each occurrence hydrogen or C1-4 alkyl, and A^2 is a 4-12 membered heterocyclyl.

[0070] Accordingly, in certain embodiments, X^1 is -C(O)N(H)-ψ. In certain embodiments, X^1 is -C(0)N(H)(Ci-6 alkylene)-ψ. In certain embodiments, X^1 is -C(0)N(H)(C(CH_3)2)-ψ or -C(0)N(H)(C(H)(CH_3))-ψ. In certain embodiments, X^1 is -C(0)N(H)(Ci-6 alkylene substituted with C1-4 alkoxyl)-ψ. In certain embodiments, X^1 is -C(0)N(H)(Ci-6 alkylene substituted with C 3-6 cycloalkyl)-ψ. In certain embodiments, X^1 is -C(0)N(H)(Ci-6 haloalkylene)-ψ. In certain embodiments, X^1 is -C(O)N(H)C(H)(CF_3)-ψ. In certain embodiments, X^1 is -C(0)N(H)(C 3-6 cycloalkylene)-ψ. In certain embodiments, X^1 is -C(0)N(H)(3-6 membered heterocycloalkylene)-\|/.

[0071] In certain embodiments, A^2 is a 5-12 membered heterocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, halogen, hydroxyl, and $-N(R^4)_2$. In certain embodiments, A^2 is a 5-6 membered heteroaryl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, halogen, hydroxyl, and $-N(R^4)_2$. In certain embodiments, A^2 is a 5-6 membered heteroaryl selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, furanyl, pyrrolyl, thiophenyl, imidazolyl, oxazolyl, isoxazolyl, isothiazolyl, and thiazolyl, each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, halogen, hydroxyl, and $-N(R^4)_2$. In certain embodiments, A^2 is a 5-6 membered heteroaryl selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, furanyl, pyrrolyl, thiophenyl, oxazolyl, isoxazolyl, and thiazolyl, each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, halogen, hydroxyl, and $-N(R^4)_2$. In certain embodiments, A^2 is pyridinyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, halogen, hydroxyl, and $-N(R^4)_2$. In certain embodiments, A^2 is 3-pyridinyl optionally substituted by 1 or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, and halogen.

[0072] In certain embodiments, A^2 is a 5-6 membered heterocycloalkyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, halogen, hydroxyl, and $-N(R^4)_2$. In certain embodiments, A^2 is a 5-6 membered heterocycloalkyl selected from the group consisting of morpholinyl, piperidinyl, pyrrolidinyl, tetrahydropyranyl, and tetrahydrofuranyl, each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, halogen, hydroxyl, and $-N(R^4)_2$.

[0073] In certain embodiments, A^2 is a 5-10 membered cycloalkyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, halogen, hydroxyl, and $-N(R^4)_2$. In certain embodiments, A^2 is a 5-6 membered cycloalkyl optionally substituted by 1, 2, or 3 substituents

independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, halogen, hydroxyl, and $-N(R^4)_2$.

[0074] In certain embodiments, A^2 is phenyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, halogen, hydroxyl, and $-N(R^4)_2$. In certain embodiments, A^2 is phenyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, and halogen. In certain embodiments, A^2 is phenyl substituted by 1 or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, and halogen.

[0075] In certain embodiments, A^2 is $-N(R^4)$(3-10 membered heterocyclyl, C_{3-10} cycloalkyl, or phenyl, each optionally substituted by 1, 2, or 3 R^6 groups) or **-0** (3-10 membered heterocyclyl, C_{3-10} cycloalkyl, or phenyl, each optionally substituted by 1, 2, or 3 R^6 groups). In certain embodiments, A^2 is $-N(R^4)$(3-10 membered heterocycloalkyl or C_{3-10} cycloalkyl, each optionally substituted by 1, 2, or 3 R^6 groups) or **-0** (3-10 membered heterocycloalkyl or C_{3-10} cycloalkyl, each optionally substituted by 1, 2, or 3 R^6 groups). In certain embodiments, A^2 is $-N(R^4)$(tetrahydropyranyl, morpholinyl, or piperidinyl, each optionally substituted by 1, 2, or 3 R^6), $-N(R^4)$(C4-6 cycloalkyl optionally substituted by 1, 2, or 3 R^6), -0-(tetrahydropyranyl, morpholinyl, or piperidinyl, each optionally substituted by 1, 2, or 3 R^6), or -0-(C_{4-6} cycloalkyl optionally substituted by 1, 2, or 3 R^6).

[0076] In certain embodiments, A^2 is located at the 2-position of the imidazo[l,5-a]pyrimidinyl. In certain embodiments, n is 1. In certain embodiments, A^2 is located at the 2-position of the imidazo[l,5-a]pyrimidinyl, n is 1, and the R^1 group is located at the 4-position of the imidazo[l,5-a]pyrimidinyl.

[0077] In certain embodiments, A^2 is located at the 4-position of the imidazo[l,5-a]pyrimidinyl. In certain embodiments, n is 1. In certain embodiments, A^2 is located at the 4-position of the imidazo[l,5-a]pyrimidinyl, n is 1, and R^1 group is located at the 2-position of the imidazo[l,5-a]pyrimidinyl.

[0078] In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{1-4} alkylene)-(2-6 membered heteroalkyl), cyclopropyl, halogen, or $-N(R^4)_2$. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4}

haloalkyl, C_{1-4} alkoxyl, cyclopropyl, cyano, chloro, or fluoro. In certain embodiments, R^1 is methyl.

[0079] In certain embodiments, R^2 is hydrogen. In certain embodiments, R^1 and R^2 each represent independently for each occurrence hydrogen or C_{1-4} alkyl.

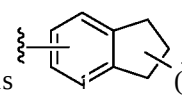
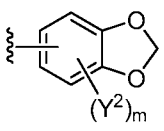
[0080] In certain embodiments, R^3 and R^4 each represent independently for each occurrence hydrogen, methyl, or ethyl.

[0081] In certain embodiments, A^1 is a 3-14 membered saturated carbocyclyl substituted by 0, 1, or 2 occurrences of Y^1 and 0, 1, 2, or 3 occurrences of Y^2. In certain embodiments, A^1 is C_{3-7} cycloalkyl substituted once by Y^1 and 0-1 occurrences of Y^2. In certain embodiments, A^1 is a 5-14 membered partially unsaturated carbocyclyl substituted by 0, 1, or 2 occurrences of Y^1 and 0, 1, 2, or 3 occurrences of Y^2. In certain embodiments, A^1 is a 8-12 membered bicyclic carbocyclyl that is partially unsaturated or a 8-12 membered bicyclic heterocyclyl, each of which is substituted by 0 or 1 occurrence of Y^1 and 0, 1, or 2 occurrences of Y^2. In certain embodiments, A^1 is phenyl substituted once by Y^1 and 0-1 occurrences of Y^2.

[0082] In certain embodiments, A^1 is a 5-6 membered heteroaryl substituted once by Y^1 and 0-1 occurrences of Y^2. In certain embodiments, A^1 is pyridinyl substituted once by Y^1 and 0-1 occurrences of Y^2.

[0083] In certain embodiments, A^1 is C_{3-7} cycloalkyl substituted by Ci-6 alkoxyl. In certain embodiments, A^1 is cyclohexyl substituted by Ci-6 alkoxyl. In certain embodiments, A^1 is C_{3-7} cycloalkyl that is not substituted. In certain embodiments, A^1 is C_{7-10} cycloalkyl that is spirocyclic and not substituted. In certain embodiments, A^1 is cyclopropyl.

[0084] In certain embodiments, A^1 is phenyl substituted by C_2 alkynyl.

[0085] In certain embodiments, A^1 is an 8-12 membered bicyclic carbocyclyl that is partially unsaturated or an 8-12 membered bicyclic heterocyclyl, each of which is substituted by 0 or 1 occurrence of Y^2 selected from the group consisting of Ci-6 alkyl, C_{3-6} cycloalkyl, halogen, Ci-6 haloalkyl, hydroxyl, and Ci-6 alkoxyl. In certain embodiments, A^1 is  or  ; wherein m is 0, 1, or 2; and Y^2 represents independently

for each occurrence C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkyl, hydroxyl, or C_{1-6} alkoxyl.

[0086] In certain embodiments, any occurrence of Y^2 is independently C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkyl, or hydroxyl. In certain embodiments, any occurrence of Y^2 is independently C_{1-3} alkyl. In certain embodiments, Y^2 is C_{1-6} haloalkyl-substituted C_{3-6} cycloalkyl.

[0087] In certain embodiments, Y^1 is a 2-8 membered heteroalkyl optionally substituted by a 6-10 membered aryl or a 3-10 membered heterocyclyl. In certain embodiments, Y^1 is a 2-8 membered heteroalkyl substituted by a 6-10 membered aryl or a 3-10 membered heterocyclyl. In certain embodiments, Y^1 is a 2-8 membered heteroalkyl substituted by a 3-10 membered heterocyclyl. In certain embodiments, Y^1 is a 2-8 membered heteroalkyl substituted by a 5-6 membered heteroaryl, such as pyrrolyl, furanyl, or pyridinyl. In certain embodiments, Y^1 is a 2-8 membered heteroalkyl.

[0088] In certain embodiments, Y^1 is **-0** -(C_{1-7} alkyl). In certain embodiments, Y^1 is -O-butyl, -O-pentyl, or -O-hexyl. In certain embodiments, Y^1 is -(C_{1-3} alkylene)**-0** -(5-6 membered heteroaryl). In certain embodiments, Y^1 is -CH_2**-0** -(5-6 membered heteroaryl). In certain embodiments, Y^1 is -CH_2**-0** -(5-6 membered heteroaryl), wherein the 5-6 membered heteroaryl is furanyl, pyrrolyl, thiophenyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, isooxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, imidazolinyl, oxazolinyl, pyrazolinyl, thiazolinyl, or triazolinyl, each of which is substituted by one or two substituents independently selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, C^haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, C_{1-6} alkoxyl, cyano, -$N(R^4)_2$, amide, and **-C0 $_2$H**.

[0089] In certain embodiments, Y^1 is a 3-10 membered heterocyclyl, 6-10 membered aryl, C_{3-7} cycloalkyl, **-0** -(3-6 membered heterocyclyl), **-0** (6-10 membered aryl), or **-0-(C2 -6** alkynyl). In certain embodiments, Y^1 is a 3-10 membered heterocyclyl selected from the group consisting of a 5-6 membered heteroaryl and a 5-6 membered heterocycloalkyl. In certain embodiments, Y^1 is 5-membered heteroaryl. In certain embodiments, Y^1 is a 5-membered heteroaryl substituted by one or two substituents independently selected from the group consisting of C_{1-6} alkyl, C_{3-7} cycloalkyl, halogen, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, C_{1-6} alkoxyl, cyano, -$N(R^4)_2$, amide, and **-CO2H.** In certain embodiments, Y^1 is a 5-membered

heteroaryl substituted by one or two substituents independently selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, Ci-6 haloalkyl, hydroxyl, and C_{1-6} alkoxyl.

[0090] In certain embodiments, Y^1 is furanyl, pyrrolyl, thiophenyl, imidazolyl, pyrazolyl, oxazolyl, or thiazolyl. In certain embodiments, Y^1 is furanyl, pyrrolyl, thiophenyl, imidazolyl, pyrazolyl, oxazolyl, or thiazolyl, each of which is substituted by one or two substituents independently selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkyl, Ci-6 hydroxyalkyl, hydroxyl, C_{1-6} alkoxyl, cyano, $-N(R^4)_2$, amide, and -CO2H.

[0091] In certain embodiments, Y^1 is pyridinyl, pyrimidinyl, pyrazinyl, isooxazolyl, isothiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, imidazolinyl, oxazolinyl, pyrazolinyl, thiazolinyl, or triazolinyl. In certain embodiments, Y^1 is pyridinyl, pyrimidinyl, pyrazinyl, isooxazolyl, isothiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, imidazolinyl, oxazolinyl, pyrazolinyl, thiazolinyl, or triazolinyl, each of which is substituted by one or two substituents independently selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkyl, Ci-6 hydroxyalkyl, hydroxyl, C_{1-6} alkoxyl, cyano, $-N(R^4)_2$, amide, and -CO2H.

[0092] In certain embodiments, Y^1 is C_{2-6} alkynyl, - C≡C-(Ci_6 alkylene)-OR 4, - C≡C-(Ci_6 alkylene)-N(R 3)2, -(C2-4 alkynylene)-(5-6 membered heteroaryl), or *C2-6* alkenyl. In certain embodiments, Y^1 is *C2-6* alkynyl. In certain embodiments, Y^1 is -C≡CH. In certain embodiments, Y^1 is -C≡C-(Ci_6 alkylene)-OR 4. In certain embodiments, Y^1 is -C≡C-(Ci_6 alky lene **)-0** -(C_{1-2} alkyl). In certain embodiments, Y^1 is -C≡C-CH_2-**0** -CH_3.

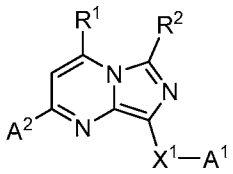
[0093] In certain embodiments, Y^1 is **-0** -(Ci_7 alkyl). In certain embodiments, Y^1 is -O-butyl, -O-pentyl, or -O-hexyl. In certain embodiments, Y^1 is *C2-6* alkynyl, - C≡C-(Ci_6 alkylene)-OR 4, - C≡C-(Ci_6 alkylene)-N(R 3)2, -(C_{2-4} alkynylene)-(5-6 membered heteroaryl), or *C2-6* alkenyl. In certain embodiments, Y^1 is -C≡CH. In certain embodiments, Y^1 is -C≡C-(Ci_6 alkylene)-OR 4. In certain embodiments, Y^1 is -C≡C-CH_2-**0** -CH_3. In certain embodiments, Y^1 is *C2-6* alkynyl.

[0094] In certain embodiments, Y^1 is a 2-8 membered heteroalkyl optionally substituted by a 6-10 membered aryl or a 3-10 membered heterocyclyl. In certain embodiments, Y^1 is -(C_{1-3} alkylene **)-0** -(5-6 membered heteroaryl). In certain embodiments, Y^1 is a 3-10 membered heterocyclyl, 6-10 membered aryl, C_{3-7} cycloalkyl, **-0** -(3-6 membered heterocyclyl), **-0** (6-10 membered aryl), or **-0** -(C_{2-6} alkynyl). In certain embodiments, Y^1 is a 3-10 membered heterocyclyl selected from the group consisting of a 5-6 membered heteroaryl and a 5-6

membered heterocycloalkyl. In certain embodiments, Y^1 is 5-membered heteroaryl. In certain embodiments, Y^1 is furanyl, pyrrolyl, thiophenyl, imidazolyl, pyrazolyl, oxazolyl, or thiazolyl.

[0095] The description above describes multiple embodiments relating to compounds of Formula I. The patent application specifically contemplates all combinations of the embodiments. For example, the invention contemplates a compound of Formula I wherein X^1 is -C(O)N(H)-ψ, R^1 and R^2 each represent independently for each occurrence hydrogen or C_{1-4} alkyl, and A^2 is a 5-12 membered heterocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, halogen, hydroxyl, and $-N(R^4)_2$.

[0096] In certain embodiments, the compound is a compound of Formula I-A:



(I-A)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is Ci-4 alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, -(C_{1-4} alkylene)-(C_{1-4} alkoxyl), cyclopropyl, chloro, or fluoro;

R^2 is hydrogen;

R^3 and R^4 each represent independently for each occurrence hydrogen or C_{1-4} alkyl;

X^1 is -C(**0**)N(H)(Ci-6 haloalkylene)-ψ or -C(**0**)N(H)(Ci$_{-6}$ alkylene)-v|/; where ψ is a bond to A^1;

A^1 is a cyclic group selected from:

- C_{3-10} cycloalkyl substituted by 0 or 1 occurrence of Y^1 and 0, 1, or 2 occurrences of Y^2; and
- phenyl substituted by 0 or 1 occurrence of Y^1 and 0, 1, or 2 occurrences of Y^2;

A^2 is phenyl or a 5-12 membered heterocyclyl, each optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, halogen, and hydroxyl;

Y^1 represents, independently for each occurrence, one of the following:

- 2-8 membered heteroalkyl or *-0-(C2-e* alkynyl); or
- C_{2-6} alkynyl or -C≡C-(Ci $_{-6}$ alkylene)-OR ^{4}; and

Y^2 represents, independently for each occurrence, Ci-6 alkyl, $_{C3-6}$ cycloalkyl, halogen, Ci-6 haloalkyl, Ci-6 hydroxyalkyl, hydroxyl, Ci-6 alkoxyl, cyano, or -$N(R^3)_2$.

[0097] Definitions of the variables in Formula I-A above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii), *e.g.* , such as where X^1 is -C(O)N(H)-ψ, R^1 is C1-4 alkyl or C1-4 haloalkyl, and A^2 is a 5-12 membered heterocyclyl.

[0098] Accordingly, in certain embodiments, R^1 represents independently for each occurrence methyl, halomethyl, -(CH $_2$)i-2-**0** -(Ci-3 alkyl), cyclopropyl, chloro, or fluoro. In certain embodiments, R^1 is C1-4 alkyl or C1-4 haloalkyl. In certain embodiments, R^1 is methyl.

[0099] In certain embodiments, A^1 is $_{C3-7}$ cycloalkyl substituted once by Y^1 and 0-1 occurrences of Y^2. In certain embodiments, A^1 is cyclohexyl substituted once by Y^1. In certain embodiments, A^1 is $_{C3-7}$ cycloalkyl that is not substituted. In certain embodiments, A^1 is $_{C\ 7\text{-}1_0}$ cycloalkyl that is spirocyclic and not substituted. In certain embodiments, A^1 is cyclopropyl.

[00100] In certain embodiments, A^1 is cyclohexyl or a 8-membered bicyclic cycloalkyl, each of which is substituted once by Y^1 and 0-1 occurrences of Y^2.

[00101] In certain embodiments, A^1 is phenyl substituted by 0 or 1 occurrence ofY^1 and 0, 1, or 2 occurrences of Y^2. In certain embodiments, A^1 is phenyl substituted by 1 occurrence of Y^1.

[00102] In certain embodiments, Y^2 is independently C1-3 alkyl, halogen, or C1-3 haloalkyl.

[00103] In certain embodiments, Y^1 is a 2-8 membered heteroalkyl. In certain embodiments, Y^1 is **-0** -(Ci-7 alkyl). In certain embodiments, Y^1 is -O-butyl, -O-pentyl, or -O-hexyl.

[00104] In certain embodiments, A^2 is a 5-12 membered heterocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C1-4 alkyl, C1-4 haloalkyl, C1-4 alkoxyl, $_{C3-5}$ cycloalkyl, cyano, halogen, and hydroxyl. In certain embodiments,

A^2 is a 5-6 membered heteroaryl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, halogen, and hydroxyl. In certain embodiments, A^2 is a 5-6 membered heteroaryl selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, furanyl, pyrrolyl, thiophenyl, imidazolyl, oxazolyl, isoxazolyl, isothiazolyl, and thiazolyl, each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C3-5 cycloalkyl, cyano, halogen, hydroxyl, and $-N(R^4)_2$. In certain embodiments, A^2 is a 5-6 membered heteroaryl selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, furanyl, pyrrolyl, thiophenyl, oxazolyl, isoxazolyl, and thiazolyl, each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C3-5 cycloalkyl, cyano, halogen, and hydroxyl. In certain embodiments, A^2 is pyridinyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C3-5 cycloalkyl, cyano, halogen, and hydroxyl. In certain embodiments, A^2 is 3-pyridinyl optionally substituted by 1 or 2 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C3-5 cycloalkyl, cyano, and halogen.

[00105] In certain embodiments, A^2 is phenyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C3-5 cycloalkyl, cyano, halogen, and hydroxyl. In certain embodiments, A^2 is phenyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C3-5 cycloalkyl, chloro, and fluoro. In certain embodiments, A^2 is phenyl substituted by 1 or 2 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C3-5 cycloalkyl, chloro, and fluoro.

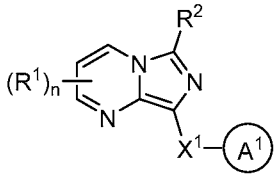
[00106] In certain embodiments, A^2 is a 5-6 membered heterocycloalkyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C3-5 cycloalkyl, cyano, halogen, and hydroxyl. In certain embodiments, A^2 is a 5-6 membered heterocycloalkyl selected from the group consisting of morpholinyl, piperidinyl, pyrrolidinyl, tetrahydropyranyl, and tetrahydrofuranyl, each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C3-5 cycloalkyl, cyano, halogen, and hydroxyl.

[00107] In certain embodiments, X^1 is -C(**0**)N(H)(Ci-6 haloalkylene)-ψ. In certain embodiments, X^1 is -C(O)N(H)C(H)(CF_3)-ψ. In certain embodiments, X^1 is -C(**0**)N(H)(Ci-6 alkylene)-ψ. In certain embodiments, X^1 is -C(**0**)N(H)(C(CH_3)$_2$)-ψ or -C(**0**)N(H)(C-(H)(**(**CH_3))-ψ.

[00108] In certain embodiments, R^1 is C 1-4 alkyl, X^1 is -C(**0**)N(H)(Ci-6 haloalkylene)-v|/; A^1 is C3-10 cycloalkyl; A^2 is phenyl substituted by 1, 2, or 3 substituents independently selected from the group consisting of C1-4 alkyl, C_{1-4} haloalkyl, and halogen.

[00109] The description above describes multiple embodiments relating to compounds of Formula I-A. The patent application specifically contemplates all combinations of the embodiments. For example, the invention contemplates a compound of Formula I-A wherein X^1 is X^1 is -C(O)N(H)C(H)(CF_3)-ψ, R^1 is C_{1-4} alkyl or C 1-4 haloalkyl, and A^2 is a 5-6 membered heteroaryl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C3-5 cycloalkyl, cyano, halogen, and hydroxyl.

[00110] In certain embodiments, the substituted imidazo[l,5-a]pyrimidinyl carboxamide or related organic compound is a compound embraced by Formula II:



(II)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} cyanoalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, cyclopropyl, cyano, halogen, hydroxyl, -N(R^4)2, **-0** -(C_{1-4} alkylene)-C_{1-6}alkoxyl, or -(Ci-4 alkylene)-(2-6 membered heteroalkyl optionally substituted by one or more halogen);

R^3 represents independently for each occurrence hydrogen, C_{1-6} alkyl, or C 3-6 cycloalkyl;

R^4 represents independently for each occurrence hydrogen, Ci-4 alkyl, cyclopropyl, or -C(0)R^3;

R^5 represents independently for each occurrence C_{1-4} alkyl or C_{3-6} cycloalkyl;

X^1 is a carbonyl-containing linker selected from -C(0)N(H)(C_{1-6} haloalkylene)-ψ, -C(0)N(H)(Ci-6 alkylene substituted with C_{1-4} alkoxyl or C_{3-6} cycloalkyl)-ψ, -C(0)N(H)(C_{3-6} cycloalkylene)-ψ, -C(0)N(H)(3-6 membered heterocycloalkylene)-ψ, -C(O)N(H)C(O)-ψ, and -C(0)N(H)C(0)(Ci-6 alkylene)-v|/; where ψ is a bond to A^1;

A^1 is one of the following:

- a cyclic group selected from a 3-14 membered saturated carbocyclyl, a 5-14 membered partially unsaturated carbocyclyl, a 3-16 membered heterocyclyl, or phenyl; each of which is substituted by 0, 1, or 2 occurrences ofY^1 and 0, 1, 2, or 3 occurrences of Y^2; or
- Ci-8 alkyl or C_{2-6} alkynyl;

Y^1 represents, independently for each occurrence, one of the following:

- 2-8 membered heteroalkyl optionally substituted by a 6-10 membered aryl, a 3-10 membered heterocyclyl, or C_{3-6} halocycloalkyl;
- 3-10 membered heterocyclyl, 6-10 membered aryl, C3-7 cycloalkyl, -O-C3-6 cycloalkyl, -0-(3-6 membered heterocyclyl), -0(6-10 membered aryl), or -O-(C_{2-6} alkynyl); or
- C_{2-6} alkynyl, -C≡C-(Ci-6 alkylene)-OR^4, -C≡C-(Ci-6 alkylene)-N(R^3)$_2$, -(C_{2-4} alkynylene)-(5-6 membered heteroaryl), or C_{2-6} alkenyl;

Y^2 represents, independently for each occurrence, Ci-6 alkyl, C_{3-6} cycloalkyl, halogen, Ci-6 haloalkyl, C_{1-6} hydroxy alkyl, hydroxyl, Ci-6 alkoxyl, -0-(Ci-8 haloalkyl), cyano, azido, -N(R^3)$_2$, -(Ci-6 alkylene)-(5-6 membered heterocyclyl), -(Ci-6 alkylene)-C0$_2$$R^3$, -C0$_2$$R^3$, -C(0)$R^5$, -S(0)$_2$$R^5$, -C(0)N($R^5$)$_2$, -C(0)N($R^3$)$_2$, or Ci-6 haloalkyl-substituted C_{3-6} cycloalkyl;

m is 1 or 2; and

n is 1, 2, or 3;

provided that when X^1 is C(0)N(H)(C_{3-6} cycloalkylene)-ψ or -C(0)N(H)(3-6 membered heterocycloalkylene)-ψ, then A^1 is not a 5-membered heterocyclyl.

[00111] Definitions of the variables in Formula II above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii), *e.g.,* such as where X^1 is -C(**0**)N(H)(Ci-6 haloalkylene)-ψ, R^1 and R^2 each represent independently for each occurrence hydrogen or C_{1-4} alkyl, and A^1 is a 3-14 membered saturated carbocyclyl.

[00112] Accordingly, in certain embodiments, X^1 is -C(**0**)N(H)(Ci-6 haloalkylene)-ψ. In certain embodiments, X^1 is -C(O)N(H)C(H)(CF_3)-ψ. In certain embodiments, X^1 is -C(**0**)N(H)(Ci-6 alkylene substituted with C_{1-4} alkoxyl)-ψ. In certain embodiments, X^1 is -C(O)N(H)C(H)(CH_2OCH_3)-ψ. In certain embodiments, X^1 is -C(**0**)N(H)(Ci_{-6} alkylene substituted with $_{C\ 3-6}$ cycloalkyl)-ψ. In certain embodiments, X^1 is -C(**0**)N(H)(C_{3-6} cycloalkylene)-ψ.

[00113] In certain embodiments, n is 2. In certain embodiments, R^1 groups are located at the 2 and 4 positions of the imidazo[l,5-a]pyrimidinyl.

[00114] In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, Ci^haloalkyl, -(C_{1-4} alkylene)-(2-6 membered heteroalkyl), cyclopropyl, halogen, or -$N(R^4)_2$. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, cyclopropyl, cyano, chloro, or fluoro. In certain embodiments, R^1 is methyl.

[00115] In certain embodiments, R^2 is hydrogen. In certain embodiments, R^1 and R^2 each represent independently for each occurrence hydrogen or C_{1-4} alkyl.

[00116] In certain embodiments, R^3 and R^4 each represent independently for each occurrence hydrogen, methyl, or ethyl.

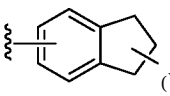
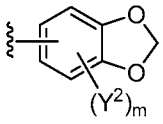
[00117] In certain embodiments, A^1 is a 3-14 membered saturated carbocyclyl substituted by 0, 1, or 2 occurrences ofY^1 and 0, 1, 2, or 3 occurrences of Y^2. In certain embodiments, A^1 is a 3-14 membered saturated carbocyclyl. In certain embodiments, A^1 is C_{3-7} cycloalkyl substituted once by Y^1 and 0-1 occurrences of Y^2. In certain embodiments, A^1 is a 5-14 membered partially unsaturated carbocyclyl substituted by 0, 1, or 2 occurrences ofY^1 and 0, 1,

2, or 3 occurrences of Y^2. In certain embodiments, A^1 is a 8-12 membered bicyclic carbocyclyl that is partially unsaturated or a 8-12 membered bicyclic heterocyclyl, each of which is substituted by 0 or 1 occurrence of Y^1 and 0, 1, or 2 occurrences of Y^2. In certain embodiments, A^1 is phenyl substituted once by Y^1 and 0-1 occurrences of Y^2.

[00118] In certain embodiments, A^1 is a 5-6 membered heteroaryl substituted once by Y^1 and 0-1 occurrences of Y^2. In certain embodiments, A^1 is pyridinyl substituted once by Y^1 and 0-1 occurrences of Y^2.

[00119] In certain embodiments, A^1 is C_{3-7} cycloalkyl substituted by C_{1-6} alkoxyl. In certain embodiments, A^1 is cyclohexyl substituted by C_{1-6} alkoxyl. In certain embodiments, A^1 is C_{3-7} cycloalkyl that is not substituted. In certain embodiments, A^1 is C_{7-10} cycloalkyl that is spirocyclic and not substituted. In certain embodiments, A^1 is cyclopropyl.

[00120] In certain embodiments, A^1 is phenyl substituted by C_2 alkynyl.

[00121] In certain embodiments, A^1 is an 8-12 membered bicyclic carbocyclyl that is partially unsaturated or an 8-12 membered bicyclic heterocyclyl, each of which is substituted by 0 or 1 occurrence of Y^2 selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, C_{1-6}haloalkyl, hydroxyl, and C_{1-6} alkoxyl. In certain embodiments, A^1 is  or  ; wherein m is 0, 1, or 2; and Y^2 represents independently for each occurrence C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, C_{1-6}haloalkyl, hydroxyl, or C_{1-6} alkoxyl.

[00122] In certain embodiments, any occurrence of Y^2 is independently C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, C_{1-6}haloalkyl, or hydroxyl. In certain embodiments, any occurrence of Y^2 is independently C_{1-3} alkyl. In certain embodiments, Y^2 is C_{1-6}haloalkyl-substituted C_{3-6} cycloalkyl.

[00123] In certain embodiments, Y^1 is **-O-**(C_{1-7} alkyl). In certain embodiments, Y^1 is -O-butyl, -O-pentyl, or -O-hexyl. In certain embodiments, Y^1 is *C2-6* alkynyl, -C≡C-(Ci_6 alkylene)-OR^4, -C≡C-(Ci_6 alkylene)-$N(R^3)_2$, -(C2-4 alkynylene)-(5-6 membered heteroaryl), or C_{2-6} alkenyl. In certain embodiments, Y^1 is -C≡CH. In certain embodiments, Y^1 is -C≡C-(Ci_6 alkylene)-OR^4. In certain embodiments, Y^1 is -C≡C-CH_2-O-CH_3. In certain embodiments, Y^1 is C_{2-6} alkynyl.

[00124] In certain embodiments, Y^1 is a 2-8 membered heteroalkyl optionally substituted by a 6-10 membered aryl or a 3-10 membered heterocyclyl. In certain embodiments, Y^1 is a 2-8 membered heteroalkyl substituted by a 6-10 membered aryl or a 3-10 membered heterocyclyl. In certain embodiments, Y^1 is a 2-8 membered heteroalkyl substituted by a 3-10 membered heterocyclyl. In certain embodiments, Y^1 is a 2-8 membered heteroalkyl substituted by a 5-6 membered heteroaryl, such as pyrrolyl, furanyl, or pyridinyl. In certain embodiments, Y^1 is a 2-8 membered heteroalkyl.

[00125] In certain embodiments, Y^1 is **-0** -(Ci_7 alkyl). In certain embodiments, Y^1 is -O-butyl, -O-pentyl, or -O-hexyl. In certain embodiments, Y^1 is -(C_{1-3} alkylene**)-0** -(5-6 membered heteroaryl). In certain embodiments, Y^1 is -CH_2**-0** -(5-6 membered heteroaryl). In certain embodiments, Y^1 is -CH_2**-0** -(5-6 membered heteroaryl), wherein the 5-6 membered heteroaryl is furanyl, pyrrolyl, thiophenyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, isooxazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, imidazolinyl, oxazolinyl, pyrazolinyl, thiazolinyl, or triazolinyl, each of which is substituted by one or two substituents independently selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, C^haloalkyl, C_{1-6} hydroxy alkyl, hydroxyl, $Ci-_6$ alkoxyl, cyano, -$N(R^4)_2$, amide, and **-C0** $_2$**H**.

[00126] In certain embodiments, Y^1 is a 3-10 membered heterocyclyl, 6-10 membered aryl, C_{3-7} cycloalkyl, **-0** -(3-6 membered heterocyclyl), **-0** (6-10 membered aryl), or ***-0-(C2-e*** alkynyl). In certain embodiments, Y^1 is a 3-10 membered heterocyclyl selected from the group consisting of a 5-6 membered heteroaryl and a 5-6 membered heterocycloalkyl. In certain embodiments, Y^1 is 5-membered heteroaryl. In certain embodiments, Y^1 is a 5-membered heteroaryl substituted by one or two substituents independently selected from the group consisting of C_{1-6} alkyl, C3-7 cycloalkyl, halogen, $Ci-_6$ haloalkyl, C_{1-6} hydroxy alkyl, hydroxyl, Ci-6 alkoxyl, cyano, -N(R 4)2, amide, and -CO2H. In certain embodiments, Y^1 is a 5-membered heteroaryl substituted by one or two substituents independently selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, $Ci-_6$ haloalkyl, hydroxyl, and C_{1-6} alkoxyl.

[00127] In certain embodiments, Y^1 is furanyl, pyrrolyl, thiophenyl, imidazolyl, pyrazolyl, oxazolyl, or thiazolyl. In certain embodiments, Y^1 is furanyl, pyrrolyl, thiophenyl, imidazolyl, pyrazolyl, oxazolyl, or thiazolyl, each of which is substituted by one or two substituents

independently selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, C_{1-6} alkoxyl, cyano, $-N(R^4)_2$, amide, and **-CO2H.**

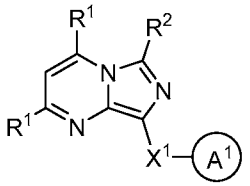
[00128] In certain embodiments, Y^1 is pyridinyl, pyrimidinyl, pyrazinyl, isooxazolyl, isothiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, imidazolinyl, oxazolinyl, pyrazolinyl, thiazolinyl, or triazolinyl. In certain embodiments, Y^1 is pyridinyl, pyrimidinyl, pyrazinyl, isooxazolyl, isothiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, imidazolinyl, oxazolinyl, pyrazolinyl, thiazolinyl, or triazolinyl, each of which is substituted by one or two substituents independently selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, C_{1-6} alkoxyl, cyano, $-N(R^4)_2$, amide, and **-CO2H.**

[00129] In certain embodiments, Y^1 is C_{2-6} alkynyl, - C≡C-(C_{1-6} alkylene)-OR^4, - C≡C-(C_{1-6} alkylene)-$N(R^3)_2$, **-(C2-4** alkynylene)-(5-6 membered heteroaryl), or C_{2-6} alkenyl. In certain embodiments, Y^1 is C_{2-6} alkynyl. In certain embodiments, Y^1 is -C≡CH. In certain embodiments, Y^1 is -C≡C-(Ci_6 alkylene)-OR^4. In certain embodiments, Y^1 is -C≡C-(Ci_6 alkylene**)-0** -(C_{1-2} alkyl). In certain embodiments, Y^1 is $-C≡C-CH_2$**-0** $-CH_3$.

[00130] In certain embodiments, Y^1 is a 2-8 membered heteroalkyl optionally substituted by a 6-10 membered aryl or a 3-10 membered heterocyclyl. In certain embodiments, Y^1 is -(C_{1-3} alkylene**)-0** -(5-6 membered heteroaryl). In certain embodiments, Y^1 is a 3-10 membered heterocyclyl, 6-10 membered aryl, C_{3-7} cycloalkyl, **-0** -(3-6 membered heterocyclyl), **-0** (6-10 membered aryl), or **-0-(C2**$_{-6}$ alkynyl). In certain embodiments, Y^1 is a 3-10 membered heterocyclyl selected from the group consisting of a 5-6 membered heteroaryl and a 5-6 membered heterocycloalkyl. In certain embodiments, Y^1 is 5-membered heteroaryl. In certain embodiments, Y^1 is furanyl, pyrrolyl, thiophenyl, imidazolyl, pyrazolyl, oxazolyl, or thiazolyl.

[00131] The description above describes multiple embodiments relating to compounds of Formula II. The patent application specifically contemplates all combinations of the embodiments. For example, the invention contemplates a compound of Formula II wherein X^1 is -C**(0**)N(H)(Ci-6 haloalkylene)-ψ, R^1 and R^2 each represent independently for each occurrence hydrogen or C_{1-4} alkyl, and A^1 is a 3-14 membered saturated carbocyclyl.

[00132] In certain embodiments, the substituted imidazo[l,5-a]pyrimidinyl carboxamide or related organic compound is a compound embraced by Formula II-A:



(II-A)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 represents independently for each occurrence C1-4 alkyl, Ci^haloalkyl, C1-4 alkoxyl, -(Ci-4 alkylene)-(Ci-4 alkoxyl), cyclopropyl, chloro, or fluoro;

R^2 is hydrogen;

R^3 and R^4 each represent independently for each occurrence hydrogen or C1-4 alkyl;

X^1 is -C(**0**)N(H)(Ci-6 haloalkylene)-ψ or -C(**0**)N(H)(Ci-6 alkylene substituted with C_{1-4} alkoxyl or C3-6 cycloalkyl)-ψ; where ψ is a bond to A^1;

A^1 is a cyclic group selected from:

- C_{3-10} cycloalkyl substituted by 0 or 1 occurrence of Y^1 and 0, 1, or 2 occurrences of Y^2; and
- phenyl substituted by 0 or 1 occurrence of Y^1 and 0, 1, or 2 occurrences of Y^2;

Y^1 represents, independently for each occurrence, one of the following:

- 2-8 membered heteroalkyl or **-0**-(C2-6 alkynyl); or
- C_{2-6} alkynyl or -C≡C-(C_{1-6} alkylene)-OR^4; and

Y^2 represents, independently for each occurrence, Ci-6 alkyl, C_{3-6} cycloalkyl, halogen, Ci-6 haloalkyl, C_{1-6} hydroxy alkyl, hydroxyl, Ci-6 alkoxyl, cyano, or -$N(R^3)_2$.

[00133] Definitions of the variables in Formula II-A above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii), *e.g.,* such as where X^1 is -C(**0**)N(H)(Ci-6 haloalkylene)-ψ, R^1 is C1-4 alkyl or Ci^haloalkyl, and A^1 is a C_{3-10} cycloalkyl substituted by 0 or 1 occurrence of Y^1 and 0, 1, or 2 occurrences of Y^2.

[00134] Accordingly, in certain embodiments, R^1 represents independently for each occurrence methyl, halomethyl, -(CH_2)i-2-**0** -(Ci-3 alkyl), cyclopropyl, chloro, or fluoro. In certain embodiments, R^1 is C_{1-4} alkyl or Ci-4haloalkyl. In certain embodiments, R^1 is methyl.

[00135] In certain embodiments, X^1 is -C(**0**)N(H)(Ci-6 haloalkylene)-ψ. In certain embodiments, X^1 is -C(**0**)N(H)C(H)(CF_3)-ψ.

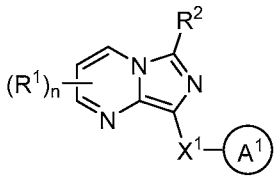
[00136] In certain embodiments, A^1 is a C3-10 cycloalkyl substituted by 0 or 1 occurrence of Y^1 and 0, 1, or 2 occurrences of Y^2. In certain embodiments, A^1 is C3-7 cycloalkyl substituted once by Y^1 and 0-1 occurrences of Y^2. In certain embodiments, A^1 is cyclohexyl substituted once by Y^1. In certain embodiments, A^1 is C3-7 cycloalkyl that is not substituted. In certain embodiments, A^1 is C_{7-10} cycloalkyl that is spirocyclic and not substituted. In certain embodiments, A^1 is cyclopropyl.

[00137] In certain embodiments, A^1 is phenyl substituted by 0 or 1 occurrence ofY^1 and 0, 1, or 2 occurrences of Y^2. In certain embodiments, A^1 is phenyl substituted by 1 occurrence of Y^1.

[00138] In certain embodiments, Y^1 is a 2-8 membered heteroalkyl. In certain embodiments, Y^1 is **-0** -(Ci-7 alkyl). In certain embodiments, Y^1 is -O-butyl, -O-pentyl, or -O-hexyl.

[00139] The description above describes multiple embodiments relating to compounds of Formula II-A. The patent application specifically contemplates all combinations of the embodiments. For example, the invention contemplates a compound of Formula II-A wherein X^1 is -C(**0**)N(H)(Ci-6 haloalkylene)-ψ, R^1 is C_{1-4} alkyl or C_{1-4} haloalkyl, and A^1 is a C3-10 cycloalkyl substituted by 0 or 1 occurrence ofY^1 and 0, 1, or 2 occurrences of Y^2.

[00140] In certain embodiments, the substituted imidazo[l,5-a]pyrimidinyl carboxamide or related organic compound is a compound embraced by Formula III:



(III)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxy alkyl, C_{1-4} cyanoalkyl, Ci-$_4$ alkoxyl, Ci^haloalkoxyl, cyclopropyl, cyano, halogen, hydroxyl, -$N(R^4)_2$, -0 -(Ci-4alkylene)-Ci-6alkoxyl, or -(Ci-$_4$ alkylene)-(2-6 membered heteroalkyl optionally substituted by one or more halogen);

R^3 represents independently for each occurrence hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl;

R^4 represents independently for each occurrence hydrogen, C_{1-4} alkyl, cyclopropyl, or -C(0)R^3;

X^1 is a carbonyl-containing linker selected from -C(0)N(H)-v|/, -C(0)N(H)(Ci$_{-6}$ alkylene optionally substituted with Ci-$_4$ alkoxyl or C_{3-6} cycloalkyl)-v|/, -C(0)N(H)(Ci_6 haloalkylene)-ψ, -C(O)N(H)(C_{3-6} cycloalkylene)-ψ, -C(0)N(H)(3-6 membered heterocycloalkylene)-ψ, -C(0)-(3-6 membered heterocycloalkylene containing at least one ring -N(H)- group)-ψ, -C(O)N(H)C(O)-ψ, and -C(0)N(H)C(0)(Ci$_{-6}$ alkylene)-ψ; where ψ is a bond to A^1;

A^1 is a C_{3-10} cycloalkyl optionally substituted with 1 or 2 C_{1-4} alkyl groups;

m is 1 or 2; and

n is 1, 2, or 3.

[00141] Definitions of the variables in Formula III above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii), *e.g.,* such as where X^1 is -C(O)N(H)-ψ, and R^1 and R^2 each represent independently for each occurrence hydrogen or C_{1-4} alkyl.

[00142] Accordingly, in certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{1-4} alkylene)-(2-6 membered heteroalkyl), cyclopropyl, halogen, or -$N(R^4)_2$. In certain embodiments, R^1 represents independently for each occurrence Ci-4 alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, cyclopropyl, cyano, chloro, or fluoro. In certain embodiments, R^1 is methyl.

[00143] In certain embodiments, n is 2. In certain embodiments, the R^1 groups are located at the 2 and 4 positions of the imidazo[l,5-a]pyrimidinyl.

[00144] In certain embodiments, R^2 is hydrogen. In certain embodiments, R^1 and R^2 each represent independently for each occurrence hydrogen or C_{1-4} alkyl.

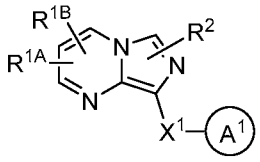
[00145] In certain embodiments, R^3 and R^4 each represent independently for each occurrence hydrogen, methyl, or ethyl.

[00146] In certain embodiments, X^1 is -C(0)N(H)(Ci-6 alkylene)-ψ. In certain embodiments, X^1 is -C(O)N(H)C(H)(CH_3)-ψ or -C(0)N(H)C(CH_3)$_2$-ψ. In certain embodiments, X^1 is -C(0)N(H)(Ci-6 haloalkylene)-ψ. In certain embodiments, X^1 is -C(O)N(H)C(H)(CF_3)-ψ. In certain embodiments, X^1 is -C(O)N(H)-ψ.

[00147] In certain embodiments, A^1 is a C_{3-1}ocycloalkyl optionally substituted with 1 or 2 Ci-4 alkyl groups. In certain embodiments, A^1 is a C_{3-1}ocycloalkyl that is not substituted. In certain embodiments, A^1 is a cyclopropyl. In certain embodiments, A^1 is a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[00148] The description above describes multiple embodiments relating to compounds of Formula III. The patent application specifically contemplates all combinations of the embodiments. For example, the invention contemplates a compound of Formula III wherein X^1 is -C(O)N(H)-ψ, and R^1 and R^2 each represent independently for each occurrence hydrogen or Ci-4 alkyl.

[00149] Another aspect of the invention provides a compound of Formula IV:



(IV)

or a pharmaceutically acceptable salt thereof, wherein:

R^{1A} is -(CM alkylene)-(2-6 membered heteroalkyl) or -N(R^3)C(0)-(C$_{6_10}$ aryl);

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

R^2 is hydrogen, C_{1-4} alkyl, or Ci^haloalkyl;

X^1 is a carbonyl-containing linker selected from -C(O)N(H)-ψ, -C(0)N(H)(Ci$_{_6}$ haloalkylene)-ψ, and -C(0)N(H)(C$_{3_6}$ cycloalkylene)-ψ; where ψ is a bond to A^1; and

A^1 is as follows:

(i) when R^{1A} is -(C M alkylene)-(2-6 membered heteroalkyl), then A^1 is monocyclic C_{3-10} cycloalkyl or bicyclic $_{C\ 5-10}$ cycloalkyl that is (a) substituted with C_{1-6} alkoxyl and (b) optionally substituted with 1 or 2 C1-4 alkyl groups; or

(ii) when R^{1A} is -$N(R^3)C(0)$-(C_{6-10} aryl), then A^1 is C3-10 cycloalkyl or bicyclic $_{C\ 5-10}$ cycloalkyl optionally substituted by 1, 2, or 3 groups independently selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, C_{1-6} alkoxyl, and -0-(C_{1-8} haloalkyl).

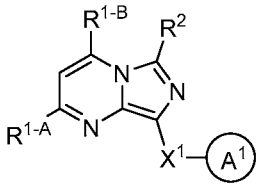
[00150] Definitions of the variables in Formula IV above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection of two or more of the chemical groups selected from those set forth above, and iii) the compound is defined by a combination of variables in which the variables are defined by (i) or (ii).

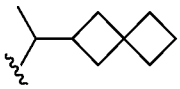
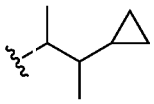
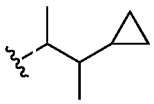
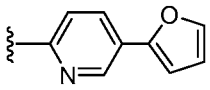
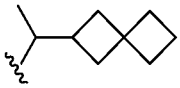
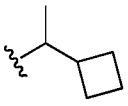
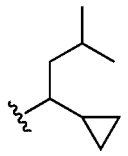
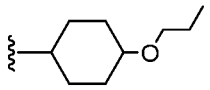
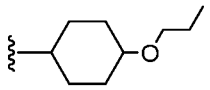
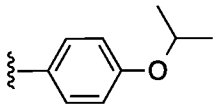
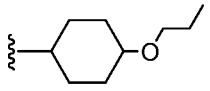
[00151] Accordingly, in certain embodiments, X^1 is -C(O)N(H)-ψ. In certain embodiments, A^1 is a monocyclic C_{3-10} cycloalkyl that is (i) substituted with C_{1-6} alkoxyl. In certain embodiments, A^1 is a bicyclic $_{C\ 5-10}$ cycloalkyl that is (i) substituted with C_{1-6} alkoxyl. In certain embodiments, R^{1A} is -(C_{1-4} alkylene)-(2-6 membered heteroalkyl). In certain embodiments, R^{1A} is -CH_2-0-CH_3. In certain embodiments, R^{1B} is methyl. In certain embodiments, R^2 is hydrogen.

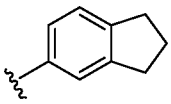
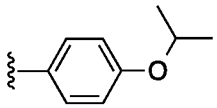
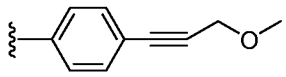
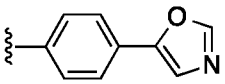
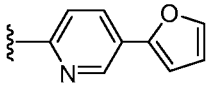
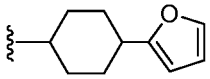
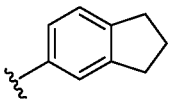
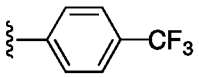
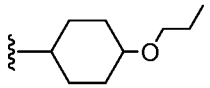
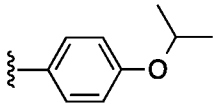
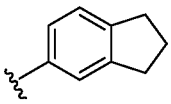
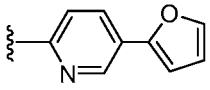
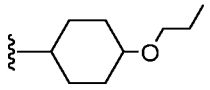
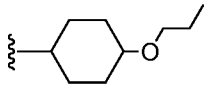
[00152] The description above describes multiple embodiments relating to compounds of Formula IV. The patent application specifically contemplates all combinations of the embodiments.

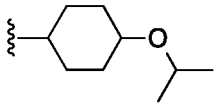
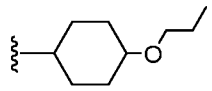
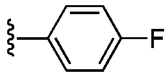
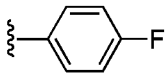
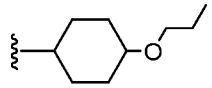
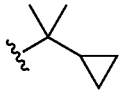
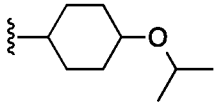
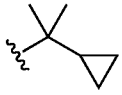
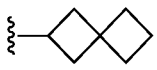
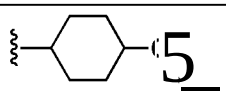
[00153] In certain embodiments, the compound is a compound described in the Examples, or a pharmaceutically acceptable salt thereof. In certain other embodiments, the compound is one of the compounds listed in Table 1 or 2 below or a pharmaceutically acceptable salt thereof.

TABLE 1.



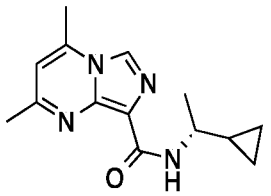
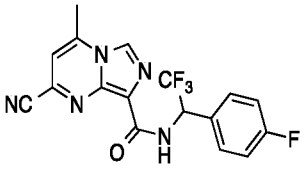
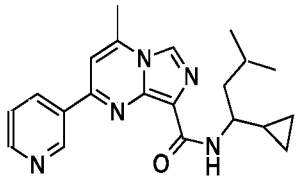
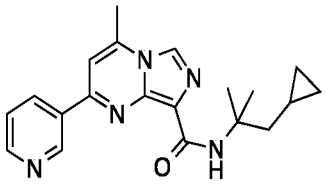
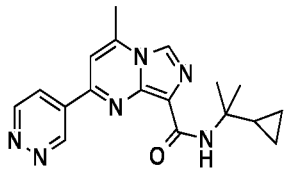
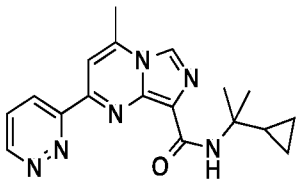
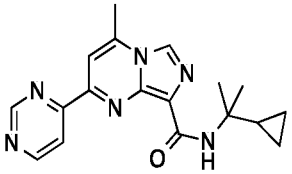
No.	R^{1-A}	R^{1-B}	R^2	X^1	A^1
I-1	-O-2-pyridinyl	ethyl	H	-C(O)N(H)-ψ	
I-2	2-pyridinyl	methyl	H	-C(O)N(H)-ψ	
I-3	3-pyridinyl	methyl	H	-C(O)N(H)-ψ	
I-4	3-pyridinyl	methyl	H	-C(O)N(H)-ψ	
I-5	-$C(Me)_2OH$	methyl	H	-C(O)N(H)-ψ	
I-6	2-thiophenyl	methyl	H	-C(O)N(H)-ψ	
I-7	-O-(4-fluoro-phenyl)	methyl	H	-C(O)N(H)-ψ	
I-8	2-thiophenyl	ethyl	H	-C(O)N(H)-ψ	
I-9	2-furanyl	methyl	H	-C(O)N(H)-ψ	
I-10	4-tetrahydropyranyl	methyl	H	-C(O)N(H)-ψ	
I-11	4-tetrahydropyranyl	methyl	H	-C(O)N(H)-ψ	

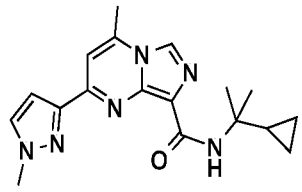
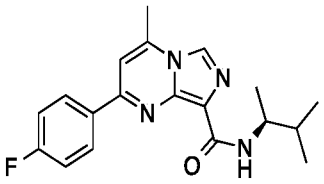
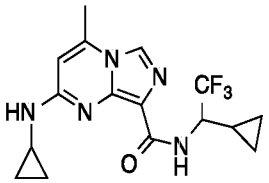
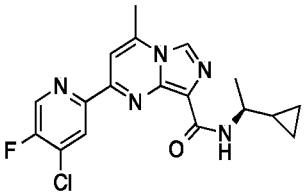
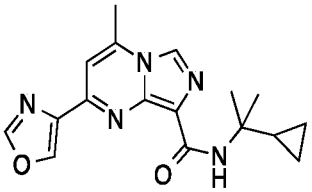
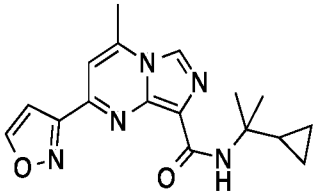
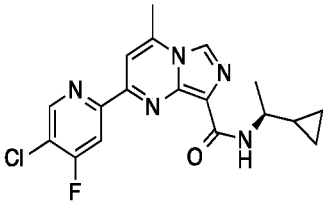
No.	R^{1-A}	R^{1-B}	R^2	X^1	A^1
I-12	4-tetrahydropyranyl	methyl	H	-C(O)N(H)-ψ	
I-13	3-pyridinyl	methyl	H	-C(O)N(H)$(CH_2)_2$-ψ	
I-14	3-pyridinyl	methyl	H	-C(O)N(H)$(CH_2)_2$-ψ	
I-15	3-pyridinyl	methyl	H	-C(O)N(H)$(CH_2)_2$-ψ	
I-16	3-pyridinyl	methyl	H	-C(O)N(H)$(CH_2)_2$-ψ	
I-17	3-pyridinyl	methyl	H	-C(O)N(H)$(CH_2)_2$-ψ	
I-18	3-pyridinyl	methyl	H	-C(O)N(H)$(CH_2)_2$-ψ	
I-19	3-pyridinyl	methyl	H	-C(O)N(H)$(CH_2)_2$-ψ	
I-20	3-pyridinyl	methyl	H	-C(O)N(H)$(CH_2)_2$-ψ	
I-21	3-pyridinyl	methyl	H	-C(O)N(H)$(CH_2)_2$-ψ	cyclopropyl
I-22	4-tetrahydropyranyl	methyl	H	-C(O)N(H)$(CH_2)_2$-ψ	
I-23	4-tetrahydropyranyl	methyl	H	-C(O)N(H)$(CH_2)_2$-ψ	
I-24	4-tetrahydropyranyl	methyl	H	-C(O)N(H)$(CH_2)_2$-ψ	
I-25	4-tetrahydropyranyl	methyl	H	-C(O)N(H)$(CH_2)_2$-ψ	
I-26	3-pyridinyl	methyl	H	-C(O)N(H)C(H)(CF_3)-ψ	2-thiophenyl
I-27	3-pyridinyl	methyl	H	-C(O)N(H)C(H)(CF_3)-ψ	

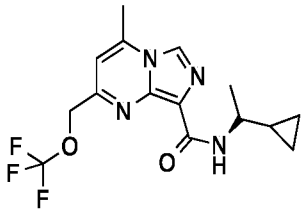
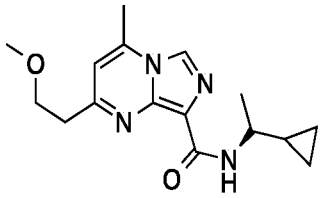
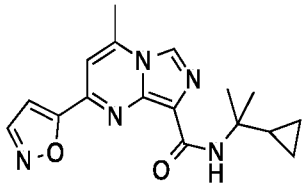
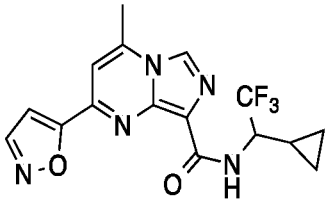
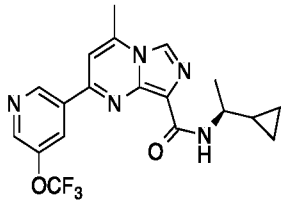
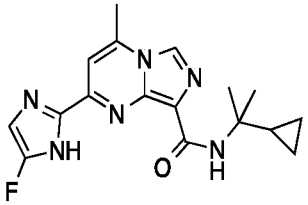
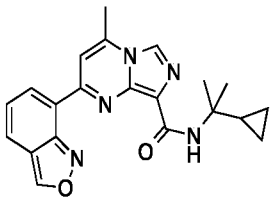
No.	R^{1-A}	R^{1-B}	R^2	X^1	A^1
I-28	4-piperidinyl	methyl	H	-C(O)N(H)C(H)(CF_3)-ψ	2-thiophenyl
I-29	4-piperidinyl	methyl	H	-C(O)N(H)C(H)(CF_3)-ψ	2-thiazolyl
I-30	4-piperidinyl	methyl	H	-C(O)N(H)C(H)(CF_3)-ψ	
I-31	3-pyridinyl	methyl	H	-C(O)N(H)C(H)(CF_3)-ψ	cyclobutyl
I-32	-C(Me)$_2$CN	methyl	H	-C(O)N(H)C(H)(CF_3)-ψ	cyclopropyl
I-33	-C(Me)$_2$OH	methyl	H	-C(O)N(H)C(H)(CF_3)-ψ	cyclopropyl
I-34	Cl	methyl	H	-C(O)N(H)C(H)(CF_3)-ψ	2-thiophenyl
I-35	Cl	methyl	H	-C(O)N(H)C(H)(CF_3)-ψ	
I-36	methyl	CN	H	-C(O)N(H)C(H)(CF_3)-ψ	
I-37	methyl	CN	H	-C(O)N(H)C(H)(CF_3)-ψ	cyclopropyl
I-38	methyl	H	F	-C(O)N(H)C(H)(CF_3)-ψ	
I-39	methyl	H	F	-C(O)N(H)C(H)(CF_3)-ψ	cyclopropyl
I-40	3-pyridinyl	methyl	H	-C(O)N(H)C(O)-ψ	
I-41	3-pyridinyl	methyl	H	-C(O)N(H)C(O)-ψ	
I-42	4-tetrahydropyranyl	methyl	H	-C(O)N(H)C(O)-ψ	
I-43	2-thiophenyl	methyl	H	-C(O)N(H)C(O)-ψ	
I-44	2-furanyl	methyl	H	-C(O)N(H)C(O)-ψ	
I-45	2-pyridinyl	methyl	H	-C(O)N(H)C(O)-ψ	
1-46	4-piperidinyl	methyl	H	-C(0)N (H)C(0)-ψ	

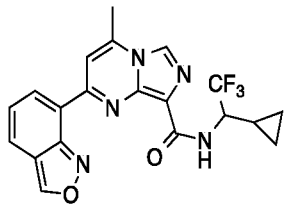
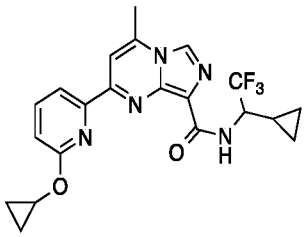
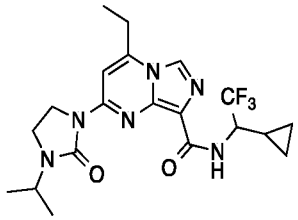
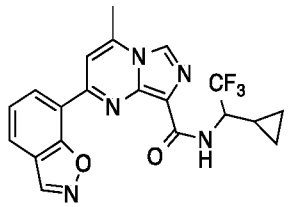
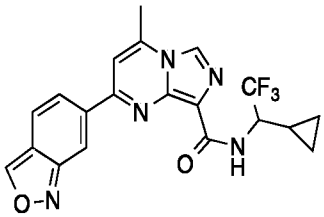
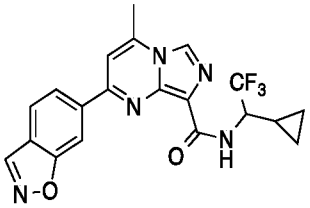
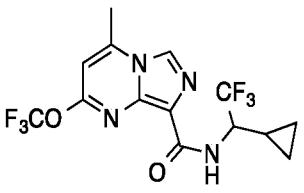
Where in Table 1, ψ **is a bond** to A^1.

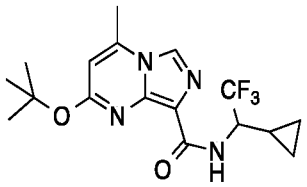
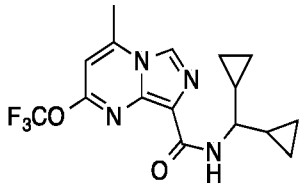
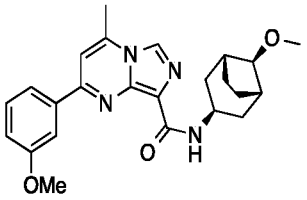
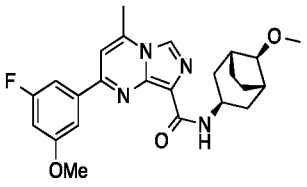
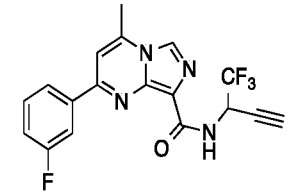
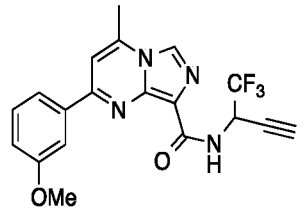
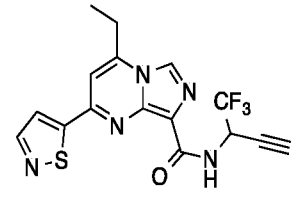
TABLE 2.

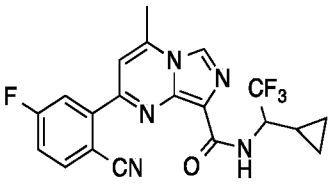
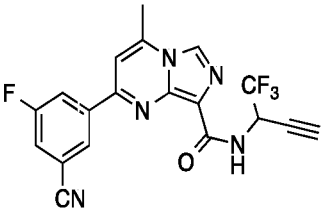
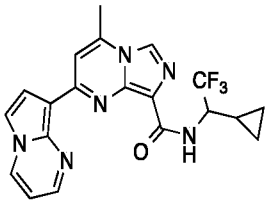
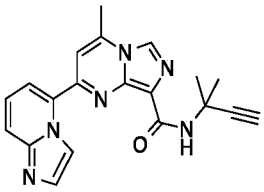
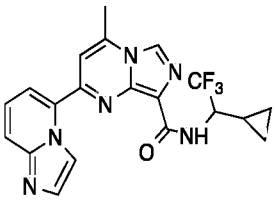
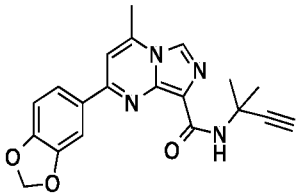
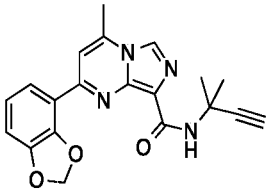
Compound No.	Compound Structure
II-1	
II-2	
II-3	
II-4	
II-5	
II-6	
II-8	

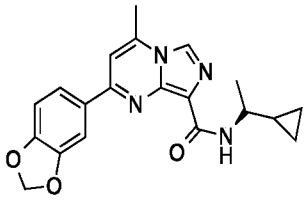
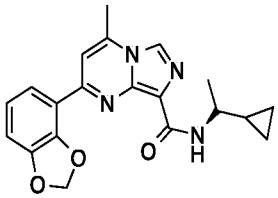
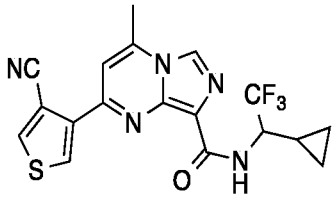
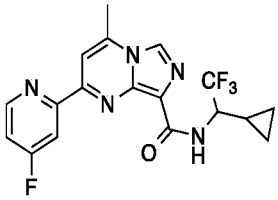
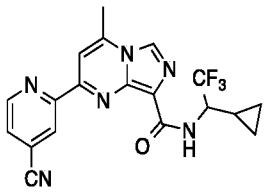
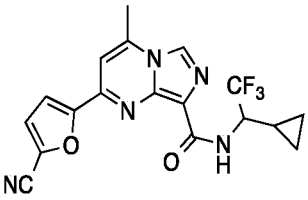
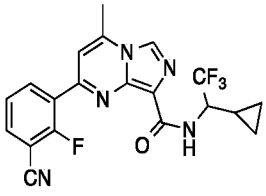
Compound No.	Compound Structure
II-9	
II-10	
II-11	
II-12	
II-13	
II-14	
II-15	

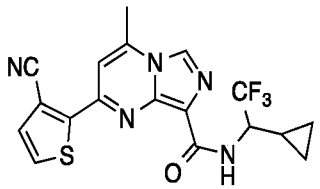
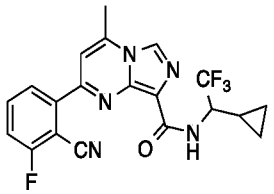
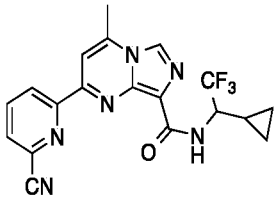
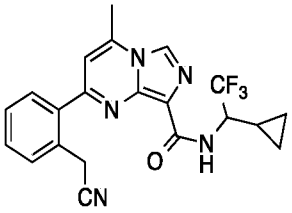
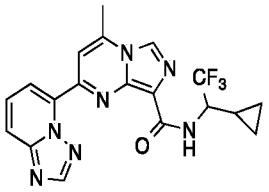
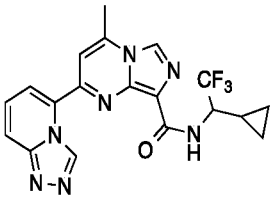
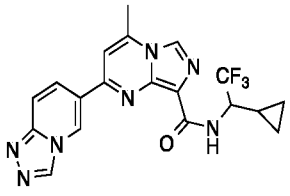
Compound No.	Compound Structure
II-16	
II-17	
II-18	
II-19	
II-21	
II-22	
II-23	

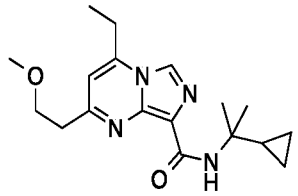
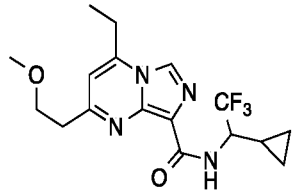
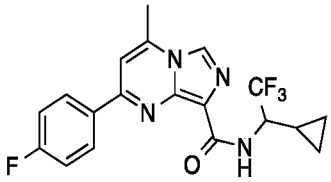
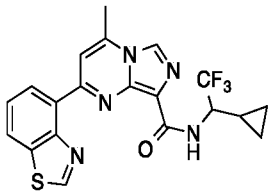
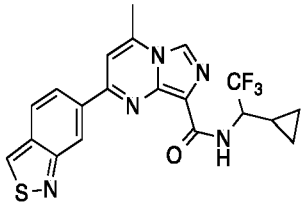
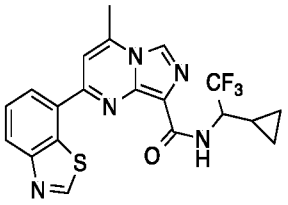
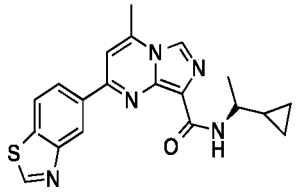
Compound No.	Compound Structure
II-24	
II-25	
II-26	
II-27	
II-28	
II-29	
II-30	

Compound No.	Compound Structure
II-31	
II-32	
II-33	
II-34	
II-35	
II-36	
II-37	

Compound No.	Compound Structure
II-38	
II-39	
II-40	
II-41	
II-42	
II-43	
II-44	

Compound No.	Compound Structure
II-45	
II-46	
II-47	
II-48	
II-49	
II-50	
II-51	

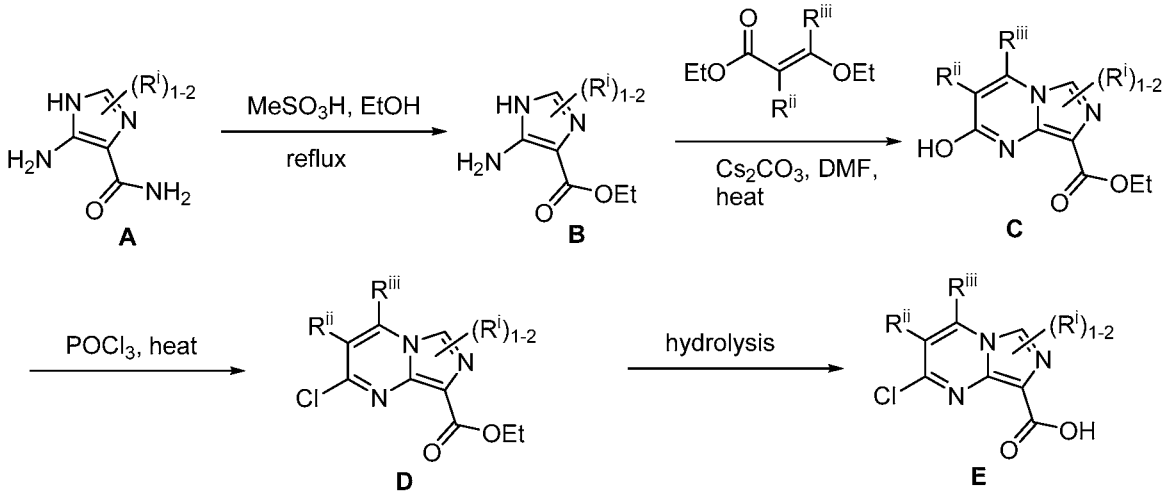
Compound No.	Compound Structure
II-52	
II-55	
II-56	
II-57	
II-58	
II-59	
II-60	

Compound No.	Compound Structure
II-61	
II-62	
II-63	
II-64	
II-65	
II-66	
II-67	

[00154] Methods for preparing compounds described herein are illustrated in the following synthetic schemes. These schemes are given for the purpose of illustrating the invention, and should not be regarded in any manner as limiting the scope or the spirit of the invention. Starting materials shown in the schemes can be obtained from commercial sources or can be prepared based on procedures described in the literature.

[00155] The synthetic route illustrated in Scheme 1 depicts an exemplary procedure for preparing substituted imidazo[l,5-a]pyrimidine compounds. In the first step, 5-amino-l*H*-imidazole-4-carboxamide (R^{i}-H) **A** is treated with methylsulfonic acid in ethanol to afforded ethyl 5-amino-l*H*-imidazole-4-carboxylate (R^{i}=H) **B** which is condensed with ethyl (£)-3-ethoxybut-2-enoate (R^{ii}=H, R^{iii}=Me) in DMF and Cs_2C0_3 to afford ethyl 2-hydroxy-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate **C**. Heating of carboxylate **C** with phosphoryl trichloride affords intermediate ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate **D**. Hydrolysis of **D** provides the intermediate 2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid **E**.

SCHEME 1.

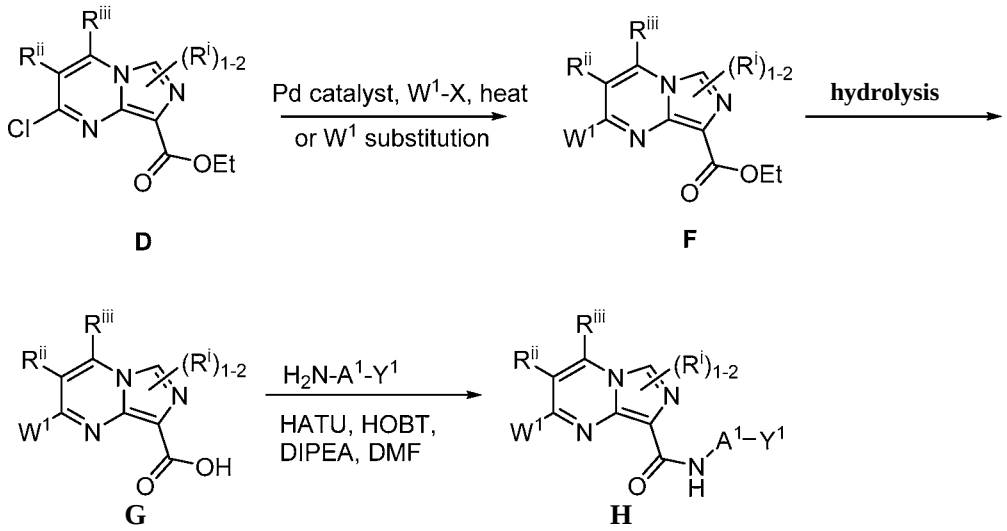


[00156] The synthetic route illustrated in Scheme 2 depicts an exemplary procedure for preparing substituted imidazo[l ,5-a]pyrimidine carboxamide compounds. In the first step, Pd-catalyzed coupling of the chloro-carboxylic ester **D** with a variety of aryl or heteroaryl boronic acids or esters or with trialkylstannyl reagents may be accomplished using standard Pd

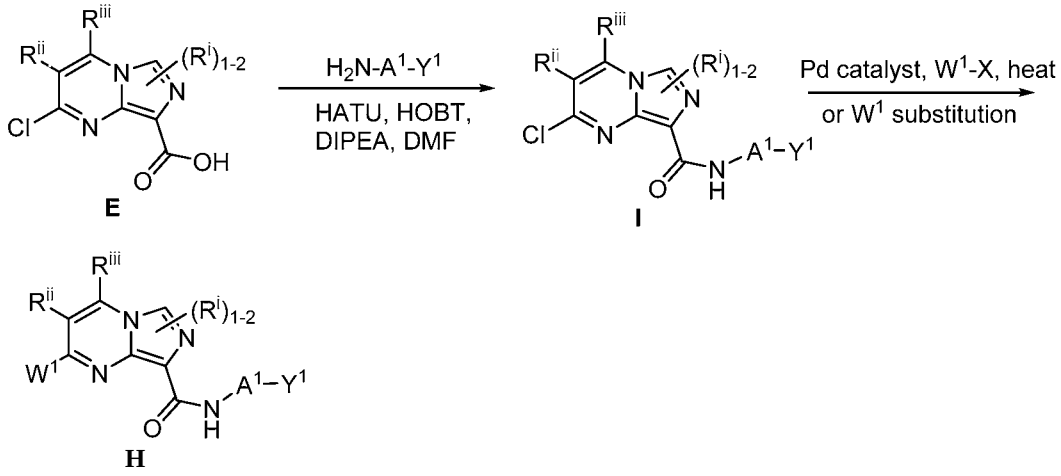
catalyzed coupling procedures such as the Suzuki and Buchwald coupling. For example, using Suzuki coupling conditions (such as $Pd(dppf)_2Cl_2 \bullet CH_2Cl_2$ in DME in the presence of K_3PO_4) affords substituted carboxylic ester **F**. Alternatively, substitution of the chloro-carboxylic ester D with a primary or secondary amine affords the substituted carboxylic ester **F**. Hydrolysis of the carboxylic acid under basic or neutral conditions then affords the carboxylic acid **G**. In the final step, coupling of carboxylic acid **G** with a variety of substituted aromatic or aliphatic amines may be accomplished using standard peptide coupling procedures(such as HATU and/or HOBT in DMF in the presence of DIPEA) to afford amide **H**.

[00157] The synthetic route illustrated in Scheme 3 depicts an exemplary procedure for preparing substituted imidazo[l,5-a]pyrimidine compounds. In the first step, coupling of carboxylic acid **E** with a variety of substituted aromatic or aliphatic amines may be accomplished using standard peptide coupling procedures(such as HATU and/or HOBT in DMF in the presence of DIPEA) to afford chloro-amide **I**. In the final step, Pd-catalyzed coupling of chloro-amide **I** with a variety of aryl or heteroaryl boronic acids or esters or with trialkylstannyl reagents may be accomplished using standard Pd-catalyzed coupling procedures such as the Suzuki or Buchwald coupling. For example, using Suzuki coupling conditions (such as, Pd(dppf)2Cl2•CH_2Cl2 in DME in the presence of **K_3PO4)** affords substituted amide **H**. Alternatively, chloro-amide **I** can be substituted with a nucleophilic N-containing group to afford substituted amide **H**.

SCHEME 2.



SCHEME 3.



[00158] The reaction procedures in Schemes 1 to 3 are contemplated to be amenable to preparing a wide variety of substituted imidazo[1 ,5-a]pyrimidine carboxamide compounds having different substituents at the A^1 and Y^1 positions. Furthermore, if a functional group that is part of the A^1 and/or Y^1 would not be amenable to a reaction condition described in Scheme 2, it is contemplated that the functional group can first be protected using standard protecting group chemistry and strategies, and then the protecting group is removed after completing the desired synthetic transformation. See, for example, Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis,* 2nd ed.; Wiley: New York, 1991, for further description of protecting chemistry and strategies. In certain other embodiments, a functional group in substituent A^1 and Y^1 can converted to another functional group using standard functional group manipulation procedures known in the art. See, for example, "Comprehensive Organic Synthesis" (B.M. Trost & I. Fleming, eds., 1991-1992).

III. THERAPEUTIC APPLICATIONS

[00159] The invention provides methods of treating medical disorders, such as Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma, multiple sclerosis, endometriosis, and multiple myeloma, using the substituted imidazo[1 ,5-a]pyrimidinyl carboxamide, related compounds, and pharmaceutical compositions described herein. Treatment methods include the use of substituted imidazo[l,5-a]pyrirnidinyl carboxamide or related organic compounds described

herein as stand-alone therapeutic agents and/or as part of a combination therapy with another therapeutic agent. Although not wishing to be bound by a particular theory, it is understood that substituted imidazo[l,5-a]pyrimidinyl carboxamide and related organic compounds described herein may activate glucocerebrosidase (Gcase).

Methods of TreatingMedical Disorders

[00160] One aspect of the invention provides a method of treating disorder selected from the group consisting of Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma, multiple sclerosis, endometriosis, and multiple myeloma. The method comprises administering to a patient in need thereof a therapeutically effective amount of a substituted imidazo[l,5-a]pyrimidinyl carboxamide or related organic compound described herein to treat the disorder. The compound may be a compound of Formula I, II, III, or IV described above in Section II.

[00161] In certain embodiments, the disorder is Gaucher disease, Parkinson's disease, Lewy body disease, dementia, or multiple system atrophy. In certain embodiments, the disorder is Gaucher disease, Parkinson's disease, Lewy body disease, dementia, or multiple system atrophy. In certain other embodiments, the disorder is Gaucher disease. In certain embodiments, the disorder is Parkinson's disease. In certain embodiments, the disorder is Lewy body disease. In certain embodiments, the disorder is dementia. In certain embodiments, the disorder is a dementia selected from the group consisting of Alzheimer's disease, frontotemporal dementia, and a Lewy body variant of Alzheimer's disease. In certain embodiments, the disorder is multiple system atrophy.

[00162] In certain embodiments, the disorder is an anxiety disorder, such as panic disorder, social anxiety disorder, or generalized anxiety disorder.

[00163] Efficacy of the compounds in treating Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma, multiple sclerosis, endometriosis, and multiple myeloma may be evaluated by testing the compounds in assays known in the art for evaluating efficacy against these diseases and/or, *e.g.*, for activation of glucocerebrosidase (Gcase), as discussed in the Examples below.

[00164] In certain embodiments, the patient is a human.

[00165] In certain embodiments, the compound is one of the generic or specific compounds described in Section II, such as a compound of Formula I, a compound embraced by one of the further embodiments describing definitions for certain variables of Formula I, a compound of Formula I-A, or a compound embraced by one of the further embodiments describing definitions for certain variables of Formula I-A. In certain other embodiments, the compound is a compound of Formula II or II-A or a compound embraced by one of the further embodiments describing definitions for certain variables of Formula II or II-A.

[00166] The description above describes multiple embodiments relating to methods of treating various disorders using certain substituted imidazo[l,5-a]pyrimidinyl carboxamide or related organic compounds. The patent application specifically contemplates all combinations of the embodiments. For example, the invention contemplates methods for treating Gaucher disease, Parkinson's disease, Lewy body disease, dementia, or multiple system atrophy by administering a therapeutically effective amount of a compound of Formula I-A.

Medical Use and Preparation of Medicament

[00167] Another aspect of the invention relates to compounds and compositions described herein for use in treating a disorder described herein. Another aspect of the invention pertains to use of a compound or composition described herein in the preparation of a medicament for treating a disorder described herein.

Combination Therapy

[00168] The invention embraces combination therapy, which includes the administration of a substituted imidazo[l,5-a]pyrimidinyl carboxamide or related compound described herein (such as compound of Formula I, I-A, II, II-A, III, or IV) and a second agent as part of a specific treatment regimen intended to provide the beneficial effect from the co-action of these therapeutic agents. The beneficial effect of the combination may include pharmacokinetic or pharmacodynamic co-action resulting from the combination of therapeutic agents.

[00169] Exemplary second agents for use in treating Gaucher disease include, for example, taliglucerase alfa, velaglucerase alfa, eliglustat, and miglustat. Exemplary second agents for use in treating Parkinson's disease include, for example, a glucosylceramide synthase inhibitor (e.g., ibiglustat), an acid ceramidase inhibitor (e.g., carmofur), an acid sphingomyelinase

activator, levodopa, pramipexole, ropinirole, rotigotine, apomorphine, or salt thereof. Additional glucosylceramide synthase inhibitors for use in combination therapies include, for example, those described in International Patent Application Publications WO 2015/089067, WO 2014/151291, WO 2014/043068, WO 2008/150486, WO 2010/014554, WO 2012/129084, WO 201 1/133915, and WO 2010/091 164; U.S. Patent Nos. US 9126993, US 8961959, US 8940776, US 8729075, and US 8309593; and U.S. Patent Application Publications US 2014/0255381 and US 2014/0336174; each of which are hereby incorporated by reference. Additional acid ceramidase inhibitors for use in combination therapies include, for example, those described in International Patent Application Publications WO 2015/173168 and WO 2015/173169, each of which are hereby incorporated by reference.

IV. PHARMACEUTICAL COMPOSITIONS

[00170] The invention provides pharmaceutical compositions comprising a substituted imidazo[l,5-a]pyrimidinyl carboxamide or related organic compound described herein, such as a compound of Formula I, I-A, II, II-A, III, or IV. In certain embodiments, the pharmaceutical compositions preferably comprise a therapeutically-effective amount of one or more of the substituted irnidazo[l,5-a]pyrirnidinyl carboxamide or related organic compounds described above, formulated together with one or more pharmaceutically acceptable carriers. As described in detail below, the pharmaceutical compositions of the present invention may be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets (e.g., those targeted for buccal, sublingual, and/or systemic absorption), boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration by, for example, subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; or (8) nasally.

[00171] The phrase "therapeutically-effective amount" as used herein means that amount of a compound, material, or composition comprising a compound of the present invention which is effective for producing some desired therapeutic effect in at least a sub-population of cells in an animal at a reasonable benefit/risk ratio applicable to any medical treatment.

[00172] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[00173] Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[00174] Examples of pharmaceutically-acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[00175] Formulations of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will vary depending upon the host being treated, the particular mode of administration.

[00176] The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 0.1 per cent to about ninety-nine percent of active ingredient, preferably from about 5 percent to about 70 percent, most preferably from about 10 percent to about 30 percent.

[00177] In certain embodiments, a formulation of the present invention comprises an excipient selected from the group consisting of cyclodextrins, celluloses, liposomes, micelle forming agents, e.g., bile acids, and polymeric carriers, e.g., polyesters and polyanhydrides; and a compound of the present invention. In certain embodiments, an aforementioned formulation renders orally bioavailable a compound of the present invention.

[00178] Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[00179] Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

[00180] In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules, trouches and the like), the active ingredient is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds and surfactants, such as poloxamer and sodium lauryl sulfate; **(7)** wetting agents, such as, for example, cetyl alcohol, glycerol monostearate, and non-ionic surfactants; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, zinc stearate, sodium stearate, stearic acid, and mixtures thereof; (10) coloring agents; and (11) controlled release agents such as crospovidone or ethyl cellulose. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-shelled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[00181] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[00182] The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical -formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be formulated for rapid release, e.g., freeze-dried. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[00183] Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

[00184] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

[00185] Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[00186] Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

[00187] Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

[00188] Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically-acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

[00189] The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[00190] Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[00191] Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

[00192] Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

[00193] Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain sugars, alcohols, antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[00194] Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[00195] These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms upon the subject compounds may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[00196] In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[00197] Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

[00198] When the compounds of the present invention are administered as pharmaceuticals, to humans and animals, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99% (more preferably, 10 to 30%) of active ingredient in combination with a pharmaceutically acceptable carrier.

[00199] The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given in forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc. administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administrations are preferred.

[00200] The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticulare, subcapsular, subarachnoid, intraspinal and intrastemal injection and infusion.

[00201] The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that

it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

[00202] These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

[00203] Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.

[00204] Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[00205] The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion or metabolism of the particular compound being employed, the rate and extent of absorption, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

[00206] A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

[00207] In general, a suitable daily dose of a compound of the invention will be that amount of the compound which is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Preferably, the compounds are administered at about 0.01 mg/kg to about 200 mg/kg, more preferably at about

0.1 mg/kg to about 100 mg/kg, even more preferably at about 0.5 mg/kg to about 50 mg/kg. When the compounds described herein are co-administered with another agent *(e.g.,* as sensitizing agents), the effective amount may be less than when the agent is used alone.

[00208] If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms. Preferred dosing is one administration per day.

V. KITS FOR USE IN MEDICAL APPLICATIONS

[00209] Another aspect of the invention provides a kit for treating a disorder. The kit comprises: i) instructions for treating a medical disorder, such as Gaucher disease, Parkinson's disease, Lewy body disease, dementia, or multiple system atrophy; and ii) a substituted imidazo[l,5-a]pyrimidinyl carboxamide or related organic compound described herein, such as a compound of Formula I, I-A, II, II-A, III, or IV. The kit may comprise one or more unit dosage forms containing an amount of a substituted imidazo[l,5-a]pyrimidinyl carboxamide or related organic compound described herein, such as a compound of Formula I, I-A, II, II-A, III, or IV, that is effective for treating said medical disorder, *e.g.,* Gaucher disease, Parkinson's disease, Lewy body disease, dementia, or multiple system atrophy.

[00210] The description above describes multiple aspects and embodiments of the invention, including substituted imidazo[l,5-a]pyrimidinyl carboxamide and related organic compounds, compositions comprising a substituted imidazo[l,5-a]pyrimidinyl carboxamide or related organic compounds, methods of using the substituted imidazo[l,5-a]pyrimidinyl carboxamide or related organic compounds, and kits. The patent application specifically contemplates all combinations and permutations of the aspects and embodiments. For example, the invention contemplates treating Gaucher disease, Parkinson's disease, Lewy body disease, dementia, or multiple system atrophy in a human patient by administering a therapeutically effective amount of a compound of Formula I-A. Further, for example, the invention contemplates a kit for treating Gaucher disease, Parkinson's disease, Lewy body disease, dementia, or multiple system atrophy, the kit comprising instructions for treating Gaucher disease, Parkinson's disease, Lewy body disease, dementia, or multiple system atrophy and ii) a substituted imidazo[l,5-a]pyrimidinyl carboxamide or related organic compound described herein, such as a compound of Formula I-A.

EXAMPLES

[00211] The invention now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention. In certain instances, the amount of compound produced by the procedure is stated alogn with the yield, which may be presented in the format of the procedure produced the title compound (10 mg; 90%) which means that 10 mg of the title compound was obtained and that corresponds to a yield of 90%.

EXAMPLE 1 - PREPARATION OF iMiDAzo [l,5-a]PYRiMiDiNE-8-CARBOXAMiDE COMPOUNDS

[00212] Imidazo[l,5-a]pyrimidine-8-carboxarnide compounds were prepared based on general procedures described in Part I below. Exemplary procedures for preparing specific amine compounds useful as synthetic intermediates in the preparation of certain imidazo[l,5-a]pyrimidine-8-carboxamide compounds are provided in Part II below. Exemplary procedures for preparing specific carboxylic ester compounds useful as synthetic intermediates in the preparation of certain imidazo[l,5-a]pyrimidine-8-carboxamide compounds are provided in Part III below. Specific inddazo[l,5-a]pyrimidine-8-carboxamide compounds prepared according to the general procedures are provided in Part IV below.

Part I - General Procedures

General Procedure A: Preparation of Amide by Coupling of a Carboxylic Acid Compound with an Amine Compound

[00213] To a stirred solution of carboxylic acid compound (1.0 equivalent), HATU (1.5 equivalents), and DIPEA (3.75 equivalents) in DCM or DMF (~4 mL/0.2 mmol) was added amine compound (1.25 - 2.0 equivalents). The reaction mixture was stirred at room temperature for 4-16 hours, and then washed with saturated aqueous NaHCCb solution (5 mL/0.2 mmol), aqueous citric acid solution (5 mL/0.2 mmol) and brine (5 mL/0.2 mmol). The combined extracts were dried over anhydrous Na_2SG-4, filtered and concentrated *in vacuo*. The resulting crude material was purified by silica gel column chromatography or preparatory HPLC to give the amide compound.

General Procedure B: Conversion of Carboxylic Ester Compound to Carboxylic Acid Compound

[00214] To a solution of carboxylic ester (1.0 equivalent) in EtOH (5.0 mL/1.0 mmol) and water (0-3.0 mL/1.0 mmol) was added NaOH (2.0-5.0 equivalents) and the mixture was heated at 80 °C for 2 hours and then concentrated. To the concentrate, 6N HCl solution was added to adjust the pH to 5-6 and then the mixture was stirred for 10 minutes and subsequently filtered. The resulting solid was collected and dried to give the carboxylic acid compound.

General Procedure B*: Conversion of Carboxylic Ester Compound to Carboxylic Acid Compound

[00215] To a solution of carboxylic ester (1.0 equivalent) in EtOH (5.0 mL/1.0 mmol) and water (0-3.0 mL/1.0 mmol) was added NaOH (2.0-5.0 equivalents) and the mixture was heated at 80 °C for 2 hours and then concentrated. To the concentrate, 6N HCl solution was added to adjust the pH to 5-6 and then the mixture was stirred for 10 minutes and subsequently filtered. The resulting solid was collected and dried to give the carboxylic acid compound.

[00216] Alternatively, to a solution of carboxylic ester (1.0 equivalent) in THF (5.0 mL/1.0 mmol) was added LiOH (1M solution, 3 equivalents) and the mixture was stirred at 60 °C for 1-2 h and then the pH was adjusted to ~ 7 with 1 N HCl. The resulting solution was lyophilized to afford the crude carboxylic acid.

General Procedure C: Preparation of Amide from a Carboxylic Acid Compound and Amine Compound

[00217] To a solution of carboxylic acid compound (1.0 equivalent) in DCM (3 mL/0.5 mmol) was added DMF (1 drop) and oxalyl chloride (2.0 equivalents). The solution was stirred at room temperature for 30 minutes and then concentrated *in vacuo.* The resulting residue was dissolved in DCM (1 mL/0.5 mmol) followed by the addition of amine compound (5.0 equivalents) and triethylamine (2.0 equivalents). The reaction mixture was stirred at RT for 2 hours and then diluted with DCM (10 mL/0.5 mmol). The organic solution was washed sequentially with ¾ **0** (10 mL/0.5 mmol) and brine (10 mL/0.5 mmol), then dried over anhydrous Na_2S0_4, and next filtered. The filtrate was concentrated *in vacuo,* and the resulting residue was purified by preparatory HPLC or silica gel chromatography to give the amide compound.

General Procedure D: Preparation of Coupled Aryl and Heteroaryl Groups Using Suzuki Catalyzed Coupling Conditions Between an Organoboronic Acid or Ester and an Aryl Halide or Heteroaryl Halide

[00218] A suspension of heteroaryl chloride (1 equivalent), organoboronic acid or organoboronic ester (1.2 equivalents), K_3PO4 (3.0 equivalents) and Pd(dppf)Cl_2•DCM (5 mol%) or $Pd_2(dba)_3$ (10 mol%) in DME or 1,4-dioxane (40 mL/mmol) was stirred at 70-100 °C for 2-6 hours under N_2. Then, the reaction mixture was quenched with water (30 mL/mmol) and resulting mixture extracted with EtOAc (30 mL/mmol x 3). The organic phases were washed with water (30 mL/mmol) and brine (30 mL/mmol), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*, and the resulting residue was purified by silica gel column chromatography to afford the coupled ring system.

General Procedure E: Preparation of Coupled Aryl and Heteroaryl Groups Using Buchwald Catalyzed Coupling Conditions Between an Organohalide in the Presence of a Tin Reagent

[00219] A solution of organobromide (1.0 equivalent), organochloride (1.0 equivalent), hexabutylditin (1.0 equivalent) and Pd(dppf)Cl_2•DCM (10 mol%) in anhydrous 1,4-dioxane (10 mL/mmol) was stirred at 100 °C under N_2 overnight, then cooled and quenched with water (20 mL/mmol). The resulting mixture was extracted with EtOAc (20 mL/mmol x 3), the organic phases were separated and dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*, and the resulting residue was purified by silica gel column chromatography or preparative-TLC to afford the coupled ring system.

General Procedure E*: Preparation of Coupled Aryl and Heteroaryl Groups Using Buchwald Catalyzed Coupling Conditions Between an Organohalide in the Presence of a Tin Reagent

[00220] A solution of organobromide (1.0 equivalent), organochloride (1.0 equivalent), hexabutylditin (1.0 equivalent) and Pd(dppf)Cl_2•DCM or Pd(t-$Bu_3P)_2$ (10 mol%) in anhydrous 1,4-dioxane (10 mL/mmol) was stirred at 100 °C under N_2 overnight, then cooled and quenched with water (20 mL/mmol). The resulting mixture was extracted with EtOAc (20 mL/mmol x 3), then the organic phases were separated and dried over anhydrous Na_2S0_4 and filtered. The filtrate was concentrated *in vacuo*, and the resulting residue was purified by silica gel column chromatography or preparative-TLC to afford the coupled ring system.

General Procedure F: Preparation of Coupled Aryl and Heteroaryl Groups Using Buchwald Catalyzed Coupling Conditions Between an Organohalide and Organotin Reagent

[00221] A solution of organochloride (1.0 equivalent) and organotin reagent (1.0 equivalent) in 1,4-dioxane (20 mL/mmol) was stirred and purged with N_2 three times at RT. Then $Pd(dppf)Cl_2$•DCM (10 mol %) was quickly added under a N_2 atmosphere to the reaction mixture, followed by additional purging with N_2 (x 3) and the resulting mixture was stirred at 120 °C for overnight. Next, the reaction mixture was cooled to RT and then quenched with water (20 mL/mmol). The resulting mixture was extracted with EA (20 mL/mmol x 3), and the organic phases were dried over anhydrous Na_2SO_4 and filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography or preparative-TLC to afford the coupled ring system.

General Procedure F*: Preparation of Coupled Aryl and Heteroaryl Groups Using Buchwald Catalyzed Coupling Conditions Between an Organohalide and Organotin Reagent

[00222] A solution of organochloride (1.0 equivalent) and organotin reagent (1.0 equivalent) in 1,4-dioxane (20 mL/mmol) was stirred and purged with N_2 three times at RT. Then $Pd(dppf)Cl_2$•DCM or $Pd(PPh_3)_2Cl_2$ (10 mol %) was quickly added under a N_2 atmosphere to the reaction mixture, followed by additional purging with N_2 (x 3) and the resulting mixture was stirred at 120 °C for overnight. Next, the reaction mixture was cooled to RT and then quenched with water (20 mL/mmol). The resulting mixture was extracted with EA (20 mL/mmol x 3), and the organic phases were dried over anhydrous Na_2SO4 and filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography or preparative-TLC to afford the coupled ring system.

General Procedure G: Preparation of an Alkoxy Heteroaryl Group Using Substitution Between an Organohalide and Aliphatic Alcohol

[00223] To a suspension of alcohol (1.5 equivalent) in anhydrous THF (10 mL/0.1 mmol) was added 60% NaH (5.0 equivalents) and the mixture was stirred at 50 °C for 30 min and then cooled to 0 °C. Organochloride (1.0 equivalent) was then added to the mixture, and the resulting mixture was stirred at 0 °C for 20 min and then concentrated *in vacuo*. The resulting crude product was purified by column chromatography on silica gel to afford the alkoxy substituted compound.

General Procedure H: Preparation of a Heteroaryl Ether Using Substitution Between an Organohalide and a Substitited Phenol or Pyridinol

[00224] To a solution of organochloride (1.0 equivalent) and alcohol (1.1 equivalent) in DMF (2 mL/0.1 mmol) was added K_2CO_3 (2.0 equivalents). The resulting mixture was stirred at 50 °C for 2-5 h under microwave conditions, then cooled to RT and diluted with DCM (50 mL/0.1 mmol). The organic phase was washed with 1N HCl (50 mL/0.1 mmol), sat. $NaHCO_3$ (50 mL/0.1 mmol), and brine (50 mL/0.1 mmol), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the resulting residue was purified by preparative-HPLC to afford the ether compound.

General Procedure I: Preparation of a Heteroaryl Amine Using Substitution Between an Organohalide and an Aliphatic Amine

[00225] A solution of organochloride (1.0 equivalent), amine hydrochloride (1.3 equivalent) and DIEA (3.0 equivalents) in DMF (5 mL/l mmol) was stirred at 60 °C for 5 h, then cooled to RT and diluted with EA (30 mL/mmol). The resulting mixture was washed with H_20 (10 mL/mmol x 3) and the organic phases were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*, and the resulting residue was purified by silica gel column chromatography to afford the amine compound.

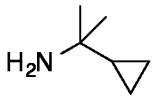
General Procedure J: Preparation of Coupled Imidazolidinyl Groups Using Buchwald Catalyzed Coupling Conditions Between an Organohalide and Imidazolidinyl Reagent

[00226] A solution of organochloride (1.0 equivalent), imidazolidinyl reagent (1.0 -2.0 equivalents), $Pd_2(dba)_3$ (10 mol%), x-antphos (20 mol%) and Cs_2CO_3 (2.1 equivalents) in dioxane (0. 3 mmol/5 mL) was stirred at 110 °C for 2 to 16 h under a N_2 atmosphere. Then, the reaction mixture was cooled to RT, quenched with saturated NH_4Cl (20 mL), and extracted with EA (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography to afford the coupled ring system.

Part II - Preparation of Specific Amine Compounds

[00227] Exemplary procedures for preparing specific amine compounds useful in the preparation of certain imidazo[l,5-a]pyrimidine-8-carboxamide compounds are provided below.

2-Cyclopropylpropan-2- amine

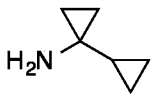


[00228] To a solution of 1-cyclopropylethan-l-one (1.0 g, 11.2 mmol) in anhydrous Et^O (5 mL) was added a solution of MgMeBr (4.4 mL, 13.2 mmol) at a rate suitable to maintain gentle reflux of the solvent, to afford the expected alcoholate as a white precipitate. The reaction mixture was maintained refiuxing for an additional 30 minutes, then stirred at RT overnight, and quenched with sat. NH_4C1 solution (5 mL). The resulting mixture was extracted with Et^O (5 mL), and the combined organic layers were washed with brine (5 mL), dried over **Na2SC)4,** and filtered. The filtrate was concentrated *in vacuo* to afford 2-cyclopropylpropan-2-ol as a pale yellow oil (1.1 g, 92%). ¾NMR (500 MHz, $CDC1_3$) δ 1.18 (s, 6H), 0.97-0.94 (m, 1H), 0.39-0.30 (m, 4H).

[00229] To a stirred solution of 2-cyclopropylpropan-2-ol (1.1 g, 11.2 mmol) in $CHCI_3$ (10 mL) was added NaN_3 (1.08 g, 15.8 mmol) and CI3CO2H (2.8 g, 17.2 mmol) successively at RT. The mixture was stirred at RT for 2 h, washed with two portions of 10% aqueous $NaHCO_3$ solution (5 mL), brine (10 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford (2-azidopropan-2-yl)cyclopropane as a clear oil (1.2 g, 85%).

[00230] To a suspension of $L1AIH_4$ (670 mg, 17.7 mmol) in anhydrous diethyl ether (6 mL) was added a solution of (2-azidopropan-2-yl)cyclopropane (1.2 g, 11.2 mmol) in 4 mL of anhydrous diethyl ether at a rate such that reflux was maintained. After refluxing for 2 h, the reaction mixture was cooled to 0 °C, quenched by careful addition of 0.67 mL of H_20 **,** 0.67 mL of 15% NaOH solution, and 2.0 mL of H_20 **,** successively. The solid was filtered off and the filtrate was concentrated *in vacuo* to afford 2-cyclopropylpropan-2-amine as a clear oil (1.0 g, 90%).

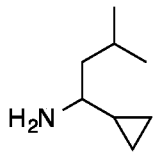
[1,1'-Bi(cyclopropan)l -1-amine



[00231] To a solution of cyclopropanecarbonitrile (1.0 g, 15 mmol) in diethyl ether (15 mL) was added $Ti(OiPr)_4$ (4.66 g, 16.4 mmol) and the solution was cooled to -78 °C and EtMgBr solution (3 M in ether, 30 mmol) was slowly added. After 10 minutes at -78° C, the slurry was

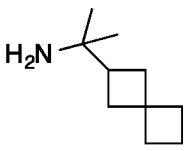
allowed to warm up to RT and stirred for 1 h. $BF_3.OEt_2$ (4.26 g, 30 mmol) was added and the mixture was stirred at RT for 18 h. To this mixture, 2N NaOH (30 mL) was slowly added at 0 °C. The organic phase was separated and extracted with 2N HC1 (30 mL). The aqueous phase was concentrated *in vacuo* and the resulting residue was triturated in diethyl ether to afford [l, 1'-bi(cyclopropan)]-l-amine (0.5 g, 34%) as the hydrochloride salt.

l-Cvclopropyl-3-methylbutan-l-amine



[00232] A mixture of cyclopropanecarbonitrile (5.0 g, 74.6 mmol) and iBuMgBr (326 mg, 2.4 mmol) in diethyl ether (10 mL) was stirred at reflux for 5 h, quenched with sat. NH_4C1 solution (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were dried over anhydrous Na2S04 and filtered. The filtrate was concentrated *in vacuo* to give crude imine (7.5 g, 80%), which was used directly in the next step. A mixture of imine (7.5 g, 60 mmol) and NaB¾ (2.28 g, 60 mmol) in MeOH (50 mL) was stirred at RT for 3 h, quenched with water (50 mL) and extracted with EtOAc (50 mL x 3). The organic layers were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo,* and the resulting residue was dissolved in HCl/dioxane (50 mL, 4M). The resulting mixture was stirred at RT for 30 min and concentrated *in vacuo.* Diethyl ether (50 mL) was added resulting in a precipitate, which was filtered and dried to give l-cyclopropyl-3-methylbutan-l -amine (1.5 g, 16%) as a pale yellow solid.

2-(Spiro [3.31heptan-2-yl)propan-2- amine



[00233] Concentrated H2SO4 (0.5 mL) was added dropwise to a solution of spiro[3.3]heptane-2-carboxylic acid (1 g, 7.14 mmol) in EtOH (30 mL) at 0 °C and the reaction mixture was refluxed for 20 h. After completion of the reaction, the solvent was removed and the reaction mixture was dissolved in EtOAc (150 mL). The organic layer was washed with saturated $NaHC0_3$ solution (100 mL), dried over anhydrous $MgS0_4$, and filtered. The filtrate

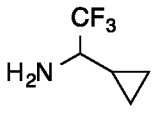
was concentrated *in vacuo* to give ethyl spiro[3.3]heptane-2-carboxylate (1.2 g, 100%) as a colorless oil which was used directly in the next step. ^{1}H NMR (500 MHz, $CDC1_3$) δ 4.04 (q, *J* = 7.0 Hz, 2H), 2.94-2.78 (m, 1H), 2.14 (p, *J* = 11.0 Hz, 4H), 1.95 (t, *J* = 7.5 Hz, 2H), 1.85 (t, *J* = 7.4 Hz, 2H), 1.73 (dd, *J* = 15.0 Hz, 7.5 Hz, 2H), 1.17 (t, *J* = 7.5 Hz, 3H).

[00234] To a solution of ethyl spiro[3.3]heptane-2-carboxylate (1.2 g, 7.14 mmol) in anhydrous THF (20 mL) at -78 °C was added dropwise a solution of MeMgBr (3.0 M in Et_20; 9.52 mL, 28.56 mmol). The reaction mixture was then stirred at RT for 18 h, poured cautiously into sat. NH_4CI solution (20 mL) and extracted with EtOAc (30 mL x 3). The combine organic layers were washed with brine (40 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to give 2-(spiro[3.3]heptan-2-yl)propan-2-ol (1.0 g, 96%) as a colorless oil, which was used in the next step without further purification. ^{1}H NMR (500 MHz, DMSO-*di)* δ 3.94 (s, 1H), 2.02-2.04 (m, 1H), 1.96 (t, *J* = 7.0 Hz, 2H), 1.87-1.80 (m, 2H), 1.78-1.73 (m, 6H), 0.93 (s, 6H).

[00235] A stirred mixture of 2-(spiro[3.3]heptan-2-yl)propan-2-ol (1.0 g, 6.49 mmol), $TMSN_3$ (2.95 g, 25.96 mmol) and molecular sieve (100 mg) in dry CH_2C1_2 (40 mL) at RT under Ar was treated with $BF_3 \cdot Et^O$ (1.8 g, 12.98 mmol). After stirring for 24 h, the resulting solution was quenched with water (100 mL). The organic layer was separated, washed with saturated $NaHCO_3$ solution (30 mL), water (30 mL) and brine (30 mL), dried over anhydrous $MgSC>4$ and filtered. The filtrate was concentrated *in vacuo.* The resulting residue was purified by silica gel column (PE/EtOAc; 3:1) to give 2-(2-azidopropan-2-yl)spiro[3.3]heptane (1.1 g) as a colorless oil.

[00236] A mixture of 2-(2-azidopropan-2-yl)spiro[3.3]heptane (1.1 g, 6.14 mmol) and Pd/C (100 mg, 10% w/w) in MeOH (5 mL) was stirred under a H_2 atmosphere at room temperature for 20 hours. The catalyst was removed by filtration through a pad of *celite* and the filtrates were concentrated to give 2-(spiro[3.3]heptan-2-yl)propan-2-amine (580 mg, 52%) as a colorless oil. LC-MS m/z: 157.2 $[M+H]^+$.

l-Cyclopropyl-2,2,2-trifluoroethan-l-amine

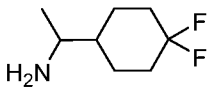


[00237] A suspension of cyclopropanecarbaldehyde (7.0 g, 100 mmol), benzylamine (11.2 g, 105 mmol) and $MgSO_4$ (62 g, 500 mmol) in DCM (200 mL) was stirred for 48 h at RT. After reaction completion the solution was filtered through celite and the filtrate was concentrated *in vacuo* to give *N*-benzyl-l-cyclopropyl methanimine as a light yellow oil (16 g, 100%). LC-MS weak MS: m/z: 159.1 $[M+H]^+$.

[00238] To a solution of *N*-benzyl-l-cyclopropyl methanimine (6.0 g, 37.7 mmol) in MeCN (70 mL) was added KHF_2 (2.35 g, 30.2 mmol), CF_3COOH (5.54 g, 48.6 mmol) and DMF (5 mL) and the mixture was stirred at RT. The reaction mixture was cooled to 0 °C for 5 minutes, and then $TMSCF_3$ (8.4 mL, 56.6 mmol) was added. After addition, the reaction mixture was stirred for 12 h at RT until the starting material was completely consumed (LCMS). Saturated Na_2CO_3 solution (20 mL) was added, stirred for 5 minutes and then 150 mL of water was added and the mixture was extracted with EtOAc (150 mL x 3). The organic phases were combined, dried over Na2S04, filtered and concentrated *in vacuo.* The resulting residue was purified by flash chromatography on silica gel (DCM:MeOH; 30:1 to 5:1) to give *N*-benzyl-l-cyclopropyl-2,2,2-trifluoroethan-l -amine as a colorless oil (3.5 g, yield: 41%). LC-MS m/z: 230.1 $[M+H]^+$. LC-MS Purity (214 nm): 97%; t_R = 1.82 minutes.

[00239] To a solution of *N*-benzyl-l-cyclopropyl-2,2,2-trifluoroethan-l-amine (3.5 g, 15.3 mmol) in MeOH (50 mL) was added 6 N HC1 (4 mL) at RT. The mixture was purged with N_2 three times and then Pd/C (350 mg, 10%, w/w) was added quickly under N_2 flow. The mixture was purged with H_2 three more times, and stirred for 16 hours at room temperature. Pd/C was removed by filtration, and the filtrate was concentrated *in vacuo* to give l-cyclopropyl-2,2,2-trifluoroethan-1 -amine as a white solid (3.5 g, 100%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.35 (s, 3H), 3.63-3.58 (m, 1H), 1.11-1.06 (m, 1H), 0.72-0.66 (m, 4H). LC-MS m/z: 140.2 $[M+H]^+$.

l-(4,4-Difluorocvclohexyl)ethan-l-amine



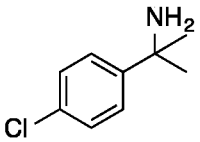
[00240] To a solution of 4,4-difiuorocyclohexane-l-carboxylic acid (1.64 g, 10 mmol) and DIPEA (2.58 g, 20 mmol) in DMF (10 mL) at 0 °C was added HATU (5.7 g, 15 mmol) and the reaction mixture was stirred at 0 °C for 30 min, followed by the addition of N,O-dimethylhydroxylamine hydrochloride (970 mg, 10 mmol). The reaction mixture was allowed to warm to RT and stirred overnight, then quenched with saturated $NaHCO_3$ solution, and

separated. The aqueous phase was extracted with EtOAc (100 mL x3), and the combined organic phases were dried over **Na2SC)4**, filtered and concentrated *in vacuo.* The resulting residue was purified by silica gel chromatography (PE/EtOAc; 4:1) to afford 4,4-difluoro -*N*-methoxy -*N*-methylcyclohexane-l-carboxamide (880 mg, 42 %) as a colorless oil. LC-MS m/z: 208.0 $[M+H]^+$. LCMS: t_R = 1.58 min.

[00241] To a solution of 4,4-difluoro -*N*-methoxy -*N*-methylcyclohexane-l-carboxamide (880 mg, 4.25 mmol) in THF (12 mL) was added a solution of MeLi in 1,2-diethoxy ethane (3 mol/L, 2 mL) dropwise at 0 °C. After the addition was complete, the reaction mixture was allowed to warm to RT and stirred overnight, then quenched with saturated NH_4C1 solution and separated. The aqueous phase was extracted with EtOAc (120 mL x 3), and the combined organic phases were dried over **Na2SC)4**, filtered and concentrated *in vacuo.* The resulting residue was purified by silica gel chromatography (PE/EA = 4:1) to afford l-(4,4-difluorocyclohexyl)ethan-l-one (400mg, 43 %) as a light yellow oil. ^1H NMR (500 MHz, $CDC1_3$) δ 2.44 (m, 1H), 2.19 (s, 3H), 2.13-2.16 (m, 2H), 1.96-1.98 (m, 2H), 1.74-1.83 (m, 4H).

[00242] A mixture of l-(4,4-difluorocyclohexyl)ethan-l-one ((200 mg, 1.23 mmol), NH_4OAc (1.9 g, 24.6 mmol) andNaBH $_3$CN (388 mg, 6.15 mmol) in i-PrOH (15 mL) was stirred at RT for 4 h and then at 90 °C for 2 h. Then, the reaction mixture was poured into water (15 mL), extracted with **CH2CI2** (30 ml, x3) and dried over **Na2SC)4**, filtered and concentrated *in vacuo.* The resulting residue was purified by silica gel chromatography (EtOAc/MeOH; 10:1) to afford l-(4,4-difluorocyclohexyl)ethan-l -amine as a colorless oil. LC-MS m/z: 164.1 $[M+H]^+$. LCMS: t_R = 1.13 min.

2-(4-Chlorophenyl)propan-2- amine



[00243] MgBrMe (3M in THF, 5 mL, 15 mmol) was added dropwise at RT to a solution of l-(4-chlorophenyl)ethan-l-one (1.54 g, 10 mol) in Et_20 (60 mL). After the addition was complete the reaction mixture was stirred at RT for 12 hours and then quenched by the careful addition of saturated NH_4C1 solution (30 mL). The resulting mixture was stirred for 1 hour and then extracted with EtOAc (100 mL χ 3). The combined organic layers were dried over $Na_2SC>4$, filtered, concentrated *in vacuo,* and purified by silica gel chromatography (PE/EtOAc;

5:1) to give 2-(4-chlorophenyl)propan-2-ol (1.365 g, 80%) as a colorless oil. ^{1}H NMR (400 MHz, $CDC1_3$) δ 7.42 (dd, *J* = 6.8 Hz, 2.0 Hz, 2H). 7.29 (dd, *J* = 6.8 Hz, 2.0 Hz, 2H), 1.78 (s, 1H), 1.56 (s, 6H).

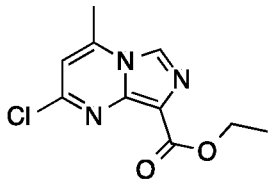
[00244] A mixture of 2-(4-chlorophenyl)propan-2-ol (1.36 g, 8 mmol), $TMSN_3$ (2.4 g, 16 mmol) and $BF_3 \cdot Et20$ (16 mL) in **CH2CI2** (20 mL) was stirred at RT for 2 h and quenched with saturated $NaHC0_3$ solution. The resulting mixture was separated, and the aqueous phase was extracted with **CH2CI2** (30 mL χ 3). The combined organic phases were dried over $Na2SC)_4$ and filtered. The filtrate was concentrated *in vacuo* to afford the target compound l-(2-azidopropan-2-yl)-4-chlorobenzene as colorless oil, which was used in the next step without further purification. LC-MS m/z: 153.0 $[M - N_3]^+$. LCMS: Purity (254 nm) : 44 %; t_R = 1.44 min.

[00245] The crude azide from the previous step was dissolved in THF (15 mL) at RT and trimethylphosphine (16 mL, 1.0 M in THF) was added. After 15 minutes, 3 mL of water was added, and the resulting mixture was stirred at RT for 2 h until the reaction was complete (monitored by LC/MS.) The solvent was removed *in vacuo* and the resulting residue was diluted with water (75 mL), extracted with **CH2CI2,** dried over sodium sulfate and filtered. The filtrate was concentrated *in vacuo,* and the resulting residue was purified by reversed-phase chromatography (0.05%TFA/MeCN) to give the desired product 2-(4-chlorophenyl)propan-2-amine (200 mg, 57% over two steps) as a pale oil. LC-MS m/z: 153.0 $[M - NH_2]^+$. LCMS: Purity (214 nm): 98%; t_R = 1.71 min.

Part III - Preparation of Specific Carboxylic Ester Compounds

[00246] Exemplary procedures for preparing specific carboxylic ester compounds useful in the preparation of certain substituted imidazo[l,5-a]pyrimidine compounds are provided below.

Ethyl 2-chloro-4-methylimidazo [1,5-al pyrimidine-8-carboxylate



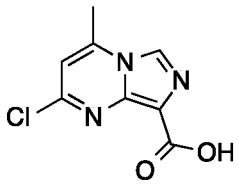
[00247] A solution of 5-amino-l *H*-imidazole-4-carboxarnide (35 g, 277 mmol) in $MeS0_3H$ (150 mL) and EtOH (560 mL) was stirred at reflux conditions for 2 days, and then concentrated

in vacuo. To the resulting residue, water (400 mL) was added and while stirring and cooling (ice/water) sodium hydroxide solution (32 %) was added until pH = 7 was reached. The water layer was saturated with sodium chloride and extracted with DCM (200 mL x 3). The combined organic layers were dried ($MgSO_4$), and filtered. The filtrate was concentrated *in vacuo* to afford ethyl 5-amino-l*H*-imidazole-4-carboxylate (13.7 g, 45%) as a white solid.

[00248] To a solution of ethyl 3-ethoxybut-2-enoate (30.6 g, 193.5 mmol) in DMF (300 mL) was added ethyl 5-amino-l*H*-imidazole-4-carboxy late (30 g, 193.5 mmol). The reaction mixture was stirred at 110 °C for 12 h, then cooled to RT, water (500 mL) added, and the resulting mixture was extracted with DCM:iPrOH = 4:1 (2500 mL x 3). The organic phases were washed with brine, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentracted *in vacuo* and the residue was purified by silica gel column (DCM:MeOH = 20: 1) to afford ethyl 2-hydroxy-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (31.8 g, 74%) as a yellow solid. LCMS: Purity (254 nm): > 99%; t_R = 0.84 min.

[00249] The solution of ethyl 2-hydroxy-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (31.8 g, 143.9 mmol) in 300 mL of $POCl_3$ was stirred at 110 °C for one hour, and concentrated *in vacuo.* The resulting residue was redissolved in DCM (50 mL) and added to saturated $NaHCO_3$ solution (2000 mL) at 0 °C. The mixture was extracted with DCM (2000 mL x 3), and the organic phases were washed with brine (1000 mL x 3), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentracted *in vacuo,* and the resulting residue was purified by silica gel column (EA:MeOH = 50:1 to 20:1) to afford ethyl 2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (26 g, 76%) as a yellow solid. LCMS: Purity (254 nm): >96%; t_R = 1.08 min.

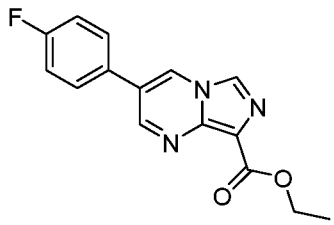
2-Chloro-4-methylimidazo [1,5-al pyrimidine-8-carboxylic acid



[00250] A mixture of ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (1.0 g, 4.18 mmol) and bis(tributyltin) oxide (6 mL, 12.5 mmol) in toluene (20 mL) was stirred at 100 °C for 2 days, then cooled and concentrated *in vacuo.* The resulting residue was dissolved in EtOAc (50 mL) and basified with saturated $NaHCO_3$ to pH ~ 8. The aqueous phase was

separated, acidified with 6M HC1 to pH ~6, and extracted with DCM (50 mL x 3). The organic phases were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (300 mg, 30 %) as a yellow solid. LC-MS m/z: 211.9 $[M+H]^+$. LCMS: t_R = 1.20 min

Ethyl 3-(4-fluorophenyl)imidazo[l,5-«lpyrimidine-8-carboxylate

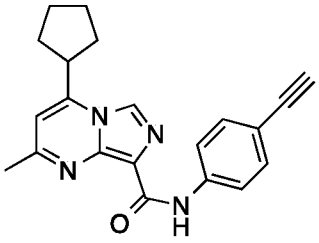


[00251] To a solution of ethyl 5-amino-l *H*-imidazole-4-carboxylate (248 mg, 1.6 mmol) in AcOH (15 mL) was added 2-(4-fluorophenyl)malonaldehyde (250 mg, 1.6 mmol) at 90 °C. Then the reaction mixture was stirred for 2 hours at 90 °C, cooled, and concentrated *in vacuo*. The resulting residue was purified by silica gel column (PE/EA = 3/1) to afford ethyl 3-(4-fluorophenyl)imidazo[l,5-a]pyrirnidine-8-carboxylate (301 mg, 66%) as a yellow solid. LC-MS m/z: 286.1 $[M+H]^+$.

Part IV- Imidazo[l,5-alpyrimidine-8-carboxamide Compounds Prepared Following General Procedures

[00252] The following compounds were prepared based on the general procedures described in Part I above.

4-Cvclopentyl-A/-(4-ethvnylphenyl)-2-methylimidazo [1,5-al pyrimidine-8-carboxamide



[00253] To a suspension of NaH (1.76 g, 43.85 mmol) in THF (50 mL) was added dropwise a solution of tert-butyl 3-oxobutanoate (6.93 g, 43.85 mmol) in THF (50 mL) at 0 °C. The mixture was stirred at RT for an hour, and a solution of cyclopentanecarbonyl chloride (1.1 g, 8.8 mmol) in THF (20 mL) was added. The mixture was stirred at RT overnight, quenched with saturated NH_4C1 (80 mL) and extracted with EtOAc (150 mL x 3). The combined organic

phases were concentrated *in vacuo,* and the resulting residue was purified by silica gel column chromatography (5% EA/PE) to afford *tert*-butyl 2-(cyclopentanecarbonyl)-3-oxobutanoate (1.6 g) as a colorless oil which was used directly in the next step. ^{1}H NMR (500 MHz, $CDCI_3$): δ 5.52 (s, 1H), 2.28 (s, 3H), 2.27 (s, 1H), 1.98-1.73 (m, 8H), 1.56 (s, 9H).

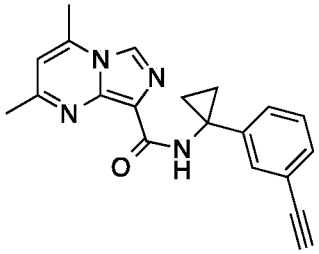
[00254] A mixture of *tert*-butyl 2-(cyclopentanecarbonyl)-3-oxobutanoate (800 mg) and p-toluenensulfonic acid monohydrate (190 mg) in toluene (20 mL) was stirred at 80 °C under N_2 overnight, and then concentrated *in vacuo.* The resulting residue was purified by silica gel column chromatography (5% EA/PE) to afford l-cyclopentylbutane-l ,3-dione (370 mg, 27.3% yield over two steps) as a colorless oil. ¾ NMR (500 MHz, $CDC1_3$): δ 15.58 (s, 1H), 5.53 (s, 1H), 2.68-2.65 (m, 1H), 2.06 (s, 3H), 1.88-1.58 (m, 8H). LC-MS m/z: 155.2 $[M+H]^+$.

[00255] A mixture of l-cyclopentylbutane-l ,3-dione (350 mg, 2.27 mmol) and ethyl 5-amino-l *H*-imidazole-4-carboxylate (352 mg, 2.27 mmol) in HOAc (20 mL) was stirred at 110 °C for 2 h, and then concentrated *in vacuo.* The crude was purified by silica gel column chromatography (PE/EA; 1/1) to afford 150 mg of the impure compound as light yellow oil, which was further purified by prep-HPLC to afford ethyl 4-cyclopentyl-2-methylimidazo[l ,5-a]pyrimidine-8-carboxylate (50 mg, 8%) as a light yellow oil. ^{1}H NMR (500 MHz, $CDC1_3$): δ 8.01 (s, 1H), 6,56 (d, J = 1.0 Hz, 1H), 4.48 (q, J = 9.0 Hz, 2H), 3.41-3.37 (m, 1H), 2.65 (s, 3H), 2.28-2.23 (m, 2H), 1.85-1.76 (m, 6H), 1.45 (t, J = 9.0 Hz, 3H). LC-MS m/z: 274.1 $[M+H]^+$.

[00256] Following general procedure B, ethyl 4-cyclopentyl-2-methylimidazo[l ,5-a]pyrimidine-8-carboxylate (50 mg, 0.18 mmol) afforded 4-cyclopentyl-2-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid ((30 mg, 68%) as a grey solid. LC-MS m/z: 246.3 $[M+H]^+$.

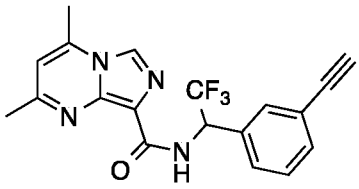
[00257] Following general procedure A, 4-cyclopentyl-2-methylimidazo[l ,5-a]pyrirnidine-8-carboxylic acid (25 mg, 0.1 mmol) and 4-ethynylaniline afforded the title compound (16 mg, 46.5%) as a grey solid. ^{1}H NMR (500 MHz, $CDC1_3$): δ 10.04 (s, 1H), 8.10 (s, 1H), 7.80 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 6.59 (s, 1H), 3.43 (m, 1H), 3.06 (s, 1H), 2.70 (s, 3H), 2.33-2.30 (m, 2H), 1.92-1.85 (m, 6H). LC-MS m/z: 345.1 $[M+H]^+$. HPLC Purity (214 nm): >99%; t_R =9.16 min.

A/-(l-(3-Ethvnylphenyl)cvclopropyl)-2,4-dimethylimidazo[l,5-alpyrimidine-8-carboxamide



[00258] Following general procedure A, 2,4-dimethylirnidazo[l,5-a]pyrirnidine-8-carboxylic acid (100 mg, 0.52 mmol) and l-(3-ethynylphenyl)cyclopropan-l -amine afforded the title compound (74.6 mg, 36%) as a white solid. ^{1}H NMR(500 MHz, *MeOO-d$_4$)* δ 8.32 (s, 1H), 7.43 (s, 1H), 7.30-7.27 (m, 3H), 6.82 (s, 1H), 3.42 (s, 1H), 2.75 (s, 3H), 2.64 (s, 3H), 1.54-1.33 (m, 4H). LC-MS m/z: 331.2 $[M+H]^+$. LCMS: t_R = 1.87 minutes. HPLC: Purity (214 nm): >96%; t_R = 9.24 min.

A/-(l-(3-Ethvnylphenyl)-2,2,2-trifluoroethyl)-24-dimethylimidazo[l,5-alpyrimidine-8-carboxamide



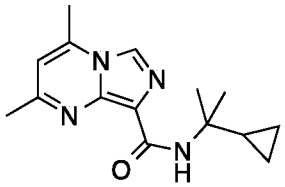
[00259] To a solution of l-(3-bromophenyl)-2,2,2-trifluoroethan-l-one (2.53 g, 10 mmol) in toluene (25 mL) at RT was added lithium bis(trimethylsilylamide) (11.17 mL, 11.17 mmol, 1 M in THF) over 10 min. The reaction mixture was stirred at RT for 30 min, and BH_3.Me2S (10 mL, 20 mmol, 2 M in toluene) was added and the reaction mixture was stirred at RT for another 30 min. After cooling to 0 °C, 2 N NaOH (10 mL) was carefully added dropwise over 5 minutes, the mixture was stirred at RT for 90 min and the layers were separated. The organic layer was washed with aqueous 2 N NaOH (10 mL), water (10 mL), dried over anhydrous Na_2SO_4 and filtered. The solution was then treated with 4 mL of 4 M HC1 in 1,4-dioxane resulting in a white precipitate. After standing at room temperature for 1 h, the slurry was filtered, and the solids were washed with Et^O (20 mL) to afford l-(3-bromophenyl)-2,2,2-trifluoroethan-1 -amine as a white powder (2.04 g, 80%). LCMS m/z: 254.0 $[M+H]^+$. LCMS: t_R = 1.96 min.

[00260] A solution of 1-(3-bromophenyl)-2,2,2-trifluoroethan-l -amine (280 mg, 0.96 mmol), trimethylsilylacetylene (190 mg, 1.93 mmol), $Pd(PPh_3)_2Cl_2$ (68 mg, 0.96 mmol) and Cul (20 mg, 0.96 mmol) in triethylamine (4 mL) was stirred at room temperature for 16 h under a N_2 atmosphere. The solution was filtered and the filtrate was concentrated *in vacuo* and purified by column chromatography on silica gel (PE/EA; 10: 1) to afford 2,2,2-trifluoro-l-(3-((trimethylsilyl)ethynyl)phenyl)ethan-l -amine as a brown solid (183 mg, 70%). LCMS m/z: 271.3 $[M+H]^+$. LCMS: t_R = 2.28 min.

[00261] Following general procedure A, 2,4-dimethylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (65 mg, 0.34 mmol) and l-(3-ethynylphenyl)-2,2,2-trifluoroethan-l-amine afforded 2,4-dimethyl -*N*-(2,2,2-trifluoro-l-(3-((trimethylsilyl)ethynyl)phenyl)ethyl)imidazo[l,5-a]pyrinddine-8-carboxaiTd de (135 mg, 90%) as a yellow solid. LCMS m/z: 444.5 $[M+H]^+$. LCMS: t_R = 2.06 min.

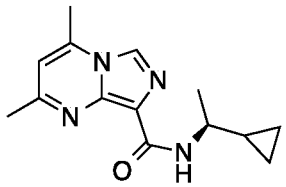
[00262] To a solution of 2,4-dimethyl -*N*-(2,2,2-trifluoro-l-(3-((trimethylsilyl)ethynyl)phenyl)ethyl)imidazo[l,5-a]pyrinddine-8-carboxamide (135 mg, 0.30 mmol) in MeOH (2 mL) was added K_2CO_3 (82 mg 0.60 mmol). The solution was stirred at RT for 2 h and then purified by prep-HPLC (10 mM NH_4HC0_3/MeCN) to provide the title compound (91 mg, 80%) as a yellow solid. ^1H NMR (500 MHz, $CDC1_3$) δ 8.97 (d, *J* = 9.5 Hz, 1H), 7.99 (s, 1H), 7.70 (s, 1H), 7.52-7.49 (m, 2H), 7.36 (t, *J* = 8.0 Hz, 1H), 6.55 (d, *J* = 1.0 Hz, 1H), 6.06-6.02 (m, 1H), 3.09 (s, 1H), 2.67 (s, 6H). LC-MS m/z: 372.3 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 9.68 min.

A/-(2-Cvclopropylpropan-2-yl)-2,4-dimethylimidazo[l,5-alpyrimidine-8-carboxamide



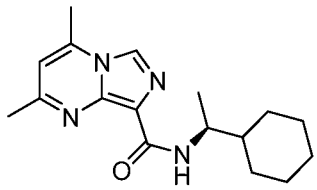
[00263] Following general procedure A, 2,4-dimethylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (40 mg, 0.2 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (20.8 mg, 28%) as ayellow solid. ^1H NMR (500 MHz, $CDC1_3$) δ 7.90 (s, 1H), 7.72 (s, 1H), 6.46 (s, 1H), 2.62 (s, 3H), 2.59 (s, 3H), 1.44 (s, 6H), 1.42-1.38 (m, 1H), 0.46 (d, *J* = 7.0 Hz, 4H). LC-MS m/z: 272.1 $[M+H]^+$. HPLC Purity (214 nm): >99%; t_R = 8.97 min.

(.s')-A/-(l-Cvclopropylethyl)-2,4-dimethylimidazo[l,5-alpyrimidine-8-carboxamide



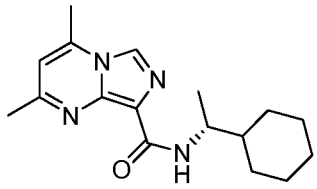
[00264] Following general procedure A, 2,4-dimethylimidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 0.16 mmol) and (<S)-l-cyclopropylethan-l -amine afforded the title compound (27.5 mg, 68 %) as a white solid. ^{1}H NMR (500 MHz, CDC1$_3$): δ 7.93 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 6.49 (s, 1H), 3.82-3.77 (m, 1H), 2.64 (s, 3H), 2.61 (s, 3H), 1.34 (d, *J* = 6.5 Hz, 3H), 0.99-0.96 (m, 1H), 0.53-0.44 (m, 3H), 0.32-0.30 (m, 1H). LCMS m/z: 259.2 [M+H]$^+$. HPLC: Purity (214 nm): >99%; t_R = 8.43 min.

^-^-(l-Cvclohexylethvn-Z^-dimethylimidazofl^-alpyrimidine-S-carboxamide



[00265] Following general procedure A, 2,4-dimethylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (50 mg, 0.26 mmol) and (5)-l-cyclohexylethanamine afforded the title compound (72 mg, 92%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-c¾): δ 8.35 (s, 1H), 8.05 (d, *J* = 9.0 Hz, 1H), 6.81 (s, 1H), 3.94-3.89 (m, 1H), 2.66 (s, 3H), 2.52 (s, 3H), 1.81-1.78 (m, 1H), 1.74-1.69 (m, 3H), 1.64-1.61 (m, 1H), 1.45-1.43 (m, 1H), 1.23-1.17 (m, 2H), 1.14 (d, *J* = 6.5 Hz, 3H), 1.11-0.99 (m, 3H). LC-MS m/z: 301.3 [M+H]$^+$. LC-MS Purity (214 nm): > 99%; t_R = 9.76 min.

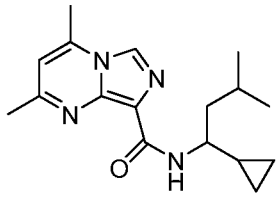
***(i*?)-A/-(l-Cvclohexylethyl)-2,4-dimethylimidazo[l,5-alpyrimidine-8-carboxamide**



[00266] Following general procedure A, 2,4-dimethylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (20 mg, 0.10 mmol) and (i?)-l-cyclohexylethanamine afforded the title compound (10 mg, 33%) as a yellow solid. ^{1}H NMR (500 MHz, CDC1$_3$): δ 8.42 (d, *J* = 8.0 Hz,

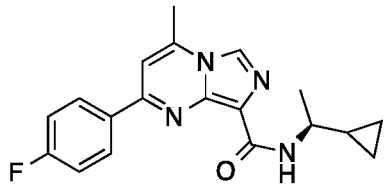
1H), 7.52 (s, 1H), 6.42 (s, 1H), 4.15-4.10 (m, 1H), 2.49 (s, 3H), 2.45 (s, 3H), 1.81 (d, J = 12.0 Hz, 1H), 1.75-1.65 (m, 3H), 1.60 (d, J = 12.5 Hz, 1H), 1.46-1.42 (m, 1H), 1.23-1.15 (m, 2H), 1.17 (d, J = 6.5 Hz, 3H), 1.11-1.02 (m, 3H). LC-MS m/z: 301.0 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 10.21 min.

A/-(l-Cvclopropyl-3-methylbuM)-2,4-dimethylimidazo[l,5-alpyrimidine-8-carboxamide



[00267] Following general procedure A, 2,4-dimethylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (100 mg, 0.50 mmol) and l-cyclopropyl-3-methylbutan-l-amine afforded the title compound (30.3 mg, 20%) as a yellow solid. ^{1}H NMR (500 MHz, $CDC1_3$) δ 7.93 (s, 1H), 7.60 (d, J = 9.0 Hz, 1H), 6.48 (s, 1H), 3.87-3.83 (m, 1H), 2.64 (s, 3H), 2.61 (s, 3H), 1.81-1.77 (m, 1H), 1.55-1.51 (m, 1H), 0.94 (d, J = 6.5 Hz, 3H), 0.93 (d, J = 6.5 Hz, 3H), 0.54-0.47 (m, 2H), 0.42-0.38 (m, 1H), 0.33-0.31 (m, 1H). LC-MS m/z: 301.2 $[M+H]^+$. HPLC: Purity (254 nm): 97%; t_R = 9.71 min.

ffl-iV-(l-Cvclopropylethyl)-2-(4-fluorophenyl)-^ -methylimidazo[1,5-*a*]pyrimidine-8-carboxamide

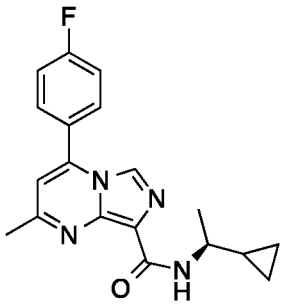


[00268] To a stirred solution of ethyl 5-amino-l *H*-imidazole-4-carboxylate (1.13g, 7.29 mmol) in 50 mL of AcOH was added l-(4-fluorophenyl)butane-l,3-dione (1.44 g, 8.01 mmol) at 110 °C. The reaction mixture was stirred at at 110 °C for 1 hr and then concentrated *in vacuo.* The resulting residue was purified by silica gel column and then by reverse phase chromatography to give ethyl 2-(4-fluorophenyl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (130 mg, 6%) and ethyl 4-(4-fluorophenyl)-2-methylinddazo[l,5-a]pyrimidine-8-carboxylate (1.1 g, 51%) as yellow solids (regiochemistry confirmed by NOESY). ^{1}H NMR (400 MHz, $CDCI_3$): δ 8.52 (s, 1H), 8.04-8.00 (m, 2H), 7.27 (td, J = 6.8 Hz, 2.0 Hz, 2H), 6.92 (s, 1H), 4.43 (q, J = 6.8 Hz, 1H), 2.77 (s, 3H), 1.43 (t, J = 6.8 Hz, 3H).

[00269] Following general procedure B, ethyl 2-(4-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate 130 mg, 0.43 mmol) afforded 2-(4-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (20 mg, 17%) as a yellow solid. LC-MS m/z: 271.9 $[M+H]^+$. LCMS: Purity (214 nm): 85%; t_R = 1.40 min.

[00270] Following general procedure A, 2-(4-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (20 mg, 0.07 mmol) and (<S)-l-cyclopropylethan-l-amine afforded the title compound (8.3 mg, 33%) as a yellow solid. ^{1}H NMR (500 MHz, $CDC1_3$): δ 8.15-8.12 (m, 2H), 8.04 (s, 1H), 7.99 (d, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 2H), 7.06 (s, 1H), 3.86-3.81 (m, 1H), 2.76 (s, 3H), 1.37 (d, *J* = 6.5 Hz, 3H), 1.04-1.01 (m, 1H), 0.54-0.44 (m, 3H), 0.38-0.35 (m, 1H). LC-MS m/z: 339.2 $[M+H]^+$. HPLC Purity (214 nm): >99%; t_R = 7.96 min.

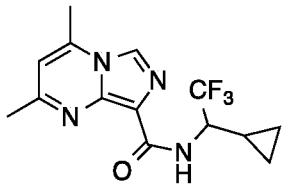
(.S^-A/-(l-Cvclopropylethyl)-4-(4-fluorophenyl)-2-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00271] Following general procedure B, ethyl 4-(4-fluorophenyl)-2-methylimidazo[l,5-a]pyrimidine-8-carboxylate (1.1 g, 3.7 mmol) afforded 4-(4-fluorophenyl)-2-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (630 mg, 62%) as a yellow solid. LC-MS m/z: 271.9 $[M+H]^+$. LC-MS: Purity (214 nm): 84.7%; t_R = 1.45 min.

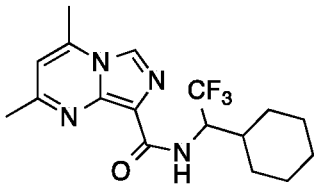
[00272] Following general procedure A, 4-(4-fluorophenyl)-2-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 0.11 mmol) and (<S)-l-cyclopropylethan-l-amine afforded the title compound (32.3 mg, 86%) as a yellow solid. ^{1}H NMR (500 MHz, $CDC1_3$): δ 8.02 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.69-7.67 (m, 2H), 7.32 (t, *J* = 8.5 Hz, 2H), 6.56 (s, 1H), 3.81-3.80 (m, 1H), 2.67 (s, 3H), 1.35 (d, *J* = 6.5 Hz, 3H), 1.00-0.98 (m, 1H), 0.54-0.45 (m, 3H), 0.34-0.32 (m, 1H). LC-MS m/z: 339.1 $[M+H]^+$. HPLC Purity (214 nm): >97%; t_R = 7.91 min.

A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-2,4-dimethylimidazo[l,5-alpyrimidine-8-carboxamide



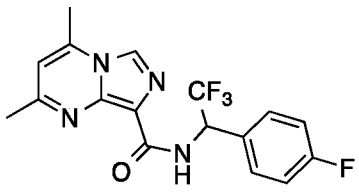
[00273] Following general procedure A, **2**,4-dimethylirnidazo[l,5-a]pyrirnidine-8-carboxylic acid (40 mg, 0.21 mmol) and l-cyclopropyl-2,2,2-trifluoroethan-l-amine afforded the title compound (34.5 mg, 53%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-c¾): δ 8.51 (d, *J* = 9.5 Hz, 1H), 8.44 (s, 1H), 6.88 (s, 1H), 4.40-4.35 (m, 1H), 2.69 (s, 3H), 2.55 (s, 3H), 1.32-1.24 (m, 1H), 0.69-0.64 (m, 1H), 0.59-0.50 (m, 2H), 0.37-0.33 (m, 1H). LC-MS m/z: 313.1 [M+H]$^+$. HPLC: Purity (214 nm): >99%; t_R = 7.23 min.

A/-(l-Cvclohexyl-2,2,2-trifluoroethyl)-2,4-dimethylimidazo[l,5-alpyrimidine-8-carboxamide



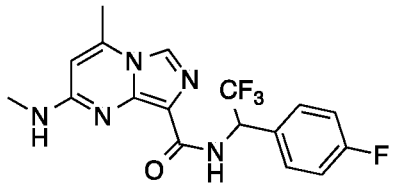
[00274] Following general procedure A, **2**,4-dimethylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (55 mg, 0.288 mmol) and l-cyclohexyl-2,2,2-trifluoroethan-l-amine afforded the title compound (33.4 mg, 32%) as a pale yellow solid. ^{1}H NMR (500 MHz, CDC1$_3$) δ 8.26 (d, *J* = 10 Hz, 1H), 7.98 (s, 1H), 6.54 (s, 1H), 4.90-4.85 (m, 1H), 2.67 (s, 3H), 2.62 (s, 3H), 1.96-1.92 (m, 2H), 1.82-1.72 (m, 3H), 1.67-1.63 (m, 1H), 1.33-1.24 (m, 4H), 1.13-1.08 (m, 1H). LC-MS m/z: 355.1 [M+H]$^+$. HPLC: Purity (214 nm): >99%; t_R = 10.23 min.

2,4-Dimethyl-A/-(2,2,2-trifluoro-l-(4-fluorophenyl)ethyl)imidazo[l,5-alpyrimidine-8-carboxamide



[00275] Following general procedure A, 2,4-dimethylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (180 mg, 0.94 mmol) and 2,2,2-trifluoro-l-(4-fluorophenyl)ethan-l -amine afforded the title compound (160 mg, 47%) as a yellow solid. ^{1}H NMR (500 MHz, $CDC1_3$): δ 8.92 (d, *J* = 10.0 Hz, 1H), 8.01 (s, 1H), 7.51 (dd, *J* = 8.5 Hz, 5.5 Hz, 2H), 7.09 (tt, *J* = 8.5 Hz, 2.0 Hz, 2H), 6.58 (d, *J* = 1.0 Hz, 1H), 6.05 (p, *J* = 8.5 Hz, 1H), 2.67 (d, *J* = 0.5 Hz, 3H), 2.65 (s, 3H). LC-MS m/z: 367.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.75 min.

4-Methyl-2-(methylamino)-A/-(2,2,2-trifluoro-l-(4-fluorophenyl)ethyl)imidazo[l,5-alpyrimidine-8-carboxamide



[00276] To a solution of ethyl 4-methyl-2-(methylthio)imidazo[l,5-a]pyrirnidine-8-carboxylate (251 mg, 1 mmol) in DCM (5 mL) was added a solution of m-CPBA (465 mg, 3.0 mmol) in DCM (5 mL). The resulting solution was stirred at RT overnight, and concentrated *in vacuo.* The resulting residue was purified by silica gel column (EtOAc:MeOH; 20: 1) to afford ethyl 4-methyl-2-(methylsulfonyl)imidazo[l,5-a]pyrimidine-8-carboxylate (266 mg, 94%) as a yellow solid. LC-MS m/z: 284.1 $[M+H]^+$. LCMS Purity: 64%.

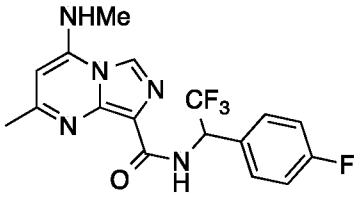
[00277] Following general procedure I, ethyl 4-methyl-2-(methylsulfonyl)imidazo[l,5-a]pyrimidine-8-carboxylate (266 mg, 1.06 mmol) and methylamine afforded ethyl 4-methyl-2-(methylandno)imidazo[l,5-a]pyrimidine-8-carboxylate (160 mg, 73%) as a brown solid. LC-MS m/z: 235.1 $[M+H]^+$. LCMS Purity: 82%.

[00278] Following general procedure B, ethyl 4-methyl-2-(methylamino)imidazo[l,5-a]pyrimidine-8-carboxylate (150 mg, 0.64 mmol) afforded 4-methyl-2-(methylandno)imidazo[l,5-a]pyrimidine-8-carboxylic acid (70 mg, 50%) as a brown solid. LC-MS m/z: 207.1 $[M+H]^+$. LCMS Purity: 99%. t_R = 0.35 min and 0.45 min.

[00279] Following general procedure A, 4-methyl-2-(methylamino)imidazo[l,5-a]pyrimidine-8-carboxylic acid (60 mg, 0.29 mmol) and 2,2,2-trifluoro-l-(4-fluorophenyl)ethan-l -amine afforded the title compound (26 mg, 23%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.34 (d, *J* = 9.5 Hz, 1H), 8.10 (d, *J* = 4.0 Hz, 1H), 8.02 (s, 1H),

7.63 (dd, J = 8.5 Hz, 5.0 Hz, 2H), 7.31 (t, J = 8.5 Hz, 2H), 6.2 (s, 1H), 6.10 (p, J = 8.5 Hz, 1H), 2.94 (d, J = 4.5 Hz, 3H), 2.55 (s, 3H). LC-MS m/z: 382.0 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 7.23 min.

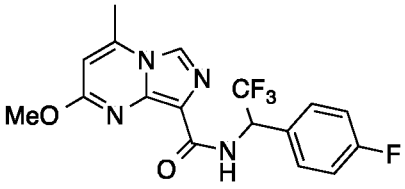
2-Methyl-4-(methylamino)-A/-(2,2,2-trifluoro-l-(4-fluorophenyl)ethyl)imidazo[l,5-a]pyrimidine-8-carboxamide



[00280] A mixture of 4-chloro-2-methyliriiidazo[l,5-a]pyrimidine-8-carboxylic acid (78 mg, 0.37 mmol), ethyl chloroformate (40 mg, 0.369 mmol) and DIPEA (95 mg, 0.74 mmol) in DMF (1 mL) was stirred at 0 °C for 1 h. 2,2,2-Trifluoro-l -(4-fluorophenyl)ethan-l -amine (85 mg, 0.44 mmol) was added at 0 °C, and the mixture was stirred at 40 °C overnight. The crude product was purified by silica gel chromatography (EA) to give 4-chloro-2-methyl -*N* -(2,2,2-trifluoro-l-(4-fluorophenyl)ethyl)inddazo[l,^ -*a*]pyrimidine-8-carboxamide (50 mg, 35 %) as a yellow solid. LC-MS m/z: 387.0 $[M+H]^+$. LCMS: t_R = 1.77 min.

[00281] A mixture of 4-chloro-2-methyl -*N* -(2,2,2-trifluoro-l-(4fluorophenyl)ethyl)imidazo[l ,5-a]pyrinddine-8-carboxamide (20 mg, 0.052 mmol) and methylamine in THF (2 mL) was stirred at 80 °C for 2 hours. The resulting solution was purified by prep-HPLC (10 mM NH_4HC0_3/MeCN) to give the title compound (14 mg, 71%) as a white solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.23 (s, 1H), 7.62 (dd, J = 8.5 Hz, 5.0 Hz, 2H), 7.22 (dd, J = 9.0 Hz, 2.0 Hz, 2H), 6.02 (s, 1H), 5.97 (q, J = 8.0 Hz, 1H), 3.11 (s, 3H), 2.61 (s, 3H). LC-MS m/z: 381.9 $[M+H]^+$. HPLC: Purity (254 nm): >99%; t_R = 7.59 min.

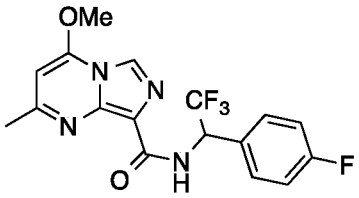
2-Methoxy-4-methyl -A/-(2,2,2-trifluoro-l-(4-fluorophenyl)ethyl)imidazo[l,5-alpyrimidine-8-carboxamide



[00282] To a suspension of ethyl 4-methyl-2-(methylthio)imidazo[l,5-a]pyrimidine-8-carboxylate (502 mg, 2 mmol) in a mixture of MeOH/H_20 (10 niL/10 niL) was added NaOH (400 mg, 10 mmol) at RT. The mixture was heated to reflux (100 °C) for 48 h, then cooled to RT and concentrated *in vacuo.* The resulting residue was suspended in 20 mL of MeOH and filtered to remove the solid. The filtrate was concentrated *in vacuo* and the resulting residue was purified by silica gel column chromatography (MeOH/EA; 1:5) to give 2-methoxy-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid as an off-white solid (240 mg, 58%). LC-MS m/z: 208.0 $[M+H]^+$. LCMS: 56% purity.

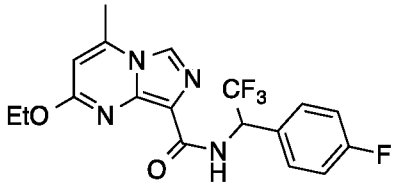
[00283] Following general procedure A, 2-methoxy-4-methyliniidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 0.145 mmol) and 2,2,2-trifluoro-l-(4-fluorophenyl)ethan-l -amine afforded the title compound (9.2 mg, 17%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-c¾) δ 8.25 (s, 1H), 7.62 (dd, *J* = 6.8 Hz, 4.4 Hz, 2H), 7.21 (dd, *J* = 6.8 Hz, 1.6 Hz, 2H), 6.52 (d, *J* = 0.8 Hz, 1 H), 6.01 (q, *J* = 6.4 Hz, 1H), 4.14 (s, 3H), 2.72 (d, *J* = 1.2 Hz, 3H). LC-MS m/z: 383.0 $[M+H]^+$. HPLC: Purity (254 nm): >98%; t_R = 9.81 min.

4-Methoxy-2-methyl -A/-(2,2,2-trifluoro-l-(4-fluorophenyl)ethyl)imidazo[l,5-alpyrimidine-8-carboxamide



[00284] A mixture of 4-chloro-2-methy l-*N*-(2,2,2-trifluoro- 1-(4-fluorophenyl)ethyl)iriiidazo[l,5-a]pyriiTddine-8-carboxamide (10 mg, 0.026 mmol) and MeONa (1.4 mg, 0.026 mmol) in methanol (1 mL) was stirred at RT overnight. The crude product was purified by prep-HPLC (10 mM NH_4HC0_3/MeCN) to give the title compound (4.0 mg, 40%) as a white solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.27 (s, 1H), 7.63 (dd, *J* = 8.5 Hz, 5.5 Hz, 2H), 7.22 (td, *J* = 8.5 Hz, 1.0 Hz, 2H), 6.51 (s, 1H), 6.00 (q, *J* = 7.5 Hz, 1H), 4.26 (s, 3H), 2.71 (s, 3H). LC-MS m/z: 382.9 $[M+H]^+$. HPLC: Purity (254 nm): >99%; t_R = 8.35 min.

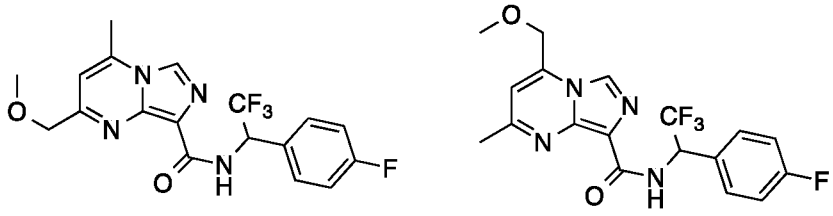
2-Ethoxy-4-methyl-iV-(2,2,2-trifluoro-l-(4-fluorophen^^)ethyl)imidazo[1,5-*a*]pyrimidine-8-carboxamide



[00285] To a suspension of ethyl 4-methyl-2-(methylthio)imidazo[l,5-a]pyrimidine-8-carboxylate (1.2 g, 4.8 mmol) in a mixed solvent of EtOH/H $_2$**0** (20 mL/20 mL) was added NaOH (383 mg, 9.6 mmol) at RT. The mixture was stirred at 80 °C for 2 h, then cooled and concentrated *in vacuo.* The resulting residue was acidified with 2N HC1 to pH = 5 and the resulting solution was extracted with EtOAc (3 x 20 mL) and then dried over MgSC>4. The filtrate was concentrated *in vacuo* to give 4-methyl-2-(ethoxy)imidazo[l,5-a]pyrirnidine-8-carboxylic acid (900 mg, 85%) as a brown solid. LC-MS m/z: 222.2 $[M+H]^+$. t_R = 0.98 min.

[00286] Following general procedure A, 4-methyl-2-(ethoxy)imidazo[l,5-a]pyrimidine-8-carboxylic acid (80 mg, 0.362 mmol) and 2,2,2-trifluoro-l-(4-fluorophenyl)ethan-l -amine afforded the title compound (58 mg, 49%) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.24 (s, 1H), 7.61 (dd, J = 8.0, 5.0 Hz, 2H), 7.21 (t, J = 8.5 Hz, 2H), 6.49 (s, 1H), 6.01 (q, J = 8.0 Hz, 1H), 4.62-4.52 (m, 2H), 2.72 (s, 3H), 1.51 (t, J = 7.0 Hz, 3H). LC-MS m/z: 397.1 $[M+H]^+$. HPLC: Purity (214 nm): >93%; t_R = 8.28 min.

2-(Methoxymethyl)-4-methyl -A/-(2,2,2-trifluoro-l-(4-fluorophenyl)ethyl)imidazo[l,5-alpyrimidine-8-carboxamide and 4-(Methoxymethyl)-2-methyl -A^-(2,2,2-trifluoro-l-(4-fluorophenyl)ethyl)imidazo[l,5-alpyrimidine-8-carboxamide



[00287] l-Methoxypentane-2,4-dione (1.0 g, 9.7 mmol) and ethyl 5-amino-l *H*-imidazole-4-carboxylate (1.2 g, 9.5 mmol) were stirred in AcOH (10 mL) at 110 °C for 1 h until the reaction was complete (TLC). The reaction mixture was concentrated and the crude was purified by

silica gel column chromatography to afford an inseparable mixture of esters that were used directly in the next step.

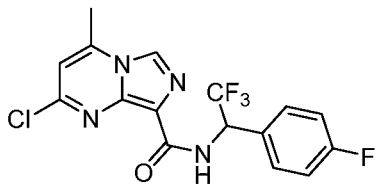
[00288] Following general procedure B, the mixture of esters afforded 2-(methoxymethyl)-4-methylirnidazo[l,5-a]pyrirnidine-8-carboxylic acid and 4-(methoxymethyl)-2-methylirnidazo[l,5-a]pyrirnidine-8-carboxylic acid as dark yellow solids (1.0 g, 50% yield over 2 steps).

[00289] Following general procedure A, a mixture of 2-(methoxymethyl)-4-methylirnidazo[l,5-a]pyrirnidine-8-carboxylic acid and 4-(methoxymethyl)-2-methylirnidazo[l,5-a]pyrirnidine-8-carboxylic acid (400 mg, 1.8 mmol) and 2,2,2-trifluoro-l-(4-fluorophenyl)ethan-l -amine afforded 2-(methoxymethyl)-4-methyl -*N*-(2,2,2-trifluoro-l-(4-fluorophenyl)ethyl)imidazo[l,5-a]pyrirnidine-8-carboxamide (8.6 mg, 1%) and 4-(methoxymethyl)-2-methyl -*N*-(2,2,2-trifluoro-l-(4-fluorophenyl)ethyl)imidazo[l,5-a]pyrimidine-8-carboxamide (1.7 mg, 1%) as white solids.

[00290] 2-(Methoxymethyl)-4-methyl -*N*-(2.2.2-trifluoro-l-(4-fluorophenyl)ethyl)inTidazo[1.5-alpyrirnidine-8-carboxarnide : 'HNMR (500 MHz, DMSO-*d6)*: δ 8.24 (d, *J* = 9.5 Hz, 1H), 8.53 (s, 1H), 7.74 (dd *J* = 8.0 Hz, 5.0 Hz, 2H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.01 (s, 1H), 6.13 (p, *J* = 9.0 Hz, 1H), 4.63 (d, *J* = 1.5 Hz, 2H), 3.45 (s, 3H), 2.76 (s, 3H). LC-MS m/z: 397.1 $[M+H]^+$. HPLC: Purity (214 nm): 98%; t_R = 7.74 min.

[00291] 4-(Methoxymethyl)-2-methyl -*N*-(2.2.2-trifluoro-l-(4-fluorophenyl)ethyl)inTidazo[1.5-alpyrirnidine-8-carboxarnide : ¾NMR (500 MHz, $CDC1_3$): δ 8.84 (d, *J* = 10.0 Hz, 1H), 8.12 (s, 1H), 7.53 (dd *J* = 9.0 Hz, 5.5 Hz, 2H), 7.11 (td *J* = 8.5 Hz, 2.0 Hz, 2H), 6.75 (s, 1H), 6.07 (p, *J* = 8.0 Hz, 1H), 4.74 (d, *J* = 0.5 Hz, 2H), 3.52 (s, 3H), 2.71 (s, 3H). LC-MS m/z: 397.0 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 7.91 min.

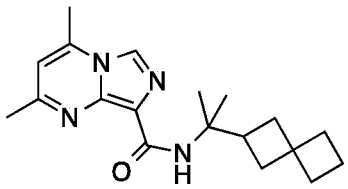
2-Chloro-4-methyl-iV-(2,2,2-trifluoro-l-(4-fluoro phenyl)ethyl)imidazo[1,5-*a*]pyrimidine-8-carboxamide



[00292] Following general procedure A, 2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (250 mg, 1.18 mmol) and 2,2,2-trifluoro-l-(4-fluorophenyl)ethanamine

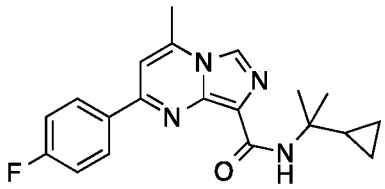
afforded the title compound (150 mg, 33 %) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.46 (s, 1H), 7.64 (dd, *J* = 9.0 Hz, 5.5 Hz, 2H), 7.22 (tt, *J* = 9.0 Hz, 2.0 Hz, 2H), 7.02 (d, *J* = 1.0 Hz, 1 H), 6.02 (q, *J* = 8.0 Hz, 1H), 2.79 (d, *J* = 0.5 Hz, 3H). LC-MS m/z: 387.0 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 7.31 min.

2,4-Dimethyl -A^-(2-(spiro[331heptan-2-vnpropan-2-vnimidazo[l,5-alpyrimidine-8-carboxamide



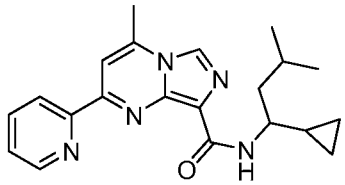
[00293] Following general procedure A, 2,4-dimethylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (70 mg, 0.366 mmol) and 2-(spiro[3.3]heptan-2-yl)propan-2-amine afforded the title compound (14.9 mg, 12%) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (s, 1H), 7.94 (s, 1H), 6.81 (d, *J* = 0.8 Hz, 1H), 2.66 (d, *J* = 0.8 Hz, 3H), 2.53 (s, 3H), 2.52-2.51 (m, 1H), 2.05-1.79 (m, 10H), 1.32 (s, 6H). LC-MS m/z: 327.2 $[M+H]^+$. HPLC: Purity (254 nm): >95%; t_R = 10.66 min.

A/-(2-Cvclopropylpropan-2-yl)-2-(4-fluorophenyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



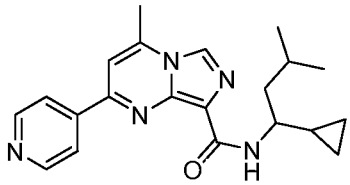
[00294] Following general procedure A, 2-(4-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (20 mg, 0.07 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (9 mg, 35%) as a white solid. ^{1}H NMR (500 MHz, $CDC1_3$): δ 8.14 (dd *J* = 8.5 Hz, 5.5 Hz, 2H), 8.02 (s, 1H), 7.98 (s, 1H), 7.20 (t, *J* = 8.5 Hz, 2H), 7.04 (s, 1H), 2.75 (s, 3H), 1.48 (s, 6H), 1.46-1.42 (m, 1H), 0.50 (d, *J* = 6.5 Hz, 4H). LC-MS m/z: 353.1 $[M+H]^+$. HPLC Purity (214 nm): >99%; t_R = 8.38 min.

A/-(l-Cvclopropyl-3-methylbuM)-4-methyl-2-(pyridin-2-yl)imidazo[l,5-alpyrimidine-8-carboxamide



[00295] Following general procedure A, 4-methyl-2-(pyridin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (100 mg, 0.40 mmol) and l-cyclopropyl-3-methylbutan-l-amine afforded the title compound (22 mg, 15%) as a yellow solid. ^{1}H NMR (400 MHz, *MeOO-d4)* δ 8.75 (d, *J* = 4.8 Hz, 1H), 8.54 (d, *J* = 6.8 Hz, 1H), 8.44 (s, 1H), 8.02 (td, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.95 (s, 1H), 7.55 (ddd, *J* = 8.0 Hz, 5.2 Hz, 0.8 Hz, 1H), 3.81-3.75 (m, 1H), 2.86 (s, 3H), 1.89-1.74 (m, 2H), 1.67-1.60 (m, 1H), 1.12-1.03 (m, 1H), 0.98 (t, *J* = 6.4 Hz, 6H), 0.62-0.57 (m, 1H), 0.52-0.47 (m, 2H), 0.36-0.32 (m, 1H). LC-MS m/z: 364.2 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 8.31 min.

A/-(l-Cvclopropyl-3-methylbuM)-4-methyl-2-(pyridin-4-yl)imidazo[l,5-alpyrimidine-8-carboxamide



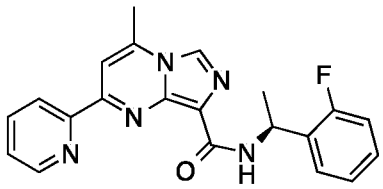
[00296] Following general procedure D, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (310 mg, 1.3 mmol) and pyridin-4-ylboronic acid afforded ethyl 4-methyl-2-(pyridin-4-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (270 mg, 75%). LC-MS m/z: 283.2 $[M+H]^+$.

[00297] Following general procedure B, ethyl 4-methyl-2-(pyridin-4-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (270 mg, 0.96 mmol) afforded 4-methyl-2-(pyridin-4-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (243 mg, 92%). LC-MS m/z: 255.1 $[M+H]^+$.

[00298] Following general procedure A, 4-methyl-2-(pyridin-4-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (40 mg, 0.16 mmol) and l-cyclopropyl-3-methylbutan-l-amine afforded the title compound (11 mg, 20%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.57 (d, *J* = 5.5 Hz, 2H), 8.27 (s, 1H), 8.02 (d, *J* = 5.5 Hz, 2H), 7.36 (s, 1H), 3.61-3.54 (m, 1H), 2.68 (s, 3H), 1.68-1.63 (m, 1H), 1.59-1.54 (m, 1H), 1.46-1.41 (m, 1H), 0.91-0.84 (m, 1H), 0.79

(d, J = 6.5 Hz ,3H), 0.78 (d, J = 6.5 Hz ,3H), 0.44-0.38 (m, 1H), 0.34-0.28 (m, 1H), 0.17-0.14 (m, 1H). LC-MS m/z: 364.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 7.14 min.

CSViV-(l-(2-Fluorophenyl)ethyl)-4-meth^^-2-(pyridin-2-yl)imidazo[1,5-*a*]pyrimidine-8-carboxamide

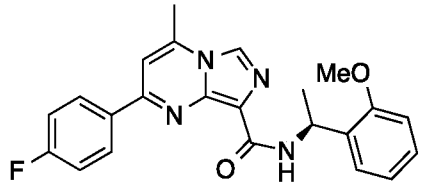


[00299] To a solution of l-(pyridin-2-yl)butane-l,3-dione (5.0 g, 28 mmol) in AcOH (100 mL) was added ethyl 5-amino-l *H*-imidazole-4-carboxylate (2.3 g, 15 mmol) at 90 °C. The mixture was stirred at 90 °C for 1 h, concentrated *in vacuo* and the residue purified by prep-HPLC (NH_4HCO_3, CH_3CN:H_20 = 5% - 95%) to obtain ethyl 4-methyl-2-(pyridin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (450 mg, 8%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-c¾): δ 8.79 (d, J = 4.0 Hz, 1H), 8.68 (d, J = 8.0 Hz, 1H), 8.51 (s, 1H), 8.05 (t, J = 7.6 Hz, 1H), 8.00 (s, 1H), 7.58 (t, J = 7.2 Hz, 1H), 4.51 (q, J = 6.8 Hz, 2H), 2.88 (s, 3H), 1.49 (t, J = 7.2 Hz, 3H). LC-MS m/z: 283.1 $[M+H]^+$. LCMS: t_R = 1.49 min.

[00300] Following general procedure B, ethyl 4-methyl-2-(pyridin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (450 mg, 1.6 mmol) afforded 4-methyl-2-(pyridin-2-yl)imidazo[l,5-a]pyrirnidine-8-carboxylic acid sodium salt (450 mg, 100%) as a yellow solid. LC-MS m/z: 255.1 $[M+H]^+$. LCMS: t_R = 1.16 min.

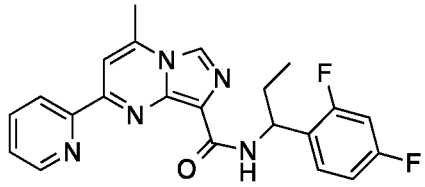
[00301] Following general procedure A, 4-methyl-2-(pyridin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid sodium salt (50 mg, 0.2 mmol) and *(S)*-\-*(2*-fluorophenyl)ethan-l -amine afforded the title compound (16.4 mg, 23%) as a pale yellow solid. ^{1}H NMR (500 MHz, *MeOO-d4)* δ 8.75 (ddd, J = 5.0 Hz, 1.5 Hz, 0.5 Hz, 1H), 8.44 (s, 1H), 8.41 (dt, J = 7.5 Hz, 0.5 Hz, 1H), 7.98 (td, J = 7.5 Hz, 1.5 Hz, 1H), 7.95 (d, J = 1.5 Hz, 1H), 7.58 (td, J = 7.5 Hz, 1.5 Hz, 1H), 7.55 (ddd, J = 7.5 Hz, 4.5 Hz, 1.0 Hz, 1H), 7.39-7.34 (m, 1H), 7.23 (td, J = 7.5 Hz, 1.0 Hz, 1H), 7.18 (ddd, J = 11.0 Hz, 8.5 Hz, 1.0 Hz, 1H), 5.59 (q, J = 7.0 Hz, 1H), 2.85 (d, J = 0.5 Hz, 3H), 1.73 (d, J = 7.0 Hz, 3H). LC-MS m/z: 376.1 $[M+H]^+$. HPLC: Purity (254 nm): >99%; t_R = 9.27 min.

(.S^-2-(4-Fluorophenyl)-A/-(l-(2-methoxyphenyl)ethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



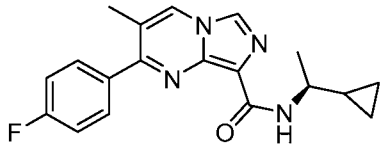
[00302] Following general procedure A, 2-(4-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (15 mg, 0.06 mmol) and (<S)-l-(2-methoxyphenyl)ethan-l-amine afforded the title compound (11.8 mg, 35%) as a white solid. ^{1}H NMR (500 MHz, $CDC1_3$): δ 8.55 (d, J = 9.0 Hz, 1H), 8.06 (dd, J = 5.5 Hz, 2.5 Hz, 2H), 8.04 (s, 3H), 7.42 (dd, J = 7.5 Hz, 2.0 Hz, 1H), 7.28-7.27 (m, 1H), 7.18 (t, J = 6.5 Hz, 2H), 7.04 (d, J = 1.0 Hz, 1H), 6.95 (t, J = 7.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 5.71-5.68 (m, 1H), 3.80 (s, 3H), 2.74 (s, 3H), 1.65 (d, J = 7.5Hz, 3H). LC-MS m/z: 405.1 $[M+H]^+$. HPLC Purity (214 nm): >97%; t_R = 8.25 min.

iV-(l-(2,4-Dif uorophenyl)propyl)-4-methyl-2-(pyr din-2-yl)imidazo[1,5-*a*]pyrimidine-8-carboxamide



[00303] Following general procedure A, 2-(4-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.2 mmol) and l-(2,4-difluorophenyl)propan-l -amine afforded the title compound (13. 1 mg, 17%) as a pale yellow solid. ^{1}H NMR (500 MHz, *MeOO-d$_4$)* δ 8.76 (d, J = 4.5 Hz, 1H), 8.45 (s, 1H), 8.38 (d, J = 8.5 Hz, 1H), 7.99 (td, J = 8.0 Hz, 1.5 Hz, 1H), 7.95 (d, J = 1.5 Hz, 1H), 7.57-7.52 (m, 3H), 7.16 (t, J = 8.5 Hz, 2H), 5.13 (t, J = 7.0 Hz, 1H), 2.86 (s, 3H), 2.13-2.11 (m, 1H), 2.05-2.02 (m, 1H), 1.05 (t, J = 7.0 Hz, 3H). LC-MS m/z: 392.3 $[M+H]^+$. HPLC: Purity (254 nm): >99%; t_R = 9.56 min.

(*S*)-*N*-(1-Cyclopropylethyl)-2-(4-fluorophenyl)-3-methylimidazo[1,5-a]pyrimidine-8-carboxamide



[00304] A solution of ethyl 3-ethoxy-2-methylacrylate (1.896 g, 12 mmol), ethyl 5-amino-1*H*-imidazole-4-carboxylate (1.55 g, 10 mol) and Cs_2CO_3 (3.9 g, 12 mmol) in DMF (20 mL) was heated at 150 °C for 3 h. Then, the solvent was removed by concentration *in vacuo*. The resulting residue was purified by silica gel column (DCM/MeOH: 9/1) to afford ethyl 2-hydroxy-3-methylimidazo[1,5-a]pyrimidine-8-carboxylate (1.2 g, 54%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) 11.24 (bs, IH), 8.33 (d, J = 1.2 Hz, IH), 7.86 (s, IH), 4.28 (q, J = 7.2 Hz, 2H), 2.95 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H). LC-MS m/z: 222.0 $[M+H]^+$. Purity (214 nm): 94%; t_R = 1.27 min.

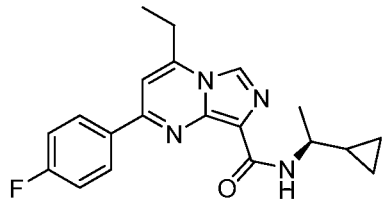
[00305] To a solution of ethyl 2-hydroxy-3-methyliimdazo[1,5-a]pyrimidine-8-carboxylate (600 mg, 2.72 mmol) in DCM (30 mL) was added $POCl_3$ (1.25 g, 8.18 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at 70 °C for 3 h, then diluted with DCM (60 mL) and poured into ice. The organic phase was separated, washed with saturated $NaHCO_3$ (30 mL) and brine (20 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* and the resulting residue was washed with PE and filtered to afford ethyl 2-chloro-3-methylinddazo[1,5-a]pyrimidine-8-carboxylate (600 mg, 70%) as a yellow solid. LC-MS m/z: 240.0 $[M+H]^+$. LCMS: Purity (214 nm): 76%; t_R = 1.52 min.

[00306] Following general procedure D, ethyl 2-chloro-3-methylimidazo[1,5-a]pyrirnidine-8-carboxylate (240 mg, 1 mmol) and 4-fluorophenylboronic acid afforded ethyl 2-(4-fluorophenyl)-3-methylinddazo[1,5-a]pyrimidine-8-carboxylate (240 mg, 80%) as a yellow solid. LC-MS m/z: 300.1 $[M+H]^+$. Purity (254 nm): 90%; t_R = 1.62 min.

[00307] Following general procedure B, ethyl 2-(4-fluorophenyl)-3-methylimidazo[1,5-a]pyrimidine-8-carboxylate (250 mg, 0.84 mmol) afforded 2-(4-fluorophenyl)-3-methylinddazo[1,5-a]pyrimidine-8-carboxylic acid (83 mg, 30%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.98 (s, IH), 7.75 (s, IH), 6.68 (s, IH), 2.45 (s, 3H), 2.43 (s, 3H). LC-MS m/z: 272.0 $[M+H]^+$. LCMS: Purity (214 nm): 95%; t_R = 1.27 min.

[00308] Following general procedure A, 2-(4-fluorophenyl)-3-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.18 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound (48 mg, 73%) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.84 (d, J = 1.0 Hz, 1H), 8.39 (s, 1H), 7.99 (d, J = 7.5 Hz, 1H), 7.83 (ddd, J = 7.0 Hz, 5.5 Hz, 2.0 Hz, 2H), 7.43 (td, J = 9.0 Hz, 2.0 Hz, 2H), 3.61-3.55 (m, 1H), 2.32 (s, 3H), 1.25 (d, J = 7.0 Hz, 3H), 1.05-1.00 (m, 1H), 0.50-0.45 (m, 1H), 0.45-0.38 (m, 1H), 0.37-0.30 (m, 1H), 0.30-0.21 (m, 1H). LC-MS m/z: 339.2 [M+H]$^+$. HPLC: Purity (214 nm): >99%; t_R = 9.60 min.

^-A^-Cl-Cvclopropylethyn-^ethyl-Z-C^fluorophenvnimidazofl^-alpyrimidine-S-carboxamide



[00309] To a solution of ethyl 3-oxopentanoate (14.4 g, 100 mmol) in EtOH (20 mL) was added *cone.* H_2SO_4 (0.02 mL) at 25 °C under N_2, followed by the dropwise addition of triethoxymethane (14.8 g, 100 mmol). The mixture was heated to 50 °C and stirred at this temperature overnight. The solvent was removed and the resulting residue was purified by silica gel column eluted with PE to afford ethyl 3-ethoxypent-2-enoate (6.4 g, 64%) as yellow oil. LC-MS m/z: 173.1 [M+H]$^+$. Purity (214 nm): > 94%; t_R = 2.04 min.

[00310] A solution of ethyl 3-ethoxypent-2-enoate (1.72 g, 10 mmol), ethyl 5-amino-lH-imidazole-4-carboxylate (1.55 g, 10 mmol) and $CS2CO_3$ (3.9 g, 12 mmol) in DMF (20 mL) was heated at 110 °C overnight, cooled, and concentrated *in vacuo.* The resulting residue was acidified to pH ~7 with diluted HC1, and extracted with EA (100 mL x 5). The organic phases were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford the crude ethyl 4-ethyl-2-hydroxyimidazo[l,5-a]pyrirnidine-8-carboxylate (1.3 g, 55%) as a yellow solid. LC-MS m/z: 236.0 [M+H]$^+$. Purity (214 nm): > 94%; t_R = 1.25 min.

[00311] A solution of ethyl 4-ethyl-2-hydroxyimidazo[l,5-a]pyrirnidine-8-carboxylate (1.3 g, 5.5 mmol) in POCI3 (2 mL) was stirred at 90 °C for 2 h, then cooled and concentrated *in vacuo.* The resulting residue was diluted with saturated $NaHCO_3$ solution (50 mL), and extracted with DCM (50 mL x 3). The organic phases were washed with H_20 (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in*

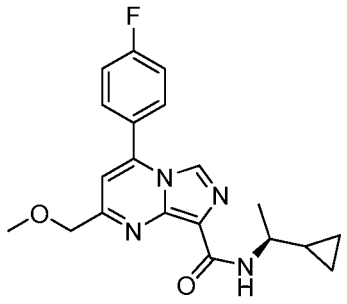
vacuo to afford ethyl 2-chloro-4-ethylimidazo[l,5-a]pyrimidine-8-carboxylate (980 mg, 70%) as ayellow solid. LC-MS m/z: 254.1 $[M+H]^+$. Purity (254 nm): > 81%; t_R = 1.50 min.

[00312] Following general procedure D, ethyl 2-chloro-4-ethylimidazo[l,5-a]pyrimidine-8-carboxylate (380 mg, 1.5 mmol) and 4-fiuorophenylboronic acid afforded ethyl 4-ethyl-2-(4-fluorophenyl)imidazo[l,5-a]pyrimidine-8-carboxylate (380 mg, 67%) as ayellow solid. LC-MS m/z: 314.1 $[M+H]^+$. Purity (214 nm): > 69%; t_R = 1.71 min.

[00313] Following general procedure B, ethyl 4-ethyl-2-(4-fluorophenyl)imidazo[l,5-a]pyrimidine-8-carboxylate (350 mg, 1.11 mmol) afforded 4-ethyl-2-(4-fluorophenyl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (340 mg, 94%) as ayellow solid. LC-MS m/z: 286.1 $[M+H]^+$. Purity (254 nm): > 99%; t_R = 1.27 min.

[00314] Following general procedure A, 4-ethyl-2-(4-fluorophenyl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (57 mg, 0.20 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound (41.6 mg, 59%) as ayellow solid. ¾NMR (500 MHz, $CDC1_3$) δ 8.15 (ddd, *J* = 9.0 Hz, 5.5 Hz, 2.5 Hz, 2H), 8.08 (s, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.23 (td, *J* = 8.5 Hz, 2.0Hz, 2H), 7.07 (s, 1H), 3.86-3.83 (m, 1H), 3.08 (qd, *J* = 7.5 Hz, 1.0 Hz, 2H), 1.56 (t, *J* = 7.5 Hz, 3H), 1.38 (d, *J* = 6.5 Hz, 3H), 1.05-1.02 (m, 1H), 0.58-0.55 (m, 1H), 0.52-0.48 (m, 2H), 0.39-0.37 (m, 1H). LC-MS m/z: 353.2 $[M+H]^+$. HPLC: Purity (214 nm): 96%; t_R = 8.16 min.

^-A^-Cl-CvclopropylethvD-^C^fluorophenvD-Z-CmethoxymethvDimidazoH^-alpyrimidine-8-carboxamide



[00315] To a solution of Meldrum's acid (5 g, 35 mmol) in DCM (50 mL) was added pyridine (5.6 mL, 70 mol) over 3 minutes in an ice-methanol bath under N_2 atmosphere. To this mixture was added dropwise a solution of methoxyacetyl chloride (4.2 g) in DCM (5 mL) over 1 h. The reaction mixture was stirred at the same temperature for 1 h and at ambient temperature for 2 h. The mixture was quenched with 1 N HC1 (50 mL). The organic layer was separated and the aqueous layer was extracted with DCM (30 mL x 3). The combined organic

layers were washed with brine (150 mL), dried over anhydrous Mg_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford 2-(methoxyacetyl)-2,2-dimethyl-l,3-dioxane-4,6-dione as dark orange oil (5.3 g, 71%). ^1H NMR (400 MHz ,$CDC1_3$) δ: 4.79 (s, 2H), 3.45 (s, 3H), 1.68 (s, 6H).

[00316] The mixture of 5-(2-methoxyacetyl)-2,2-dimethyl-l,3-dioxane-4,6-dione (5.3 g, 24.5 mmol) and ethyl 5-amino- l*H*-imidazole-4-carboxy late (2.6 g, 17.2 mmol) in 20 mL of MeCN was heated to reflux overnight under N_2, cooled and concentrated *in vacuo.* The resulting residue was purified by silica gel column chromatography (PE/EA = 1:4) to afford ethyl 5-amino-l-(4-methoxy-3-oxobutanoyl)-l *H*-imidazole-4-carboxylate as a yellow solid (3.4 g, 64%). LC-MS m/z: 270.1 $[M+H]^+$.

[00317] The solution of ethyl 5-amino-l-(4-methoxy-3-oxobutanoyl)-l *H*-imidazole-4-carboxylate (3.4 g, 12.6 mmol) in glacial AcOH (10 mL) was stirred at 110 °C overnight, and concentrated *in vacuo.* The resulting residue was purified by silica gel column chromatography (EA/MeOH = 20/1) to afford ethyl 4-hydroxy-2-(methoxymethyl)imidazo[l,5-a]pyrimidine-8-carboxylate (1.5 g, 42%) as a yellow solid. LC-MS m/z: 252.2 $[M+H]^+$.

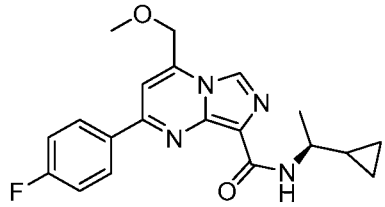
[00318] The solution of ethyl 4-hydroxy-2-(methoxymethyl)imidazo[l,5-a]pyrirnidine-8-carboxylate (1.5 g, 6 mmol) in $POCI_3$ (20 mL) was stirred at 110 °C for 2 h, and concentrated *in vacuo.* The resulting residue was quenched with saturated $NaHCO_3$ solution, and extracted with EA (50 mL x 3). The organic phases were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo,* and the resulting residue was purified by silica gel column chromatography (EA/MeOH = 10/1) to afford ethyl 4-chloro-2-(methoxymethyl)imidazo[l,5-a]pyrimidine-8-carboxylate (100 mg, 7%) as a yellow solid. LC-MS m/z: 270.2 $[M+H]^+$.

[00319] Following general procedure D, ethyl 4-chloro-2-(methoxymethyl)imidazo[l,5-a]pyrimidine-8-carboxylate (100 mg, 0.37 mmol) and 4-fluorophenylboronic acid afforded ethyl 4-(4-fluorophenyl)-2-(methoxymethyl)inddazo[l,5-a]pyrimidine-8-carboxylate (100 mg, 82%) as a yellow solid. LC-MS m/z: 330.2 $[M+H]^+$.

[00320] Following general procedure B, ethyl 4-(4-fluorophenyl)-2-(methoxymethyl)imidazo[l,5-a]pyrirnidine-8-carboxylate (100 mg, 0.30 mmol) afforded 4-(4-fluorophenyl)-2-(methoxymethyl)inddazo[l,5-a]pyrimidine-8-carboxylic acid (100 mg, 79%) as a yellow solid. LC-MS m/z: 302.2 $[M+H]^+$.

[00321] Following general procedure A, 4-(4-fluorophenyl)-2-(methoxymethyl)imidazo[l,5-a]pyrirnidine-8-carboxylic acid (100 mg, 0.24 mmol) and (*s*')- 1-cyclopropylethanamine afforded the title compound (7.5 mg, 8.7%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.20 (s, 1H), 7.81 (dd, *J* = 9.0 Hz, 5.5 Hz, 2H), 7.32 (tt, *J* = 9.0 Hz, 2.0 Hz, 2H), 6.96 (s, 1H), 4.58 (s, 2H), 3.61-3.56 (m, 1H), 3.44 (s, 3H), 1.26 (d, *J* = 7.0 Hz, 3H), 0.99-0.92 (m, 1H), 0.50-0.43 (m, 1H), 0.42-0.38 (m, 1H), 0.37-0.30 (m, 1H), 0.25-0.19 (m, 1H). LC-MS m/z: 369.1 [M+H]+. HPLC: Purity (254 nm): > 99%; t_R = 7.62 min.

(*s*')-A/-(l-Cvclopropylethyl)-2-(4-fluorophenyl)-4-(methoxymethyl)imidazo[l,5-*a*\pyrimidine-8-carboxamide

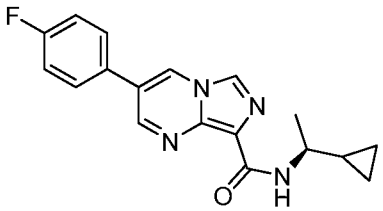


[00322] Following general procedure D, ethyl 2-chloro-4-(methoxymethyl)imidazo[l,5-a]pyrimidine-8-carboxylate (150 mg, 0.55 mmol) and 4-fluorophenylboronic acid afforded ethyl 2-(4-fluorophenyl)-4-(methoxymethyl)imidazo[l,5-a]pyrimidine-8-carboxylate (110 mg, 53%) as a yellow solid. LC-MS m/z: 330.1 $[M+H]^+$. t_R = 1.82 min.

[00323] Following general procedure B, ethyl 2-(4-fluorophenyl)-4-(methoxymethyl)imidazo[l,5-a]pyrimidine-8-carboxylate (110 mg, 0.38 mmol) afforded 2-(4-fluorophenyl)-4-(methoxymethyl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 80%) as a yellow solid. LC-MS m/z: 302.1 $[M+H]^+$. t_R = 0.91 min.

[00324] Following general procedure A, 2-(4-fluorophenyl)-4-(methoxymethyl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.17 mmol) and *(S)*-\-cyclopropylethanamine afforded the title compound (8.9 mg, 15%) as a yellow solid. 'HNMR (500 MHz, MeOD-c¾): δ 8.48 (d, *J* = 8.0 Hz, 1H), 8.39 (s, 1H), 8.33 (dd, *J* = 8.5 Hz, 5.5 Hz, 2H), 7.63 (s, 1H), 7.35 (t, *J* = 8.5 Hz, 2H), 4.96 (s, 2H), 3.78-3.68 (m, 1H), 3.57 (s, 3H), 1.41 (d, *J* = 6.5 Hz, 3H), 1.18-1.12 (m, 1H), 0.68-0.52 (m, 2H), 0.51-0.42 (m, 1H), 0.41-0.38 (m, 1H). LC-MS m/z: 369.2 $[M+H]^+$. HPLC Purity (214 nm): 96%; t_R = 9.84 min.

***(S)*-A/-(l-Cvclopropylethyl)-3-(4-fluorophenyl)imidazo[l,5-alpyrimidine-8-carboxamide**

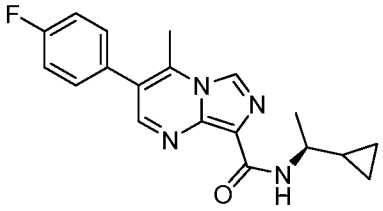


[00325] To a solution of ethyl 5-amino-l *H*-imidazole-4-carboxylate (248 mg, 1.6 mmol) in AcOH (15 mL) was added 2-(4-fluorophenyl)malonaldehyde (250 mg, 1.6 mmol) at 90 °C. Then the reaction mixture was stirred for 2 h at 90 °C, then cooled, and concentrated *in vacuo.* The resulting residue was purified by silica gel column (PE/EA = 3/1) to afford ethyl 3-(4-fluorophenyl)imidazo[l ,5-a]pyrirnidine-8-carboxylate (301 mg, 66%) as a yellow solid. LC-MS m/z: 286. 1 $[M+H]^+$.

[00326] Following general procedure B, ethyl 3-(4-fluorophenyl)imidazo[l,5-a]pyrimidine-8-carboxylate (150 mg, 0.53 mmol) afforded 3-(4-fluorophenyl)imidazo[l ,5-a]pyrirnidine-8-carboxylic acid (80 mg, 59%) as a white solid. LC-MS m/z: 239.9 $[M-OH]^+$.

[00327] Following general procedure A, 3-(4-fluorophenyl)imidazo[l,5-a]pyrirnidine-8-carboxylic acid (40 mg, 0.16 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (23 mg, 44%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-i¾): δ 9.18 (d, *J* = 2.5 Hz, 1H), 8.88 (d, *J* = 2.5 Hz, 1H), 8.39 (s, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.86 (ddd, *J* = 8.5 Hz, 5.0 Hz, 2.0 Hz, 2H), 7.41 (tt, *J* = 9.5 Hz, 2.0 Hz, 2H), 3.60-3.51 (m, 1H), 1.25 (d, *J* = 6.5 Hz, 3H), 1.05-1.00 (m, 1H), 0.50-0.46 (m, 1H), 0.42-0.38 (m, 1H), 0.33-0.27 (m, 1H), 0.26-0.22 (m, 1H). LC-MS m/z: 325. 1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.57 min.

***(S)*-A/-(l-Cvclopropylethyl)-3-(4-fluorophenyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide**



[00328] To a suspension of NaH (480 mg, 12 mmol) in anhydrous THF (5 mL) was added dropwise a solution of l-(4-fiuorophenyl)propan-2-one (1.52 g, 10 mmol) in anhydrous THF at 0 °C and the mixture was stirred for 30 min followed by the addition of a solution of ethyl formate (814 mg, 11 mmol) in anhydrous THF. The reaction mixture was stirred at RT

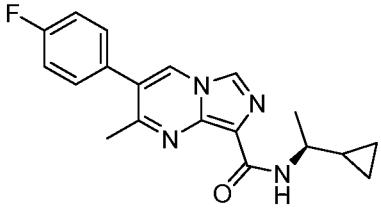
overnight, quenched with H_20 (50 mL) at 0 °C and extracted with DCM (10 mL x 3). The aqueous phase was then acidified with 4M HC1 to pH ~ 4, and extracted with DCM (30 mL x 3). The organic phases were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford crude 2-(4-fluorophenyl)-3-oxobutanal (1.2 g, 68%) as yellow oil. LC-MS m/z: 181.1 $[M+H]^+$. Purity (254 nm): 60%; t_R = 1.17 min.

[00329] A solution of 2-(4-fluorophenyl)-3-oxobutanal (800 mg, 4.44 mmol), ethyl 5-amino-l*H*-imidazole-4-carboxylate (480 mg, 3.11 mmol) in HOAc (10 mL) was stirred at 110 °C for 2 h, and concentrated *in vacuo*. The resulting residue was purified by prep-HPLC (MeCN/TFA) to afford ethyl 3-(4-fluorophenyl)-4-methylinddazo[l,5-a]pyrimidine-8-carboxylate (220 mg, 25%) as ayellow solid. ^{1}H NMR (500 MHz, $CDC1_3$): δ 8.51 (s, IH), 8.11 (s, IH), 7.35 (ddd, *J* = 7.5 Hz, 5.5 Hz, 2.5 Hz, 2H), 7.24 (tt, *J* = 9.0 Hz, 2.0 Hz, 2H), 4.54 (q, *J* = 7.0 Hz, 2H), 2.67 (s, 3H), 1.48 (t, *J* = 7.5 Hz, 3H). LC-MS m/z: 299.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 1.65 min.

[00330] Following general procedure B, ethyl 3-(4-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (220 mg, 0.74 mmol) afforded 3-(4-fluorophenyl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (120 mg, 60%) as ayellow solid. LC-MS m/z: 300.1 $[M+H]^+$. LCMS: Purity (214 nm): 95%; t_R = 1.84 min.

[00331] Following general procedure A, 3-(4-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 0.10 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound (5.8 mg, 15%) as a yellow solid. ^{1}H NMR (500 MHz, $CDC1_3$): δ 8.56 (s, IH), 8.46 (s, IH), 7.96 (d, *J* = 8.5 Hz, IH), 7.58 (ddd, *J* = 12.0 Hz, 5.0 Hz, 1.5 Hz, 2H), 7.39 (tt, *J* = 8.5 Hz, 2.0 Hz, 2H), 3.57 (m, *J* =7.5 Hz, IH), 2.65 (s, 3H), 1.26 (d, *J* = 6.5Hz, 3H), 1.05-1.02 (m, IH), 0.48-0.41 (m, 2H), 0.33-0.23 (m, 2H). HPLC m/z: 339.1 $[M+H]^+$. LCMS Purity (214 nm): > 99%; t_R = 1.83 min.

(*S*)-A/-(l-Cvclopropylethyl)-3-(4-fluorophenyl)-2-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00332] To a solution of ethyl 2-(4-fluorophenyl)acetate (3.64 g, 20 mmol) in THF (100 mL) was added NaH (960 mg, 24 mmol) at 0 °C in portions. The mixture was stirred at RT for 2 h and then EtOAc (2.64 g, 30 mmol) was added at 0 °C and the reaction mixture was stirred at reflux overnight, cooled, and partitioned between sat. NH_4Cl (100 mL) and EA (200 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo,* and the resulting residue was purified by silica gel column chromatography (petroleum ether /ethyl acetate = 20/1) to afford ethyl 2-(4-fluorophenyl)-3-oxobutanoate (780 mg, 18%) as a colorless oil. LC-MS m/z: 225.1 $[M+H]^+$. Purity (254 nm): > 90% t_R = 1.74 min.

[00333] To a solution of ethyl 5-amino-l *H*-imidazole-4-carboxylate (500 mg, 3.2 mmol) in AcOH (10 mL) was added ethyl 2-(4-fluorophenyl)-3-oxobutanoate (700 mg, 3.1 mmol) at 110 °C. Then the reaction mixture was stirred for 10 h at 110 °C, cooled, and concentrated *in vacuo* to afford ethyl 3-(4-fluorophenyl)-4-hydroxy-2-methylimidazo[l,5-a]pyrimidine-8-carboxylate (800 mg, 80%). ^1H NMR (500 MHz, DMSO-c¾), δ 11.75 (s, 1H), 8.20 (s, 1H), 7.39-7.36 (m, 2H), 7.29-7.25 (m, 2H), 4.35 (q, *J* = 7.0 Hz, 2H), 2.29 (s, 3H), 1.34 (t, *J* = 7.0 Hz, 3H). LC-MS m/z: 316.0 $[M+H]^+$; Purity (254 nm): >90%; t_R = 1.51 min.

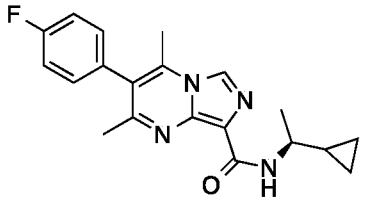
[00334] A mixture of ethyl 3-(4-fluorophenyl)-4-hydroxy-2-methylimidazo[l,5-a]pyrimidine-8-carboxylate (800 mg, 2.54 mmol) in phosphorus oxychloride (15 mL) was stirred at 110 °C for 16 h. The reaction mixture was concentrated to afford ethyl 4-chloro-3-(4-fluorophenyl)-2-methylinddazo[l,5-a]pyrimidine-8-carboxylate as dark oil, which was used directly. LC-MS m/z: 334.1 $[M+H]^+$. t_R = 1.65min.

[00335] A mixture of ethyl 4-chloro-3-(4-fluorophenyl)-2-methylinddazo[l,5-a]pyrimidine-8-carboxylate (700 mg, 2.10 mmol), Pd/C (70 mg) and Et_3N (3 mL) in EtOAc (15 mL) was stirred at RT for 3 h under H_2. The reaction mixture was filtered and the filtrate was concentrated *in vacuo.* The resulting residue was purified by flash chromatography to afford ethyl 3-(4-fluorophenyl)-2-methylinddazo[l,5-a]pyrimidine-8-carboxylate (130 mg, 20%) as a yellow solid. LC-MS m/z: 300.1 $[M+H]^+$. Purity (254 nm): > 95%; t_R = 1.58 min.

[00336] Following general procedure B, ethyl 3-(4-fluorophenyl)-2-methylimidazo[l,5-a]pyrimidine-8-carboxylate (130 mg, 0.43 mmol) afforded 3-(4-fluorophenyl)-2-methylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (100 mg, 85%) as a yellow solid. LC-MS m/z: 272.1 $[M+H]^+$. Purity (254 nm): > 80%; t_R = 1.23 min.

[00337] Following general procedure A, 3-(4-fluorophenyl)-2-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (100 mg, 0.37 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound (10 mg, 12%) as a yellow solid. ^{1}H NMR (500 MHz, *OMSO-d $_6$)* δ 8.74 (s, 1H), 8.28 (s, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.58 (dd, *J* = 8.5 Hz, 5.5 Hz, 2H), 7.37 (t, *J* = 8.5 Hz, 2H), 3.61-3.56 (m, 1H), 2.44 (s, 3H), 1.25 (d, *J* = 6.5 Hz, 3H), 1.07-0.99 (m, 1H), 0.50-0.38 (m, 2H), 0.36-0.32 (m, 1H), 0.28-0.21 (m, 1H). LC-MS m/z: 339.2 $[M+H]^+$. HPLC: Purity (254 nm): >99%; t_R = 7.87 min.

f.y)-iV-(l-Cvclopropylethyl)-3-(4-fluorophen^^)-2,4-dimethylimidazo[1,5-*a*]pyrimidine-8-carboxamide

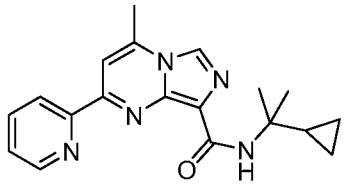


[00338] To a solution of ethyl 5-amino-l *H*-imidazole-4-carboxylate (1.2 g, 7.7 mmol) in AcOH (10 mL) was added 3-(4-fluorophenyl)pentane-2,4-dione (2.5 g, 12.88 mmol) at 110 °C. The reaction mixture was stirred for 0.5 h at 110 °C, then cooled, and concentrated *in vacuo*. The resulting residue was purified by silica gel column (PE/EA = 1/1 to EA) to afford ethyl 3-(4-fluorophenyl)-2,4-dimethylinddazo[l,5-a]pyrimidine-8-carboxylate (1.5 g, 36%) as a grey solid. LC-MS m/z: 314.1 $[M+H]^+$. t_R = 1.63 min.

[00339] Following general procedure B, ethyl 3-(4-fluorophenyl)-2,4-dimethylimidazo[l,5-a]pyrimidine-8-carboxylate (1.4 g, 4.47 mmol) afforded 3-(4-fluorophenyl)-2,4-dimethyliiTiidazo[l,5-a]pyrirnidine-8-carboxylic acid (610 mg, 48%) as a grey solid. LC-MS m/z: 285.9 $[M+H]^+$. t_R = 1.53 min.

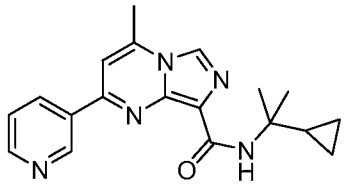
[00340] Following general procedure A, 3-(4-fluorophenyl)-2,4-dimethylimidazo[l,5-a]pyrimidine-8-carboxylic acid (100 mg, 0.35 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound (36 mg, 58%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.39 (d, *J* = 8.0 Hz, 1H), 8.33 (s, 1H), 7.43-7.39 (m, 2H), 7.32 (tt, *J* = 9.0 Hz, 2.0 Hz, 2H), 3.75-3.71 (m, 1H), 2.49 (s, 3H), 2.37 (s, 3H), 1.39 (d, *J* = 6.5 Hz, 3H), 1.11-1.04 (m, 1H), 0.62-0.50 (m, 2H), 0.49-0.44 (m, 1H), 0.36-0.32 (m, 1H). LC-MS m/z: 353.2 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 9.99 min.

A/-(2-Cvclopropylpropan-2-yl)-4-methyl-2-(pyridin-2-yl)imidazo[l,5-alpyrimidine-8-carboxamide



[00341] Following general procedure A, 4-methyl-2-(pyridin-2-yl)imidazo[l ,5-a]pyrimidine-8-carboxylic acid (100 mg, 0.40 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (9 mg, 7%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-c¾): δ 8.75 (d, *J* = 4.4 Hz, 1H), 8.55 (d, *J* = 8.0 Hz, 1H), 8.41 (s, 1H), 7.99 (td, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.93 (d, *J* = 0.8 Hz, 1H), 7.54 (ddd, *J* = 7.2 Hz, 4.8 Hz, 0.8 Hz, 1H), 2.85 (s, 3H), 1.49 (s, 6H), 1.49-1 .47 (m, 1H), 0.58-0.56 (m, 4H). LC-MS m/z: 336.0 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 8.14 min.

A/-(2-Cvclopropylpropan -2-yl)-4-methyl -2-(pyridin-3-yl)imidazo[l,5-alpyrimidine-8-carboxamide



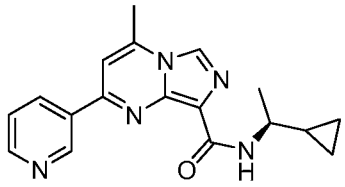
[00342] Following general procedure D, ethyl 2-chloro-4-methylimidazo[l ,5-a]pyrirnidine-8-carboxylate (800 mg, 3.35 mmol) and pyridin-3-ylboronic acid afforded ethyl 4-methyl-2-(pyridin-3-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (600 mg, 64%) as a yellow solid. LC-MS m/z: 283.7 $[M+H]^+$. t_R = 1.54 min.

[00343] Following general procedure B, ethyl 4-methyl-2-(pyridin-3-yl)imidazo[l ,5-a]pyrimidine-8-carboxylate (600 mg, 2.1 mmol) afforded 4-methyl-2-(pyridin-3-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (533 mg 100%) as a yellow solid. LC-MS m/z: 255.7 $[M+H]^+$. t_R = 0.84 min.

[00344] Following general procedure A, 4-methyl-2-(pyridin-3-yl)imidazo[l ,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.19 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (2.4 mg, 3.7%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 9.44 (d, *J* = 2.5 Hz, 1H), 8.73 (dd, *J* = 5.0 Hz, 1.5 Hz, 1H), 8.67 (dt, *J* = 8.5 Hz, 2.0 Hz, 1H), 8.44 (s, 1H), 8.39 (s, 1H), 7.66 (dd, *J* = 8.0 Hz, 5.0 Hz, 1H), 7.56 (s, 1H), 2.88 (s, 3H), 1.50 (s, 6H),

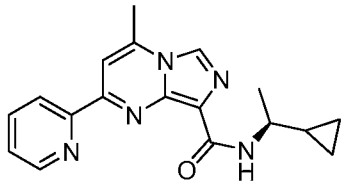
1.50-1.42 (m, 1H), 0.60-0.56 (m, 4H). LC-MS m/z: 336.0 $[M+H]^+$. HPLC: Purity (254 nm): 99%; t_R = 7.11 min.

f.y)-iV-(l-Cvclopropylethyl)-4-methyl-2-(py^^din-3-yl)imidazo[1,5-*a*]pyrimidine-8-carboxamide



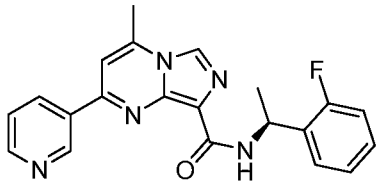
[00345] Following general procedure A, 4-methyl-2-(pyridin-3-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.20 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound (2. 1 mg, 3.2%) as a white solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 9.44 (d, *J* = 1.5 Hz, 1H), 8.74 (dd, *J* = 5.0 Hz, 1.5 Hz, 1H), 8.68 (tt, *J* = 7.5 Hz, 2.0 Hz, 1H), 8.46 (s, 1H), 7.68 (ddd, *J* = 8.0 Hz, 5.0 Hz, 1.0 Hz, 1H), 7.57 (d, *J* = 1.0 Hz, 1H), 3.74-3.68 (m, 1H), 2.88 (d, *J* = 1.0 Hz, 3H), 1.42 (d, *J* = 6.5 Hz, 3H), 1.17-1.10 (m, 1H), 0.67-0.55 (m, 2H), 0.51-0.46 (m, 1H), 0.42-0.37 (m, 1H). LC-MS m/z: 322.1 $[M+H]^+$. HPLC: Purity (214 nm): 98.4%; t_R = 6.68 min.

f.y)-iV-(l-Cvclopropylethyl)-4-methyl-2-(py^^din-2-yl)imidazo[1,5-*a*]pyrimidine-8-carboxamide



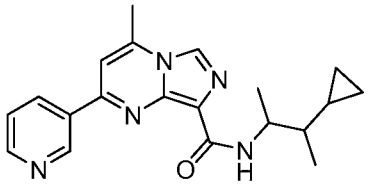
[00346] Following general procedure A, 4-methyl-2-(pyridin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.20 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound (7 mg, 11%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.75 (dd, *J* = 5.0 Hz, 1.0 Hz, 1H), 8.55 (d, *J* = 8.0 Hz, 1H), 8.43 (s, 1H), 8.02 (td, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.95 (d, *J* = 1.0 Hz, 1H), 7.55 (ddd, *J* = 7.5 Hz, 5.0 Hz, 1.0 Hz, 1H), 3.74-3.68 (m, 1H), 2.86 (s, 3H), 1.44 (d, *J* = 6.5 Hz, 3H), 1.20-1.13 (m, 1H), 0.67-0.55 (m, 2H), 0.52-0.47 (m, 1H), 0.42-0.37 (m, 1H). LC-MS m/z: 322.2 $[M+H]^+$. HPLC: Purity (214 nm): 96%; t_R = 8.71 min.

f.y)-iV-(l-(2-Fluorophenyl)ethyl)-4-meth^^-2-(pyridin-3-yl)imidazo[1,5-*a*]pyrimidine-8-carboxamide



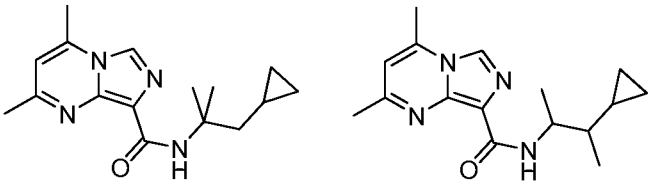
[00347] Following general procedure A, 4-methyl-2-(pyridin-3-yl)imidazo[l ,5-a]pyrirnidine-8-carboxylic acid (70 mg, 0.28 mmol) and (<S)-l-(2-fluorophenyl)ethanamine afforded the title compound (17 mg, 16%) as yellow solid. ^{1}H NMR (400 MHz, MeOD-c¾) δ 9.40 (d, *J* = 2.0 Hz, 1H), 8.73 (dd, *J* = 4.8 Hz, 1.2 Hz, 1H), 8.61 (dt, *J* = 8.4 Hz, 2.0 Hz, 1H), 8.46 (s, 1H), 7.65 (dd, *J* = 8.0 Hz, 4.8 Hz, 1H), 7.57 (s, 1H), 7.53 (dt, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.36-7.30 (m, 1H), 7.22-7. 14 (m,2H), 5.57 (q, *J* = 6.8 Hz, 1H), 2.87 (s, 3H), 1.69 (d, *J* = 6.8 Hz, 3H). LC-MS m/z: 376.2 $[M+H]^+$. HPLC: Purity (214 nm): 92%; t_R = 6.58 min.

A/-(3-Cvclopropylbutan-2-yl)-4-methyl-2-(pyridin-3-yl)imidazo [1,5-alpyrimidine-8-carboxamide



[00348] Following general procedure A, 4-methyl-2-(pyridin-3-yl)imidazo[l ,5-a]pyrimidine-8-carboxylic acid (30 mg, 0.12 mmol) and the mixture of 3-cyclopropylbutan-2-amine (major) and l-cyclopropyl-2-methylpropan-2-amine (minor) afforded the title compound (14 mg, 39%) as a yellow solid. ^{1}H NMR (500 MHz, $CDC1_3$) δ 9.32 (d, *J* = 2.5 Hz, 1H), 8.78 (dd, *J* = 5.0 Hz, 1.5 Hz, 1H), 8.49 (dt, *J* = 8.0 Hz, 2.0 Hz, 1H), 8.12 (s, 1H), 7.91 (d, *J* = 9.5 Hz, 1H), 7.50 (ddd, *J* = 8.5 Hz, 5.0 Hz, 1.0 Hz, 1H), 7.13 (d, *J* = 1.0 Hz, 1H), 3.68-3.64 (m, 1H), 2.82 (d, *J* = 1.0 Hz, 3H), 2.11-2.09 (m, 1H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.03-0.98 (m, 1H), 0.62-0.57 (m, 2H), 0.52-0.40 (m, 3H). LC-MS m/z: 350.2 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 6.70 min.

A/-(l-Cvclopropyl-2-methylpropan-2-yl)-2,4-dimethylimidazo[l,5-alpyrimidine-8-carboxamide & A/-(3-Cvclopropylbutan-2-vn-24-dimethylimidazo[l,5-alpyrimidine-8-carboxamide

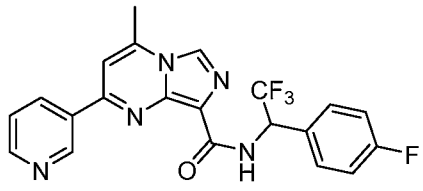


[00349] Following general procedure A, 2,4-dimethylirnidazo[l,5-a]pyrirnidine-8-carboxylic acid (25 mg, 0.13 mmol) and a mixture of l-cyclopropyl-2-methylpropan-2-amine and 3-cyclopropylbutan-2-amine afforded ***N***-(l-cyclopropyl-2-methylpropan-2-yl)-2,4-dimethylimidazo[l,5-a]pyrimidine-8-carboxamide (3.0 mg, 1.6%) and ***N***-(3-cyclopropylbutan-2-yl)-2,4-dimethylimidazo[l,5-a]pyrirnidine-8-carboxarnide (7.3 mg, 3.2%) as white solids.

[00350] ***N***-(l-Cvclopropyl-2-methylpropan-2-yl)-2^-dimethylimidazo[1.5-alpyrimidine-8-carboxamide : ^{1}H NMR (500 MHz, CDC1$_3$) δ 7.92 (s, 1H), 7.71 (bs, 1H), 6.48 (d, ***J*** = 1.0 Hz, 1H), 2.64 (**d, *J*** = 1.0 Hz, 3H), 2.62 (s, 3H), 1.82 (**d, *J*** = 7.0 Hz, 2H), 1.57 (s, 6H), 0.81-0.78 (m, 1H), 0.48-0.44 (m, 2H), 0.17-0.14 (m, 2H). LC-MS m/z: 287.2 $[M+H]^+$. HPLC: Purity (214 nm): > 98%; t_R =7.58 min.

[00351] ***N***-(3-Cvclopropylbutan-2-yl)-2^-dimethylimidazo[1.5-alpyrimidine-8-carboxamide : ^{1}H NMR (500 MHz, CDC1$_3$) *δ* 7.97 (s, 1H), 7.91 (**d, *J*** = 9.5 Hz, 1H), 6.51 (**d, *J*** = 1.0 Hz, 1H), 3.69-3.64 (m, 1H), 2.66 (**d, *J*** = 1.5 Hz, 3H), 2.62 (s, 3H), 2.07-2.03 (m, 1H), 1.09 (**d, *J*** = 6.5 Hz, 3H), 1.07 (**d, *J*** = 6.5 Hz, 3H), 1.00-0.95 (m, 1H), 0.56-0.49 (m, 2H), 0.44-0.36 (m, 2H). LC-MS m/z: 287.2 $[M+H]^+$. HPLC: Purity (214 nm): > 97%; t_R =7.38 min.

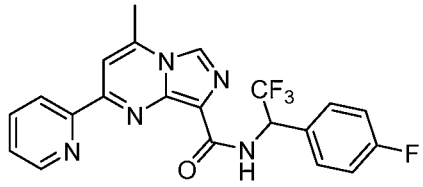
4-Methyl-2-(pyridin-3-yl)-iV-(2,2,2-trifluoro-l-(4-fluorophenyl)ethyl)imidazo [1,5-*a*\pyrimidine-8-carboxamide



[00352] Following general procedure A, 4-methyl-2-(pyridin-3-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.19 mmol) and 2,2,2-trifluoro- 1-(4-fluorophenyl)ethanamine afforded the title compound (3.5 mg, 4.1%) as a white solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 9.43 (**d, *J*** = 1.5 Hz, 1H), 8.78(dd, ***J*** = 4.5 Hz, 1.5 Hz, 1H), 8.66 (dt, ***J*** =

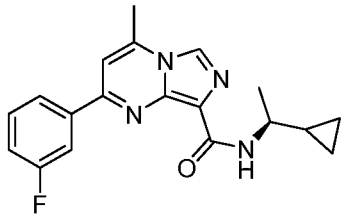
8.0 Hz, 2.0 Hz, 1H), 8.53 (s, 1H), 7.71-7.65 (m, 3H), 7.63 (d, *J* = 1.0 Hz, 1H), 7.23 (tt, *J* = 8.5 Hz, 2.0 Hz, 2H), 6.08 (q, *J* = 8.0 Hz, 1H), 2.91 (d, *J* = 1.0 Hz, 3H). LC-MS m/z: 429.8[M+H]$^+$. HPLC: Purity (214 nm): 97%; t_R = 7.83 min.

4-Methyl-2-(pyridin-2-yl)-iV-(2,2,2-trifluoro-l-(4-fluorophenyl)ethyl)imidazo[1,5-«ıpyrimidine-8-carboxamide



[00353] Following general procedure A, 4-methyl-2-(pyridin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (100 mg, 0.40 mmol) and 2,2,2-trifiuoro-l-(4-fluorophenyl)ethanamine afforded the title compound (44 mg, 26%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-c¾): δ 8.78 (d, *J* = 4.8 Hz, 1H), 8.50 (t, *J* = 4.0 Hz, 2H), 8.04 (t, *J* = 8.0 Hz, 1H), 8.00 (s, 1H), 7.68 (dd, *J* = 8.4 Hz, 4.8 Hz, 2H), 7.57 (dd, *J* = 7.6 Hz, 4.8 Hz, 1H), 7.22 (tt, *J* = 8.0 Hz, 2.0 Hz, 2H), 6.08 (q, *J* = 8.0 Hz, 1H), 2.88 (s, 3H). LC-MS m/z: 429.8 [M+H]$^+$. HPLC: Purity (214 nm): 98%; t_R = 8.18 min.

***(s')*-A/-(l-Cvclopropylethyl)-2-(3-fluorophenyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide**



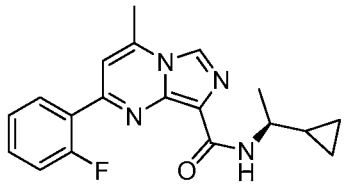
[00354] Following general procedure **D,** ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (100 mg, 0.418 mmol) and 3-fluorophenylboronic acid afforded ethyl 2-(3-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (100 mg, 80%) as ayellow solid. LC-MS m/z: 300.0 [M+H]$^+$. t_R = 1.67 min.

[00355] Following general procedure B, ethyl 2-(3-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (100 mg, 0.334 mmol) afforded crude 2-(3-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid. LC-MS m/z: 272.0 [M+H]$^+$. t_R = 1.22 min.

[00356] Following general procedure A, 2-(3-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (crude, previous step) and (<S)-l-cyclopropylethanamine

afforded the title compound (62 mg, 53% over 2 steps) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) ıδ 8.50 (d, *J* = 3.0 Hz, 1H), 8.41 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 8.02 (dt, *J* = 10.0 Hz, 2.0 Hz, 1H), 7.60 (ddd, *J* = 14.0 Hz, 8.0 Hz, 2.0 Hz, 1H), 7.51 (d, *J* = 0.5 Hz, 1H), 7.33 (td, *J* = 9.0 Hz, 2.0 Hz, 1H), 3.76-3.68 (m, 1H), 2.85 (s, 3H), 1.41 (d, *J* = 7.0 Hz, 3H), 1.16-1.09 (m, 1H), 0.67-0.56 (m, 2H), 0.52-0.47 (m, 1H), 0.42-0.37 (m, 1H). LC-MS m/z: 339.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 7.77 min.

^-A^-Cl-Cvclopropylethyn-Z-CZ-fluorophenvn^-methylimidazofl^-alpyrimidine-S-carboxamide

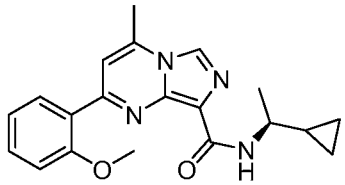


[00357] Following general procedure **D,** ethyl 2-chloro-4-methylimidazo[l ,5-a]pyrirnidine-8-carboxylate (60 mg, 0.251 mmol) and 2-fluorophenylboronic acid afforded ethyl 2-(2-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (28 mg, 37%) as a yellow solid. LC-MS m/z: 300.1 $[M+H]^+$. t_R = 1.74 min.

[00358] Following general procedure B, ethyl 2-(2-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (28 mg, 0.094 mmol) afforded crude 2-(2-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid. LC-MS m/z: 272.0 $[M+H]^+$. t_R = 1.32 min.

[00359] Following general procedure A, 2-(2-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (crude, previous step) and (<S)-l-cyclopropylethanamine afforded the title compound (2.6 mg, 8% over 2 steps) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) *δ* 8.44 (s, 1H), 8.14 (td, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.63-7.59 (m, 1H), 7.42 (td, *J* = 7.5 Hz, 1.0 Hz, 1H), 7.38-7.37 (m, 1H), 7.35 (ddd, *J* = 12.0 Hz, 8.5 Hz, 1.0 Hz, 1H), 3.76-3.70 (m, 1H), 2.85 (s, 3H), 1.38 (d, *J* = 7.0 Hz, 3H), 1.11-1.04 (m, 1H), 0.62-0.57 (m, 1H), 0.55-0.50 (m, 1H), 0.48-0.44 (m, 1H), 0.38-0.33 (m, 1H). LC-MS m/z: 339.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.78 min.

f.y)-iV-(l-Cvclopropylethyl)-2-(2-methoxyphen^ l)-4-methylimidazo[1,5-*a*]pyrimidine-8-carboxamide

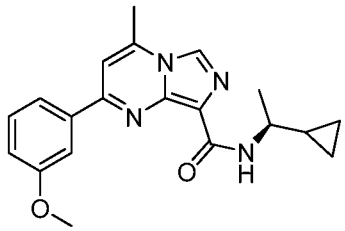


[00360] Following general procedure D, ethyl 2-chloro-4-methylimidazo[l ,5-a]pyrimidine-8-carboxylate (100 mg, 0.42 mmol) and 2-methoxyphenylboronic acid afforded ethyl 2-(2-methoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (124 mg, 95%) as a yellow solid. LC-MS m/z: 312.1 $[M+H]^+$. t_R = 1.64 min.

[00361] Following general procedure B, ethyl 2-(2-methoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (124 mg, 0.40 mmol) afforded 2-(2-methoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid sodium salt (110 mg, 92%) as a light yellow solid. LC-MS m/z: 283.9 $[M+H]^+$. LCMS: t_R = 1.50 min.

[00362] Following general procedure A, 2-(2-methoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.18 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound (13.3 mg, 22%) as a white solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.57 (d, *J* = 8.0 Hz, 1H), 8.38(s, 1H), 7.93 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.55 (ddd, *J* = 9.0 Hz, 7.0 Hz, 2.0 Hz, 1H), 7.46 (d, *J* = 1.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.15 (td, *J* = 7.5 Hz, 0.5 Hζ,IH), 3.98 (s, 3H), 3.78-3.70 (m, 1H), 2.82 (d, *J* = 1.0 Hz, 3H), 1.36 (d, *J* = 6.5 Hz, 3H), 1.08-1.01 (m, 1H), 0.60-0.43 (m,3H), 0.37-0.32 (m, 1H). LC-MS m/z: 351.1 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 8.52 min.

***(.s')*-A/-(l-Cvclopropylethyl)-2-(3-methoxyphenyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide**



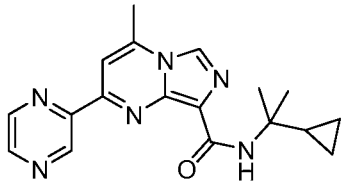
[00363] Following general procedure **D,** ethyl 2-chloro-4-methylimidazo[l ,5-a]pyrirnidine-8-carboxylate (100 mg, 0.42 mmol) and 3-methoxyphenylboronic acid afforded ethyl 2-(3-

methoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (101 mg, 67%) as a yellow solid. LC-MS m/z: 312.2 $[M+H]^+$. t_R = 1.63 min.

[00364] Following general procedure B, ethyl 2-(3-methoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (100 mg, 0.32 mmol) afforded 2-(3-methoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (80, mg, 88%). LC-MS m/z: 284.0 $[M+H]^+$. t_R = 1.21 min.

[00365] Following general procedure A, 2-(3-methoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (80 mg, 0.28 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound (48 mg, 48%) as a white solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.54 (d, J = 8.0 Hz, 1H), 8.38 (s, 1H), 7.81-7.78 (m, 2H), 7.50-7.47 (m, 2H), 7.15 (ddd, J = 8.5 Hz, 2.5 Hz, 1.0 Hz, 1H), 3.93 (s, 3H), 3.78-3.71 (m, 1H), 2.84 (s, 3H), 1.41 (d, J = 6.5 Hz, 3H), 1.14-1.07 (m, 1H), 0.66-0.54 (m, 2H), 0.51-0.46 (m, 1H), 0.40-0.36 (m, 1H). LC-MS m/z: 351.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 9.66 min.

A/-(2-Cvclopropylpropan-2-yl)-4-methyl-2-(pyrazin-2-yl)imidazo[l,5-alpyrimidine-8-carboxamide



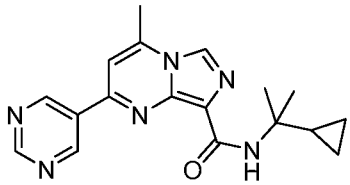
[00366] Following general procedure F, ethyl 2-chloro-4-methylimidazo[l ,5-a]pyrirnidine-8-carboxylate (200 mg, 0.8 mmol) and 2-(tributylstannyl)pyrazine afforded ethyl 4-methyl-2-(pyrazin-2-yl)imidazo[l ,5-a]pyrimidine-8-carboxylate (150 mg, 63%) as a yellow solid. LC-MS m/z: 284.7 $[M+H]^+$. LCMS : t_R = 1.40 min.

[00367] Following general procedure B, ethyl 4-methyl-2-(pyrazin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (150 mg, 0.53 mmol) afforded 4-methyl-2-(pyrazin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (135 mg, 100%) as a yellow solid. LC-MS m/z: 256.7 $[M+H]^+$. LCMS : t_R = 0.86 min.

[00368] Following general procedure A, 4-methyl-2-(pyrazin-2-yl)imidazo[l ,5-a]pyrimidine-8-carboxylic acid (80 mg, 0.31 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (11.8 mg, 11%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.59 (d, J = 1.5 Hz, 1H), 8.84-8.82 (m, 2H), 8.56 (s, 1H), 8.04 (s, 1H), 7.78 (d, J = 1.0 Hz, 1H), 2.83 (d,

J = 0.5 Hz, 3H), 1.48-1.42 (m, 1H), 1.39 (s, 6H), 0.50-0.45 (m, 4H). LC-MS m/z: 337.1 $[M+H]^+$. HPLC: Purity (254 nm): 98%; t_R = 8.89 min.

iV-(2-Cvclopropylpropan-2-yl)-4-methyl-2-(pyrimid^ n-5-yl)imidazo[1,5-*a*]pyrimidine-8-carboxamide

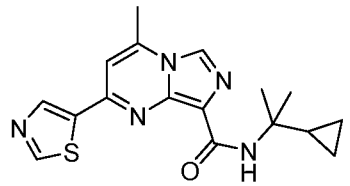


[00369] Following general procedure D, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (110 mg, 0.46 mmol) and pyrimidin-5-ylboronic acid afforded ethyl 4-methyl-2-(pyrirnidin-5-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (83 mg, 64%) as a yellow solid. LC-MS m/z: 283.9 $[M+H]^+$. LCMS: t_R = 1.33 min.

[00370] Following general procedure B, ethyl 4-methyl-2-(pyrimidin-5-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (20 mg, 0.071 mmol) afforded 4-methyl-2-(pyrimidin-5-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (27 mg, crude). LC-MS m/z: 256.0 $[M+H]^+$. LCMS: t_R = 0.37 min.

[00371] Following general procedure A, 4-methyl-2-(pyrimidin-5-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (27 mg, 0.096 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (6.8 mg, 21% over 2 steps) as an off-white solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 9.62 (s, 2H), 9.32 (s, 1H), 8.47 (s, 1H), 8.28 (s, 1H), 7.59 (d, *J* = 1.0 Hz, 1H), 2.89 (d, *J* = 1.5 Hz, 3H), 1.49 (s, 6H), 1.49-1.46 (m, 1H), 0.59-0.55 (m, 4H). LC-MS m/z: 336.9 $[M+H]^+$. HPLC: Purity (214 nm): 97%; t_R = 7.14 min.

A/-(2-Cvclopropylpropan-2-yl)-4-methyl-2-(thiazol-5-yl)imidazo[l,5-alpyrimidine-8-carboxamide



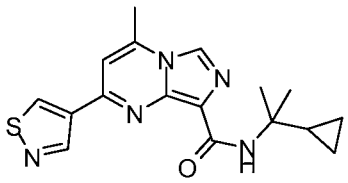
[00372] Following general procedure F, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (250 mg, 1.05 mmol) and 5-(tributylstannyl)thiazole afforded ethyl 2-(4-methyl-

2-(thiazol-5-yl)imidazo[l,5-a]pyrimidin-8-carboxylate (180 mg, 50%) as a yellow solid. LC-MS m/z: 289.0 $[M+H]^+$. t_R = 1.36 min.

[00373] Following general procedure B, ethyl 2-(4-methyl-2-(thiazol-5-yl)imidazo[l,5-a]pyrimidin-8-carboxylate (30 mg, 0.104 mmol) afforded 2-(4-methyl-2-(thiazol-5-yl)imidazo[l,5-a]pyrimidin-8-carboxylic acid (45 mg crude). LC-MS m/z: 261.1 $[M+H]^+$. LCMS: t_R = 0.37 min.

[00374] Following general procedure A, 2-(4-methyl-2-(thiazol-5-yl)imidazo[l,5-a]pyrimidin-8-carboxylic acid (45 mg, 0.17 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (9.2 mg, 16% over 2 steps) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4) *δ 9.22* (s, 1H), 8.73 (s, 1H), 8.40 (s, 1H), 8.18 (s, 1H), 7.50 (d, *J* = 0.5 Hz, 1H), 2.84 (d, *J* = 0.5 Hz, 3H), 1.51 (s, 6H), 1.51-1.46 (m, 1H), 0.61-0.54 (m, 4H). LC-MS m/z: 342.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 6.05 min.

A/-(2-Cvclopropylpropan-2-yl)-2-(isothiazol-4-yl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00375] To a solution of isothiazole (5.0 g, 58.82 mmol) in AcOH (37 mL) was added Br_2 (12.5 g, 78. 12 mmol) dropwise at 95 °C over 20 min and the mixture was stirred for 6 h at 95 °C, then cooled to RT, and poured into ice water (100 mL). The resulting mixture was extracted with Et^O (200 mL x 2). The organic phases were washed with 6N NaOH to pH at 7-8, dried over anhydrous Na2SC>4 and filtered. The filtrate was concentrated *in vacuo,* and the resulting residue was purified by distillation to afford 4-bromoisothiazole as a white solid (1.5 g, 15%).

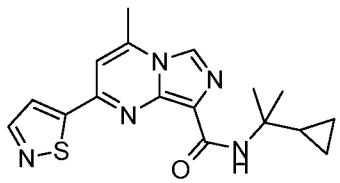
[00376] Following general procedure E, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (102 mg, 0.427 mmol) and 4-bromoisothiazole afforded ethyl 2-(isothiazol-4-yl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (70 mg, 57%) as a yellow solid. LC-MS m/z: 289.0 $[M+H]^+$. t_R = 1.44 min.

[00377] Following general procedure B, ethyl 2-(isothiazol-4-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (70 mg, 0.243 mmol) afforded crude 2-(isothiazol-4-yl)-4-

methylimidazo[l,5-a]pyrimidine-8-carboxylic acid as a yellow solid. LC-MS m/z: 261.0 $[M+H]^+$. t_R = 0.92 min.

[00378] Following general procedure A, 2-(isothiazol-4-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (crude, from previous step) and 2-cyclopropylpropan-2-amine afforded the title compound (4.4 mg, 5% over 2 steps) as a yellow solid. ^{1}H NMR (500 MHz, *MeOO-d_4)* δ 9.70 (s, 1H), 9.31 (s, 1H), 8.39 (s, 1H), 8.26 (s, 1H), 7.43 (s, 1H), 2.84 (s, 3H), 1.50 (s, 6H), 1.50-1.46 (m, 1H), 0.59-0.56 (m, 4H). LC-MS m/z: 342.1.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.14 min.

A/-(2-Cvclopropylpropan-2-yl)-2-(isothiazol-5-yl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



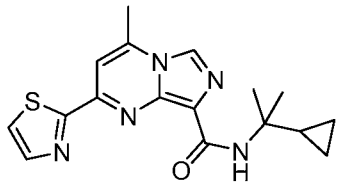
[00379] To a solution of isothiazole (5 g, 0.06 mol) in anhydrous THF (50 mL) was added n-BuLi (28.2 mL, 0.07 mol) dropwise at -70 °C over 1 h. After stirring at -70 °C for 1 h, Br_2 (6 mL, 0.12 mol) was added dropwise over 30 min and the resulting mixture was allowed to warm to RT and poured into an excess of cold 2N HCl solution. The organic layer was separated and the aqueous layer was extracted with Et^O (200 mL x 3). The combined organic extracts were washed with saturated sodium dithionite solution (200 mL x 2), dried over anhydrous Na2SC>4, and filtered. The filtrate was concentrated *in vacuo,* and the resulting residue was distilled to afford 5-bromoisothiazole (2 g, 21%) as yellow oil. ^{1}H NMR (400 MHz, $CDC1_3$) δ 8.33 (d, J = 1.6 Hz, 1H), 7.28 (d, J = 1.6 Hz, 1H).

[00380] Following general procedure E, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (218 mg, 0.9 mmol) and 5-bromoisothiazole afforded ethyl 2-(isothiazol-5-yl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (80 mg, 45%) as a white solid. LC-MS m/z: 289.2 $[M+H]^+$.

[00381] Following general procedure B, ethyl 2-(isothiazol-5-yl)-4-methylimidazo [1,5-a]pyrimidine-8-carboxylate (80 mg, 0.28 mmol) afforded 2-(isothiazol-5-yl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (100 mg, 99%) as a brown solid. LC-MS m/z: 261.2 $[M+H]^+$.

[00382] Following general procedure A, 2-(isothiazol-5-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (100 mg, 0.26 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (13 mg, 15%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.65 (d, *J* = 2.0 Hz, 1H), 8.45 (s, 1H), 8.12 (bs, 1H), 8.06 (d, *J* = 2.0 Hz, 1H), 7.45 (d, *J* = 0.5 Hz, 1H), 2.86 (d, *J* = 1.0 Hz, 3H), 1.52-1.47 (m, 1H), 1.51 (s, 6H), 0.61-0.55 (m, 4H). LC-MS m/z: 342.2 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 7.18 min.

A/-(2-Cvclopropylpropan-2-yl)-4-methyl-2-(thiazol-2-yl)imidazo[l,5-alpyrimidine-8-carboxamide

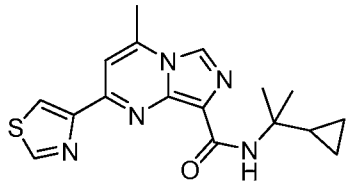


[00383] Following general procedure F, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (142 mg, 0.594 mmol) and 2-(tributylstannyl)thiazole afforded ethyl 2-(4-methyl-2-(thiazol-2-yl)imidazo[l,5-a]pyrimidin-8-carboxylate as a light brown solid (160 mg, 88%). LC-MS m/z: 208 $[M+H]^+$. LCMS Purity (214 nm): 80.5 %.

[00384] Following general procedure B, ethyl 2-(4-methyl-2-(thiazol-2-yl)imidazo[l,5-a]pyrimidin-8-carboxylate (260 mg, 0.90 mmol) afforded 2-(4-methyl-2-(thiazol-2-yl)imidazo[l,5-a]pyrimidin-8-carboxylic acid (71 mg, 30 %). LC-MS m/z: 261 $[M+H]^+$. LCMS Purity (214 nm): 96.3 %.

[00385] Following general procedure A, 2-(4-methyl-2-(thiazol-2-yl)imidazo[l,5-a]pyrimidin-8-carboxylic acid (70 mg, 0.27 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (42 mg, 46%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.12 (d, *J* = 3.0 Hz, 1H), 8.07 (d, *J* = 3.0 Hz, 1H), 7.88 (s, 1H), 7.62 (d, *J* = 1.5 Hz, 1H), 2.81 (s, 3H), 1.46-1.40 (m, 1H), 1.39 (s, 6H), 0.50-0.44 (m, 4H). LC-MS m/z: 342.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.32 min.

A/-(2-Cvclopropylpropan-2-yl)-4-methyl-2-(thiazol-4-yl)imidazo[l,5-alpyrimidine-8-carboxamide

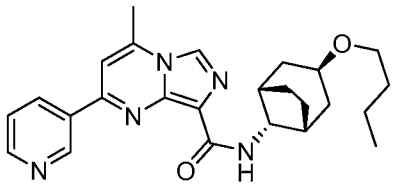


[00386] Following general procedure F, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (200 mg, 0.8 mmol) and 4-(tributylstannyl)thiazole afforded ethyl 2-(4-methyl-2-(thiazol-4-yl)imidazo[l,5-a]pyrimidin-8-carboxylate (200 mg, 83%) as a yellow solid. LC-MS m/z: 289.7 $[M+H]^+$. LCMS: t_R = 1.42 min.

[00387] Following general procedure B, ethyl 2-(4-methyl-2-(thiazol-4-yl)imidazo[l,5-a]pyrimidin-8-carboxylate (200 mg, 0.70 mmol) afforded 2-(4-methyl-2-(thiazol-4-yl)imidazo[l,5-a]pyrimidin-8-carboxylic acid (300 mg, 100%) as a yellow solid. LC-MS m/z: 261.7 $[M+H]^+$. LCMS: t_R = 0.97 min.

[00388] Following general procedure A, 2-(4-methyl-2-(thiazol-4-yl)imidazo[l,5-a]pyrimidin-8-carboxylic acid (100 mg, 0.38 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (22 mg, 17%) as a yellow solid. ^{1}H NMR (500 MHz, *OMSO-d_6)* δ 9.32 (d, *J* = 2.0 Hz, 1H), 8.46 (s, 1H), 8.45 (d, *J* = 2.0 Hz, 1H), 8.05 (s, 1H), 7.63 (d, *J* = 1.0 Hz, 1H), 2.79 (d, *J* = 1.0 Hz, 3H), 1.48-1.42 (m, 1H), 1.38 (s, 6H), 0.47-0.44 (m, 4H). LC-MS m/z: 342.2 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 9.19 min.

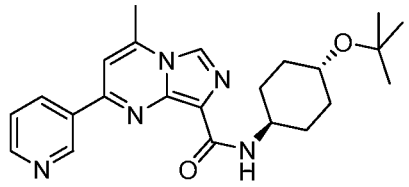
***N*-((1*R*,3*R*,5*S*,8*R*)-3-Butoxybicyclo[3.2.1]octan-8-yl)-4-methyl-2-(pyridin-3-yl)imidazo[1,5-« 1pyrimidine-8-carboxamide**



[00389] Following general procedure A, 4-methyl-2-(pyridin-3-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (51 mg, 0.20 mmol) and *(lR,3R,5S)-3*-butoxybicyclo[3.2.1]octan-8-amine afforded the title compound (14 mg, 16%) as a white solid. ^{1}H NMR (400 MHz, *MeOO-d_4)* δ 9.30 (d, *J* = 2.0 Hz, 1H), 8.74 (dd, *J* = 4.0 Hz, 1.2 Hz, 1H), 8.54 (tt, *J* = 6.0 Hz, 1.6 Hz, 1H), 8.46 (s, 1H), 7.65 (ddd, *J* = 6.4 Hz, 4.0 Hz, 0.8 Hz, 1H), 7.52 (d, *J* = 0.8 Hz, 1H), 4.20 (t, *J* = 4.8 Hz, 1H), 3.55 (t, *J* = 4.8 Hz, 1H), 3.41 (t, *J* = 6.4 Hz, 2H),

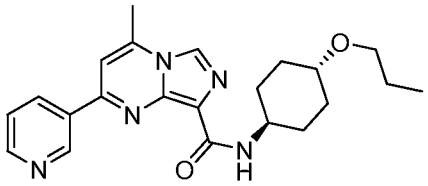
2.88 (s, 3H), 2.27-2.21 (m, 2H), 2.08-2.02 (m, 4H), 1.94-1.87 (m, 2H), 1.86-1.79 (m, 2H), 1.59-1.51 (m, 2H), 1.48-1.39 (m, 2H), 0.96 (t, J = 7.6 Hz, 3H). LC-MS m/z: 434.2 $[M+H]^+$. HPLC: Purity (214 nm): 96.8%; t_R = 8.34 min.

A/-((*Ji?,4i?*)-4-tert-Butoxycyclohexyl)-4-methyl-2-(pyr din-3-yl)imidazo[l,5-alpyr midine-8-carboxamide



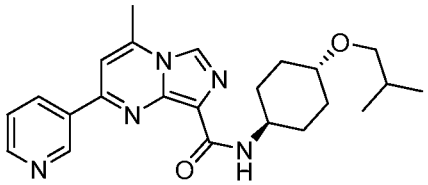
[00390] Following general procedure A, 4-methyl-2-(pyridin-3-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (51 mg, 0.20 mmol) and *(1R,4R)-4-tcrt*-butoxycyclohexanamine afforded the title compound (33 mg, 40%) as a yellow solid. ^{1}H NMR (500 MHz,$CDCl_3$) δ 9.33 (d, J = 2.0 Hz, 1H), 8.79 (dd, J = 5.0 Hz, 2.0 Hz, 1H), 8.45 (dt, J = 7.5 Hz, 1.5 Hz, 1H), 8.10 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.53 (ddd, J = 8.0 Hz, 4.5 Hz, 0.5 Hz, 1H), 7.13 (d, J = 1.0 Hz, 1H), 4.12-4.03 (m, 1H), 3.50-3.43 (m, 1H), 2.81 (s, 3H), 2.26-2.22 (m, 2H), 1.92-1.88 (m, 2H), 1.56-1.53 (m, 2H), 1.42-1.39 (m, 2H), 1.23 (s, 9H). LC-MS m/z: 408.3 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 6.85 min.

4-Methyl-A/-((7i?,^i?)-4-propoxycyclohexyl)-2-(pyridin-3-yl)imidazo[l,5-alpyrimidine-8-carboxamide



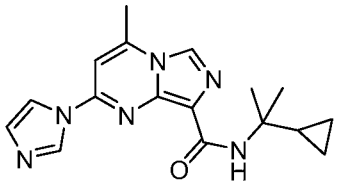
[00391] Following general procedure A, 4-methyl-2-(pyridin-3-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.19 mmol) and (7i?,4i?)-4-propoxycyclohexanamine afforded the title compound (24 mg, 36%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾): δ 9.41 (t, J = 1.0 Hz, 1H), 8.74 (dd, J = 4.5 Hz, 1.5 Hz, 1H), 8.66 (dt, J = 8.5 Hz, 2.0 Hz, 1H), 8.45 (s, 1H), 7.68 (ddd, J = 8.0 Hz, 5.0 Hz, 0.5 Hz, 1H), 7.57 (d, J = 1.0 Hz, 1H), 4.03-3.99 (m, 1H), 3.51 (t, J = 6.0 Hz, 2H), 3.43-3.39 (m, 1H), 2.88 (d, J = 1.0 Hz, 3H), 2.22-2.13 (m, 4H), 1.63-1.57 (m, 2H), 1.56-1.47 (m, 4H), 0.97 (t, J = 7.5 Hz, 3H). LC-MS m/z: 394.2 $[M+H]^+$. HPLC Purity (214 nm): 99%; t_R = 6.64 min.

iV-((*Ii*?,*4i*?)-4-isoButoxycvclohexyl)-4-methyl-2-(pyridin-3-yl)imidazo[1,5-*a*]pyrimidine-8-carboxamide



[00392] Following general procedure A, 4-methyl-2-(pyridin-3-yl)imidazo[l ,5-a]pyrimidine-8-carboxylic acid (51 mg, 0.20 mmol) and (7i?, 4i?)-4-isobutoxycyclohexanamine afforded the title compound (13.5 mg, 17%) as a white solid. ^{1}H NMR (500 MHz, CDC1$_3$) δ 9.32 (d, J = 1.5 Hz, 1H), 8.79 (dd, J = 5.0 Hz, 1.5 Hz, 1H), 8.46 (dt, J = 8.0 Hz, 2.0 Hz, 1H), 8.10 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.52 (ddd, J = 8.0 Hz, 5.0 Hz, 1.0 Hz, 1H), 7.13 (d, J = 1.0 Hz, 1H), 4.20-4. 15 (m, 1H), 3.3 1-3.25 (m, 1H), 3.25 (d, J = 7.0 Hz, 2H), 2.82 (d, J = 1.0 Hz, 3H), 2.26-2.24 (m, 2H), 2.12-2.08 (m, 2H), 1.90-1 .81 (m, 1H), 1.58-1 .48 (m, 2H), 1.42-1.38 (m, 2H), 0.93 (d, J = 7.0Hz, 6H). LC-MS m/z: 408.3 [M+H]$^+$. HPLC: Purity (254 nm): >99%; t_R = 7.27min.

A/-(2-Cvclopropylpropan-2-yl)-2-(l *H* -imidazol-l-yl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



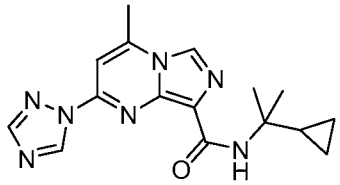
[00393] A mixture of ethyl 2-chloro-4-methylimidazo[l ,5-a]pyrimidine-8-carboxylate (500 mg, 2.09 mmol), I*H*-imidazole (426 mg, 6.27 mmol) and K_2C0_3 (576 mg, 4.18 mmol) in DMF (10 mL) was stirred at 60 °C for 5 h, cooled, poured into H_20 (100 mL) and extracted with EA (150 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo,* and the resulting residue was purified by silica gel column chromatography (EA/MeOH = 5/1) to afford ethyl 2-(l *H*-imidazol-l -yl)-4-methylinddazo[l,5-a]pyrimidine-8-carboxylate (250 mg, 40%) as a brown solid. LC-MS m/z: 272. 1 [M+H]$^+$. Purity (254 nm): > 95%; t_R = 0.95 min.

[00394] A mixture of ethyl 2-(l *H*-irrddazol-l -yl)-4-methylirrddazo[l ,5-a]pyrimidine-8-carboxylate (100 mg, 0.37 mmol) and bis(tri-n-butyltin)oxide (440 mg,0.74 mmol) in toluene (5 mL) was stirred at 110 °C for 16 h, cooled to RT and poured into a solution of 1 M Na_2C0_3

(2 mL) and EA (10 mL). The aqueous phase was separated, acidified to pH ~5 with 4M HC1 and lyophilized to afforded 2-(l *H*-imidazol-l-yl)-4-methylinddazo[l ,5-a]pyrimidine-8-carboxylic acid (200 mg, crude) as a yellow solid. LC-MS m/z: 244. 1 $[M+H]^+$. Purity (254 nm): > 80%; t_R = 0.35 min.

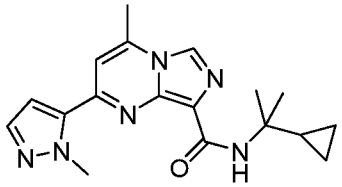
[00395] Following general procedure A, 2-(l *H*-imidazol-l -yl)-4-methylimidazo[l ,5-a]pyrimidine-8-carboxylic acid (20 mg, 0.08 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (2.5 mg, 10%) as a yellow solid. ¾ NMR (500 MHz, *OMSO-d_6)* δ 8.64 (s, IH), 8.47 (s, IH), 7.96 (s, IH), 7.61 (s, IH), 7.52 (d, *J* = 1.5 Hz, IH), 7.24 (s, IH), 2.77 (s, 3H), 1.44-1 .41 (m, IH), 1.35 (s, 6H), 0.45-0.43 (m, 4H). LC-MS m/z: 325.2 $[M+H]^+$, HPLC : Purity (214 nm): > 99%; t_R = 6.08 min.

A/-(2-Cvclopropylpropan-2-yl)-4-methyl-2-(l *H* -l,2,4-triazol-l-yl)imidazo[l,5-*a*]pyrimidine-8-carboxamide



[00396] A mixture of 2-chloro-*N*-(2-cyclopropylpropan-2-yl)-4-methylimidazo[l ,5-a]pyrimidine-8-carboxarnide (70 mg, 0.21 mmol), l*H*-l,2,4-triazole (32.2 mg, 0.42 mmol), K_2C0_3 (58. 1 mg, 0.42 mmol), and KI (3.5 mg, 0.02 mmol) in 5 mL of DMF was stirred at 100 °C for 1 h under microwave condition. The crude product was further purified by prep-HPLC (MeCN/l OmM NH4HCO3) to afford the title compound (21 mg, 29%) as a yellow solid. ^{1}H NMR (500 MHz, *MeOO-d_4)*: δ 9.74 (s, IH), 8.42 (s, IH), 8.28 (s, IH), 7.70 (s, IH), 7.55 (d, *J* = 1.0 Hz, IH), 2.88 (d, *J* = 1.0 Hz, 3H), 1.49-1 .47 (m, IH), 1.49 (s, 6H), 1.49-1 .47 (m, IH), 0.55-0.54 (m, 4H). LC-MS m/z: 326. 1 $[M+H]^+$. HPLC: Purity (214 nm): 98.9%; t_R = 6.37 min.

A/-(2-Cvclopropylpropan-2-yl)-4-methyl-2-(l-methyl-l *H*-pyrazol-5-yl)imidazo[l,5-«1pyrimidine-8-carboxamide



[00397] Following general procedure D, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (120 mg, 0.5 mmol) and 1-methyl-l*H*-pyrazol-5-ylboronic acid to afford crude ethyl 4-methyl-2-(l-methyl-l *H*-pyrazol-5-yl)irnidazo[l,5-a]pyrimidine-8-carboxylate (143 mg, quantitative) as a brown solid. LC-MS m/z: 286.1 $[M+H]^+$.

[00398] Following general procedure B, ethyl 4-methyl-2-(l -methyl-l*H*-pyrazol-5-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (143 mg, 0.5 mmol) afforded 4-methyl-2-(l-methyl-l *H*-pyrazol-5-yl)irnidazo[l,5-a]pyrimidine-8-carboxylic acid (110 mg, 84%) as a brown solid. LC-MS m/z: 258.1 $[M+H]^+$.

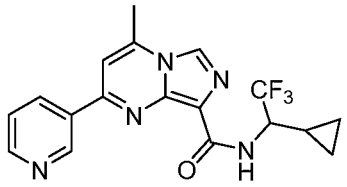
[00399] Following general procedure A, 4-methyl-2-(l -methyl-l*H*-pyrazol-5-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (52 mg, 0.20 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (27 mg, 30%) as a yellow solid. ^{1}H NMR (500 MHz, $CDC1_3$): δ 8.02 (s, 1H), 7.57 (d, *J* = 2.5 Hz, 1H), 7.44 (s, 1H), 6.89 (d, *J* = 1.0 Hz, 1H), 6.78 (d, *J* = 2.5 Hz, 1H), 4.48 (s, 3H), 2.74 (d, *J* = 1.0 Hz, 3H), 1.48-1.44 (m, 1H), 1.46 (s, 6H), 0.50-0.45 (m, 4H). LC-MS m/z: 339.2 $[M+H]^+$. HPLC Purity (214 nm): 96%; t_R = 6.73 min.

[00400] A mixture of ethyl 2-(l*H*-imidazol-l-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (100 mg, 0.37 mmol) and bis(tri-n-butyltin)oxide (440 mg,0.74 mmol) in toluene (5 mL) was stirred at 110 °C for 16 h, cooled and poured into 1 M Na_2C0_3 (2 mL) and EA (10 mL). The aqueous phase was separated, acidified to pH ~5 with 4M HC1 and lyophilized to afforded 2-(l*H*-inddazol-l-yl)-4-methylinddazo[l,5-a]pyrimidine-8-carboxylic acid (200 mg, crude) as a yellow solid. LC-MS m/z: 244.1 $[M+H]^+$. Purity (254 nm): > 80%; t_R = 0.35 min.

[00401] Following general procedure A, 2-(l*H*-imidazol-l-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (20 mg, 0.08 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (2.5 mg, 10%) as a yellow solid. ¾ NMR (500 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.47 (s, 1H), 7.96 (s, 1H), 7.61 (s, 1H), 7.52 (d, *J* = 1.5 Hz, 1H), 7.24 (s, 1H), 2.77 (s, 3H),

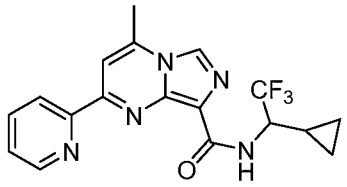
1.44-1.41 (m, 1H), 1.35 (s, 6H), 0.45-0.43 (m, 4H). LC-MS m/z: 325.2 $[M+H]^+$, HPLC : Purity (214 nm): > 99%; t_R = 6.08 min.

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-4-methyl-2-(pyridin-3-yl)imidazo[l,5-alpyrimidine-8-carboxamide



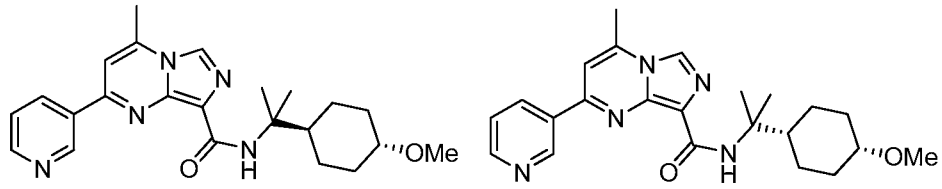
[00402] Following general procedure A, 4-methyl-2-(pyridin-3-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.19 mmol) and l-cyclopropyl-2,2,2-trifluoroethanamine afforded the title compound (14 mg, 19%) as a white solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 9.42 (d, J = 2.5 Hz, 1H), 8.74 (dd, J = 5.0 Hz, 1.5 Hz, 1H), 8.65 (dt, J = 8.0 Hz, 2.5 Hz, 1H), 8.51 (s, 1H), 7.68 (dd, J = 8.5 Hz, 5.0 Hz, 1H), 7.62 (d, J = 0.5 Hz, 1H), 4.48-4.38 (m, 1H), 2.90 (d, J = 1.0 Hz, 3H), 1.38-1.30 (m, 1H), 0.82-0.76 (m, 1H), 0.70-0.59 (m, 2H), 0.55-0.48 (m, 1H). LC-MS m/z: 376.1 $[M+H]^+$. HPLC: Purity (254 nm): 99%; t_R = 6.69 min.

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-4-methyl-2-(pyridin-2-yl)imidazo[l,5-*a*\pyrimidine-8-carboxamide



[00403] Following general procedure A, 4-methyl-2-(pyridin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (100 mg, 0.40 mmol) and l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (39 mg, 26%) as a yellow solid. ^{1}H NMR (400 MHz, *MeOO-d4):* δ 8.75 (d, J = 4.4 Hz, 1H), 8.51 (d, J = 8.0 Hz, 1H), 8.48 (s, 1H), 8.02 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.99 (s, 1H), 7.55 (dd, J = 7.6 Hz, 5.2 Hz, 1H), 4.47-4.39 (m, 1H), 2.87 (s, 3H), 1.40-1.33 (m, 1H), 0.83-0.76 (m, 1H), 0.70-0.58 (m, 2H), 0.55-0.50 (m, 1H). LC-MS m/z: 376.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 7.66 min.

A/-(2-((7i?,^i?)-4-Methoxycvclohexyl)propan-2-yl)-4-methyl-2-(pyridin-3-yl)imidazo[l,5-alpyrimidine-8-carboxamide & *N*-(2-((*1S,4S*)-4-Meihoχvcvcïohexγl)ρrθPaη-2-yl)-4-methyl-2-(pyridin-3-vnimidazo[l,5-alpyrimidine-8-carboxamide

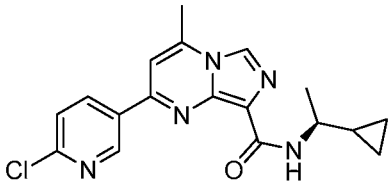


[00404] Following general procedure A, 4-methyl-2-(pyridin-3-yl)imidazo[l ,5-a]pyrirnidine-8-carboxylic acid (130 mg, 0.49 mmol) and 2-(4-methoxycyclohexyl)propan-2-amine afforded the *N*-(2-((7i?, 4i?)-4-methoxycyclohexyl)propan-2-yl)-4-methyl-2-(pyridin-3-yl)imidazo[l,5-a]pyrimidine-8-carboxamide (18.1 mg, 8.7%) and *N-(2-((lS, 4S*)-4-methoxycyclohexyl)propan-2-yl)-4-methyl-2-(pyridin-3-yl)imidazo[l ,5-a]pyrimidine-8-carboxamide (19 mg, 9.1%) as white solids.

[00405] *N-(*2-((*R*,4i?)-4-Methoxycvclohexyl)propan-2-yl)-4-methyl-2-(pyridin-3-yl)imidazori.5-alpyrimidine-8-carboxamide: ¾ NMR (500 MHz, MeOD-c¾) δ 9.35 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 8.72 (dd, *J* = 6.0 Hz, 2.0 Hz, 1H), 8.60 (dt, *J* = 10.0 Hz, 2.5 Hz, 1H), 8.42 (s, 1H), 8.15 (s, 1H), 7.65 (ddd, *J* = 10.5 Hz, 6.0 Hz, 0.5 Hz, 1H), 7.51 (d, *J* = 1.0 Hz, 1H), 3.33 (s, 3H), 3.17-3.10 (m, 1H), 2.87 (s, 3H), 2.18-2.10 (m, 3H), 1.99-1.92 (m, 2H), 1.53 (s, 6H), 1.30-1.18 (m, 4H). LC-MS m/z: 408.1 $[M+H]^+$. HPLC: Purity (214 nm): 89%; t_R = 8.36 min.

[00406] *N-(2-((lS,* 4SV4-Methoxycvclohexyl)propan-2-yl)-4-methyl-2-(pyridin-3-yl)imidazori.5-alpyrimidine-8-carboxamide: ^{1}H NMR (500 MHz, MeOD-c¾) δ 9.23 (dd, *J* = 2.5 Hz, 0.5 Hz, 1H), 8.60 (dd, *J* = 6.5 Hz, 2.0 Hz, 1H), 8.47 (ddd, *J* = 10.0 Hz, 7.5 Hz, 2.0 Hz, 1H), 8.28 (s, 1H), 8.03 (s, 1H), 7.52 (ddd, *J* = 10.5 Hz, 6.5 Hz, 0.5 Hz, 1H), 7.40 (d, *J* = 1.5 Hz, 1H), 3.38-3.35 (m, 1H), 3.17 (s, 3H), 2.74 (s, 3H), 1.93-1.87 (m, 2H), 1.55-1.47 (m, 2H), 1.39 (s, 6H), 1.38-1.32 (m, 5H). LC-MS m/z: 408.1 $[M+H]^+$. HPLC: Purity (254 nm): 95%; t_R = 6.70 min.

f.y)-2-(6-Chloropyridin-3-yl)-iV-(l-cvclopropyk^^ yl)-4-methylimidazo[1,5-*a*]pyrimidine-8-carboxamide

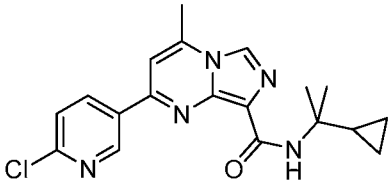


[00407] Following general procedure D, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (480 mg, 2 mmol) and 6-chloropyridin-3-ylboronic acid afforded ethyl 2-(6-chloropyridin-3-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate as a yellow solid (300 mg, 27%). LC-MS m/z: 317.1 $[M+H]^+$. Purity (214 nm): 68%; t_R = 1.24 min.

[00408] A mixture of ethyl 2-(6-chloropyridin-3-yl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (200 mg, 0.47 mmol) and $(Bu_3Sn)_2O$ (465 mg, 0.95 mmol) in toluene (2 mL) was stirred at 110 °C for 15 h until the reaction was complete. The mixture was cooled and concentrated *in vacuo.* The resulting residue was purified by column chromatography on silica gel (DCM/MeOH: 10/1) to afford 2-(6-chloropyridin-3-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid as a yellow solid (200 mg, >90%). LC-MS m/z: 289.0 $[M+H]^+$. Purity (214 nm): 59%; t_R = 0.82 min.

[00409] Following general procedure A, 2-(6-chloropyridin-3-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (55 mg, 0.19 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound (35 mg, 51%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO^) δ 9.22 (d, ***J*** = 2.4 Hz, 1H), 8.61 (dd, ***J*** = 8.4 Hz, 2.4 Hz, 1H), 8.53 (s, 1H), 8.09 (d, ***J*** = 8.0 Hz, 1H), 7.79 (d, ***J*** = 8.4 Hz, 1H), 7.69 (s, 1H), 3.60-3.50 (m, 1H), 2.78 (s, 3H), 1.27 (d, ***J*** = 6.4 Hz, 3H), 1.13-1.05 (m, 1H), 0.50-0.40 (m, 2H), 0.40-0.20 (m, 2H). LC-MS m/z: 356.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.23 min.

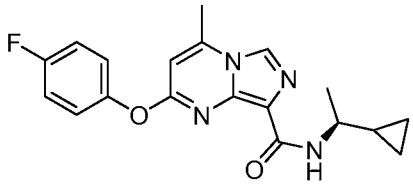
2-(6-Chloropyridin-3-yl)-A/-(2-cvclopropylpropan-2-yl)-4-methylimidazo[l,5-*a*\pyrimidine-8-carboxamide



[00410] Following general procedure A, 2-(6-chloropyridin-3-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (55 mg, 0.19 mmol) and 2-cyclopropylpropan-2-amine afforded

the title compound (33 mg, 47%) as yellow solid. ^{1}H NMR (400 MHz, *OMSO-d_6)* δ 9.22 (d, *J* = 2.4 Hz, 1H), 8.59 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 8.52 (s, 1H), 8.03 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.68 (s, 1H), 2.78 (s, 3H), 1.40-1.36 (m, 1H), 1.36 (s, 6H), 0.48-0.42 (m, 4H). LC-MS m/z: 370.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.73 min.

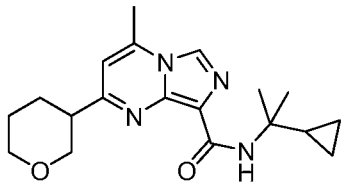
(*S*')-A/-(l-Cvclopropylethyl)-2-(4-fluorophenoxy)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00411] Following general procedure A, 2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (120 mg, 0.60 mmol) and (<S)-l-cyclopropylethanamine afforded (5)-2-chloro-*N*-(l-cyclopropylemyl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxamide as a yellow solid (150 mg, 80%). LC-MS m/z: 279.1 $[M+H]^+$. HPLC: Purity (254 nm): 80%; t_R = 1.28 min.

[00412] Following general procedure H, (5)-2-chloro -*N*-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (150 mg, 0.66 mmol) and 4-fluorophenol afforded the title compound (50 mg, 26%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.32 (s, 1H), 7.38-7.36 (m, 4H), 7.17 (d, *J* = 9.0 Hz 1H), 6.83 (s, 1H), 3.46-3.41 (m, 1H), 2.72 (s, 3H), 0.93 (d, *J* = 6.5 Hz ,3H), 0.56-0.50 (m, 1H), 0.35-0.30 (m, 1H) 0.22-0.17 (m, 1H), 0.07-0.01 (m, 2H). LC-MS m/z: 355.2 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 7.55 min.

A/-(2-Cvclopropylpropan-2-yl)-4-methyl-2-(tetrahvdro-2 *H* -pyran-3-yl)imidazo[l,5-alpyrimidine-8-carboxamide



[00413] To a stirred solution of KHMDS (0.5 mol/L in toluene, 12.0 mL) in THF (5 mL) was added slowly dihydro-2*H*-pyran-3(4*H*)-one (500 mg, 5.0 mmol) in THF (5 mL) at -78 °C under N_2. The mixture was stirred for an additional 15 min before the careful addition of PhN(Tf)2 (2.15 g, 6.0 mmol) in THF (5 mL), and stirred at -78 °C for another 15 min and then at RT for 1 h. Then, the reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution (200 mL), and extracted with EA (160 mL x 3). The combined organic phases were

dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the resulting residue was purified by silica gel chromatography (PE/EA = 10:1) to afford 5,6-dihydro-2*H*-pyran-3-yl trifluoromethanesulfonate (840 mg, crude) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.96-5.95 (m, 1H), 4.19-4.17 (m, 2H), 3.80 (t, J = 5.5 Hz, 2H), 2.40-2.37 (m, 2H).

[00414] A mixture of 5,6-dihydro-2*H*-pyran-3-yl trifluoromethanesulfonate (840 mg, crude), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(l,3,2-dioxaborolane) (1.01 g, 3.98 mmol), Pd(dppf)Cl_2 CH_2Cl_2 (90 mg, 0.11 mmol) and KOAc (1.07 g, 10.86 mmol) in 1,4-dioxane (8 mL) was stirred in a sealed tube at 80 °C under N_2 for 17 h. The mixture was poured into H_2O (20 mL), and extracted with EA (40 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the resulting residue was purified by silica gel chromatography (PE/EA = 9:1) to afford 2-(5,6-dihydro-2*H*-pyran-3-yl)-4,4,5,5-tetramethyl-l,3,2-dioxaborolane (1.06 g, crude) as a yellow oil. ¾NMR (500 MHz, $CDCl_3$): δ 6.68-6.67 (m, 1H), 4.27-4.26 (m, 2H), 3.80 (t, J = 5.5 Hz, 2H), 2.24-2.21 (m, 2H), 1.27 (s, 12H).

[00415] A mixture of 2-(5,6-dihydro-2*H*-pyran-3-yl)-4,4,5,5-tetramethyl-l,3,2-dioxaborolane (850 mg, 4.04 mmol), ethyl 2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (483 mg, 2.02 mmol), $Pd(PPh_3)_4$ (466 mg, 0.4 mmol), and 2 mL of saturated Na_2CO_3 aqueous solution in DME(10 mL) was stirred at 80 °C under N_2 overnight, then poured into H_2O (30 mL), and extracted with EA (40 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the resulting residue was purified by silica gel chromatography (1% MeOH in EA) to afford ethyl 2-(5,6-dihydro-2*H*-pyran-3-yl)-4-methylinddazo[l,5-a]pyrimidine-8-carboxylate (450 mg, crude) as a yellow oil. LC-MS m/z: 288.1 $[M+H]^+$. t_R = 1.45 min.

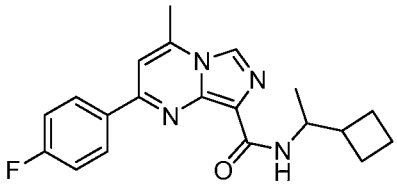
[00416] A mixture of ethyl 2-(5,6-dihydro-2*H*-pyran-3-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (300 mg, crude) and Pd/C (100 mg) in MeOH (10 mL) was stirred at room temperature under H_2 for 2 h. Pd/C was filtered off. The filtrate was concentrated *in vacuo* to afford ethyl 4-methyl-2-(tetrahydro-2*H*-pyran-3-yl)-l,2,3,4-tetrahydroimidazo[l,5-a]pyrimidine-8-carboxylate (305 mg, crude) as light green oil. LC-MS m/z: 294.2 $[M+H]^+$. t_R = 1.14 min.

[00417] A mixture of ethyl 4-methyl-2-(tetrahydro-2 *H*-pyran-3-yl)- 1,2,3,4-tetrahydroimidazo[l,5-a]pyrimidine-8-carboxylate (305 mg, crude) and MnO_2 (1.74 g, 20.0 mmol) in CH2CI2 (15 mL) was stirred at RT for 48 h. MnO_2 was filtered off. The filtrate was concentrated *in vacuo,* and the residual was purified by silica gel column chromatography (100% EA) to afford ethyl 4-methyl-2-(tetrahydro-2H-pyran-3-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (120 mg, 60% over 2 steps) as a light green oil. LC-MS m/z: 290.3 $[M+H]^+$. t_R = I.10 min.

[00418] Following general procedure B, ethyl 4-methyl-2-(tetrahydro-2 *H*-pyran-3-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (120 mg, 0.4 mmol) afforded 4-methyl-2-(tetrahydro-2 *H*-pyran-3-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 28%) as an orange oil. LC-MS m/z: 262.2 $[M+H]^+$. t_R = 0.76 min.

[00419] Following general procedure A, 4-methyl-2-(tetrahydro-2 *H*-pyran-3-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (25 mg, 0.086 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (9 mg, 31%) as a light yellow solid. ¾ NMR (500 MHz, DMSO-d_6): δ 8.37 (s, 1H), 8.08 (s, 1H), 6.95 (s, 1H), 4.11 (dd, J = 11.0 Hz, 2.0 Hz, 1H), 3.88 (d, J = II. 0 Hz, 1H), 3.54 (t, J = 10.5 Hz, 1H), 3.38-3.36 (m, 1H), 3.03-2.99 (m, 1H), 2.69 (s, 3H), 2.14-2.11 (m, 1H), 1.88-1.83 (m, 1H), 1.70-1.66 (m, 2H), 1.38-1.32 (m, 7H), 0.44-0.42 (m, 4H). LC-MS m/z: 343.2 $[M+H]^+$. HPLC: Purity (214 nm): >96%; t_R = 7.10 min.

A/-(l-Cvclobutylethyl)-2-(4-fluorophenyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



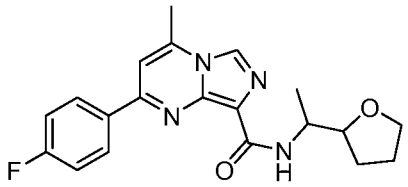
[00420] Following general procedure D, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (2.0 g, 8.36 mmol) and 4-fluorophenylboronic acid afforded ethyl 2-(4-fluorophenyl)-4-methylinddazo[l,5-a]pyrimidine-8-carboxylate (2.3 g, 92%) as a brown solid. LC-MS m/z: 300.0 $[M+H]^+$. Purity (254 nm): > 93%; t_R = 1.32 min.

[00421] Following general procedure B, ethyl 2-(4-fluorophenyl)-4-methylirnidazo[l,5-a]pyrimidine-8-carboxylate (2.1 g, 7.02 mmol) afforded 2-(4-fluorophenyl)-4-

methylirnidazo[l,5-a]pyrimidine-8-carboxylic acid (1.9 g, 99%) as a yellow solid. LC-MS m/z: 272.1 $[M+H]^+$. Purity (254 nm): > 84%; t_R = 0.88 min.

[00422] Following general procedure A, 2-(4-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (35 mg, 0.13 mmol) and 1-cyclobutylethanamine afforded the title compound (9.4 mg, 21%) as a yellow solid. ^{1}H NMR (500 MHz, *OMSO-d_6)*: δ 8.47 (s, 1H), 8.27 (td, *J* = 6.0 Hz, 2.0 Hz, 2H), 7.97 (d, *J* = 7.5 Hz, 1H), 7.60 (d, *J* = 1.0 Hz, 1H), 7.46 (t, *J* = 9.0 Hz, 2H), 4.09-4.05 (m, 1H), 2.78 (s, 3H), 2.01-1.96 (m, 2H), 1.86-1.75 (m, 5H), 1.12 (d, *J* = 6.5 Hz, 3H). LC-MS m/z: 353.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.23 min.

2-(4-Fluorophenyl)-4-methyl-A/-(l-(tetrahvdrofuran-2-yl)ethyl)imidazo[l,5-alpyrimidine-8-carboxamide

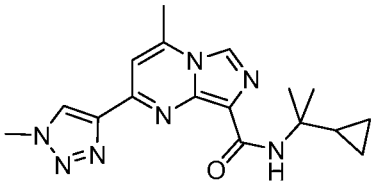


[00423] Following general procedure A, 2-(4-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (32 mg, 0.12 mmol) and l-(tetrahydrofuran-2-yl)ethanamine afforded the title compound as a mixture of diastereoisomers A (5.3 mg, 12%) and **B** (3.2 mg, 7%) as yellow solids.

[00424] Diastereoisomer A: ^{1}H NMR (500 MHz, DMSO-i¾) δ 8.49 (s, 1H), 8.38-8.35 (m, 3H), 7.66 (s, 1H), 7.47 (t, *J* = 9.0 Hz, 2H), 4.23-4.17 (m, 1H), 3.91 (td, *J* = 7.5 Hz, 3.0 Hz, 1H), 3.80 (q, *J* = 7.0 Hz, 1H), 3.68 (q, *J* = 7.5 Hz, 1H), 2.78 (s, 3H), 1.96-1.89 (m, 1H), 1.84-1.69 (m, 2H), 1.60-1.53 (m, 1H), 1.27 (d, *J* = 7.0 Hz, 3H). LC-MS m/z: 369.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.27 min.

[00425] Diastereoisomer **B**: ^{1}H NMR (500 MHz, *OMSO-d_6)* δ 8.48 (s, 1H), 8.43 (d, *J* = 9.0 Hz, 1H), 8.38 (dd, *J* = 8.5 Hz, 5.5 Hz, 2H), 7.65 (s, 1H), 7.45 (t, *J* = 9.0 Hz, 2H), 4.17-4.10 (m, 1H), 3.98-3.89 (m, 2H), 3.75 (q, *J* = 7.5 Hz, 1H), 2.78 (s, 3H), 1.99-1.92 (m, 1H), 1.90-1.85 (m, 2H), 1.76-1.71 (m, 1H), 1.19 (d, *J* = 6.5 Hz, 3H). LC-MS m/z: 369.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.43 min.

A/-(2-Cvclopropylpropan-2-yl)-4-methyl-2-(l-methyl-l *H*-l,2,3-triazol-4-yl)imidazo[l,5-alpyrimidine-8-carboxamide

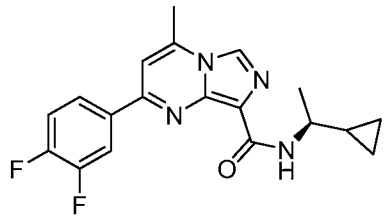


[00426] Following general procedure E, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (200 mg, 0.83 mmol) and 4-bromo-l-methyl-l *H*-l,2,3-triazole afforded ethyl 4-methyl-2-(l-methyl-l *H*-l,2,34riazol-4-yl)imidazo[l,5-a]pyrimidine-8-carboxylate as a yellow solid (100 mg, 42%). LC-MS m/z: 287.1 $[M+H]^+$.

[00427] Following general procedure B, ethyl 4-methyl-2-(l-methyl-l *H*-l,2,3-triazol-4-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (100 mg, 0.35 mmol) afforded 4-methyl-2-(l-methyl-l *H*-l,2,34riazol-4-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (60 mg, 67%) as a yellow solid. LC-MS m/z: 259.1 $[M+H]^+$.

[00428] Following general procedure A, 4-methyl-2-(l-methyl-l *H*-l,2,3-triazol-4-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (60 mg, 0.23 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (15 mg, 19%) as a yellow solid. ^{1}H NMR (500 MHz, $CDC1_3$): δ 8.42 (s, 1H), 7.97 (s, 1H), 7.60 *(d, J* = 0.5 Hz, 1H), 7.53 (s, 1H), 4.19 (s, 3H), 2.73 (s, 3H), 1.46 (s, 6H). 1.46-1.43 (m, 1H), 0.51-0.47 (m, 4H). LC-MS m/z: 340.2 $[M+H]^+$. HPLC Purity (214 nm): > 92%; t_R = 6.41 min.

f.y)-iV-(l-Cvclopropylethyl)-2-(3,4-difluorop henyl)-4-methylimidazo[1,5-*a*]pyrimidine-8-carboxamide

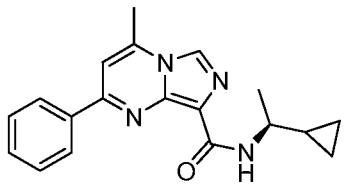


[00429] Following general procedure D, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (200 mg, 0.8 mmol) and 3,4-difluorophenylboronic acid afforded ethyl 2-(3,4-difluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (200 mg, 75%) as a yellow solid. LC-MS m/z: 318.1 $[M+H]^+$. LCMS: t_R = 1.91 min.

[00430] Following general procedure B, ethyl 2-(3,4-difluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (200 mg, 0.63 mmol) afforded 2-(3,4-difluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (182 mg, 100%) as ayellow solid. LC-MS m/z: 290.7 $[M+H]^+$. LCMS: t_R = 0.94 min.

[00431] Following general procedure A, 2-(3,4-difluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (100 mg, 0.35 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound (8.3 mg, 6.7%) as ayellow solid. ^{1}H NMR (500 MHz, *OMSO-d_6)* δ 8.50 (s, 1H), 8.27 (ddd, J = 11.5 Hz, 7.5 Hz, 1.5 Hz, 1H), 8.13-8.10 (m, 2H), 7.70 (ddd, J = 27.5 Hz, 9.5 Hz, 8.5 Hz, 2.0 Hz, 1H), 7.65 (d, J = 0.5 Hz, 1H), 3.62-3.55 (m, 1H), 2.78 (d, J = 0.5 Hz, 3H), 1.28 (d, J = 6.6 Hz, 3H), 1.16-1.04 (m, 1H), 0.54-0.42 (m, 2H), 0.38-0.34 (m, 1H), 0.34-0.27 (m, 1H). LC-MS m/z: 357.1 $[M+H]^+$. HPLC: Purity (254 nm): > 97%; t_R = 7.94 min.

(*S*)-A/-(l-Cvclopropylethyl)-4-methyl-2-phenylimidazo[l,5-alpyrimidine-8-carboxamide

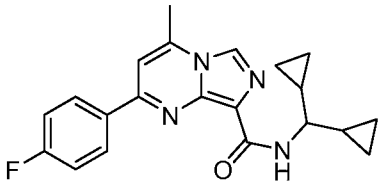


[00432] Following general procedure D, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (200 mg, 0.835 mmol) and phenylboronic acid afforded ethyl 4-methyl-2-phenylimidazo[l,5-a]pyrimidine-8-carboxylate as ayellow solid (155 mg, 66%). LC-MS m/z: 282.1 $[M+H]^+$. LCMS Purity (214 nm): 95%.

[00433] Following general procedure B, ethyl 4-methyl-2-phenylimidazo[l,5-a]pyrirnidine-8-carboxylate (155 mg, 0.55 mmol) afforded 4-methyl-2-phenylirnidazo[l,5-a]pyrirnidine-8-carboxylic acid (95 mg, 68%). LC-MS m/z: 261. 1 $[M+H]^+$. LCMS Purity (214 nm): 88%.

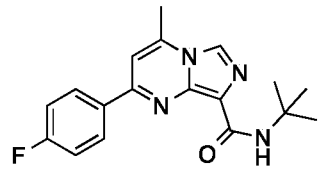
[00434] Following general procedure A, 4-methyl-2-phenylimidazo[l,5-a]pyrimidine-8-carboxylic acid (95 mg, 0.38 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound (42 mg, 71%) as ayellow solid. ^{1}H NMR (500 MHz, DMSO-i¾) δ 8.47 (s, 1H), 8.24-8.21 (m, 3H), 7.62-7.56 (m, 4H), 3.64-3.58 (m, 1H), 2.79 (s, 3H), 1.28 (d, J = 6.5 Hz, 3H), 1.12-1.05 (m, 1H), 0.52-0.40 (m, 2H), 0.40-0.33 (m, 1H), 0.33-0.28 (m, 1 H). LC-MS m/z: 321.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.66 min.

iV-(Dicvclopropylmethyl)-2-(4-fluorophenyl)-4-methylimidazo [1,5-«1 pyrimidine-8-carboxamide



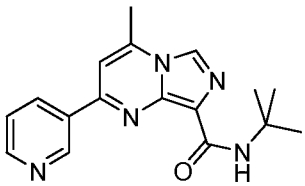
[00435] Following general procedure A, 2-(4-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.18 mmol) and dicyclopropylmethanamine afforded the title compound (15 mg, 22%) as a light yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.40 (s, 1H), 8.32 (dd, *J* = 8.5 Hz, 5.5 Hz, 2H), 7.50 (d, *J* = 1.0 Hz, 1H), 7.34 (t, *J* = 9.0 Hz, 2H), 3.51 (t, *J* = 7.5 Hz, 1H), 2.86 (d, *J* = 1.0 Hz, 3H), 1.20-1.14 (m, 2H), 0.64-0.59 (m, 2H), 0.54-0.49 (m, 4H), 0.49-0.43 (m, 2H). LC-MS m/z: 365.2 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 8.15 min.

A/-ferf-Butyl-2-(4-fluorophenyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00436] Following general procedure A, 2-(4-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.18 mmol) and 2-methylpropan-2-amine afforded the title compound (10.3 mg, 17%) as ayellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.37 (s, 1H), 8.30 (dd, *J* = 8.5 Hz, 5.5 Hz, 2H), 7.48 (s, 1H), 7.33 (t, *J* = 8.5 Hz, 2H), 2.84 (s, 3H), 1.59 (s, 9H). LC-MS m/z: 327.1 $[M+H]^+$. HPLC: Purity (254 nm): 99.30%; t_R = 9.78 min.

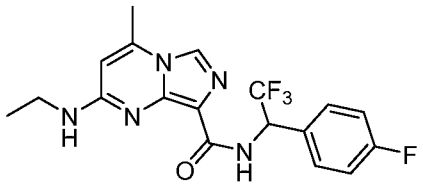
iV-fert-Butyl-4-methyl-2-(pyridin-3-yl)imidazo[1,5-al pyrimidine-8-carboxamide



[00437] Following general procedure A, 4-methyl-2-(pyridin-3-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.20 mmol) and 2-methylpropan-2-amine afforded the title compound (27 mg, 44%) as a white solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 9.40 (d, *J* = 2.0 Hz, 1H), 8.72 (dd, *J* = 5.0 Hz, 1.5 Hz, 1H), 8.65 (dt, *J* = 8.0 Hz, 1.5 Hz, 1H), 8.41 (s, 1H),

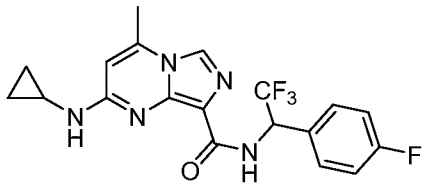
8.27 (bs, 1H), 7.65 (dd, ***J*** = 8.5 Hz, 5.0 Hz, 1H), 7.54 (s, 1H), 2.86 (s, 3H), 1.59 (s, 9H). LC-MS m/z: 310.0 $[M+H]^+$. HPLC: Purity (254 nm): 99%; t_R = 6.69 min.

2-(Ethylamino)-4-methyl-A/-(2,2,2-trifluoro-l-(4-fluorophenyl)ethyl)imidazo[l,5-alpyrimidine-8-carboxamide



[00438] Following general procedure I, 2-chloro-4-methyl -***N***-(2,2,2-trifluoro-l-(4-fluorophenyl)ethyl)imidazo[l,5-a]pyrirnidine-8-carboxamide (26 mg, 0.067 mmol) and ethylamine afforded the title compound (10 mg, 37%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.24 (d, ***J*** = 9.5 Hz, 1H), 8.10 (t, ***J*** = 5.0 Hz, 1H), 8.01 (s, 1H), 7.60 (dd, ***J*** = 8.0 Hz, 5.0 Hz, 2H), 7.31 (tt, ***J*** = 9.0 Hz, 2.0 Hz, 2H), 6.17 (s, 1H), 6.09 (q, ***J*** = 9 Hz, 1H), 3.42-3.39 (m, 2H), 2.54 (s, 3H), 1.22 (t, ***J*** = 7.5 Hz, 3H). LC-MS m/z: 396.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 7.98 min.

2-(Cvclopropylamino)-4-methyl-A/-(2,2,2-trifluoro-l-(4-fluorophenyl)ethyl)imidazo[l,5-*a*\pyrimidine-8-carboxamide



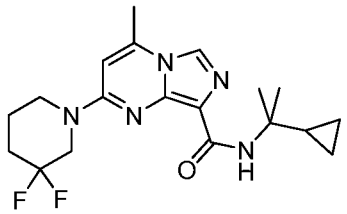
[00439] Following general procedure I, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (239 mg, 1 mmol) and cyclopropanamine afforded crude ethyl 2-(cyclopropylainino)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (260 mg, quantitative) as a white solid. LC-MS m/z: 261.2 $[M+H]^+$. Purity (214 nm): 80%; t_R = 1.03 min.

[00440] Following general procedure B, ethyl 2-(cyclopropylamino)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (260 mg, 1 mmol) afforded 2-(cyclopropylamino)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (120 mg, 50%) as a white solid. LC-MS m/z: 233.1 $[M+H]^+$. Purity (214 nm): > 99%; t_R = 0.98 min.

[00441] Following general procedure A, 2-(cyclopropylamino)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (46 mg, 0.18 mmol) and 2,2,2-trifluoro-l-(4-

fluorophenyl)ethanamine afforded the title compound (49 mg, 60%) as a yellow solid. ^{1}H NMR (500 MHz, **DMSO-i¾):** δ 9.41 (d, ***J*** = 10.0 Hz, 1H), 8.28 (s, 1H), 8.05 (s, 1H), 7.63-7.60 (m, 2H), 7.30 (**t, *J*** = 9.0 Hz, 2H), 7.20-7.15 (m, 2H), 2.81-2.78 (m, 1H), 2.56 (s, 3H), 0.81-0.76 (m, 2H), 0.62-0.58 (m, 2H). LC-MS m/z: 408.1 $[M+H]^+$. HPLC Purity (254 nm): > 99%; t_R = 7.54 min.

A/-(2-Cvclopropylpropan-2-yl)-2-(33-difluoropiperidin-l-yl)-4-methylimidazo[l,5-*a*\pyrimidine-8-carboxamide

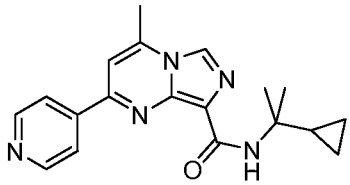


[00442] Following general procedure I, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (150 mg, 0.63 mmol) and 3,3-difluoropiperidine hydrochloride afforded ethyl 2-(3,3-difluoropiperidin-l-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (140 mg, 68%) as a yellow solid. LC-MS m/z: 325.1 $[M+H]^+$. Purity (254 nm): > 80%; t_R = 1.21 min.

[00443] Following general procedure B, ethyl 2-(3,3-difluoropiperidin-l-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (140 mg, 0.43 mmol) afforded 2-(3,3-difluoropiperidin-l-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (80 mg, 63%) as a white solid. LC-MS m/z: 297.9 $[M+H]^+$.

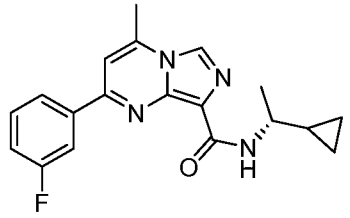
[00444] Following general procedure A, 2-(3,3-difiuoropiperidin-l-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (40 mg, 0.13 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (18 mg, 35%). ^{1}H NMR (500 MHz, DMSO-c¾): δ 8.02 (s, 1H), 7.84 (s, 1H), 6.88 (s, 1H), 4.10 (d, ***J*** = 12.0 Hz, 2H), 3.77 (d, ***J*** = 5.0 Hz, 2H), 2.59 (s, 3H), 2.15-2.12 (m, 2H), 1.80-1.74 (m, 2H), 1.33 (s, 6H), 1.33-1.29 (m, 1H), 0.38 (d, ***J*** = 7.0 Hz, 4H). LC-MS m/z: 378.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.37 min.

A/-(2-Cvclopropylpropan-2-yl)-4-methyl-2-(pyridin-4-yl)imidazo[l,5-alpyrimidine-8-carboxamide



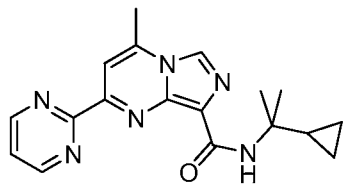
[00445] Following general procedure A, 4-methyl-2-(pyridin-4-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (40 mg, 0.16 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (2.9 mg, 5.5%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.65 (dd, *J* = 4.5 Hz, 1.5 Hz, 2H), 8.34 (s, 1H), 8.20 (bs,lH), 8.11 (dd, *J* = 4.5 Hz, 1.5 Hz, 2H), 7.44 (s, 1H), 2.76 (s, 3H), 1.38 (s, 6H), 1.38-1.33 (m, 1H), 0.47-0.43 (m, 4H). LC-MS m/z: 336.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 6.41 min.

***(i?)*-A/-(l-Cvclopropylethyl)-2-(3-fluorophenyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide**



[00446] Following general procedure A, 2-(3-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (25 mg, 0.10 mmol) and (i?)-l-cyclopropylethanamine afforded the title compound (3.4 mg, 10%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾): *δ* 8.43 (s,lH), 8.08 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 10.0 Hz, 1H), 7.64-7.60 (m, 1H), 7.53 (s, 1H), 7.42 (td, *J* = 8.0 Hz, *J* = 2.5 Hz, 1H), 3.73 (m, *J* = 7.5 Hz, 1H), 2.87 (s, 3H), 1.42 (d, *J* = 7.0 Hz, 3H), 1.14-1.12 (m, 1H), 0.66-0.57 (m, 2H), 0.51-048 (m, 1H), 0.41-0.39 (m, 1H). LC-MS m/z: 339.1 $[M+H]^+$. HPLC Purity (214 nm): 99%; t_R = 7.75 min.

iV-(2-Cvclopropylpropan-2-yl)-4-methyl-2-(pyrimidin-2-yl)imidazo[1,5-*a*]pyrimidine-8-carboxamide

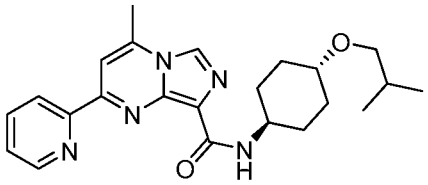


[00447] Following general procedure F, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (200 mg, 0.835 mmol) and 2-(tributylstannyl)pyrimidine (462 mg, 1.853 mmol) afforded ethyl 4-methyl-2-(pyrirnidin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylate as a brown solid (95 mg, 40%). LC-MS m/z: 284 $[M+H]^+$. LCMS Purity (214 nm): 58%.

[00448] Following general procedure B, ethyl 4-methyl-2-(pyrimidin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (90 mg, 0.32 mmol) afforded 4-methyl-2-(pyrimidin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (36 mg, 44%) as a yellow solid. LC-MS m/z: 256.1 $[M+H]^+$. LCMS Purity (214 nm): 94%.

[00449] Following general procedure A, 4-methyl-2-(pyrimidin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (35 mg, 0.14 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (7.5 mg, 25%) as a yellow solid. ^{1}H NMR (500 MHz, $CDC1_3$) δ 8.95 (d, J = 5.0 Hz, 2H), 8.09 (s, 1H), 7.98 (s, 1H), 7.82 (s, 1H), 7.41 (t, J = 5.0 Hz, 1H), 2.79 (s, 3H), 1.47 (s, 6H), 1.47-1.44 (m, 1H), 0.50 (d, J = 7.0 Hz, 4H). LC-MS m/z: 337.1 $[M+H]^+$. HPLC Purity (254 nm): 96%; t_R = 6.73min

A/-^7i?,^i?)-4-isoButoxycvclohexyl)-4-methyl-2-(pyridin-2-yl)imidazo[l,5-alpyrim idine-8-carboxamide



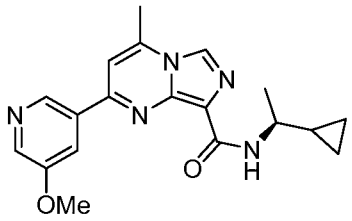
[00450] Following general procedure F, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (100 mg, 0.418 mmol) and 2-(tributylstannyl)pyridine afforded ethyl 4-methyl-2-(pyridin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (45 mg, 38%) as a yellow solid. LC-MS m/z: 283.1 $[M+H]^+$. t_R = 1.51 min.

[00451] Following general procedure B, ethyl 4-methyl-2-(pyridin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (45 mg, 0.16 mmol) afforded crude 4-methyl-2-(pyridin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid as a yellow solid, which was used directly. LC-MS m/z: 255.1 $[M+H]^+$. t_R = 1.08 min.

[00452] Following general procedure A, 4-methyl-2-(pyridin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (crude, from previous step) and *(JR,4R)-4-*isobutoxycyclohexanamine afforded the title compound (14 mg, 21% two steps). ^{1}H NMR (500

MHz, *MeOO-d4)* δ 8.76 (d, *J* = 4.0 Hz, 1H), 8.52 (d, *J* = 7.5 Hz, 1H), 8.44 (s, 1H), 8.05 (td, *J* = 7.5 Hz, 1.0 Hz, 1H), 7.95 (s, 1H), 7.56 (dd, *J* = 7.5 Hz, 5.5 Hz, 1H), 4.05-3.99 (m, 1H), 3.44-3.36 (m, 1H), 3.31 (d, *J* = 7.0 Hz, 2H), 2.86 (s, 3H), 2.22-2.14 (m, 4H), 1.84 (m, *J* = 6.5 Hz, 1H), 1.60-1.43 (m, 4H), 0.93 (d, *J* = 7.0 Hz, 6H). LC-MS m/z: 408.3 $[M+H]^+$. HPLC: Purity (214 nm): 91.88%; t_R = 8.73 min.

(.S^-A/-(l-Cvclopropylethvn-2-(5-methoxypyridin-3-yl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide

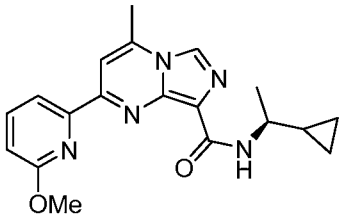


[00453] Following general procedure D, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (150 mg, 0.63 mmol) and 3-methoxy-5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine afforded ethyl 2-(5-methoxypyridin-3-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (55 mg, 28%) as a white solid. LC-MS m/z: 313.1 $[M+H]^+$. LC-MS Purity (214 nm): > 98%; t_R = 1.42 min.

[00454] Following general procedure B, ethyl 2-(5-methoxypyridin-3-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (55 mg, 0.17 mmol) afforded 2-(5-methoxypyridin-3-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 73%) as a yellow solid. LC-MS m/z: 285.1 $[M+H]^+$. LC-MS Purity (214 nm): > 93%; t_R = 0.77 min.

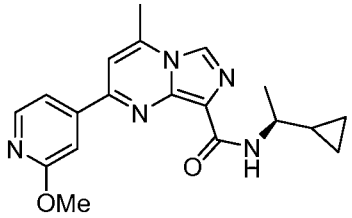
[00455] Following general procedure A, 2-(5-methoxypyridin-3-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 0.10 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound (11.4 mg, 30%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾): δ 8.99 (s, 1H), 8.44 (*d, J* = 8.5 Hz, 2H), 8.40 (d, *J* = 6.5 Hz, 1H), 8.26 (s,lH), 7.59 (s, 1H), 4.04 (s, 3H), 3.71 (m, *J* = 7.0 Hz, 1H), 2.88 (s, 3H), 1.42 (d, *J* = 6.5 Hz, 3H), 1.13-1.10 (m, 1H), 0.64-0.55 (m, 2H), 0.47-0.46 (m, 1H), 0.40-0.36 (m, 1H). LC-MS m/z: 352.1 $[M+H]^+$. HPLC Purity (214 nm): 99%; t_R = 6.45 min.

f*S*)-iV-(l-Cvclopropylethyl)-2-(6-methoxypyr din-2-yl)-4-methylimidazo[1,5-*a*]pyrimidine-8-carboxamide



[00456] Following general procedure F, (5)-2-chloro-*N*-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (30 mg, 0.108 mmol) and 2-methoxy-6-(tributylstannyl)pyridine afforded the title compound (7 mg, 18%) as a yellow solid. 'HNMR (500 MHz, MeOD-c¾) δ 8.42 (s, 1H), 8.14 (d, *J* = 7.5 Hz, 1H), 7.93 (d, *J* = 0.5 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 4.10 (s, 3H), 3.77-3.68 (m, 1H), 2.87 (s, 3H), 1.42 (d, *J* = 6.5 Hz, 3H), 1.19-1.15 (m, 1H), 0.63-0.58 (m, 2H), 0.51-0.43 (m, 1H), 0.42-0.38 (m, 1H). LC-MS m/z: 352.2 $[M+H]^+$. HPLC: Purity (214 nm): > 98%; t_R = 7.88 min.

(*S*)-iV-(l-Cvclopropylethyl)-2-(2-methoxypyr din-4-yl)-4-methylimidazo[1,5-*a*]pyrimidine-8-carboxamide



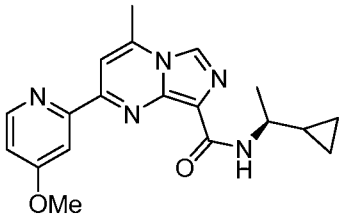
[00457] Following general procedure D, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (100 mg, 0.42 mmol) and 2-methoxypyridin-4-ylboronic acid afforded ethyl 2-(2-methoxypyridin-4-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (53 mg, 40%) as a yellow solid. LC-MS m/z: 322.1 $[M+H]^+$. Purity (214nm): > 99%; t_R = 1.32 min.

[00458] Following general procedure B, ethyl 2-(2-methoxypyridin-4-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (53 mg, 0.17 mmol) afforded 2-(2-methoxypyridin-4-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (48 mg, 90%) as a yellow solid. LC-MS m/z: 285.0 $[M+H]^+$. LC-MS Purity (254 nm): > 94%; t_R = 1.16 min.

[00459] Following general procedure A, 2-(2-methoxypyridin-4-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (25 mg, 0.09 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound (4.7 mg, 16%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.54 (s,

1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 7.0 Hz, 1H), 7.64 (s, 1H), 7.25 (d, *J* = 2.5 Hz, 1 H), 6.99 (dd, *J* = 7.0 Hz, 2.0 Hz, 1H), 3.57 (q, *J* = 7.0 Hz, 1H), 3.49 (s, 3H), 2.76 (s, 3H), 1.27 (d, *J* = 6.5 Hz, 3H), 1.10-1.05 (m, 1H), 0.51-0.43 (m, 2H), 0.36-0.27 (m, 2H). LC-MS m/z: 352.2 $[M+H]^+$. HPLC: Purity (214 nm): >91%; t_R = 5.54 min.

(.s')-A/-(l-Cvclopropylethvn-2-(4-methoxypyridin-2-yl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide

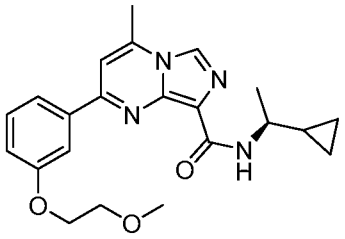


[00460] Following general procedure E, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (154 mg, 0.64 mmol) and 2-bromo-4-methoxypyridine afforded ethyl 2-(4-methoxypyridin-2-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (72 mg, 37%) as a pale solid. LC-MS m/z: 313.1 $[M+H]^+$. LC-MS Purity (214 nm): 79%. t_R = 1.35 min.

[00461] Following general procedure B, ethyl 2-(4-methoxypyridin-2-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (72 mg, 0.23 mmol) afforded 2-(4-methoxypyridin-2-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 77%) as a pale solid. LC-MS m/z: 285.1 $[M+H]^+$. LCMS Purity (214 nm): 78%. t_R = 0.82 min.

[00462] Following general procedure A, 2-(4-methoxypyridin-2-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.175 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound (22 mg, 36%) as pale yellow solid. ^{1}H NMR (500 MHz, $CDC1_3$) δ 8.59 (d, *J* = 4.5 Hz, 1H), 8.53 (s, 1 H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.98 (d, *J* = 2.5 Hz, 1H), 7.88 (s, 1 H), 7.19 (dd, *J* = 6.0 Hz, 2.5 Hz, 1H), 3.95 (s, 3H), 3.62-3.58 (m, 1H), 2.81 (s, 3H), 1.30 (d, *J* = 6.5 Hz, 3H), 1.11-1.08 (m, 1H), 0.526-0.36 (m, 3H), 0.30-0.28 (m, 1H). LC-MS m/z: 352.1 $[M+H]^+$. HPLC: Purity (214 nm): 96.7%; t_R = 7.05 min.

***(S)-N-(* 1-Cyclop ropylethyl)-2-(3-(2-methoxyethoxy)phenyl)-4-methylimid azo [1,5-*a*]pyrimidine-8-carboxamide**



[00463] The suspension of 3-iodophenol (6.0 g, 28.0 mmol), l-bromo-2-methoxy ethane (5.90 g, 42.0 mmol) and K_2C0_3 (11.59 g, 84.0 mmol) in DMF (50 mL) was stirred at 50 °C for 3 hours, then cooled, quenched with water (200 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford l-iodo-3-(2-methoxyethoxy)benzene (5.9 g, 76%) as ayellow oil. ¾NMR (500 MHz, DMSO-d_6) δ 7.31 (s, 1H), 7.30 (d, J = 6.5 Hz, 1H), 7.08 (t, J = 8.5 Hz, 1H), 6.99-6.96 (m, 1H), 4.10-4.08 (m, 2H), 3.65-3.63 (m, 2H), 3.30 (s, 3H). LCMS Purity (214 nm): 89%; t_R = 1.59 min.

[00464] Following general procedure D, l-iodo-3-(2-methoxyethoxy)benzene (2.50 g, 8.99 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(l,3,2-dioxaborolane) afforded 2-(3-(2-methoxyethoxy)phenyl)-4,4,5,5-tetramethyl-l,3,2-dioxaborolane as ayellow oil (1.80 g, 72%). LC-MS m/z: 296.3 $[M+H]^+$. LCMS Purity (214 nm): 82%; t_R = 1.63 min.

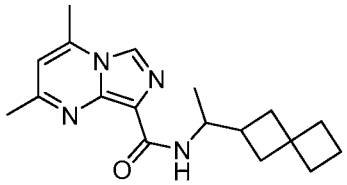
[00465] Following general procedure D, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (400 mg, 1.673 mmol) and 2-(3-(2-methoxyethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane afforded ethyl 2-(3-(2-methoxyethoxy)phenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate as a black solid (500 mg, 84%). LC-MS m/z: 356.2 $[M+H]^+$. LCMS Purity (214 nm): 50%; t_R = 1.28 min.

[00466] Following general procedure B, ethyl 2-(3-(2-methoxyethoxy)phenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (500 mg, 1.41 mmol) afforded 2-(3-(2-methoxyethoxy)phenyl)-4-methylinddazo[l,5-a]pyrimidine-8-carboxylic acid (100 mg, 22%). LC-MS m/z: 328.1 $[M+H]^+$. LCMS Purity (214 nm): 54%; t_R = 0.90 min.

[00467] Following general procedure A, 2-(3-(2-methoxyethoxy)phenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (100 mg, 0.31 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (14 mg, 12%) as ayellow solid. ^{1}H NMR

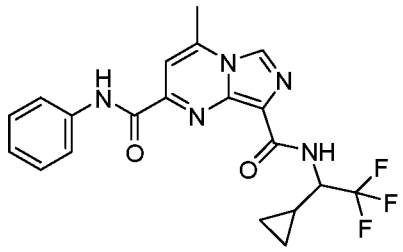
(500 MHz, DMSO-c¾): δ 8.48 (s, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.81 (s, 1H), 7.66 (s, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.17 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 4.22 (dd, *J* = 5.5 Hz, 3.5 Hz, 2H), 3.71 (t, *J* = 4.5 Hz, 1H), 3.64-3.59 (m, 1H), 3.34 (s, 3H), 2.79 (s, 3H), 1.29 (d, *J* = 6.5 Hz, 3H), 1.10-1.02 (m, 1H), 0.56-0.41 (m, 2H), 0.38-0.31 (m, 1H), 0.31-0.25 (m, 1H). LC-MS m/z: 395.2 $[M+H]^+$. HPLC Purity (214 nm): 98%; t_R = 7.45 min.

2,4-Dimethyl-A^-(l-(spiro[331heptan-2-vnethvnimidazo[l,5-alpyrimidine-8-carboxamide



[00468] Following general procedure A, 2,4-dimethylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (109 mg, 0.57 mmol) and (l-(spiro[3.3]heptan-2-yl)ethanamine afforded the title compound (100 mg, 38% yield) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 6.81 (s, 1H), 3.99-3.94 (m, 1H), 2.66 (s, 3H), 2.52 (s, 3H), 2.28-2.23 (m, 1H), 2.06-1.92 (m, 4H), 1.89-1.66 (m, 6H), 1.05 (d, *J* = 6.5 Hz, 3H). LC-MS m/z: 313.2 $[M+H]^+$. HPLC: Purity (214 nm): 97.78%; t_R = 8.24 min.

A^-(l-Cvclopropyl-2,2,2-trifluoroethyl)-4-methyl-A^-phenylimidazo[l,5-alpyrimidine-2,^-dicarboxamide



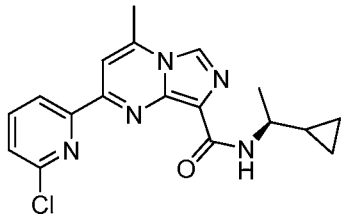
[00469] Following general procedure A, 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (240 mg, 1.0 mmol) and l-cyclopropyl-2,2,2-trifluoroethanamine afforded 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxamide (300 mg, 87%) as a yellow solid. LC-MS m/z: 333.1 $[M+H]^+$. Purity (254 nm): > 95%; t_R = 1.36 min.

[00470] A mixture of 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxamide (120 mg, 0.36 mmol), Et_3N (**13** mg, 0.12 mmol), MeOH (10 mg, 0.72 mmol), and $Pd(dppf)Cl_2$.DCM (33 mg, 0.04 mmol) in MeCN (10 mL) was stirred at 80 °C for 16 h under CO (10 atm.), then cooled and filtered. The filtrate was acidified with IN HCl to

pH = 6 and lyophilized. The resulting solid was dissolved in EA (100 mL), filtered and concentrated *in vacuo* to afford crude 8-(l-cyclopropyl-2,2,2-trifluoroethylcarbamoyl)-4-methylimidazo[l,5-a]pyrimidine-2-carboxylic acid (60 mg, 48%) as a yellow solid. LC-MS m/z: 343.1 $[M+H]^+$. Purity (254 nm): > 90%; t_R = 0.92 min.

[00471] Following general procedure A, 8-(l-cyclopropyl-2,2,2-trifluoroethylcarbamoyl)-4-methylinridazo[l,5-a]pyrinridine-2-carboxylic acid (60 mg, 0.18 mmol) and aniline afforded the title compound (30 mg, 30%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.66 (s, 1H), 8.74 (d, J = 9.5 Hz, 1H), 8.71 (s, 1H), 7.83 (d, J = 8.0 Hz, 2H), 7.53 (s, 1H), 7.42 (t, J = 8.0 Hz, 2H), 7.17 (t, J = 7.0 Hz 1H), 4.26-4.19 (m, 1H), 2.84 (s, 3H), 1.52-1.46 (m, 1H), 0.76-0.69 (m, 1H), 0.66-0.59 (m, 1H), 0.58-0.50 (m, 1H), 0.40-0.34 (m, 1H). LC-MS m/z: 418.2 $[M+H]^+$. HPLC : Purity (214 nm): 97%; t_R = 8.07 min.

CSV2-(6-Chloropyridin-2-yl)-iV-(l-cvclopropy^^thyl)-4-methylimidazo[1,5-*a*]pyrimidine-8-carboxamide



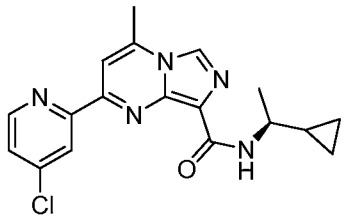
[00472] Following general procedure D, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (500 mg, 2.1 mmol) and 2-chloro-6-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)pyridine afforded ethyl 2-(6-chloropyridin-2-yl)-4-methylinddazo[l,5-a]pyrimidine-8-carboxylate (500 mg, 75%) as a yellow solid. LC-MS m/z: 317.2 $[M+H]^+$.

[00473] The mixture of ethyl 2-(6-chloropyridin-2-yl)-4-methylinddazo[l,5-a]pyrimidine-8-carboxylate (500 mg, 1.58 mmol) and $(Bu_3Sn)_20$ (4.7 g, 7.91 mmol) in toluene (10 mL) was stirred at 110 °C for 3 days, then cooled and poured into saturated $NaHCO_3$ solution (20 mL). The aqueous phase was washed with EA (5 mL x 3), acidified to pH value to 6 with 6N HC1 and extracted with EA (50 mL x 3). The organic phases were dried over anhydrous Na_2S0_4 and filtered. The filtrate was concentrated *in vacuo* to afford 2-(6-chloropyridin-2-yl)-4-methylinridazo[l,5-a]pyrinridine-8-carboxylic acid as a yellow solid (100 mg, 26%). LC-MS m/z: 289.1 $[M+H]^+$.

[00474] Following general procedure A, 2-(6-chloropyridin-2-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.17 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound (26.3 mg, 43%) as a yellow solid. 'HNMR (500 MHz, MeOD-c¾): δ 8.52

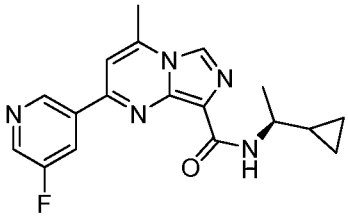
(**d**, ***J*** = 7.5 Hz, 1H), 8.44 (s, 1H), 8.38 (**d**, ***J*** = 8.0 Hz, 1H), 8.02 (t, ***J*** = 7.5 Hz, 1H), 7.88 (s, 1H), 7.59 (**d**, ***J*** = 8.0 Hz, 1H), 3.72-3.68 (m, 1H), 2.86 (s, 3H), 1.43 (**d**, ***J*** = 6.5 Hz, 3H), 1.20-1.12 (m, 1H), 0.68-0.54 (m, 2H), 0.51-0.48 (m, 1H), 0.41-0.36 (m, 1H). LC-MS m/z: 356.0 $[M+H]^+$. LC-MS Purity (214 nm): > 99%; t_R = 9.89 min.

CSV2-(4-Chloropyridin-2-yl)-iV-(l-cvclopro pylethyl)-4-methylimidazo[1,5-*a*]pyrimidine-8-carboxamide



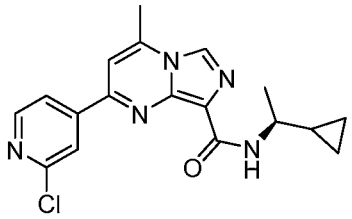
[00475] Following general procedure F, (5)-2-chloro -***N***-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (40 mg, 0.14 mmol) and 4-chloro-2-(tributylstannyl)pyridine afforded the title compound (20 mg, 39%) as a yellow solid. ^{1}H NMR (500 MHz, $CDC1_3$): δ 8.607 (s, 1H), 8.606 (d, ***J*** = 5.5 Hz, 1H), 8.09 (s, 1H), 7.86 (s, 1H), 7.84 (d, ***J*** =8.0 Hz, 1H), 7.42 (dd, ***J*** = 5.5 Hz, 2.5 Hz, 1H), 3.84-3.79 (m, 1H), 2.78 (d, ***J*** = 0.5 Hz, 3H), 1.39 (**d**, ***J*** = 7.0 Hz, 3H), 1.10-1.04 (m, 1H), 0.64-0.53 (m, 2H), 0.53-0.48 (m, 1H), 0.41-0.37 (m, 1H). LC-MS m/z: 356.1 $[M+H]^+$. LC-MS Purity (254 nm): > 99%; t_R = 7.85 min.

***(S)-N-(* 1-Cyclop ropylethyl)-2-(5-fluorop yridin-3-yl)-4-methylimid azo[1,5-*a*]pyrimidine-8-carboxamide**



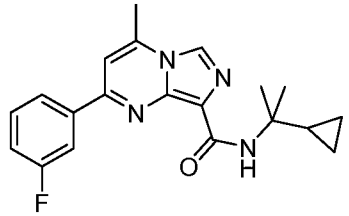
[00476] Following general procedure D, (5)-2-chloro -***N***-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (50 mg, 0.18 mmol) and 5-fluoropyridin-3-ylboronic acid afforded the title compound (6 mg, 10%) as a yellow solid. ^{1}H NMR (500 MHz, **DMSO-i¾)** δ 9.31 (s, 1H), 8.78 (**d**, ***J*** = 3.0 Hz, 1H), 8.55 (s, 1H), 8.46 (dt, ***J*** = 9.5 Hz, 2.0 Hz, 1H), 8.10 (**d**, ***J*** = 8.0 Hz, 1H), 7.73 (s, 1H), 3.61-3.56 (m, 1H), 2.80 (s, 3H), 1.28 (**d**, ***J*** = 6.5 Hz, 3H), 1.15-1.07 (m, 1H), 0.53-0.48 (m, 1H), 0.46-0.40 (m, 1H), 0.39-0.34 (m, 1H), 0.32-0.26 (m, 1H). LC-MS m/z: 340.2 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 6.59 min.

CSV2-(2-Chloropyridin-4-yl)-iV-(l-cvclopropyleth^l)-4-methylimidazo[1,5-*a*]pyrimidine-8-carboxamide



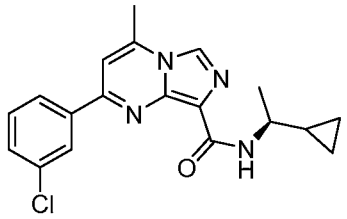
[00477] Following general procedure D, (5)-2-chloro-*N*-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (40 mg, 0.144 mmol) and 2-chloropyridin-4-ylboronic acid afforded the title compound (15 mg, 29%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.60 (s, 1H), 8.59 (s, 1H), 8.34 (d, *J* = 1.0 Hz, 1H), 8.17 (dd, *J* = 5.5 Hz, 1.5 Hz, 1H). 7.59 (s, 1H), 3.72-3.68 (m, 1H), 2.89 (s, 3H), 1.42 (d, *J* = 6.5 Hz, 3H), 1.18-1.10 (m, 1H), 0.68-0.58 (m, 2H), 0.50-0.42 (m, 1H), 0.41-0.38 (m, 1H). LC-MS m/z: 356.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 7.04 min.

A/-(2-Cvclopropylpropan-2-yl)-2-(3-fluorophenyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



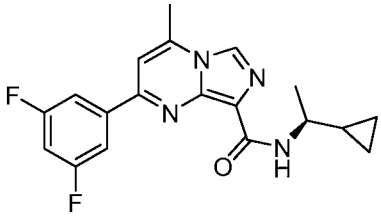
[00478] Following general procedure A, 2-(3-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (25 mg, 0.10 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (19.4 mg, 60%) as a yellow solid. ¾NMR (500 MHz, MeOD-c¾): δ 8.46 (d, *J* = 4.0 Hz, 1H), 8.40 (d, *J* = 5.0 Hz, 1H), 8.08-8.04 (m, 2H), 7.61-7.59 (m, 1H), 7.51 (d, *J* = 4.5 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 2.85 (d, *J* = 2.5 Hz, 3H), 1.50 (s, 6H), 1.47-1.44 (m, 1H), 0.61-0.

(*S*)-2-(3-Chlorophenyl)-iV-(l-cyclopropylethyl)-4-methylimidazo[1,5-*a*]pyrimidine-8-carboxamide



[00479] Following general procedure A, 2-(3-chlorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.17 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (10.2 mg, 16 % yield) as a yellow solid. ^{1}H NMR (500 MHz, *OMSO-d_6)* δ 8.51 (s, 1H), 8.30 (s, 1H), 8.21-8.20 (m, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.68 (s, 1H), 7.65 (s, 1H), 7.65-7.64 (m, 1H), 3.63-3.56 (m, 1H), 2.79 (s, 3H), 1.28 (d, J = 6.5 Hz, 3H), 1.13-1.06 (m, 1H), 0.55-0.44 (m, 2H), 0.39-0.34 (m, 1H), 0.33-0.28 (m, 1H). LC-MS m/z: 355.0 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 8.26 min.

CSViV-(l-Cyclopropylethyl)-2-(3,5-difluoroph^^yl)-4-methylimidazo[1,5-a]pyrimidine-8-carboxamide



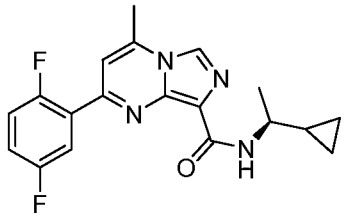
[00480] Following general procedure D, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (240 mg, 1.0 mmol) and 3,5-difiuorophenylboronic acid afforded ethyl 2-(3,5-difluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (135 mg, 42%) as a brown solid. LC-MS m/z: 318.1 $[M+H]^+$. LC-MS Purity (254 nm): > 93%; t_R = 1.81 min.

[00481] Following general procedure B, ethyl 2-(3,5-difluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (135 mg, 0.42 mmol) afforded 2-(3,5-difluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 41%) as a yellow solid. LC-MS m/z: 290.1 $[M+H]^+$. LC-MS Purity (254 nm): > 90%; t_R = 1.54 min.

[00482] Following general procedure A, 2-(3,5-difluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.17 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound (7.6 mg, 12%) as a light yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ

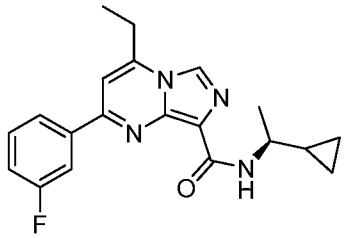
8.52 (s, 1H), 8.11 (d, *J* = 9.5 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 2H), 7.69 (s, 1H), 7.49 (t, *J* = 11.0 Hz, 1H), 3.58 (m, *J* = 8.5 Hz, 1H), 2.77 (s, 3H), 1.26 (d, *J* = 8.5 Hz, 3H), 1.11-1.05 (m, 1H), 0.51- 0.42 (m, 2H), 0.40- 0.27 (m, 2H). LC-MS m/z: 357.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.98 min.

(,SViV-(l-Cvclopropylethyl)-2-(2,5-difluorophen^ -4-methylimidazo[1,5-*a*]pyrimidine-8-carboxamide



[00483] Following general procedure D, (5)-2-chloro-*N*-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxarnide (50 mg, 0.18 mmol) and 2,5-difluorophenylboromc acid afforded the title compound (9.9 mg, 15%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.88-7.84 (m, 1H), 7.55-7.47 (m, 2H), 7.37 (s, 1H), 3.64-3.57 (m, 1H), 2.79 (s, 3H), 1.25 (d, *J* = 6.5 Hz, 3H), 1.08-1.01 (m, 1H), 0.50-0.45 (m, 1H), 0.43-0.38 (m, 1H), 0.37-0.32 (m, 1H), 0.29-0.24 (m, 1H). LC-MS m/z: 357.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 7.79 min.

(*s*')-A/-(l-Cvclopropylethyl)-4-ethyl-2-(3-fluorophenyl)imidazo[l,5-alpyrimidine-8-carboxamide



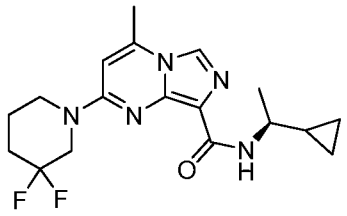
[00484] Following general procedure D, ethyl 2-chloro-4-ethylimidazo[l,5-a]pyrimidine-8-carboxylate (253 mg, 1.0 mmol) and 3-fluorophenylboronic acid afforded ethyl 4-ethyl-2-(3-fluorophenyl)imidazo[l,5-a]pyrimidine-8-carboxylate (310 mg, 97%) as ayellow solid. LC-MS m/z: 314.1 $[M+H]^+$. LC-MS: Purity (254 nm): 80%.

[00485] Following general procedure B, ethyl 4-ethyl-2-(3-fluorophenyl)imidazo[l,5-a]pyrimidine-8-carboxylate (310 mg, 0.99 mmol) afforded 4-ethyl-2-(3-

fluorophenyl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (230 mg, 80%) as a yellow solid. LC-MS m/z: 286.1 $[M+H]^+$. LCMS: Purity (214 nm): 90%.

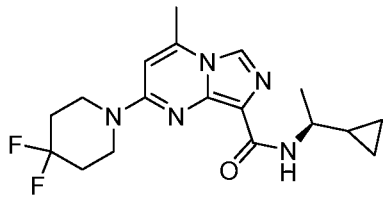
[00486] Following general procedure A, 4-ethyl-2-(3-fluorophenyl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (55 mg, 0.19 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (31 mg, 45%) as ayellow solid. 'HNMR (500 MHz, $CDC1_3$): δ 8.13 (s, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.92-7.87 (m, 2H), 7.53 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 7.28-7.25 (m, 1H), 7.09 (s, 1H), 3.88-3.82 (m, 1H), 3.11 (q, *J* = 7.0 Hz, 2H), 1.58 (t, *J* = 7.0 Hz, 3H), 1.40 (d, *J* = 7.0 Hz, 3H), 1.10-1.02 (m, 1H), 0.62-0.48 (m, 3H), 0.41-0.38 (m, 1H). LC-MS m/z: 353.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.10 min.

(*S*)-A^-Cl-Cvclopropylethyn-Z-CS^-difluoropiperidin-l-vn^-methylimidazofl^-*a*\pyrimidine-8-carboxamide



[00487] Following general procedure A, 2-(3,3-difluoropiperidin-l-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (40 mg, 0.135 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (9.5 mg, 19%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.01 (s, 1H), 6.77 (s, 1H), 4.12 (q, *J* = 12.5 Hz, 2H), 3.86 (t, *J* = 5.0 Hz, 2H), 3.68-3.62 (m, 1H), 2.67 (s, 3H), 2.22-2.17 (m, 2H), 1.92-1.89 (m, 2H), 1.34 (d, *J* = 6.5 Hz, 3H), 1.04-0.99 (m, 1H), 0.60-0.48 (m, 2H), 0.42-0.39 (m, 1H), 0.38-0.33 (m, 1H). LC-MS m/z: 364.1 $[M+H]^+$. HPLC: Purity (254 nm): >99%; t_R = 6.98 min.

(*S*)-A/-(l-Cvclopropylethyl)-2-(4,4-difluoropiperidin-l-yl)-4-methylimidazo[l,5-*a*\pyrimidine-8-carboxamide

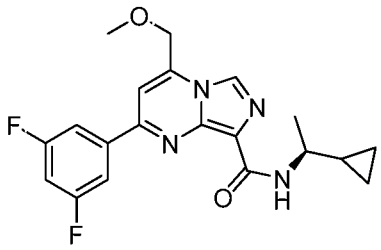


[00488] Following general procedure A, 2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (120 mg, 0.568 mmol) and *(S)*-\ -cyclopropylethanamine afforded (5)-2-chloro-

N-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxamide (66 mg, 42 %) as a yellow solid. LC-MS m/z: 279.0 $[M+H]^+$. LCMS: t_R = 1.26 min.

[00489] Following general procedure I, (<S)-2-chloro-*N*-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (20 mg, 0.072 mmol) and 4,4-difiuoropiperidine hydrochloride afforded the title compound (11 mg, 41%) as a white solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.01 (s, 1H), 6.77 (s, 1H), 3.96 (t, J = 5.5 Hz, 4H), 3.67-3.62 (m, 1H), 2.67 (s, 3H), 2.18-2.09 (m, 4H), 1.34 (d, J = 6.5 Hz, 3H), 1.07-1.02 (m, 1H), 0.60-0.48 (m, 2H), 0.42-0.38 (m, 1H), 0.37-0.33 (m, 1H). LC-MS m/z: 364.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.15 min.

(,S)-A^-(l-Cvclopropylethyl)-2-(3,5-difluorophenyl)-4-(methoxymethyl)imidazo[l,5-*a*\pyrimidine-8-carboxamide



[00490] The mixture of methyl 3-ethoxy-4-methoxybut-2-enoate (3 g, 17.2 mmol), ethyl 5-amino-l *H*-imidazole-4-carboxylate (2.6 g, 17.2 mmol) and CS2CO $_3$ (6.7 g, 20.6 mmol) in 20 mL of DMF was stirred at 110 °C for 16 h, and the resulting product purified by prep-HPLC (10 mM NH_4HC0_3/MeCN) to afford ethyl 2-hydroxy-4-(methoxymethyl)imidazo[l,5-a]pyrimidine-8-carboxylate (1.6 g, 37%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-c¾): δ 7.87 (s, 1H), 6.12 (s, 1H), 4.59 (s, 2H), 4.30 (q, J = 8.5 Hz, 2H), 3.39 (s, 3H), 1.29 (t, J = 8.5 Hz, 3H). LC-MS m/z: 252.1 $[M+H]^+$. LCMS: t_R = 0.80 min.

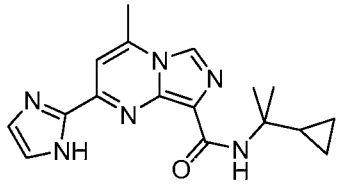
[00491] The solution of ethyl 2-hydroxy-4-(methoxymethyl)iniidazo[l,5-a]pyrimidine-8-carboxylate (1.2 g, 4.78 mmol) in 10 mL of phenylphosphonic dichloride was stirred at 80 °C for 2 hours, cooled and poured into ice water (200 mL). The mixture was extracted with EA (50 mL x 3). The organic phases were dried over annydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo,* and the residue was purified by pre-TLC (PE/EA =1/1) to afford ethyl 2-chloro-4-(methoxymethyl)inddazo[l,5-a]pyrimidine-8-carboxylate (800 mg, 62%) as ayellow solid. LC-MS m/z: 270.0 $[M+H]^+$.LCMS: t_R = 1.48 min.

[00492] Following general procedure **D,** ethyl 2-chloro-4-(methoxymethyl)imidazo[l ,5-a]pyrimidine-8-carboxylate (100 mg, 0.4 mmol) and 3,5-difluorophenylboronic acid afforded ethyl 2-(3,5-difluorophenyl)-4-(methoxymethyl)imidazo[l ,5-a]pyrimidine-8-carboxylate (68 mg, 53%) as a yellow solid. LC-MS m/z: 348. 1 $[M+H]^+$.LCMS: t_R = 1.42 min.

[00493] Following general procedure B, ethyl 2-(3,5-difluorophenyl)-4-(methoxymethyl)imidazo[l ,5-a]pyrimidine-8-carboxylate (68 mg, 0.2 mmol) afforded crude 2-(3,5-difluorophenyl)-4-(methoxymethyl)imidazo[l ,5-a]pyrimidine-8-carboxylic acid (50 mg, 80%). LC-MS m/z: 320. 1 $[M+H]^+$.LCMS: t_R = 0.95 min.

[00494] Following general procedure A, 2-(3,5-difluorophenyl)-4-(methoxymethyl)imidazo[l ,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.16 mmol) and (*S*)-\-cyclopropylethanamine afforded the title compound (7.3 mg, 12%) as a white solid. ^{1}H NMR (500 MHz, *MeOO-d4):* δ 8.44 (s, 1H), 7.94 (dd, *J* = 9.0 Hz, 2.0 Hz, 1H), 7.65 (s, 1H), 7.22 (tt, *J* = 8.5 Hz, 2.5 Hz, 1H), 4.97 (s, 2H), 3.75-3.68 (m, 1H), 3.56 (s, 3H), 1.41 (d, *J* = 6.5 Hz, 3H), 1.17-1.10 (m, 1H), 0.68-0.56 (m, 2H), 0.52-0.47 (m, 1H), 0.43-0.36 (m, 1H). LC-MS m/z: 387. 1 $[M+H]^+$. LC-MS Purity (214 nm): 90%; t_R = 10.08 min.

A/-(2-Cvclopropylpropan-2-yl)-2-(l *H* -imidazol-2-yl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



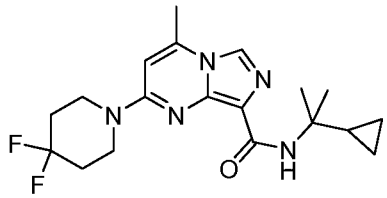
[00495] Following general procedure **D,** ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (300 mg, 1.26 mmol) and l*H*-imidazol-2-ylboronic acid afforded ethyl 2-(l *H*-imidazol-2-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (105 mg, 25%) as a yellow solid. LC-MS m/z: 272. 1 $[M+H]^+$; Purity (254 nm): > 90%; t_R = 0.94 min.

[00496] A mixture of ethyl 2-(l *H*-imidazol-2-yl)-4-methylimidazo[l ,5-a]pyrirnidine-8-carboxylate (95 mg, 0.35 mmol), and bis(tri-n-butyltin) oxide (418 mg,0.70 mmol) in toluene (5 mL) was stirred at 110 °C for 16 h, cooled and concentrated *in vacuo* to afford 2-(l *H*-imidazol-2-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (80 mg, 90 %) as a brown solid. LC-MS m/z: 244.0 $[M+H]^+$; Purity (254 nm): > 80%; t_R = 0.36 min.

[00497] Following general procedure A, 2-(l *H*-irnidazol-2-yl)-4-methylimidazo[l ,5-a]pyrimidine-8-carboxylic acid (70 mg, 0.29 mmol) and 2-cyclopropylpropan-2-amine afforded

the title compound (2.2 mg, 3%) as a yellow solid. ^{1}H NMR (500 MHz, **DMSO-i¾)** δ 8.64 (s, IH), 8.48 (s, IH), 7.99 (s, IH), 7.63 (s, IH), 7.53 (s, IH), 7.24 (s, IH), 2.78 (s, 3H), 1.44-1.39 (m, IH), 1.35 (s, 6H), 0.46-0.42 (m, 4H). LC-MS m/z: 325.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 6.14 min.

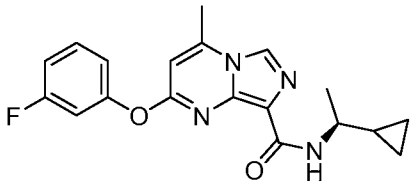
A/-(2-Cvclopropylpropan-2-yl)-2-(4,4-difluoropiperidin-l-yl)-4-methylimidazo[l,5-*a*\pyrimidine-8-carboxamide



[00498] Following general procedure A, 2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (236 mg, 1.12 mmol) and 2-cyclopropylpropan-2-amine afforded 2-chloro-*N*-(2-cyclopropylpropan-2-yl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxamide (140 mg, 43%) as a yellow solid. LC-MS m/z: 293.0 $[M+H]^+$. LCMS: t_R = 1.37 min.

[00499] Following general procedure **I,** 2-chloro-*N*-(2-cyclopropylpropan-2-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (10 mg, 0.034 mmol) and 4,4-difiuoropiperidine hydrochloride afforded the title compound (5.8 mg, 46%) as a white solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.07 (s, IH), 7.97 (s, IH), 6.71 (s, IH), 3.95 (t, J = 5.5 Hz, 4H), 2.65 (s, 3H), 2.15-2.05 (m, 4H), 1.42 (s, 6H), 1.42-1.36 (m, IH), 0.509-0.47 (m, 4H). LC-MS m/z: 378.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 7.55 min.

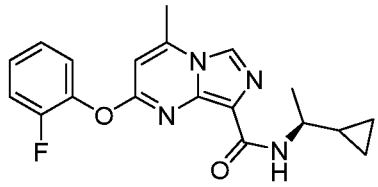
(*S*')-A/-(l-Cvclopropylethyl)-2-(3-fluorophenoxy)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00500] Following general procedure H, (5)-2-chloro-*N*-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (30 mg, 0.107 mmol) and 3-fiuorophenol afforded the title compound (20 mg, 53%) as a grey solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.34 (s, IH), 7.57 (q, J = 7.5 Hz, IH), 7.36 (tt, J = 8.5 Hz, 2.5 Hz, IH), 7.24-7.19 (m, 3H), 6.84 (d, J = 1.0 Hz, IH), 3.49 -3.41 (m, IH), 2.73 (s, 2H), 0.93 (d, J = 6.5 Hz, 3H), 0.57-0.48 (m,

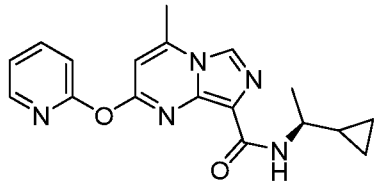
1H), 0.35-0.30 (m, 1H), 0.20-0.13 (m, 1H), 0.07-0.00 (m, 2H). LC-MS m/z: 355.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.60 min.

(.S^-A/-(l-Cvclopropylethyl)-2-(2-fluorophenoxy)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



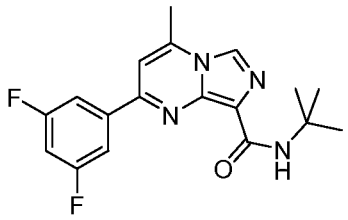
[00501] Following general procedure H, (5)-2-chloro-*N*-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (30 mg, 0.107 mmol) and 2-fluorophenol afforded the title compound (23 mg, 61%) as a grey solid. ^{1}H NMR (500 MHz, **DMSO-i¾)** δ 8.36 (s, 1H), 7.50 (ddd, *J* = 16.0 Hz, 8.0 Hz, 1.5 Hz, 2H), 7.44-7.38 (m, 1H), 7.35 (tt, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.92 (s, 1H), 3.45-3.38 (m, 1H), 2.74 (s, 3H), 0.89 (d, *J* = 6.5 Hz, 2H), 0.52-0.45 (m, 1H), 0.35-0.30 (m, 1H), 0.20-0.15 (m, 1H), 0.06-0.04 (m, 2H). LC-MS m/z: 355.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.52 min.

(.S^-A/-(l-Cvclopropylethyl)-4-methyl-2-(pyridin-2-yloxy)imidazo[l,5-alpyrimidine-8-carboxamide



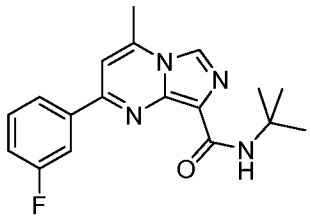
[00502] Following general procedure H, (5)-2-chloro-*N*-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (25 mg, 0.089 mmol) and pyridin-2-ol afforded the title compound (2 mg, 3.4 %) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.82 (d, *J* = 8.0 Hz, 2H), 8.45 (s, 1H), 7.39 (s, 1H), 6.60 (d, *J* = 8.0 Hz, 2H), 3.67-3.60 (m, 1H), 2.89 (s, 3H), 1.38 (d, *J* = 6.5 Hz, 3H), 0.62-0.57 (m, 1H), 0.57-0.49 (m, 1H), 0.47-0.42 (m, 1H), 0.38-0.34 (m, 1H). LC-MS m/z: 338.1 $[M+H]^+$. HPLC: Purity (214 nm): 97%; t_R = 5.15 min.

jV-fert-Butyl-2-(3,5-difluorophenyl)-4-methylimid azo[1,5-*a*]pyrimidine-8-carboxamide



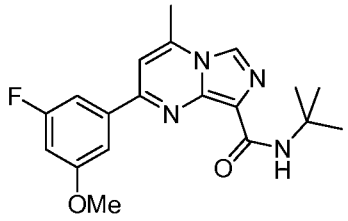
[00503] Following general procedure A, 2-(3,5-difluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (40 mg, 0.14 mmol) and 2-methylpropan-2-amine afforded the title compound (24.7 mg, 51%) as ayellow solid. ^{1}H NMR (400 MHz, *OMSO-d_6)* δ 8.52 (s, 1H), 7.99 (s, 1H), 7.94 (d, J = 7.2 Hz, 2H), 7.70 (s, 1H), 7.51 (t, J = 8.8 Hz 1 H), 2.78 (s, 3H), 1.47 (s, 9 H). LC-MS m/z: 345.2 $[M+H]^+$. HPLC: Purity (254 nm): > 98%; t_R = 8.12 min.

A/-ferf-Butyl-2-(3-fluorophenyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00504] Following general procedure A, 2-(3-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.18 mmol) and 2-methylpropan-2-amine afforded the title compound (31 mg, 50%) as ayellow solid. ^{1}H NMR (500 MHz, *OMSO-d_6)* δ 8.49 (s, 1H), 8.08-8.01 (m, 3H), 7.68-7.63 (m, 2H), 7.44 (td, J = 9.0 Hz, 2.5 Hz, 1H), 2.78 (s, 3H), 1.48 (s, 9H). LC-MS m/z: 327.2 $[M+H]^+$, HPLC Purity (214 nm): > 99%; t_R = 7.87 min.

A/-ferf-Butyl-2-(3-fluoro-5-methoxyphenyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide

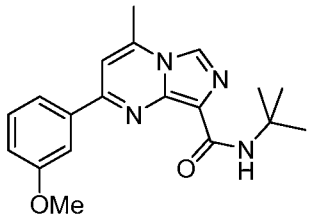


[00505] Following general procedure **D,** ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (308 mg, 1.3 mmol) and 3-fluoro-5-methoxyphenylboronic acid afforded ethyl 2-(3-fluoro-5-methoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate as a light brown solid (170 mg, 40%). LC-MS m/z: 330.1 $[M+H]^+$. t_R = 1.37 min.

[00506] Following general procedure B, ethyl 2-(3-fluoro-5-methoxyphenyl)-4-methylirnidazo[l,5-a]pyrirnidine-8-carboxylate (170 mg, 0.52 mmol) afforded 2-(3-fluoro-5-methoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (105 mg, 67 %) as a yellow solid. LC-MS m/z: 302.1 $[M+H]^+$. t_R = 0.94 min.

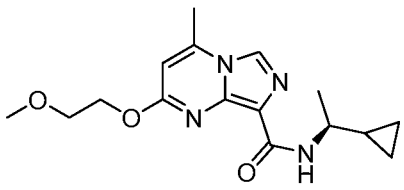
[00507] Following general procedure A, 2-(3-fluoro-5-methoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (48 mg, 0.16 mmol) and 2-methylpropan-2-amine afforded the title compound (11 mg, 19%) as ayellow solid. ^{1}H NMR (500 MHz, DMSO-i¾) δ 8.49 (s, 1H), 8.04 (s, 1H), 7.67 (s, 1H), 7.62 (s, 1H), 7.61 (d, *J* = 10.5 Hz, 1H), 7.07 (dt, *J* = 10.5 Hz, 1.5 Hz, 1H), 3.89 (s, 3H), 2.78 (s, 3H), 1.48 (s, 9H). LC-MS m/z: 357.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.06 min.

iV-fert-Butyl-2-(3-methoxyphenyl)-4-methylimidazo [1,5-al pyrimidine-8-carboxamide



[00508] Following general procedure A, 2-(3-methoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 0.11 mmol) and 2-methylpropan-2-amine afforded the title compound (17.6 mg, 48% yield) as ayellow solid. ^{1}H NMR (500 MHz, DMSO-i¾): δ 8.46 (s, 1H), 8.12 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.75 (s, 1H), 7.63 (s, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.15 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 3.87 (s, 3H), 2.78 (s, 3H), 1.48 (s, 9H). LC-MS m/z: 339.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.79 min.

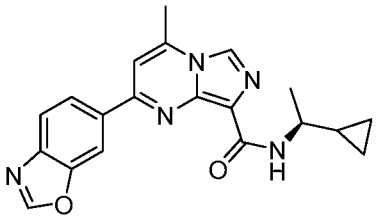
(.s')-A/-(l-Cvclopropylethyl)-2-(2-methoxyethoxy)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00509] Following general procedure G, (<S)-2-chloro-*N*-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (25 mg, 0.09 mmol) and 2-methoxyethanol afforded the title compound (26 mg, 93% yield) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.24 (s, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 6.53 (s, 1H), 4.52 (bs, 2H), 3.73 (bs, 2H), 3.56-3.50

(m, 1H), 3.32 (s, 3H), 2.64 (s, 3H), 1.23 (d, J = 6.5 Hz, 3H), 1.06-1.01 (m, 1H), 0.49-0.37 (m, 2H), 0.33-0.28 (m, 1H), 0.27-0.22 (m, 1H). LC-MS m/z: 319.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 6.43 min.

CSV2-(Benzo[</1oxazol-6-yl)-iV-(l-cvclopropy^^thyl)-4-methylimidazo[1,5-*a*]pyrimidine-8-carboxamide

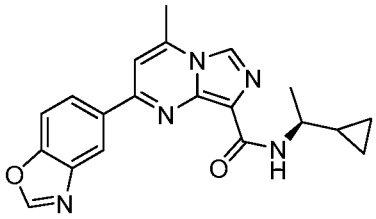


[00510] A mixture of 2-amino-5-bromophenol (1.0 g, 5.34 mmol), p-toluene sulphonic acid (100 mg, 0.581 mmol) and trimethoxymethane (6 mL) was stirred at 80 °C under N2 for 1 h, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE/EA = 9:1) to afford 6-bromobenzo[cf]oxazole (980 mg, 93%) as a brown solid. LC-MS m/z: no mass. t_R = 1.73 min.

[00511] Following general procedure D, 6-bromobenzo[cf]oxazole (980 mg, 4.97 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(l,3,2-dioxaborolane) afforded 6-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)benzo[cf]oxazole (1.1 g, 90%) as a light yellow solid. LC-MS m/z: 246.2 $[M+H]^+$. t_R = 1.92 min.

[00512] Following general procedure D, (5)-2-chloro-*N*-(l-cyclopropylethyl)-4-methylinddazo[l,5-a]pyrinddine-8-carboxamide (30 mg, 0.107 mmol) and 6-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)benzo[cf]oxazole afforded the title compound (8 mg, 21%) as a yellow green solid. ¾NMR (500 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.64 (s, 1H), 8.50 (s, 1H), 8.35 (d, J = 8.0 Hz, 1H), 8.21 (d, J = 7.5 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.75 (s, 1H), 3.64-3.60 (m, 1H), 2.81 (s, 3H), 1.30 (d, J = 7.0 Hz, 3H), 1.16-1.10 (m, 1H), 0.58-0.42 (m, 2H), 0.41-0.36 (m, 1H), 0.36-0.30 (m, 1H). LC-MS m/z: 362.2 $[M+H]^+$. HPLC: Purity (214 nm): 97%; t_R = 6.69 min.

CSV2-(Benzo[dloxazol-5-yl)-iV-(l-cvclopropylefo yl)-4-methylimidazo[1,5-*a*]pyrimidine-8-carboxamide

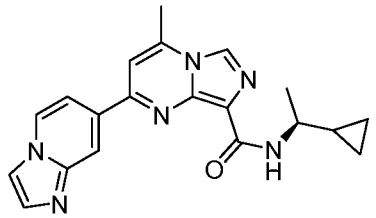


[00513] Following general procedure D, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (200 mg, 0.84 mmol) and 5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)benzo[cf]oxazole afforded ethyl 2-(benzo[i¾oxazol-5-yl)-4-methylirrddazo[l,5-a]pyrirnidine-8-carboxylate as ayellow solid (150 mg, 52%). LC-MS m/z: 323.7 $[M+H]^+$. t_R = 1.16 min.

[00514] To a solution of ethyl 2-(benzo[<i]oxazol-5-yl)-4-methylirnidazo[l,5-a]pyrirnidine-8-carboxylate (100 mg, 0.31 mmol) in toluene (15 mL) was added $(Bu_3Sn)_2O$ (557 mg, 0.93 mmol. The resulting mixture was stirred at 110 °C for 2 days. The solution was concentrated *in vacuo.* The residue was filtered, and washed with Et^O to collect 2-(benzo[cf]oxazol-5-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid as a gray solid (127 mg, 70%). LC-MS m/z: 295.7 $[M+H]^+$; t_R = 1.15 min.

[00515] Following general procedure A, 2-(benzo[cf]oxazol-5-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (80 mg, 0.14 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound as ayellow solid (2.7 mg, 5.5%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.89 (s, 1H), 8.69 (s, 1H), 8.49 (s, 1H), 8.38 (dd, ***J*** = 8.5 Hz, 1.5 Hz, 1H), 8.23 (d, ***J*** = 7.5 Hz, 1H), 8.02 (d, ***J*** = 8.5 Hz, 1H), 7.78 (s, 1H), 3.64-3.59 (m, 1H), 2.80 (s, 3H), 1.29 (d, ***J*** = 6.5 Hz, 3H), 1.14-1.08 (m, 1H), 0.56-0.46 (m, 2H), 0.41-0.36 (m, 1H), 0.34-0.29 (m, 1H). LC-MS m/z: 362.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 6.80 min.

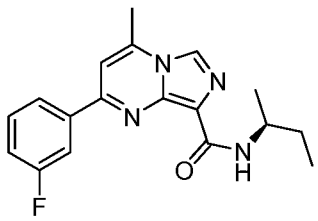
***(.s')*-A/-(l-Cvclopropylethyl)-2-(imidazo[l,2-alpyridin -7-yl)-4-methylimidazo[l,5-*a*\pyrimidine-8-carboxamide**



[00516] A mixture of 7-bromoimidazo[l,2-a]pyridine (40 mg, 0.164 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(l,3,2-dioxaborolane) (40 mg, 0.136 mmol), KOAc (93 mg, 0.34 mmol) and $Pd(dppf)Cl_2$.DCM (14 mg, 0.019 mmol) in dioxane (2 mL) was stirred at 90 °C for 2 h under N_2 atmosphere. The reaction was concentrated *in vacuo* and the crude mixture of 7-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)imidazo[l,2-a]pyridine was used in the next step without purification. LC-MS m/z: 245.2 $[M+H]^+$. t_R = 1.17 min.

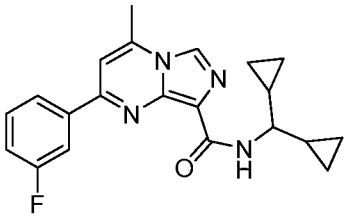
[00517] Following general procedure D, (5)-2-chloro-*N*-(l-cyclopropylethyl)-4-methylinddazo[l,5-a]pyrimidine-8-carboxamide (40 mg, 0.136 mmol) and 7-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)imidazo[l,2-a]pyridine afforded the title compound (18 mg, 37% over two steps) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.75 (d, *J* = 7.5 Hz, 1H), 8.55 (s, 1H), 8.51 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 8.10 (s, 1H), 7.85 (s, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.76 (s, 1H), 3.62-3.58 (m, 1H), 2.79 (s, 3H), 1.30 (d, *J* = 6.5 Hz, 3H), 1.15-1.09 (m, 1H), 0.58-0.45 (m, 2H), 0.40-0.36 (m, 1H), 0.34-0.29 (m, 1H). LC-MS m/z: 361.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 6.07 min.

(.S^-A/-$gc-BuM-2-(3-fluorophenyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



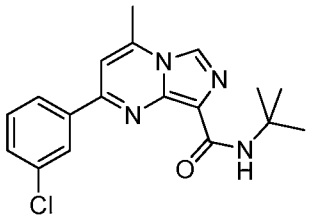
[00518] Following general procedure A, 2-(3-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.18 mmol) and (<S)-butan-2-amine afforded the title compound (35 mg, 55%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50 (s, 1H), 8.07 (d, *J* = 7.5 Hz, 1H), 8.03-7.99 (m, 2H), 7.68-7.64 (m,2H), 7.45-7.42 (td, *J* = 8.5 Hz, 2.0 Hz, 1H), 4.03-3.98 (m, 1H), 2.78 (s, 3H), 1.64-1.58 (m, 1H), 1.22 (d, *J* = 6.5 Hz, 3H), 0.94 (t, *J* = 7.5 Hz, 3H). LC-MS m/z: 327.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.69 min.

A/-(Dicvclopropylmethyl)-2-(3-fluorophenyl)-4-methylimidazo [1,5-«1 pyrimidine-8-carboxamide



[00519] Following general procedure A, 2-(3-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (46 mg, 0.17 mmol) and dicyclopropylmethanamine afforded the title compound (31 mg, 50%) as a light yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.52 (s, 1H), 8.17 (d, J = 8.0 Hz, 1H), 8.11-8.04 (m, 2H), 7.67 (s, 2H), 7.44 (s, 1H), 3.35-3.32 (m, 1H), 2.79 (s, 3H), 1.18-1.05 (m, 2H), 0.60-0.48 (m, 2H), 0.48-0.30 (m, 6H). LC-MS m/z: 365.1 [M+H]$^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.17 min.

A/-ferf-Butyl-2-(3-chlorophenyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



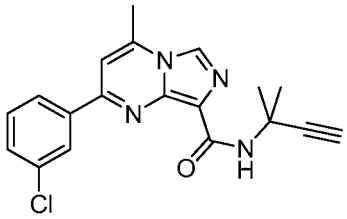
[00520] Following general procedure D, ethyl 2-chloro-4-methylimidazo[l ,5-a]pyrirnidine-8-carboxylate (500 mg, 2.09 mmol) and 3-chlorophenylboronic acid afforded ethyl 2-(3-chlorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (452 mg, 62%) as a brown oil. LC-MS m/z: 316.1 [M+H]$^+$. Purity (254 nm): > 68%; t_R = 1.41 min.

[00521] Following general procedure B, ethyl 2-(3-chlorophenyl)-4-methylimidazo[l ,5-a]pyrimidine-8-carboxylate (452 mg, 1.43 mmol) afforded 2-(3-chlorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (240 mg, 58%) as a yellow solid. LC-MS m/z: 288.1 [M+H]$^+$.Purity (254 nm): > 67%; t_R = 0.95 min.

[00522] Following general procedure A, 2-(3-chlorophenyl)-4-methylimidazo[l ,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.17 mmol) and 2-methylpropan-2-amine afforded the title compound (12.9 mg, 22 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50 (s, 1H), 8.30-8.29 (m, 1H), 8.18 (dt, J = 7.0 Hz, 1.5 Hz, 1H), 8.08 (s, 1H), 7.69 (d, J = 0.5 Hz,

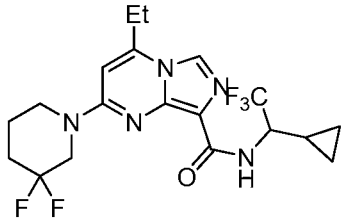
1H), 7.66-7.62 (m, 2H), 2.79 (s, 3H), 1.48 (s, 9H). LC-MS m/z: 343.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.40 min.

2-(3-Chlorophenyl)-4-methyl -A/- (2-methylbut-3-vn -2-yl)imidazo[l,5-alpyrimidine-8-carboxamide



[00523] Following general procedure A, 2-(3-chlorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 0.10 mmol) and 2-methylbut-3-yn-2-amine afforded the title compound (7.2 mg, 20%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.40 (s, 1H), 8.31 (s, 1H), 8.22 (d, J = 6.0 Hz, 1H), 7.72 (s, 1H), 7.66 (d, J = 6.0 Hz, 2H), 4.05 (s, 1H), 2.79 (s, 3H), 1.75 (s, 6H). LC-MS m/z: 353.1 $[M+H]^+$. HPLC: Purity (254 nm): 98 %; t_R = 8.08 min.

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(33-difluoropiperidin-l-yl)-4-ethylimidazo[l,5-alpyrimidine-8-carboxamide



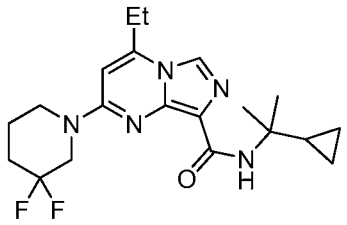
[00524] Following general procedure I, ethyl 2-chloro-4-ethylimidazo[l,5-a]pyrirnidine-8-carboxylate (200 mg, 0.79 mmol) and 3,3-difluoropiperidine afforded crude ethyl 2-(3,3-difluoropiperidin-l-yl)-4-ethylimidazo[l,5-a]pyrimidine-8-carboxylate (180 mg, 67%) as a yellow solid. LC-MS m/z: 339.1 $[M+H]^+$. Purity (214 nm): 85%, t_R = 1.59 min.

[00525] Following general procedure B, ethyl 2-(3,3-difluoropiperidin-l-yl)-4-ethylimidazo[l,5-a]pyrimidine-8-carboxylate (150 mg, 0.44 mmol) afforded 2-(3,3-difluoropiperidin-l-yl)-4-ethylimidazo[l,5-a]pyrimidine-8-carboxylic acid (100 mg, 73%) as a grey solid. LC-MS m/z: 311.1 $[M+H]^+$. Purity (214 nm): 86%; t_R = 0.91 min.

[00526] Following general procedure A, 2-(3,3-difluoropiperidin-l-yl)-4-ethylimidazo[l,5-a]pyrimidine-8-carboxylic acid (40 mg, 0.13 mmol) and l-cyclopropyl-2,2,2-

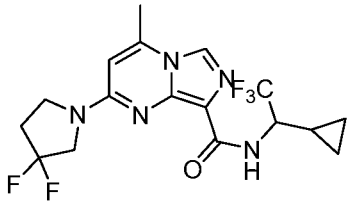
trifluoroethanamine afforded the title compound (14 mg, 25%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-i¾) δ 8.34 (d, *J* = 9.5 Hz, 1H), 8.19 (s, 1H), 6.81 (s, 1H), 4.43-4.39 (m, 1H), 4.14 (td, *J* = 12.5 Hz, 4.0 Hz, 2H), 3.81-3.79 (m, 2H), 2.98 (q, *J* = 7.5 Hz, 2H), 2.20-2.14 (m, 2H), 1.80-1.76 (m, 2H), 1.33 (t, *J* = 7.5 Hz, 3H), 1.20-1.16 (m, 1H), 0.68-0.62 (m, 1H), 0.58-0.42 (m, 2H), 0.38 0.30 (m, 1H). LC-MS m/z: 432.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.71 min.

A/-(2-Cvclopropylpropan-2-yl)-2-(3,3-difluoropiperidin-l-yl)-4-ethylimidazo[l,5-alpyrimidine-8-carboxamide



[00527] Following general procedure A, 2-(3,3-difluoropiperidin-l-yl)-4-ethylimidazo[l,5-a]pyrimidine-8-carboxylic acid (40 mg, 0.13 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (12 mg, 24%) as a yellow solid. ¾ NMR (500 MHz, DMSO-d_6) δ 8.11 (s, 1H), 7.85 (s, 1H), 6.75 (s, 1H), 4.12 (t, *J* = 11.5 Hz, 2H), 3.79 (t, *J* = 5.5 Hz, 2H), 2.96 (q, *J* = 7.5 Hz, 2H), 2.20-2.10 (m, 2H), 1.80-1.76 (m, 2H), 1.313 (t, *J* = 7.5 Hz, 3H), 1.308 (s, 6H), 1.31-1.30 (m, 1H), 0.39 (d, *J* = 6.5 Hz, 4H). LC-MS m/z: 392.3 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.67 min.

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(3,3-difluoropyrrolidin-l-yl)-4-methylimidazo [1,5-«1 pyrimidine-8-carboxamide

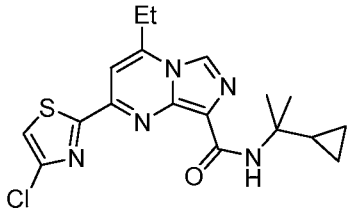


[00528] Following general procedure I, ethyl 5-chloro-7-methylimidazo[l,5-a]pyrimidine-3-carboxylate (200 mg, 0.84 mmol) and 3,3-difluoropyrrolidine hydrochloride afforded ethyl 5-(3,3-difluoropyrrolidin-l-yl)-7-methylimidazo[l,5-a]pyrimidine-3-carboxylate (156 mg, 50%) as a yellow solid. LC-MS m/z: 311.1 $[M+H]^+$, t_R = 1.49 min.

[00529] Following general procedure B, ethyl 5-(3,3-difluoropyrrolidin-l-yl)-7-methylimidazo[l,5-a]pyrimidine-3-carboxylate (80 mg, 0.26 mmol) afforded 5-(3,3-difluoropyrrolidin-l-yl)-7-methylimidazo[l,5-a]pyrimidine-3-carboxylic acid (50 mg, 69%) as an earth yellow solid. LC-MS m/z: 283.0 $[M+H]^+$. t_R = 1.11 min.

[00530] Following general procedure A, 5-(3,3-difluoropyrrolidin-l-yl)-7-methylimidazo[l,5-a]pyrimidine-3-carboxylic acid (50 mg, 0.18 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine afforded the title compound (9.6 mg, 14%) as a white solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.60 (br, 1H), 8.07 (s, 1H), 6.49 (s, 1H), 4.45-4.40 (m, 1H), 4.02 (t, J = 12.5 Hz, 2H), 3.91 (t, J = 7.0 Hz, 2H), 2.70 (s, 3H), 2.68-2.60 (m, 2H), 1.28-1.20 (m, 1H), 0.79-0.72 (m, 1H), 0.63-0.60 (m, 1H), 0.59-0.43 (m, 2H). LC-MS m/z: 404.1 $[M+H]^+$. HPLC: Purity (254 nm): 99%; t_R = 7.48 min.

2-(4-Chlorothiazol-2-yl)-iV-(2-cyclopropylpropan-2-yl)-4-ethylimidazo[1,5-*a*]pyrimidine-8-carboxamide



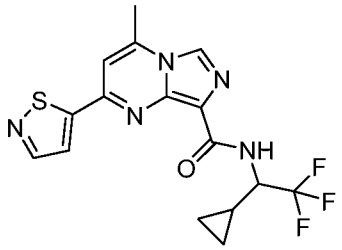
[00531] Following general procedure E, ethyl 2-chloro-4-ethylimidazo[l,5-a]pyrirnidine-8-carboxylate (50 mg, 0.20 mmol) and 2,4-dichlorothiazole afforded ethyl 2-(4-chlorothiazol-2-yl)-4-ethylimidazo[l,5-a]pyrimidine-8-carboxylate (15 mg, 22%) as ayellow solid. LC-MS m/z: 337.0 $[M+H]^+$.

[00532] To a solution of ethyl 2-(4-chlorothiazol-2-yl)-4-ethylirnidazo[l,5-a]pyrirnidine-8-carboxylate (30 mg, 0.089 mmol) in toluene (1.0 mL) was added $(nBu_3Sn)_20$ (106 mg, 0.18 mmol). The reaction mixture was stirred at 120 °C for 48 h, and concentrated *in vacuo*. The residue was washed with PE and then filtered to afford 2-(4-chlorothiazol-2-yl)-4-ethylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (20 mg, 74%) as ayellow solid. LC-MS m/z: 309.1 $[M+H]^+$.

[00533] Following general procedure A, 2-(4-chlorothiazol-2-yl)-4-ethylimidazo[l,5-a]pyrimidine-8-carboxylic acid (20 mg, 0.065 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (5 mg, 20%) as ayellow solid. ^{1}H NMR (500 MHz, $CDC1_3$): δ 8.13 (s, 1H), 7.72 (s, 1H), 7.53 (s, 1H), 7.34 (s, 1H), 3.07 (q, J = 7.5 Hz, 1H), 1.55 (t, J = 7.5 Hz,

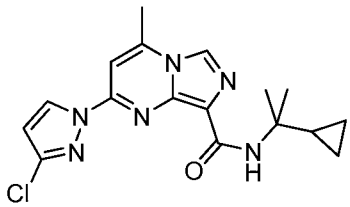
3H), 1.51-1.45 (m, 1H), 1.47 (s, 3H), 0.52-0.48 (m, 4H). LC-MS m/z: 390.0 $[M+H]^+$. HPLC Purity (214nm): > 80%; t_R = 7.91 min.

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(isothiazol-5-yl)-4-methylimidazo[l,5-*a*\pyrimidine-8-carboxamide



[00534] Following general procedure A, 2-(isothiazol-5-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (26 mg, 0.10 mmol) and l-cyclopropyl-2,2,2-trifluoroethanamine afforded the title compound (13 mg, 32%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.67 (d, *J* = 2.0 Hz, 1H), 8.52 (s, 1H), 8.09 (d, *J* = 2.0 Hz, 1H), 7.52 (s, 1H), 4.47-4.42 (m, 1H), 2.88 (s, 3H), 1.40-1.32 (m, 1H), 0.85-0.78 (m, 1H), 0.72-0.62 (m, 1H), 0.61-0.50 (m, 2H). LC-MS m/z: 382.0 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.29 min.

2-(3-Chloro-l *H*-pyrazol-l-yl)-A/-(2-cvclopropylpropan-2-yl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



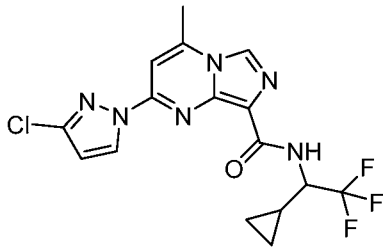
[00535] To a stirred solution of ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (300 mg, 1.25 mmol) in DMF (2.0 mL) was added 3-chloro-l *H*-pyrazole (255 mg, 2.5 mmol) and K2CO $_3$ (345 mg, 2.5 mmol). The reaction mixture was stirred at 60 °C for 3 h, cooled to RT and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by reverse phase flash chromatography (MeCN/H$_2$**0)** to afford ethyl 2-(3-chloro-l *H*-pyrazol-l-yl)-4-methyliiTiidazo[l,5-a]pyrirnidine-8-carboxylate (150 mg, 39%) as a red solid. LC-MS m/z: 306.1 $[M+H]^+$.

[00536] To a solution of ethyl 2-(3-chloro-l *H*-pyrazol-l-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (150 mg, 0.49 mmol) in toluene (1.0 mL) was added (nBu3Sn)$_2$**0** (586 mg, 0.98 mmol). The reaction mixture was stirred at 120 °C for 48 h, and concentrated *in*

vacuo. The residue was washed with PE and then filtered to afford 2-(3-chloro-l *H*-pyrazol-l-yl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (70 mg, 51%) as a black solid. LC-MS m/z: 278.1 $[M+H]^+$.

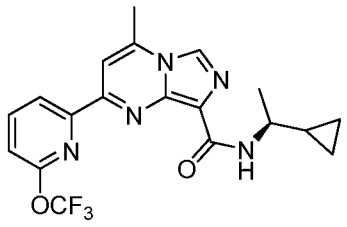
[00537] Following general procedure A, 2-(3-chloro-l *H*-pyrazol-l-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (70 mg, 0.25 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (10 mg, 12%). ¾ NMR (500 MHz, $CDC1_3$): δ 8.71 (d, *J* = 3.0 Hz, 1H), 7.93 (s, 1H), 7.46 (s, 1H), 7.30 (s, 1H), 6.47 (d, *J* = 3.0 Hz, 1H), 2.74 (s, 3H), 1.54 (s, 9H). LC-MS m/z: 333.1 $[M+H]^+$. HPLC Purity (214nm): > 66%; t_R = 7.72 min.

2-(3-Chloro-l *H*-pyrazol-l-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-*a*\pyrimidine-8-carboxamide



[00538] Following general procedure A, 2-(3-chloro-l *H*-pyrazol-l-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (70 mg, 0.25 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine afforded the title compound (6 mg, 6%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCI_3$) δ 8.61 (d, *J* = 2.5 Hz, 1H), 8.02 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 0.5 Hz, 1H), 6.51 (d, *J* = 3.0 Hz, 1H), 4.46-4.37 (m, 1H), 2.78 (s, 3H), 1.25-1.15 (m, 1H), 0.78-0.71 (m, 1H), 0.62-0.56 (m, 2H), 0.54-0.49 (m, 1H). LC-MS m/z: 399.0 $[M+H]^+$. HPLC: Purity (214 nm): 95%; t_R = 8.14 min.

(.S^-A/-(l-Cvclopropylethyl)-4-methyl-2-(6-(trifluoromethoxy)pyridin-2-yl)imidazo[l,5-*a*\pyrimidine-8-carboxamide



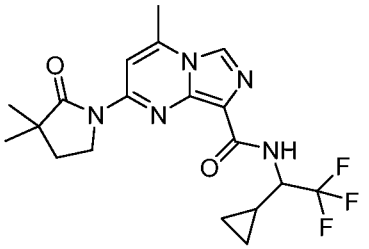
[00539] Following general procedure E, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (300 mg, 1.25 mmol) and 2-chloro-6-(trifluoromethoxy)pyridine afforded ethyl

4-methyl-2-(6-(trifluoromethoxy)pyridin-2-yl)imidazo[l ,5-a]pyrimidine-8-carboxylate (81 mg, 17%) as a a yellow solid. LC-MS m/z: 367. 1 $[M+H]^+$. Purity (214 nm): > 96%; t_R = 1.47 min.

[00540] Following general procedure B, ethyl 4-methyl-2-(6-(trifluoromethoxy)pyridin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (73 mg, 0.20 mmol) afforded 4-methyl-2-(6-(trifluoromethoxy)pyridin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (43 mg, 64%) as a yellow solid. LC-MS m/z: 339. 1 $[M+H]^+$. Purity (214 nm): > 93%; t_R = 1.02 min.

[00541] Following general procedure A, 4-methyl-2-(6-(trifluoromethoxy)pyridin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (38 mg, 0.11 mmol) and (<S)-1 - cyclopropylethanamine afforded the title compound (4.3 mg, 9%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.56 (d, *J* = 8.0 Hz, 1H), 8.46 (s, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 8.19 (t, *J* = 8.0 Hz, 1H), 7.79 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 3.73-3.68 (m, 1H), 2.87 (s, 3H), 1.43 (d, *J* = 6.5 Hz, 3H), 1.20-1 .13 (m, 1H), 0.68-0.52 (m, 2H), 0.5 1-0.47 (m, 1H), 0.41 -0.37 (m, 1H). LC-MS m/z: 406. 1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.42 min.

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(3,3-dimethyl-2-oxopyrrolidin-l-yl)-4-methyliniidazo [1,5-al pyrimidine-8-carboxamide



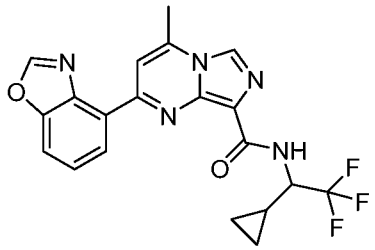
[00542] A mixture of ethyl 2-chloro-4-methylimidazo[l ,5-a]pyrimidine-8-carboxylate (480 mg, 2.0 mmol), 4,4-dimethylpyrrolidin-2-one (226 mg, 2.0 mmol), $Pd_2(dba)_3$ (92 mg, 0.1 mmol), $CS2CO_3$ (975 mg, 3.0 mmol), and Xantphos (174 mg, 0.3 mmol) in 1,4-dioxane (10 mL) was stirred at 100 °C under N2 overnight, poured into H2O (20 mL), and extracted with EA (40 mL x 3). The combined organic phases were dried over anhydrous MgSC^ and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (100% EA) to afford ethyl 2-(3,3-dimethyl-2-oxopyrrolidin-l -yl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (200 mg, 32% yield) as an orange solid. LC-MS m/z: 317.2$[M+H]^+$; t_R = 1.26 min.

[00543] A mixture of ethyl 2-(3,3-dimethyl-2-oxopyrrolidin-l -yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (160 mg, 0.5 1 mmol) and $(Bu_3Sn)_20$ (591 mg, 1.02 mmol) in

toluene (4 mL) was stirred at 120 °C overnight, and concentrated to dryness. The residue was dissolved in H_20 (10 mL), basified to pH 10-1 1 with 6*N* NaOH, and washed with EA (20 mL x 3). The aqueous phase was then acidified to pH 1-2 with 4*N* HC1 aqueous solution, and extracted with EA (30 mL x 3). The combined organic phases were dried over anhydrous MgSC>4, and filtered. The filtrate was concentrated in vauo to afford 2-(3,3-dimethyl-2-oxopyrrolidin-l-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (35 mg, 21 %) as light yellow oil. LC-MS m/z: 289.1 $[M+H]^+$, t_R = 0.83 min.

[00544] Following general procedure A, 2-(3,3-dimethyl-2-oxopyrrolidin-l-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 0.11 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (6.0 mg, 12% yield) as an off-white solid. '**HNMR** (500 MHz, CD_3OD): δ 8.33 (s, 1H), 8.15 (s, 1H), 4.40-4.36 (m, 1H), 4.16-4.07 (m, 2H), 2.79 (s, 3H), 2.11 (t, *J* = 7.0 Hz, 2H), 1.30 (s, 6H), 0.93-0.90 (m, 1H), 0.79-0.76 (m, 1H), 0.66-0.57 (m, 2H), 0.50-0.47 (m, 1H). LC-MS m/z: 410.1 $[M+H]^+$. HPLC: Purity (214 nm): 97%; t_R = 7.98 min.

2-(Benzo[</loxazol-4-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-« 1pyrimidine-8-carboxamide

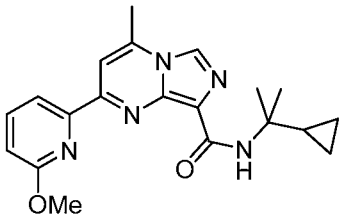


[00545] To 2-amino-3-bromophenol trimethoxymethane (1.5 g, 8 mmol) was added trimethoxymethane (4.24 g, 40 mmol) and *p*-TsOH (68.8 mg, 0.4 mmol). The reaction mixture was stirred at 100 °C overnight, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (PE/EA; 1/2) to afford 4-bromobenzo[cf]oxazole (1.5 g, 94%) as a red solid.

[00546] Following general procedure D, 4-bromobenzo[cf]oxazole (1.2 g, 6.06 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(l,3,2-dioxaborolane) afforded 4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)benzo[cf]oxazole (400 mg, 27%) as a yellow oil. LC-MS m/z: 246.0 $[M+H]^+$. t_R = 1.46 min.

[00547] Following general procedure **D,** 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (60 mg, 0.18 mmol) and 4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)benzo [*d*]oxazole afforded the title compound (26 mg, 34%) as ayellow solid. ^{1}H NMR (500 MHz, *OMSO-d$_6$)* δ 9.02 (s, 1H), 8.89 (d, *J* = 9.5 Hz, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 8.19 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.69 (t, *J* = 8.0 Hz, 1H), 4.40-4.36 (m, 1H), 2.86 (s, 3H), 1.41-1.37 (m, 1H), 0.74-0.68 (m, 1H), 0.61-0.52 (m, 2H), 0.41-0.36 (m, 1H). LC-MS m/z: 416.0 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.84 min.

A/-(2-Cvclopropylpropan-2-yl)-2-(6-methoxypyridin-2-yl)-4-methylimidazo[l,5-*a*\pyrimidine-8-carboxamide

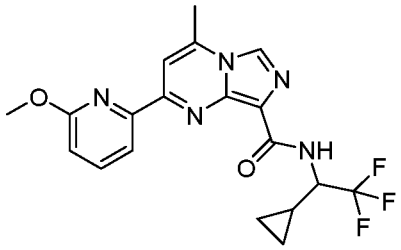


[00548] Following general procedure F, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (350 mg, 1.46 mmol) and 2-methoxy-6-(tributylstannyl)pyridine afforded ethyl 2-(6-methoxypyridin-2-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate as a brown solid (400 mg, 82%). LC-MS m/z: 313.1 $[M+H]^+$. LC-MS Purity (214 nm): 93.5%; t_R = 1.68 min.

[00549] Following general procedure B, ethyl 2-(6-methoxypyridin-2-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (360 mg, 1.15 mmol) afforded 2-(6-methoxypyridin-2-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (265 mg, 73%) as a yellow solid. LC-MS m/z: 285.1 $[M+H]^+$. LC-MS Purity (254 nm): 94.7%; t_R = 1.45 min.

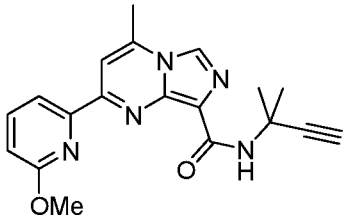
[00550] Following general procedure A, 2-(6-methoxypyridin-2-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (70 mg, 0.25 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (16 mg, 18%) as ayellow solid. ¾NMR (500 MHz, **DMSO-c¾):** δ 8.53 (s, 1H), 8.10 (s, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.97 (t, *J* = 8.0 Hz, 1H), 7.85 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 4.05 (s, 3H), 2.83 (s, 3H), 1.46-1.41 (m, 1H), 1.39 (s, 6H), 0.49-0.47 (m, 4H). LC-MS m/z: 366.1 $[M+H]^+$. HPLC: Purity (214 nm): 97.79%; t_R = 8.42 min.

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(6-methoxypyridin-2-yl)-4-methylimidazo[l,5-« 1pyrimidine-8-carboxamide



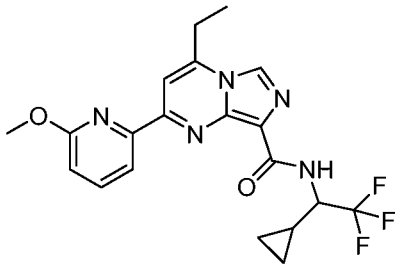
[00551] Following general procedure A, 2-(6-methoxypyridin-2-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (70 mg, 0.25 mmol) and l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (20 mg, 20%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-c¾): δ 8.65 (d, *J* = 9.0 Hz, 1H), 8.60 (s, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.97 (t, *J* = 7.5 Hz, 1H), 7.89 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 1H),4.40-4.36 (m, 1H), 4.05 (s, 3H), 2.84 (s, 3H), 1.40-1.37 (m, 1H), 0.72-0.62 (m, 1H), 0.60-0.56 (m, 2H), 0.40-0.37 (m, 1H). LC-MS m/z: 406.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.41 min.

2-(6-Methoxypyridin -2-yl)-4-methyl -A/-(2-methylbut-3-vn -2-yl)imidazo[l,5-alpyrimidine-8-carboxamide



[00552] Following general procedure A, 2-(6-methoxypyridin-2-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (79 mg, 0.28 mmol) and 2-methylbut-3-yn-2-amine afforded the title compound (9.4 mg, 10%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.42 (s, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.97 (t, *J* = 7.5 Hz, 1H), 7.84 (s, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 4.04 (s, 3H), 3.40 (s, 1H), 2.82 (s, 3H), 1.76 (s, 6H). LC-MS m/z: 350.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.76 min.

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-4-ethyl-2-(6-methoxypyridin-2-yl)imidazo[l,5-«1pyrimidine-8-carboxamide

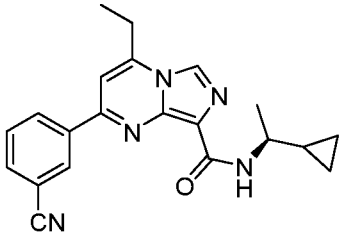


[00553] Following general procedure F, ethyl 2-chloro-4-ethylimidazo[l,5-a]pyrimidine-8-carboxylate (200 mg, 0.79 mmol) and 2-methoxy-6-(tributylstannyl)pyridine afforded ethyl 4-ethyl-2-(6-methoxypyridin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (255 mg, 99%) as a yellow solid. LC-MS m/z: 327.1 $[M+H]^+$. Purity (214nm): > 89%; t_R = 1.89 min.

[00554] Following general procedure B, ethyl 4-ethyl-2-(6-methoxypyridin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (245 mg, 0.75 mmol) afforded 4-ethyl-2-(6-methoxypyridin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (200 mg, 89%) as a yellow solid. LC-MS m/z: 299.1 $[M+H]^+$. LC-MS Purity (214 nm): > 88%; t_R = 1.67 min.

[00555] Following general procedure A, 4-ethyl-2-(6-methoxypyridin-2-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (35 mg, 0.12 mmol) and l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (25.4 mg, 51%) as a yellow solid. ^{1}H NMR (400 MHz, *OMSO-d_6)* δ 8.68 (s, 1H), 8.65 (d, J = 9.6 Hz, 1H), 8.03 (dd, J = 7.2 Hz, 0.8 Hz, 1H), 7.98 (t, J = 7.6 Hz, 1H), 7.85 (s, 1H), 7.05 (t, J = 8.0 Hz, 1H), 4.40-4.29 (m, 1H), 4.04 (s, 3H), 3.20 (q, J = 7.6 Hz, 2H), 1.43 (t, J = 7.6 Hz, 3H), 1.40-1.34 (m, 1H), 0.73-0.68 (m, 1H), 0.62-0.54 (m, 2H), 0.39-0.33 (m, 1H). LC-MS m/z: 420.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.81 min.

(.s')-2-(3-Cvanophenyl)-A/-(l-cvclopropylethyl)-4-ethylimidazo[l,5-alpyrimidine-8-carboxamide

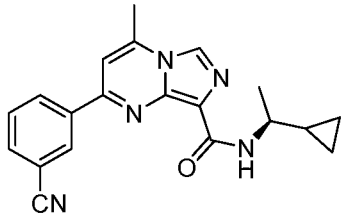


[00556] A mixture of ethyl 2-chloro-4-ethylirnidazo[l ,5-a]pyrimidine-8-carboxylate (1.1 g 4.89 mmol) and Bu_6Sn_20 (5.82 g, 9.78mmol) in 10 mL of toluene was stirred at 110 °C for 2 days, cooled to RT, and diluted with water. The mixture was basified with 5N NaOH solution to pH~8, and washed with EA (15 mL x 2). The aqueous phase was acified with 2N HC1 to pH~4, and extracted with EA (40 mL x 4). The organic phases were washed with brine (100 mL), dried over anhydrous Na2SC>4, and filtered. The filtrate was concentrated *in vacuo*, and the residue was further purified by silica chromatography (EA/MeOH = 95/5) to afford 2-chloro-4-ethylimidazo[l ,5-a]pyrirnidine-8-carboxylic acid (352 mg, 22%) as a yellow solid. LC-MS m/z: 226. 1 $[M+H]^+$.

[00557] Following general procedure A, 2-chloro-4-ethylimidazo[l ,5-a]pyrirnidine-8-carboxylic acid (98 mg, 0.43 mmol) and (*S*)-1-cyclopropylethanamine afforded (5)-2-chloro -*N*-(l-cyclopropylethyl)-4-ethylinddazo[l,5-a]pyrinddine-8-carboxamide as a yellow solid (87 mg, 67%). LC-MS m/z: 293. 1 $[M+H]^+$.

[00558] Following general procedure D, (5)-2-chloro -*N*-(l-cyclopropylethyl)-4-ethylinddazo[l ,5-a]pyrimidine-8-carboxamide (40 mg, 0.14 mmol) and 3-cyanophenylboronic acid afforded the title compoound (1.4 mg, 3%) as a yellow solid. ^1H NMR (500 MHz, MeOD-d_4) δ 8.7*l* (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 8.51 (s, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.79 (t, J = 8.0 Hz, 1H), 7.52 (s, 1H), 3.73-3.68 (m, 1H), 3.23 (q, J = 7.5 Hz, 2H), 1.57 (t, J = 7.5 Hz, 3H), 1.42 (d, J = 7.0 Hz, 3H), 1.20-1.12 (m, 1H), 0.67-0.60 (m, 2H), 0.51-0.47 (m, 1H), 0.43-0.38 (m, 1H). LC-MS m/z: 360. 1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.53 min.

(.S^-2-(3-Cvanophenyl)-A/-(l-cvclopropylethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide

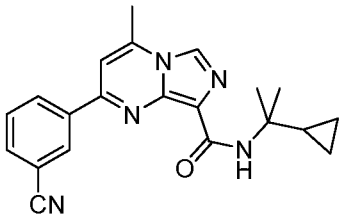


[00559] Following general procedure **D,** a mixture of ethyl 2-chloro-4-methylimidazo[l ,5-a]pyrimidine-8-carboxylate (500 mg, 2.09 mmol) and 3-cyanophenylboronic acid afforded ethyl 2-(3-cyanophenyl)-4-methylimidazo[l ,5-a]pyrimidine-8-carboxylate (450 mg, 70 %) as a brown solid. LC-MS m/z: 307. 1$[M+H]^+$. Purity (254 nm): > 72%; t_R = 1.57 min.

[00560] To a solution of ethyl 2-(3-cyanophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (450 mg, 1.47 mmol) in 10 mL of MeOH/H_2O was added IN LiOH (4.4 mL, 4.41 mmol). The reaction mixture was stirred at RT overnight, and concentrated *in vacuo*. The residue was acidified with aqueous HC1 (2N) to pH = 5. The mixture was extracted with EtOAc (50 mL x 3). The combined organic extracts were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford 2-(3-cyanophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (100 mg, 27%) as a yellow solid. LC-MS m/z: 279.1 $[M+H]^+$. Purity (254 nm): > 78%; t_R = 0.83 min.

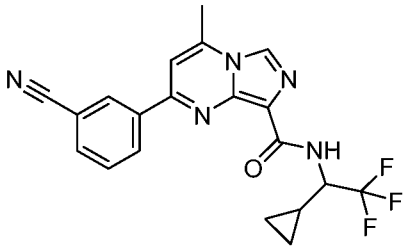
[00561] Following general procedure A, 2-(3-cyanophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 0.11 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound (11 mg, 29 %) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-c¾) δ 8.68 (s, 1H), 8.54 (d, J = 8.0 Hz, 1H), 8.44 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.78 (t, J = 8.0 Hz, 1H), 7.57 (s, 1H), 3.72-3.68 (m, 1H), 2.86 (s, 3H), 1.40 (d, J = 6.4 Hz, 3H), 1.15-1.11 (m, 1H), 0.65-0.58 (m, 2H), 0.50-0.42 (m, 1H), 0.41-0.36 (m, 1H). LC-MS m/z: 346.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.11 min.

2-(3-Cvanophenyl)-A/-(2-cvclopropylpropan-2-yl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



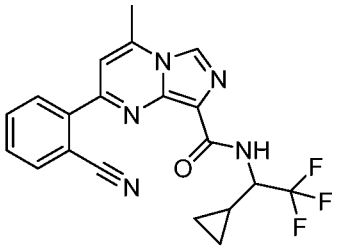
[00562] Following general procedure A, 2-(3-cyanophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 0.11 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (8 mg, 21 %) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.53 (d, J = 8.4 Hz, 2H), 8.51 (s, 1H), 8.08 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.81 (t, J = 8.0 Hz, 1H), 7.72 (s, 1H), 2.78 (s, 3H), 1.44-1.37 (m, 1H), 1.37 (s, 6H), 0.46 (d, J = 6.8 Hz, 4H). LC-MS m/z: 360.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.52 min.

2-(3-Cvanophenyl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-« 1pyrimidine-8-carboxamide



[00563] Following general procedure A, 2-(3-cyanophenyl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (30 mg, 0.11 mmol) and 1-cyclopropy 1-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (10 mg, 23%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.62 (d, ***J*** = 10.0 Hz, 1H), 8.60 (s, 1H), 8.54 (d, ***J*** = 8.0 Hz, 1H), 8.06 (**d**, ***J*** = 7.5 Hz, 1H), 7.83 (**d**, ***J*** = 8.0 Hz, 1H), 7.79 (s, 1H), 4.40-4.31 (m, 1H), 2.82 (s, 3H), 1.40-1.33 (m, 1H), 0.74-0.66 (m, 1H), 0.60-0.53 (m, 2H), 0.39-0.32 (m, 1H). LC-MS m/z: 400.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 7.66 min.

2-(2-Cvanophenyl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-*a*\pyrimidine-8-carboxamide



[00564] Following general procedure D, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (240 mg, 1.0 mmol) and 2-cyanophenylboronic acid afforded ethyl 2-(2-cyanophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (40 mg, 13%) as ayellow solid and ethyl 2-(2-carbamoylphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (170 mg, 52%) as a brown solid.

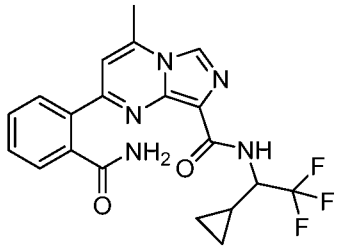
[00565] Ethyl 2-(2-cyanophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate: LC-MS m/z: 306.1 $[M+H]^+$. Purity (214 nm): > 60%; t_R = 1.64 min.

[00566] Ethyl 2-(2-carbamoylphenyl)-4-methylimidazo[l ,5-a]pyrimidine-8-carboxylate: LC-MS m/z: 324.1 $[M+H]^+$. Purity (214nm): > 93%; t_R = 1.41 min.

[00567] **A** suspension of ethyl 2-(2-cyanophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (20 mg, 0.065 mmol) and lMLiOH (0.7 mL, 0.65 mmol) aqueous solution in MeOH (2 mL) was stirred at RT for 4 days, and neutralized to pH 6-7 with dilute HCl at 0 °C. The slurry was filtered, washed with minimum water and diethyl ether, and dried *in vacuo* to afford 2-(2-cyanophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (20 mg, 64%) as a brown solid. LC-MS m/z: 278.0 $[M+H]^+$. LC-MS Purity (254 nm): > 78%; t_R = 1.47 min.

[00568] Following general procedure **A,** 2-(2-cyanophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (20 mg, 0.09 mmol) and l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (9.4 mg, 32%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.47 (d, *J* = 9.6 Hz, 1H), 8.11 (d, *J* = 7.6 Hz, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 7.94 (t, *J* = 8.0 Hz, 1H), 7.78 (t, *J* = 8.0 Hz, 1H), 7.50 (s, 1H), 4.30-4.23 (m, 1H), 2.83 (s, 3H), 1.39-1.34 (m, 1H), 0.71-0.67 (m, 1H), 0.61-0.57 (m, 1H), 0.50-0.46 (m, 1H), 0.33-0.29 (m, 1H). LC-MS m/z: 400.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.53 min.

2-(2-Carbamoylphenyl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-« ıpyrimidine-8-carboxamide

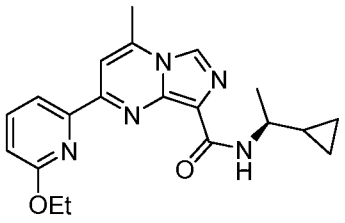


[00569] Following general procedure B, ethyl 2-(2-carbamoylphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (170 mg, 0.52 mmol) afforded 2-(2-carbamoylphenyl)-4-methylinddazo[l,5-a]pyrimidine-8-carboxylic acid (80 mg, 52%) as a yellow solid. LC-MS m/z: 296.0 $[M+H]^+$. Purity (214 nm): > 88%; t_R = 1.29 min.

[00570] Following general procedure **A,** 2-(2-carbamoylphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (27 mg, 0.09 mmol) and l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (28 mg, 73%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.46 (d, *J* = 9.6 Hz, 1H), 8.00 (s, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.65-7.59 (m, 3H), 7.35 (s, 1H), 7.11 (s, 1H), 4.30-4.22 (m, 1H), 2.77 (s, 3H),

1.41 - 1.34 (m, 1H), 0.66-0.62 (m, 1H), 0.57-0.54 (m, 2H), 0.3 1-0.26 (m, 1H). LC-MS m/z: 4 18.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 6.41 min.

CSViV-(l-Cvclopropylethyl)-2-(6-ethoxypyridin-2-^ -4-methylimidazo[1,5-*a*]pyrimidine-8-carboxamide

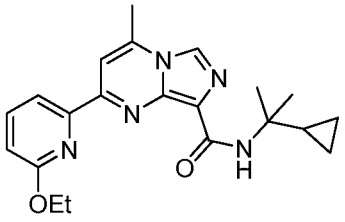


[00571] Following general procedure **E,** ethyl 2-chloro-4-methylimidazo[l ,5-a]pyrimidine-8-carboxylate (98 1 mg, 4.10 mmol) and 2-chloro-6-ethoxypyridine afforded ethyl 2-(6-ethoxypyridin-2-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (75 mg, 6%) as a bright yellow solid. LC-MS m/z: 327.2 $[M+H]^+$. t_R = 1.43 min.

[00572] Following general procedure B, ethyl 2-(6-ethoxypyri din-2-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (75 mg, 0.23 mmol) afforded 2-(6-ethoxypyridin-2-yl)-4-methylirnidazo[l,5-a]pyrimidine-8-carboxylic acid (66 mg, 96%) as a bright yellow solid. LC-MS m/z: 299. 1 $[M+H]^+$. t_R = 0.98 min.

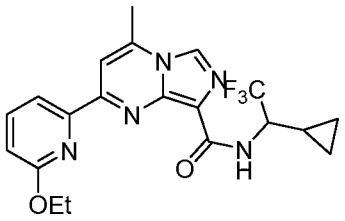
[00573] Following general procedure A, 2-(6-ethoxypyridin-2-yl)-4-methylimidazo[l ,5-a]pyrimidine-8-carboxylic acid (40 mg, 0.13 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound (12. 8 mg, 26%) as a yellow solid. ¾ **NMR** (500 MHz, *OMSO-d6)* δ 8.53 (s, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.96 (t, *J* = 8.0 Hz, 1H), 7.80 (s, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 4.5 1 (q, *J* = 7.0 Hz, 2H), 3.63-3.55 (m, 1H), 2.82 (s, 3H), 1.41 (t, *J* = 7.0 Hz, 3H), 1.30 (d, *J* = 6.5 Hz, 3H), 1.17-1 .08 (m, 1H), 0.54-0.41 (m, 2H), 0.40-0.32 (m, 1H), 0.3 1-0.27 (m, 1H). LC-MS m/z: 366. 1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.41 min.

A/-(2-Cvclopropylpropan-2-yl)-2-(6-ethoxypyridin-2-yl)-4-methylimidazo[l,5-*a*\pyrimidine-8-carboxamide



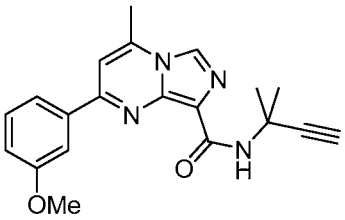
[00574] Following general procedure A, 2-(6-ethoxypyridin-2-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (49 mg, 0.16 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (14.4 mg, 23%) as a yellow solid. ¾NMR (500 MHz, *OMSO-d_6)* δ 8.52 (s, 1H), 8.09 (s, 1H), 8.02 (d, J = 7.5 Hz, 1H), 7.95 (t, J = 8.0 Hz, 1H), 7.78 (s, 1H), 6.99 (d, J = 8.0 Hz, 1H), 4.50 (q, J = 7.0 Hz, 2H), 2.82 (s, 3H), 1.41 (t, J = 7.0 Hz, 3H), 1.39 (s, 6H), 1.47-1.37 (m, 1H), 0.49-0.46 (m, 4H). LC-MS m/z: 380.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.93 min.

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(6-ethoxypyridin-2-yl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00575] Following general procedure A, 2-(6-ethoxypyridin-2-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (34 mg, 0.11 mmol) and l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (10.7 mg, 22%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, J = 9.2 Hz, 1H), 8.60 (s, 1H), 7.79 (d, J = 7.2 Hz, 1H), 7.96 (t, J = 7.2 Hz, 1H), 7.84 (s, 1H), 7.00 (d, J = 7.2 Hz, 1H), 4.50 (q, J = 6.8 Hz, 2H), 4.37-4.28 (m, 1H), 2.83 (s, 3H), 1.40 (t, J = 6.8 Hz, 3H), 1.38-1.32 (m, 1H), 0.72-0.61 (m, 1H), 0.60-0.52 (m, 2H), 0.39-0.32 (m, 1H). LC-MS m/z: 420.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.86 min.

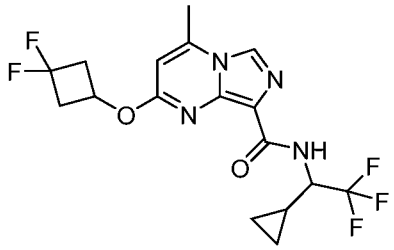
2-(3-Methoxyphenyl)-4-methyl -A^-(2-methylbut-3-vn-2-yl)imidazo[l,5-alpyrimidine-8-carboxamide



[00576] Following general procedure A, 2-(3-methoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (47 mg, 0.17 mmol) and 2-methylbut-3-yn-2-amine afforded

the title compound (3.9 mg, 7%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-i¾) δ 8.50 (s, 1H), 8.44 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.78 (s, 1H), 7.67 (s, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.17 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 3.89 (s, 3H), 3.29 (s, 1H), 2.80 (s, 3H), 1.75 (s, 6H). LC-MS m/z: 349.1 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 7.54 min.

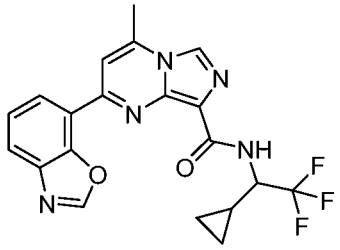
A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(3,3-difluorocvclobutoxy)-4-methylimidazo[l,5-«1pyrimidine-8-carboxamide



[00577] Following general procedure A, 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (704 mg, 2.94 mmol) and l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxamide (360 mg, 37 %) as a yellow solid. LC-MS m/z: 333.1 $[M+H]^+$, t_R = 1.35 min.

[00578] A mixture of 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxamide (10 mg, 0.03 mmol), 3,3-difluorocyclobutanol (25 mg, 0.23 mmol), potassium hydroxide (4.2 mg, 0.075 mmol), and 18-crown-6 (2 mg, 0.006 mmol) in THF (1 mL) was stirred at 100 °C for 16 h, cooled to RT, diluted with ice water (8 mL), and extracted with EA (10 mL x 3). The organic layers were washed brine (50 mL), dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated *in vacuo,* and the residue was purified by prep-HPLC (10 mM NH_4HC0_3/MeCN) to afford the title compound (2.4 mg, 20%) as a pink solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.26 (s, 1H), 6.53 (s, 1H), 5.35-5.30 (m, 1H), 4.37-4.31 (m, 1H), 3.26-3.18 (m, 2H), 2.91-2.82 (m, 2H), 2.73 (s, 3H), 1.31-1.23 (m, 1H), 0.83-0.77 (m, 1H), 0.68-0.58 (m, 2H), 0.50-0.45 (m, 1H), 0.33-0.29 (m, 1H). LC-MS m/z: 405.1 $[M+H]^+$. HPLC: Purity (214 nm): > 98%; t_R = 7.86 min.

2-(Benzo[dloxazol-7-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide

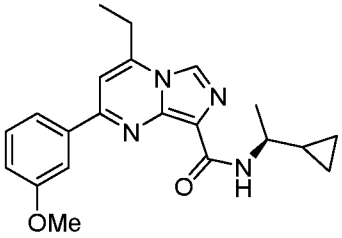


[00579] A mixture of 2-amino-6-bromophenol (500 mg, 2.67 mmol), p-TsOH (50 mg, 0.29 mmol) and trimethoxymethane (4 mL) was stirred at 80 °C under N_2 for 1 h, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE/EA = 9:1) to afford 7-bromobenzo[cf]oxazole (48 1 mg, 92%) as a white solid.

[00580] Following general procedure D, 7-bromobenzo[cf]oxazole (48 1 mg, 4.97 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(l ,3,2-dioxaborolane) afforded 7-(4,4,5,5-tetramethyl-l ,3,2-dioxaborolan-2-yl)benzo[cf]oxazole (0.9 g, 75%) as a light yellow solid. LC-MS m/z: 246.2 $[M+H]^+$.

[00581] Following general procedure D, 2-chloro -*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylinridazo[l,5-a]pyrinridine-8-carboxamide (49.8 mg, 0.15mmol) and 7-(4,4,5,5-tetramethyl-l ,3,2-dioxaborolan-2-yl)benzo[cf]oxazole afforded the title compound (1.3 mg, 1.5% yield) as a white solid. ^{1}H NMR (500 MHz, $CDC1_3$) δ 8.45 (d, J = 10.0 Hz, 1H), 8.20 (s, 1H), 8.16 (d, J = 7.5 Hz, 1H), 8.08 (s, 1H), 7.92 (d, J = 7.5 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.48 (s, 1H), 4.60-4.52 (m, 1H), 2.78 (s, 3H), 1.18-1.11 (m, 1H), 0.68-0.60 (m, 1H), 0.52-0.40 (m, 3H). LC-MS m/z: 416.0 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 7.30 min.

(,S)-A/-(l-Cvclopropylethyl)-4-ethyl-2-(3-methoxyphenyl)imidazo[l,5-alpyrimidine-8-carboxamide

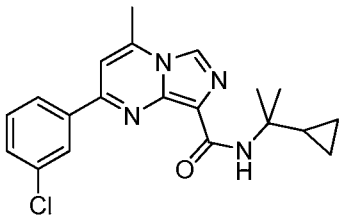


[00582] Following general procedure D, ethyl 2-chloro-4-ethylirnidazo[l,5-a]pyrirnidine-8-carboxylate (200 mg, 0.79 mmol) and 3-methoxyphenylboronic acid afforded ethyl 4-ethyl-2-(3-methoxyphenyl)imidazo[l,5-a]pyrimidine-8-carboxylate (86 mg, 33%) as a white solid. LC-MS m/z: 326.1 $[M+H]^+$. Purity (214 nm): > 96%; t_R = 1.37 min.

[00583] Following general procedure B, ethyl 4-ethyl-2-(3-methoxyphenyl)imidazo[l,5-a]pyrimidine-8-carboxylate (76 mg, 0.23 mmol) afforded 4-ethyl-2-(3-methoxyphenyl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (40 mg, 51%) as a yellow solid. LC-MS m/z: 298.1 $[M+H]^+$. Purity (214 nm): > 93%; t_R = 0.94 min.

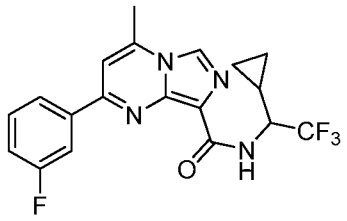
[00584] Following general procedure **A,** 4-ethyl-2-(3-methoxyphenyl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 0.10 mmol) and (<S)-l-cyclopropylethanamine afforded the title compound (20.5 mg, 55%) as a yellow solid. ¾NMR (500 MHz, MeOD-c¾) δ 8.54 (d, *J* = 7.5 Hz, 1H), 8.44 (s, 1H), 7.80 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.40 (s, 1H), 7.15 (dd, *J* = 8.0 Hz, 2.5 Hz, 1H), 3.93 (s, 3H), 3.90-3.72 (m, 1H), 3.19 (q, *J* = 7.0 Hz, 2H), 1.55 (t, *J* = 7.0 Hz, 3H), 1.41 (d, *J* = 6.5 Hz, 3H), 1.12-1.06 (m, 1H), 0.66-0.51 (m, 2H), 0.50-0.46 (m, 1H), 0.40-0.36 (m, 1H). LC-MS m/z: 365.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.08 min.

2-(3-Chlorophenyl)-A/-(2-cvclopropylpropan-2-yl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



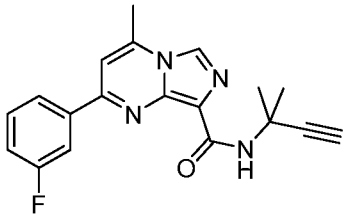
[00585] Following general procedure **A,** 2-(3-chlorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 0.10 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (7 mg, 18%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.37 (s, 1H), 8.28 (s, 1H), 8.12 (d, *J* = 7.0 Hz, 1H), 7.57-7.52 (m, 2H), 7.47 (s, 1H), 2.84 (s, 3H), 1.49 (s, 6H), 1.49-1.40 (m, 1H), 0.62-0.59 (m, 2H), 0.58-0.55 (m, 2H). LC-MS m/z: 369.2$[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.77 min.

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(3-fluorophenyl)-4-methylimidazo[l,5-« 1pyrimidine-8-carboxamide



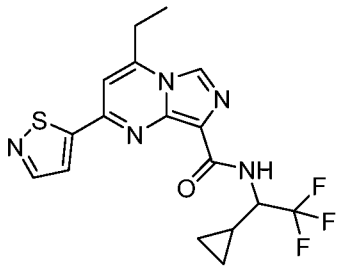
[00586] Following general procedure A, 2-(3-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (40 mg, 0.15 mmol) and l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (12.5 mg, 21%) as ayellow solid. ^{1}H NMR (500 MHz, MeOD-c¾): δ 8.48 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 8.03 (dt, J = 10.5 Hz, 2.0 Hz, 1H), 7.64-7.60 (m, 1H), 7.57 (s, 1H), 7.35 (td, J = 8.5 Hz, 2.5 Hz 1H), 4.48 (p, J = 8.0 Hz, 1H), 2.88 (s, 3H), 1.34-1.30 (m, 1H), 0.81-0.77 (m, 1H), 0.67-0.63 (m, 1H), 0.62-0.58 (m, 1H), 0.57-0.52 (m, 1H). LC-MS m/z: 393.1 $[M+H]^+$. HPLC Purity (214 nm): 91%; t_R = 8.19 min.

2-(3-Fluorophenyl)-4-methyl-A/-(2-methylbut-3-vn-2-yl)imidazo[l,5-alpyrimidine-8-carboxamide



[00587] Following general procedure A, 2-(3-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (40 mg, 0.15 mmol) and but-3-yn-2-amine afforded the title compound (14.4 mg, 29%) as ayellow solid. ^{1}H NMR (500 MHz, *MeOO-d4):* δ 8.40 (s, 1H), 8.08 (d, J = 7.5 Hz, 1H), 8.06 (dt, J = 10.0 Hz, 2.0 Hz, 1H), 7.60 (ddd, J = 14.5 Hz, 7.0 Hz, 2.5 Hz, 1H), 7.53 (s, 1H), 7.33 (td, J = 8.0 Hz, 2.0 Hz, 1H), 2.86 (s, 3H), 2.85 (s, 1H), 1.86 (s, 6H).

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-4-ethyl-2-(isothiazol-5-yl)imidazo[l,5-«1pyrimidine-8-carboxamide

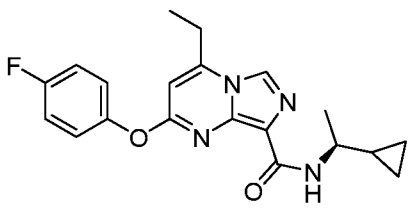


[00588] Following general procedure E, ethyl 2-chloro-4-ethylimidazo[l,5-a]pyrimidine-8-carboxylate (200 mg, 0.79 mmol) and 5-bromoisothiazole afforded ethyl 4-ethyl-2-(isothiazol-5-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (160 mg, 68%). LC-MS m/z: 303.0 $[M+H]^+$. t_R = 1.56 min.

[00589] Following general procedure B, ethyl 4-ethyl-2-(isothiazol-5-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (160 mg, 0.53 mmol) at 30 °C afforded 4-ethyl-2-(isothiazol-5-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid sodium salt (100 mg, 63%) as ayellow solid. LC-MS m/z: 275.0 $[M+H]^+$. t_R = 1.45 min.

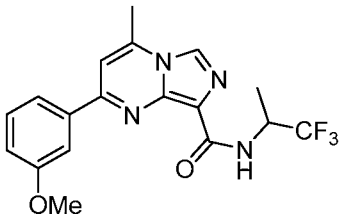
[00590] Following general procedure A, 4-ethyl-2-(isothiazol-5-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (25 mg, 0.09 mmol) and l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (2.6 mg, 15%) as ayellow solid. ^{1}H NMR (500 MHz, *MeOO-d4)* δ 8.68 (d, *J* = 2.5 Hz, 1H), 8.58 (s, 1H), 8.16 (d, *J* = 2.0 Hz, 1H), 7.47 (s, 1H), 4.47-4.42 (m, 1H), 3.24 (q, *J* = 7.0 Hz, 2H), 1.57 (t, *J* = 7.0 Hz, 3H), 1.40-1.34 (m, 1H), 0.82-0.79 (m, 1H), 0.71-0.66 (m, 1H), 0.64-0.51 (m, 2H). LC-MS m/z: 396.0 $[M+H]^+$. HPLC: Purity (214 nm): 94%; t_R = 9.61 min.

(.s')-A/-(l-Cvclopropylethyl)-4-ethyl -2-(4-fluorophenoxy)imidazo[l,5-alpyrimidine-8-carboxamide



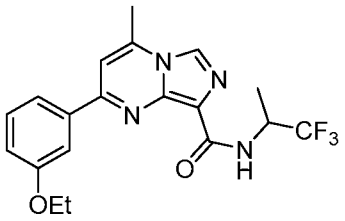
[00591] Following general procedure H, (5)-2-chloro -*N* -(l-cyclopropylethyl)-4-ethylimidazo[l ,5-a]pyrirnidine-8-carboxamide (30 mg, 0.10 mmol) and 4-fluorophenol afforded the title compound (7 mg, 19%) as a yellow solid. ^{1}H NMR (500 MHz, $CDC1_3$) δ 7.97 (s, 1H), 7.22-7.20 (m, 2H), 7.17-7.11 (m, 3H), 6.46 (s, 1H), 3.68-3.60 (m, 1H), 3.02 (q, J = 7.5 Hz, 2H), 1.51 (t, J = 7.5 Hz, 3H), 1.04 (d, J = 7.0 Hz, 3H), 0.54-0.49 (m, 1H), 0.42-0.37 (m, 1H), 0.24-0.19 (m, 1H), 0.18-0.10 (m, 1H). LC-MS m/z: 369.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.98 min.

2-(3-Methoxyphenyl)-4-methyl-iV-(144-triflu^ ropropan-2-yl)imidazo[1,5-*a*]pyrimidine-8-carboxamide



[00592] Following general procedure A, 2-(3-methoxyphenyl)-4-methylimidazo[l ,5-a]pyrimidine-8-carboxylic acid (51 mg, 0.18 mmol) and l,l,l-trifluoropropan-2-amine hydrochloride afforded the title compound (12.3 mg, 18%) as a light yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) 8.57 (d, J = 9.5 Hz, 1H), 8.55 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.77 (t, J = 2.0 Hz, 1H), 7.69 (s, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.17 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 5.01-4.94 (m, 1H), 3.88 (s, 3H), 2.81 (s, 3H), 1.44 (d, J = 7.0 Hz, 3H). LC-MS m/z: 379.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.81 min.

2-(3-Ethoxyphenyl)-4-methyl-A/-(144-trifluoropropan-2-yl)imidazo[l,5-alpyrimidine-8-carboxamide



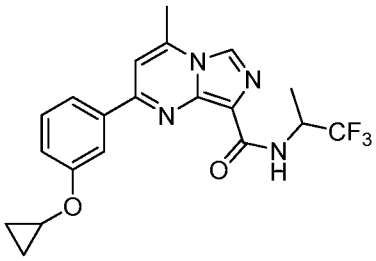
[00593] Following general procedure **D,** ethyl 2-chloro-4-methylimidazo[l ,5-a]pyrimidine-8-carboxylate (200 mg, 0.83 mmol) and 2-(3-ethoxyphenyl)-4,4,5,5-tetramethyl-l ,3,2-dioxaborolane afforded ethyl 2-(3-ethoxyphenyl)-4-methylimidazo[l ,5-a]pyrimidine-8-

carboxylate (120 mg, 35%) as a white solid. LC-MS m/z: 326.1 [M+Hf . LC-MS Purity (214 nm): > 96%; t_R = 1.39 min.

[00594] Following general procedure B, ethyl 2-(3-ethoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (105 mg, 0.31 mmol) afforded 2-(3-ethoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (60 mg, 55%) as a yellow solid. LC-MS m/z: 298.1 $[M+H]^+$. LC-MS Purity (214 nm): > 93%; t_R = 0.94 min.

[00595] Following general procedure A, 2-(3-ethoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.17 mmol) and l,l,l-trifluoropropan-2-amine hydrochloride afforded the title compound (43 mg, 65%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾): δ 8.42 (s, 1H), 7.75 (s, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.50 (s, *J* = 2.0 Hz, 1H), 7.46 (dt, *J* = 7.5 Hz, 1H), 7.14 (dd, *J* = 7.5 Hz, 2.0 Hz 1H), 5.01 (p, *J* = 7.5 Hz 1H), 4.168 (qd, *J* = 7.5 Hz, 2.0 Hz, 2H), 2.85 (s, 3H), 1.53 (d, *J* = 7.0 Hz, 3H), 1.46 (t, *J* = 7.0 Hz, 3H). LC-MS m/z: 393.2 $[M+H]^+$. HPLC Purity (214 nm): 93%; t_R = 8.26 min.

2-(3-Cvclopropoxyphenyl)-4-methyl -A/-(l,l,l-trifluoropropan-2-yl)imidazo[l,5-alpyrimidine-8-carboxamide



[00596] A mixture of 3-bromophenol (9.5 g, 55.2 mmol), bromocyclopropane (13.3 g, 110.5 mmol), and Cs_2C0_3 (36 g, 110.5 mmol) in DME (80 mL) was stirred at 140 °C for 12 h, cooled, diluted with water (50 mL) and extracted with EtOAc (50 mL χ 3). The organic layers were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo.* The residue was purified by silica gel column (PE) to afford give l-bromo-3-cyclopropoxybenzene (1.86 g, 16%) as a colorless oil. LC-MS t_R = 2.0 min.

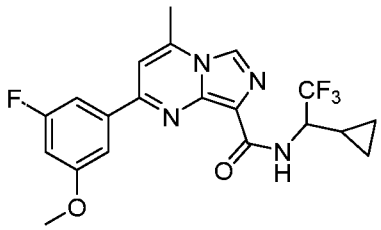
[00597] Following general procedure D, l-bromo-3-cyclopropoxybenzene (1 g, 4.7 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(l,3,2-dioxaborolane) afforded crude 2-(3-cyclopropoxyphenyl)-4,4,5,5-tetramethyl-l,3,2-dioxaborolane (1.8 g, 100%) as a black solid which was directly in the next step. LC-MS m/z: 261.2 $[M+H]^+$; t_R = 2.20 min.

[00598] Following general procedure D, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (200 mg, 0.84 mmol) and 2-(3-cyclopropoxyphenyl)-4,4,5,5-tetramethyl-l,3,2-dioxaborolane afforded ethyl 2-(3-cyclopropoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (150 mg, 51%) as ayellow solid. LC-MS m/z: 338.7 $[M+H]^+$; t_R = 1.75 min.

[00599] Following general procedure B, ethyl 2-(3-cyclopropoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (150 mg, 0.45 mmol) afforded 2-(3-cyclopropoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (200 mg, 100%) as a gray solid. LC-MS m/z: 310.7 $[M+H]^+$; t_R = 1.34 min.

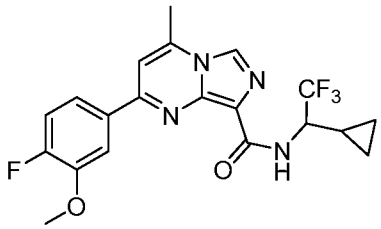
[00600] Following general procedure A, 2-(3-cyclopropoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (100 mg, 0.32 mmol) and l,l,l-trifluoropropan-2-amine hydrochloride afforded the title compound (8.1 mg, 6% yield) as ayellow solid. 'HNMR (500 MHz, DMSO-i¾) δ 8.55-8.53 (m, 2H), 7.85 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.66 (s, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.29 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 5.00-4.90 (m, 1H), 4.00-3.94 (m, 1H), 2.80 (s, 3H), 1.42 (d, *J* = 7.0 Hz, 3H), 0.86-0.81 (m, 2H), 0.74-0.68 (m, 2H). LC-MS m/z: 405.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.37 min.

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(3-fluoro-5-methoxyphenyl)-4-methylimidazo [1,5-al pyrimidine-8-carboxamide



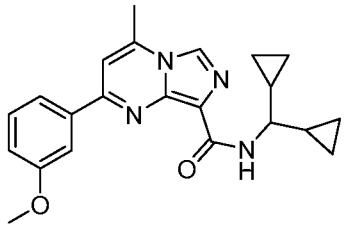
[00601] Following general procedure D, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (50 mg, 0.15 mmol) and 3-fluoro-5-methoxyphenylboronic acid afforded the title compound (5.5 mg, 8 %) as ayellow solid. ^{1}H NMR (400 MHz, MeOD-c¾) *δ* 8.47 (s, 1H), 7.63 (s, 1H), 7.56 (d, *J* = 10.4 Hz, 1H), 7.54 (s, 1H), 6.94 (dt, *J* = 10.4 Hz, 2.0 Hz, 1H), 4.52-4.43 (m, 1H), 3.93 (s, 3H), 2.86 (s, 3H), 1.34-1.25 (m, 1H), 0.81-0.74 (m, 1H), 0.68-0.50 (m, 3H). LC-MS m/z: 423.0 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 8.35 min.

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(4-fluoro-3-methoxyphenyl)-4-methylimidazo [1,5-al pyrimidine-8-carboxamide



[00602] Following general procedure D, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (50 mg, 0.15 mmol) and 4-fluoro-3-methoxyphenylboronic acid afforded the title compound (5.2 mg, 8%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-c¾) δ 8.45 (s, 1H), 7.98 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.80-7.77 (m, 1H), 7.55 (s, 1H), 7.30 (dd, *J* = 10.8 Hz, 8.4 Hz, 1H), 4.52-4.44 (m, 1H), 4.02 (s, 3H), 2.85 (s, 3H), 1.30-1.27 (m, 1H), 0.78-0.76 (m, 1H), 0.65-0.39 (m, 3H). LC-MS m/z: 423.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 9.00 min.

A/-(Dicvclopropylmethyl)-2-(3-methoxyphenyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide

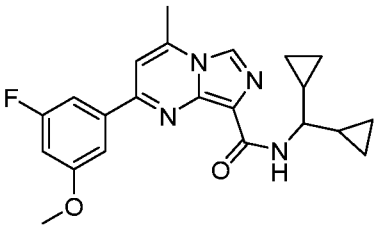


[00603] Following general procedure A, 2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (633 mg, 3 mmol) and dicyclopropylmethanamine afforded 2-chloro-*N*-(dicyclopropylmethyl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxamide (750 mg, 82 %) as a brown solid. LC-MS m/z: 305.1 $[M+H]^+$. Purity (254 nm): > 90%; t_R = 1.341 min.

[00604] Following general procedure D, 2-chloro-*N*-(dicyclopropylmethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (50 mg,0.16 mmol) and 3-methoxyphenylboronic acid afforded the title compound (9.1 mg, 15%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.54 (d, *J* = 9.0 Hz, 1H), 8.39 (s, 1H), 7.80 (s, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.494 (t, *J* = 8.0 Hz, 1H), 7.488 (s, 1H), 7.16 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 3.93 (s,

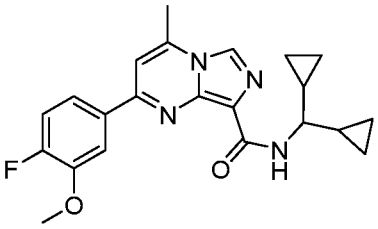
3H), 3.56-3.5 1 (m, 1H), 2.85 (s, 3H), 1.20-1.12 (m, 2H), 0.64-0.59 (m, 2H), 0.54-0.48 (m, 4H), 0.47-0.42 (m, 2H). LC-MS m/z: 377. 1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.05 min.

A/-(Dicvclopropylmethyl)-2-(3-fluoro-5-methoxyphenyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



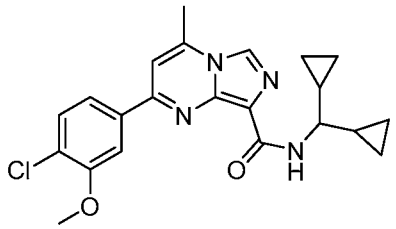
[00605] Following general procedure D, 2-chloro-*N*-(dicyclopropylmethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (50 mg, 0.16 mmol) and 3-fluoro-5-methoxyphenylboronic acid afforded the tilte compound (10.5 mg, 16%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-c¾) δ 8.46 (d, *J* = 8.0 Hz, 1H), 8.42 (s, 1H), 7.65 (s, 1H), 7.59 (d, *J* = 9.6 Hz, 1H), 7.50 (s, 1H), 6.94 (dt, *J* = 10.8 Hz, 2.0 Hz, 1H), 3.93 (s, 3H), 3.50(t, *J* = 8.0 Hz, 1H), 2.85 (s, 3H), 1.16-1.12 (m, 2H), 0.63-0.56 (m, 2H), 0.54-0.41 (m, 6H). LC-MS m/z: 395. 1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 9.17 min.

A/-(Dicvclopropylmethyl)-2-(4-fluoro-3-methoxyphenyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



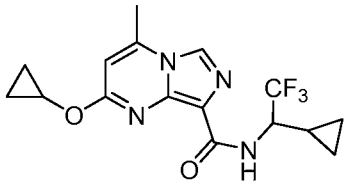
[00606] Following general procedure D, 2-chloro-*N*-(dicyclopropylmethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (50 mg, 0.16 mmol) and 4-fluoro-3-methoxyphenylboronic acid afforded the title compound (15.4 mg, 24%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-c¾) δ 8.41 (d, *J* = 10.0 Hz, 1H), 8.39 (s, 1H), 7.99 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.82-7.78 (m, 1H), 7.50 (s, 1H), 7.30 (dd, *J* = 10.4 Hz, 8.0 Hz, 1H), 4.03 (s, 3H), 3.47 (q, *J* = 8.4 Hz, 1H), 2.84 (s, 3H), 1.18-1.13 (m, 2H), 0.62-0.57 (m, 2H), 0.51-0.41 (m, 6H). LC-MS m/z: 395.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.92 min.

A/-(Dicvclopropylmethyl)-2-(4-chloro-3-methoxyphenyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



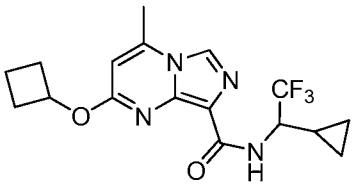
[00607] Following general procedure D, 2-chloro-*N*-(dicyclopropylmethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (50 mg, 0.16 mmol) and 4-chloro-3-methoxyphenylboronic acid afforded the title compound (10.9 mg, 16%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-c¾) δ 8.41 (s, 1H), 8.40 (d, *J* = 8.0 Hζ,IH), 7.94 (d, *J* = 1.6 Hz, 1H), 7.78 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.52 (s, 1H), 4.05 (s, 3H), 3.48 (q, *J* = 8.4 Hz, 1H), 2.85 (s, 3H), 1.18-1.13 (m, 2H), 0.62-0.57 (m, 2H), 0.51-0.39 (m, 6H). LC-MS m/z: 411.1 $[M+H]^+$. HPLC: Purity (214 nm): > 98%; t_R = 9.39 min.

2-Cvclopropoxy-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



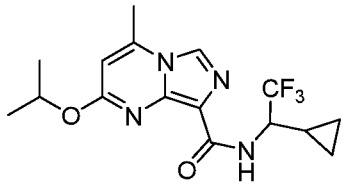
[00608] Following general procedure G, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (60 mg, 0.18 mmol) and cyclopropanol afforded the title compound (1.5 mg, 2.3%) as a pink solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.25 (s, 1H), 6.45 (d, *J* = 0.5 Hz, 1H), 4.43-4.35 (m, 2H), 2.72 (s, 3H), 1.25-1.23 (m, 1H), 0.93-0.86 (m, 4H), 0.76-0.75 (m, 1H), 0.63-0.49 (m, 3H). LC-MS m/z: 355.0 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 7.76 min.

2-Cvclobutoxy -A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



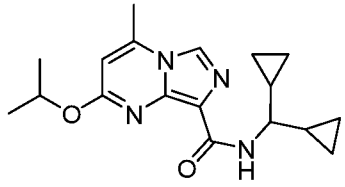
[00609] Folloing general procedure G, 2-chloro -*N* -(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (20 mg, 0.066 mmol) and cyclobutanol afforded the title compound (5.0 mg, 23%) as a white solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.23 (s, 1H), 6.46 (d, *J* = 1.0 Hz, 1H), 5.35-5.29 (m, 1H), 4.40-4.34 (m, 1H), 2.7 1 (s, 3H), 2.60-2.55 (m, 2H), 2.32-2.21 (m, 2H), 1.98-1 .92 (m, 1H), 1.82-1 .73 (m, 1H), 1.28-1 .21 (m, 1H), 0.85-0.77 (m, 1H), 0.68-0.56 (m, 2H), 0.52-0.47 (m, 1H). LC-MS m/z: 369. 1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 8.27 min.

iV-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-isopropoxy-4-m ethylimidazo[1,5-*a*]pyrimidine-8-carboxamide



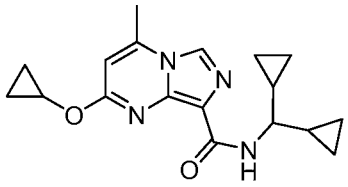
[00610] Following general procedure G, 2-chloro -*N* -(l -cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (30 mg, 0.09 mmol) and propan-2-ol afforded the title compound (9.3 mg, 29%) as a pink solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.15 (s, 1H), 6.35 (s, 1H), 5.34-5.3 1 (m, 1H), 4.32-4.28 (m, 1H), 2.63 (s, 3H), 1.40 (d, *J* = 6.0 Hz, 3H), 1.39 (d, *J* = 6.0 Hz, 3H), 1.20-1 .13 (m, 1H), 0.7 1-0.67 (m, 1H), 0.58-0.48 (m, 2H), 0.43-0.39 (m, 1H). LC-MS m/z: 357. 1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.05 min.

A/-**(Dicvclopropylmethyl)-2-isopropoxy-4-methylimidazo[l,5-alpyrimidine-8-carboxamide**



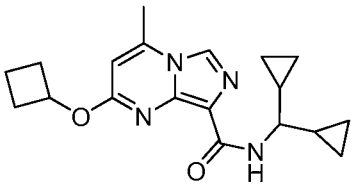
[00611] Following general procedure G, 2-chloro-*N*-(dicyclopropylmethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (50 mg, 0.16 mmol) and propan-2-ol afforded the title compound (16.6 mg, 31%) as a pink solid. ¾ NMR (500 MHz, MeOD-c¾) δ 8.19 (s, 1H), 6.40 (s, 1H), 5.47-5.41 (m, 1H), 3.47-3.42 (m, 1H), 2.70 (s, 3H), 1.48 (d, *J* = 7.0 Hz, 6H), 1.12-1.06 (m, 2H), 0.60-0.55 (m, 2H), 0.50-0.39 (m, 6H). LC-MS m/z: 329.1 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 7.92 min.

2-Cvclopropoxy-A/-(dicvclopropylmethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



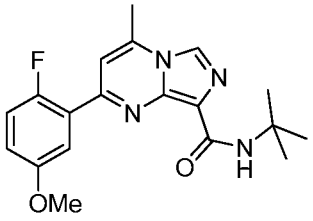
[00612] Following general procedure G, 2-chloro-*N*-(dicyclopropylmethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (50 mg, 0.16 mmol) and cyclopropanol afforded the title compound (14.3 mg, 27 %) as a pink solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.09 (s, 1H), 8.06 (d, *J* = 8.5 Hz, 2H), 6.31 (s, 1H), 4.32-4.29 (m, 1H), 3.36-3.32 (m, 1H), 2.59 (s, 3H), 1.05-0.91 (m, 2H), 0.85-0.73 (m, 4H), 0.48-0.43 (m, 2H), 0.38-0.30 (m, 4H), 0.30-0.24 (m, 2H). LC-MS m/z: 327.1 $[M+H]^+$. HPLC: Purity (254 nm): 98%; t_R = 7.59 min.

2-Cvclobutoxy-A/-(dicvclopropylmethyl)-4-methylimidazo [1,5-al pyrimidine-8-carboxamide



[00613] Following general procedure G, 2-chloro-*N*-(dicyclopropylmethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (40 mg, 0.132 mmol) and cyclobutanol afforded the title compound (7.1 mg, 16%) as a white solid. ^{1}H NMR (400 MHz, MeOD-c¾) δ 8.15 (s, 1H), 6.40 (s, 1H), 5.31 (m, *J* = 7.2 Hz, 1H), 3.42 (t, *J* = 9.0 Hz, 1H), 2.68 (s, 3H), 2.63-2.55 (m, 2H), 2.28-2.23 (m, 2H), 1.97-0.90 (m, 1H), 1.83-1.71 (m, 1H), 1.10-1.06 (m, 2H), 0.62-0.56 (m, 2H), 0.51-0.40 (m, 6H). LC-MS m/z: 341.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 8.15 min.

A/-ferf-Butyl-2-(2-fluoro-5-methoxyphenyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide

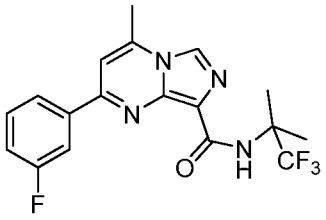


[00614] Following general procedure D, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (300 mg, 1.25 mmol) and 2-fluoro-5-methoxyphenylboronic acid afforded ethyl 2-(2-fluoro-5-methoxyphenyl)-4-methylirnidazo[l,5-a]pyrimidine-8-carboxylate (280 mg, 69.6%) as a brown solid. LC-MS m/z: 330.1 $[M+H]^+$. LC-MS Purity (254 nm): 72.3%; t_R = 1.34 min.

[00615] Following general procedure B, ethyl 2-(2-fluoro-5-methoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (280 mg, 0.85 mmol) afforded 2-(2-fluoro-5-methoxyphenyl)-4-methylirnidazo[l,5-a]pyrimidine-8-carboxylic acid (152 mg, 57%) as a brown solid. LC-MS m/z: 302.2 $[M+H]^+$. LC-MS Purity (254 nm): 92.7%; t_R = 1.59 min.

[00616] Following general procedure A, 2-(2-fluoro-5-methoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 0.10 mmol) and 2-methylpropan-2-amine afforded the title compound (27.2 mg, 76%) as a yellow solid. ^{1}H NMR (500 MHz, $CDC1_3$) δ 8.05 (s, 1H), 7.90 (s, 1H), 7.59 (dd, J = 6.0 Hz, 3.0 Hz, 1H), 7.17 (s, 1H), 7.12 (dd, J = 10.5 Hz, 9.0 Hz, 1H), 7.10 (tt, J = 9.0 Hz, 3.0 Hz, 1H), 3.87 (s, 3H), 2.74 (s, 3H), 1.55 (s, 9H). LC-MS m/z: 357.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.87 min.

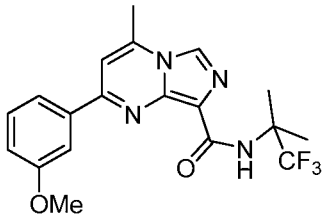
2-(3-Fluorophenyl)-4-methyl -A^-(l,l.,l-trifluoro-2-methylpropan-2-yl)imidazo[l,5-alpyrimidine-8-carboxamide



[00617] Following general procedure A, 2-(3-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (26 mg, 0.10 mmol) and l,l,l-trifluoro-2-methylpropan-2-

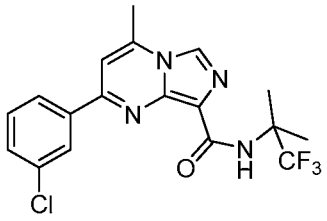
amine afforded the title compound (3.7 mg, 10%) as ayellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.45 (s, 1H), 8.05 (d, *J* = 7.5 Hz, 1H), 8.00 (d, *J* = 10.0 Hz, 1H), 7.64-7.59 (m, 1H), 7.55 (s, 1H), 7.35 (td, *J* = 8.0 Hz, 2.5 Hz, 1H), 2.89 (s, 3H), 1.82 (s, 6H). LC-MS m/z: 381.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.21 min.

2-(3-Methoxyphenyl)-4-methyl -A/-(1 ,1 ,1 -trifluoro-2-methylpropan-2-yl)imidazo [1 ,5-alpyrimidine-8-carboxamide



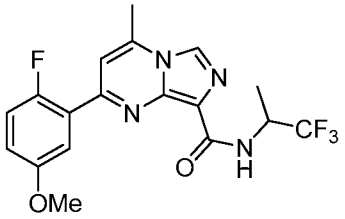
[00618] Following general procedure A, 2-(3-methoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.176 mmol) and l,l,l-trifluoro-2-methylpropan-2-amine afforded the title compound (7.5 mg, 11%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 8.42 (s, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 2.0 Hz, 1H), 7.68 (d, *J* = 0.8 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.18 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 3.88 (s, 3H), 2.80 (s, 3H), 1.73 (s, 6H). LC-MS m/z: 393.2$[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.13 min.

2-(3-Chlorophenyl)-4-methyl -A/-(1 ,1 ,1 -trifluoro-2-methylpropan-2-yl)imidazo [1 ,5-alpyrimidine-8-carboxamide



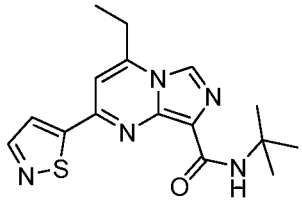
[00619] Following general procedure A, 2-(3-chlorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.174 mmol) and l,l,l-trifluoro-2-methylpropan-2-amine afforded the title compound (10.2 mg, 15%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.38 (s, 1H), 8.27 (d, *J* = 1.6 Hz, 1H), 8.17 (dt, *J* = 7.2 Hz, 1.6 Hz, 1H), 7.73 (d, *J* = 0.8 Hz, 1H), 7.67-7.64 (m, 2H), 2.80 (s, 3H), 1.73 (s, 6H). LC-MS m/z: 397.0 $[M+H]^+$. Purity (254 nm): 97%; t_R = 1.57 min.

2-(2-Fluoro-5-methoxyphenyl)-4-methyl -A^-(l,l..l-trifluoropropan-2-yl)imidazo[l,5-« 1pyrimidine-8-carboxamide



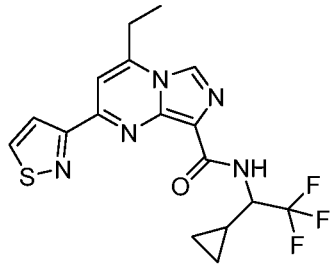
[00620] Following general procedure A, 2-(2-fluoro-5-methoxyphenyl)-4-methylirnidazo[l,5-a]pyrirnidine-8-carboxylic acid (30 mg, 0.10 mmol) and 1,1,1-trifluoropropan-2-amine hydrochloride afforded the title compound (14 mg, 36%) as a yellow solid. ^{1}H NMR (500 MHz, CDC1$_3$) δ 8.30 (d, *J* = 9.0 Hz, 1H), 8.12 (s, 1H), 7.54 (dd, *J* = 6.0 Hz, 3.5 Hz, 1H), 7.24 (s, 1H), 7.14 (dd, *J* = 10.5 Hz, 9.0 Hz, 1H), 7.05 (tt, *J* = 9.0 Hz, 3.5 Hz, 1H), 5.13-5.08 (m, 1H), 3.88 (s, 3H), 2.78 (s, 3H), 1.46 (d, *J* = 7.0 Hz, 3H). LC-MS m/z: 397.1 [M+H]$^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.84 min.

A/-ferf-Butyl-4-ethyl-2-(isothiazol-5-yl)imidazo[l,5-alpyrimidine-8-carboxamide



[00621] Following general procedure A, 4-ethyl-2-(isothiazol-5-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (40 mg, 0.15 mmol) and 2-methylpropan-2-amine afforded the title compound (3.3 mg, 7%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.66 (s, 1H), 8.51 (s, 1H), 8.15 (s, 1H), 8.13 (d, *J* = 1.5 Hz, 1H), 7.41 (s, 1H), 3.21 (q, *J* = 7.0 Hz, 1H), 1.60 (s, 9H), 1.56 (t, *J* = 7.0 Hz, 3H). LC-MS m/z: 330.0 [M+H]$^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.18 min.

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-4-ethyl-2-(isothiazol-3-yl)imidazo[l,5-«1pyrimidine-8-carboxamide

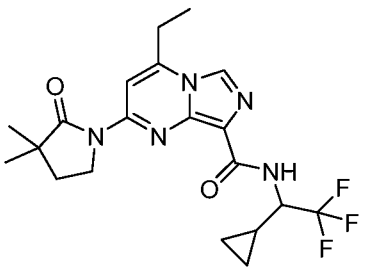


[00622] Following general procedure E, ethyl 2-chloro-4-ethylimidazo[l,5-a]pyrimidine-8-carboxylate (200 mg, 0.8 mmol) and 3-bromoisothiazole afforded ethyl 4-ethyl-2-(isothiazol-3-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (190 mg, 78%) as ayellow solid. LC-MS m/z: 303.2 $[M+H]^+$.

[00623] Following general procedure B, ethyl 4-ethyl-2-(isothiazol-3-yl)imidazo[l,5-a]pyrimidine-8-carboxylate (190 mg, 0.59 mmol) at room temperature afforded 4-ethyl-2-(isothiazol-3-yl)irnidazo[l,5-a]pyrimidine-8-carboxylic acid (80 mg, 50%) as ayellow solid. LC-MS m/z: 275.0 $[M+H]^+$. LCMS: t_R = 1.21 min.

[00624] Following general procedure A, 4-ethyl-2-(isothiazol-3-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (25 mg, 0.09 mmol) and 1-cyclopropy 1-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (18.2 mg, 18%) as ayellow solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ **9.**11 (d, J = 4.5 Hz, 1H), 8.55 (s, 1H), 8.21 (d, J = 4.5 Hz, 1H), 7.82 (s, 1H), 4.47-4.40 (m, 1H), 3.22 (q, J = 7.5 Hz, 2H), 1.57 (t, J = 7.5 Hz, 3H), 1.40-1.35 (m, 1H), 0.81-0.77 (m, 1H), 0.70-0.59 (m, 2H), 0.58-0.51 (m, 1H). LC-MS m/z: 396.1 $[M+H]^+$. HPLC: Purity (214 nm): 98%; t_R = 10.06 min.

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(3,3-dimethyl-2-oxopyrrolidin-l-yl)-4-ethylimidazo [1,5-alpyrimidine-8-carboxamide

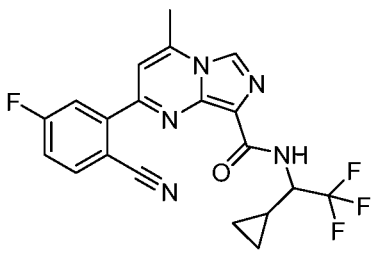


[00625] **A** mixture of ethyl 2-chloro-4-ethylirnidazo[l,5-a]pyrimidine-8-carboxylate (185 mg, 0.73 mmol), 3,3-dimethylpyrrolidin-2-one (83 mg, 0.73 mmol), $Pd_2(dba)_3$ (67 mg, 0.073 mmol), CS2CO3 (475 mg, 1.46 mmol), and Xantphos (85 mg, 0.146 mmol) in 1,4-dioxane (8 mL) was stirred at 100 °C under N_2 overnight, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (1% MeOH in **EA)** to afford ethyl 2-(3,3-dimethyl-2-oxopyrrolidin-l-yl)-4-ethylimidazo[l,5-a]pyrimidine-8-carboxylate (310 mg, 76%) as a red oil. LC-MS m/z: 331.1[M+H] $^+$. Purity: 52% (254 nm); t_R = 1.35 min.

[00626] **A** mixture of ethyl 2-(3,3-dimethyl-2-oxopyrrolidin-l-yl)-4-ethylimidazo[l,5-a]pyrimidine-8-carboxylate (310 mg, 0.94 mmol), and $(Bu_3Sn)_2O$ (1.68 g, 2.82 mmol) in toluene (10 mL) was stirred at 120 °C overnight, and concentrated *in vacuo.* The residue was dissolved in 3 mL of saturated $NaHCO_3$ aqueous solution, and extracted with **EA** (10 mL x 3). The aqueous phase was acidified to pH 1-2 with dilute HC1 aqueous solution, and extracted with **EA** (40 mL x 3). The organic phases were dried over anhydrous Na2SC>4 and filtered. The filtrate was concentrated *in vacuo* to afford 2-(3,3-dimethyl-2-oxopyrrolidin-l-yl)-4-ethylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (55 mg, 19%) as a yellow oil. LC-MS m/z: 303.2 [M+H] $^+$. t_R = 0.93 min.

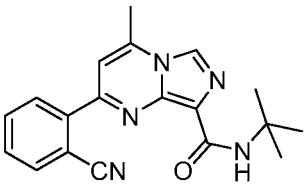
[00627] Following general procedure **A,** 2-(3,3-dimethyl-2-oxopyrrolidin-l-yl)-4-ethylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (40 mg, 0.13 mmol) and l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (11.0 mg, 14%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.32 (d, J = 9.5 Hz, 1H), 8.02 (s, 1H), 4.35-4.29 (m, 1H), 4.18-3.92 (m, 2H), 3.10 (q, J = 7.5 Hz, 2H), 2.02 (t, J = 7.0 Hz, 2H), 1.34 (t, J = 7.5 Hz, 3H), 1.33-1.24 (m, 1H), 1.21 (s, 6H), 0.70-0.65 (m, 1H), 0.60-0.52 (m, 2H), 0.36-0.31 (m, 1H). LC-MS m/z: 424.2 [M+H] $^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.32 min.

2-(2-Cvano-5-fluorophenyl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-*a*]pyrimidine-8-carboxamide



[00628] Following general procedure D, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (40 mg, 0.12 mmol) and 2-cyano-5-fluorophenylboronic acid afforded the title compound (25 mg, 49%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-i¾): δ 8.68 (s, 1H), 8.44 (d, *J* = 9.5 Hz, 1H), 8.22 (dd, *J* = 9.0 Hz, 6.0 Hz, 1H), 7.99 (dd, *J* = 9.5 Hz, 2.5 Hz, 1H), 7.68 (td, *J* = 9.0 Hz, 2.5 Hz, 1H), 7.54 (s, 1H), 4.30-4.22 (m, 1H), 2.83 (s, 3H), 1.42-1.35 (m, 1H), 0.73-0.67 (m, 1H), 0.63-0.58 (m, 1H), 0.51-0.46 (m, 1H), 0.34-0.28 (m, 1H). HPLC m/z: 418.0 $[M+H]^+$. LC-MS Purity (214 nm): > 99%; t_R = 7.67 min.

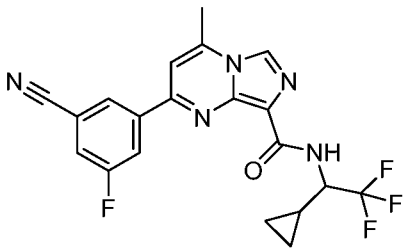
A/-ferf-Butyl-2-(2-cvanophenyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00629] Following general procedure A, 2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (1 g, 2 mmol) and 2-methylpropan-2-amine afforded *N*-fer/-butyl-2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (250 mg, 47%) as a yellow solid. LCMS : Purity (254 nm): > 86%; t_R = 1.28 min.

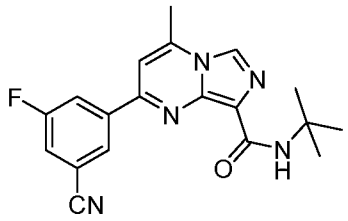
[00630] Following general procedure D, *N*-teri-butyl-2-chloro-4-methylimidazo[l ,5-a]pyrimidine-8-carboxamide (60 mg, 0.23 mmol) and 2-cyanophenylboronic acid afforded the title compound (9.9 mg, 16%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾): δ 8.49 (s, 1H), 8.36 (brs, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 7.0 Hz, 1H), 7.89 (t, *J* = 7.5 Hz, 1H), 7.75 (t, *J* = 7.5 Hz, 1H), 7.32 (s, 1H), 2.88 (s, 3H), 1.55 (s, 9H). LC-MS m/z: 334.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.08 min.

2-(3-Cvano-5-fluorophenyl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



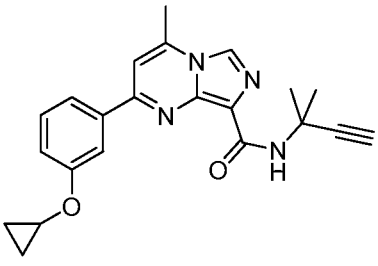
[00631] Following general procedure D, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (60 mg, 0.18 mmol) and 3-cyano-5-fluorophenylboronic acid afforded the title compound (14.6 mg, 19%) as ayellow solid. ^{1}H NMR (500 MHz, *MeOO-d4)*: δ 8.63 (s, 1H), 8.62 (d, *J* = 10.0 Hz, 1H), 8.55 (s, 1H), 8.39 (d, *J* = 10.0 Hz, 1H), 8.11 (d, *J* = 7.0 Hz, 1H), 7.82 (s, 1H), 4.36-4.31 (m, 1H), 2.81 (s, 3H), 1.38-1.34 (m, 1H), 0.73-0.67 (m, 1H), 0.60-0.52 (m, 2H), 0.39-0.33 (m, 1H). LC-MS m/z: 418.0 $[M+H]^+$. HPLC Purity (214 nm): 98%; t_R = 7.93 min.

iV-fert-Butyl-2-(3-cvano-5-fluorophenyl)-4-methylimidazo [1,5-al pyrimidine-8-carboxamide



[00632] Following general procedure **D,** *N*-teri-butyl-2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxamide (50 mg, 0.19 mmol) and 3-cyano-5-fluorophenylboronic acid afforded the title compound (13.3 mg, 20%) as ayellow solid. ^{1}H NMR (500 MHz, *OMSO-d6)*: δ 8.542 (s, 1H), 8.537 (s, 1H), 8.38 (d, *J* = 10.5 Hz, 1H), 8.10 (d, *J* = 7.5 Hz, 1H), 7.96 (s, 1H), 7.76 (s, 1H), 2.78 (s, 3H), 1.48 (s, 9H). LC-MS m/z: 352.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.56 min.

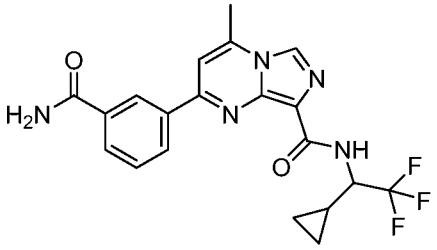
2-(3-Cvclopropoxyphenyl)-4-methyl-A^-(2-methylbut-3-vn-2-yl)imidazo[l,5-alpyrimidine-8-carboxamide



[00633] Following general procedure A, 2-(3-cyclopropoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (100 mg, 0.32 mmol) and 2-methylbut-3-yn-2-amine afforded the title compound (22.6 mg, 19%) as ayellow solid. ¾NMR (500 MHz, DMSO-*d6*) δ 8.49 (s, 1H), 8.43 (s, 1H), 7.87-7.84 (m, 2H), 7.64 (s, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.30 (dd, *J* = 8.0

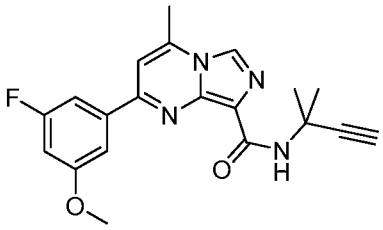
Hz, 2.5 Hz, 1H), 4.01-3.98 (m, 1H), 3.28 (s, 1H), 2.79 (s, 3H), 1.73 (s, 6H), 0.87-0.83 (m, 2H), 0.73-0.70 (m, 2H). LC-MS m/z: 375.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.17 min.

2-(3-Carbamoylphenyl)-A/-(l-cvclopropyl -2,2,2-trifluoroethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



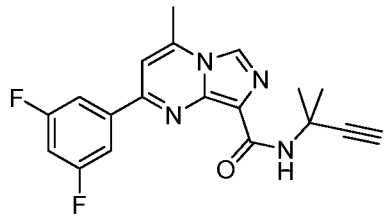
[00634] Following general procedure D, 2-chloro -*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (60 mg, 0.18 mmol) and 3-carbamoylphenylboronic acid afforded the title compound (10 mg, 13 %) as a yellow solid. ^{1}H NMR (500 MHz, *MOSO-d_6)*: δ 8.73 (s, 1H), 8.72 (d, *J* = 8.5 Hz, 1H), 8.58 (s, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 8.16 (s, 1H), 8.06 (d, *J* = 7.5 Hz, 1H), 7.74 (s, 1H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.58 (s, 1H), 4.36-4.28 (m, 1H), 2.83 (s, 3H), 1.44-1.38 (m, 1H), 0.73-0.67 (m, 1H), 0.60-0.52 (m, 2H), 0.39-0.33 (m, 1H). LC-MS m/z: 418.1 $[M+H]^+$. HPLC Purity (214 nm): 99%; t_R = 6.35 min.

2-(3-Fluoro-5-methoxyphenyl)-4-methyl-A/-(2-methylbut-3-vn-2-yl)imidazo[l,5-« ıpyrimidine-8-carboxamide



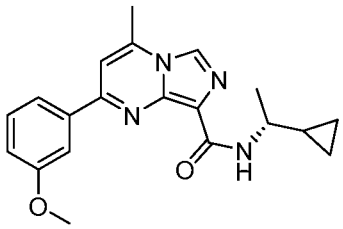
[00635] Following general procedure A, 2-(3-fluoro-5-methoxyphenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.167 mmol) and 2-methylbut-3-yn-2-amine afforded the title compound (3.5 mg, 5.8%) as a pink solid. ^{1}H NMR (400 MHz, DMSO-c¾): δ 8.53 (s, 1H), 8.34 (s, 1H), 7.71 (s, 1H), 7.67-7.64 (m, 2H), 7.09 (dt, *J* = 6.4 Hz, 2.0 Hz, 1H), 3.90 (s, 3H), 3.24 (s, 1H), 2.79 (s, 3H), 1.76 (s, 6H). LC-MS m/z: 367.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.83 min.

2-(3,5-Difluorophenyl)-4-methyl -A^-(2-methylbut-3-vn-2-yl)imidazo[l,5-alpyrimidine-8-carboxamide



[00636] Following general procedure A, 2-(3,5-difluorophenyl)-4-methylimidazo[l ,5-a]pyrimidine-8-carboxylic acid (30 mg, 0.10 mmol) and 2-methylbut-3-yn-2-amine afforded the title compound (13.1 mg, 37%) as a yellow solid. ¾ NMR (500 MHz, *OMSO-d6):* δ 8.55 (s, 1H), 8.30 (s, 1H), 7.97 *(d, J* = 7.0 Hz, 1H), 7.73 (s, 2H), 7.52 (t, *J* = 8.5 Hz, 1H), 3.254 (s, 1H), 2.79 (s, 3H), 1.74 (s, 6H). LC-MS m/z: 355.1 $[M+H]^+$. HPLC Purity (214 nm): 97%; t_R = 7.88 min.

(i?)-A/-(l-Cvclopropylethyl)-2-(3-methoxyphenyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide

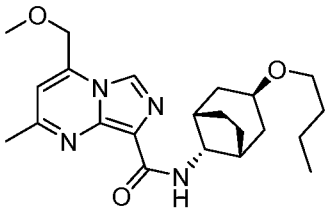


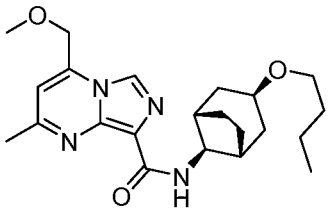
[00637] Following general procedure B*, 2-chloro-4-methylimidazo[l ,5-a]pyrirnidine-8-carboxylic acid (1.0 g, 2.0 mmol) and (i?)-l -cyclopropylethanamine (204 mg, 2.4 mmol) afforded (i?)-2-chloro-*N*-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxamide as a yellow solid (327 mg, 59 %). LC-MS m/z: 279.1 $[M+H]^+$. Purity (214 nm): > 99%; t_R = 1.60 min.

[00638] Following general procedure D, (i?)-2-chloro-*N*-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (80 mg, 0.29 mmol) and 3-methoxyphenylboronic acid afforded the title compound (22.2 mg, 22%) as a yellow solid. ^1H NMR (500 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 7.5 Hz, 1H), 7.78 (t, *J* = 2.0 Hz, 1H), 7.65 (d, *J* = 1.0 Hz, 1H), 7.53 (t, *J* = 8.5 Hz, 1H), 7.17 (dd, *J* = 8.0 Hz, 2.5 Hz, 1H), 3.88 (s, 3H), 3.65-3.61 (m, 1H), 2.79 (d, *J* = 1.0 Hz, 3H), 1.29 (d, *J* = 6.5 Hz, 3H),

1.11-1.06 (m, 1H), 0.52-0.48 (m, 1H), 0.46-0.42 (m, 1H), 0.38-0.34 (m, 1H), 0.30-0.26 (m, 1H). LC-MS m/z: 351.2 $[M+H]^+$. HPLC: Purity (214 nm): 97%; t_R = 7.90 min.

7v-((mii?,5^,gi?)-3-Butoxybicvclo[3.2.11octan-8-vn-4-(methoxymethvn-2-methylimidazo[l,5-«lpyrimidine-8-carboxamide &*N-((lR,3R,5S,8S)-3-butoxybicvclo [3.2.1]octan-8-yl)-4-(methoxymethyl)-2-methylimid azo [1,5-«l pyrimidine-8-carboxamide



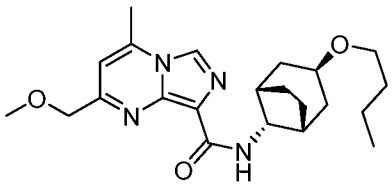


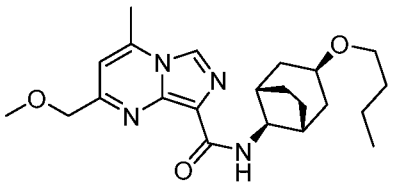
[00639] Following general procedure A, 4-(methoxymethyl)-2-methyl imidazo[l,5-a]pyrimidine-8-carboxylic acid (29 mg, 0.13 mmol) and *(lR3R5S)-3-*butoxybicyclo[3.2.1]octan-8-amine afforded *N*-^^^J^^-S-butoxybicycloP^.^octan-S-yl)-4-(methoxymethyl)-2-methylimidazo[l,5-a]pyrirnidine-8-carboxamide (28 mg, 54%) as a yellow solid and *N*-((7i?,3i?,55;S5)-3-butoxybicyclo[3.2.1]octan-8-yl)-4-(methoxymethyl)-2-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (8.3 mg, 16%) as a white solid.

[00640] *N*-((7i?,3i?,55',Si?)-3-butoxybicyclo[3.2.1]octan-8-yl)-4-(methoxymethyl)-2-methylimidazo[l,5-a]pyrirnidine-8-carboxarnide: ^{1}H NMR (500 MHz, MeOD-*d*4) δ 8.32 (s, 1H), 7.01 (s, 1H), 4.87 (s, 2H), 4.18 (t, ***J*** **=** 4.5 Hz, 1H), 3.59 (t, ***J*** **=** 4.5 Hz, 1H), 3.53 (s, 3H), 3.44 (t, ***J*** **=** 6.0 Hz, 2H), 2.66 (s, 3H), 2.22 (brs, 2H), 2.14-2.00 (m, 4H), 1.94-1.91 (m, 2H), 1.87-1.77 (m, 2H), 1.64-1.52 (m, 2H), 1.48-1.45 (m, 2H), 0.98 (**t, *J*** **=** 7.5 Hz, 3H). LC-MS m/z: 401.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 9.11 min.

[00641] *N*-((77?,37?,55',S5)-3-butoxybicyclo[3.2.1]octan-8-yl)-4-(methoxymethyl)-2-methylimidazo[l,5-a]pyrirnidine-8-carboxarnide: ¾NMR (500 MHz, MeOD-*d*4) δ 8.31 (s, 1H), 6.99 (s, 1H), 4.86 (s, 2H), 4.06-4.02 (m, 1H), 3.52 (s, 3H), 3.52-3.51 (m, 1H), 3.41 (t, ***J*** **=** 6.5 Hz, 3H), 2.65 (s, 3H), 2.25 (brs, 2H), 2.16-2.08 (m, 4H), 1.92-1.90 (m, 4H), 1.58-1.56 (m, 2H), 1.51-1.41 (m, 2H), 0.98 (t, ***J*** **=** 7.5 Hz, 3H). LC-MS m/z: 401.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 9.14 min.

^-((mii?,5^,gi?)-3-Butoxybicvclo[3.2.11octan-8-vn-2-(methoxymethvn-4-methylimidazo[l,5-«lpyrimidine-8-carboxamide & *N-((1R,3R, 5S,8S)*-3-Butoxybicvclo[3.2.11octan-8 -vn-2-(methoxymethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



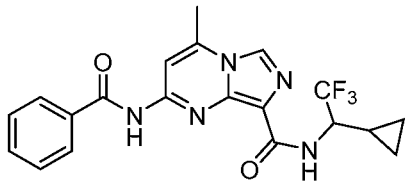


[00642] Following general procedure A, 2-(methoxymethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (29 mg, 0.13 mmol) and *(lR3R5S)-3*-butoxybicyclo[3.2.1]octan-8-amine afforded *N-((lR3R5S,8R)-3-butoxybicyc\o[3.*2.l]octan-8-yl)-2-(methoxymethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxamide (33 mg, 63%) as a yellow solid and *N-((lR3R5S,8S)-3-butoxybicyclo[3.2.* l]octan-8-yl)-2-(methoxymethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (8.4 mg, 16%) as a white solid.

[00643] *N*-((7i?,3i?,55',Si?)-3-butoxybicyclo[3.2.1]octan-8-yl)-2-(methoxymethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxamide: 'HNMR (500 MHz, MeOD-*d4*) δ 8.40 (s, 1H), 7.00 (s, 1H), 4.61 (s, 2H), 4.18 (t, J = 4.5 Hz, 1H), 3.59 (t, J = 4.5 Hz, 1H), 3.52 (s, 3H), 3.44 (t, J = 6.5 Hz, 2H), 2.80 (s, 3H), 2.22 (brs, 2H), 2.12-2.03 (m, 4H), 1.92-1.89 (m, 2H), 1.83-1.81 (m, 2H), 1.64-1.53 (m, 2H), 1.48-1.44 (m, 2H), 0.98 (t, J = 7.5 Hz, 3H). LC-MS m/z: 401.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.79 min.

[00644] *N*-((7i?,3i?,55',S5)-3-butoxybicyclo[3.2.1]octan-8-yl)-2-(methoxymethyl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxarnide: 'HNMR (500 MHz, MeOD-*d4*) δ 8.26 (s, 1H), 6.88 (s, 1H), 4.49 (s, 2H), 3.91 (brs, 1H), 3.39 (s, 4H), 3.29 (t, J = 6.5 Hz, 2H), 2.68 (s, 3H), 2.13 (brs, 2H), 2.02-1.95 (m, 4H), 1.80-1.78 (m, 4H), 1.46-1.43 (m, 2H), 1.35-1.31 (m, 2H), 0.86 (t, J = 7.0 Hz, 3H). LC-MS: m/z, 401.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.81 min.

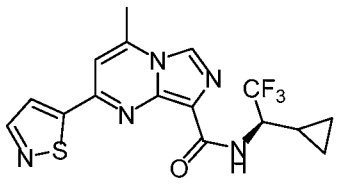
2-Benzamido -iV-(l-cvclopropyl -2,2,2-trifluoroethyl)-^ -methylimidazo[1,5-*a*]pyrimidine-8-carboxamide



[00645] A mixture of 2-chloro -*N*-(l -cyclopropyl-2,2,2-trifluoroethyl)-4-methylirnidazo[l ,5-a]pyrimidine-8-carboxamide (400 mg, 1.20 mmol), NH_4Cl (325 mg, 6.02 mmol), DIPEA (1.55 g, 12.0 mmol) in DMF (20 mL) was stirred at 40 °C for 2 days. The mixture was partitioned between EA (100 mL) and $\mathbf{H_20}$ (100 mL), the organic layer was dried over anhydrous Na2SC>4 and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by flash chromatography (100% EA) to afford 2-amino -*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylinddazo[l,5-a]pyrimidine-8-carboxamide (250 mg, 58%) as a yellow solid LC-MS m/z: 314.1 $[M+H]^+$. Purity (254 nm): >90%; t_R = 1.12 min.

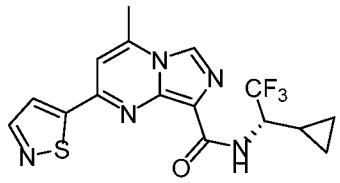
[00646] A mixture of 2-andno -*N*-(l -cyclopropyl-2,2,24rifluoroethyl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxarnide (150 mg, 0.48 mmol), pyridine (370 mg, 4.80 mmol) in benzoyl chloride (5 mL) was stirred at RT for 2 h. Then EA (50 mL) was added and the organic layer was washed with IN HCl (50 mL), saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na2SC>4 and filtered and the filtrate was concentrated *in vacuo*, and the residue purified by silica gel chromatography (PE/EA= 1/1) to afford the title compound (5 mg, 3%) as a yellow solid. ^1H NMR (400 MHz, *OMSO-d*$_6$): δ 11.27 (s, 1H), 8.49 (d, *J* = 9.2 Hz, 1H), 8.42 (s, 1H), 7.99 (d, *J* = 7.2 Hz, 2H), 7.68-7.64 (m, 1H), 7.57 (t, *J* = 7.2 Hz, 2H), 7.54 (s, 1H),4.26-4. 18 (m, 1H), 2.75 (s, 3H), 1.41-1.33 (m, 1H), 0.72-0.64 (m, 1H), 0.60-0.49 (m, 2H), 0.36-0.30 (m, 1H). LC-MS m/z: 418.1 $[M+H]^+$. HPLC Purity (214 nm): 93%; t_R = 7.76 min.

(i?)-A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(isothiazol-5-yl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



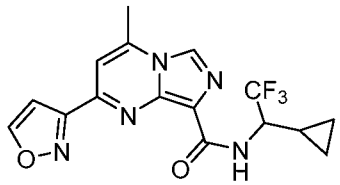
[00647] Following general procedure A, 2-(isothiazol-5-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (100 mg, 0.38 mmol) and (R)-l-cyclopropy 1-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (27 mg, 19 %) as a yellow solid. ^{1}H NMR (500 MHz, *MeOO-d$_4$)* δ 8.67 (d, *J* = 1.5 Hz, 1H), 8.53 (s, 1H), 8.09 (d, *J* = 1.5 Hz, 1H), 7.52 (s, 1H), 4.47-4.42 (m, 1H), 2.89 (s, 3H), 1.40-1.32 (m, 1H), 0.85-0.78 (m, 1H), 0.72-0.62 (m, 1H), 0.61-0.50 (m, 2H). LC-MS m/z: 382.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.77 min.

(.S^-A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(isothiazol-5-yl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00648] Following general procedure A, 2-(isothiazol-5-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (100 mg, 0.38 mmol) and (<S)-l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (21 mg, 15 %) as a yellow solid. ^{1}H NMR (500 MHz, CDC1$_3$) *δ* 8.61 (d, *J* = 2.0 Hz, 1H), 8.15 (s, 1H), 8.14 (s, 1H), 7.73 (d, *J* = 2.0 Hz, 1H), 7.00 (s, 1H), 4.57-4.49 (m, 1H), 2.81 (s, 3H), 1.30-1.23 (m, 1H), 0.78-0.72 (m, 1H), 0.63-0.55 (m, 3H). LC-MS m/z: 382.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.46 min.

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(isoxazol-3-yl)-4-methylimidazo[l,5-*a*\pyrimidine-8-carboxamide



[00649] Following general procedure F*, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (436 mg, 1.82 mmol) and tributyl(vinyl)stannane afforded ethyl 4-methyl-2-vinylimidazo[l,5-a]pyrimidine-8-carboxylate (150 mg, 32%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 8.16 (s, 1H), 6.97-6.91 (m, 2H), 6.31 (d, *J* = 17.5 Hz, 1H), 5.84 (d, *J* =

10.5 Hz, 1H), 4.50 (q, *J* = 7.0 Hz, 1H), 2.73 (s, 3H), 1.47 (t, *J* = 7.5 Hz, 3H). LC-MS m/z: 232.1 $[M+H]^+$. Purity (254 nm): 86.3%; t_R = 1.52 min.

[00650] To a solution of ethyl 4-methyl-2-vinylimidazo[l,5-a]pyrimidine-8-carboxylate (150 mg, 0.649 mmol) and OsO_4 (2 mg, 0.007 mmol) in THF/H_2O (10 mL/ 3 mL) was added $NaIO_4$ (278 mg, 1.298 mmol). The resulting mixture was stirred at RT for 12 h, treated with water (50 mL) and extracted with EA (20 mL χ 3). The combined EA layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford crude ethyl 2-formyl-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (90 mg) as an oil, which was used directly in the next. LC-MS m/z: 234.1 $[M+H]^+$. Purity (254 nm): 64%; t_R = 1.21 min.

[00651] To a solution of ethyl 2-formyl-4-methylinddazo[l,5-a]pyrimidine-8-carboxylate (90 mg) in MeOH (5 mL) was added $OHNH_4Cl$ (54 mg, 0.77 mmol) and Et_3N (116 mg, 1.16 mmol). The reaction mixture was stirred at RT for 2 h, concentrated *in vacuo* and purified by reverse-phase chromatography (0.01%TFA/MeCN) to afford ethyl 2-((hydroxyimino)methyl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (60 mg, 38% over two steps) as ayellow solid. LC-MS m/z: 249.1 $[M+H]^+$. Purity (214 nm): 78%; t_R = 1.41 min.

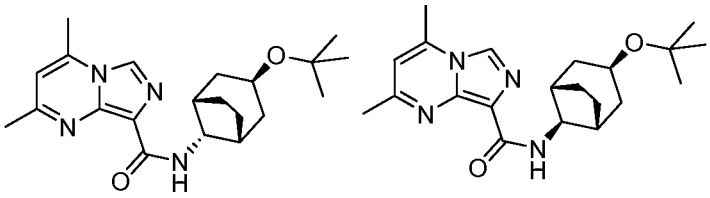
[00652] To a solution ethyl 2-((hydroxyindno)methyl)-4-methylinddazo[l,5-a]pyrimidine-8-carboxylate (60 mg, 0.24 mmol) and ethynyltrimethylsilane (47 mg, 0.48 mmol) in MeCN (5 mL) was added CrC_2 (201 mg, 2.4 mmol). The reaction mixture was stirred at 80 °C for 2 h, and filtered through a Celite bed. The filtrate was concentrated *in vacuo*, and the residue was purified was purified by reverse-phase chromatography (0.01%TFA/MeCN) to afford ethyl 4-methyl-2-(5-(trimethylsilyl)isoxazol-3-yl)inddazo[l,5-a]pyrimidine-8-carboxylate (21 mg, 25%) as ayellow solid. ^1H NMR (500 MHz, $CDC1_3$) δ 8.04 (s, 1H), 7.45 (s, 1H), 7.26 (s, 1H), 4.47 (q, *J* = 7.0 Hz, 2H), 2.71 (s, 3H), 1.43 (t, *J* = 7.0 Hz, 3H), 0.33 (s, 9H). LC-MS m/z: 345.1 $[M+H]^+$. Purity (214 nm): 86%; t_R = 1.86 min.

[00653] Following general procedure B*, ethyl 4-methyl-2-(5-(trimethylsilyl)isoxazol-3-yl)imidazo[l,5-a]pyrirnidine-8-carboxylate (20 mg, 0.058 mmol) afforded crude 2-(isoxazol-3-yl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (15 mg) as an oil which was used directly in the next step. LC-MS m/z: 245.1 $[M+H]^+$. Purity (254 nm): 74%; t_R = 1.39 min.

[00654] Following general procedure A, 2-(isoxazol-3-yl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (15 mg, crude) and l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride

afforded the title compound (2.2 mg, 10% over two steps) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.20 (d, *J* = 1.2 Hz, 1H), 8.66 (s, 1H), 8.59 (d, *J* = 9.2 Hz, 1H), 7.55 (s, 1H), 7.09 (d, *J* = 1.2 Hz, 1H), 4.32-4.26 (m, 1H), 2.82 (s, 3H), 1.41-1.35 (m, 1H), 0.71-0.66 (m, 1H), 0.60-0.51 (m, 2H), 0.38-0.31 (m, 1H). LC-MS m/z: 366.0 $[M+H]^+$. HPLC: Purity (214 nm): 95%; t_R = 7.44 min.

N-((lRJR,5S,8R)-3-tert-butoxybicycio* [3.2.11 octan-8-yl)-2,4-dimethylimidazo[l,5-alpyrimidine-8-carboxamide *& N-((lR,3R,5S,8S)-3-tert-butoxybicycio\3 .2.1]octan-8-yi)-2,4-dimethylimidazo[l,5-alpyrimidine-8-carboxamide

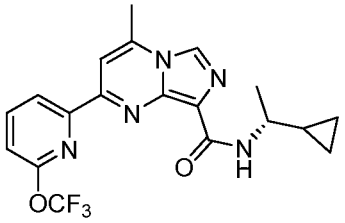


[00655] Following general procedure A, 2,4-dimethylimidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.26 mmol) and (7i?,3i?,55)-3-teri-butoxybicyclo[3.2.1]octan-8-amine afforded *N-((lR,3R,5S,8R)-3-tert-butoxybicyc\o[32A]octm-8-y\)-2,4-dimQlfay*limidazo[1,5-*a*]pyrimidine-8-carboxamide (12.4 mg, 33%) and *N*-((77?,37?,55',S5)-3-tert-butoxybicyclo[3.2.1]octan-8-yl)-2,4-dimethylimidazo[l,5-a]pyrirnidine-8-carboxarnide (3.6 mg, 10 %) as yellow solids.

[00656] *N-((lR,3R,5S,8R)-3-tert-butoxybicydo[3.2.* l]octan-8-yl)-2,4-dimethylimidazo[l,5-a]pyrimidine-8-carboxamide: ^{1}H NMR (400 MHz, MeOD-c¾) δ 8.32 (s, 1H), 6.85 (d, *J* = 0.8 Hz, 1H), 4.13 (t, *J* = 4.4 Hz, 1H), 3.82 (t, *J* = 4.4 Hz, 1H), 2.75 (d, *J* = 0.8 Hz, 3H), 2.64 (s, 3H), 2.26-2.15 (m, 6H), 1.82-1.78 (m, 2H), 1.72-1.65 (m, 2H), 1.18 (s, 9H). LC-MS m/z: 371.1 $[M+H]^+$. HPLC: Purity (214 nm): 98.63%; t_R = 9.06 min.

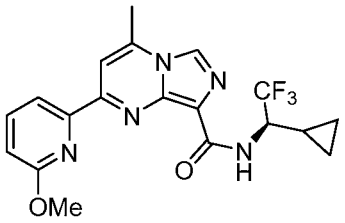
[00657] *N*-((77?,37?,55',S5)-3-terr-butoxybicyclo[3.2.1]octan-8-yl)-2,4-dimethylimidazo[l,5-a]pyrimidine-8-carboxamide: 1H NMR (400 MHz, MeOD-c¾) δ 8.29 (s, 1H), 6.81 (d, *J* = 0.8 Hz, 1H), 3.98-3.96 (m, 1H), 3.77 (t, *J* = 4.8 Hz, 1H), 2.73 (d, *J* = 0.8 Hz, 3H), 2.64 (s, 3H), 2.34-2.30 (m, 2H), 2.23-2.20 (m, 2H), 2.06-2.01 (m, 2H), 1.88-1.82 (m, 4H), 1.18 (s, 9H). LC-MS: m/z, 371.1 $[M+H]^+$. HPLC: Purity (214 nm): 92.73%; t_R = 9.17 min.

(i?)-A/-(l-Cvclopropylethyl)-4-methyl-2-(6-(trifluoromethoxy)pyridin-2-yl)imidazo[l,5-« 1pyrimidine-8-carboxamide



[00658] Following general procedure E, (i?)-2-chloro-*N*-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (65 mg, 0.23 mmol) and 2-chloro-6-(trifluoromethoxy)pyridine afforded the title compound (6.4 mg, 6%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.58 (d, *J* = 7.5 Hz, 1H), 8.48 (s, 1H), 8.20 (d, *J* = 7.5 Hz, 1H), 7.81 (s, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 3.73-3.68 (m, 1H), 2.88 (s, 3H), 1.43 (d, *J* = 7.0 Hz, 3H), 1.20-1.13 (m, 1H), 0.68-0.52 (m, 2H), 0.51-0.47 (m, 1H), 0.41-0.37 (m, 1H). LC-MS m/z: 406.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.62 min.

(i?)-A/-(l-Cvclopropyl-2,2,2-trifluoroethvn-2-(6-methoxypyridin-2-vn-4-methylimidazo [1,5-al pyrimidine-8-carboxamide

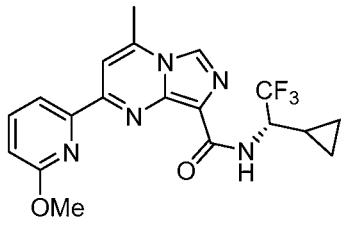


[00659] Following general procedure A, 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (300 mg, 1.42 mmol) and (i?)-l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded (i?)-2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (310 mg, 66 %) as a yellow solid. LC-MS m/z: 333.1 $[M+H]^+$. Purity (214 nm): 86%; t_R = 1.80 min.

[00660] Following general procedure F*, (i?)-2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (80 mg, 0.24 mmol) and 2-methoxy-6-(tributylstannyl)pyridine afforded the title compound (26.7 mg, 27 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-c¾): δ 8.64 (d, *J* = 9.5 Hz, 1H), 8.60 (s, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.97 (t, *J* = 7.5 Hz, 1H), 7.89 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 4.37-4.32 (m, 1H), 4.05 (s, 3H),

2.84 (s, 3H), 1.40-1.35 (m, 1H), 0.72-0.69 (m, 1H), 0.60-0.56 (m, 2H), 0.36-0.34 (m, 1H). LC-MS m/z: 406.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.57 min.

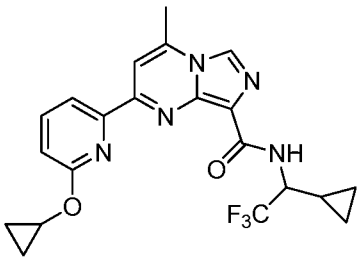
(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-2-(6-methoxypyridin-2-yl)-4-methylimidazo[1,5-a]pyrimidine-8-carboxamide



[00661] Following general procedure A, 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (700 mg, 1.40 mmol) and (5)-l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded (5)-2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (230 mg, 49 %) as a yellow solid. LC-MS m/z: 333.1 $[M+H]^+$. Purity (254 nm): 93%; t_R = 1.69 min.

[00662] Following general procedure F*, (5)-2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (70 mg, 0.21 mmol) and 2-methoxy-6-(tributylstannyl)pyridine afforded the title compound (25 mg, 30 %) as a yellow solid. ^{1}H NMR (500 MHz, **DMSO-d$_6$):** δ 8.64 (d, *J* = 9.5 Hz, 1H), 8.60 (s, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.97 (t, *J* = 7.5 Hz, 1H), 7.89 (s, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 4.37-4.32 (m, 1H), 4.05 (s, 3H), 2.84 (s, 3H), 1.40-1.35 (m, 1H), 0.72-0.69 (m, 1H), 0.60-0.56 (m, 2H), 0.36-0.34 (m, 1H). LC-MS m/z: 406.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.61 min.

2-(6-Cyclopropoxypyridin-2-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[1,5-a]pyrimidine-8-carboxamide

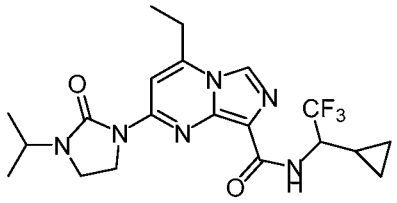


[00663] A mixture of 2-bromo-6-fluoropyridine (371 mg, 2.1 mmol) and cyclopropanol (350 mg, 6.0 mmol) in NMP (6 mL) was stirred for 5 minutes at 0 °C. Then to the solution was

added dropwise a solution of t-BuOK in THF (1M, 0.6 mL, 0.6 mmol) at 0 °C. After addition, the reaction mixture was warmed to RT and stirred for 2 h. The reaction mixture was poured into a mixed solvent of PE/EA/water (50 mL/50mL/100 mL). The organic layer was separated, washed with 5% of LiCl aqueous solution (20 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo,* and the residue was purified by silica gel column (5% ~ 10% EA/PE) to afford 2-bromo-6-cyclopropoxypyridine (374 mg, 83%) as a colorless oil. LC-MS m/z: 216&218 $[M+H]^+$. Purity (214 nm): 99.6%.

[00664] Following general procedure E, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylinddazo[l,5-a]pyrimidine-8-carboxamide (100 mg, 0.3 mmol) and 2-bromo-6-cyclopropoxypyridine afforded the title compound (22 mg, 17%) as a yellow solid. ^1H NMR (500 MHz, MeOD-c¾) δ 8.48 (s, 1H), 8.15 (d, J = 7.5 Hz, 1H), 7.99 (s, 1H), 7.91 (t, J = 7.5 Hz, 1H), 7.02 (d, J = 7.5 Hz, 1H), 4.47-4.42 (m, 2H), 2.88 (s, 3H), 1.38-1.35 (m, 1H), 0.93-0.89 (m, 2H), 0.81-0.77 (m, 3H), 0.70-0.60 (m, 2H), 0.56-0.51 (m, 1H). LC-MS m/z: 432.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.76 min.

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-4-ethyl-2-(3-¾o-propyl-2-oxoimidazolidin-l-vDimidazo [1,5-al pyrimidine-8-carb oxamide



[00665] To a mixture of l-chloro-2-isocyanatoethane (6.0 g, 57. 14 mmol) in G¾CN (30 mL) was added wo-PrNH $_2$ (3.37 g, 57. 14 mmol). The mixture was stirred at room temperature for 2 h, and filtered to collect l-(2-chloroethyl)-3-wo-propylurea (7.0 g, 74%) as a white solid. LC-MS m/z: 165.1 $[M+H]^+$. t_R = 1.32 min.

[00666] To a mixture of l-(2-chloroethyl)-3-z ˙so-propylurea (3.0 g, 18.29 mmol) in THF (30 mL) was added NaH (1.46 g, 21.95 mmol) and the mixture was stirred at RT overnight, quenched with H_20 (30 mL) and extracted with EA (30 mL x 3). The organic phases were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo,* and the residue was purified by silica gel column (PE:EA = 4:1 to 1:1) to afford \-*iso*-

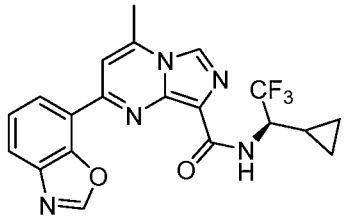
propylimidazolidin-2-one (1.5 g, 65%) as a white solid. LC-MS m/z: 129.1 $[M+H]^+$. t_R = 1.23 min.

[00667] Following general Procedure J, ethyl 2-chloro-4-ethylimidazo[l,5-a]pyrirnidine-8-carboxylate (200 mg, 0.836 mmol) and l-zso-propylimidazolidin-2-one afforded ethyl 4-ethyl-2-(3-zso-propyl-2-oxoiinidazolidin-l -yl)imidazo[l,5-a]pyrirnidine-8-carboxylat^ (150 mg, 50%) as a yellow solid. LC-MS m/z: 346.1 $[M+H]^+$. t_R = 1.62 min.

[00668] Following general procedure B*, ethyl 4-ethyl-2-(3-zso-propyl-2-oxoimidazolidin-l -yl)imidazo[l,5-a]pyrimidine-8-carboxylate (130 mg, 0.377 mmol) afforded crude 4-ethyl-2-(3-wo-propyl^-oxoiinidazolidin-l -y^imidazofl ^-^pyrirnidine-S-carboxylic acid (120 mg, 100%). LC-MS m/z: 318.1 $[M+H]^+$. t_R = 1.245 min.

[00669] Following general procedure A, 4-ethyl-2-(3-iso-propyl-2-oxoimidazolidin-l -yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (120 mg, 0.377 mmol) and l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (46 mg, 24%) as a yellow solid. ^{1}H NMR (500 MHz, *MeOO-d4)* δ 8.28 (s, 1H), 8.15 (s, 1H), 4.38-4.32 (m, 1H), 4.28-4.22 (m, 1H), 4.18-4.11 (m, 2H), 3.64 (t, *J* = 8.0 Hz, 2H), 3.10 (q, *J* = 7.5 Hz, 2H), 1.48 (t, *J* = 7.5 Hz, 3H), 1.31-1.28 (m, 1H), 1.27 (d, *J* = 6.5 Hz, 6H), 0.80-0.74 (m, 1H), 0.78-0.55 (m, 2H), 0.51-0.46 (m, 1H). LC-MS m/z: 439.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.10 min.

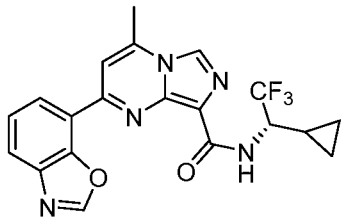
(i?)-2-(Benzo[</loxazol-7-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00670] Following general procedure **D,** (i?)-2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l ,5-a]pyrimidine-8-carboxarnide (80 mg, 0.24 mmol) and **7**-(4,4,5,5-tetramethyl-l ,3,2-dioxaborolan-2-yl)benzo[cf]oxazole afforded the title compound (30 mg, 31%) as a green solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.91 (s, 1H), 8.80 (d, *J* = 10.0 Hz, 1H), 8.63 (s, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.78 (s, 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 4.46-4.38 (m, 1H), 2.86 (s, 3H), 1.38-1.31 (m, 1H), 0.73-0.70 (m, 1H), 0.61-0.54

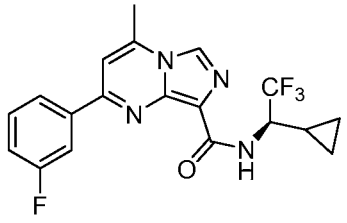
(m, 2H), 0.38-0.33 (m, 1H). LC-MS m/z: 416.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.44 min.

CSV2-(Benzo[</|oxazol-7-yl)-iV-(l-cvclopropyl-2,2,2-M fluoroethyl)-4-methylimidazo[1,5-alpyrimidine-8-carboxamide



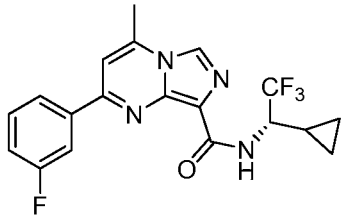
[00671] Following general procedure D, (5)-2-chloro -*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxarnide (100 mg, 0.30 mmol) and 7-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)benzo[cf]oxazole afforded the title compound (44 mg, 35 %) as a green solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.91 (s, 1H), 8.80 (d, J = 10.0 Hz, 1H), 8.63 (s, 1H), 8.26 (d, J = 8.0 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.78 (s, 1H), 7.65 (t, J = 8.0 Hz, 1H), 4.46-4.38 (m, 1H), 2.86 (s, 3H), 1.38-1.31 (m, 1H), 0.73-0.70 (m, 1H), 0.61-0.54 (m, 2H), 0.38-0.33 (m, 1H). LC-MS m/z: 416.1 $[M+H]^+$. HPLC: Purity (214 nm): 97%; t_R = 7.48 min.

(i?)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-2-(3-fluorophenyl)-4-methylimidazo[l,5-*a*\pyrimidine-8-carboxamide



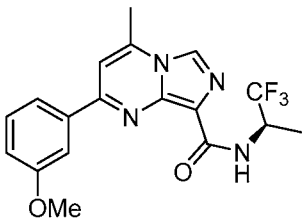
[00672] Following general procedure A, 2-(3-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (100 mg, 0.37 mmol) and (i?)-l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (48 mg, 55 %) as a yellow solid. ^{1}H NMR (500 MHz, *OMSO-d_6)* δ 8.65 (d, J = 9.5 Hz, 1H), 8.59 (s, 1H), 8.09 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 10.5 Hz, 1H), 7.73 (s, 1H), 7.67 (q, J = 7.5 Hz, 1H), 7.45 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 4.43-4.35 (m, 1H), 2.81 (s, 3H), 1.37-1.30 (m, 1H), 0.74-0.67 (m, 1H), 0.61-0.54 (m, 2H), 0.39-0.34 (m, 1H). LC-MS m/z: 393.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.43 min.

(.S^-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-2-(3-fluorophenyl)-4-methylimidazo[l,5-« 1pyrimidine-8-carboxamide



[00673] Following general procedure A, 2-(3-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (100 mg, 0.37 mmol) and (<S)-l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (52.0 mg, 37 %) as a yellow solid. ^{1}H NMR (500 MHz, *OMSO-d$_6$)* δ 8.65 (d, *J* = 9.5 Hz, 1H), 8.59 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 8.03 (d, *J* = 10.5 Hz, 1H), 7.73 (s, 1H), 7.67 (q, *J* = 7.5 Hz, 1H), 7.45 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 4.43-4.35 (m, 1H), 2.81 (s, 3H), 1.37-1.30 (m, 1H), 0.74-0.67 (m, 1H), 0.61-0.54 (m, 2H), 0.39-0.34 (m, 1H). LC-MS m/z: 393.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.43 min.

(i?)-2-(3-Methoxyphenyl)-4-methyl-A^-(l,l..l-trifluoropropan-2-yl)imidazo[l,5-« 1pyrimidine-8-carboxamide

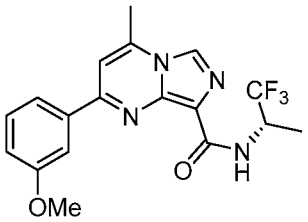


[00674] Following general procedure A, 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylic acid (1.0 g, 2.0 mmol) and (i?)-l,l,l-trifluoropropan-2-amine hydrochloride afforded (i?)-2-chloro-4-methyl -*N*-(l,l,l-trifluoropropan-2-yl)imidazo[l,5-a]pyrimidine-8-carboxamide (380 mg, 62 %) as a yellow solid. LC-MS m/z: 307.1$[M+H]^+$. Purity (214 nm): 91%; t_R = 1.60 min.

[00675] Following general procedure D, (i?)-2-chloro-4-methyl -*N*-(l,l,l-trifluoropropan-2-yl)imidazo[l,5-a]pyrimidine-8-carboxarnide (80 mg, 0.27 mmol), and 3-methoxyphenylboronic acid afforded the title compound (10.4 mg, 11 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56(d, *J* = 9.5 Hz, 1H), 8.54 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.77 (t, *J* = 2.0 Hz,

1H), 7.68 (d, J = 0.5 Hz, 1H), 7.52 (t, J = 8.5 Hz, 1H), 7.17 (dd, J = 8.0 Hz, 2.5 Hz, 1H), 4.99-4.94 (m, 1H), 3.88 (s, 3H), 2.80 (s, 3H), 1.43 (d, J = 6.5 Hz, 3H). LC-MS m/z: 379.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.97 min.

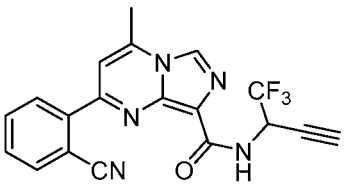
(.S^-2-(3-Methoxyphenyl)-4-methyl-A/-(l,l,l-trifluoropropan-2-yl)imidazo[l,5-*a*]pyrimidine-8-carboxamide



[00676] Following general procedure A, 2-chloro-4-methylimidazo[l ,5-a]pyrirnidine-8-carboxylic acid (1.0 g, 2 mmol) and (*S*)-1,1,1-trifluoropropan-2-amine hydrochloride afforded (<S)-2-chloro-4-methyl-*N*-(1,1,14rifluoropropa n-2-yl)imidazo[1,5-*a*]pyrimidine-8-carboxamide (572 mg, 93 %) as a yellow solid. LC-MS m/z: 307.0$[M+H]^+$. Purity (214 nm): 79%; t_R = 1.60 min.

[00677] Following general procedure D, (5)-2-chloro-4-methyl -*N*-(l ,l ,l-trifluoropropan-2-yl)imidazo[l,5-a]pyrimidine-8-carboxarnide (80 mg, 0.26 mmol) and 3-methoxyphenylboronic acid afforded the title compound (21 mg, 24 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56 (d, J = 8.5 Hz, 1H), 8.54 (s, 1H), 7.81 (d, J = 7.5 Hz, 1H), 7.77 (t, J = 2.5 Hz, 1H), 7.69 (d, J = 1.0 Hz, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.18 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 4.99-4.95 (m, 1H), 3.89 (s, 3H), 2.81 (s, 3H), 1.44 (d, J = 6.5 Hz, 3H). LC-MS m/z: 379.1 $[M+H]^+$. HPLC: Purity (214 nm): 98%; t_R = 7.97 min.

2-(2-Cvanophenyl)-4-methyl -A/-(14J-trifluorobut-3-vn-2-yl)imidazo[l,5-alpyrimidine-8-carboxamide



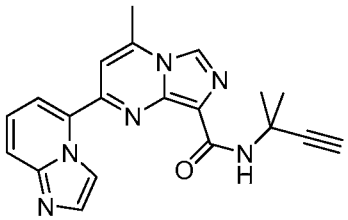
[00678] Following general procedure **D,** ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (300 mg, 1.25 mmol) and 2-cyanophenylboronic acid afforded ethyl 2-(2-

cyanophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (110 mg, 48 %) as a yellow solid. LC-MS m/z: 307.0 $[M+H]^+$. Purity (214 nm): 98%; t_R = 1.51 min.

[00679] Following general procedure B*, ethyl 2-(2-cyanophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (110 mg, 0.36 mmol) afforded 2-(2-cyanophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (61 mg, 60 %) as a yellow solid. LC-MS m/z: 279.0 $[M+H]^+$. Purity (214 nm): 80%; t_R = 1.20 min.

[00680] Following general procedure A, 2-(2-cyanophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (45 mg, 0.16 mmol) and l,l,l-trifluorobut-3-yn-2-amine hydrochloride afforded the title compound (12 mg, 20 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.71 (d, J = 9.5 Hz, 1H), 8.68 (s, 1H), 8.11 (d, J = 7.5 Hz, 1H), 8.05 (d, J = 7.5 Hz, 1H), 7.93 (t, J = 7.5 Hz, 1H), 7.78 (t, J = 7.5 Hz, 1H), 7.51 (s, 1H), 5.98-5.92 (m, 1H), 3.70 (d, J = 2.5 Hz, 1H), 2.84 (s, 3H). LC-MS m/z: 384.0 $[M+H]^+$. HPLC Purity (214 nm): 94%; t_R = 7.58 min.

2-(Iniidazo [1,2-«1pyridin-5-yl)-4-methyl-A^-(2-methylbut-3-vn-2-yl)imidazo [1,5-alpyrimidine-8-carboxamide



[00681] To a solution of 5-bromoimidazo[l,2-a]pyridine (2.50 g, 12.70 mmol) in THF (40 mL) was added a solution of n-BuLi (1.6 M in hexane, 8.7 mL, 13.90 mmol) dropwise at -78 °C. The mixture was stirred at -78 °C for 20 minutes, and then $Sn(Bu)_3Cl$ (4.13 g, 12.70 mmol) was added. The reaction mixture was stirred at RT for 2 h, diluted with DCM (50 mL), and then filtered through a Celite pad using KF (5: 1). The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (1:2 PE: EA) to afford 5-(tributylstannyl)imidazo[l,2-a]pyridine (1.7 g, 33%) as a colorless oil. LC-MS: m/z, 409.1 $[M+H]^+$;Purity (214 nm): 96%; t_R = 1.94 min.

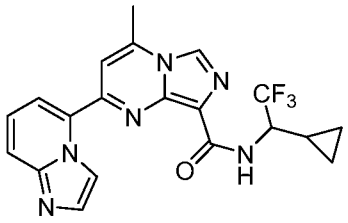
[00682] Following general procedure F*, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (360 mg, 1.51 mmol) and 5-(tributylstannyl)imidazo[l,2-a]pyridine afforded ethyl

2-(imidazo[l ,2-a]pyridin-5-yl)-4-methylimidazo[l ,5-a]pyrimidine-8-carboxylate (310 mg, 64%) as a yellow solid. LC-MS m/z: 322. 1 $[M+H]^+$. Purity (214 nm): 86%; t_R = 1.36 min.

[00683] Following general procedure B*, ethyl 2-(imidazo[l ,2-a]pyridin-5-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (180 mg, 0.56 mmol) afforded 2-(imidazo[l ,2-a]pyridin-5-yl)-4-methylimidazo[l ,5-a]pyrimidine-8-carboxylic acid (120 mg, 73%) as a yellow solid. LC-MS : m/z, 294. 1 $[M+H]^+$;Purity (214 nm): 98%; t_R = 1.25 min.

[00684] Following general procedure A, 2-(imidazo[l ,2-a]pyridin-5-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (40 mg, 0.14 mmol) and 2-methylbut-3-yn-2-amine afforded the title compound (18 mg, 33%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.78 (s, 1H), 8.58 (s, 1H), 7.96 (d, J = 7.5 Hz, 1H), 7.89 (d, J = 7.5 Hz, 1H), 7.88 (s, 1H), 7.82 (s, 1H), 7.74 (s, 1H), 7.47 (t, J = 7.5 Hz, 1H), 3.21 (s, 1H), 2.80 (s, 3H), 1.69 (s, 6H). LC-MS m/z: 359. 1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 5.97 min

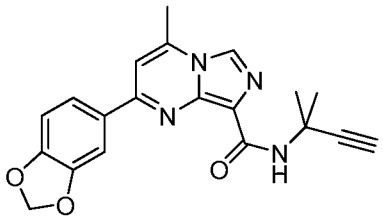
A/-(l-cyclopropyl-2,2,2-trifluoroethyl)-2-(imidazo[l,2-alpyridin-5-yl)-4-methylimidazo [1,5-alpyrimidine-8-carboxamide



[00685] Following general procedure A, 2-(imidazo[l ,2-a]pyridin-5-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (40 mg, 0.14 mmol) and l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (14.7 mg, 25%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.98 (s, 1H), 8.69 (d, J = 9.5 Hz, 1H), 8.66 (s, 1H), 8.06 (d, J = 7.5 Hz, 1H), 7.91 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.49 (t, J = 8.0 Hz, 1H), 4.36-4.21 (m, 1H), 2.81 (s, 3H), 1.48-1.33 (m, 1H), 0.81-0.22 (m, 4H). LC-MS m/z: 415. 1 $[M+H]^+$. HPLC: Purity (214 nm): 97%; t_R = 6.70 min.

2-(Benzo[</l [l,31dioxol-5-yl)-4-methyl -A^-(2-methylbut-3-vn-2-yl)imidazo[l,5-

« 1pyrimidine-8-carboxamide

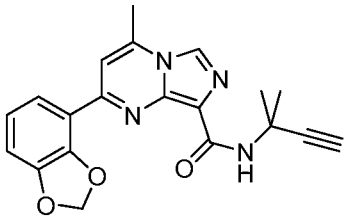


[00686] Following general procedure A, 2-chloro-4-methylimidazo[l ,5-a]pyrimidine-8-carboxylic acid (422 mg, 2.0 mmol) and 2-methylbut-3-yn-2-amine afforded 2-chloro-4-methyl-*N*-(2-methylbut-3-yn-2-yl)imidazo[l ,5-a]pyrirnidine-8-carboxarnide (400 mg, 72%) as a yellow solid. LC-MS: m/z: 277. 1 $[M+H]^+$. Purity (254 nm): 98.23%; t_R = 1.67 min.

[00687] Following general procedure D, 2-chloro-4-methyl-*N*-(2-methylbut-3-yn-2-yl)imidazo[l,5-a]pyrimidine-8-carboxarnide (50 mg, 0.18 mmol) and 2-(benzo[cf][l,3]dioxol-5-yl)-4,4,5,5-tetramethyl-l ,3,2-dioxaborolane afforded the title compound (5.3 mg, 8%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.50 (s, 1H), 8.44 (s, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.80 (s, 1H), 7.60 (s, 1H), 7.16 (*d, J* = 8.5 Hz, 1H), 6.16 (s, 2H), 3.31 (s, 1H), 2.76 (s, 3H), 1.74 (s, 6H). LC-MS m/z: 363. 1 $[M+H]^+$. HPLC: Purity (214 nm): 98%; t_R = 7.39 min.

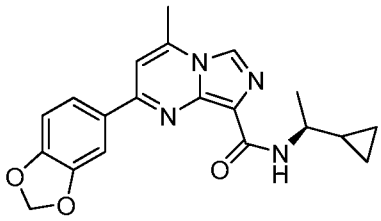
2-(Benzo *d*] [1,31 dioxol-4-yl)-4-methyl -A/-(2-methylbut-3-vn-2-yl)imidazo [1,5-

alpyrimidine-8-carboxamide



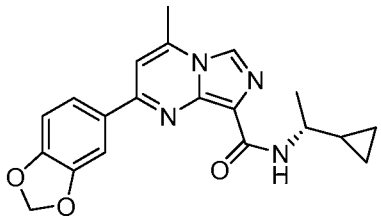
[00688] Following general procedure D, 2-chloro-4-methyl-*N*-(2-methylbut-3-yn-2-yl)imidazo[l,5-a]pyrimidine-8-carboxarnide (60 mg, 0.23 mmol) and benzo[cf| [l ,3]dioxol-4-ylboronic acid afforded the title compound (5.6 mg, 6%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-dg) δ 8.50 (s, 1H), 8.41 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.51 (s, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.21 (s, 2H), 3.37 (s, 1H), 2.78 (s, 3H), 1.72 (s, 6H). LC-MS m/z: 363. 1 $[M+H]^+$. HPLC: Purity (214 nm): 98%; t_R = 8.30 min.

(^-Z-fBenzofrflH^ldioxol-S-vD-A^-d-cvclopropylethvD-^methylimidazoH^-alpyrimidine-8-carboxamide



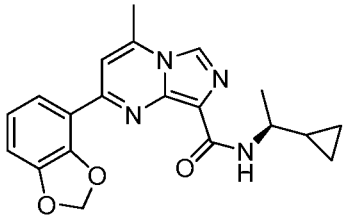
[00689] Following general procedure D, (5)-2-chloro-*N*-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (100 mg, 0.36 mmol) and 2-(benzo[ci|[l,3]dioxol-5-yl)-4,4,5,5-tetramethyl-l,3,2-dioxaborolane afforded the title compound (16.7 mg, 13%) as ayellow solid. ^{1}H NMR (500 MHz, MeOD-d$_4$) δ 8.34 (s, 1H), 7.79 *(d, J* = 7.5 Hz, 1H), 7.78 (s, 1H), 7.42 (s, 1H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.10 (s, 2H), 3.73-3.70 (m, 1H), 2.82 (s, 3H), 1.40 (d, *J* = 6.5 Hz, 3H), 1.13-1.10 (m, 1H), 0.68-0.56 (m, 2H), 0.51-0.46 (m, 1H), 0.42-0.37 (m, 1H). LC-MS m/z: 365.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.51 min.

(i?)-2-(Benzo \d\ \1,31 dioxol-5-yl)-iV-(l-cvclopropylethyl)-4-methylimidazo [1,5-alpyrimidine-8-carboxamide



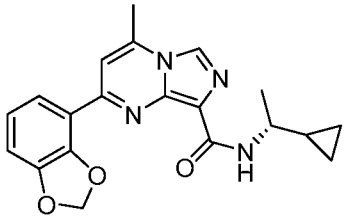
[00690] Following general procedure D, (i?)-2-chloro-*N*-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (80 mg, 0.28 mmol) and 2-(benzo[cf|[l,3]dioxol-5-yl)-4,4,5,5-tetramethyl-l,3,2-dioxaborolane afforded the title compound (19.8 mg, 19 %) as ayellow solid. ^{1}H NMR (400 MHz, MeOD-c¾) δ 8.02 (s, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.41 (s, 1H), 7.08 (s, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 5.83 (s, 2H), 3.46-3.44 (m, 1H), 2.52 (s, 3H), 1.14 (d, *J* = 6.8 Hz, 3H), 0.86-0.84 (m, 1H), 0.36-0.32 (m, 2H), 0.24-0.22 (m, 1H), 0.16-0.13 (m, 1H). LC-MS m/z: 365.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 7.60 min.

(*S*)-2-(Benzo[*d*][1,3]dioxol-4-yl)-*N*-(1-cyclopropylethyl)-4-methylimidazo[1,5-*a*]pyrimidine-8-carboxamide



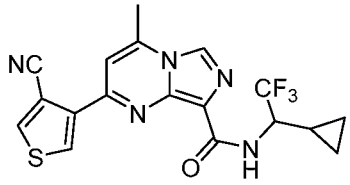
[00691] Following general procedure D, (5)-2-chloro-*N*-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (70 mg, 0.25 mmol) and benzo[cf][l,3]dioxol-4-ylboronic acid afforded the title compound (43.6 mg, 47%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.48 (s, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.50 (s, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.05 (t, *J* = 8.0 Hz, 1H), 6.22 (d, *J* = 2.0 Hz, 2H), 3.65-3.59 (m, 1H), 2.76 (s, 3H), 1.26 (d, *J* = 6.4 Hz, 3H), 1.08-1.00 (m, 1H), 0.51-0.39 (m, 2H), 0.38-0.30 (m, 1H), 0.29-0.20 (m, 1H). LC-MS m/z: 365.2 [M+H]$^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.70 min.

(i?)-2-(Benzo*d*][1,31dioxol-4-yl)-iV-(l-cvclopropylethyl)-4-methylimidazo[1,5-alpyrimidine-8-carboxamide



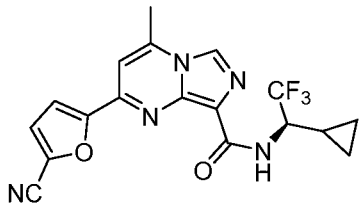
[00692] Following general procedure D, (i?)-2-chloro-*N*-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (80 mg, 0.29 mmol) and benzo[cf][l,3]dioxol-4-ylboronic acid afforded the title compound (37.4 mg, 36 %) as a light yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.25 (d, *J* = 8.5 Hz, 1H), 7.69 (dd, *J* = 8.0 Hz, 1.0 Hz, 1H), 7.50 (d, *J* = 1.5 Hz, 1H), 7.12 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.06 (t, *J* = 8.0 Hz 1H), 6.23 (d, *J* = 0.5 Hz, 2H), 3.65-3.60 (m, 1H), 2.78 (s, 3H), 1.27 (d, *J* = 7.0 Hz, 3H), 1.27-1.01 (m, 1H), 0.50-0.47 (m, 1H), 0.45-0.41 (m, 1H), 0.38-0.31 (m, 1H), 0.29-0.22 (m, 1H). LC-MS m/z: 365.1 [M+H]$^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.77 min.

2-(4-Cvanothiophen-3-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-« 1pyrimidine-8-carboxamide



[00693] Following general procedure E, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (100 mg, 0.30 mmol) and 4-bromothiophene-3-carbonitrile afforded the title compound (5 mg, 4%) as a brown solid. ^{1}H NMR (400 MHz, *MeOO-d4)* δ 8.53-8.48 (m, 3H), 7.44 (s, 1H), 4.20-4.14 (m, 1H), 2.85 (s, 3H), 1.68-1.62 (m, 1H), 0.78-0.74 (m, 1H), 0.62-0.54 (m, 2H), 0.39-0.36 (m, 1H). LC-MS m/z: 406.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.42 min.

(i?)-2-(5-Cvanofuran-2-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



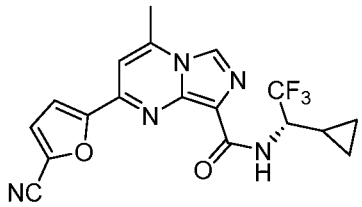
[00694] A mixture of 5-bromofuran-2-carboxylic acid (4.95 g, 25.93 mmol), HATU (9.84 g, 25.88 mmol) and DIEA (18 mL, 109.12 mmol) in DMF (16 mL) was stirred at RT for 30 minutes. Then NH_4C1 (4. 12 g, 77.70 mmol) was added, and the reaction mixture was stirred at RT for another 2 h. The mixture was neutralized with diluted HC1 to pH~7, and partitioned between EA (240 mL) and H_20 (100 mL). The organic layer was washed with H_20 (70 mL x 3), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford crude 5-bromofuran-2-carboxamide (3.2 g, 64%) as a dark brown solid. LC-MS m/z: 190.0, 192.0 $[M+H]^+$. t_R = 1.23 min.

[00695] A mixture of 5-bromofuran-2-carboxamide (3.17 g, 16.66 mmol) and Eï$_3$N (4.89 mL, 35.25 mmol) in DCM (30 mL) was stirred at 0 °C for 30 minutes. Then TFAA (5.13 g, 24.43 mmol) was added dropwise under N_2 and the mixture was stirred at 0 °C for 1 hour. The solution was diluted with DCM (100 mL) and neutralized to pH = 6-7 with saturated NaHCCh.

The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford crude 5-bromofuran-2-carbonitrile (917 mg, 32%) as a black solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, J = 4.5 Hz, 1H), 6.50 (d, J = 5.0 Hz, 1H). t_R = 1.72 min.

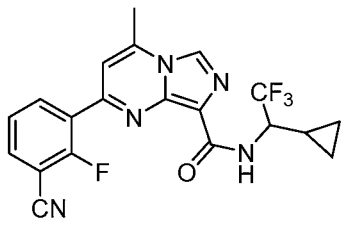
[00696] Following general procedure E, (i?)-2-chloro -*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrinddine-8-carboxamide (120 mg, 0.36 mmol) and 5-bromofuran-2-carbonitrile afforded the title compound (11.4 mg, 8 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-c¾): δ 8.62 (s, 1H), 8.59 (d, J = 9.6 Hz, 1H), 7.87 (d, J = 4.0 Hz, 1H), 7.61 (d, J = 4.0 Hz, 1H), 7.53 (s, 1H), 4.43-4.32 (m, 1H), 2.79 (s, 3H), 1.40-1.30 (m, 1H), 0.70-0.64 (m, 1H), 0.60-0.50 (m, 2H), 0.43-0.30 (m, 1H). LC-MS m/z: 390.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.75 min.

(.S^-2-(5-Cvanofuran-2-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



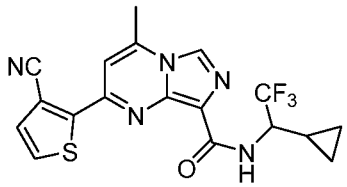
[00697] Following general procedure E, (5)-2-chloro -*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylinddazo[l,5-a]pyrimidine-8-carboxamide (60 mg, 0.18 mmol) and 5-bromofuran-2-carbonitrile afforded the title compound (9 mg, 6 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-i¾): δ 8.61 (s, 1H), 8.58 (d, J = 9.5 Hz, 1H), 7.86 (d, J = 3.5 Hz, 1H), 7.61 (d, J = 3.5 Hz, 1H), 7.53 (s, 1H), 4.43-4.32 (m, 1H), 2.79 (s, 3H), 1.40-1.30 (m, 1H), 0.70-0.64 (m, 1H), 0.60-0.50 (m, 2H), 0.43-0.30 (m, 1H). LC-MS m/z: 390.1 $[M+H]^+$. HPLC Purity (214 nm): 95%; t_R = 7.82 min.

2-(3-Cvano-2-fluorophenyl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



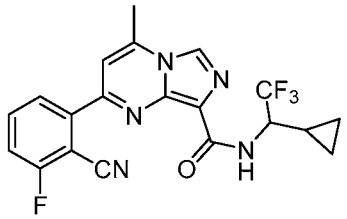
[00698] Following general procedure D, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (80 mg, 0.24 mmol) and 3-cyano-2-fluorophenylboronic acid afforded the title compound (6.6 mg, 7%) as a yellow solid. ^{1}H NMR (500 MHz, **DMSO-i¾)** δ 8.64 (s, 1H), 8.61 (d, *J* = 9.0 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 7.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.46 (s, 1H), 4.36-4.27 (m, 1H), 2.82 (s, 3H), 1.34-1.27 (m, 1H), 0.71-0.64 (m, 1H), 0.59-0.50 (m, 2H), 0.35-0.28 (m, 1H). LC-MS m/z: 418.1 $[M+H]^+$. HPLC: Purity (214 nm): 96%; t_R = 7.83 min.

2-(3-Cvanothiophen-2-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00699] Following general procedure E, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (120 mg, 0.36 mmol) and 2-bromothiophene-3-carbonitrile afforded the title compound (10.1 mg, 7%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-c¾) δ 8.54 (s, 1H), 7.94 (d, *J* = 5.2 Hz, 1H), 7.579 (s, 1H), 7.577 (d, *J* = 5.2 Hz, 1H), 4.34-4.28 (m, 1H), 2.88 (s, 3H), 1.52-1.46 (m, 1H), 0.82-0.76 (m, 1H), 0.65-0.56 (m, 2H), 0.49-0.42 (m, 1H). LC-MS m/z: 406.1 $[M+H]^+$. HPLC: Purity (254 nm): 97%; t_R = 9.59 min.

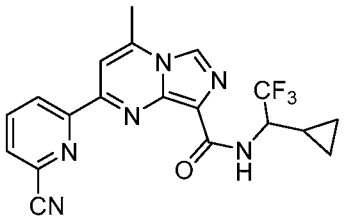
2-(2-Cvano-3-fluorophenyl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00700] Following general procedure D, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (100 mg, 0.30 mmol) and 2-fluoro-6-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)benzonitrile afforded the title compound (14.7 mg, 12%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-c¾) δ 8.57 (s, 1H), 7.94-7.90 (m, 2H), 7.63-7.58 (m, 1H), 7.43 (s, 1H), 4.29-4.20 (m, 1H), 2.90 (s, 3H), 1.50-1.41 (m, 1H), 0.82-0.76 (m, 1H),

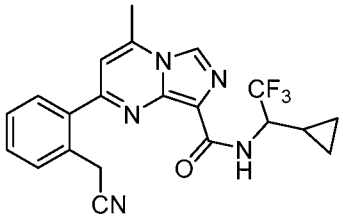
0.63-0.56 (m, 2H), 0.49-0.42 (m, 1H). LC-MS m/z: 418.1 $[M+H]^+$. HPLC: Purity (254 nm): 99%; t_R = 9.53 min.

2-(6-Cvanopyridin-2-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



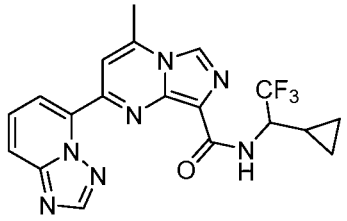
[00701] Following general procedure E, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (70 mg, 0.21 mmol) and 6-bromopicolinonitrile afforded the title compound (8 mg, 10%) as a yellow solid. ^{1}H NMR (400 MHz, **DMSO-i¾):** δ 8.67 (d, *J* = 7.6 Hz, 1H), 8.65 (s, 1H), 8.64 (d, *J* = 7.6 Hz, 1H), 8.34 (t, *J* = 7.6 Hz, 1H), 8.24 (d, *J* = 7.6 Hz, 1H), 7.85 (s, 1H), 4.28-4.22 (m, 1H), 2.86 (s, 3H), 1.46-1.38 (m, 1H), 0.71-0.62 (m, 1H), 0.60-0.51 (m, 2H), 0.38-0.31 (m, 1H). LC-MS m/z: 401.0 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.83 min.

2-(2-(Cvanomethyl)phenyl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00702] Following general procedure D, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (44 mg, 0.132 mmol) and 2-(2-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl)acetonitrile afforded the title compound (6.9 mg, 13%) as ayellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.51 (s, 1H), 7.78 (dd, *J* = 7.5 Hz, 2.5 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.62-7.58 (m, 2H), 7.23 (s, 1H), 4.40 (d, *J* = 18.5 Hz, 1H), 4.34 (d, *J* = 18.5 Hz, 1H), 4.34-4.29 (m, 1H), 2.88 (s, 3H), 1.33-1.26 (m, 1H), 0.80-0.74 (m, 1H), 0.64-0.56 (m, 2H), 0.46-0.40 (m, 1H). LC-MS m/z: 414.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.74 min.

2-([l,2,41Triazolo[l,5-alpyridin-5-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo [1,5-al pyrimidine-8-carboxamide

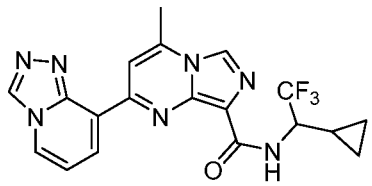


[00703] Following general procedure E, ethyl 2-chloro-4-methylirnidazo[l,5-a]pyrirnidine-8-carboxylate (386 mg, 1.62 mmol) and 5-bromo-[l,2,4]triazolo[l,5-a]pyridine afforded ethyl 2-([l,2,4]triazolo[l,5-a]pyridin-5-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (127 mg, 24 %) as ayellow solid. LC-MS m/z: 323.2 $[M+H]^+$. t_R = 1.36 min.

[00704] Following general procedure B*, ethyl 2-([l,2,4]triazolo[l,5-a]pyridin-5-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (127 mg, 0.39 mmol) afforded crude 2-([l,2,4]triazolo[l,5-a]pyridin-5-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid sodium salt (127 mg) as ayellow solid. LC-MS m/z: 295.1 $[M+H]^+$. t_R = 0.99 min.

[00705] Following general procedure A, 2-([l,2,4]triazolo[l,5-a]pyridin-5-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (127 mg) and l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (31 mg, 19% over two steps) as ayellow solid.. ^{1}H NMR (500 MHz, **DMSO-i¾)** δ 9.23 (d, *J* = 6.5 Hz, 1H), 8.89 (d, *J* = 9.5 Hz, 1H), 8.71 (s, 1H), 8.64 (s, 1H), 8.62 (d, *J* = 7.5 Hz, 1H), 8.38 (s, 1H), 7.50 (t, *J* = 6.5 Hz, 1H), 4.36-4.30 (m, 1H), 2.87 (s, 3H), 1.46-1.42 (m, 1H), 0.76-0.70 (m, 1H), 0.63-0.52 (m, 2H), 0.39-0.32 (m, 1H). LC-MS m/z: 416.1 $[M+H]^+$. HPLC: Purity (214 nm): 97%; t_R = 6.98 min.

2-([1,2,41 Triazolo [4,3-al Pyridin-8-yl)-iV(1-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo [1,5-al pyrimidine-8-carboxamide



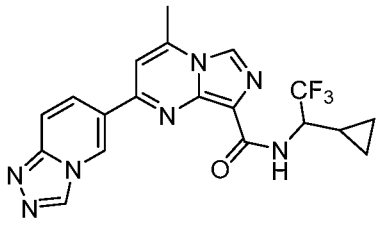
[00706] Following general procedure E, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxylate (480 mg, 2.0 mmol) and 8-bromo-[l,2,4]triazolo[4,3-a]pyridine afford ethyl 2-

([l,2,4]triazolo[4,3-a]pyridin-8-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (360 mg, 39 %) as an orange solid. LC-MS m/z: 323.1[M+H] $^+$. Purity (214 nm): 69%; t_R = 1.32 min.

[00707] Following general procedure B*, ethyl 2-([l,2,4]triazolo[4,3-a]pyridin-8-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (360 mg, 1.12 mmol) afforded 2-([l,2,4]triazolo[4,3-a]pyridin-8-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (350 mg, 100%) as a grey solid. LC-MS m/z: 295.1[M+H] $^+$, t_R = 1.03 min.

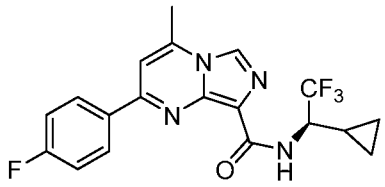
[00708] Following general procedure A, 2-([l,2,4]triazolo[4,3-a]pyridin-8-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (150 mg, 0.51 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (8 mg, 4%) as a yellow solid. ^{1}H NMR (500 MHz, *OMSO-d6)*: δ 9.22 (d, *J* = 6.5 Hz, 1H), 8.89 (d, *J* = 9.5 Hz, 1H), 8.71 (s, 1H), 8.64 (s, 1H), 8.62 (d, *J* = 7.5 Hz, 1H), 8.38 (s, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 4.35-4.30 (m, 1H), 2.86 (s, 3H), 1.46-1.42 (m, 1H), 0.74-0.70 (m, 1H), 0.62-0.55 (m, 2H), 0.38-0.34 (m, 1H). LC-MS m/z: 416.1 [M+H] $^+$. HPLC: Purity (214 nm): 97%; t_R = 6.98 min.

2-([1,2,41 Triazolo [4,3-«l pyridin-6-yl)-iV-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methyliniidazo [1,5-al pyrimidine-8-carboxamide



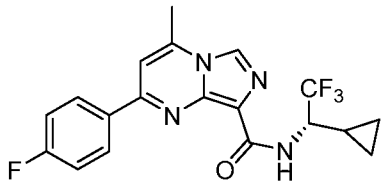
[00709] Following general procedure E, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (100 mg, 0.3 mmol) and 6-bromo-[l,2,4]triazolo[4,3-a]pyridine afforded the title compound (38.3 mg, 31%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 9.47 (s, 1H), 9.32 (s, 1H), 8.51 (s, 1H), 8.38 (d, *J* = 10.0 Hz, 1H), 7.94 (d, *J* = 10.0 Hz, 1H), 7.56 (s, 1H), 4.40-4.36 (m, 1H), 2.90 (s, 3H), 1.41-1.37 (m, 1H), 0.84-0.78 (m, 1H), 0.69-0.60 (m, 2H), 0.54-0.48 (m, 1H). LC-MS m/z: 416.1 [M+H] $^+$. HPLC: Purity (214 nm): 97%; t_R = 6.39 min.

(i?)-A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(4-fluorophenyl)-4-methylimidazo[l,5-« 1pyrimidine-8-carboxamide



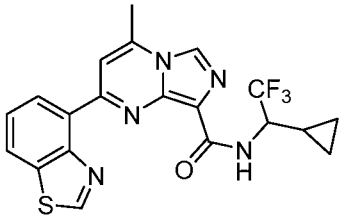
[00710] Following general procedure A, 2-(4-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 0.11 mmol) and (i?)-l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (15 mg, 38 %) as a yellow solid. ^{1}H NMR (500 MHz, *OMSO-d6):* δ 8.63 (d, *J* = 9.5 Hz, 1H), 8.54 (s, 1H), 8.28 (dd, *J* = 9.0 Hz, 5.5 Hz, 2H), 7.68 (s, 1H), 7.47 (t, *J* = 9.0 Hz, 2H), 4.40-4.29 (m, 1H), 2.80 (s, 3H), 1.38-1.29 (m, 1H), 0.70-0.64 (m, 1H), 0.60-0.52 (m, 2H), 0.38-0.30 (m, 1H). LC-MS m/z: 393. 1 $[M+H]^+$. HPLC Purity (214 nm): 98%; t_R = 8.47 min.

(.s')-A/-(l-Cvclopropyl -2,2,2-trifluoroethvn -2-(4-fluorophenvn-4-methylimidazo[l,5-*a*\pyrimidine-8-carboxamide



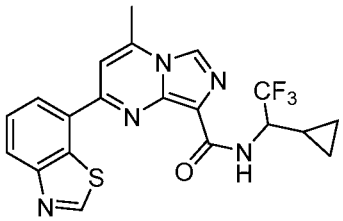
[00711] Following general procedure A, 2-(4-fluorophenyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 0.11 mmol) and (<S)-l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (21.5 mg, 55 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-c¾): δ 8.63 (d, *J* = 9.5 Hz, 1H), 8.54 (s, 1H), 8.28 (dd, *J* = 9.0 Hz, 5.5 Hz, 2H), 7.68 (s, 1H), 7.47 (t, *J* = 9.0 Hz, 2H), 4.40-4.29 (m, 1H), 2.80 (s, 3H), 1.38-1.29 (m, 1H), 0.70-0.64 (m, 1H), 0.60-0.52 (m, 2H), 0.38-0.30 (m, 1H). LC-MS m/z: 393. 1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.44 min.

2-(Benzo[</lthiazol-4-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-« 1pyrimidine-8-carboxamide



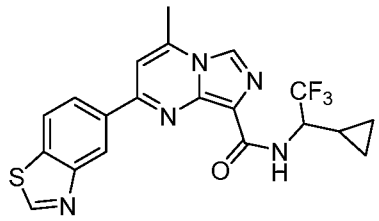
[00712] Following general procedure E, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (100 mg, 0.30 mmol) and 4-bromobenzo[cf]thiazole afforded the title compound (3.1 mg, 2 %) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 9.43 (s, 1H), 8.51 (s, 1H), 8.34 (dd, *J* = 7.5 Hz, 5.0 Hz, 2H), 8.22 (s, 1H), 7.71 (t, *J* = 7.5 Hz, 1H), 4.48-4.46 (m, 1H), 2.91 (s, 3H), 1.31-1.27 (m, 1H), 0.77-0.74 (m, 1H), 0.63-0.52 (m, 2H), 0.51-0.49 (m, 1H). LC-MS m/z: 432.0 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.25 min.

2-(Benzo[</lthiazol-7-vn-A/-(l-cvclopropyl-2,2,2-trifluoroethvn-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



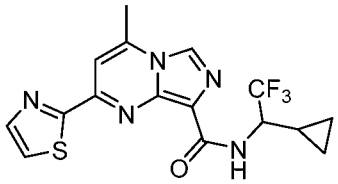
[00713] Following general procedure E, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (124 mg, 0.373 mmol) and 7-bromobenzo[cf]thiazole afforded the title compound (7.1 mg, 4 %) as a yellow solid. ^{1}HNMR (500 MHz, DMSO-d_6) δ 9.64 (s, 1H), 8.62 (s, 1H), 8.52 (d, *J* = 9.5 Hz, 1H), 8.48 (d, *J* = 7.5 Hz, 1H), 8.34 (d, *J* = 8.0 Hz, 1H), 7.95 (s, 1H), 7.81 (t, *J* = 7.5 Hz, 1H), 4.32-4.26 (m, 1H), 2.85 (s, 3H), 1.46-1.42 (m, 1 H), 0.75-0.73 (m, 1 H), 0.69-0.65 (m, 1H), 0.59-0.56 (m, 1H), 0.36-0.32 (m, 1H). LC-MS m/z: 432.0 $[M+H]^+$. HPLC Purity (214 nm): 98.2%; t_R = 7.53 min.

2-(Benzo[dlthiazol-5-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



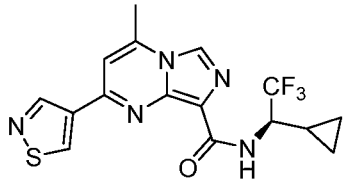
[00714] Following general procedure D, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (100 mg, 0.30 mmol) and 5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)benzo[cf]thiazole afforded the title compound (8.0 mg, 6%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.53 (s, IH), 8.96 (s, IH), 8.72 (d, J = 9.6 Hz, IH), 8.57 (s, IH), 8.40 (d, J = 8.4 Hz, IH), 8.36 (dd, J = 8.8 Hz, 1.2 Hz, IH), 7.89 (s, IH), 4.42-4.38 (m, IH), 2.82 (s, 3H), 1.35-1.30 (m, IH), 0.70-0.67 (m, IH), 0.58-0.52 (m, 2H), 0.38-0.36 (m, IH). LC-MS m/z: 434.0 $[M+H]^+$. HPLC: Purity (214 nm): 94%; t_R = 7.74 min.

iV-(l-Cvclopropyl-2,2,2-trifluoroethyl)-4-meth^ 2-(thiazol-2-yl)imidazo[1,5-*a*]pyrimidine-8-carboxamide



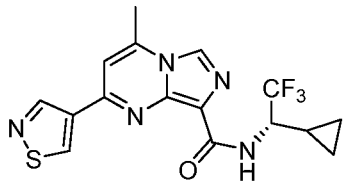
[00715] Following general procedure F*, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (50 mg, 0.15 mmol) and 2-(tributylstannyl)thiazole afforded the title compound (1.5 mg, 3%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.53 (s, IH), 8.10 (d, J = 3.5 Hz, IH), 7.93 (d, J = 3.5 Hz, IH), 7.75 (s, IH), 4.48-4.42 (m, IH), 2.89 (s, 3H), 1.40-1.35 (m, IH), 0.82-0.75 (m, IH), 0.72-0.62 (m, IH), 0.61-0.51 (m, 2H). LC-MS m/z: 382.0 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.57 min.

(i?)-A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(isothiazol-4-yl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



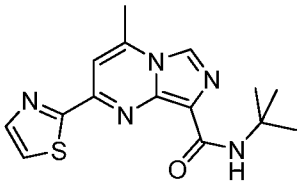
[00716] Following general procedure A, 2-(isothiazol-4-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 11.4 mmol) and (i?)-l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (4.4 mg, 10 %) as a yellow solid. ^{1}H NMR (500 MHz, *MeOO-d$_4$)* δ 9.62 (s, IH), 9.17 (s, IH), 8.34 (s, IH), 7.38 (s, IH), 4.33-4.25 (m, IH), 2.75 (s, 3H), 1.26-1.21 (m, IH), 0.69-0.65 (m, IH), 0.56-0.49 (m, 2H), 0.40-0.38 (m, IH). LC-MS m/z: 382.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.44 min.

CSViV-(l-Cvclopropyl-2,2,2-trifluoroethyl)-^-(isothiazol-4-yl)-4-methylimidazo[1,5-alpyrimidine-8-carboxamide



[00717] Following general procedure A, 2-(isothiazol-4-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 11.4 mmol) and (<S)-l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (4.6 mg, 11 %) as a yellow solid. ^{1}H NMR (500 MHz, *MeOO-d$_4$)* δ 9.62 (s, IH), 9.17 (s, IH), 8.34 (s, IH), 7.38 (s, IH), 4.33-4.25 (m, IH), 2.75 (s, 3H), 1.26-1.21 (m, IH), 0.69-0.65 (m, IH), 0.56-0.49 (m, 2H), 0.40-0.38 (m, IH). LC-MS m/z: 382.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.45 min.

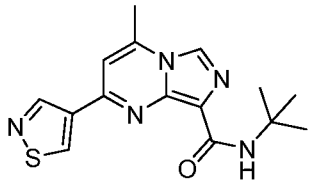
A^-ferf-buM-4-methyl-2-(thiazol-2-yl)imidazo[l,5-alpyrimidine-8-carboxamide



[00718] Following general procedure A, 2-chloro-4-methylirnidazo[l,5-a]pyrirnidine-8-carboxylic acid (500 mg, 2.37 mmol) and 2-methylpropan-2-amine afforded *N-tert-buty\-2-*chloro-4-methylimidazo[l,5-a]pyrirnidine-8-carboxamide (180 mg, 30%) as a white solid.

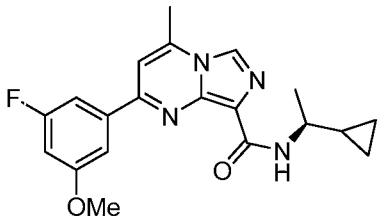
[00719] Following general procedure F*, *N*-teri-butyl-2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxamide (50 mg, 0.18 mmol) and 2-(tributylstannyl)thiazole afforded the title compound (1.2 mg, 2 %) as a yellow solid. ^{1}H NMR (500 MHz, *MeOO-d_4)* δ 8.34 (s, IH), 7.96 (d, *J* = 3.0 Hz, IH), 7.78 (d, *J* = 3.0 Hz, IH), 7.57 (s, IH), 2.75 (s, 3H), 1.78 (s, 9H). LC-MS m/z: 316.0 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.07 min.

A/-ferf-buM-2-(isothiazol-4-yl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00720] Following general procedure A, 2-(isothiazol-4-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 0.1 1 mmol) and 2-methylpropan-2-amine afforded the title compound (3.3 mg, 9%) as a yellow solid. ^{1}H NMR (500 MHz, *OMSO-d_6)* δ 9.91 (s, IH), 9.29 (s, IH), 8.40 (s, IH), 2.84 (s, 3H), 1.59 (s, 9H). LC-MS m/z: 316.0 $[M+H]^+$. HPLC: Purity (254 nm): 94%; t_R = 7.65 min.

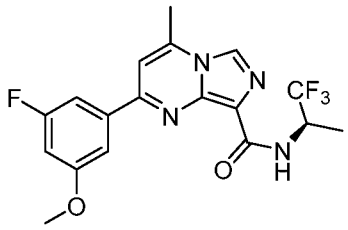
(*S*)-*N*-(1-Cyc˜opr˜eihy1)-2-(3-fluor˜-5-ineihoxypheny1)-4-ineihy1imidaζo[1,5-alpyrimidine-8-carboxamide



[00721] Following general procedure D, (5)-2-chloro -*N*-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (84 mg, 0.302 mmol) and 3-fluoro-5-methoxyphenylboronic acid afforded the title compound (20 mg, 18%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (s, IH), 8.15 (d, *J* = 6.5 Hz, IH), 7.68-7.62 (m, 3H), 7.09-7.06 (m, IH), 3.90 (s, 3H), 3.62-3.60 (m, IH), 2.75 (s, 3H), 1.28 (d, *J* = 4.5 Hz, 3H), 1.10-1.07

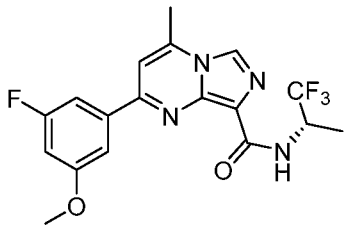
(m, 1H), 0.55-0.42 (m, 2H), 0.40-0.30 (m, 1H), 0.30-0.25 (m, 1H). LC-MS m/z: 369. 1 $[M+H]^+$. HPLC: Purity (214 nm): 91%; t_R = 8.08 min.

(i?)-2-(3-Fluoro-5-methoxyphenyl)-4-methyl-A^-(144-trifluoropropan-2-yl)imidazo[l,5-alpyrimidine-8-carboxamide



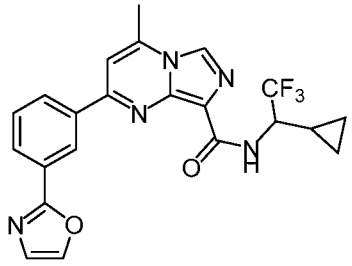
[00722] Following general procedure **D,** (i?)-2-chloro-4-methyl -*N*-(l, l,l-trifluoropropan-2-yl)iinidazo[l,5-a]pyrirnidine-8-carboxamide (70 mg, 0.23 mmol) and 3-fluoro-5-methoxyphenylboronic acid afforded the title compound (30 mg, 33%) as a yellow solid. ^{1}H NMR (400 MHz, *OMSO-d_6)* δ 8.57 (s, 1H), 8.54 (d, *J* = 9.6 Hz, 1H), 7.73 (s, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.63 (d, *J* = 10.4 Hz, 1H), 7.09 (dt, *J* = 10.4 Hz, 2.4 Hz, 1H), 5.01-4.94 (m, 1H), 3.89 (s, 3H), 2.79 (s, 3H), 1.43 (d, *J* = 7.2 Hz, 3H). LC-MS m/z: 397. 1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.19 min.

(.S^-2-(3-Fluoro-5-methoxyphenyl)-4-methyl-A/-(144-trifluoropropan-2-yl)imidazo[l,5-alpyrimidine-8-carboxamide



[00723] Following general procedure D, (5)-2-chloro-4-methyl -*N*-(l ,l ,l-trifluoropropan-2-yl)iinidazo[l,5-a]pyrimidine-8-carboxarnide (80 mg, 0.26 mmol) and 3-fluoro-5-methoxyphenylboronic acid afforded the title compound (15 mg, 17 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.52 (d, *J* = 9.0 Hz, 1H), 7.73 (s, 1H), 7.65 (d, *J* = 2.5 Hz, 1H), 7.64 (d, *J* = 12.0 Hz, 1H), 7.09 (dt, *J* = 12.0 Hz, 2.5 Hz, 1H), 5.01-4.94 (m, 1H), 3.89 (s, 3H), 2.79 (s, 3H), 1.43 (d, *J* = 7.0 Hz, 3H). LC-MS m/z: 397. 1 $[M+H]^+$. HPLC: Purity (214 nm): 97%; t_R = 8.19 min.

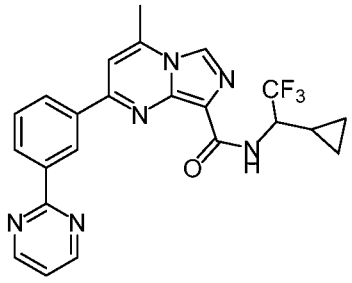
A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-4-methyl-2-(3-(oxazol-2-yl)phenyl)imidazo[l,5-alpyrimidine-8-carboxamide



[00724] Following general procedure D, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (300 mg, 0.90 mmol) and 3-bromophenylboronic acid afforded the title compound 2-(3-bromophenyl)-*N*-(l-cyclopropyl-2,2,24rifluoroethyl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxamide (100 mg, 30%) as a yellow solid. LC-MS m/z: 453.1 $[M+H]^+$. Purity (214 nm): 95%; t_R = 1.88 min.

[00725] Following general procedure F*, 2-(3-bromophenyl)-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxamide (70 mg, 0.16 mmol) and 2-(tributylstannyl)oxazole afforded the title compound (8.9 mg, 10 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-i¾) δ 8.88 (s, 1H), 8.74 (d, *J* = 9.2 Hz, 1H), 8.59 (s, 1H), 8.36 (d, *J* = 8.0 Hz, 1H), 8.29 (s, 1H), 8.19 (d, *J* = 7.6 Hz, 1H), 7.80-7.76 (m, 2H), 7.46 (s, 1H), 4.39-4.28 (m, 1H), 2.84 (s, 3H), 1.48-1.39 (m, 1H), 0.78-0.72 (m, 1H), 0.65-0.55 (m, 2H), 0.42-0.32 (m, 1H). LC-MS m/z: 419.1 $[M+H]^+$. HPLC: Purity (214 nm): 96%; t_R = 8.00 min.

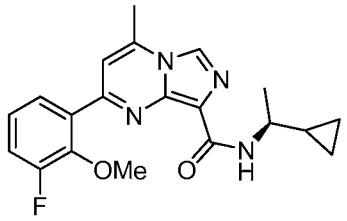
iV-(l-Cvclopropyl-2,2,2-trifluoroethyl)-4-meth^ 2-(3-(pyrimidin-2-yl)phenyl)imidazo[1,5-alpyrimidine-8-carboxamide



[00726] Following general procedure F*, 2-(3-bromophenyl)-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxamide (100 mg, 0.22 mmol) and 2-(tributylstannyl)pyrimidine afforded the title compound (2 mg, 2%) as a yellow solid. ^{1}H NMR

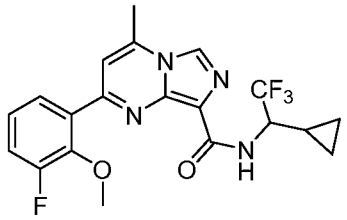
(500 MHz, DMSO-i¾) δ 9.34 (s, 1H), 8.92 (d, J = 4.8 Hz, 2H), 8.81 (d, J = 9.6 Hz, 1H), 8.585 (d, J = 7.2 Hz, 1H), 8.576 (s, 1H), 8.37 (d, J = 8.0 Hz, 1H), 7.77 (t, J = 8.0 Hz, 1H), 7.76 (s, 1H), 7.52 (t, J = 4.8 Hz, 1H), 4.36-4.30 (m, 1H), 2.83 (s, 3H), 1.52-1.46 (m, 1H), 0.78-0.71 (m, 1H), 0.64-0.54 (m, 2H), 0.40-0.35 (m, 1H). LC-MS m/z: 453.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.21 min.

(*S*)-*N*-(1-Cyclopropylethyl)-2-(3-fluoro-2-methoxyphenyl)-4-methylimidazo[1,5-a]pyrimidine-8-carboxamide



[00727] Following general procedure **D,** (5)-2-chloro-*N*-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (80 mg, 0.287 mmol) and 3-fluoro-2-methoxyphenylboronic acid afforded the title compound (18 mg, 17%) as a yellow solid. ^{1}H NMR (500 MHz, *OMSO-d_6)* δ 8.51 (s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.49 (dd, J = 10.0 Hz, 8.0 Hz, 1H), 7.34-7.30 (m, 1H), 7.29 (s, 1H), 3.90 (s, 3H), 3.59-3.56 (m, 1H), 2.79 (s, 3H), 1.24 (d, J = 6.5 Hz, 3H), 1.04-1.00 (m, 1H), 0.49-0.41 (m, 1H), 0.41-0.38 (m, 1H), 0.38-0.29 (m, 1H), 0.29-0.21 (m, 1H). LC-MS m/z: 369.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.78 min.

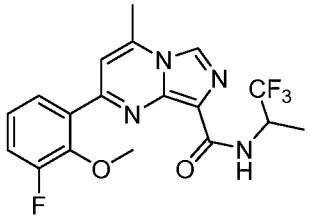
A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(3-fluoro-2-methoxyphenyl)-4-methylimidazo [1,5-alpyrimidine-8-carboxamide



[00728] Following general procedure **D,** 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (100 mg, 0.30 mmol) and 3-fluoro-2-methoxyphenylboronic afforded the title compound (40 mg, 31 %) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-c¾) δ 8.48 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.43 (s, 1H), 7.39 (t, J = 10.0

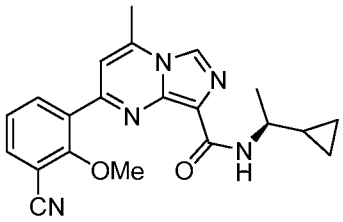
Hz, 1H), 7.29-7.25 (m, 1H), 4.46-4.42 (m, 1H), 3.96 (d, J = 1.0 Hz, 3H), 2.86 (s, 3H), 1.27-1.24 (m, 1H), 0.77-0.74 (m, 1H), 0.63-0.50 (m, 2H), 0.49-0.46 (m, 1H). LC-MS m/z: 423.0 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.50 min.

2-(3-Fluoro-2-methoxyphenyl)-4-methyl-A^-(l,l..l-trifluoropropan-2-yl)imidazo[l,5-alpyrimidine-8-carboxamide



[00729] Following general procedure **D,** 2-chloro-4-methyl -*N-(* 1,1,1 -trifluoropropan-2-yl)imidazo[l,5-a]pyrimidine-8-carboxarnide (100 mg, 0.33 mmol) and 3-fluoro-2-methoxyphenylboronic acid afforded the title compound (12.4 mg, 10 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.52 (d, J = 9.5 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.53-7.47 (m, 1H), 7.33 (s, 1H), 7.33-7.28 (m, 1H), 4.92-4.89 (m, 1H), 3.90 (s, 3H), 2.80 (s, 3H), 1.39 (d, J = 7.0 Hz, 3H). LC-MS m/z: 397.0 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.14 min.

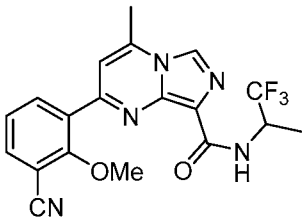
(„S)-2-(3-Cvano-2-methoxyphenyl)-A/-(l-cvclopropylethyl)-4-methylimidazo[l,5-« 1pyrimidine-8-carboxamide



[00730] Following general procedure **D,** (5)-2-chloro -*N* -(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (60 mg, 0.22 mmol) and 2-methoxy-3-(4,4,5, 5-tetramethyl-l,3,2-dioxaborolan-2-yl)benzonitrile afforded the title compound (21 mg, 69 %) as ayellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.13 (dd, J = 10.0 Hz, 2.0 Hz, 1H), 8.08 (d, J = 10.5 Hz, 1H), 8.01 (dd, J = 7.5 Hz, 2.0 Hz, 1H), 7.52 (t, J = 9.5 Hz, 1H), 7.34 (s, 1H), 3.89 (s, 3H), 3.56-3.53 (m, 1H), 2.79 (s, 3H), 1.24 (d, J = 8.0 Hz, 3H), 1.05-

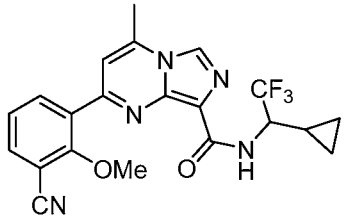
1.03 (m, 1H), 0.47-0.23 (m, 4H). LC-MS m/z: 376.0 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.44 min.

2-(3-Cvano-2-methoxyphenyl)-4-methyl-A^-(l,l..l-trifluoropropan-2-yl)imidazo[l,5-alpyrimidine-8-carboxamide



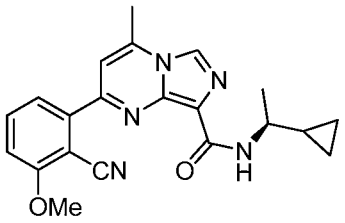
[00731] Following general procedure D, 2-chloro-4-methyl -*N*-(1,1,1-trifluoropropan-2-yl)imidazo[l,5-a]pyrimidine-8-carboxarnide (80 mg, 0.18 mmol) and 2-methoxy-3-(4,4,5,5-tetramethyl-l ,3,2-dioxaborolan-2-yl)benzonitrile afforded the title compound (35 mg, 49 %) as a yellow solid. ^{1}H NMR (500 MHz, *OMSO-d6)* δ 8.60 (s, 1 H), 8.51 (d, *J* = 9.5 Hz, 1H), 8.10 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 8.02 (dd, *J* = 8.0 Hz, 1.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.38 (s, 1 H), 4.93-4.88 (m, 1H), 3.89 (s, 3H), 2.80 (s, 3H), 1.39 (d, *J* = 7.0 Hz, 3H). LC-MS m/z: 404.1 $[M+H]^+$. HPLC: Purity (214 nm): 98.2%; t_R = 7.56 min.

2-(3-Cvano-2-methoxyphenvn-A/-(l-cvclopropyl-2,2,2-trifluoroethvn-4-methylimidazo [1,5-alpyrimidine-8-carboxamide



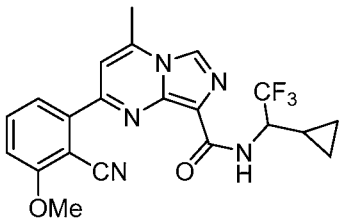
[00732] Following general procedure D, 2-chloro-*N*-(l -cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (60 mg, 0.18 mmol) and 2-methoxy-3-(4,4,5,5-tetramethyl-l ,3,2-dioxaborolan-2-yl)benzonitrile afforded the title compound (8 mg, 10 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.60 (s, 1H), 8.57 (d, *J* = 9.6 Hz, 1H), 8.08 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 8.01 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.37 (s, 1H), 4.33-4.23 (m, 1H), 3.88 (s, 3H), 2.80 (s, 3H), 1.34-1.25 (m, 1H), 0.70-0.62 (m, 1H), 0.58-0.48 (m, 2H), 0.34-0.27 (m, 1H). LC-MS m/z: 430.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.91 min.

(S)-2-(2-cvano-3-methoxyphenyl)-A/-(l-cvclopropylethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



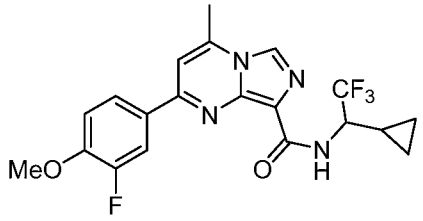
[00733] Following general procedure D, (5)-2-chloro-*N*-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (80 mg, 0.29 mmol) and 2-(5,5-dimethyl-l,3,2-dioxaborinan-2-yl)-6-methoxybenzonitrile afforded the title compound (30 mg, 28%) as a yellow solid. 'HNMR (500 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.15 (d, J = 8.5 Hz, 1H), 7.86 (t, J = 8.5 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.40 (s, 1H), 4.02 (s, 3H), 3.58-3.52 (m, 1H), 2.80 (s, 3H), 1.27 (d, J = 6.5 Hz, 3H), 1.10-1.05 (m, 1 H), 0.47-0.41 (m, 1H), 0.38-0.30 (m, 2H), 0.25-0.20 (m, 1H) LC-MS m/z: 376.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 7.03 min.

2-(2-Cvano-3-methoxyphenyl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo [1,5-al pyrimidine-8-carboxamide



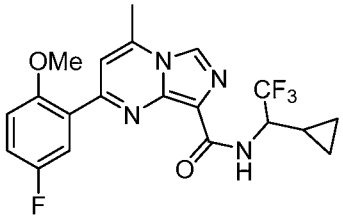
[00734] Following general procedure D, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (80 mg, 0.24 mmol) and 2-cyano-3-methoxyphenylboronic acid afforded the title compound (10 mg, 10 %) as ayellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.48 (d, J = 9.5 Hz, 1H), 7.87 (t, J = 8.0 Hz, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.48 (d, J = 9.0 Hz, 1H), 7.45 (s, 1H), 4.30-4.22 (m, 1H), 4.02 (s, 3H), 2.82 (s, 3H), 1.39-1.34 (m, 1H), 0.72-0.66 (m, 1H), 0.61-0.58 (m, 1H), 0.50-0.47 (m, 1H), 0.33-0.30 (m, 1H). LC-MS m/z: 430.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.24 min.

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(3-fluoro-4-methoxyphenyl)-4-methylimidazo [1,5-al pyrimidine-8-carboxamide



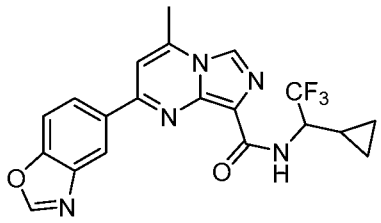
[00735] Following general procedure **D,** 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (80 mg, 0.24 mmol) and 3-fluoro-4-methoxyphenylboronic acid afforded the title compound (28 mg, 20 %) as a yellow solid. ^{1}H NMR (400 MHz, *OMSO-d$_6$)* δ 8.65 (d, *J* = 10.0 Hz, 1H), 8.52 (s, 1H), 8.09 (s, 1H), 8.06 (s, 1H), 7.68 (s, 1H), 7.41 (t, *J* = 8.8 Hz, 1H), 4.43-4.36 (m, 1H), 3.96 (s, 3H), 2.78 (s, 3H), 1.36-1.28 (m, 1H), 0.72-0.66 (m, 1H), 0.60-0.53 (m, 2H), 0.39-0.32 (m, 1H). LC-MS m/z: 423.1 [M+H]$^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.19 min.

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(5-fluoro-2-methoxyphenyl)-4-methylimidazo [1,5-al pyrimidine-8-carboxamide



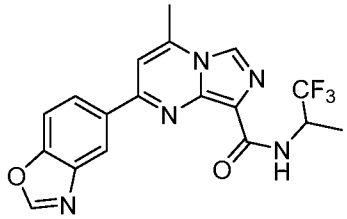
[00736] Following general procedure D, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (100 mg, 0.3 mmol) and 5-fluoro-2-methoxyphenylboronic acid afforded the title compound (68 mg, 54%) as a yellow solid. ^{1}HNMR (500 MHz, MeOD-c¾) δ 8.46 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 3.0 Hz, 1H), 7.54 (s, 1H), 7.32-7.28 (m, 1H), 7.24-7.21 (m, 1H), 4.49-4.45 (m, 1H), 3.97 (s, 3H), 2.84 (s, 3H), 1.28-1.23 (m, 1H), 0.78-0.73 (m, 1H), 0.65-0.54 (m, 2H), 0.53-0.49 (m, 1H). LC-MS m/z: 423.1 [M+H]$^+$. HPLC Purity (214 nm): > 99%; t_R = 9.02 min.

2-(Benzo[dloxazol-5-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



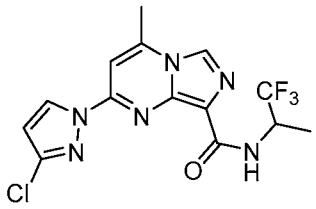
[00737] Following general procedure **D,** 2-chloro -*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (100 mg, 0.30 mmol) and 5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)benzo[cf]oxazole afforded the title compound (27 mg, 22 %) as ayellow solid. 'HNMR (500 MHz, *MeOO-d*$_4$) δ 8.64 (s, IH), 8.63 (s, IH), 8.48 (s, IH), 8.39 (d, *J* = 8.5 Hz, IH), 7.90 (d, *J* = 8.5 Hz, IH), 7.66 (s, IH), 4.46-4.44 (m, IH), 2.90 (s, 3H), 1.38-1.34 (m, IH), 0.81-0.79 (m, IH), 0.69-0.66 (m, IH), 0.62-0.60 (m, IH), 0.55-0.52 (m, IH). LC-MS m/z: 416.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.23 min.

2-(Benzo[</loxazol-5-vn-4-methyl-A/-(14J-trifluoropropan-2-ylMmidazo[l,5-alpyrimidine-8-carboxamide



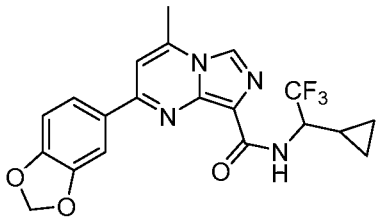
[00738] Following general procedure **D,** 2-chloro-4-methyl -*N*-*(*1,1,1-trifluoropropan-2-yl)imidazo[l,5-a]pyrimidine-8-carboxarnide (50 mg, 0.16 mmol) and 5-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)benzo[cf]oxazole afforded the title compound (10.7 mg, 17 %) as a yellow solid. ^{1}H NMR (500 MHz, *OMSO-d*$_6$) δ 8.90 (s, IH), 8.68 (d, *J* = 1.5 Hz, IH), 8.60 (d, *J* = 9.0 Hz, IH), 8.55 (s, IH), 8.37 (dd, *J* = 9.0 Hz, 1.5 Hz, IH), 8.02 (d, *J* = 9.0 Hz, IH), 7.83 (s, IH), 5.00-4.94 (m, IH), 2.81 (s, 3H), 1.45 (t, *J* = 7.5 Hz, 3H). LC-MS m/z: 390.1 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 7.01 min.

2-(3-Chloro-1*H*-pyrazol-1-yl)-4-methyl-*N*-(1,1,1-trifluoropropan-2-yl)imidazo[1,5-a]pyrimidine-8-carboxamide



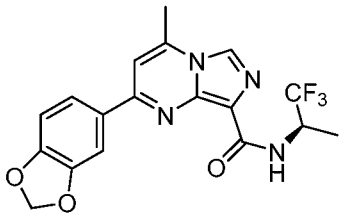
[00739] To a solution of 2-chloro-4-methyl-*N*-(1,1,1-trifluoropropan-2-yl)imidazo[1,5-a]pyrimidine-8-carboxamide (70 mg, 0.23 mmol) in DMF (5 mL) was added K_2CO_3 (63 mg, 0.46 mmol) and 3-chloro-1*H*-pyrazole (36 mg, 0.35 mmol). Then the mixture was stirred at 70 °C for 2 h, and purified by *prep*-HPLC (10 mM NH_4HCO_3/MeCN) to afford the title compound (7 mg, 7 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (d, J = 3.0 Hz, 1H), 8.54 (s, 1H), 8.32 (d, J = 9.5 Hz, 1H), 7.55 (d, J = 1.0 Hz, 1H), 6.88 (d, J = 3.0 Hz, 1H), 4.92-4.86 (m, 1H), 2.83 (s, 3H), 1.42 (d, J = 7.5 Hz, 3H). LC-MS m/z: 373.0 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 7.85 min.

2-(Benzo[<//[131dioxol-5-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[1,5-alpyrimidine-8-carboxamide



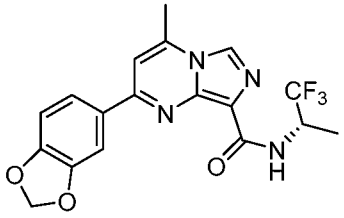
[00740] Following general procedure **D,** 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylinddazo[l,5-a]pyrimidine-8-carboxamide (120 mg, 0.36 mmol) and 2-(benzo[cf][l,3]dioxol-5-yl)-4,4,5,5-tetramethyl-l,3,2-dioxaborolane afforded the title compound (55 mg, 36 %) as ayellow solid. ^{1}H NMR (400 MHz, *MeOO-d4)* δ 8.38 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.70 (s, 1H), 7.44 (s, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.09 (s, 2H), 4.48-4.44 (m, 1H), 2.82 (s, 3H), 1.32-1.28 (m, 1H), 0.80-0.74 (m, 1H), 0.68-0.46 (m, 3H). LC-MS m/z: 419.0 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 9.80 min.

(i?)-2-(Benzo[</l[131dioxol-5-yl)-4-methyl-A^-(144-trifluoropropan-2-yl)imidazo[l,5-alpyrimidine-8-carboxamide



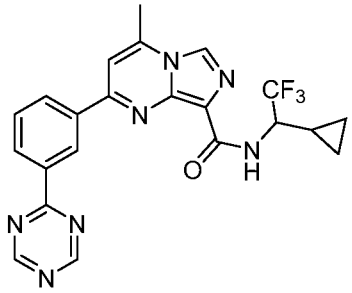
[00741] Following general procedure D, (i?)-2-chloro-4-methyl -*N*-(l, l,l-trifluoropropan-2-yl)irnidazo[l,5-a]pyrirnidine-8-carboxamide (80 mg, 0.26 mmol) and 2-(benzo[cf][l,3]dioxol-5-yl)-4,4,5,5-tetramethyl-l ,3,2-dioxaborolane afforded the title compound (52 mg, 51 %) as a yellow solid. ¾ NMR (500 MHz, *MeOO-d4)* δ 8.39 (s, 1H), 7.78 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.73 (d, *J* = 1.6 Hz, 1H), 7.46 (s, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.10 (s, 2H), 5.01-4.96 (m, 1H), 2.82 (s, 3H), 1.52 (d, *J* = 7.2 Hz, 3H). LC-MS m/z: 393.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 7.67 min.

(.S^-2-(Benzo[</|[131dioxol-5-yl)-4-methyl-A/-(144-trifluoropropan-2-yl)imidazo[l,5-alpyrimidine-8-carboxamide



[00742] Following general procedure D, (S)-2-chloro-4-methyl -*N*-(l ,l ,l-trifluoropropan-2-yl)imidazo[l,5-a]pyrimidine-8-carboxarnide (80 mg, 0.26 mmol) and 2-(benzo[cf][l,3]dioxol-5-yl)-4,4,5,5-tetramethyl-l ,3,2-dioxaborolane afforded the title compound (36 mg, 35 %) as a yellow solid. ¾ NMR (500 MHz, DMSO-d_6) δ 8.55 (d, *J* = 9.5 Hz, 1H), 8.49 (s, 1H), 7.83 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 7.76 (d, *J* = 2.0 Hz, 1H), 7.61 (s, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.17 (s, 2H), 4.97-4.92 (m, 1H), 2.77 (s, 3H), 1.43 (d, *J* = 7.5 Hz, 3H). LC-MS m/z: 393.1 $[M+H]^+$. HPLC Purity (214 nm): 99.65%; t_R = 7.68 min.

2-(3-(l,3-.5-Triazin-2-yl)phenyl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo [1,5-al pyrimidine-8-carboxamide



[00743] A mixture of 3-bromobenzonitrile (1.81 g, 10.0 mmol), and HC1 (4M in dioxane, 2.5 mL, 50.0 mmol) in MeOH (0.6 mL, 20 mmol) was stirred at RT for 20 h, and concentrated *in vacuo*. The residue was triturated with Et20 (30 mL) once and filtered to afford methyl 3-bromobenzimidate hydrochloride (1.7 g, 70%) as a white solid. LC-MS m/z: 214.0 $[M+H]^+$. Purity (254 nm): 98.62%; t_R = 1.32 min.

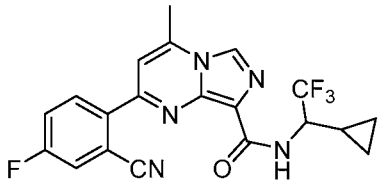
[00744] To a solution of methyl 3-bromobenzimidate hydrochloride (2.0 g, 9.38 mmol) in EtOH (10 mL) were added 1,3,5-triazine (760 mg, 9.38 mmol) and AcOH (112 mg, 1.87 mmol). Then the mixture was stirred under reflux for 20 h, and concentrated *in vacuo.* The residue was crystallized from EtOH (10 mL) to afford 2-(3-bromophenyl)-l,3,5-triazine (2.0 g, 91%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.42 (s, 2H), 8.55 (s, 1H), 8.44 (d, J = 7.5 Hz, 1H), 7.90 (d, J = 7.5 Hz, 1H), 7.59 (t, J = 7.5 Hz, 1H). LC-MS m/z: 236.1 $[M+H]^+$. Purity (214 nm): 96.81%; t_R = 1.98 min.

[00745] A mixture of 2-(3-bromophenyl)-l,3,5-triazine (1.06 g, 4.54 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(l,3,2-dioxaborolane) (1.15 g, 4.54 mmol), $PdCl_2(PPh_3)_2$ (315 mg, 0.45 mmol) and KOAc (908 mg, 9.08 mmol) in dioxane (30 mL) was stirred at 100 °C for 20 h under N_2, and concentrated *in vacuo.* The residue was purified by column chromatography on silica gel (PE/EA = 21/5) to afford 2-(3-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl)-1,3,5-triazine (720 mg, 56%) as a white solid. LC-MS m/z: 284.2 $[M+H]^+$. Purity (214 nm): 88.15%; t_R = 2.12 min.

[00746] Following general procedure D, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylinddazo[l,5-a]pyrimidine-8-carboxamide (93 mg, 0.28 mmol) and 2-(3-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)phenyl)-l,3,5-triazine afforded the title compound (38 mg, 30%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.41 (s, 2H), 9.36 (s, 1H), 8.75 (d, J

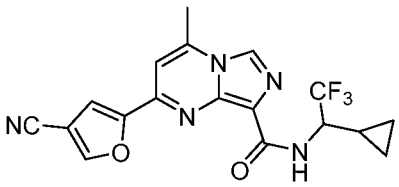
= 9.5 Hz, 1H), 8.65 (d, *J* = 8.0 Hz, 1H), 8.60 (s, 1H), 8.50 (d, *J* = 7.5 Hz, 1H), 7.85 (t, *J* = 7.5 Hz, 1H), 7.78 (s, 1H), 4.36-4.32 (m, 1H), 2.84 (s, 3H), 1.49-1.43 (m, 1H), 0.80-0.74 (m, 1H), 0.62-0.58 (m, 2H), 0.39-0.34 (m, 1H). LC-MS m/z: 454.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.94 min.

2-(2-Cvano-4-fluorophenvn -/V-(l-cvclopropyl -2,2,2-trifluoroethvn-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00747] Following general procedure **D,** 2-chloro -*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (100 mg, 0.30 mmol) and 5-fluoro-2-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)benzonitrile afforded the title compound (15.6 mg, 12 %) as a yellow solid. ^{1}H NMR (500 MHz, *OMSO-d 6)* δ 8.66 (s, 1H), 8.44 (d, *J* = 9.0 Hz, 1H), 8.17-8.11 (m, 2H), 7.85 (t, *J* = 7.5 Hz, 1H), 7.49 (s, 1H), 4.32-4.22 (m, 1H), 2.83 (s, 3H), 1.42-1.32 (m, 1H), 0.72-0.66 (m, 1H), 0.63-0.57 (m, 1H), 0.52-0.45 (m, 1H), 0.35-0.28 (m, 1H). LC-MS m/z: 418.0 $[M+H]^+$. HPLC: Purity (214 nm): 97%; t_R = 7.89 min.

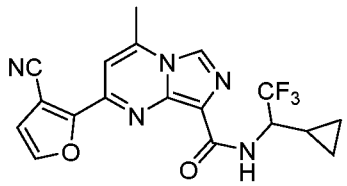
2-(4-Cvanofuran-2-yl)-A^-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00748] To a solution of 5-bromofuran-3-carboxamide (400 mg, 2.10 mmol), and Eï$_3$N (1.7 g, 16.8 mmol) in DCM (20 mL) was dropwise added $POCl_3$ (964 mg, 6.3 mmol) at 0 °C under N_2 atmosphere. The mixture was then allowed to warm to RT and stirred for 2 h. The solvent was reduced, and the resulting residue was dissolved with EtOAc (20 mL) and washed with saturated $NaHCO_3$ solution (10 mL x 3). The combined organic layers were dried (Na2S04), and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (PE/EA: 4/1) to afford 5-bromofuran-3-carbonitrile (270 mg, 75%) as a white solid. ^{1}H NMR (500 MHz, $CDC1_3$) δ 7.93 (s, 1H), 6.56 (s, 1H).

[00749] Following general procedure E, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (100 mg, 0.30 mmol) and 5-bromofuran-3-carbonitrile afforded the title compound (25 mg, 21%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.59 (s, 1H), 8.56 (d, J = 9.0 Hz, 1H), 7.86 (s, 1H), 7.42 (s, 1H), 4.36-4.32 (m, 1H), 2.78 (s, 3H), 1.40-1.36 (m, 1H), 0.70-0.66 (m, 1H), 0.59-0.52 (m, 2H), 0.39-0.35 (m, 1H). LC-MS m/z: 390.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.81 min.

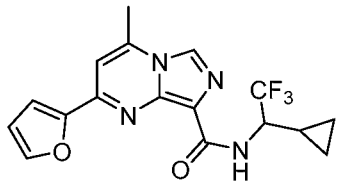
2-(3-Cvanofuran-2-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00750] To an ice cold solution of 2,2,6,6-tetramethylpiperidine (1.9 g, 13.5 mmol) in THF (15 mL) was slowly added n-BuLi (2.5 M in hexanes, 4.8 mL, 12.0 mmol). The solution was stirred at 0 °C for 30 minutes, and cooled to -78 °C. A solution of furan-3-carbonitrile (1.4 g, 15.0 mmol) in THF (10 mL) was added dropwise over 30 minutes and the mixture was stirred for 2 h at -78 °C. A solution of tributyltin chloride in THF (5 mL) was added dropwise over 30 min and the mixture was stirred overnight with the temperature rising to RT. The reaction was quenched with saturated NH_4Cl (20 mL) and extracted with DCM (30 mL x 3). The organic layers were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo,* and the residue was purified by silica gel column chromatography (PE/EA = 100: 1) to afford 2-(tributylstannyl)furan-3-carbonitrile (3.7 g, 63%) as colorless oil. LC-MS m/z: no MS signal. t_R = 2.65 min.

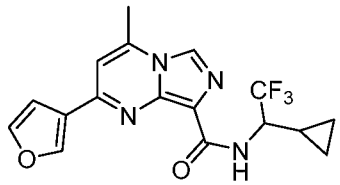
[00751] Following general procedure F*, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylinddazo[l,5-a]pyrimidine-8-carboxamide (109 mg, 0.33 mmol) and 2-(tributylstannyl)furan-3-carbonitrile afforded the title compound (23 mg, 18%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.28 (d, J = 2.0 Hz, 1H), 8.18 (d, J = 9.2 Hz, 1H), 7.42 (s, 1H), 7.32 (d, J = 2.0 Hz, 1H), 4.24-4.09 (m, 1H), 2.82 (s, 3H), 1.61-1.52 (m, 1 H), 0.75-0.60 (m, 2H), 0.55-0.48 (m, 1H), 0.28-0.22 (m, 1H). LC-MS m/z: 390.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.82 min.

iV-(l-Cvclopropyl-2,2,2-tr f uoroethyl)-2-(furan-2-yl)-4-methylimidazo[1,5-*a*]pyrimidine-8-carboxamide



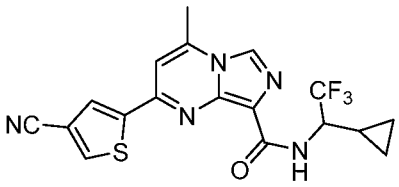
[00752] Following general procedure F*, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (60 mg, 0.18 mmol) and tributyl(furan-2-yl)stannane afforded the title compound (29 mg, 44%) as a yellow solid. ^{1}H NMR (500 MHz DMSO-c¾): δ 8.61 (d, *J* = 9.0 Hz, 1H), 8.51 (s, 1H), 8.07 (s, 1H), 7.44 (d, *J* = 3.5 Hz, 1H), 7.40 (s, 1H), 6.81 (q, *J* = 2.0 Hz, 1H), 4.46-4.42 (m, 1H), 2.76 (s, 3H), 1.35-1.30 (m, 1H), 0.68-0.64 (m, 1H), 0.60-0.49 (m, 2H), 0.45-0.40 (m, 1H). LC-MS m/z: 365.1 $[M+H]^+$. HPLC Purity (254 nm): > 99%; t_R = 7.79 min.

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(furan-3-yl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



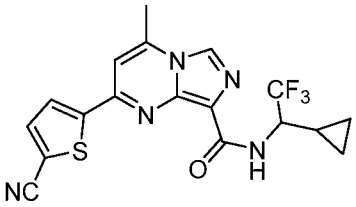
[00753] Following general procedure D, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (80 mg, 0.24 mmol) and furan-3-ylboronic acid afforded the title compound (32 mg, 37 %) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-d_4) *δ 8.45* (s, 1H), 8.38 (s, 1H), 7.73 (d, *J* = 1.6 Hz, 1H), 7.28 (s, 1H), 7.09 (d, *J* = 1.6 Hz, 1H), 4.46-4.42 (m, 1H), 2.80 (s, 3H), 1.33-1.31 (m, 1H), 0.78-0.76 (m, 1H), 0.67-0.64 (m, 1H), 0.57-0.52 (m, 2H). LC-MS m/z: 365.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 9.77 min.

2-(4-Cvanothiophen-2-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-«1pyrimidine-8-carboxamide



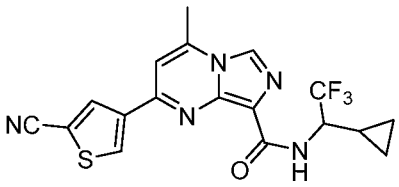
[00754] Following general procedure E, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (90 mg, 0.27 mmol) and 5-bromothiophene-3-carbonitrile afforded the title compound (13.8 mg, 10%) as a yellow solid. ^{1}H NMR (400 MHz, *MeOO-d4)* δ 8.54 (d, *J* = 0.4 Hz, 1H), 8.46 (s, 1H), 8.27 (d, *J* = 0.4 Hz, 1H), 7.51 (s, 1H), 4.44-4.37 (m, 1H), 2.85 (s, 3H), 1.37-1.29 (m, 1H), 0.82-0.75 (m, 1H), 0.69-0.49 (m, 3H). LC-MS m/z: 406.1 $[M+H]^+$. HPLC: Purity (214 nm): 97%; t_R = 7.69 min.

2-(5-Cvanothiophen-2-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00755] Following general procedure D, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (80 mg, 0.24 mmol) and 5-cyanothiophen-2-ylboronic acid afforded the title compound (23.3 mg, 24 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.46 (d, *J* = 9.5 Hz, 1H), 8.18 (d, *J* = 4.0 Hz, 1H), 8.13 (d, *J* = 4.0 Hz, 1H), 7.71 (s, 1H), 4.35-4.27 (m, 1H), 2.79 (s, 3H), 1.43-1.31 (m, 1H), 0.75-0.67 (m, 1H), 0.62-0.57 (m, 2H), 0.38-0.33 (m, 1H). LC-MS m/z: 406.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.77 min.

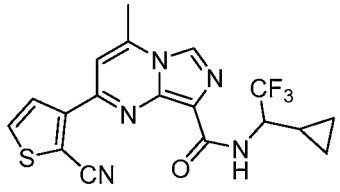
2-(5-Cvanothiophen-3-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00756] Following general procedure E, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (100 mg, 0.3 mmol) and 4-bromothiophene-2-carbonitrile afforded the title compound (40 mg, 15%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.56 (s, 1H), 8.55 (d, *J* = 9.5 Hz, 1H), 8.54 (s, 1H), 7.58 (s, 1H),

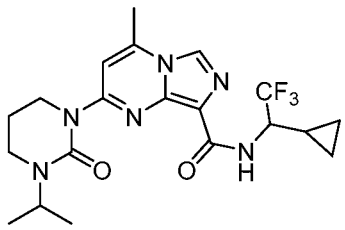
4.31-4.27 (m, 1H), 2.78 (s, 3H), 1.46-1.42 (m, 1H), 0.74-0.66 (m, 1H), 0.60-0.55 (m, 2H), 0.36-0.33 (m, 1H). LC-MS m/z: 406.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.81 min.

2-(2-Cvanothiophen-3-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-alpyrimidine-8-carboxamide



[00757] Following general procedure E, 2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxarnide (80 mg, 0.24 mmol) and 3-bromothiophene-2-carbonitrile afforded the title compound (12.7 mg, 10%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-i¾) δ 8.64 (s, 1H), 8.32 (d, *J* = 9.5 Hz, 1H), 8.27 (d, *J* = 5.5 Hz, 1H), 7.96 (d, *J* = 5.0 Hz, 1H), 7.57 (s, 1H), 4.25-4.18 (m, 1H), 2.81 (s, 3H), 1.53-1.50 (m, 1H), 0.72-0.66 (m, 1H), 0.64-0.60 (m, 1H), 0.52-0.49 (m, 1H), 0.30-0.25 (m, 1H). LC-MS m/z: 406.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.79 min.

A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-2-(3-¾o-propyl-2-oxotetrahvdropyrimidin-l(2*H*)-vD-4-methylimidazo [1,5-al pyrimidine-8-carboxamide



[00758] A mixture of l-chloro-3-isocyanatopropane (2.67 g, 22.3 mmol) and propan-2-amine (1.2 g, 20.3 mmol) in MeCN (40 mL) was stirred at RT for 2 h, and concentrated *in vacuo* to afford crude l-(3-chloropropyl)-3-wo-propylurea (3.95 g) as a white solid, which was used in the next step without further purification. LC-MS m/z: 179.1$[M+H]^+$, t_R = 1.39 min.

[00759] To a solution of l-(3-chloropropyl)-3-wo-propylurea (3.95 g) in THF (100 mL) was added NaH (2.4 g, 100.0 mmol) at 0 °C. The mixture was stirred at RT overnight, quenched with saturated NH4CI solution, and extracted with EtOAc (120 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo,*

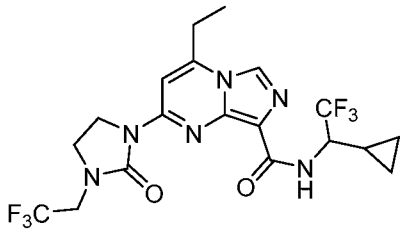
and the residue was purified by silica gel column chromatography (PE/EA = 4/1) to afford 1-wo-propyltetrahydropyrimidin-2(l *H*)-one (2.2 g, 76%) as a pink solid. LC-MS m/z: 143.2[M+H]$^+$, t_R = 1.27 min.

[00760] Following general Procedure J, ethyl 2-chloro-4-methylimidazo[l,5-a]pyrimidine-8-carboxylate (239 mg, 1.0 mmol) and l-*iso*-propyltetrahydropyrimidin-2(l *H*)-one afforded ethyl 2-(3-*iso*-propyl-2-oxotetrahydropyrirnidin-l (2*H*)-yl)-4-methylimidazo[l ,5-a]pyrimidine-8-carboxylate (80 mg, 21%) as a grey yellow solid. LC-MS m/z: 346.2 [M+H]$^+$, t_R = 1.55 min.

[00761] Following general procedure B*, ethyl 2-(3-*iso*-propyl-2-oxotetrahydropyrimidin-l(2*H*)-yl)-4-methylinddazo[l,5-a]pyrimidine-8-carboxylate (70 mg, 0.2 mmol) afforded 2-(3-*iso*-propyl-2-oxotetrahydropyriiTridin-l(2 *H*)-y^)-4-methylimidazo[1,5-*a*]pyrimidine-8-carboxylic acid sodium salt (59 mg, 100%) as a grey solid. LC-MS m/z: 318.2[M+H]$^+$, t_R = 1.18 min.

[00762] Following general procedure A, 2-(3-*iso*-propyl-2-oxotetrahydropyrimidin-l(2 *H*)-yl)-4-methylinddazo[l,5-a]pyrimidine-8-carboxylic acid (59 mg, 0.2 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (9.0 mg, 10%) as an off-white solid. ¾ NMR (500 MHz, *OMSO-d6)*: δ 8.33 (d, *J* = 10.0 Hz, 1H), 8.31 (s, 1H), 7.52 (d, *J* = 0.5 Hz, 1H), 4.64-4.58 (m, 1H), 4.34-4.29 (m, 1H), 3.96-3.87 (m, 2H), 3.27 (t, *J* = 6.0 Hz, 2H), 2.67 (s, 3H), 2.04-1.99 (m, 2H), 1.27-1.23 (m, 1H), 1.14 (d, *J* = 6.5 Hz, 6H), 0.69-0.64 (m, 1H), 0.56-0.52 (m, 2H), 0.34-0.30 (m, 1H). LC-MS m/z: 439.2 [M+H]$^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.92 min.

A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-ethyl-2-(2-oxo-3-(2,2,2-trifluoroethyl)imidazolidin-l-yl)imidazo[l,5-alpyrimidine-8-carboxamide

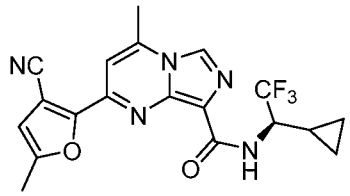


[00763] Following general Procedure J, ethyl 2-chloro-4-ethylimidazo[l,5-a]pyrimidine-8-carboxylate (60 mg, 0.24 mmol) and l-(2,2,2-trifluoroethyl)irnidazolidin-2-one afforded ethyl 4-ethyl-2-(2-oxo-3-(2,2,2-trifluoroethyl)iimidazolidin-1-yl)imidazo[1,5-*a*]pyrimidine-8-carboxylate (90 mg, 49%) as a yellow solid. LC-MS m/z: 386.0 [M+H]$^+$.

[00764] Following general procedure B*, ethyl 4-ethyl-2-(2-oxo-3-(2,2,2-trifluoroethyl)irnidazolidin-l-yl)imidazo[l,5-a]pyrirnidine-8-carboxylate (90 mg, 0.23 mmol) afforded 4-ethyl-2-(2-oxo-3-(2,2,24rifluoroethyl)irmdazolidm -1-yl)imidazo[1,5-*a*]pyrimidine-8-carboxylic acid (50 mg, 60%) as a white solid. LC-MS m/z: 332.2 $[M+H]^+$.

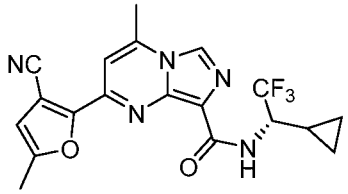
[00765] Following general procedure A, 4-ethyl-2-(2-oxo-3-(2,2,2-trifluoroethyl)imidazolidin-l-yl)imidazo[l,5-a]pyrimidine-8-carboxylic acid (50 mg, 0.15 mmol) and l-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (8.6 mg, 13%) as a white solid. ^{1}H NMR (500 MHz, $CDC1_3$): δ 8.02 (s, 1H), 7.96 (s, 1H), 7.91 (d, J = 9.5Hz, 1H), 4.51-4.45 (m, 1H), 4.25-4.20 (m, 2H), 4.00-3.92 (m, 2H), 3.78-3.75 (m, 2H), 2.99 (q, J = 8.0 Hz, 2H), 1.48 (t, J = 8.0 Hz, 3H), 1.14-1.11 (m, 1H), 0.71-0.68 (m, 1H), 0.56-0.52 (m, 3H). LC-MS m/z: 479.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.09 min.

(i?)-2-(3-Cvano-5-methylfuran-2-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo [1,5-al pyrimidine-8-carboxamide



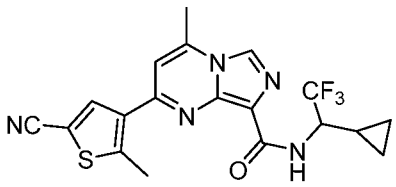
[00766] A mixture of (i?)-2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (67 mg, 0.20 mmol), 5-methyl-2-(tributylstannyl)furan-3-carbonitrile (88 mg, 0.24 mmol), $Pd(PPli_3)_4$(23 mg, 0.02 mmol) and CuBr (2 mg, 0.02 mmol) in dioxane (2 mL) was heated at 120 °C under nitrogen atmosphere for 12 hours, cooled to room temperature and filtered. The cake was washed with EtOAc (10 mL), and the combined filtrate was concentrated *in vacuo*. The residue was crystallized with DCM/Et_20 (1/4) to afford the title compound (60 mg, 75%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.17 (d, J = 9.6 Hz, 1H), 7.37 (s, 1H), 6.94 (s, 1H), 4.24-4.17 (m, 1H), 2.81 (s, 3H), 2.47 (s, 3H), 1.58-1.55 (m, 1H), 0.71-0.60 (m, 2H), 0.54-0.51 (m, 1H), 0.28-0.25 (m, 1H). LC-MS m/z: 404.1 $[M+H]^+$. HPLC: Purity (214 nm): 95.18%; t_R = 7.94 min.

(*S*)-2-(3-Cvano-5-methylfuran-2-yl)-A/-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo [1,5-al pyrimidine-8-carboxamide



[00767] A mixture of (5)-2-chloro -*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (67 mg, 0.20 mmol), 5-methyl-2-(tributylstannyl)furan-3-carbonitrile (88 mg, 0.24 mmol), Pd(PPh3)4(23 mg, 0.02 mmol) and CuBr (2 mg, 0.02 mmol) in dioxane (2 mL) was heated at 120 °C under nitrogen atmosphere for 12 hours, cooled to room temperature and filtered. The cake was washed with EtOAc (10 mL), and the combined filtrate was concentrated *in vacuo.* The residue was crystallized with DCM/Et_20 (1/4) to afford the title compound (50 mg, 63%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.65 (s, IH), 8.18 (d, *J* = 9.0 Hz, IH), 7.38 (s, IH), 6.94 (s, IH), 4.24-4.19 (m, 1 H), 2.82 (s, 3H), 2.47 (s, 3H), 1.58-1.55 (m, IH), 0.71-0.62 (m, 2H), 0.53-0.51 (m, IH), 0.27-0.25 (m, IH). LC-MS m/z: 404.1 $[M+H]^+$. HPLC: Purity (214 nm): 94.29%; t_R = 7.96 min

2-(5-Cvano-2-methylthiophen-3-yl)-jV-(l-cvclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo [1,5-al pyrimidine-8-carboxamide



[00768] To a mixture of 5-methylthiophene-2-carboxylic acid (2 g, 14. 1 mmol) and FeC¾ (456 mg, 2.81 mmol) in AcOH (28 mL) was added a solution of Br_2 (725 uL, 14.1 mmol) in AcOH (2.8 mL) at 25 °C. After 5 h, the mixture was poured into ice and the precipitate was filtered and washed with water affording 4-bromo-5-methylthiophene-2-carboxylic acid (2.7 g, 87 %) as a yellow solid. ^{1}H NMR (500 MHz, $CDC1_3$) δ 13.33 (s, IH), 7.61 (s, IH), 2.41 (s, 3H). LC-MS m/z: 220.9 $[M+H]^+$. LCMS: Purity (254nm): 92.7%; t_R = 1.76 min.

[00769] To a mixture of 4-bromo-5-methylthiophene-2-carboxylic acid (2.21 g, 10 mmol), HOBt (1.49 g, 11 mmol), EDCI (2.11 g, 11 mmol) and DIPEA (1.9 g, 15 mmol) in DMF (10

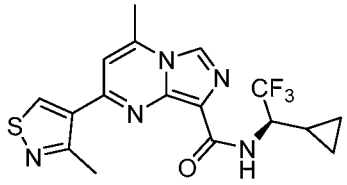
mL) stirred at RT for 0.5 h was added NH_4Cl (1.6 g, 30 mmol). The reaction mixture was stirred at RT for 10 h, and concentrated *in vacuo*. The residue was dissolved in EtOAc (50 mL), washed with NaOH (IN, 40 mL χ 3), HC1 (IN, 40 mL χ 3), and brine (50 mL) and dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo*, and the residue was crystallized with Et^O (10 mL) to afford 4-bromo-5-methylthiophene-2-carboxamide (1.7 g, 76%) as a white solid. ^1H NMR (500 MHz, DMSO-d_6) δ 7.96 (s, 1H), 7.69 (s, 1H), 7.50 (s, 1H), 2.38 (s, 3H). LC-MS m/z: 220.0 $[M+H]^+$. LCMS: Purity (254 nm): 96.0%; t_R = 1.60 min.

[00770] To a solution of 4-bromo-5-methylthiophene-2-carboxamide (1.1 g, 5.0 mmol), and Et_3N (5.1 g, 40 mmol) in DCM (20 mL) was added $POCl_3$ (2445 mg, 15 mmol) dropwise at 0°C under N_2 atmosphere. The mixture was stirred at RT for 2 h, and concentrated *in vacuo*. The residue was dissolved with EtOAc (20 mL) and washed with saturated $NaHCO_3$ solution (20 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated *in vacuo*, and the residue purified by silica gel column (PE/EA: 10/1) to afford 4-bromo-5-methylthiophene-2-carbonitrile (863 mg, 86 %) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.26 (s, 1H), 2.46 (s, 3H).

[00771] A mixture of 4-bromo-5-methylthiophene-2-carbonitrile (404 mg, 2 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(l,3,2-dioxaborolane) (610 mg, 2.4 mmol), KOAc (490 mg, 5 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (163 mg, 0.2 mmol) was flushed with N_2 three times, followed by the addition of dioxane (20 mL). The reaction mixture was stirred at 90 °C for 1 hour, and filtered. The filtrate was concentrated *in vacuo*, /-propyl ether (60 mL) was added and the resulting precipitate was filtered. The filtrate was concentrated *in vacuo* to afford 5-methyl-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)thiophene-2-carbonitrile (424 mg) as a black oil. LC-MS m/z: 250.2 $[M+H]^+$. LCMS: Purity (214 nm): 55.0%; t_R = 1.64 min.

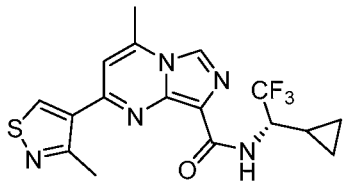
[00772] Following general procedure D, 2-chloro -*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylinddazo[l,5-a]pyrimidine-8-carboxamide (64 mg, 0.2 mmol) and 5-methyl-4-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)thiophene-2-carbonitrile afforded the title compound (28 mg, 34 %) as a white solid. ^1H NMR (400 MHz, DMSO-i¾) δ 8.56 (s, 1H), 8.50 (s, 1H),8.40 (d, *J* = 9.2 Hz, 1H), 7.44 (s, 1H), 4.27-4.24 (m, 1H), 2.94 (s, 3H), 2.77 (s, 3H), 1.32-1.28 (m, 1H), 0.73-0.69 (m, 1H), 0.62-0.60 (m, 1H), 0.54-0.53 (m, 1H), 0.30-0.28 (m, 1H). LC-MS m/z: 420.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.24 min.

(i?)-A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-4-methyl-2-(3-methylisothiazol-4-vDimidazo[l,5-«lpyrimidine-8-carboxamide



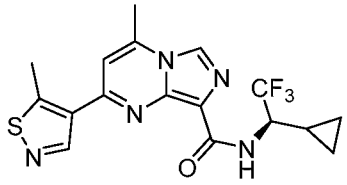
[00773] Following general procedure E*, (i?)-2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxarnide (60 mg, 0.18 mmol) and 4-bromo-3-methylisothiazole (96 mg, 0.54 mmol) afforded the title compound (4.4 mg, 6%) as a grayish solid. ^{1}H NMR (500 MHz, *OMSO-d$_6$)* δ 9.75 (s, 1H), 8.56 (s, 1H), 8.41 (d, *J* = 10.0 Hz, 1H), 7.49 (s, 1H), 4.29-4.21 (m, 1H), 2.85 (s, 3H), 2.78 (s, 3H), 1.30-1.20 (m, 1H), 0.76-0.46 (m, 3H), 0.31-0.24 (m, 1H). LC-MS m/z: 396.0 $[M+H]^+$. HPLC Purity (214 nm): 96.53%; t_R = 7.63 min.

(*S*)-*N*-(1-CycïορΓθρν1-2,2,2-íη fluorθeí hyl)-4-ιneí hy1-2-(3-ιneí hy1sθí híaζo1-4-yl)imidazo[l,5-«lpyrimidine-8-carboxamide



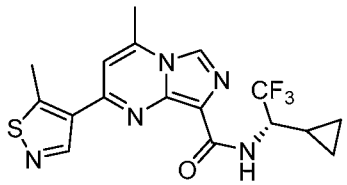
[00774] Following general procedure E*, (5)-2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (60 mg, 0.18 mmol) and 4-bromo-3-methylisothiazole afforded the title compound (11.3 mg, 16%) as a grayish solid. ^{1}H NMR (500 MHz, DMSO-*d$_6$*) δ 9.75 (s, 1H), 8.56 (s, 1H), 8.41 (d, *J* = 9.5 Hz, 1H), 7.49 (s, 1H), 4.29-4.21 (m, 1H), 2.85 (s, 3H), 2.78 (s, 3H), 1.30-1.20 (m, 1H), 0.72-0.68 (m, 1H), 0.62-0.60 (m, 1H), 0.59-0.52 (m, 1H), 0.30-0.22 (m, 1H). LC-MS m/z: 396.0 $[M+H]^+$. HPLC Purity (214 nm): 96.53%; t_R = 9.97 min.

(i?)-A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-4-methyl-2-(5-methylisothiazol-4-vDimidazo[1,5-alpyrimidine-8-carb oxamide



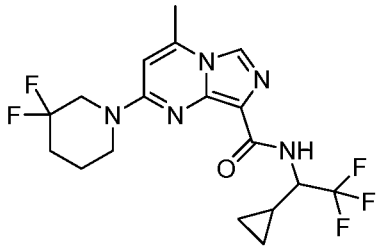
[00775] Following general procedure E*, (i?)-2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxarnide (100 mg, 0.3 mmol) and 4-bromo-5-methylisothiazole afforded the title compound (19.4 mg, 15%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.56 (s, 1H), 8.41 (d, J = 9.5 Hz, 1H), 7.53 (s, 1H), 4.30-4.25 (m, 1H), 2.96 (s, 3H), 2.79 (s, 3H), 1.30-1.24 (m, 1H), 0.73-0.68 (m, 1H), 0.63-0.61 (m, 1H), 0.6-0.53 (m, 1H), 0.32-0.27 (m, 1H). LC-MS m/z: 396.0 $[M+H]^+$. HPLC Purity (214 nm): >99%; t_R = 7.77 min.

(*S*)-*N*-(1-CvcïορΓθρν1-2,2,2-ίηfluorθeihyl)-4-ιneihy1-2-(5-ιneihy1sθihiaζo1-4-yl)imidazo[l,5-«lpyrimidine-8-carboxamide



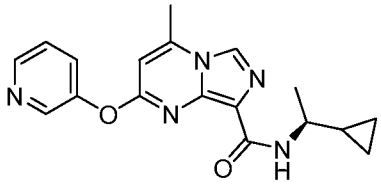
[00776] Following general procedure E*, (5)-2-chloro-*N*-(l-cyclopropyl-2,2,2-trifluoroethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (100 mg, 0.3 mmol) and 4-bromo-5-methylisothiazole afforded the title compound (7.9 mg, 7%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-cd_6) ιδ 9.12 (s, 1H), 8.56 (s, 1H), 8.41 (d, J = 9.0 Hz, 1H), 7.54 (s, 1H), 4.37-4.22 (m, 1H), 2.96 (s, 3H), 2.79 (s, 3H), 1.33-1.21 (m, 1H), 0.76-0.48 (m, 4H), 0.31-0.28 (m, 1H). LC-MS m/z: 396.0 $[M+H]^+$. HPLC Purity (214 nm): >99%; t_R = 7.77 min.

A/-(l-Cvclopropyl-2,2,2-trifluoroethyl)-2-(3,3-difluoropiperidin-l-yl)-4-methylimidazo [1,5-al pyrimidine-8-carboxamide



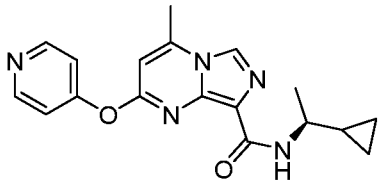
[00777] Following general procedure A, 2-(3,3-difluoropiperidin-l-yl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxylic acid (30 mg, 0.16 mmol) and l-cyclopropyl-2,2,2-trifluoroethanamine afforded the title compound (29 mg, 45%) as a yellow solid. ^{1}H NMR (500 MHz, **DMSO-i¾):** δ 8.34 (d, *J* = 10.0 Hz, 1H), 8.11 (s, 1H), 6.94 (s, 1H), 4.43-4.38 (m, 1H), 4.14-4.08 (m, 2H), 3.78 (s, 2H), 2.61 (s, 3H), 2.18-2.10 (m, 2H), 1.78-1.75 (m, 2H), 1.19-1.15 (m, 1H), 0.66-0.62 (m, 1H), 0.54-0.46 (m, 2H), 0.34-0.32 (m, 1H). LC-MS m/z: 418.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.46 min.

(.S^-A/-(l-Cvclopropylethyl)-4-methyl-2-(pyridin-3-yloxy)imidazo[l,5-alpyrimidine-8-carboxamide



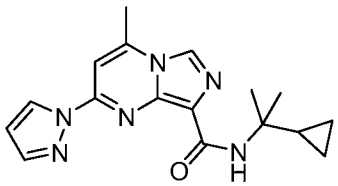
[00778] Following general procedure H, (5)-2-chloro -*N* -(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (30 mg, 0.1lmmol) and pyridin-3-ol afforded the title compound (10.6 mg, 29%) as a yellow solid. ¾NMR (400 MHz, MeOD-c¾) δ 8.47 (s, 1H), 8.14 (dd, *J* = 7.2 Hz, 1.6 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.66 (ddd, *J* = 9.2 Hz, 6.4 Hz, 2.0 Hz, 1H), 7.34 (d, *J* = 0.8 Hz, 1H), 6.66 (d, *J* = 9.2 Hz, 1H), 6.56 (td, *J* = 7.2 Hz, 1.2 Hz, 1H), 3.68-3.58 (m, 1H), 2.83 (d, *J* = 0.8 Hz, 3H), 1.35 (d, *J* = 6.4 Hz, 3H), 1.09-1.01 (m, 1H), 0.60-0.47 (m, 2H), 0.46-0.40 (m, 1H), 0.35-0.28 (m, 1H). LC-MS m/z: 338.1$[M+H]^+$. HPLC: Purity (214 nm): > 92%; t_R = 5.92 min.

CSViV-(l-Cvclopropylethyl)-4-methyl-2-(py^^ din-4-yloxy)imidazo[1,5-*a*]pyrimidine-8-carboxamide



[00779] Following general procedure H, (5)-2-chloro-*N*-(l-cyclopropylethyl)-4-methylimidazo[l,5-a]pyrimidine-8-carboxarnide (30 mg, 0.11 mmol) and pyridin-4-ol afforded the title compound (11 mg, 31%) as a gray solid. ^{1}H NMR (500 MHz, *OMSO-d$_6$)* δ 8.65 (d, *J* = 3.0 Hz, 1H), 8.56 (dd, *J* = 4.5 Hz, 1.0 Hz, 1H), 8.34 (s, 1H), 7.86 (ddd, *J* = 8.0 Hz, 2.5 Hz, 1.0 Hz, 1H), 7.59 (dd, *J* = 8.0 Hz, 4.5 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 6.89 (s, 1H), 3.43-3.37 (m, 1H), 2.74 (s, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.56-0.49 (m, 1H), 0.36-0.30 (m, 1H), 0.20-0.15 (m, 1H), 0.07- -0.03 (m, 1H). LC-MS m/z: 338.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 6.06 min.

EXAMPLE 2 - PREPARATION OFiV-(2-CYCLOPROPYLPROPAN-2-YL)-4-METHYL-2-(*H*-PYRAZOL-1-YL)IMIDAZO[1,5-*a*]PYRIMIDINE-8-CARBOXAMIDE



[00780] A mixture of 2-chloro-*N*-(2-cyclopropylpropan-2-yl)-4-methylimidazo[l,5-a]pyrirnidine-8-carboxarnide (70 mg, 0.21 mmol), l*H*-pyrazole (32.2 mg, 0.42 mmol), K_2CO_3 (58.1 mg, 0.42 mmol), and KI (3.5 mg, 0.02 mmol) in 5 mL of DMF was stirred at 100 °C for 1 h under microwave condition. The crude product was further purified by prep-HPLC (MeCN/lOmM NH_4HCO_3) to afford the title compound (19.5 mg, 29%) as a yellow solid. ^{1}H NMR (500 MHz, *MeOO-d$_4$)*: δ 8.78 (d, *J* = 3.0 Hz, 1H), 8.33 (s, 1H), 7.87 (d, *J* = 1.5 Hz, 1H), 7.83 (s, 1H), 7.62 (d, *J* = 1.0 Hz, 1H), 6.66 (dd, *J* = 3.0 Hz, 1.5 Hz, 1H), 2.84 (d, *J* = 1.0 Hz, 3H), 1.48 (s, 6H), 1.49-1.47 (m, 1H), 0.57-0.55 (m, 4H). LC-MS m/z: 325.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.30 min.

EXAMPLE 3 - BIOLOGICAL ACTIVITY EVALUATION

[00781] The ability of exemplary compounds to activate glucocerebrosidase (Gcase) was measured. Experimental procedures and results are provided below.

Part I: Assay Procedure

[00782] A 484 μL aliquot of a 1.0 mg/mL solution of phosphatidylserine (PS) (Sigma P7769) in chloroform was evaporated under a stream of nitrogen for 1 hour. The lipid film was dissolved over 4 minutes of vigorous vortexing in 40 mL of 176 mM K_2HPO_4/50 mM citric acid (pH 4.7) containing 7.5 μL of triton X-100, resulting in a mixed micellar preparation with a composition of 0.32 mM triton and 0.37 mol% PS. 4-Methylumbelliferyl-beta-D-glucopyranoside (ACROS-337025000) was dissolved in the micellar solution to a final concentration of 2 mM for use as the reaction substrate.

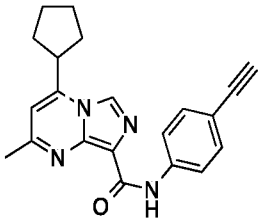
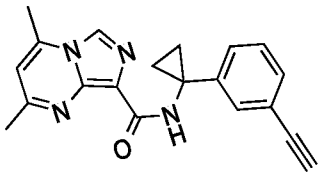
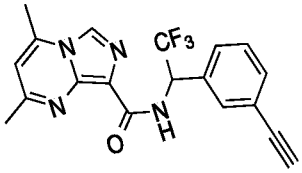
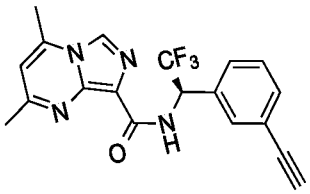
[00783] Test compounds were diluted to the desired concentrations with dimethylsulfoxide (DMSO) from 10 mM stocks, and 0.41 μL of the DMSO compound mixture was added to 100 μL of micellar solution containing 10 nM GCase and 100 nM saposin C (Enzo ALX-201-262-C050). Pre-incubation was allowed to occur for 30 minutes at room temperature, after which the reaction was initiated by combining 25 μL of substrate solution with 25 μL of compound/GCase/saposin mixture. The reaction proceeded for 15 minutes at room temperature and was stopped by adding 150 μL of 1M glycine, pH 12.5. The endpoint of the reaction was monitored by measuring fluorescence intensity (excitation: 365 nm; emission: 440 nm) on a SpectraMax i3 instrument (Molecular Devices). Test compounds were screened at 1.0 and 0.1 μM final concentration, and subsequent 8-point dose response curves were obtained using 3-fold dilutions from a maximum final concentration of 5 μM.

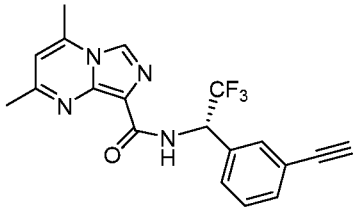
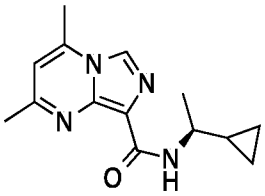
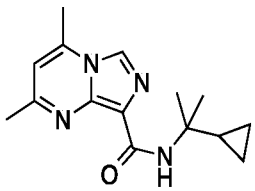
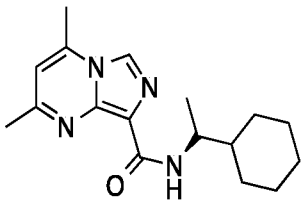
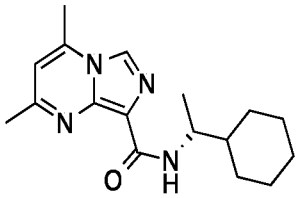
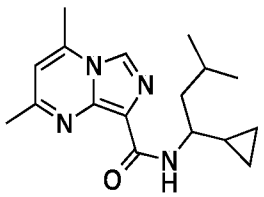
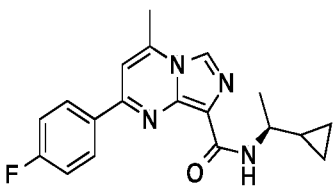
Part II: Results

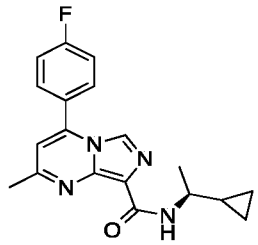
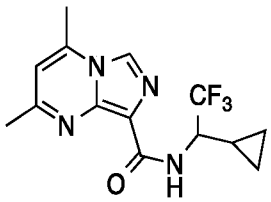
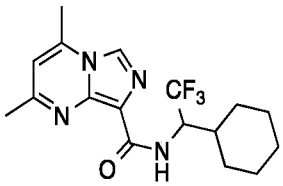
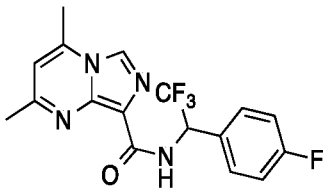
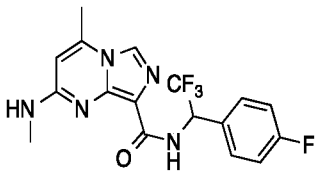
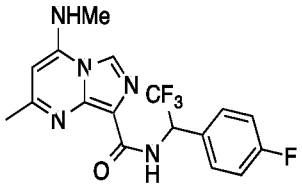
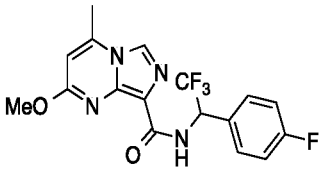
[00784] Gcase activation values for tested compounds are provided in Tables 3 and 4 below, along with cLogP, PSA, and compound solubility in water. For experiments in which the test compound was used at a concentration of 1.0 μM, the symbol "+" indicates less than 30% Gcase activation; the symbol "++" indicates Gcase activation in the range of 30% up to 60%; and the symbol "+++" indicates Gcase activation greater than 60%. For experiments in which the test compound was used at a concentration of 0.1 μM, the symbol "*" indicates less than

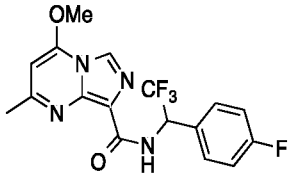
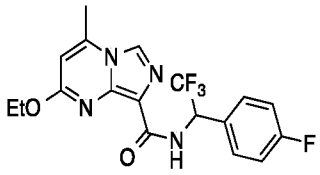
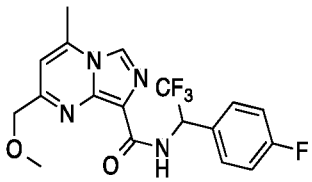
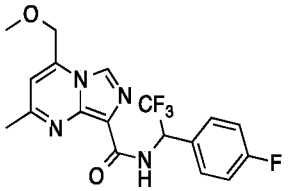
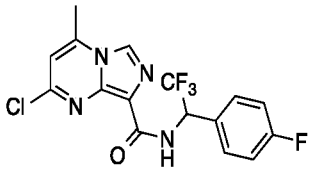
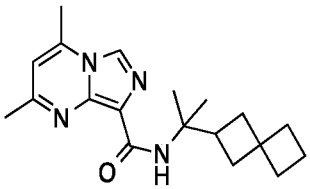
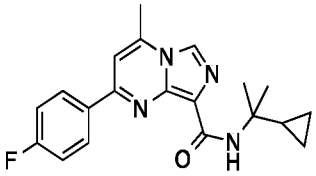
10% Gcase activation; the symbol "**" indicates Gcase activation in the range of 10% up to 20%; and the symbol "***" indicates greater than 20% Gcase activation.

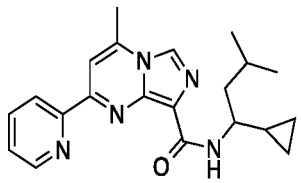
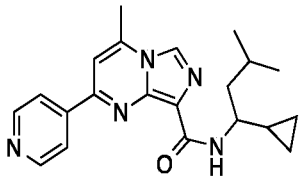
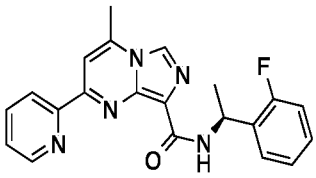
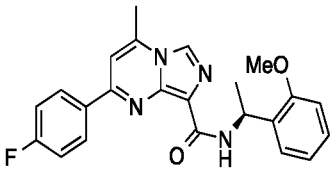
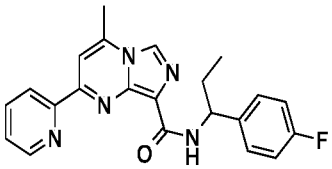
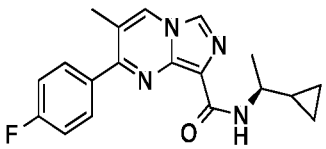
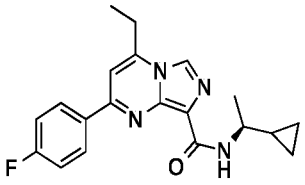
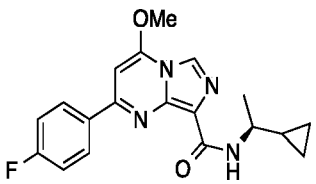
TABLE 3

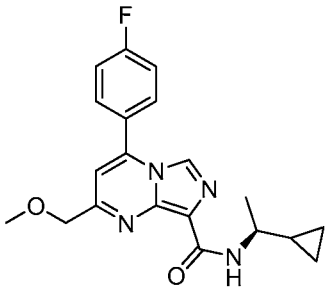
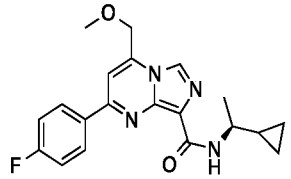
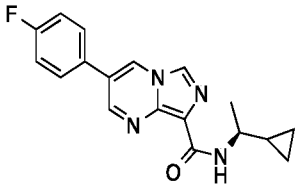
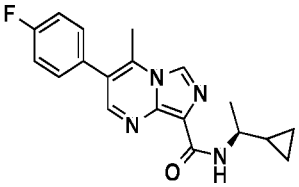
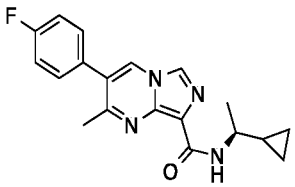
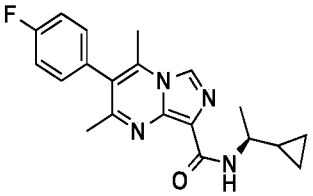
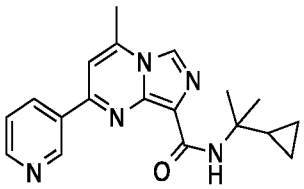
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-1		4.8	57.1	0.2	++	**
III-2		3.8	57.1	19.7	++	*
III-3		4.2	57.1	2.2	+++	***
III-4		4.2	57.1	6.1	+++	***

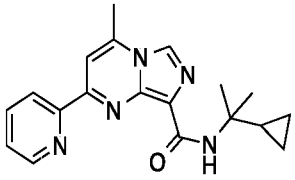
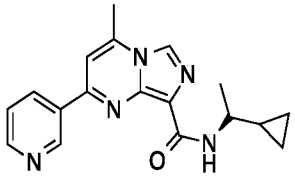
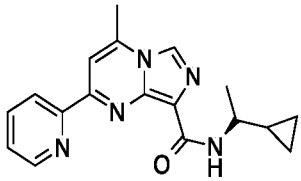
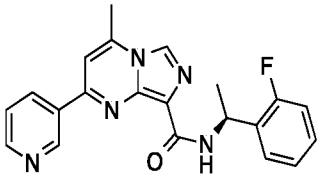
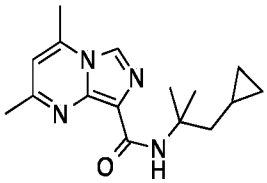
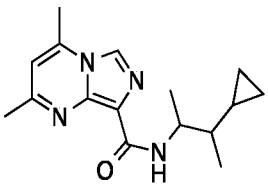
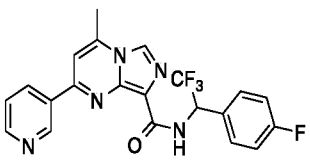
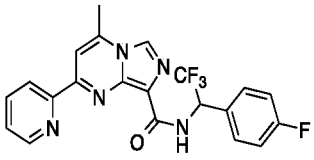
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-5		4.2	57.1	5.9	+++	***
III-6		2.5	57.1	24.4	+	*
III-8		2.9	57.1	25.2	+	*
III-9		4.2	57.1	14.3	+++	*
III-10		4.2	57.1	23.0	+++	**
III-11		3.9	57.1	32.6	+++	**
III-12		4.2	57.1	9.3	+++	**

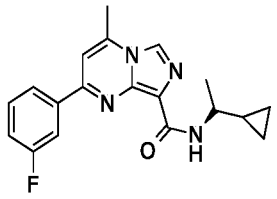
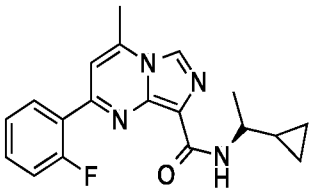
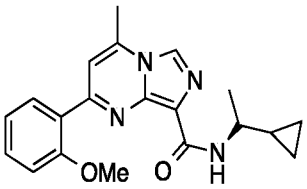
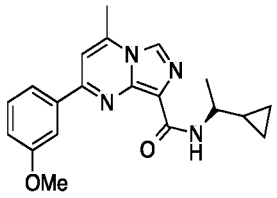
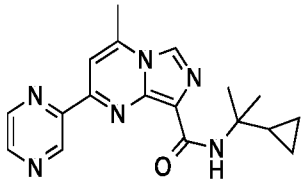
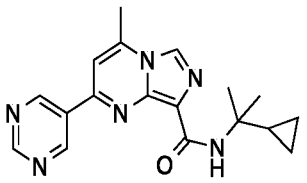
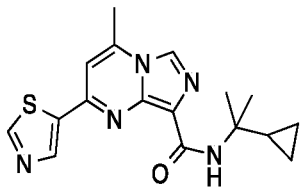
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-13		4.2	57.1	25.0	+	*
III-14		2.8	57.1	37.8	++	*
III-15		4.4	57.1	4.0	+++	***
III-16		3.5	57.1	24.3	+++	**
III-17		3.7	69.1	0.9	+++	***
III-18		3.7	69.1	1.7	+++	***
III-19		3.5	66.3	8.7	+++	**

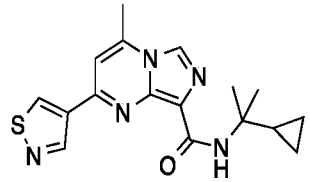
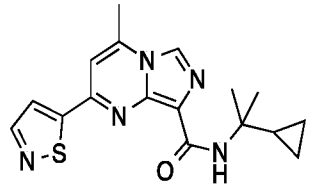
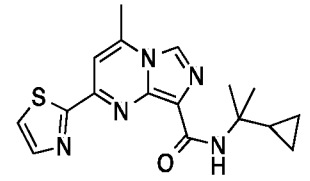
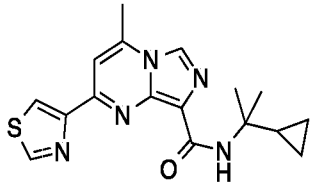
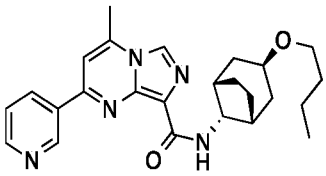
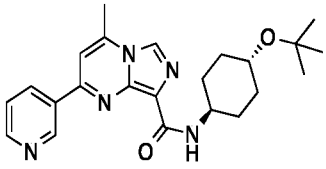
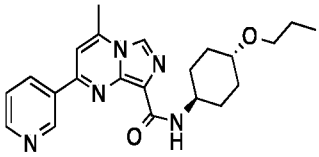
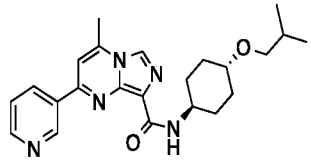
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-20		3.5	66.3	6.9	+++	*
III-21		3.9	66.3	1.1	+++	***
III-22		2.8	66.3	24.7	+++	*
III-23		2.8	66.3	10.9	+++	***
III-24		3.7	57.1	10.4	+++	**
III-25		4.3	57.1	1.5	+++	***
III-26		4.6	57.1	1.6	+++	***

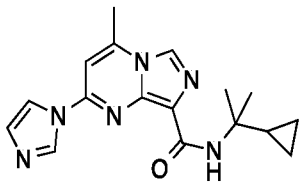
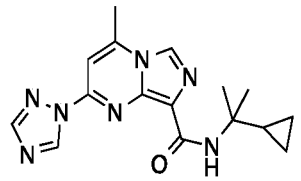
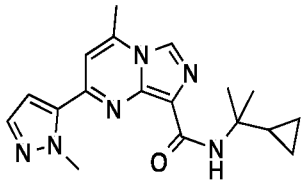
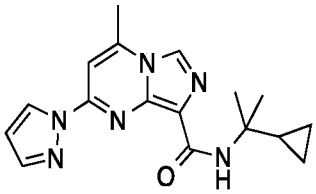
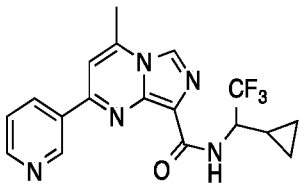
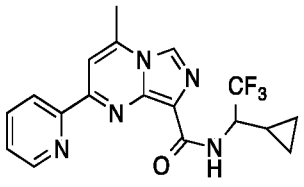
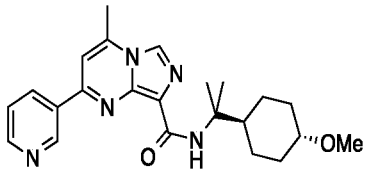
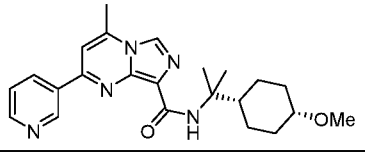
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-27		4.3	69.4	4.6	+++	***
III-28		4.1	69.4	19.7	+++	*
III-29		4.0	69.4	0.9	+++	**
III-30		5.1	66.2	1.3	+++	**
III-31		4.5	69.4	2.7	+++	**
III-32		3.9	57.1	N/A	+	*
III-33		4.8	57.1	10.5	+++	***
III-34		4.2	66.3	0.2	+	*

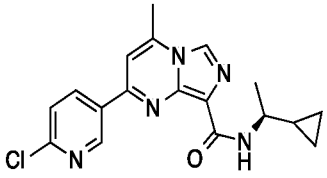
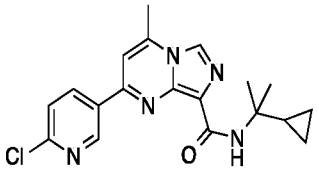
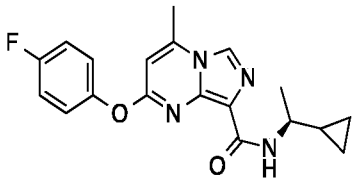
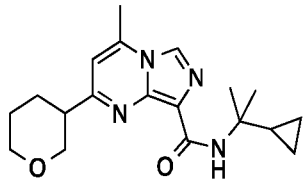
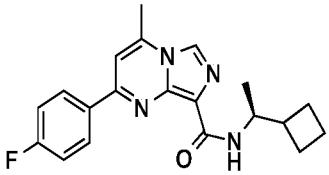
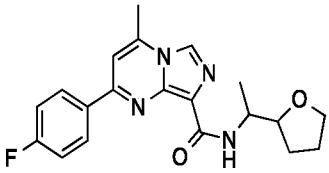
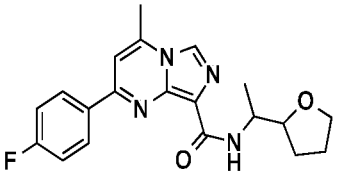
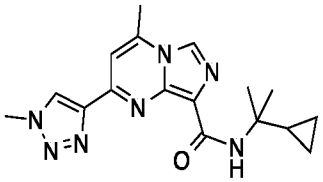
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-35		3.5	66.3	43.5	+	*
III-36		3.5	66.3	22.0	+++	**
III-37		3.5	57.1	2.2	+	*
III-38		3.7	57.1	N/A	+	*
III-39		3.7	57.1	N/A	+	*
III-40		3.0	69.4	N/A	+	*
III-41		3.3	69.4	27.1	++	*

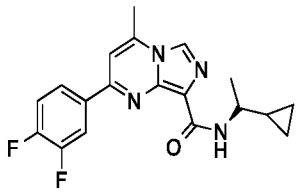
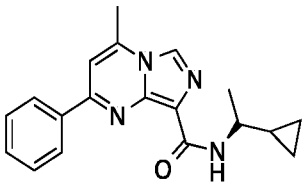
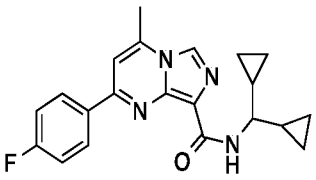
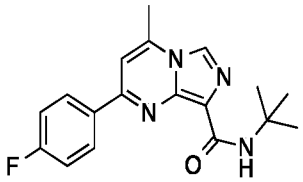
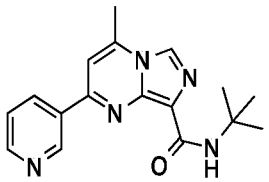
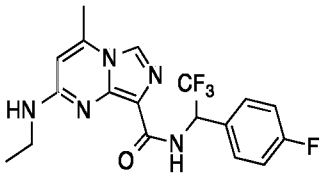
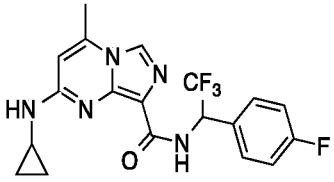
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-42		3.3	69.4	4.0	+++	*
III-43		2.9	69.4	31.1	+	*
III-44		2.9	69.4	26.0	+	*
III-45		3.8	69.4	5.0	++	*
III-46		3.4	57.1	12.0	+++	*
III-47		3.4	57.1	24.2	++	*
III-48		3.6	69.4	7.1	+++	***
III-49		3.6	69.4	6.7	+++	***

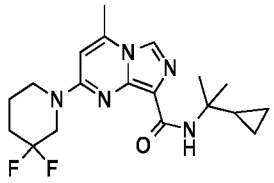
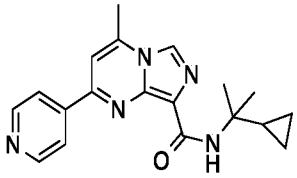
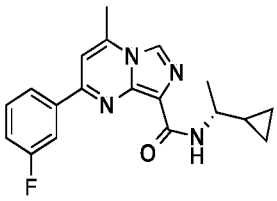
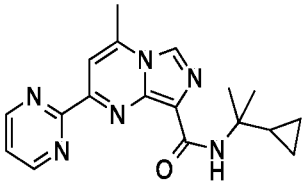
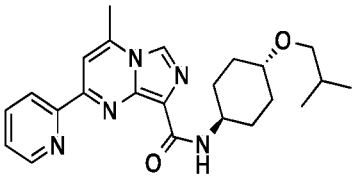
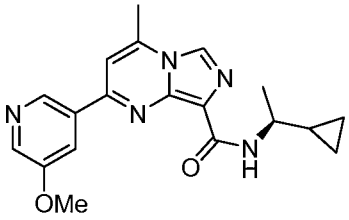
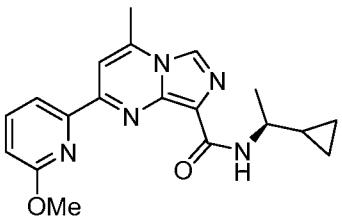
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-50		4.2	57.1	33.3	+++	***
III-51		4.2	57.1	22.7	+++	*
III-52		3.5	66.3	11.6	+++	***
III-55		4.1	66.3	7.8	+++	***
III-56		2.3	81.8	16.2	++	*
III-57		2.1	81.8	23.4	+	*
III-58		3.1	69.4	44.4	+++	*

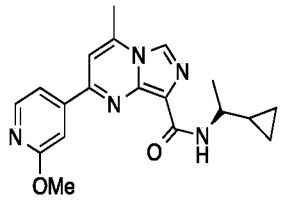
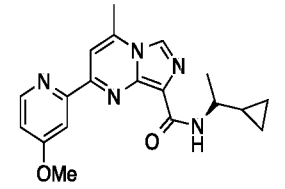
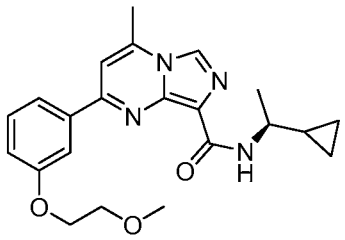
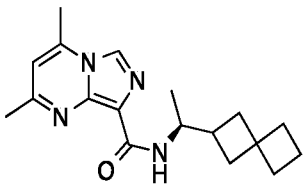
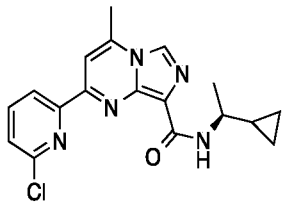
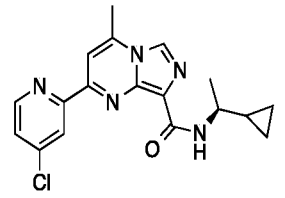
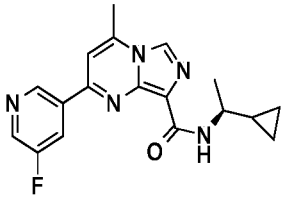
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-59		3.3	69.4	2.1	+++	**
III-60		3.5	69.4	4.0	+++	**
III-61		2.7	69.4	5.5	+++	**
III-62		2.7	69.4	6.3	+++	*
III-63		4.3	78.7	3.5	+++	***
III-64		3.1	78.7	32.2	+	*
III-65		2.9	78.7	15.4	+	*
III-66		3.3	78.7	16.0	++	*

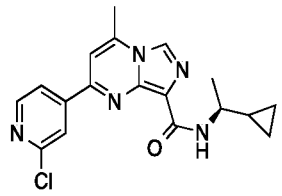
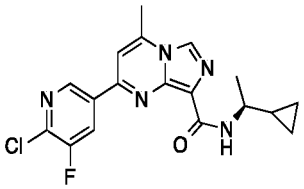
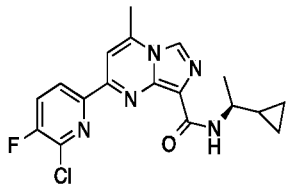
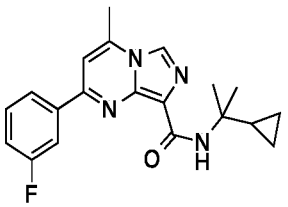
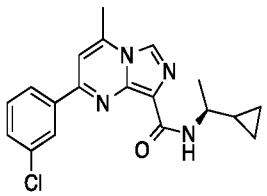
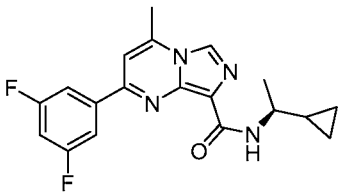
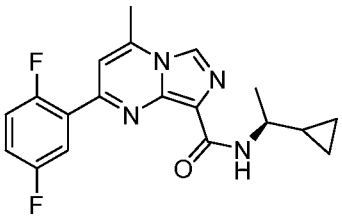
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-67		2.4	72.7	23.4	+	*
III-68		1.4	85.0	27.3	+	*
III-69		2.9	72.7	8.5	+	*
III-70		2.8	72.7	10.5	++	*
III-71		2.9	69.4	22.5	+++	*
III-72		2.9	69.4	4.7	+++	**
III-73		3.4	78.7	19.3	+	*
III-74		3.4	78.7	19.3	++	*

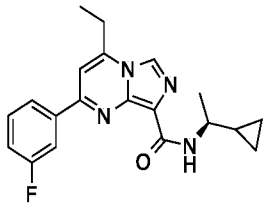
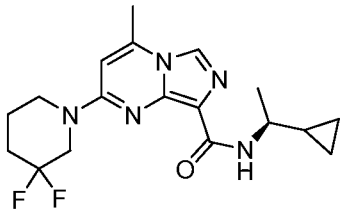
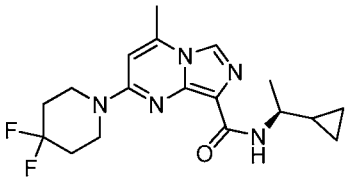
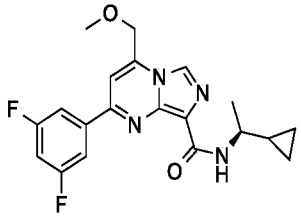
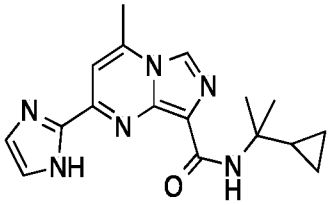
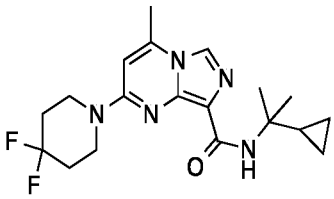
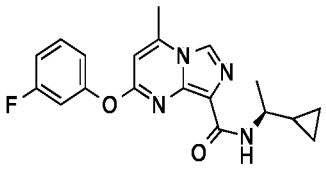
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-75		3.4	69.4	4.9	++	*
III-76		3.8	69.4	1.1	+++	**
III-77		4.2	66.3	10.6	++	*
III-78		2.8	66.3	23.2	+	*
III-79		4.8	57.1	3.0	+++	**
III-80		3.9	66.3	14.5	+	*
III-81		3.9	66.3	N/A	+	*
III-82		2.2	85.0	22.8	+	*

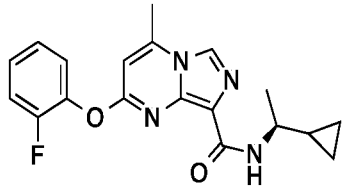
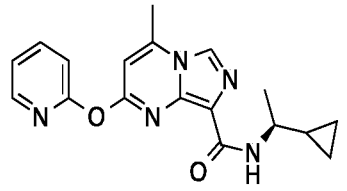
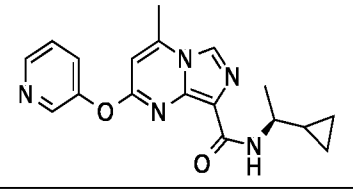
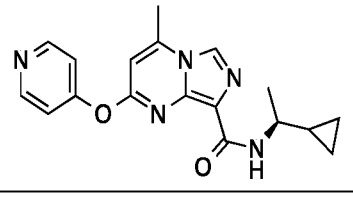
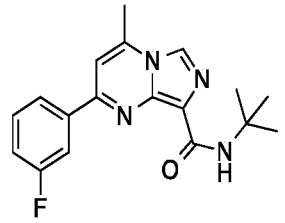
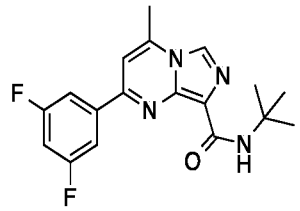
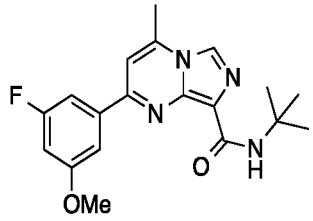
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-85		4.3	57.1	1.2	+++	***
III-86		4.1	57.1	13.1	+++	***
III-87		4.7	57.1	2.2	+++	***
III-88		4.2	57.1	2.0	+++	*
III-89		2.6	69.4	24.5	+	*
III-90		4.2	69.1	2.2	+++	***
III-91		4.3	60.1	0.8	+++	***

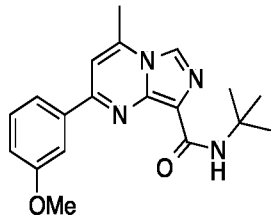
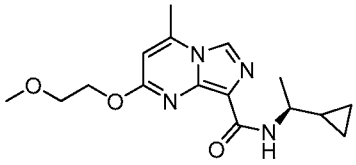
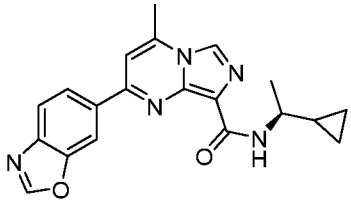
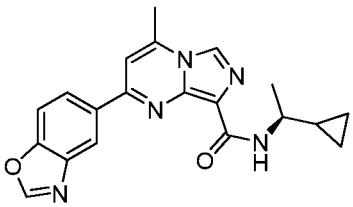
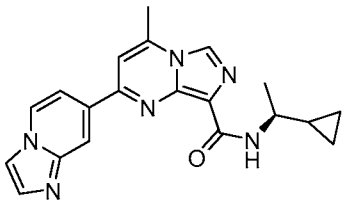
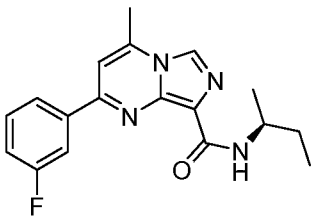
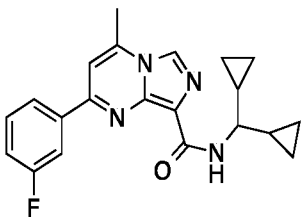
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-92		4.2	60.3	9.6	+++	**
III-93		3.0	69.4	18.8	+	*
III-94		4.2	57.1	8.4	+++	**
III-95		2.3	81.8	6.4	+	*
III-96		3.6	78.7	6.6	++	*
III-97		3.1	78.7	17.3	++	*
III-98		3.7	78.7	5.2	+++	**

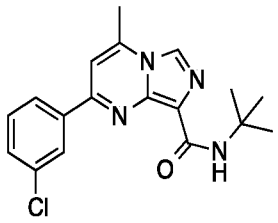
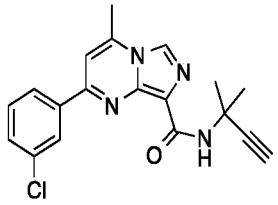
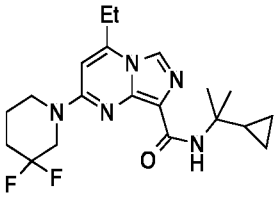
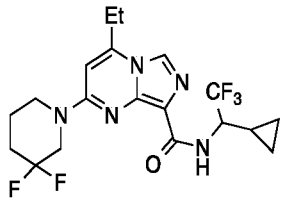
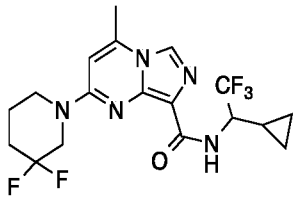
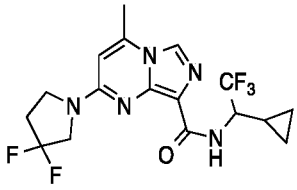
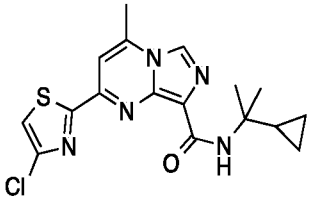
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-99		3.5	78.7	25.6	+	*
III-100		3.3	78.7	7.2	++	*
III-101		4.0	75.5	16.0	+++	**
III-102		3.9	57.1	12.1	+++	*
III-103		3.6	69.4	3.8	+++	*
III-104		3.6	69.4	8.0	+++	**
III-105		2.8	69.4	24.9	++	*

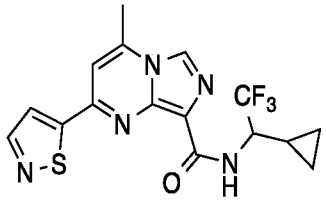
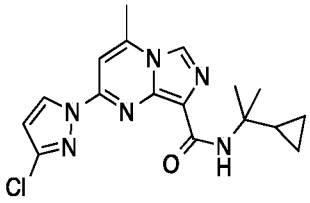
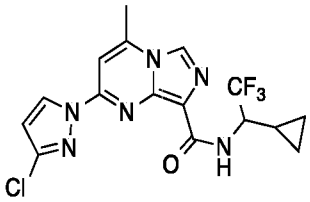
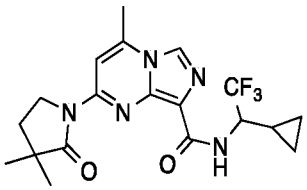
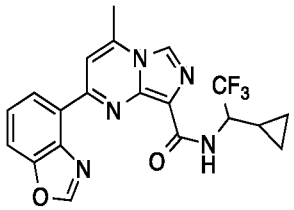
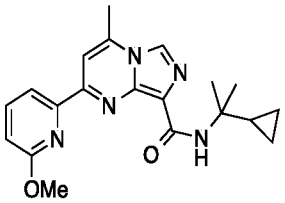
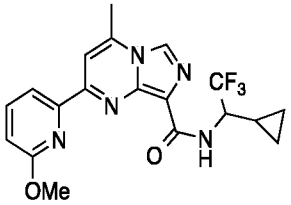
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-106		3.6	69.4	12.8	++	*
III-107		3.6	69.4	1.9	++	*
III-108		2.9	69.4	14.5	++	*
III-109		4.6	57.1	1.1	+++	***
III-110		4.8	57.1	3.6	+++	***
III-111		4.4	57.1	1.3	+++	***
III-112		4.4	57.1	5.5	+++	***

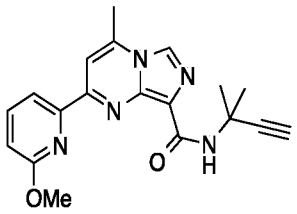
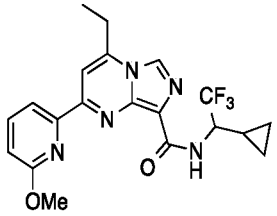
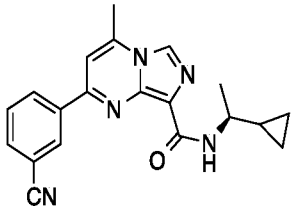
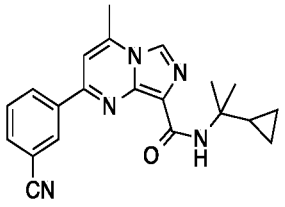
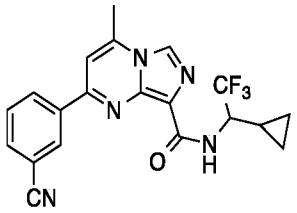
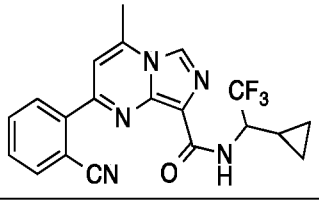
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-113		4.8	57.1	1.7	+++	***
III-114		3.8	60.3	26.0	+++	**
III-115		2.9	60.3	20.5	+	*
III-116		3.7	66.3	0.6	+++	**
III-117		2.6	81.5	20.5	+	*
III-118		3.3	60.3	9.7	++	*
III-119		4.2	66.3	8.8	++	*

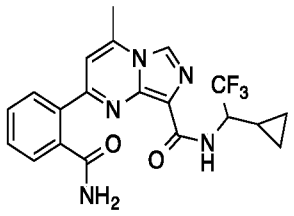
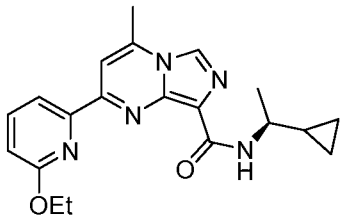
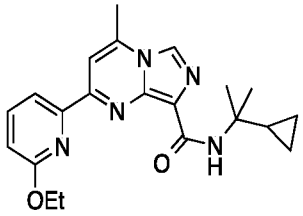
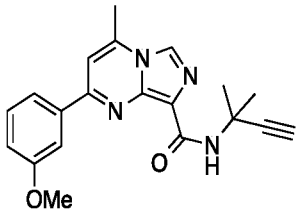
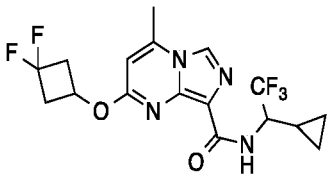
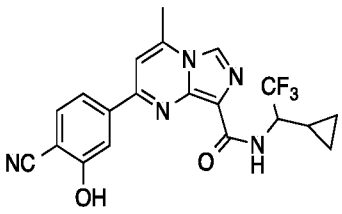
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-120		4.0	66.3	27.7	++	*
III-121		2.6	78.7	34.9	+	*
III-122		2.6	78.7	32.8	+	*
III-123		2.6	78.7	29.6	+	*
III-124		4.2	57.1	3.4	+++	***
III-125		4.3	57.1	0.2	+++	***
III-126		4.3	66.3	0.1	+++	***

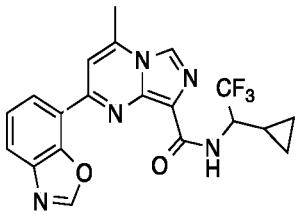
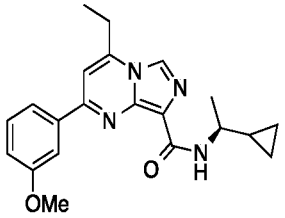
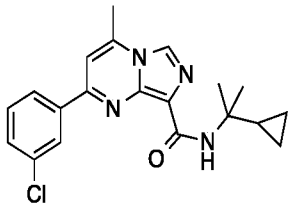
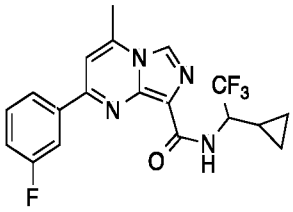
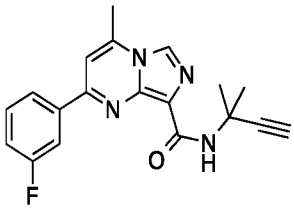
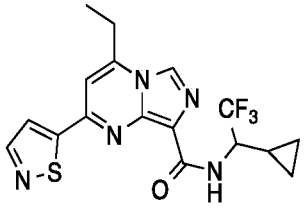
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-127		4.1	66.3	1.4	+++	***
III-128		1.9	75.5	34.1	+	*
III-129		3.4	78.7	6.1	+++	*
III-130		3.4	78.7	7.7	+++	***
III-131		3.4	72.7	2.8	+	*
III-132		4.3	57.1	18.6	+++	**
III-133		4.7	57.1	1.5	+++	***

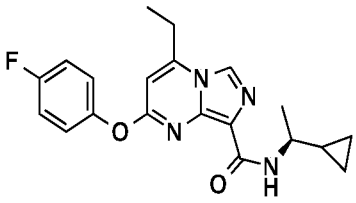
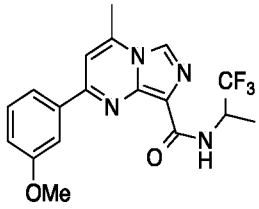
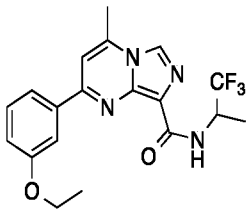
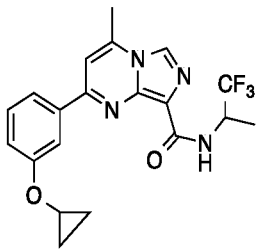
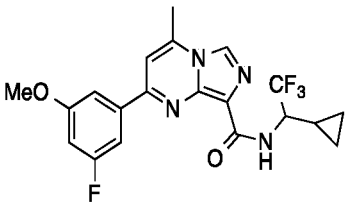
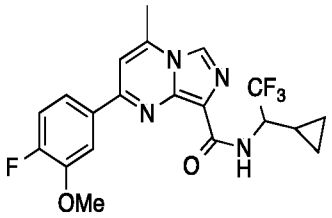
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-134		4.8	57.1	2.4	+++	***
III-135		4.8	57.1	0.3	+++	***
III-136		4.7	60.3	17.2	+++	***
III-137		4.6	60.3	12.0	+++	**
III-138		4.1	60.3	17.2	+++	***
III-139		3.5	60.3	1.8	+++	***
III-140		3.8	69.4	0.8	+	*

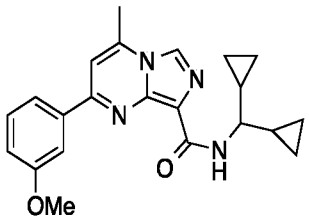
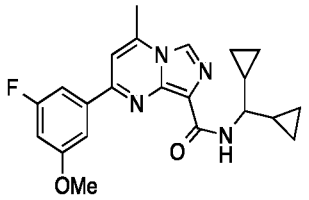
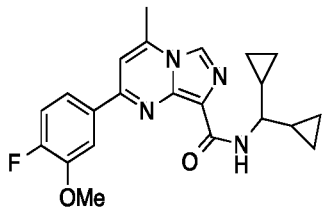
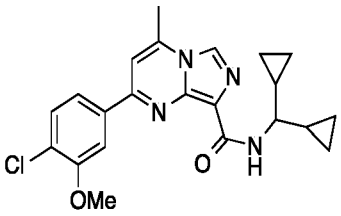
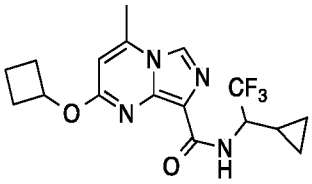
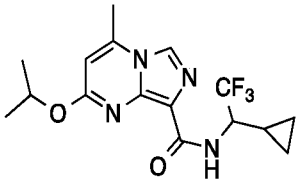
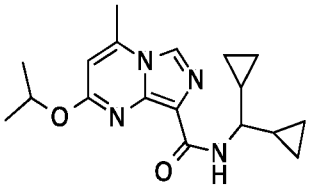
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-141		3.3	69.4	18.0	+++	***
III-142		3.5	72.7	14.9	+	*
III-143		3.4	72.7	4.2	+++	**
III-144		3.3	77.4	20.5	++	*
III-145		3.6	78.7	1.6	+++	***
III-146		4.1	78.7	0.9	+++	***
III-147		3.9	78.7	0.5	+++	***

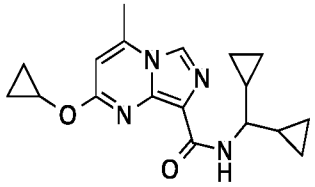
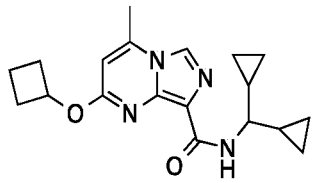
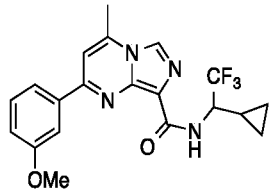
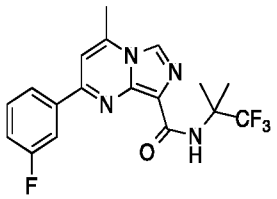
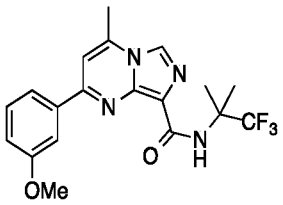
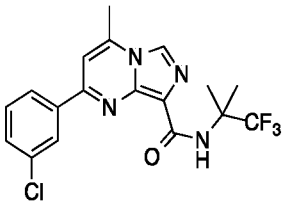
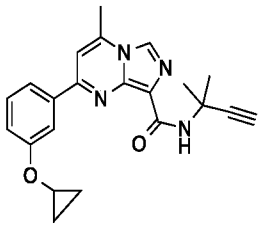
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-148		3.7	78.7	4.9	++	*
III-149		4.5	78.7	0.7	+++	***
III-150		3.5	80.9	10.1	+++	**
III-151		3.9	80.9	4.3	+++	***
III-152		3.8	80.9	3.8	+++	***
III-153		3.8	80.9	0.5	+++	***

Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-154		2.5	100.2	28.1	+	*
III-155		4.2	78.7	1.7	++	*
III-156		4.6	78.7	0.8	++	*
III-157		4.1	66.3	2.1	+++	***
III-158		3.4	66.3	21.9	++	*
III-159		3.9	101.1		+	*

Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-160		3.6	78.7	8.9	+++	***
III-161		4.6	66.3	1.8	+++	***
III-162		5.2	57.1	0.2	+++	***
III-163		4.5	57.1	0.4	+++	***
III-164		4.3	57.1	4.5	+++	***
III-165		3.9	69.4	4.7	+++	***

Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-166		4.8	66.3	10.8	++	*
III-167		3.9	66.3	2.9	+++	***
III-168		4.4	66.3	1.4	+++	***
III-169		4.5	66.3	0.7	+++	***
III-170		4.6	66.3	0.1	+++	***
III-171		4.4	66.3	0.6	+++	***

Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-172		4.5	66.3	4.2	+++	***
III-173		4.8	66.3	1.7	+++	***
III-174		4.6	66.3	0.3	+++	***
III-175		5.1	66.3	0.2	+++	**
III-176		4.0	66.3	5.5	+++	***
III-177		4.0	66.3	25.4	++	**
III-178		4.1	66.3	17.4	+++	**

Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-179		3.9	66.3	14.3	++	*
III-180		4.2	66.3	23.3	+++	**
III-182		4.3	66.3	1.5	+++	***
III-183		3.6	66.3	0.6	+++	***
III-184		3.7	81.8	4.3	+++	***
III-185		2.7	85.0	3.7	+++	***
III-186		4.7	66.3	1.5	+++	***

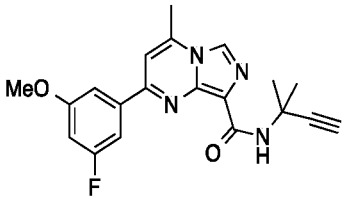
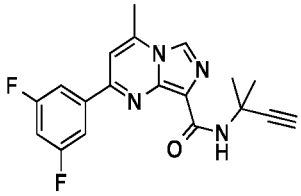
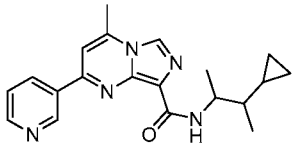
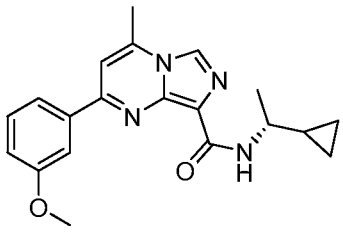
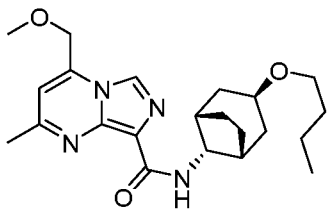
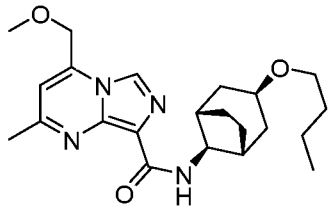
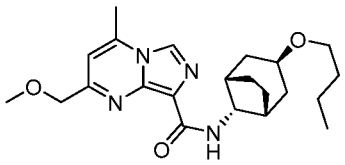
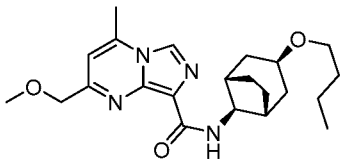
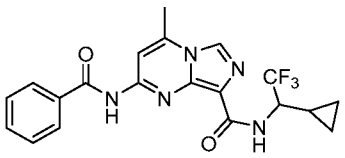
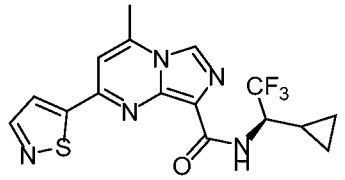
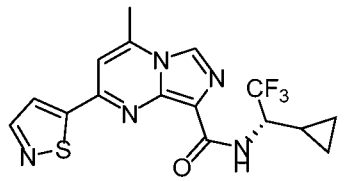
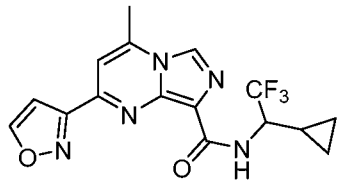
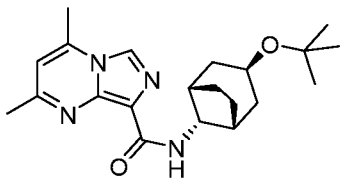
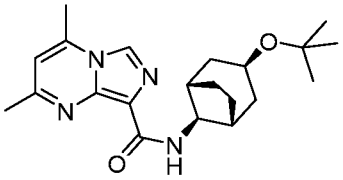
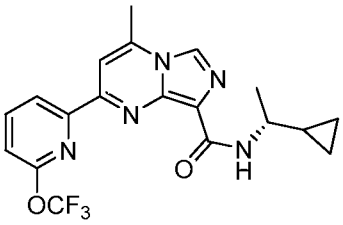
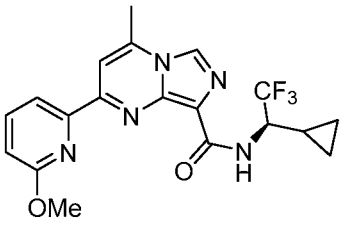
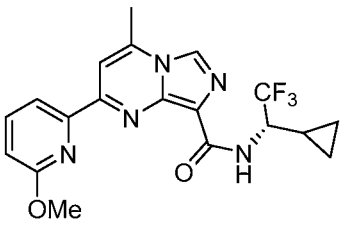
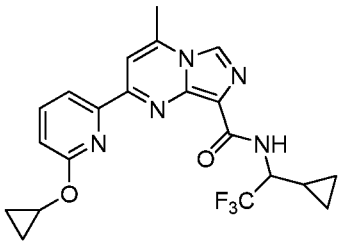
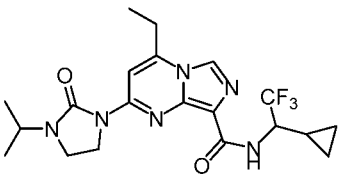
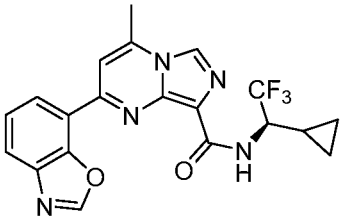
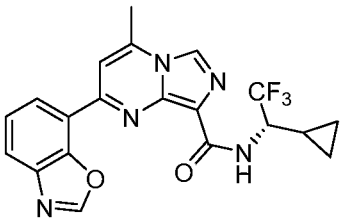
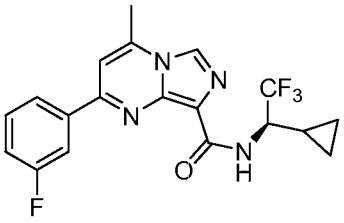
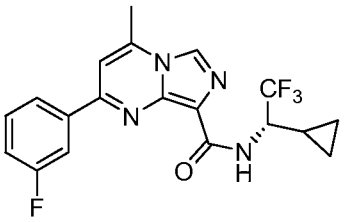
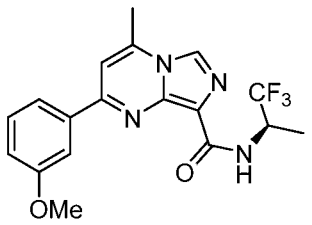
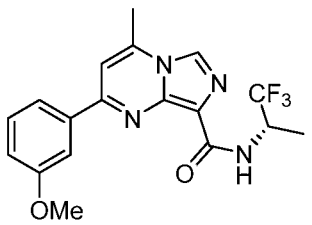
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-187		4.3	66.3	0.9	+++	***
III-188		4.4	57.1	0.3	+++	**
III-189		N/A	N/A	N/A	++	*

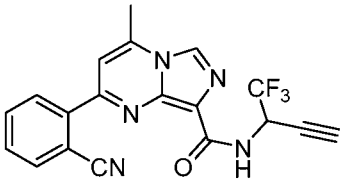
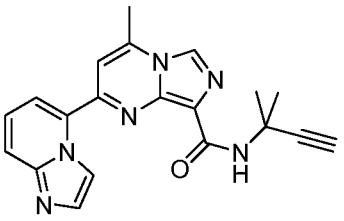
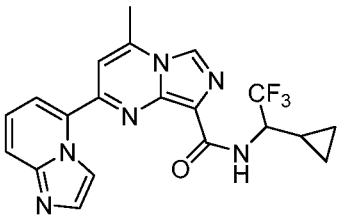
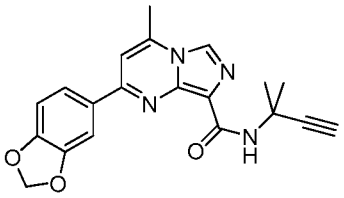
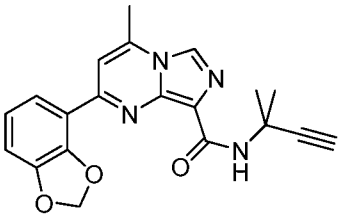
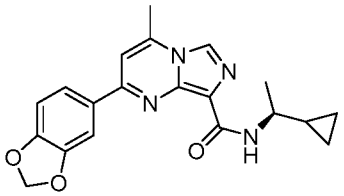
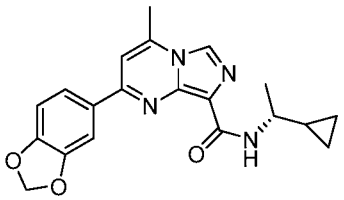
TABLE 4.

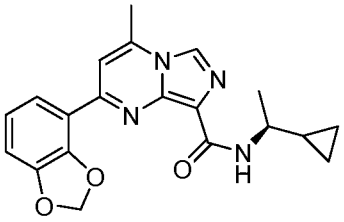
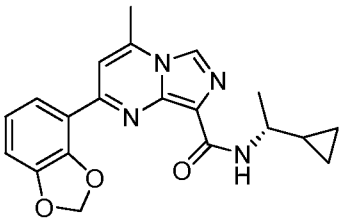
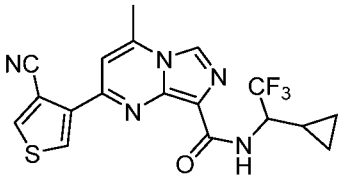
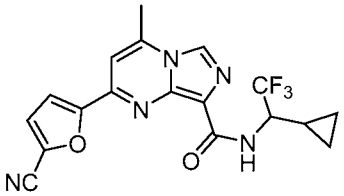
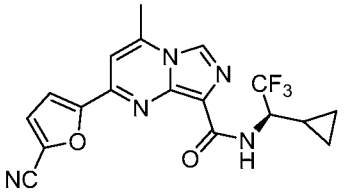
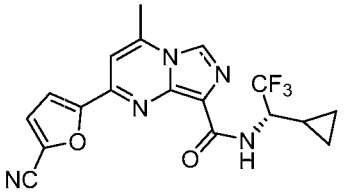
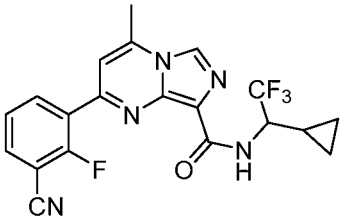
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
IV-1		N/A	N/A	8.3	+++	**
IV-2		3.4	75.5	27.5	+++	***

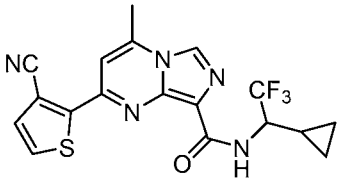
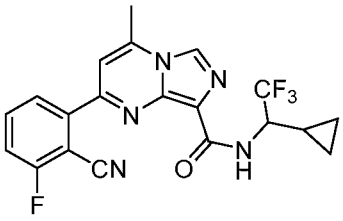
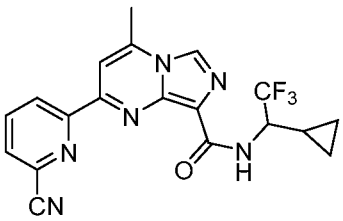
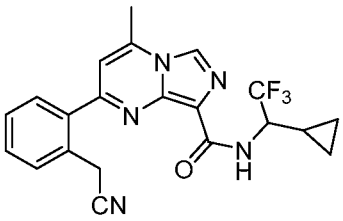
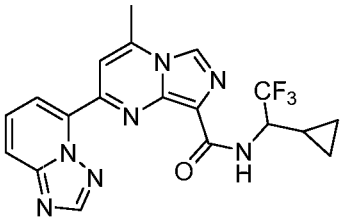
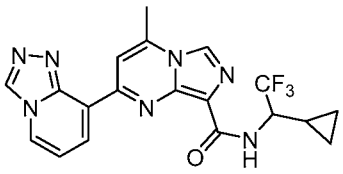
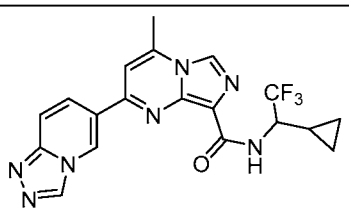
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
IV-3		3.4	75.5	15.3	++	*
IV-4		3.4	75.5	16.4	+++	***
IV-5		3.4	75.5	24.3	+++	*
IV-6		3.8	86.2	15.1	++	*
IV-7		3.3	69.4	9.9	+++	**
IV-8		3.3	69.4	19.7	+++	**
IV-9		2.7	78.7	3.9	++	*
IV-10		3.8	66.3	1.0	+++	***

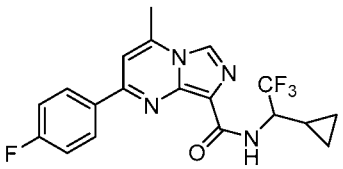
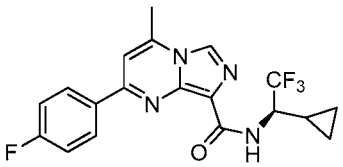
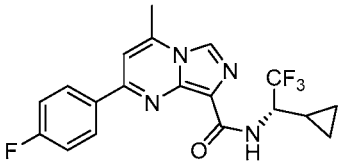
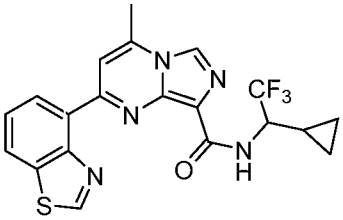
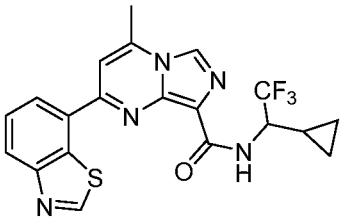
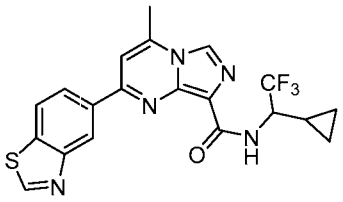
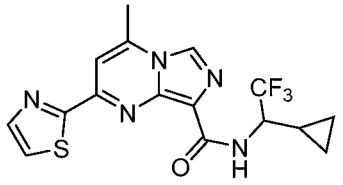
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
IV-11		3.8	66.3	4.9	+++	***
IV-12		N/A	N/A	N/A	++	*
IV-13		N/A	N/A	1.9	+++	***
IV-14		N/A	N/A	3.2	+++	***
IV-15		4.5	78.7	2.1	+++	**
IV-16		3.2	80.6	24.6	+++	**

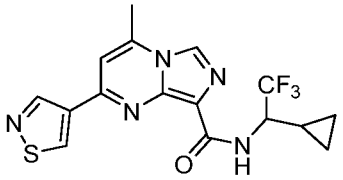
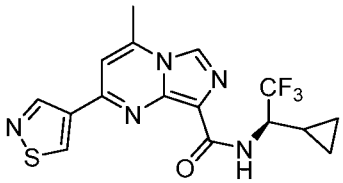
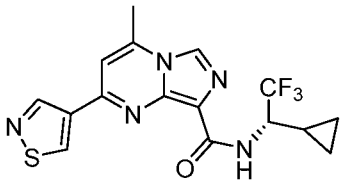
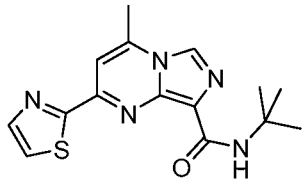
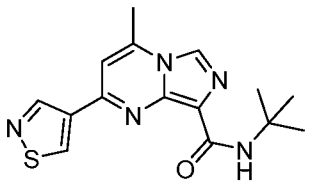
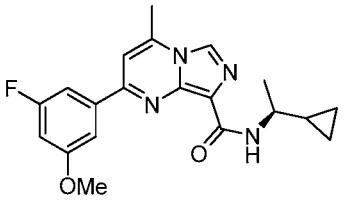
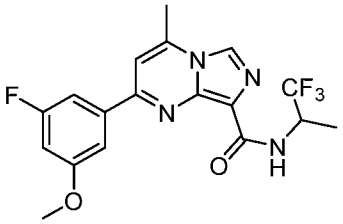
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
IV-17		N/A	N/A	1.1	+++	***
IV-18		N/A	N/A	0.4	+++	***
IV-19		4.5	57.1	0.7	+++	***
IV-20		4.5	57.1	0.7	+++	***
IV-21		N/A	N/A	2.7	+++	**
IV-22		N/A	N/A	1.7	+++	***

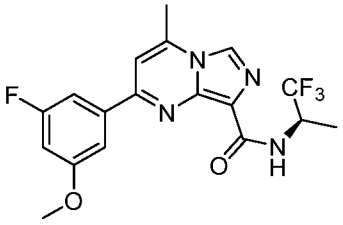
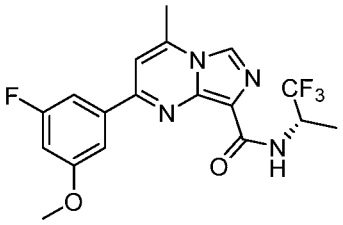
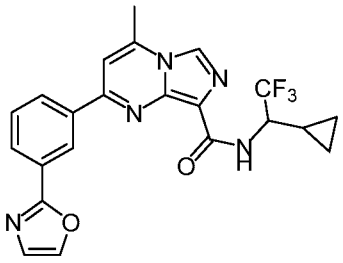
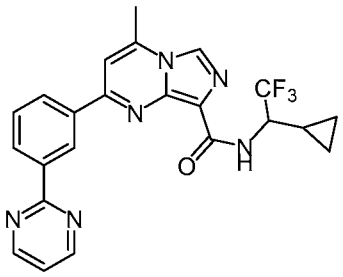
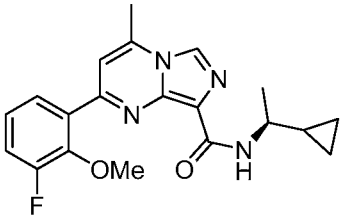
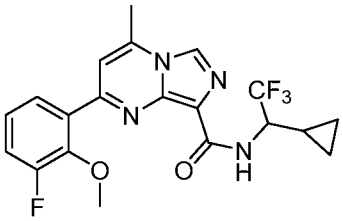
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
IV-23		3.5	80.9	0.6	+++	**
IV-24		3.6	72.7	2.5	+	*
IV-25		3.4	72.7	3.3	+	*
IV-26		4.1	75.5	0.5	+++	**
IV-27		4.1	75.5	1.1	+	*
IV-28		4.1	75.5	1.1	+++	***
IV-29		N/A	N/A	1.1	+++	***

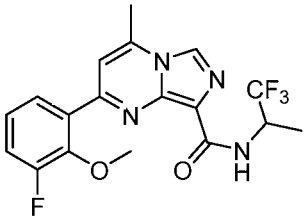
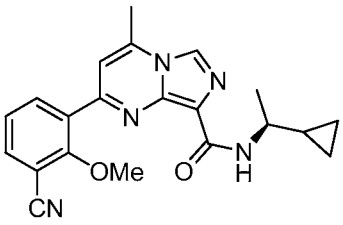
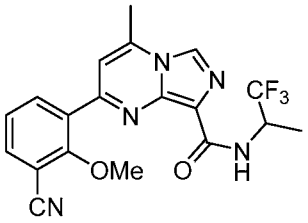
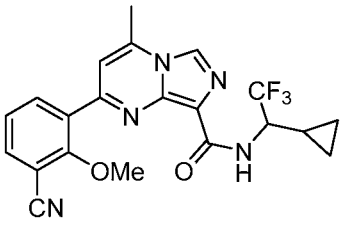
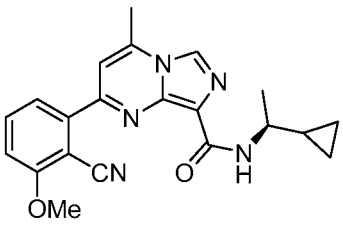
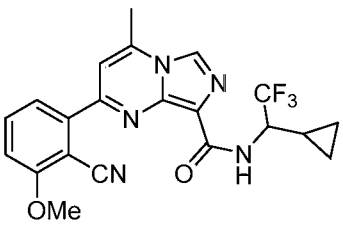
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
IV-30		4.1	75.5	0.5	+++	***
IV-31		N/A	N/A	1.4	+++	**
IV-32		3.5	80.7	0.6	+++	***
IV-33		3.2	90.1	0.7	+++	***
IV-34		N/A	N/A	N/A	+++	***
IV-35		N/A	N/A	N/A	+++	***
IV-36		3.9	80.9	0.5	+++	***

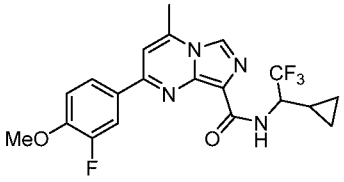
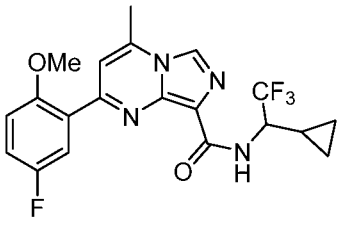
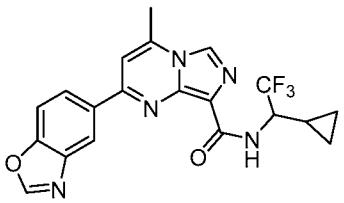
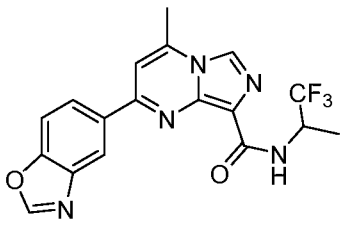
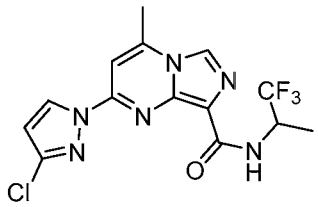
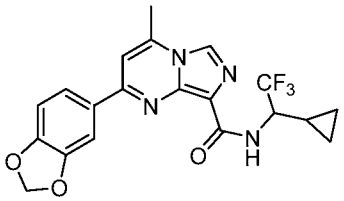
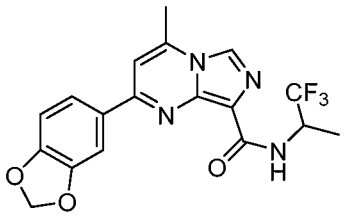
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
IV-37		3.7	80.9	2.4	+++	***
IV-38		3.9	80.9	0.4	+++	***
IV-39		2.9	93.2	0.3	++	*
IV-40		3.5	80.9	15.4	++	*
IV-41		2.9	85.0	3.5	++	*
IV-42		2.7	85.0	2.1	+++	*
IV-43		2.5	85.0	17.5	+	*

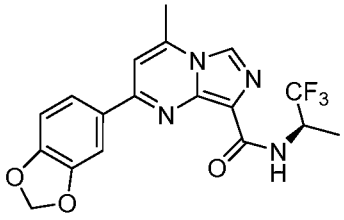
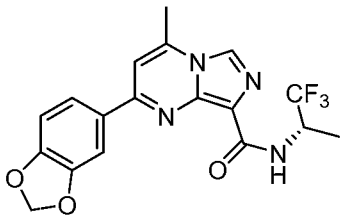
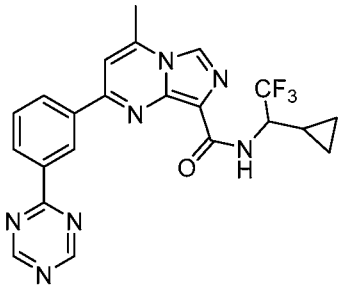
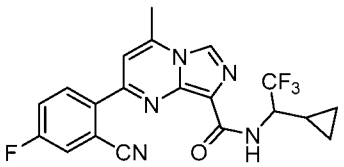
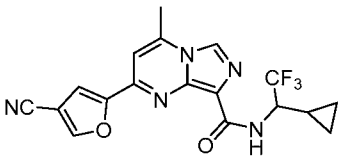
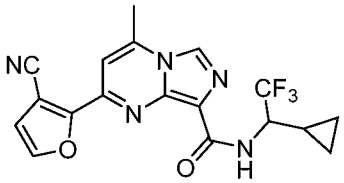
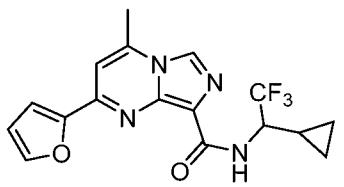
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
IV-44		4.5	57.1	0.8	+++	***
IV-45		4.5	57.1	2.5	+++	***
IV-46		4.5	57.1	0.8	+++	***
IV-47		4.3	69.4	3.8	++	*
IV-48		4.3	69.4	0.4	+++	**
IV-49		4.0	69.4	0.6	+++	***
IV-50		2.9	69.4	1.5	+++	**

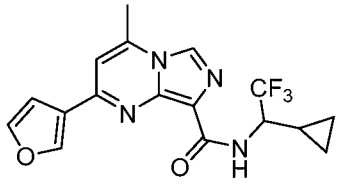
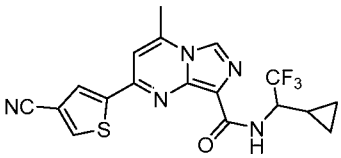
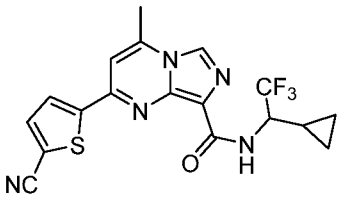
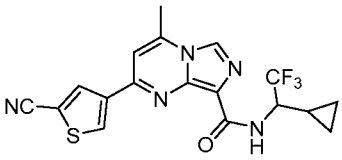
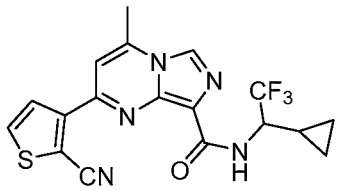
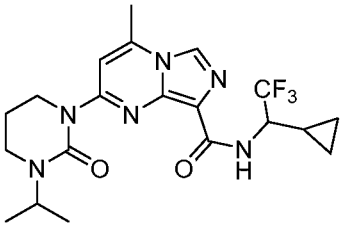
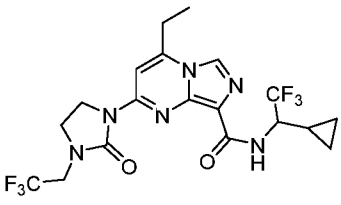
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
IV-51		3.1	69.4	2.1	+++	***
IV-52		3.1	69.4	15.4	+++	**
IV-53		3.1	69.4	13.2	+++	**
IV-54		2.6	69.4	N/A	+	*
IV-55		2.8	69.4	8.2	+++	*
IV-56		4.3	66.3	3.7	+++	***
IV-57		4.1	66.3	1.2	+++	***

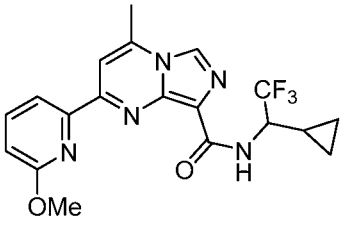
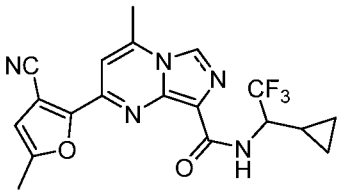
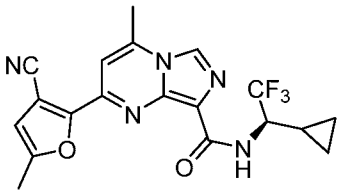
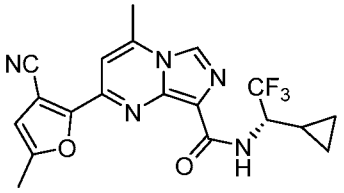
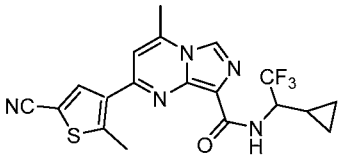
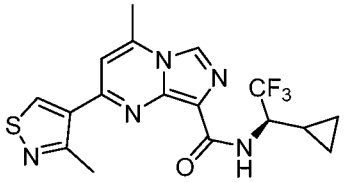
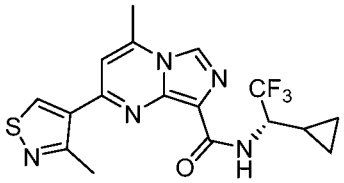
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
IV-58		N/A	N/A	2.3	+++	***
IV-59		N/A	N/A	2.2	+++	***
IV-60		4.1	78.7	2.3	+++	***
IV-61		4.0	81.8	1.1	+++	***
IV-62		3.6	66.3	16.0	+++	*
IV-63		3.8	66.3	3.1	+++	**

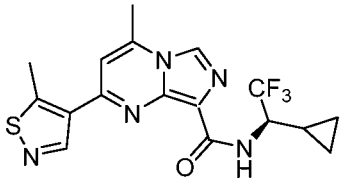
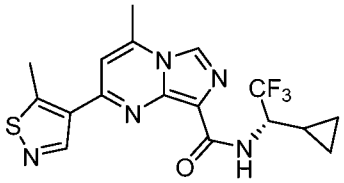
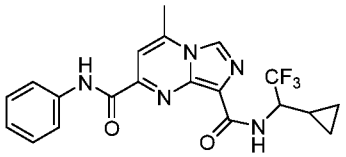
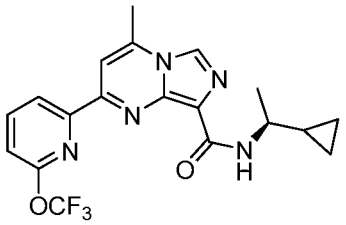
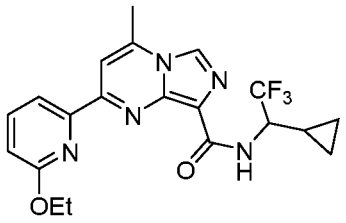
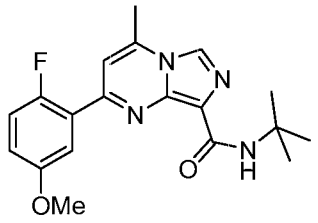
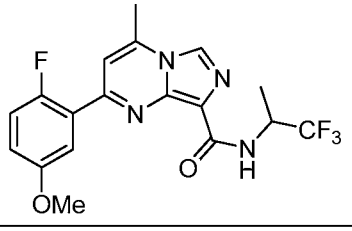
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
IV-64		3.4	66.3	21.0	++	*
IV-65		3.2	90.1	15.6	+	*
IV-66		3.1	90.1	23.9	+	*
IV-67		3.5	90.1	13.5	++	*
IV-68		3.8	90.1	0.7	+++	***
IV-69		4.1	90.1	1.3	+++	***

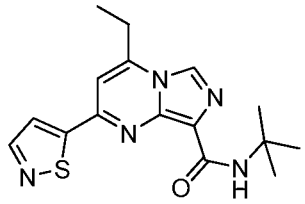
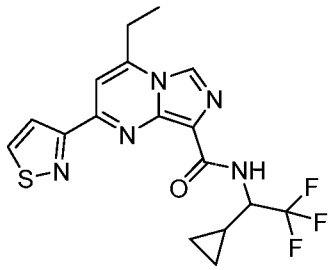
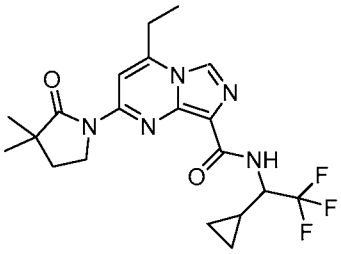
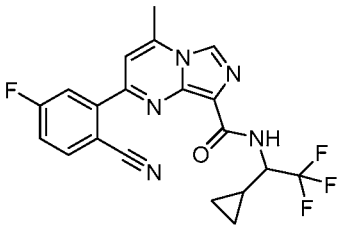
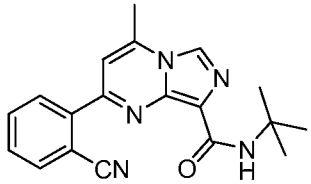
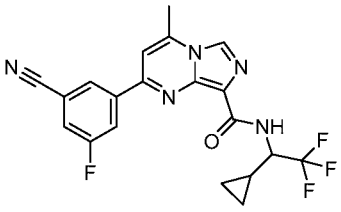
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
IV-70		4.4	66.3	1.5	+++	***
IV-71		4.0	66.3	1.5	+++	***
IV-72		3.6	78.7	1.1	+++	***
IV-73		3.2	78.7	2.1	+++	***
IV-74		2.9	72.7	4.2	++	*
IV-75		4.4	75.5	0.5	+++	***
IV-76		3.9	75.5	1.2	+++	***

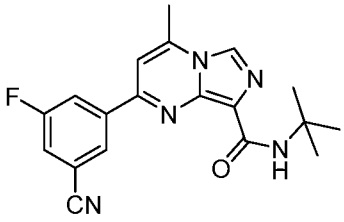
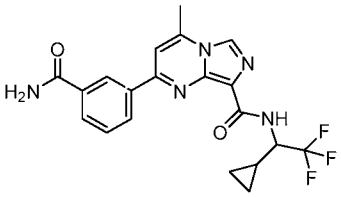
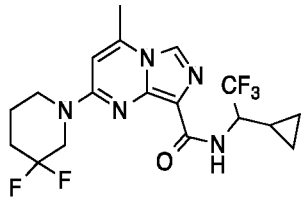
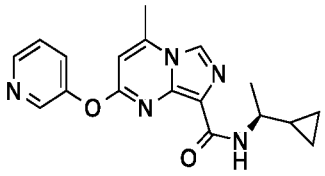
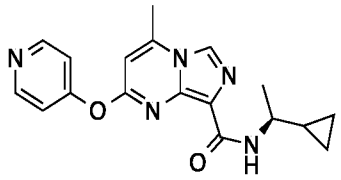
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
IV-77		N/A	N/A	1.3	+++	***
IV-78		N/A	N/A	3.3	+++	***
IV-79		3.1	94.1	0.5	+++	***
IV-80		3.9	80.9	3.7	+++	***
IV-81		3.2	90.1	1.0	+++	**
IV-82		3.2	90.1	1.9	+++	***
IV-83		3.7	66.7	1.2	+++	***

Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
IV-84		3.5	66.7	3.2	+++	***
IV-85		3.7	80.9	5.9	+++	***
IV-86		3.7	80.9	3.6	+++	***
IV-87		3.5	80.9	9.2	+++	***
IV-88		3.5	80.9	0.3	+++	***
IV-89		3.3	80.6	25.6	+	*
IV-90		2.7	80.6	25.6	+++	**

Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
IV-91		3.9	78.7	1.4	N/A	N/A
IV-92		3.7	90.1	0.3	+++	***
IV-93		N/A	N/A	N/A	+++	***
IV-94		N/A	N/A	N/A	+++	***
IV-95		3.7	80.9	2.5	+++	***
IV-96		3.3	69.4	N/A	+++	**
IV-97		3.3	69.4	N/A	+++	**

Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
IV-98		3.3	69.4	N/A	+++	***
IV-99		3.3	69.4	N/A	+++	***
IV-100		3.9	86.2	6.2	+	*
IV-101		4.8	78.7	1.5	+++	***
IV-102		4.5	78.7	7.8	+++	***
IV-103		4.3	66.3	0.7	+++	**
IV-104		3.8	72.7	0.7	+++	***

Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
IV-105		3.5	69.4	15.9	+++	**
IV-106		3.9	69.4	0.6	+++	***
IV-107		3.8	77.4	29.6	+++	**
IV-108		3.9	80.9	0.7	+++	***
IV-109		3.5	80.9	2.5	++	*
IV-110		3.9	80.9	1.2	+++	***

Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
IV-111		3.6	80.9	0.9	+++	**
IV-112		3.0	100.2	1.1	+++	**
IV-113		4.14	60.3	17.2	+++	***
IV-114		2.6	78.7	32.8	+	*
IV-115		2.6	78.7	29.6	+	*

INCORPORATION BY REFERENCE

[00785] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

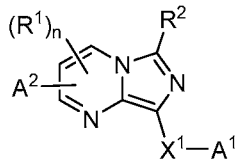
EQUIVALENTS

[00786] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be

considered in all respects illustrative rather than limiting the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

What is claimed is:

1. A compound of Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 each represent independently for each occurrence hydrogen, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} cyanoalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, cyclopropyl, cyano, halogen, hydroxyl, $-N(R^4)_2$, -0-(C_{1-4} alkylene)-C_{1-6} alkoxyl, or -(C_{1-4} alkylene)-(2-6 membered heteroalkyl optionally substituted by one or more halogen);

R^3 represents independently for each occurrence hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl;

R^4 represents independently for each occurrence hydrogen, C_{1-4} alkyl, cyclopropyl, or $-C(O)R^3$;

R^5 represents independently for each occurrence C_{1-4} alkyl or C_{3-6} cycloalkyl;

R^6 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, cyano, halogen, hydroxyl, or $-N(R^4)_2$;

X^1 is a carbonyl-containing linker selected from -C(O)N(H)-ψ, -C(O)N(H)(C_{1-6} alkylene optionally substituted with C_{1-4} alkoxyl or C_{3-6} cycloalkyl)-v|/, -C(O)N(H)(C_{1-6} haloalkylene)-ψ, -C(O)N(H)(C_{3-6} cycloalkylene)-ψ, -C(O)N(H)(3-6 membered heterocycloalkylene)-ψ, -C(O)-(3-6 membered heterocycloalkylene containing at least one ring -N(H)- group)-ψ, -C(O)N(H)C(O)-v|/, and -C(O)N(H)C(O)(C_{1-6} alkylene)-v|/; where ψ is a bond to A^1;

A^1 is one of the following:

- a cyclic group selected from a 3-14 membered saturated carbocyclyl, a 5-14 membered partially unsaturated carbocyclyl, a 3-16 membered heterocyclyl, or phenyl; each of which is substituted by 0, 1, or 2 occurrences of Y^1 and 0, 1, 2, or 3 occurrences of Y^2; or
- C_{1-8} alkyl or C_{2-6} alkynyl;

A^2 is one of the following:

- a cyclic group selected from a 3-12 membered heterocyclyl, 4-12 membered oxoheterocyclyl, 4-10 membered cycloalkyl, or phenyl; each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of halogen, hydroxyl, cyano, C_{1-4} alkyl, Ci_{-4} haloalkyl, C_{1-4} alkoxyl, Ci_{-4} haloalkoxyl, C_{3-6} cycloalkyl, -0-(C3-6 cycloalkyl), -0-(Ci_6 alkylene)-Ci-6 alkoxyl, -(Ci_{-6} alkylene)-CN, -$N(R^4)_2$, -$C(0)N(R^4)_2$, and heteroaryl;
- -$N(R^4)$(3-10 membered heterocyclyl, C_{3-1}ocycloalkyl, or phenyl, each optionally substituted by 1, 2, or 3 R^6 groups) or -0(3-10 membered heterocyclyl, C_{3-1}o cycloalkyl, or phenyl, each optionally substituted by 1, 2, or 3 R^6 groups); or
- -$C(0)N(R^4)$(aryl or heteroaryl);

Y^1 represents, independently for each occurrence, one of the following:

- 2-8 membered heteroalkyl optionally substituted by a 6-10 membered aryl, a 3-10 membered heterocyclyl, or C_{3-6} halocycloalkyl;
- 3-10 membered heterocyclyl, 6-10 membered aryl, C3-7 cycloalkyl, -O-C3-6 cycloalkyl, -0-(3-6 membered heterocyclyl), -0(6-10 membered aryl), or -O-(C_{2-6} alkynyl); or
- C_{2-6} alkynyl, -C≡C-(C_W alkylene)-OR^4, -C≡C-(C_W alkylene)-$N(R^3)_2$, -(C_{2-4} alkynylene)-(5-6 membered heteroaryl), or C_{2-6} alkenyl;

Y^2 represents, independently for each occurrence, C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, Ci-6 haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, C_{1-6} alkoxyl, -0-(Ci-8 haloalkyl), cyano, azido, -$N(R^3)_2$, -(Ci-6 alkylene)-(5-6 membered heterocyclyl), -(C_{1-6} alkylene)-$C0_2R^3$, -$C0_2R^3$, -$C(0)R^5$, -$S(0)_2R^5$, -$C(0)N(R^5)_2$, -$C(0)N(R^3)_2$, or Ci_{-6} haloalkyl-substituted C_{3-6} cycloalkyl; and

n is i, 2, or 3;

wherein R^1 is other than hydrogen, when $X^A{}^1$ is -C(0)N(H)-(5-6 membered heteroaryl containing at least 1 nitrogen atom, wherein the heteroaryl is substituted by 0, 1, or 2 occurrences of Y^1 and 0, 1, 2, or 3 occurrences of Y^2).

2. The compound of claim 1, wherein X^1 is -C(O)N(H)-ψ.

3. The compound of claim 1, wherein X^1 is -C(0)N(H)(Ci_6 alkylene)-\|/.

4. The compound of claim 1, wherein X^1 is -C(O)N(H)(C(CH_3)$_2$)-ψ or -C(0)N(H)(C-(H)(CH$_3$))-Y|/.

5. The compound of claim 1, wherein X^1 is -C(O)N(H)(C_{1-6} haloalkylene)-ψ.

6. The compound of claim 1, wherein X^1 is -C(O)N(H)C(H)(CF_3)-ψ.

7. The compound of any one of claims 1-6, wherein A^2 is a 5-12 membered heterocyclyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, halogen, hydroxyl, and -N(R^4)$_2$.

8. The compound of any one of claims 1-6, wherein A^2 is a 5-6 membered heteroaryl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, halogen, hydroxyl, and -N(R^4)$_2$.

9. The compound of any one of claims 1-6, wherein A^2 is a 5-6 membered heteroaryl selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, furanyl, pyrrolyl, thiophenyl, imidazolyl, oxazolyl, isoxazolyl, isothiazolyl, and thiazolyl, each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, halogen, hydroxyl, and -N(R^4)$_2$.

10. The compound of any one of claims 1-6, wherein A^2 is pyridinyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, halogen, hydroxyl, and -N(R^4)$_2$.

11. The compound of any one of claims 1-6, wherein A^2 is 3-pyridinyl optionally substituted by 1 or 2 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, and halogen.

12. The compound of any one of claims 1-6, wherein A^2 is a 5-6 membered heterocycloalkyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, halogen, hydroxyl, and -N(R^4)$_2$.

13. The compound of any one of claims 1-5, wherein $\mathbf{A^2}$ is a 5-6 membered heterocycloalkyl selected from the group consisting of morpholinyl, piperidinyl, pyrrolidinyl, tetrahydropyranyl, and tetrahydrofuranyl, each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, **Ci-4** alkoxyl, $_{C\ 3-5}$ cycloalkyl, cyano, halogen, hydroxyl, and $\mathbf{-N}(R^4)_2$.

14. The compound of any one of claims 1-6, wherein $\mathbf{A^2}$ is phenyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, $_{C3-5}$ cycloalkyl, cyano, halogen, hydroxyl, and $\mathbf{-N}(R^4)_2$.

15. The compound of any one of claims 1-6, wherein $\mathbf{A^2}$ is $\mathbf{-N}(R^4)$(3-10 membered heterocycloalkyl or $_{C3-10}$ cycloalkyl, each optionally substituted by 1, 2, or 3 R^6 groups) or -0(3-10 membered heterocycloalkyl or C_{3-1}ocycloalkyl, each optionally substituted by 1, 2, or 3 R^6 groups).

16. The compound of any one of claims 1-15, wherein $\mathbf{A^2}$ is located at the 2-position of the imidazo[l,5-a]pyrimidinyl.

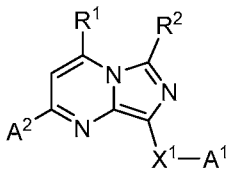
17. The compound of any one of claims 1-15, wherein $\mathbf{A^2}$ is located at the 4-position of the imidazo[l,5-a]pyrimidinyl.

18. The compound of any one of claims 1-17, wherein n is 1.

19. The compound of claim 16, wherein n is 1, and the R^1 group is located at the 4-position of the imidazo[l,5-a]pyrimidinyl.

20. The compound of claim 17, wherein n is 1, and the R^1 group is located at the 2-position of the imidazo[l,5-a]pyrimidinyl.

21. The compound of claim 1, wherein the compound is represented by Formula **I-A:**



(I-A)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is Ci-4 alkyl, C1-4 haloalkyl, C_{1-4} alkoxyl, -(C_{1-4} alkylene)-(Ci-4 alkoxyl), cyclopropyl, chloro, or fluoro;

R^2 is hydrogen;

R^3 and R^4 each represent independently for each occurrence hydrogen or C_{1-4} alkyl;

X^1 is -C(0)N(H)(Ci-6 haloalkylene)-ψ or -C(0)N(H)(Ci$_{-6}$ alkylene)-v|/; where ψ is a bond to A^1;

A^1 is a cyclic group selected from:

- C_{3-10} cycloalkyl substituted by 0 or 1 occurrence ofY^1 and 0, 1, or 2 occurrences of Y^2; and
- phenyl substituted by 0 or 1 occurrence ofY^1 and 0, 1, or 2 occurrences of Y^2;

A^2 is phenyl or a 5-12 membered heterocyclyl, each optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C3-5 cycloalkyl, cyano, halogen, and hydroxyl;

Y^1 represents, independently for each occurrence, one of the following:

- 2-8 membered heteroalkyl or -*0-(C2*$_{-6}$ alkynyl); or
- C_{2-6} alkynyl or -C≡C-(Ci$_{-6}$ alkylene)-OR^4; and

Y^2 represents, independently for each occurrence, C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, Ci-6 haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, C_{1-6} alkoxyl, cyano, or -$N(R^3)_2$.

22. The compound of claim 21, wherein R^1 represents independently for each occurrence methyl, halomethyl, -(CH_2)i-2-0-(Ci-3 alkyl), cyclopropyl, chloro, or fluoro.

23. The compound of claim 21 or 22, wherein A^1 is C3-7 cycloalkyl substituted once by Y^1 and 0-1 occurrences ofY^2.

24. The compound of claim 21 or 22, wherein A^1 is cyclohexyl substituted once by Y^1.

25. The compound of claim 21 or 22, wherein A^1 is C3-7 cycloalkyl that is not substituted.

26. The compound of claim 21 or 22, wherein A^1 is cyclopropyl.

27. The compound of any one of claims 21-23, wherein any occurrence ofY^2 is independently Ci-3 alkyl, halogen, or C_{1-3} haloalkyl.

28. The compound of any one of claims 21-24 or 27, wherein Y^1 is a 2-8 membered heteroalkyl optionally substituted by a 6-10 membered aryl or a 3-10 membered heterocyclyl.

29. The compound of any one of claims 21-24 or 27, wherein Y^1 is -0-(Ci_7 alkyl).

30. The compound of any one of claims 21-24 or 27, wherein Y^1 is -O-butyl, -O-pentyl, or -O-hexyl.

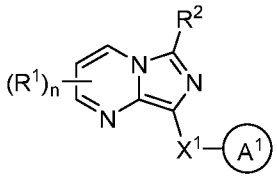
31. The compound of any one of claims 21-30, wherein A^2 is a 5-6 membered heteroaryl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C1-4 alkyl, C1-4 haloalkyl, C1-4 alkoxyl, C3-5 cycloalkyl, cyano, halogen, hydroxyl, and $-N(R^4)_2$.

32. The compound of any one of claims 21-30, wherein A^2 is a 5-6 membered heteroaryl selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl, furanyl, pyrrolyl, thiophenyl, imidazolyl, oxazolyl, isoxazolyl, isothiazolyl, and thiazolyl, each of which is optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C1-4 alkyl, C1-4 haloalkyl, C1-4 alkoxyl, C3-5 cycloalkyl, cyano, halogen, hydroxyl, and $-N(R^4)_2$.

33. The compound of any one of claims 21-30, wherein A^2 is pyridinyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C1-4 alkyl, C1-4 haloalkyl, C1-4 alkoxyl, C3-5 cycloalkyl, cyano, halogen, hydroxyl, and $-N(R^4)_2$.

34. The compound of any one of claims 21-30, wherein A^2 is phenyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C1-4 alkyl, C1-4 haloalkyl, C1-4 alkoxyl, C3-5 cycloalkyl, cyano, halogen, and hydroxyl.

35. A compound of Formula II:



(II)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 each represent independently for each occurrence hydrogen, C1-4 alkyl, C_{1-4} haloalkyl, Ci^hydroxyalkyl, C_{1-4} cyanoalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, cyclopropyl, cyano, halogen, hydroxyl, $-N(R^4)_2$, -0-(C_{1-4} alkylene)-Ci-6 alkoxyl, or -(Ci_$_4$ alkylene)-(2-6 membered heteroalkyl optionally substituted by one or more halogen);

R^3 represents independently for each occurrence hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl;

R^4 represents independently for each occurrence hydrogen, C_{1-4} alkyl, cyclopropyl, or -C(0)R^3;

R^5 represents independently for each occurrence C_{1-4} alkyl or C_{3-6} cycloalkyl;

X^1 is a carbonyl-containing linker selected from -C(0)N(H)(C_{1-6} haloalkylene)-ψ, -C(0)N(H)(Ci-6 alkylene substituted with C_{1-4} alkoxyl or C_{3-6} cycloalkyl)-ψ, -C(0)N(H)(C_{3-6} cycloalkylene)-ψ, -C(0)N(H)(3-6 membered heterocycloalkylene)-ψ, -C(O)N(H)C(O)-ψ, and -C(0)N(H)C(0)(Ci$_{-6}$ alkylene)-v|/; where ψ is a bond to A^1;

A^1 is one of the following:

- a cyclic group selected from a 3-14 membered saturated carbocyclyl, a 5-14 membered partially unsaturated carbocyclyl, a 3-16 membered heterocyclyl, or phenyl; each of which is substituted by 0, 1, or 2 occurrences ofY^1 and 0, 1, 2, or 3 occurrences of Y^2; or
- Ci-8 alkyl or C_{2-6} alkynyl;

Y^1 represents, independently for each occurrence, one of the following:

- 2-8 membered heteroalkyl optionally substituted by a 6-10 membered aryl, a 3-10 membered heterocyclyl, or C_{3-6} halocycloalkyl;
- 3-10 membered heterocyclyl, 6-10 membered aryl, C_{3-7} cycloalkyl, -O-C3-6 cycloalkyl, -0-(3-6 membered heterocyclyl), -0(6-10 membered aryl), or -O-$(C_{2-6}$ alkynyl); or
- C_{2-6} alkynyl, -C≡C-(Ci$_{-6}$ alkylene)-OR^4, -C≡C-(C_W alkylene)-N(R^3)$_2$, -(C_{2-4} alkynylene)-(5-6 membered heteroaryl), or C_{2-6} alkenyl;

Y^2 represents, independently for each occurrence, C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, Ci-6 haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, C_{1-6} alkoxyl, -0-(Ci_8 haloalkyl), cyano, azido, -N(R^3)$_2$, -(Ci$_{-6}$ alkylene)-(5-6 membered heterocyclyl), -(C_{1-6} alkylene)-C0$_2R^3$, -C0$_2R^3$, -C(0)R^5, -S(0)$_2R^5$, -C(0)N(R^5)$_2$, -C(0)N(R^3)$_2$, or Ci$_{-6}$ haloalkyl-substituted C_{3-6} cycloalkyl;

m is 1 or 2; and

n is i, 2, or 3;

provided that when X^1 is C(0)N(H)(C_{3-6} cycloalkylene)-ψ or -C(0)N(H)(3-6 membered heterocycloalkylene)-ψ, then A^1 is not a 5-membered heterocyclyl.

36. The compound of claim 35, wherein X^1 is -C(0)N(H)(Ci_6 haloalkylene)-\|/.

37. The compound of claim 35, wherein X^1 is -C(0)N(H)C(H)(CF_3)-ψ.

38. The compound of claim 35, wherein X^1 is -**C(0)N(H)(Ci-6** alkylene substituted with $\mathbf{C_{1-4}}$ alkoxyl)-ψ.

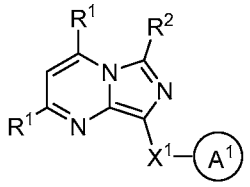
39. The compound of claim 35, wherein X^1 is -**C(0)N(H)(Ci-6** alkylene substituted with $\mathbf{C_{3-6}}$ cycloalkyl)-ψ.

40. The compound of claim 35, wherein X^1 is -**C(0)N(H)(C3-6** cycloalkylene)-ψ.

41. The compound of any one of claims 35-40, wherein n is 2.

42. The compound of claim 41, wherein the **R1** groups are located at the 2 and 4 positions of the imidazo[1 ,5-a]pyrimidinyl.

43. The compound of claim 35, wherein the compound is represented by Formula II-A:



(II-A)

or a pharmaceutically acceptable salt thereof, wherein:

R1 represents independently for each occurrence $\mathbf{C_{1-4}}$ alkyl, $\mathbf{C_{1-4}}$ haloalkyl, $\mathbf{C_{1-4}}$ alkoxyl, **-(Ci-4** alky**lene)-(C 1-4** alkoxyl), cyclopropyl, chloro, or fluoro;

R2 is hydrogen;

R3 and **R4** each represent independently for each occurrence hydrogen or $\mathbf{C_{1-4}}$ alkyl;

X^1 is -**C(0)N(H)(Ci-6** haloalkylene)-ψ or -**C(0)N(H)(Ci-6** alkylene substituted with $\mathbf{C_{1-4}}$ alkoxyl or $\mathbf{C_{3-6}}$ cycloalkyl)-ψ; where ψ is a bond to A^1;

A^1 is a cyclic group selected from:

- $\mathbf{C_{3-10}}$ cycloalkyl substituted by 0 or 1 occurrence of Y^1 and 0, 1, or 2 occurrences of Y^2; and
- phenyl substituted by 0 or 1 occurrence ofY^1 and 0, 1, or 2 occurrences of Y^2;

Y^1 represents, independently for each occurrence, one of the following:

- 2-8 membered heteroalkyl or -***0-(C2-6*** alkynyl); or
- $\mathbf{C_{2-6}}$ alkynyl or -**C≡C-**(C_{1-6} alkylene)**-OR4;** and

Y^2 represents, independently for each occurrence, C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, C_{1-6} alkoxyl, cyano, or $-N(R^3)_2$.

44. The compound of claim 43, wherein R^1 represents independently for each occurrence methyl, halomethyl, $-(CH_2)_{1-2}-O-(C_{1-3}$ alkyl), cyclopropyl, chloro, or fluoro.

45. The compound of claim 43 or 44, wherein X^1 is $-C(O)N(H)(C_{1-6}$ haloalkylene)-ψ.

46. The compound of claim 43 or 44, wherein X^1 is $-C(O)N(H)C(H)(CF_3)$-ψ.

47. The compound of any one of claims 43-46, wherein A^1 is C_{3-7} cycloalkyl substituted once by Y^1 and 0-1 occurrences of Y^2.

48. The compound of any one of claims 43-46, wherein A^1 is cyclohexyl substituted once by Y^1.

49. The compound of any one of claims 43-46, wherein A^1 is C_{3-7} cycloalkyl that is not substituted.

50. The compound of any one of claims 43-46, wherein A^1 is cyclopropyl.

51. The compound of any one of claims 43-48, wherein Y^1 is $-O-(C_{1-7}$ alkyl).

52. The compound of any one of claims 43-48, wherein Y^1 is -O-butyl, -O-pentyl, or -O-hexyl.

53. The compound of any one of claims 1-20 or 35-42, wherein R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, $-(C_{1-4}$ alkylene)-(2-6 membered heteroalkyl), cyclopropyl, halogen, or $-N(R^4)_2$.

54. The compound of any one of claims 1-20 or 35-42, wherein R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, cyclopropyl, cyano, chloro, or fluoro.

55. The compound of any one of claims 1-20 or 35-42, wherein R^1 is methyl.

56. The compound of any one of claims 1-20, 35-42, or 53-55, wherein R^2 is hydrogen.

57. The compound of any one of claims 1-20, 35-42, or 53-56, wherein R^3 and R^4 each represent independently for each occurrence hydrogen, methyl, or ethyl.

58. The compound of any one of claims 1-20, 35-42, or 53-57, wherein A^1 is a 3-14 membered saturated carbocyclyl substituted by 0, 1, or 2 occurrences of Y^1 and 0, 1, 2, or 3 occurrences of Y^2.

59. The compound of any one of claims 1-20, 35-42, or 53-57, wherein A^1 is C_{3-7} cycloalkyl substituted once by Y^1 and 0-1 occurrences of Y^2.

60. The compound of any one of claims 1-20, 35-42, or 53-57, wherein A^1 is a 5-14 membered partially unsaturated carbocyclyl substituted by 0, 1, or 2 occurrences of Y^1 and 0, 1, 2, or 3 occurrences of Y^2.

61. The compound of any one of claims 1-20, 35-42, or 53-57, wherein A^1 is a 8-12 membered bicyclic carbocyclyl that is partially unsaturated or a 8-12 membered bicyclic heterocyclyl, each of which is substituted by 0 or 1 occurrence of Y^1 and 0, 1, or 2 occurrences of Y^2.

62. The compound of any one of claims 1-20, 35-42, or 53-57, wherein A^1 is phenyl substituted once by Y^1 and 0-1 occurrences of Y^2.

63. The compound of any one of claims 1-20, 35-42, or 53-57, wherein A^1 is C_{3-7} cycloalkyl substituted by Ci-6 alkoxyl.

64. The compound of any one of claims 1-20, 35-42, or 53-57, wherein A^1 is cyclohexyl substituted by Ci-6 alkoxyl.

65. The compound of any one of claims 1-20, 35-42, or 53-57, wherein A^1 is C_{3-7} cycloalkyl that is not substituted.

66. The compound of any one of claims 1-20, 35-42, or 53-57, wherein A^1 is cyclopropyl.

67. The compound of any one of claims 1-20, 35-42, or 53-57, wherein A^1 is phenyl substituted by C_2 alkynyl.

68. The compound of any one of claims 1-20, 35-42, or 53-62, wherein any occurrence of Y^2 is independently Ci-6 alkyl, C_{3-6} cycloalkyl, halogen, Ci-6 haloalkyl, or hydroxyl.

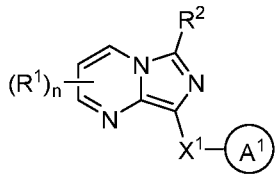
69. The compound of any one of claims 1-20, 35-42, or 53-62, wherein any occurrence of Y^2 is independently C_{1-3} alkyl.

70. The compound of any one of claims 1-20, 35-42, 53-62, 68, or 69, wherein Y^1 is -0-(Ci_7 alkyl).

71. The compound of any one of claims 1-20, 35-42, 53-62, 68, or 69, Y^1 is -O-butyl, -O-pentyl, or -O-hexyl.

72. The compound of any one of claims 1-20, 35-42, 53-62, 68, or 69, wherein Y^1 is C_{2-6} alkynyl.

73. A compound of Formula III:



(III)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 each represent independently for each occurrence hydrogen, C1-4 alkyl, C_{1-4} haloalkyl, Ci^ hydroxyalkyl, C_{1-4} cyanoalkyl, C_{1-4} alkoxyl, Ci^ haloalkoxyl, cyclopropyl, cyano, halogen, hydroxyl, $-N(R^4)_2$, -0-(Ci_4 alkylene)-Ci-6 alkoxyl, or -(Ci_4 alkylene)-(2-6 membered heteroalkyl optionally substituted by one or more halogen);

R^3 represents independently for each occurrence hydrogen, C_{1-6} alkyl, or C_{3-6} cycloalkyl;

R^4 represents independently for each occurrence hydrogen, C_{1-4} alkyl, cyclopropyl, or $-C(0)R^3$;

X^1 is a carbonyl-containing linker selected from -C(O)N(H)-ψ, -C(O)N(H)(Ci_6 alkylene optionally substituted with C_{1-4} alkoxyl or C_{3-6} cycloalkyl)-ψ, -C(0)N(H)(Ci-6 haloalkylene)-ψ, -C(O)N(H)(C_{3-6} cycloalkylene)-ψ, -C(0)N(H)(3-6 membered heterocycloalkylene)-ψ, -C(0)-(3-6 membered heterocycloalkylene containing at least one ring -N(H)- group)-ψ, -C(O)N(H)C(O)-ψ, and -C(0)N(H)C(0)(Ci_6 alkylene)-y; where ψ is a bond to A^1;

A^1 is a C_{3-10} cycloalkyl optionally substituted with 1 or 2 C_{1-4} alkyl groups;

m is 1 or 2; and

n is i, 2, or 3.

74. The compound of claim 73, wherein R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{1-4} alkylene)-(2-6 membered heteroalkyl), cyclopropyl, halogen, or $-N(R^4)_2$.

75. The compound of claim 73, wherein R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, cyclopropyl, cyano, chloro, or fluoro.

76. The compound of claim 73, wherein R^1 is methyl.

77. The compound of any one of claims 73-76, wherein n is 2.

78. The compound of claim 77, wherein the R^1 groups are located at the 2 and 4 positions of the imidazo[l,5-a]pyrimidinyl.

79. The compound of any one of claims 73-78, wherein R^2 is hydrogen.

80. The compound of any one of claims 73-79, wherein R^3 and R^4 each represent independently for each occurrence hydrogen, methyl, or ethyl.

81. The compound of any one of claims 73-80, wherein X^1 is -C(0)N(H)(Ci_6 alkylene)-ψ.

82. The compound of any one of claims 73-80, wherein X^1 is -C(O)N(H)C(H)(CH_3)-ψ or -C(0)N(H)C(CH_3)$_2$-ψ.

83. The compound of any one of claims 73-80, wherein X^1 is -C(O)N(H)(C_{1-6} haloalkylene)-ψ.

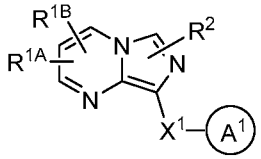
84. The compound of any one of claims 73-80, wherein X^1 is -C(O)N(H)C(H)(CF_3)-ψ.

85. The compound of any one of claims 73-80, wherein X^1 is -C(O)N(H)-ψ.

86. The compound of any one of claims 73-85, wherein A^1 is a cyclopropyl.

87. A compound in any one of Tables 1, 2, or 3 herein, or a pharmaceutically acceptable salt thereof.

88. A compound of Formula IV:



(IV)

or a pharmaceutically acceptable salt thereof, wherein:

R^{1A} is -(CM alkylene)-(2-6 membered heteroalkyl) or -N(R^3)C(0)-(C_{6-10} aryl);

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

R^2 is hydrogen, C_{1-4} alkyl, or Ci^haloalkyl;

X^1 is a carbonyl-containing linker selected from -C(O)N(H)-ψ, -C(0)N(H)(Ci_6 haloalkylene)-ψ, and -C(0)N(H)(C_{3-6} cycloalkylene)-ψ; where ψ is a bond to A^1; and

A^1 is as follows:

(i) when R^{1A} is -(C_{1-4} alkylene)-(2-6 membered heteroalkyl), then A^1 is monocyclic C_{3-10} cycloalkyl or bicyclic C_{5-10} cycloalkyl that is (a) substituted with C_{1-6} alkoxyl and (b) optionally substituted with 1 or 2 C_{1-4} alkyl groups; or

(ii) when R^{1A} is -$N(R^3)C(O)$-(C_{6-10} aryl), then A^1 is C3-10 cycloalkyl or bicyclic C_{5-10} cycloalkyl optionally substituted by 1, 2, or 3 groups independently selected from the group consisting of C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, C_{1-6} alkoxyl, and -O-(C_{1-8} haloalkyl).

89. A compound in Table 4 herein, or a pharmaceutically acceptable salt thereof.

90. A pharmaceutical composition, comprising a compound of any one of claims 1-87 and a pharmaceutically acceptable carrier.

91. A pharmaceutical composition, comprising a compound of claims 88 or 89 and a pharmaceutically acceptable carrier.

92. A method of treating a disorder selected from the group consisting of Gaucher disease, Parkinson's disease, Lewy body disease, dementia, multiple system atrophy, epilepsy, bipolar disorder, schizophrenia, an anxiety disorder, major depression, polycystic kidney disease, type 2 diabetes, open angle glaucoma, multiple sclerosis, endometriosis, and multiple myeloma, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of any one of claims 1-89 to treat the disorder.

93. The method of claim 92, wherein the disorder is Gaucher disease.

94. The method of claim 92, wherein the disorder is Parkinson's disease.

95. The method of claim 92, wherein the disorder is Lewy body disease.

96. The method of claim 92, wherein the disorder is dementia.

97. The method of claim 92, wherein the disorder is multiple system atrophy.

98. The method of any one of claims 92-97, wherein the patient is a human.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/026282

A. CLASSIFICATION OF SUBJECT MATTER

C07D 487/14 (2006.01) A61K 31/519 (2006.01) A61P 25/16 (2006.01) A61P 27/06 (2006.01) A61P 3/10 (2006.01) A61P 13/12 (2006.01) A61P 25/24 (2006.01) A61P 25/28 (2006.01) A61P 25/08 (2006.01) A61P 25/18 (2006.01) A61P 25/22 (2006.01) A61P 43/00 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

ESPACENET Search using title/abstract keywords "imidazo" "pyrimidin" "glucocerebrosidase" combined with Applicant name (LYSOSOMAL THERAPEUTICS INC.) and/or Inventor names (SKERLJ; BOURQUE; LANSBURY; GREENLEE; GOOD).

STN REGISTRY, CAPLUS search based on Formulae I, II, III and IV.

Applicant(s)/Inventor(s) name search in internal databases provided by IP Australia and AusPat: Applicant name = "LYSOSOMAL THERAPEUTICS INC." AND Inventor name = "SKERLJ" OR "BOURQUE" OR "LANSBURY" OR "GREENLEE" OR "GOOD".

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 May 2017	25 May 2017
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	George Nikolakopoulos AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61 3 99359639

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/US2017/026282**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/073889 A1 (LYSOSOMAL THERAPEUTICS INC.) 12 May 2016 see page 2 para [0006]; page 41 para [0147] - page 43 para [0149]; examples 1-38 on pages 56-108; page 47 para [0161]-[0199]; Example 38 para [00335]-[00338]; para [00150]-[00160]	88 and 91
A	DE 102004049363 A1 (HENKEL KGAA) 13 April 2006 see abstract; para [0112] and claims	1-86, 88 and 90-98
A	WO 2013/059587 A1 (SIRTRIS PHARMACEUTICALS, INC.) 25 April 2013 see abstract and claims	1-86, 88 and 90-98
P,X	WO 2016/073889 A1 (LYSOSOMAL THERAPEUTICS INC.) 12 May 2016 see para [0006]-[0008]; Example 38 para [00335]-[00338]; claims 1-58	1-86, 90 and 92-98

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/026282

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

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
the subject matter listed in Rule 39 on which, under Article 17(2)(a)(i), an international search is not required to be carried out, including

2. ☒ Claims Nos.: **87 and 89**
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
See Supplemental Box

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

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

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

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

Remark on Protest

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

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

☐ No protest accompanied the payment of additional search fees.

Supplemental Box

Continuation of **Box II**
The claims do not comply with Rule 6.2(a) because they rely on references to the description and/or drawings.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2017/026282

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2016/073889 A1	12 May 2016	WO 2016073889 A1	12 May 2016
DE 102004049363 A1	13 April 2006	DE 102004049363 A1	13 Apr 2006
		EP 1796627 A1	20 Jun 2007
		EP 1796627 B1	04 Mar 2009
		JP 2008515829 A	15 May 2008
		US 2008189877 A1	14 Aug 2008
		US 7473280 B2	06 Jan 2009
		WO 2006040015 A1	20 Apr 2006
WO 2013/059587 A1	25 April 2013	WO 2013059587 A1	25 Apr 2013
		AU 2012325909 A1	15 May 2014
		AU 2012325909 B2	09 Jun 2016
		CA 2852936 A1	25 Apr 2013
		CN 104394869 A	04 Mar 2015
		EP 2768509 A1	27 Aug 2014
		EP 2768509 B1	22 Mar 2017
		JP 2014530869 A	20 Nov 2014
		JP 6073343 B2	01 Feb 2017
		KR 20140077963 A	24 Jun 2014
		RU 2014120166 A	27 Nov 2015
		US 2014349993 A1	27 Nov 2014
WO 2016/073889 A1	12 May 2016	WO 2016073889 A1	12 May 2016

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.