PYRAZOLO[1,5-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 62/318,929, filed April 6, 2016, the contents of which are hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The invention provides substituted pyrazolo[1,5-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.

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

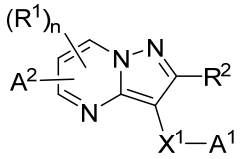
disease, while sometimes also producing a movement disorder side effect called dyskinesia. Diffuse Lewy Body disease is a dementia that is sometimes confused with Alzheimer's disease.

[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 present disclosure provides substituted pyrazolo[1,5-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 examples of the present disclosure are described in further detail below.

[0006a] In one aspect of the present disclosure, there is provided a compound of Formula I:



(I)

or a pharmaceutically acceptable salt thereof, 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;

R^2 is hydrogen;

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^7 represents independently for each occurrence halogen, hydroxyl, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{3-6} cycloalkyl, -O-(C_{3-6} cycloalkyl), -O-(C_{1-6} alkylene)-C_{1-6} alkoxyl, -(C_{1-6} alkylene)-CN, -N(R^4)$_2$, -C(O)N(R^4)$_2$, or heteroaryl;

R^8 is a bond or C_{1-6} alkylene;

R^9 is hydrogen or C_{1-6} alkyl;

X^1-A^1 is one of the following:

- X^1 is -C(O)N(H)(C_{1-6} haloalkylene)-ψ, where ψ is a bond to A^1; wherein A^1 is one of the following:
  - (i) 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; or
  - (ii) C_{1-8} alkyl; or
- X^1 is -C(O)N(H)C(C_{1-6} alkyl)$_2$-R^8-ψ or -C(O)N(H)C(C_{1-6} alkyl)(R^9)-R^8-ψ, where ψ is a bond to A^1, and A^1 is a 3-5 membered saturated carbocyclyl substituted by 0, 1, or 2 occurrences of Y^1 and 0, 1, 2, or 3 occurrences of Y^2;

A^2 is one of the following:

- phenyl substituted by 1, 2, or 3 occurrences of R^7; or
- a cyclic group selected from a 3-12 membered heterocyclyl, 4-12 membered oxoheterocyclyl, or 4-10 membered cycloalkyl; each of which is optionally substituted by 1, 2, or 3 occurrences of R^7;

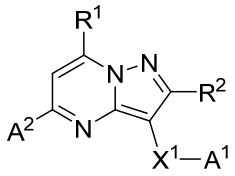
Y^1 represents, independently for each occurrence, -O-(C_{1-7} alkyl);

Y^2 represents, independently for each occurrence, C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, or hydroxyl; and

n is 1;

wherein A^2 is located at the 5-position of the pyrazolo[1,5-a]pyrimidinyl, and the R^1 group is located at the 7-position of the pyrazolo[1,5-a]pyrimidinyl.

[0006b] In another aspect of the present disclosure, there is provided a compound represented by Formula I-A:



(I-A)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is methyl;

R^2 is hydrogen;

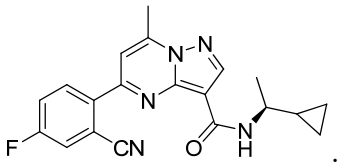
X^1 is -C(O)N(H)C(H)(CF_3)-ψ, -C(O)N(H)($C(CH_3)_2$)-ψ, or -C(O)N(H)(C(H)(CH_3))-ψ, where ψ is a bond to A^1;

A^1 is cyclopropyl; and

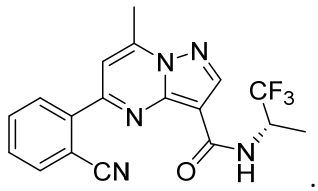
A^2 is a cyclic group selected from:

- phenyl 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; and
- 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.

[0006c] In a further aspect of the present disclosure, there is provided a compound having the following formula or a pharmaceutically acceptable salt thereof:



[0006d] In another aspect of the present disclosure, there is provided a compound having the following formula or a pharmaceutically acceptable salt thereof:

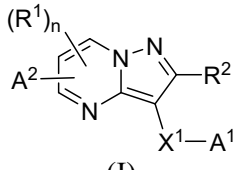


[0006e] In a further aspect of the present disclosure, there is provided a pharmaceutical composition, comprising a compound disclosed herein and a pharmaceutically acceptable carrier.

[0006f] In another aspect of the present disclosure, there is provided a compound disclosed herein for use in 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.

[0006g] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for 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.

[0007] Accordingly, one example of the present disclosure provides a family of substituted pyrazolo[1,5-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:

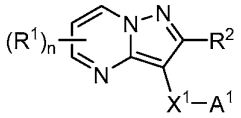


(I)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in the detailed description. Further description of additional collections of substituted pyrazolo[1,5-a]pyrimidinyl carboxamide and related organic compounds embraced by Formula I are described in the detailed description.

[0008] Another example of the present disclosure provides a family of substituted pyrazolo[1,5-a]pyrimidinyl carboxamide and related organic compounds embraced by Formula II that may

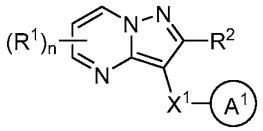
be used in the methods, compositions, and kits described herein, wherein Formula II is represented by:



(II)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in the detailed description. Further description of additional collections of substituted pyrazolo[1,5-a]pyrimidinyl carboxamide and related organic compounds embraced by Formula II are described in the detailed description

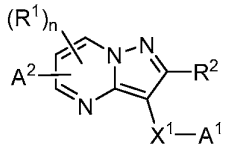
[0009] Another aspect of the invention provides a family of substituted pyrazolo[1,5-a]pyrimidinyl carboxamide and related organic compounds embraced by Formula III that may be used in the methods, compositions, and kits described herein, wherein Formula III is represented by:



(III)

or a pharmaceutically acceptable salt thereof, wherein the variables are as defined in the detailed description. Further description of additional collections of substituted pyrazolo[1,5-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 pyrazolo[1,5-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 pyrazolo[1,5-a]pyrimidinyl 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 pyrazolo[1,5-a]pyrimidinyl carboxamide or related organic compound described herein, such as a compound of Formula I, I-1, I-A, II, II-A, 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 pyrazolo[1,5-a]pyrimidinyl carboxamide or related organic compound described herein, such as a compound of Formula I, I-1, I-A, II, II-A, 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 pyrazolo[1,5-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 *et al.*, 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 C_1-C_{12}alkyl, C_1-C_{10}alkyl, and C_1-C_6alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-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 $–CH_2CH_2-$.

[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.

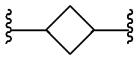
[0021] The term "heteroalkyl" as used herein refers to an "alkyl" group in which at least one carbon atom has been replaced with a heteroatom (e.g., an O, N, or S atom). The heteroalkyl may be, for example, an $–O-C_1$-C_{10}alkyl group, an $-C_1$-C_6alkylene-$O-C_1$-C_6alkyl group, or a C_1-C_6 alkylene-OH 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 C_2-C_{12}alkenyl, C_2-C_{10}alkenyl, and C_2-C_6alkenyl, 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 C_2-C_{12}alkynyl, C_2-C_{10}alkynyl, and C_2-C_6alkynyl, respectively. Exemplary alkynyl groups include ethynyl, prop-1-yn-1-yl, and but-1-yn-1-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.

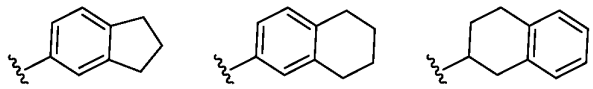
[0025] The term "cycloalkylene" refers to a diradical of an cycloalkyl group. An exemplary cycloalkylene group is  .

[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 "C_{4-8}cycloalkenyl," 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(O)alkyl, -CO_2alkyl, 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.

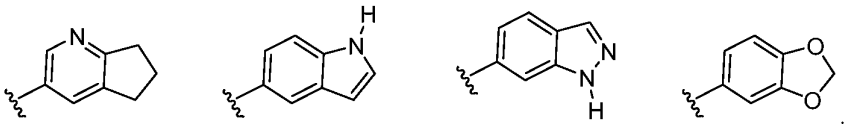
[0029] The term "bicyclic carbocyclyl that is partially unsaturated" refers to a bicyclic carbocyclic group containing at least one double bond between ring atoms and at least one ring in the bicyclic carbocyclic group is not aromatic. Representative examples of a bicyclic carbocyclyl that is partially 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-C_7heterocyclyl 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 "C_3-C_7" 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 C_3heterocyclyl is aziridinyl. Heterocycles may also be 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.

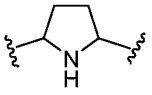
[0032] The term "bicyclic heterocyclyl" refers to a heterocyclyl group that contains two rings that are fused together. Representative examples of a bicyclic heterocyclyl include, for example:



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., =O). In certain embodiments, the oxoheterocyclyl is substituted with 1 or 2 oxo groups. In certain embodiments, 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(O)alkyl, -CO_2alkyl, 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, -O-$(CH_2)_m$-R_{61}, where m and R_{61} are described above. The term "haloalkoxyl" refers to an alkoxyl group that is substituted with at least one halogen. For example, -O-CH_2F, -O-CHF_2, -O-CF_3, and the like. In certain embodiments, the haloalkoxyl is an alkoxyl group

that is substituted with at least one fluoro group. In certain embodiments, 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 $-R_gOC(O)N(R_h)-$, $-R_gOC(O)N(R_h)R_i-$, or $-OC(O)NR_hR_i$, wherein R_g, 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 R_g, 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(O)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 $-R_aC(O)N(R_b)-$, $-R_aC(O)N(R_b)R_c-$, $-C(O)NR_bR_c$, or $-C(O)NH_2$, wherein R_a, R_b and 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, R_b, R_c, or R_a. The amide also may be cyclic, for example R_b and R_c, R_a and R_b, or R_a and 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 "=O" 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 $-N(R_r)-S(O)_2-R_s-$ or $-S(O)_2-N(R_r)R_s$, 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_uSO_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 $\overset{\cdots\cdots}{\text{———}}$ 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}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, 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.

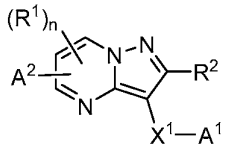
[0065] Abbreviations as used herein include *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU); diisopropylethylamine (DIPEA); dimethylformamide (DMF); methylene chloride (DCM); tert-butoxycarbonyl (Boc); tetrahydrofuran (THF); trifluoroacetic acid (TFA); N-methylmorpholine (NMM); triethylamine (TEA); Boc anhydride ($(Boc)_2O$); dimethylsulfoxide (DMSO); diisopropylethylamine (DIEA); ethyl acetate (EA); 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 PYRAZOLO[1,5-a]PYRIMIDINYL CARBOXAMIDE AND RELATED ORGANIC COMPOUNDS

[0068] One aspect of the invention provides substituted pyrazolo[1,5-a]pyrimidinyl carboxamide and related organic compounds. The substituted pyrazolo[1,5-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 pyrazolo[1,5-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} hydroxyalkyl, C_{1-4} cyanoalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, cyclopropyl, cyano, halogen, hydroxyl, $-N(R^4)_2$, $-O-(C_{1-4}$ 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 $-N(R^4)_2$;

R^7 represents independently for each occurrence halogen, hydroxyl, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{3-6} cycloalkyl, -O-(C_{3-6} cycloalkyl), -O-(C_{1-6} alkylene)-C_{1-6} alkoxyl, -(C_{1-6} alkylene)-CN, $-N(R^4)_2$, $-C(O)N(R^4)_2$, or heteroaryl;

R^8 is a bond or C_{1-6} alkylene;

R^9 is hydrogen or C_{1-6} alkyl;

X^1-A^1 is one of the following:

- X^1 is a carbonyl-containing linker selected from -C(O)N(H)(C_{1-6} haloalkylene)-ψ, -C(O)N(H)(C_{1-6} alkylene substituted with C_{1-4} alkoxyl or C_{3-6} cycloalkyl)-ψ, -C(O)N(H)(C_{3-6} cycloalkylene)-ψ, -C(O)N(H)(3-6 membered heterocycloalkylene)-ψ, and -C(O)-(3-6 membered heterocycloalkylene containing at least one ring -N(H)- group)-ψ, where ψ is a bond to A^1; wherein A^1 is one of the following:
  (i) 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
  (ii) C_{1-8} alkyl or C_{2-6} alkynyl;
- X^1 is -C(O)N(H)(C_{1-6} alkylene)-ψ, where ψ is a bond to A^1, and A^1 is (i) a cyclic group selected from 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 (ii) C_{2-6} alkynyl;
- X^1 is -C(O)N(H)-ψ, where ψ is a bond to A^1, and A^1 is cyclic group selected from 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; and provided that R^1 is not hydrogen;
- X^1 is -C(O)N(H)-ψ, where ψ is a bond to A^1, and A^1 is C_{2-6} alkynyl;
- X^1 is -C(O)N(H)(C_{1-6} alkylene)-ψ or -C(O)N(H)-ψ, where ψ is a bond to A^1, and A^1 is a 6-14 membered saturated carbocyclyl substituted by 0, 1, or 2

occurrences of Y^1 and 0, 1, 2, or 3 occurrences of Y^2; provided that A^2 is not a 5-membered heteroaryl optionally substituted by 1, 2, or 3 occurrences of R^7;

- X^1 is -C(O)N(H)(C_{1-6} alkylene)-ψ or -C(O)N(H)-ψ, where ψ is a bond to A^1, and A^1 is a 6-14 membered saturated spirocyclic carbocyclyl substituted by 0, 1, or 2 occurrences of Y^1 and 0, 1, 2, or 3 occurrences of Y^2;
- X^1 is -C(O)N(H)C(C_{1-6} alkyl)$_2$-R^8-ψ or -C(O)N(H)C(C_{1-6} alkyl)(R^9)-R^8-ψ, where ψ is a bond to A^1, and A^1 is a 3-5 membered saturated carbocyclyl substituted by 0, 1, or 2 occurrences of Y^1 and 0, 1, 2, or 3 occurrences of Y^2; or
- X^1 is -C(O)N(H)C(O)-ψ or -C(O)N(H)C(O)(C_{1-6} alkylene)-ψ, where ψ is a bond to A^1; and A^1 is (i) 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 (ii) C_{1-8} alkyl or C_{2-6} alkynyl;

A^2 is one of the following:

- phenyl substituted by 1, 2, or 3 occurrences of R^7;
- a cyclic group selected from a 3-12 membered heterocyclyl, 4-12 membered oxoheterocyclyl, or 4-10 membered cycloalkyl; each of which is optionally substituted by 1, 2, or 3 occurrences of R^7; or
- -N(R^4)(3-10 membered heterocyclyl, C_{3-10} cycloalkyl, or phenyl, each optionally substituted by 1, 2, or 3 occurrences of R^6) or -O-(3-10 membered heterocyclyl, C_{3-10} cycloalkyl, or phenyl, each optionally substituted by 1, 2, or 3 occurrences of R^6);

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-C_{3-6} cycloalkyl, -O-(3-6 membered heterocyclyl), -O-(6-10 membered aryl), or -O-(C_{2-6} alkynyl); or
- C_{2-6} alkynyl, -C≡C-(C_{1-6} alkylene)-OR^4, -C≡C-(C_{1-6} 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, C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, C_{1-6} alkoxyl, -O-(C_{1-8} haloalkyl), cyano, azido, -$N(R^3)_2$, -(C_{1-6} alkylene)-(5-6 membered heterocyclyl), -(C_{1-6} alkylene)-CO_2R^3, -CO_2R^3, -$C(O)R^5$, -$S(O)_2R^5$, -$C(O)N(R^5)_2$, -$C(O)N(R^3)_2$, or C_{1-6} haloalkyl-substituted C_{3-6} cycloalkyl; and

n is 1, 2, or 3;

provided that when A^2 is a 5-6 membered heterocycloalkyl and X^1 is -C(O)N(H)-ψ, then A^1 is not -phenyl-(C_{1-6} alkyl).

[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)(C_{1-6} haloalkylene)-ψ, R^1 and R^2 each represent independently for each occurrence hydrogen or C_{1-4} alkyl, and A^2 is phenyl substituted by 1 or 2 R^7.

[0070] Accordingly, in certain embodiments, X^1 is -C(O)N(H)(C_{1-6} 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)(C_{1-6} alkylene)-ψ. In certain embodiments, X^1 is -C(O)N(H)($C(CH_3)_2$)-ψ or -C(O)N(H)(C(H)(CH_3))-ψ. In certain embodiments, X^1 is -C(O)N(H)(C_{1-6} alkylene substituted with C_{1-4} alkoxyl)-ψ. In certain embodiments, X^1 is -C(O)N(H)(C_{1-6} alkylene substituted with C_{3-6} cycloalkyl)-ψ. In certain embodiments, X^1 is -C(O)N(H)(C_{3-6} cycloalkylene)-ψ. In certain embodiments, X^1 is -C(O)N(H)(3-6 membered heterocycloalkylene)-ψ. In certain embodiments, X^1 is -C(O)N(H)-ψ.

[0071] In certain embodiments, A^2 is phenyl 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 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, and halogen, wherein there is at least one substituent at a meta-position on the phenyl group. In certain embodiments, A^2 is phenyl substituted at one meta-position by C_{1-4} alkoxyl, cyano, or halogen, and optionally substituted

elsewhere on the phenyl group by C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, or halogen. In certain embodiments, A^2 is phenyl substituted by C_{1-4} alkoxyl, cyano, or halogen. In certain embodiments, A^2 is phenyl substituted at one meta-position by C_{1-4} alkoxyl, cyano, or halogen.

[0072] 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.

[0073] 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, thiazolyl, isothiazolyl, pyrazolyl, and oxadiazolyl 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 $-N(R^4)_2$.

[0074] In certain embodiments, A^2 is a bicyclic heteroaryl selected from the group consisting of benzimidazolyl, benzoxazolyl, benzodioxolyl, and benzothiazolyl, 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 $-N(R^4)_2$.

[0075] 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 $-N(R^4)_2$.

[0076] In certain embodiments, A^2 is a 4-12 membered oxoheterocyclyl 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 oxoheterocyclyl 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 oxoheterocyclyl selected from the group consisting of oxoimidazolidinyl, oxotetrahydropyrimidinyl, oxooxazolidinyl, oxopyrrolidinyl, and oxotetrahydrofuranyl, each of which is optionally substituted by 1, 2, or 3 substituents 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 oxoheterocyclyl selected from the group consisting of oxoimidazolidinyl, oxotetrahydropyrimidin-1(2*H*)-yl, oxooxazolidinyl, and oxopyrrolidinyl, each of which is optionally substituted by 1, 2, or 3 substituents selected from the group consisting of C_{1-4} alkyl and C_{1-4} haloalkyl.

[0077] 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 $-N(R^4)_2$.

[0078] 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 occurrences of R^6) or -O-(3-10 membered heterocyclyl, C_{3-10} cycloalkyl, or phenyl, each optionally substituted by 1, 2, or 3 occurrences of R^6). 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 occurrences of R^6) or -O-(3-10 membered heterocycloalkyl or C_{3-10} cycloalkyl, each optionally substituted by 1, 2, or 3 occurrences of R^6). In certain embodiments, A^2 is -N(R^4)(tetrahydropyranyl, morpholinyl, or piperidinyl, each optionally substituted by 1, 2, or 3 occurrences of R^6), -N(R^4)(C_{4-6} cycloalkyl optionally substituted by 1, 2, or 3 occurrences of R^6), -O-(tetrahydropyranyl, morpholinyl, or piperidinyl, each optionally substituted by 1, 2, or 3 occurrences of R^6), or -O-(C_{4-6} cycloalkyl optionally substituted by 1, 2, or 3 occurrences of R^6).

[0079] In certain embodiments, A^2 is located at the 5-position of the pyrazolo[1,5-a]pyrimidinyl. In certain embodiments, n is 1. In certain embodiments, A^2 is located at the 5-position of the pyrazolo[1,5-a]pyrimidinyl, n is 1, and the R^1 group is located at the 7-position of the pyrazolo[1,5-a]pyrimidinyl.

[0080] In certain embodiments, A^2 is located at the 7-position of the pyrazolo[1,5-a]pyrimidinyl. In certain embodiments, n is 1. In certain embodiments, A^2 is located at the 7-position of the pyrazolo[1,5-a]pyrimidinyl, n is 1, and R^1 group is located at the 5-position of the pyrazolo[1,5-a]pyrimidinyl.

[0081] 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.

[0082] 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.

[0083] In certain embodiments, R^3 and R^4 each represent independently for each occurrence hydrogen, methyl, or ethyl.

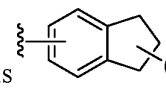
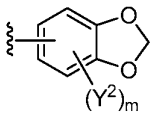
[0084] In certain embodiments, A^1 is (i) 3-5 membered saturated carbocyclyl, or (ii) a 6-14 membered saturated spirocyclic carbocyclyl, each optionally substituted with 1 or 2 C_{1-4} alkyl

groups. 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.

[0085] 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.

[0086] 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.

[0087] In certain embodiments, A^1 is phenyl substituted by C_2 alkynyl.

[0088] 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.

[0089] 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.

[0090] 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.

[0091] 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 -(C_{1-3} alkylene)-O-(5-6 membered heteroaryl). In certain embodiments, Y^1 is -CH_2-O-(5-6 membered heteroaryl). In certain embodiments, Y^1 is -CH_2-O-(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_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, C_{1-6} alkoxyl, cyano, -$N(R^4)_2$, amide, and -CO_2H.

[0092] In certain embodiments, Y^1 is a 3-10 membered heterocyclyl, 6-10 membered aryl, C_{3-7} cycloalkyl, -O-(3-6 membered heterocyclyl), -O-(6-10 membered aryl), or -O-(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 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 -CO_2H. 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, C_{1-6} haloalkyl, hydroxyl, and C_{1-6} alkoxyl.

[0093] 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 $-CO_2H$.

[0094] 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 $-CO_2H$.

[0095] In certain embodiments, Y^1 is C_{2-6} alkynyl, $-C\equiv C-(C_{1-6}$ alkylene)-OR^4, $-C\equiv C-(C_{1-6}$ alkylene)-$N(R^3)_2$, -(C_{2-4} 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 $-C\equiv CH$. In certain embodiments, Y^1 is $-C\equiv C-(C_{1-6}$ alkylene)-OR^4. In certain embodiments, Y^1 is $-C\equiv C-(C_{1-6}$ alkylene)-O-(C_{1-2} alkyl). In certain embodiments, Y^1 is $-C\equiv C-CH_2-O-CH_3$.

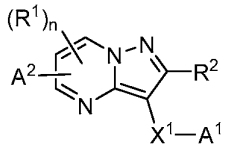
[0096] In certain embodiments, Y^1 is -O-(C_{1-7} alkyl). In certain embodiments, Y^1 is -O-butyl, -O-pentyl, or -O-hexyl. In certain embodiments, Y^1 is C_{2-6} alkynyl, $-C\equiv C-(C_{1-6}$ alkylene)-OR^4, $-C\equiv C-(C_{1-6}$ alkylene)-$N(R^3)_2$, -(C_{2-4} alkynylene)-(5-6 membered heteroaryl), or C_{2-6} alkenyl. In certain embodiments, Y^1 is $-C\equiv CH$. In certain embodiments, Y^1 is $-C\equiv C-(C_{1-6}$ alkylene)-OR^4. In certain embodiments, Y^1 is $-C\equiv C-CH_2-O-CH_3$. In certain embodiments, Y^1 is C_{2-6} alkynyl.

[0097] 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)-O-(5-6 membered heteroaryl). In certain embodiments, Y^1 is a 3-10 membered heterocyclyl, 6-10 membered aryl, C_{3-7} cycloalkyl, -O-(3-6 membered heterocyclyl), -O-(6-10 membered aryl), or -O-(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.

[0098] 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)C(H)(CF_3)-ψ, R^1 and R^2 each represent independently for each occurrence hydrogen or C_{1-4} alkyl, and A^2 is phenyl 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 -$N(R^4)_2$.

[0099] In certain embodiments, the compound is a compound of Formula I-1:



(I-1)

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, -$N(R^4)_2$, -O-(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 -$N(R^4)_2$;

R^7 represents independently for each occurrence halogen, hydroxyl, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{3-6} cycloalkyl, -O-(C_{3-6} cycloalkyl), -O-(C_{1-6} alkylene)-C_{1-6} alkoxyl, -(C_{1-6} alkylene)-CN, -$N(R^4)_2$, -$C(O)N(R^4)_2$, or or heteroaryl;

X^1 is a carbonyl-containing linker selected from -C(O)N(H)(C_{1-6} haloalkylene)-ψ, -C(O)N(H)(C_{1-6} alkylene optionally substituted with C_{1-4} alkoxyl or C_{3-6} cycloalkyl)-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, and -C(O)N(H)-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
- C_{1-8} alkyl or C_{2-6} alkynyl;

A^2 is one of the following:

- phenyl substituted by 1, 2, or 3 occurrences of R^7;
- a cyclic group selected from a 3-12 membered heterocyclyl, 4-12 membered oxoheterocyclyl, or 4-10 membered cycloalkyl; each of which is optionally substituted by 1, 2, or 3 occurrences of R^7; or
- $-N(R^4)$(3-10 membered heterocyclyl, C_{3-10} cycloalkyl, or phenyl, each optionally substituted by 1, 2, or 3 occurrences of R^6) or -O-(3-10 membered heterocyclyl, C_{3-10} cycloalkyl, or phenyl, each optionally substituted by 1, 2, or 3 occurrences of R^6);

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-C_{3-6} cycloalkyl, -O-(3-6 membered heterocyclyl), -O-(6-10 membered aryl), or -O-(C_{2-6} alkynyl); or
- C_{2-6} alkynyl, $-C\equiv C-(C_{1-6}$ alkylene)-OR^4, $-C\equiv C-(C_{1-6}$ 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, C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, C_{1-6} alkoxyl, -O-(C_{1-8} haloalkyl), cyano, azido, $-N(R^3)_2$, -(C_{1-6} alkylene)-(5-6 membered heterocyclyl), -(C_{1-6} alkylene)-CO_2R^3, $-CO_2R^3$, $-C(O)R^5$, $-S(O)_2R^5$, $-C(O)N(R^5)_2$, $-C(O)N(R^3)_2$, or C_{1-6} haloalkyl-substituted C_{3-6} cycloalkyl; and

n is 1, 2, or 3;

provided that when A^2 is a 5-6 membered heterocycloalkyl and X^1 is -C(O)N(H)-ψ, then A^1 is not -phenyl-(C_{1-6} alkyl).

[00100] Definitions of the variables in Formula I-1 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)(C_{1-6} haloalkylene)-ψ, R^1 and R^2 each represent independently for each occurrence hydrogen or C_{1-4} alkyl, and A^2 is phenyl substituted by 1 or 2 R^7.

[00101] Accordingly, in certain embodiments, X^1 is -C(O)N(H)(C_{1-6} 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)(C_{1-6} alkylene)-ψ. In certain embodiments, X^1 is -C(O)N(H)(C(CH_3)$_2$)-ψ or -C(O)N(H)(C(H)(CH_3))-ψ. In certain embodiments, X^1 is -C(O)N(H)(C_{1-6} alkylene substituted with C_{1-4} alkoxyl)-ψ. In certain embodiments, X^1 is -C(O)N(H)(C_{1-6} alkylene substituted with C_{3-6} cycloalkyl)-ψ. In certain embodiments, X^1 is -C(O)N(H)(C_{3-6} cycloalkylene)-ψ. In certain embodiments, X^1 is -C(O)N(H)(3-6 membered heterocycloalkylene)-ψ. In certain embodiments, X^1 is -C(O)N(H)-ψ.

[00102] In certain embodiments, A^2 is phenyl 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 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, and halogen, wherein there is at least one substituent at a meta-position on the phenyl group. In certain embodiments, A^2 is phenyl substituted at one meta-position by C_{1-4} alkoxyl, cyano, or halogen, and optionally substituted elsewhere on the phenyl group by C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, or halogen. In certain embodiments, A^2 is phenyl substituted by C_{1-4} alkoxyl, cyano, or halogen. In certain embodiments, A^2 is phenyl substituted at one meta-position by C_{1-4} alkoxyl, cyano, or halogen.

[00103] 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, 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.

[00104] 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 $-N(R^4)_2$.

[00105] 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 $-N(R^4)_2$.

[00106] 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 occurrences of R^6) or -O-(3-10 membered heterocyclyl, C_{3-10} cycloalkyl, or phenyl, each optionally substituted by 1, 2, or 3 occurrences of R^6). 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 occurrences of R^6) or -O-(3-10 membered heterocycloalkyl or C_{3-10} cycloalkyl, each optionally substituted by 1, 2, or 3 occurrences of

R^6). In certain embodiments, A^2 is -N(R^4)(tetrahydropyranyl, morpholinyl, or piperidinyl, each optionally substituted by 1, 2, or 3 occurrences of R^6), -N(R^4)(C_{4-6} cycloalkyl optionally substituted by 1, 2, or 3 occurrences of R^6), -O-(tetrahydropyranyl, morpholinyl, or piperidinyl, each optionally substituted by 1, 2, or 3 occurrences of R^6), or -O-(C_{4-6} cycloalkyl optionally substituted by 1, 2, or 3 occurrences of R^6).

[00107] In certain embodiments, A^2 is located at the 5-position of the pyrazolo[1,5-a]pyrimidinyl. In certain embodiments, n is 1. In certain embodiments, A^2 is located at the 5-position of the pyrazolo[1,5-a]pyrimidinyl, n is 1, and the R^1 group is located at the 7-position of the pyrazolo[1,5-a]pyrimidinyl.

[00108] In certain embodiments, A^2 is located at the 7-position of the pyrazolo[1,5-a]pyrimidinyl. In certain embodiments, n is 1. In certain embodiments, A^2 is located at the 7-position of the pyrazolo[1,5-a]pyrimidinyl, n is 1, and R^1 group is located at the 5-position of the pyrazolo[1,5-a]pyrimidinyl.

[00109] 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.

[00110] 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.

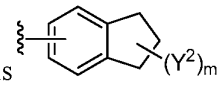
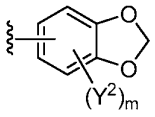
[00111] In certain embodiments, R^3 and R^4 each represent independently for each occurrence hydrogen, methyl, or ethyl.

[00112] 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.

[00113] 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.

[00114] 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.

[00115] In certain embodiments, A^1 is phenyl substituted by C_2 alkynyl.

[00116] 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.

[00117] 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.

[00118] 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.

[00119] 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 -(C_{1-3} alkylene)-O-(5-6 membered

heteroaryl). In certain embodiments, Y^1 is -CH_2-O-(5-6 membered heteroaryl). In certain embodiments, Y^1 is -CH_2-O-(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_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, C_{1-6} alkoxyl, cyano, -$N(R^4)_2$, amide, and -CO_2H.

[00120] In certain embodiments, Y^1 is a 3-10 membered heterocyclyl, 6-10 membered aryl, C_{3-7} cycloalkyl, -O-(3-6 membered heterocyclyl), -O-(6-10 membered aryl), or -O-(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 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 -CO_2H. 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, C_{1-6} haloalkyl, hydroxyl, and C_{1-6} alkoxyl.

[00121] 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 -CO_2H.

[00122] 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 -CO_2H.

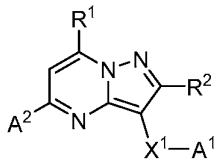
[00123] In certain embodiments, Y^1 is C_{2-6} alkynyl, –C≡C-(C_{1-6} alkylene)-OR^4, –C≡C-(C_{1-6} alkylene)-$N(R^3)_2$, -(C_{2-4} alkynylene)-(5-6 membered heteroaryl), or C_{2-6} alkenyl. In certain embodiments, Y^1 is C_{2-6} alkynyl. In certain embodiments, Y^1 is -C≡CH. In certain embodiments,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

[00124] 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 C_{2-6} alkynyl, –C≡C-(C_{1-6} alkylene)-OR^4, –C≡C-(C_{1-6} alkylene)-$N(R^3)_2$, -(C_{2-4} 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-(C_{1-6} 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.

[00125] 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)-O-(5-6 membered heteroaryl). In certain embodiments, Y^1 is a 3-10 membered heterocyclyl, 6-10 membered aryl, C_{3-7} cycloalkyl, -O-(3-6 membered heterocyclyl), -O-(6-10 membered aryl), or -O-(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.

[00126] The description above describes multiple embodiments relating to compounds of Formula I-1. The patent application specifically contemplates all combinations of the embodiments. For example, the invention contemplates a compound of Formula I-1 wherein X^1 is -C(O)N(H)C(H)(CF_3)-ψ, R^1 and R^2 each represent independently for each occurrence hydrogen or C_{1-4} alkyl, and A^2 is phenyl 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 $-N(R^4)_2$.

[00127] In certain embodiments, the compound is a compound of Formula I-A:



(I-A)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is C_{1-4} 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(O)N(H)(C_{1-6} haloalkylene)-ψ or -C(O)N(H)(C_{1-6} alkylene)-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;

A^2 is a cyclic group selected from:

- phenyl 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; and
- 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, and hydroxyl;

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

- 2-8 membered heteroalkyl or -O-(C_{2-6} alkynyl); or
- C_{2-6} alkynyl or -C≡C-(C_{1-6} alkylene)-OR^4; 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 -$N(R^3)_2$;

provided that when X^1-A^1 is -C(O)N(H)(C_{1-6} alkylene)-(unsubstituted C_{5-8} cycloalkyl), A^2 is not a 5 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.

[00128] 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 -C(O)N(H)(C_{1-6} haloalkylene)-ψ, R^1 is C_{1-4} alkyl or C_{1-4} haloalkyl, and A^2 is phenyl substituted by 1 or 2 substituents independently selected from the group consisting of C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, and halogen.

[00129] Accordingly, in certain embodiments, R^1 represents independently for each occurrence methyl, halomethyl, -$(CH_2)_{1-2}$-O-(C_{1-3} alkyl), cyclopropyl, chloro, or fluoro. In certain embodiments, R^1 is C_{1-4} alkyl or C_{1-4} haloalkyl. In certain embodiments, R^1 is methyl.

[00130] 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 cyclohexyl substituted once by Y^1. 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.

[00131] 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.

[00132] In certain embodiments, A^1 is phenyl 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 by 1 occurrence of Y^1.

[00133] In certain embodiments, Y^2 is independently C_{1-3} alkyl, halogen, or C_{1-3} haloalkyl.

[00134] In certain embodiments, Y^1 is a 2-8 membered heteroalkyl. In certain embodiments, Y^1 is -O-(C_{1-7} alkyl). In certain embodiments, Y^1 is -O-butyl, -O-pentyl, or -O-hexyl.

[00135] In certain embodiments, A^2 is phenyl substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, and halogen. In certain embodiments, A^2 is phenyl 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, and halogen, wherein there is at least one substituent at a meta-position on

the phenyl group. In certain embodiments, A^2 is phenyl substituted at one meta-position by C_{1-4} alkoxyl, cyano, or halogen, and optionally substituted elsewhere on the phenyl group by C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, or halogen. In certain embodiments, A^2 is phenyl substituted by C_{1-4} alkoxyl, cyano, or halogen. In certain embodiments, A^2 is phenyl substituted at one meta-position by C_{1-4} alkoxyl, cyano, or halogen.

[00136] 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, 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, 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, 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, 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, C_{3-5} 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, C_{3-5} cycloalkyl, cyano, and halogen.

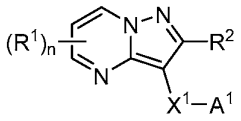
[00137] In certain embodiments, A^2 is a 5-6 membered heterocycloalkyl optionally substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, halogen, and hydroxyl. In certain embodiments, A^2 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, C_{3-5} cycloalkyl, cyano, halogen, and hydroxyl.

[00138] In certain embodiments, X^1 is -C(O)N(H)(C_{1-6} 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)(C_{1-6} alkylene)-ψ. In certain embodiments, X^1 is -C(O)N(H)($C(CH_3)_2$)-ψ or -C(O)N(H)(C(H)(CH_3))-ψ.

[00139] 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 -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 phenyl substituted at one meta-position by C_{1-4} alkoxyl, cyano, or halogen, and optionally substituted elsewhere on the phenyl group by C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, or halogen.

[00140] In certain embodiments, the substituted pyrazolo[1,5-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)$_2$, -O-(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;

X^1 is a carbonyl-containing linker selected from -C(O)N(H)(C_{1-6} haloalkylene)-ψ, -C(O)N(H)(C_{1-6} alkylene substituted with C_{1-4} alkoxyl or C_{3-6} cycloalkyl)-ψ, -C(O)N(H)(C_{3-6} cycloalkylene)-ψ, -C(O)N(H)(3-6 membered heterocycloalkylene)-ψ, -C(O)N(H)C(O)-ψ, and -C(O)N(H)C(O)(C_{1-6} 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
- C_{1-8} 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-C_{3-6} cycloalkyl, -O-(3-6 membered heterocyclyl), -O-(6-10 membered aryl), or -O-(C_{2-6} alkynyl); or
- C_{2-6} alkynyl, -C≡C-(C_{1-6} alkylene)-OR^4, -C≡C-(C_{1-6} 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, C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, C_{1-6} alkoxyl, -O-(C_{1-8} haloalkyl), cyano, azido, $-N(R^3)_2$, -(C_{1-6} alkylene)-(5-6 membered heterocyclyl), -(C_{1-6} alkylene)-CO_2R^3, $-CO_2R^3$, $-C(O)R^5$, $-S(O)_2R^5$, $-C(O)N(R^5)_2$, $-C(O)N(R^3)_2$, or C_{1-6} 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(O)N(H)(C_{3-6} cycloalkylene)-ψ or -C(O)N(H)(3-6 membered heterocycloalkylene)-ψ, then A^1 is not a 5-membered heterocyclyl, C_{1-8} alkyl, or C_2 alkynyl.

[00141] 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 where X^1 is -C(O)N(H)(C_{1-6} 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.

[00142] Accordingly, in certain embodiments, X^1 is -C(O)N(H)(C_{1-6} 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)(C_{1-6} 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(O)N(H)(C_{1-6} alkylene substituted with C_{3-6} cycloalkyl)-ψ. In certain embodiments, X^1 is -C(O)N(H)(C_{3-6} cycloalkylene)-ψ.

[00143] In certain embodiments, n is 2. In certain embodiments, R^1 groups are located at the 5 and 7 positions of the pyrazolo[1,5-a]pyrimidinyl.

[00144] 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.

[00145] 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.

[00146] In certain embodiments, R^3 and R^4 each represent independently for each occurrence hydrogen, methyl, or ethyl.

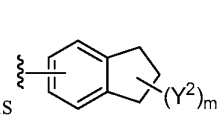
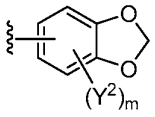
[00147] In certain embodiments, A^1 is a 3-14 membered saturated carbocyclyl substituted by 0, 1, or 2 occurrences of Y^1 and 0, 1, 2, or 3 occurrences of Y^2. In certain embodiments, A^1 is a 3-14 membered saturated carbocyclyl. In certain embodiments, A^1 is C_{3-7} cycloalkyl substituted once by Y^1 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 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.

[00148] 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.

[00149] 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.

[00150] In certain embodiments, A^1 is phenyl substituted by C_2 alkynyl.

[00151] 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.

[00152] 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.

[00153] 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 C_{2-6} alkynyl, –C≡C-(C_{1-6} alkylene)-OR^4, –C≡C-(C_{1-6} alkylene)-$N(R^3)_2$, -(C_{2-4} 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-(C_{1-6} 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.

[00154] 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.

[00155] 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 -(C_{1-3} alkylene)-O-(5-6 membered heteroaryl). In certain embodiments, Y^1 is -CH_2-O-(5-6 membered heteroaryl). In certain embodiments, Y^1 is -CH_2-O-(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_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, hydroxyl, C_{1-6} alkoxyl, cyano, -$N(R^4)_2$, amide, and -CO_2H.

[00156] In certain embodiments, Y^1 is a 3-10 membered heterocyclyl, 6-10 membered aryl, C_{3-7} cycloalkyl, -O-(3-6 membered heterocyclyl), -O-(6-10 membered aryl), or -O-(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 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 -CO_2H. 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, C_{1-6} haloalkyl, hydroxyl, and C_{1-6} alkoxyl.

[00157] 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 $-CO_2H$.

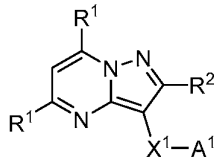
[00158] In certain embodiments, Y^1 is pyridinyl, pyrimidinyl, pyrazinyl, isooxazolyl, isothiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, imidazolinyl, oxazolinyl, pyrazolinyl, thiazolinyl, or triazolinyl. In certain embodiments, Y^1 is pyridinyl, pyrimidinyl, pyrazinyl, isooxazolyl, isothiazolyl, 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 $-CO_2H$.

[00159] In certain embodiments, Y^1 is C_{2-6} alkynyl, $-C\equiv C-(C_{1-6}$ alkylene)-OR^4, $-C\equiv C-(C_{1-6}$ alkylene)-$N(R^3)_2$, $-(C_{2-4}$ 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 $-C\equiv CH$. In certain embodiments, Y^1 is $-C\equiv C-(C_{1-6}$ alkylene)-OR^4. In certain embodiments, Y^1 is $-C\equiv C-(C_{1-6}$ alkylene)-O-(C_{1-2} alkyl). In certain embodiments, Y^1 is $-C\equiv C-CH_2-O-CH_3$.

[00160] 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)-O-(5-6 membered heteroaryl). In certain embodiments, Y^1 is a 3-10 membered heterocyclyl, 6-10 membered aryl, C_{3-7} cycloalkyl, -O-(3-6 membered heterocyclyl), -O-(6-10 membered aryl), or $-O-(C_{2-6}$ 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.

[00161] 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 $-C(O)N(H)(C_{1-6}$ 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.

[00162] In certain embodiments, the substituted pyrazolo[1,5-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 C_{1-4} 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(O)N(H)(C_{1-6} haloalkylene)-ψ or -C(O)N(H)(C_{1-6} alkylene substituted with C_{1-4} alkoxyl or C_{3-6} 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 -O-(C_{2-6} alkynyl); or
- C_{2-6} alkynyl or -C≡C-(C_{1-6} alkylene)-OR^4; 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 -$N(R^3)_2$.

[00163] 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(O)N(H)(C_{1-6} haloalkylene)-ψ, R^1 is C_{1-4} alkyl or C_{1-4} 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.

[00164] Accordingly, in certain embodiments, R^1 represents independently for each occurrence methyl, halomethyl, -$(CH_2)_{1-2}$-O-(C_{1-3} alkyl), cyclopropyl, chloro, or fluoro. In certain embodiments, R^1 is C_{1-4} alkyl or C_{1-4} haloalkyl. In certain embodiments, R^1 is methyl.

[00165] In certain embodiments, X^1 is -C(O)N(H)(C_{1-6} haloalkylene)-ψ. In certain embodiments, X^1 is -C(O)N(H)C(H)(CF_3)-ψ.

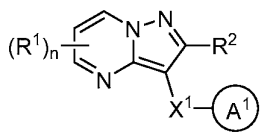
[00166] In certain embodiments, A^1 is a C_{3-10} cycloalkyl substituted by 0 or 1 occurrence of Y^1 and 0, 1, or 2 occurrences of Y^2. In certain embodiments, A^1 is C_{3-7} cycloalkyl substituted once by Y^1 and 0-1 occurrences of Y^2. In certain embodiments, A^1 is cyclohexyl substituted once by Y^1. 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.

[00167] In certain embodiments, A^1 is phenyl 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 by 1 occurrence of Y^1.

[00168] In certain embodiments, Y^1 is a 2-8 membered heteroalkyl. In certain embodiments, Y^1 is -O-(C_{1-7} alkyl). In certain embodiments, Y^1 is -O-butyl, -O-pentyl, or -O-hexyl.

[00169] 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(O)N(H)(C_{1-6} haloalkylene)-ψ, R^1 is C_{1-4} alkyl or C_{1-4} 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.

[00170] In certain embodiments, the substituted pyrazolo[1,5-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} hydroxyalkyl, C_{1-4} cyanoalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, cyclopropyl, cyano, halogen, hydroxyl, $-N(R^4)_2$, $-O-(C_{1-4}$ 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 is hydrogen or C_{1-6} alkyl;

R^6 is a bond or C_{1-6} alkylene;

X^1-A^1 is one of the following:

- $-C(O)N(H)(C_{1-6}$ haloalkylene)-A^1, $-C(O)N(H)(C_{1-6}$ alkylene substituted with C_{1-4} alkoxyl)-A^1, $-C(O)N(H)(C_{3-6}$ cycloalkylene)-A^1, $-C(O)N(H)$(3-6 membered heterocycloalkylene)-A^1, $-C(O)-$(3-6 membered heterocycloalkylene containing at least one ring -N(H)- group)-A^1, or $-C(O)N(H)-A^1$, where A^1 is C_{3-10} cycloalkyl optionally substituted with 1 or 2 C_{1-4} alkyl groups;
- $-C(O)N(H)C(C_{1-6}$ alkyl$)_2-R^6-A^1$ or $-C(O)N(H)C(C_{3-6}$ alkyl$)(R^5)-R^6-A^1$, where A^1 is C_{3-10} cycloalkyl optionally substituted with 1 or 2 C_{1-4} alkyl groups;
- $-C(O)N(H)(C_{1-6}$ alkylene)-A^1 or $-C(O)N(H)(C_{1-6}$ alkylene substituted with C_{3-6} cycloalkyl)-A^1, where A^1 is a C_{6-10} monocyclic or spirocyclic cycloalkyl optionally substituted with 1 or 2 C_{1-4} alkyl groups;
- $-C(O)N(H)C(O)-A^1$ or $-C(O)N(H)C(O)(C_{1-6}$ alkylene)-A^1, where A^1 is a C_{6-10} monocyclic or spirocyclic cycloalkyl optionally substituted with 1 or 2 C_{1-4} alkyl groups;

m is 1 or 2; and

n is 1, 2, or 3;

provided that when X is $-C(O)N(H)-\psi$ and A^1 is a C_{5-7} cycloalkyl optionally substituted with 1 or 2 C_{1-4} alkyl groups; then R^1 is other than C_{1-4} alkyl and C_{1-4} haloalkyl.

[00171] 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)(C_{1-6} alkylene)-ψ, and R^1 and R^2 each represent independently for each occurrence hydrogen or C_{1-4} alkyl.

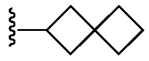
[00172] Accordingly, in certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, -(C_{1-4} alkylene)-(2-6 membered heteroalkyl), cyclopropyl, halogen, or -$N(R^4)_2$. In certain embodiments, R^1 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, cyclopropyl, cyano, chloro, or fluoro. In certain embodiments, R^1 is methyl.

[00173] In certain embodiments, n is 2. In certain embodiments, the R^1 groups are located at the 5 and 7 positions of the pyrazolo[1,5-a]pyrimidinyl.

[00174] 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.

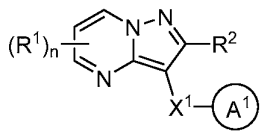
[00175] In certain embodiments, R^3 and R^4 each represent independently for each occurrence hydrogen, methyl, or ethyl.

[00176] In certain embodiments, The description above describes multiple embodiments relating to compounds of Formula III. The patent application specifically contemplates all combinations of the embodiments.

[00177] In certain embodiments, X^1-A^1 is -C(O)N(H)(C_{1-6} haloalkylene)-A^1, where A^1 is C_{3-10} cycloalkyl optionally substituted with 1 or 2 C_{1-4} alkyl groups. In certain embodiments, X^1-A^1 is -C(O)N(H)C(H)(CF_3)-A^1, where A^1 is C_{3-10} cycloalkyl optionally substituted with 1 or 2 C_{1-4} alkyl groups. In certain embodiments, X^1-A^1 is -C(O)N(H)C(C_{1-6} alkyl)$_2$-R^6-A^1, where A^1 is C_{3-10} cycloalkyl optionally substituted with 1 or 2 C_{1-4} alkyl groups. In certain embodiments, X^1-A^1 is -C(O)N(H)C(CH_3)$_2$-A^1; where A^1 is C_{3-10} cycloalkyl optionally substituted with 1 or 2 C_{1-4} alkyl groups. In certain embodiments, A^1 is cyclopropyl. In certain embodiments, A^1 is  .

[00178] The description above describes multiple embodiments relating to compounds of Formula III. The patent application specifically contemplates all combinations of the embodiments.

[00179] In certain embodiments, the substituted pyrazolo[1,5-a]pyrimidinyl carboxamide or related organic compound is a compound embraced by Formula III-1:



(III-1)

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} alkoxyl, C_{1-4} haloalkoxyl, cyclopropyl, cyano, halogen, hydroxyl, $-N(R^4)_2$, -O-(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 $-C(O)R^3$;

X^1 is a carbonyl-containing linker selected from -C(O)N(H)(C_{1-6} alkylene optionally substituted with C_{1-4} alkoxyl or C_{3-6} cycloalkyl)-ψ, -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, and -C(O)N(H)-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;

provided that when X^1 is -C(O)N(H)-ψ and A^1 is a C_{5-7} cycloalkyl optionally substituted with 1 or 2 C_{1-4} alkyl groups; then R^1 is other than C_{1-4} alkyl and C_{1-4} haloalkyl.

[00180] Definitions of the variables in Formula III-1 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)(C_{1-6} alkylene)-ψ, and R^1 and R^2 each represent independently for each occurrence hydrogen or C_{1-4} alkyl.

[00181] 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 C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, cyclopropyl, cyano, chloro, or fluoro. In certain embodiments, R^1 is methyl.

[00182] In certain embodiments, n is 2. In certain embodiments, the R^1 groups are located at the 5 and 7 positions of the pyrazolo[1,5-a]pyrimidinyl.

[00183] 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.

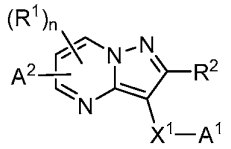
[00184] In certain embodiments, R^3 and R^4 each represent independently for each occurrence hydrogen, methyl, or ethyl.

[00185] In certain embodiments, X^1 is -C(O)N(H)(C_{1-6} alkylene)-ψ. In certain embodiments, X^1 is -C(O)N(H)C(H)(CH_3)-ψ or -C(O)N(H)C(CH_3)$_2$-ψ. In certain embodiments, X^1 is -C(O)N(H)(C_{1-6} 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.

[00186] In certain embodiments, A^1 is a C_{3-10} cycloalkyl optionally substituted with 1 or 2 C_{1-4} alkyl groups. In certain embodiments, A^1 is a C_{3-10} cycloalkyl that is not substituted. In certain embodiments, A^1 is a cyclopropyl. In certain embodiments, A^1 is a cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[00187] The description above describes multiple embodiments relating to compounds of Formula III-1. The patent application specifically contemplates all combinations of the embodiments. For example, the invention contemplates a compound of Formula III-1 wherein X^1 is -C(O)N(H)(C_{1-6} alkylene)-ψ, and R^1 and R^2 each represent independently for each occurrence hydrogen or C_{1-4} alkyl.

[00188] In certain embodiments, the substituted pyrazolo[1,5-a]pyrimidinyl carboxamide or related organic compound is a compound embraced by Formula IV:



(IV)

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, or C_{1-4} cyanoalkyl;

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^7 represents independently for each occurrence halogen, hydroxyl, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{3-6} cycloalkyl, -O-(C_{3-6} cycloalkyl), -O-(C_{1-6} alkylene)-C_{1-6} alkoxyl, -O-(heteroaryl), -(C_{1-6} alkylene)-CN, $-N(R^4)_2$, $-C(O)N(R^4)_2$, 3-8 membered heterocycloalkyl, phenyl, or heteroaryl;

A^2 is one of the following:

- phenyl;
- 4-12 membered oxoheterocyclyl optionally substituted by 1, 2, or 3 occurrences of R^7; or
- 6-membered heteroaryl that is (i) substituted by C_{2-4} alkynyl and (ii) optionally substituted by 1, 2, or 3 occurrences of R^7;

X^1-A^1 is as follows:

(i) when A^2 is phenyl, then X^1-A^1 is -C(O)N(H)C(H)(C_{1-2} alkyl)-cyclopropyl, or X^1-A^1 is -C(O)N(H)(C_{1-6} haloalkylene)-cyclopropyl;

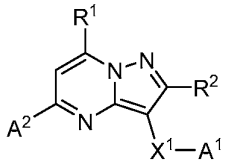
(ii) when A^2 is a 4-12 membered oxoheterocyclyl optionally substituted by 1, 2, or 3 occurrences of R^7, then X^1-A^1 is -C(O)N(H)(C_{1-6} alkyl), -C(O)N(H)(C_{1-6} haloalkylene)-(C_{3-6} cycloalkyl), -C(O)N(H)(C_{1-6} haloalkylene)-(C_{1-6} alkyl), -C(O)N(H)(C_{1-6} alkylene)-(C_{3-6} cycloalkyl), or -C(O)N(H)-(C_{3-6} cycloalkyl); or

(iii) when A^2 is a 6-membered heteroaryl that is (i) substituted by C_{2-4} alkynyl and (ii) optionally substituted by 1, 2, or 3 occurrences of R^7, then X^1-A^1 is -C(O)N(H)(C_{1-6} haloalkylene)-(C_{3-6} cycloalkyl), -C(O)N(H)(C_{1-6} haloalkylene)-(C_{1-6} alkyl), or -C(O)N(H)(C_{1-6} alkylene)-(C_{3-6} cycloalkyl); and

n is 1, 2, or 3.

[00189] 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).

[00190] In certain embodiments, the substituted pyrazolo[1,5-a]pyrimidinyl carboxamide or related organic compound is a compound embraced by Formula IV-A:



(IV-A)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 each represent independently hydrogen, C_{1-4} alkyl, or C_{1-4} haloalkyl;

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^7 represents independently for each occurrence halogen, hydroxyl, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{3-6} cycloalkyl, -O-(C_{3-6} cycloalkyl), -O-(C_{1-6} alkylene)-C_{1-6} alkoxyl, -O-(heteroaryl), -(C_{1-6} alkylene)-CN, -N(R^4)$_2$, -C(O)N(R^4)$_2$, 3-8 membered heterocycloalkyl, phenyl, or heteroaryl;

A^2 is one of the following:

- phenyl;

- 4-12 membered oxoheterocyclyl optionally substituted by 1, 2, or 3 occurrences of R^7; or
- 6-membered heteroaryl that is (i) substituted by C_{2-4} alkynyl and (ii) optionally substituted by 1, 2, or 3 occurrences of R^7; and

X^1-A^1 is as follows:

(i) when A^2 is phenyl, then X^1-A^1 is -C(O)N(H)C(H)(C_{1-2} alkyl)-cyclopropyl, or X^1-A^1 is -C(O)N(H)(C_{1-6} haloalkylene)-cyclopropyl;

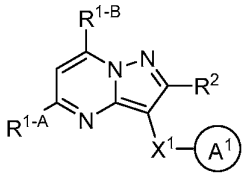
(ii) when A^2 is a 4-12 membered oxoheterocyclyl optionally substituted by 1, 2, or 3 occurrences of R^7, then X^1-A^1 is -C(O)N(H)(C_{1-6} alkyl), -C(O)N(H)(C_{1-6} haloalkylene)-(C_{3-6} cycloalkyl), -C(O)N(H)(C_{1-6} haloalkylene)-(C_{1-6} alkyl), -C(O)N(H)(C_{1-6} alkylene)-(C_{3-6} cycloalkyl), or -C(O)N(H)-(C_{3-6} cycloalkyl); or

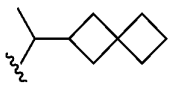
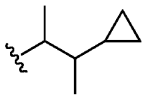
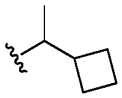
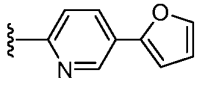
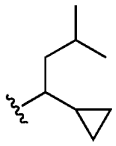
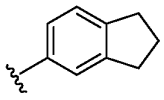
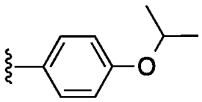
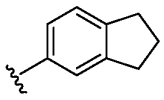
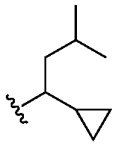
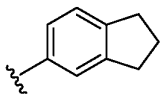
(iii) when A^2 is a 6-membered heteroaryl that is (i) substituted by C_{2-4} alkynyl and (ii) optionally substituted by 1, 2, or 3 occurrences of R^7, then X^1-A^1 is -C(O)N(H)(C_{1-6} haloalkylene)-(C_{3-6} cycloalkyl), -C(O)N(H)(C_{1-6} haloalkylene)-(C_{1-6} alkyl), or -C(O)N(H)(C_{1-6} alkylene)-(C_{3-6} cycloalkyl).

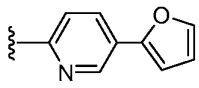
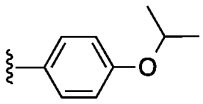
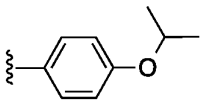
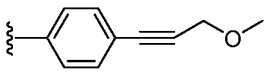
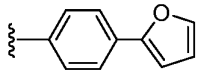
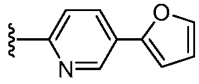
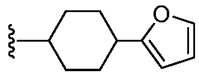
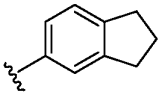
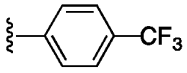
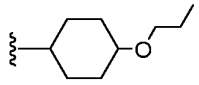
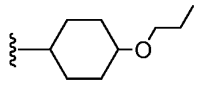
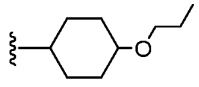
[00191] Definitions of the variables in Formula IV-A above encompass multiple chemical groups. The application contemplates embodiments where, for example, i) the definition of a variable is a single chemical group selected from those chemical groups set forth above, ii) the definition is a collection 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).

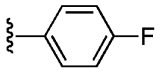
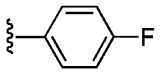
[00192] In certain other embodiments, the compound is a compound described in the Examples, or a pharmaceutically acceptable salt thereof. In certain other embodiments, the compound is one of the compounds listed in Table 1, 2, or 3A below or a pharmaceutically acceptable salt thereof. In certain other embodiments, the compound is one of the compounds listed in Table 3B below 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.



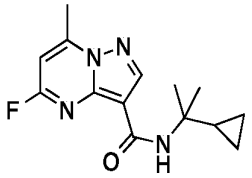
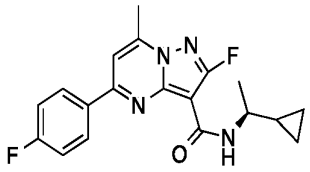
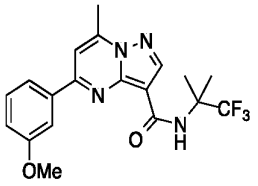
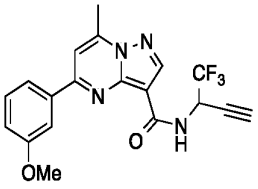
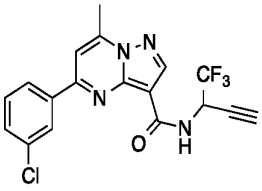
No.	R^{1-A}	R^{1-B}	R^2	X^1	A^1
I-1	2-pyridinyl	ethyl	H	-C(O)N(H)-ψ	
I-2	2-pyridinyl	methyl	H	-C(O)N(H)-ψ	
I-3	2-pyridinyl	methyl	H	-C(O)N(H)-ψ	
I-4	2-pyridinyl	methyl	H	-C(O)N(H)-ψ	
I-5	2-pyridinyl	methyl	H	-C(O)N(H)-ψ	
I-6	2-pyridinyl	methyl	H	-C(O)N(H)-ψ	
I-7	2-pyridinyl	methyl	H	-C(O)N(H)-ψ	
I-8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

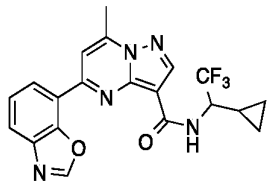
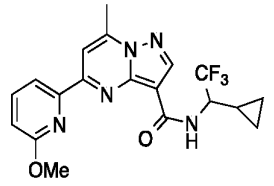
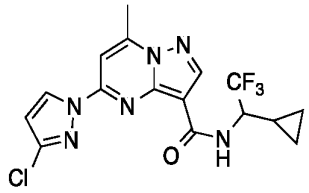
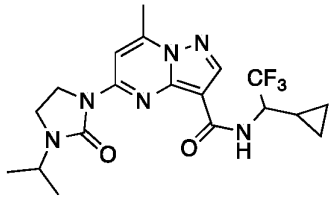
No.	R^{1-A}	R^{1-B}	R^2	X^1	A^1
I-11	4-tetrahydropyranyl	methyl	H	-C(O)N(H)-ψ	
I-12	4-tetrahydropyranyl	methyl	H	-C(O)N(H)-ψ	
I-13	3-pyridinyl	methyl	H	-C(O)N(H)$(CH_2)_2$-ψ	
I-14	3-pyridinyl	methyl	H	-C(O)N(H)$(CH_2)_2$-ψ	
I-15	3-pyridinyl	methyl	H	-C(O)N(H)$(CH_2)_2$-ψ	
I-16	3-pyridinyl	methyl	H	-C(O)N(H)$(CH_2)_2$-ψ	
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	3-pyridinyl	methyl	H	-C(O)N(H)C(H)(CF_3)-ψ	2-thiophenyl
I-23	4-piperidinyl	methyl	H	-C(O)N(H)C(H)(CF_3)-ψ	
I-24	4-piperidinyl	methyl	H	-C(O)N(H)C(H)(CF_3)-ψ	2-thiophenyl
I-25	-$C(Me)_2$CN	methyl	H	-C(O)N(H)C(H)(CF_3)-ψ	cyclopropyl
I-26	-$C(Me)_2$OH	methyl	H	-C(O)N(H)C(H)(CF_3)-ψ	cyclopropyl
I-27	Cl	methyl	H	-C(O)N(H)C(H)(CF_3)-ψ	2-furanyl
I-28	Cl	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-29	methyl	CN	H	-C(O)N(H)C(H)(CF_3)-ψ	
I-30	methyl	CN	H	-C(O)N(H)C(H)(CF_3)-ψ	cyclopropyl
I-31	methyl	H	F	-C(O)N(H)C(H)(CF_3)-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	

Compound No.	Compound Structure
II-6	
II-8	
II-9	
II-10	

[00193] 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.

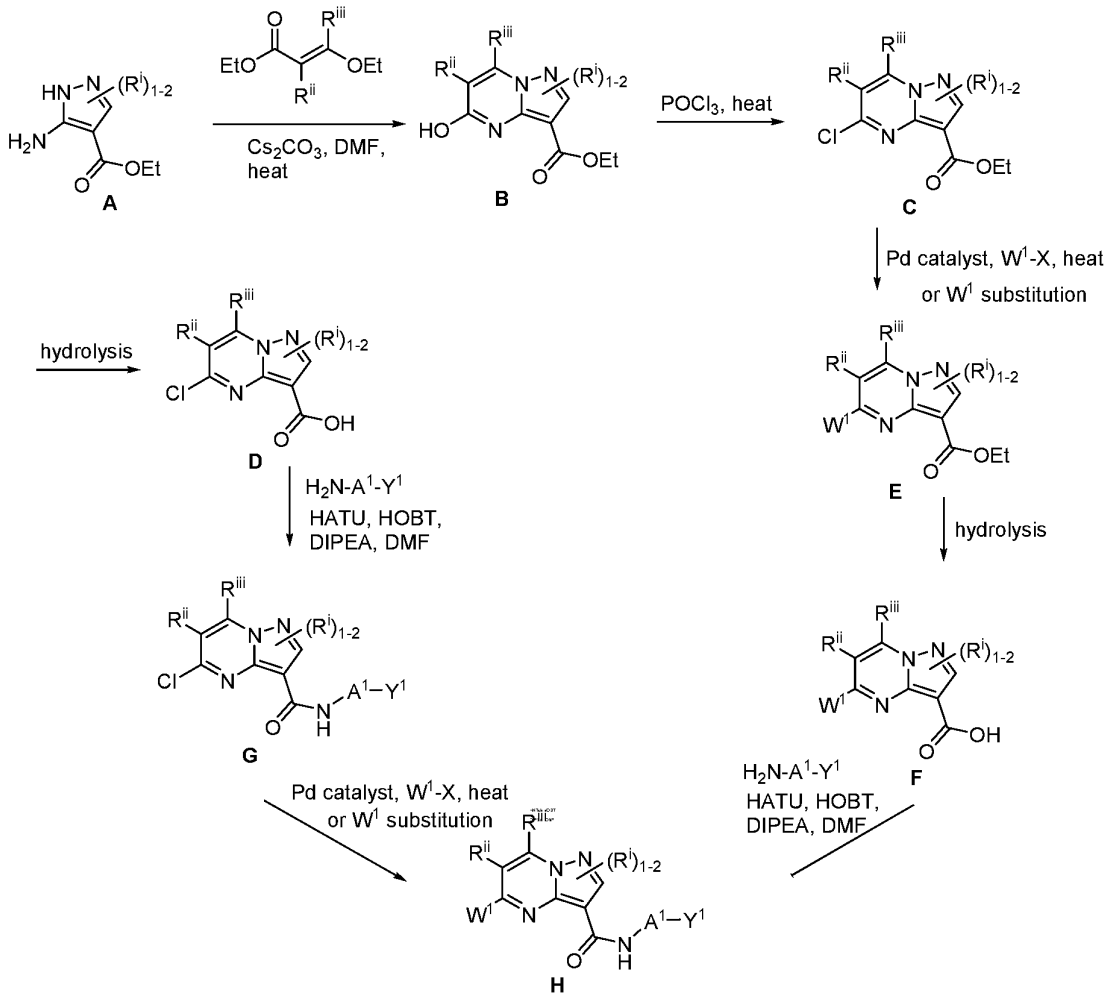
[00194] The synthetic route illustrated in Scheme 1 depicts an exemplary procedure for preparing substituted pyrazolo[1,5-a]pyrimidine compounds. In the first step, ethyl 5-amino-1*H*-pyrazole-4-carboxylate (R^{i}=H) **A** is condensed with ethyl (*E*)-3-ethoxybut-2-enoate (R^{ii}=H, R^{iii}=Me) in DMF at Cs_2CO_3 to afford ethyl 5-hydroxy-7-methylpyrazolo[1,5-a]pyrimidine-3-carboxylate **B**. Heating of carboxylate **B** with phosphoryl trichloride affords the intermediate ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate **C**. Hydrolysis of chloro ester

C under basic conditions provides ethyl 5-chloro-7-methylpyrazolo[1,5-a]pyrimidine-3-carboxylic acid **D**.

[00195] Carboxylic acid **D** can be treated with a variety of substituted aromatic or aliphatic amines using standard peptide coupling procedures, such as HATU and/or HOBT in DMF in the presence of DIPEA to afford chloro amide **G**. In the final step, Pd-catalyzed coupling of chloro amide **G** with a variety of aromatic or heteraromatic boronic acids or esters or with trialkylstannyl reagents may be accomplished using standard Pd-catalyzed coupling procedures such as Suzuki and Buchwald coupling. For example, using Suzuki coupling conditions (such as $Pd(dppf)_2Cl_2 \cdot CH_2Cl_2$ in DME in the presence of K_3PO_4) affords substituted amide **H**. In some cases, substitution of the chloro amide **G** with a primary or secondary amine affords the substituted amide **H**.

[00196] Alternatively chloro carboxylic ester **C** can undergo Pd-catalyzed coupling with a variety of aromatic/heteraromatic boronic acids or esters or with trialkylstannyl reagents using standard Pd-catalyzed coupling procedures such as Suzuki and Buchwald coupling. For example, using Suzuki coupling conditions (such as $Pd(dppf)_2Cl_2 \cdot CH_2Cl_2$ in DME in the presence of K_3PO_4) affords substituted carboxylic ester **E**. Alternatively, substitution of the chloro carboxylic ester **C** with a primary or secondary amine affords the substituted carboxylic ester **E**. Hydrolysis of carboxylic ester **E** under basic or neutral conditions affords carboxylic acid **F**. In the final step, coupling of carboxylic acid **F** 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**.

SCHEME 1



[00197] The reaction procedures in Scheme 1 are contemplated to be amenable to preparing a wide variety of substituted pyrazolo[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 1, 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

[00198] 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 pyrazolo[1,5-a]pyrimidinyl carboxamide, related compounds, and pharmaceutical compositions described herein. Treatment methods include the use of substituted pyrazolo[1,5-a]pyrimidinyl 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 pyrazolo[1,5-a]pyrimidinyl carboxamide and related organic compounds described herein may activate glucocerebrosidase (Gcase).

Methods of Treating Medical Disorders

[00199] 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 pyrazolo[1,5-a]pyrimidinyl carboxamide or related organic compound described herein to treat the disorder. The compound may be a compound of Formula I, I-1, I-A, II, II-A, III, III-1, or IV described above in Section II.

[00200] In certain embodiments, the compound is a compound of Formula I. In certain embodiments, the compound is a compound of Formula II. In certain embodiments, the compound is a compound of Formula III.

[00201] 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.

[00202] In certain embodiments, the disorder is an anxiety disorder, such as panic disorder, social anxiety disorder, or generalized anxiety disorder.

[00203] 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.

[00204] In certain embodiments, the patient is a human.

[00205] 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.

[00206] The description above describes multiple embodiments relating to methods of treating various disorders using certain substituted pyrazolo[1,5-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

[00207] 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

[00208] The invention embraces combination therapy, which includes the administration of a substituted pyrazolo[1,5-a]pyrimidinyl carboxamide or related compound described herein (such as compound of Formula I, I-1, I-A, II, II-A, III, III-1, 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.

[00209] 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 2011/133915, and WO 2010/091164; 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

[00210] The invention provides pharmaceutical compositions comprising a substituted pyrazolo[1,5-a]pyrimidinyl carboxamide or related organic compound described herein, such as

a compound of Formula I, I-1, I-A, II, II-A, III, III-1, or IV. In certain embodiments, the pharmaceutical compositions preferably comprise a therapeutically-effective amount of one or more of the substituted pyrazolo[1,5-a]pyrimidinyl carboxamide or related organic compounds described above, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. 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.

[00211] 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.

[00212] 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.

[00213] 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.

[00214] 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.

[00215] 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.

[00216] 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.

[00217] 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.

[00218] 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.

[00219] 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.

[00220] 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.

[00221] 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.

[00222] 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.

[00223] 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.

[00224] 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.

[00225] 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.

[00226] 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.

[00227] 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.

[00228] 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.

[00229] 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.

[00230] 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.

[00231] 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.

[00232] Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

[00233] 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.

[00234] 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.

[00235] 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.

[00236] 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.

[00237] 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.

[00238] 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.

[00239] 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.

[00240] 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 intrasternal injection and infusion.

[00241] 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.

[00242] 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.

[00243] 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.

[00244] 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.

[00245] 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.

[00246] 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.

[00247] 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.

[00248] 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

[00249] 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 pyrazolo[1,5-a]pyrimidinyl carboxamide or related organic compound described herein, such as

a compound of Formula I, I-1, I-A, II, II-A, III, III-1, or IV. The kit may comprise one or more unit dosage forms containing an amount of a substituted pyrazolo[1,5-a]pyrimidinyl carboxamide or related organic compound described herein, such as a compound of Formula I, that is effective for treating said medical disorder, *e.g.*, Gaucher disease, Parkinson's disease, Lewy body disease, dementia, or multiple system atrophy.

[00250] The description above describes multiple aspects and embodiments of the invention, including substituted pyrazolo[1,5-a]pyrimidinyl carboxamide and related organic compounds, compositions comprising a substituted pyrazolo[1,5-a]pyrimidinyl carboxamide or related organic compounds, methods of using the substituted pyrazolo[1,5-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 pyrazolo[1,5-a]pyrimidinyl carboxamide or related organic compound described herein, such as a compound of Formula I-A.

EXAMPLES

[00251] 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.

EXAMPLE 1 – PREPARATION OF PYRAZOLO[1,5-a]PYRIMIDINYL CARBOXAMIDE COMPOUNDS

[00252] Pyrazolo[1,5-a]pyrimidine-3-carboxamide compounds were prepared based on the general procedures described in Part I below. Exemplary procedures for preparing specific amine compounds useful as synthetic intermediates in the preparation of certain pyrazolo[1,5-a]pyrimidine-3-carboxamide compounds are provided in Part II below. Exemplary procedures for preparing specific carboxylic acid compounds useful as synthetic intermediates in the preparation of certain pyrazolo[1,5-a]pyrimidine-3-carboxamide compounds are provided in

Part III below. Specific pyrazolo[1,5-a]pyrimidine-3-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

[00253] 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 RT for 4-16 h, and then washed with saturated aqueous $NaHCO_3$ 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_2SO_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

[00254] 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 h 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

[00255] 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 h 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.

[00256] 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

[00257] 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 RT 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 h and then diluted with DCM (10 mL/0.5 mmol). The organic solution was washed sequentially with H_2O (10 mL/0.5 mmol) and brine (10 mL/0.5 mmol), then dried over anhydrous Na_2SO_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

[00258] A suspension of heteroaryl chloride (1 equivalent), organoboronic acid or organoboronic ester (1.2 equivalents), K_3PO_4 (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 concentrated *in vacuo* and the resulting residue 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

[00259] 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 the reaction 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

[00260] A solution of organobromide (1.0 equivalent), organochloride (1.0 equivalent), hexabutylditin (1.0 equivalent), and $Pd(dppf)Cl_2$•DCM or $Pd(t\text{-}Bu_3P)_2$ (10 mol%) in anhydrous 1,4-dioxane (10 mL/mmol) was stirred at 100 °C under N_2 overnight, then cooled and the reaction was 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_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 F: Preparation of Coupled Aryl and Heteroaryl Groups Using Buchwald Catalyzed Coupling Conditions Between an Organohalide and Organotin Reagent

[00261] 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 then the mixture was stirred at 120 °C overnight. Next, the reaction 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 G: Preparation of a Heteroaryl Amine Using Substitution Between an Organohalide and Aliphatic Amine

[00262] A solution of organochloride (1.0 equivalent), amine hydrochloride (1.3 equivalent) and DIEA (3.0 equivalents) in DMF (5 mL/1 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_2O (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.

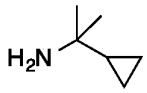
[00263] General Procedure H: Preparation of Coupled Imidazolidinyl Groups Using Buchwald Catalyzed Coupling Conditions Between an Organohalide and Imidazolidinyl Reagent

[00264] 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 2-16 h under a N_2 atmosphere. The reaction mixture was then cooled to RT, quenched with saturated NH_4Cl (20 mL), and extracted with EA (30 mL × 3). The combined organic layers were washed with brine (30 mL), 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.

Part II – Preparation of Specific Amine Compounds

[00265] Exemplary procedures for preparing specific amine compounds useful in the preparation of certain pyrazolo[1,5-a]pyrimidine-3-carboxamide compounds are provided below.

2-Cyclopropylpropan-2-amine



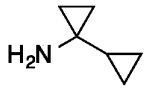
[00266] To a solution of 1-cyclopropylethan-1-one (1.0 g, 11.2 mmol) in anhydrous Et_2O (5 mL) was added a solution of MgMeBr (4.4 mL, 13.2 mmol) at a rate suitable to maintain gentle reflux of the solvent, to afford the expected alcoholate as a white precipitate. The reaction mixture was maintained refluxing for an additional 30 minutes, then stirred at RT overnight, and quenched with sat. NH_4Cl solution (5 mL). The resulting mixture was extracted with Et_2O (5 mL), and the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford 2-cyclopropylpropan-2-ol as a pale yellow oil (1.1 g, 92%). ^1H NMR (500 MHz, $CDCl_3$) δ 1.18 (s, 6H), 0.97-0.94 (m, 1H), 0.39-0.30 (m, 4H).

[00267] To a stirred solution of 2-cyclopropylpropan-2-ol (1.1 g, 11.2 mmol) in $CHCl_3$ (10 mL) was added NaN_3 (1.08 g, 15.8 mmol) and Cl_3CO_2H (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%).

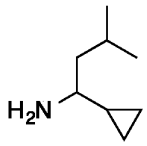
[00268] To a suspension of $LiAlH_4$ (670 mg, 17.7 mmol) in anhydrous diethyl ether (6 mL) was added a solution of (2-azidopropan-2-yl)cyclopropane (1.2 g, 11.2 mmol) in 4 mL of anhydrous diethyl ether at a rate such that reflux was maintained. After refluxing for 2 h, the reaction mixture was cooled to 0 °C, quenched by careful addition of 0.67 mL of H_2O, 0.67 mL of 15% NaOH solution, and 2.0 mL of H_2O, 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)]-1-amine



[00269] 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 HCl (30 mL). The aqueous phase was concentrated *in vacuo* and the resulting residue was triturated in diethyl ether to afford [1,1'-bi(cyclopropan)]-1-amine (0.5 g, 34%) as the hydrochloride salt.

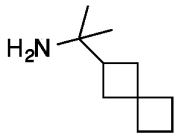
1-Cyclopropyl-3-methylbutan-1-amine



[00270] 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_4Cl solution (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 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 $NaBH_4$ (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 1-cyclopropyl-3-methylbutan-1-amine (1.5 g, 16%) as a pale yellow solid.

2-(Spiro[3.3]heptan-2-yl)propan-2-amine



[00271] Concentrated H_2SO_4 (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 $NaHCO_3$ solution (100 mL), dried over anhydrous $MgSO_4$, 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, $CDCl_3$) 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).

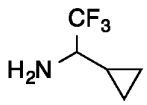
[00272] To a solution of ethyl spiro[3.3]heptane-2-carboxylate (1.2 g, 7.14 mmol) in anhydrous THF (20 mL) at -78 °C was added dropwise a solution of MeMgBr (3.0 M in Et_2O; 9.52 mL, 28.56 mmol). The reaction mixture was then stirred at RT for 18 h, poured cautiously into sat. NH_4Cl solution (20 mL) 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-d_6) 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).

[00273] 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_2Cl_2 (40 mL) at RT under Ar was treated with $BF_3 \cdot Et_2O$ (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 $MgSO_4$ 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.

[00274] 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 $[M+H]^+$.

1-Cyclopropyl-2,2,2-trifluoroethan-1-amine

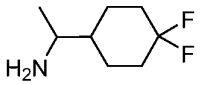


[00275] A suspension of cyclopropanecarbaldehyde (7.0 g, 100 mmol), benzylamine (11.2 g, 105 mmol) and $MgSO_4$ (62 g, 500 mmol) in DCM (200 mL) was stirred for 48 h at RT. After reaction completion the solution was filtered through celite and the filtrate was concentrated *in vacuo* to give *N*-benzyl-1-cyclopropyl methanimine as a light yellow oil (16 g, 100%). LC-MS weak MS: m/z: 159.1 $[M+H]^+$.

[00276] To a solution of *N*-benzyl-1-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 Na_2SO_4, 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-1-cyclopropyl-2,2,2-trifluoroethan-1-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.

[00277] To a solution of *N*-benzyl-1-cyclopropyl-2,2,2-trifluoroethan-1-amine (3.5 g, 15.3 mmol) in MeOH (50 mL) was added 6 N HCl (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 1-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 $[M+H]^+$.

1-(4,4-Difluorocyclohexyl)ethan-1-amine



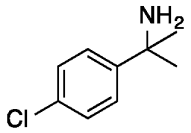
[00278] To a solution of 4,4-difluorocyclohexane-1-carboxylic acid (1.64 g, 10 mmol) and DIPEA (2.58 g, 20 mmol) in DMF (10 mL) at 0 °C was added HATU (5.7 g, 15 mmol) and the reaction mixture was stirred at 0 °C for 30 min, followed by the addition of *N,O*-dimethylhydroxylamine hydrochloride (970 mg, 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 Na_2SO_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-1-carboxamide (880 mg, 42 %) as a colorless oil. LC-MS m/z: 208.0 $[M+H]^+$. LCMS: t_R = 1.58 min.

[00279] To a solution of 4,4-difluoro-*N*-methoxy-*N*-methylcyclohexane-1-carboxamide (880 mg, 4.25 mmol) in THF (12 mL) was added a solution of MeLi in 1,2-diethoxyethane (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_4Cl solution and separated. The aqueous phase was extracted with EtOAc (120 mL x 3), and the combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (PE/EA = 4:1) to afford 1-(4,4-difluorocyclohexyl)ethan-1-one (400mg, 43 %) as a light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) 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).

[00280] A mixture of 1-(4,4-difluorocyclohexyl)ethan-1-one ((200 mg, 1.23 mmol), NH_4OAc (1.9 g, 24.6 mmol) and $NaBH_3CN$ (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 CH_2Cl_2 (30 ml, x3) and dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (EtOAc/MeOH; 10:1) to afford 1-(4,4-difluorocyclohexyl)ethan-1-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



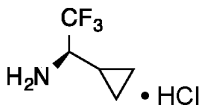
[00281] MgBrMe (3M in THF, 5 mL, 15 mmol) was added dropwise at RT to a solution of 1-(4-chlorophenyl)ethan-1-one (1.54 g, 10 mol) in Et_2O (60 mL). After the addition was complete the reaction mixture was stirred at RT for 12 hours and then quenched by the careful addition of saturated NH_4Cl solution (30 mL). The resulting mixture was stirred for 1 hour and then extracted with EtOAc (100 mL × 3). The combined organic layers were dried over Na_2SO_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. ^1H NMR (400 MHz, $CDCl_3$) 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).

[00282] A mixture of 2-(4-chlorophenyl)propan-2-ol (1.36 g, 8 mmol), $TMSN_3$ (2.4 g, 16 mmol) and $BF_3 \cdot Et_2O$ (16 mL) in CH_2Cl_2 (20 mL) was stirred at RT for 2 h and quenched with saturated $NaHCO_3$ solution. The resulting mixture was separated, and the aqueous phase was extracted with CH_2Cl_2 (30 mL × 3). The combined organic phases were dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the target compound 1-(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.

[00283] 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 CH_2Cl_2, 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.

(*R*)-1-Cyclopropyl-2,2,2-trifluoroethan-1-amine hydrochloride

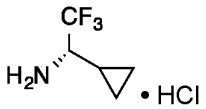


[00284] To a mixture of 1-ethoxy-2,2,2-trifluoroethan-1-ol (10 g, 69.4 mmol) and (*R*)-2-methylpropane-2-sulfinamide (9.3 g, 76.7 mmol) was added $Ti(OEt)_4$ (24 g, 105.3 mmol) and the mixture was stirred at 70 °C for 2 days, cooled, diluted with EA (200 mL) and poured into brine (700 mL). The resulting mixture was stirred vigorously for several minutes and filtered through celite. The cake was washed with EA, and the filtrate was extracted with EA (200 mL x 3). The combined organic layers were washed with brine (400 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (20–50% EA/PE) to afford stereoisomer A (8 g, 47%) and stereoisomer B (4 g, 23%) whose stereochemistry was unassigned. Stereoisomer A (less polar): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.75-4.70 (m, 1H), 4.09-4.03 (m, 1H), 3.9 (d, J = 6.0 Hz, 1H), 3.68-3.62 (m, 1H), 1.3-1.25 (m, 12H). LC-MS: m/z: no MS signal, t_R = 1.655 min. Stereoisomer B (less polar): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.81-4.76 (m, 1H), 4.3 (d, J = 9.0 Hz, 1H), 3.94-3.88 (m, 1H), 3.66-3.60 (m, 1H), 1.28-1.14 (m, 12H). m/z: no MS signal, t_R = 1.614 min.

[00285] To a solution of stereoisomer A (5 g, 20.2 mmol) in 75 mL of DCM was added dropwise *c*PrMgBr in THF (1M, 61 mL, 61 mmol) at -60 °C and the mixture was stirred for 10 minutes and then allowed to warm slowly to -20 °C over 2 h, during which time the reaction was complete. The reaction mixture was quenched with saturated NH_4Cl solution (120 mL) and extracted with DCM (120 mL x 3). The combined organic extracts were washed with brine (160 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by preparative HPLC to afford (*R*)-*N*-((*R*)-1-cyclopropyl-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide (1.8 g, 37%). LC-MS m/z: 244.1 $[M+H]^+$, t_R = 1.74 min.

[00286] To a solution of (*R*)-*N*-((*R*)-1-cyclopropyl-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide (2.4 g, 9.9 mmol) in MeOH (5 mL) was added 4M HCl in dioxane (5 mL, 20 mmol). The reaction mixture was stirred for 2 h at RT and concentrated *in vacuo*. The residue was triturated with Et_2O (10 mL x 2) to afford the title compound (1.2 g, 71%) as a white solid. ^1H NMR (500 MHz, DMSO-d_6) δ 9.46-9.26 (s, 3H), 3.63-3.56 (m, 1H), 1.12-1.05 (m, 1H), 0.73-0.58 (m, 4H).

(*S*)-1-cyclopropyl-2,2,2-trifluoroethan-1-amine hydrochloride



[00287] To a mixture of 1-ethoxy-2,2,2-trifluoroethan-1-ol (20 g, 138.9 mmol) and (*S*)-2-methylpropane-2-sulfinamide (18.4 g, 152.8 mmol) was added $Ti(OEt)_4$ (48 g, 208.3 mmol). The mixture was stirred at 70 °C for 2 d, then cooled, diluted with EA (200 mL), and poured into brine (1.4 L) The resulting mixture was stirred vigorously for several minutes and filtered through celite. The cake was washed with EA, and the filtrate was extracted with EA (400 mL x 3). The combined organic phases were washed with brine (800 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (20–50% EA/PE) to afford stereoisomer C (11 g, 32%) and stereoisomer D (5.1 g, 15%) whose stereochemistry was unassigned. Stereoisomer C (less polar): LC-MS m/z: no MS signal, t_R = 1.669 min. Stereoisomer C (more polar): LC-MS m/z: no MS signal, t_R = 1.626 min.

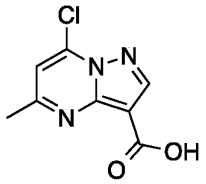
[00288] To a solution of stereoisomer C (9 g, 36.4 mmol) in 150 mL of DCM was added dropwise *c*PrMgBr in THF (1M, 109.3 mL, 109.3 mmol) at -60 °C and the mixture was stirred for 10 minutes and allowed to warm slowly to -20 °C over 2 h, during which time the reaction was complete. The reaction mixture was quenched with saturated NH_4Cl solution (80 mL) and extracted with DCM (120 mL x 3). The combined organic extracts were washed with brine (160 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by preparative HPLC to afford (*S*)-*N*-((*S*)-1-cyclopropyl-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide (3.5 g, 40%). LC-MS m/z: 244.1 $[M+H]^+$, t_R = 1.19 min.

[00289] To a solution of (*S*)-*N*-((*S*)-1-cyclopropyl-2,2,2-trifluoroethyl)-2-methylpropane-2-sulfinamide (1.16 g, 4.8 mmol) in MeOH (5 mL) was added 4M HCl in dioxane (5 mL, 20 mmol). The reaction mixture was stirred for 30 min at RT and concentrated to half volume. Et_2O was added to the mixture, and the resulting precipitate was filtered to afford the title compound (725 mg, 40%) as a white solid. ^{1}H NMR: (500 MHz, DMSO-d_6) δ 9.30-9.00 (m, 3H), 3.62-3.57 (m, 1H), 1.12-1.03 (m, 1H), 0.74-0.59 (m, 4H).

Part III – Preparation of Specific Carboxylic Acid Compounds

[00290] Exemplary procedures for preparing specific carboxylic acid compounds useful in the preparation of certain substituted pyrazolo[1,5-a]pyrimidinyl carboxamide compounds are provided below.

7-Chloro-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid



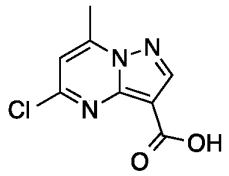
[00291] To a solution of ethyl 3-amino-1*H*-pyrazole-4-carboxylate (10 g, 64.5 mmol) in HOAc (50 mL) was added 4-methyleneoxetan-2-one (27 g, 322.5 mmol). The mixture was stirred at 110 °C for 2 h, then cooled and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (PE/EA; 10:3) to afford ethyl 7-hydroxy-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (8.0 g, 57%) and ethyl 5-hydroxy-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (3.1 g, 21%) as white solids. **7-hydroxy product**: LC-MS m/z: 221.0 $[M+H]^+$, Purity (214 nm): >90%, t_R = 1.26 min; **5-hydroxy product**: LC-MS m/z: 221.0 $[M+H]^+$, Purity (214 nm): >92%, t_R = 1.46 min.

[00292] A solution of ethyl 7-hydroxy-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (4.4 g, 20 mmol) in $POCl_3$ (30 mL) was stirred at 95 °C for 1 h and then concentrated *in vacuo*. The residue was dissolved in EtOAc (20 mL) and basified with *sat.* $NaHCO_3$ solution (20 mL) to pH~7. The resulting mixture was separated, and the aqueous phase was extracted with EtOAc (15 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; 1:1) to give ethyl 7-chloro-5-methylpyrazolo[1,5-

a]pyrimidine-3-carboxylate (1.0 g, 21%) as a white solid. LC-MS m/z: 239.0 $[M+H]^+$, Purity (254 nm): >82%, t_R = 1.55 min.

[00293] To a solution of ethyl 7-chloro-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (1.0 g, 4.18 mmol) in toluene (10 mL) was added $(Bu_3Sn)_2O$ (5.0 g, 8.36 mmol). The reaction mixture was stirred at 120 °C for 2 days, and then concentrated *in vacuo*. The resulting residue was dissolved in EtOAc (10 mL), and basified with *sat.* $NaHCO_3$ solution (10 mL) to pH~8-9. The aqueous phase was separated and acidified with 6N HCl (10 mL) to pH~5. The solution was extracted with EtOAc (10 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 chromatography (PE/EA; 1:1) to give 7-chloro-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (230 mg, 26%) as a white solid. LC-MS m/z: 211.0 $[M+H]^+$, Purity (214 nm): >97%, t_R = 1.23min.

5-Chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid

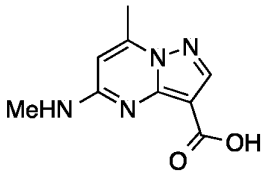


[00294] A solution of ethyl 5-hydroxy-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (2.8 g, 12.6 mmol) in $POCl_3$ (30 mL) was stirred at 70 °C for 2 hr and then concentrated *in vacuo*. The resulting residue was dissolved in EtOAc (20 mL) and basified with *sat.* $NaHCO_3$ solution (15 mL) to pH~7. The resulting mixture was separated, and the aqueous phase was extracted with EtOAc (10 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; 1:1) to give ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (2.7 g, 90%) as a white solid. LC-MS m/z: 239.0 $[M+H]^+$, Purity (214 nm): >99%, t_R = 1.74 min.

[00295] To a solution of ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (1.0 g, 4.18 mmol) in toluene (10 mL) was added $(Bu_3Sn)_2O$ (5.0 g, 8.36 mmol). The reaction mixture was stirred at 120 °C for 2 days, and then concentrated *in vacuo*. The resulting residue was dissolved in EtOAc (10 mL), and basified with *sat.* $NaHCO_3$ solution (10 mL) to pH~8-9. The aqueous phase was separated and acidified with 6N HCl (10 mL) to pH~5. The solution

was extracted with EtOAc (10 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 chromatography (PE/EA; 1:1) to give 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (330 mg, 37%) as a white solid. LC-MS m/z: 211.0 $[M+H]^+$, Purity (214 nm): >97%, t_R = 1.28 min.

7-Methyl-5-(methylamino)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid



[00296] A solution of acetone (0.96 mL, 13.1 mmol) in carbon disulfide (1 g, 13.1 mmol) was added to a suspension of sodium tert-butoxide (2.5 g, 26.2 mmol) in THF (30 mL) while not allowing the temperature to exceed 10 °C. The reaction mixture was stirred at RT for 3 h and MeI (1.6 mL, 26.2 mmol) was added at 10 °C and the resulting solution was stirred overnight at RT. The reaction mixture was diluted with EtOAc (100 mL), washed with water (30 mL x 2) and the organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo* and the crude was purified by triturating with PE (30 mL) to give 4,4-bis(methylthio)but-3-en-2-one (500 mg, 61%) as a yellow solid.

[00297] To a solution of 4,4-bis(methylthio)but-3-en-2-one (0.5 g, 3.08 mmol) in a mixture of acetic acid/water (3:1, 48 mL) was added ethyl 3-amino-1*H*-pyrazole-4-carboxylate (0.36 g, 2.37 mmol) and a catalytic amount of piperidine (2 drops). The resulting solution was heated at reflux for 20 h then, after cooling, water was added (10 mL). The precipitated solid was collected by filtration and recrystallized from a mixture of PE/ether (3:1) to furnish ethyl 7-methyl-5-(methylthio)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (500 mg, 62%) as a yellow solid.

[00298] A suspension of m-CPBA (823 mg, 4.7 mmol) in DCM (5 mL) was added to a stirred solution of ethyl 7-methyl-5-(methylthio)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (400 mg, 1.59 mmol) in DCM (5 mL). The resulting solution was stirred at RT overnight, the solvent was removed *in vacuo* and EtOH (15 mL) was added to the residue. The solid was collected by filtration, washed with cold EtOH and dried to give ethyl 7-methyl-5-(methylsulfonyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (400 mg, 89%) as a white solid.

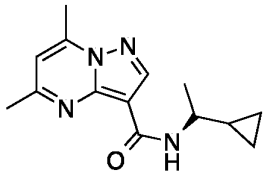
[00299] A mixture of ethyl 7-methyl-5-(methylsulfonyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (400 mg, 1.4 mmol) and $MeNH_2$ in MeOH (15 mL) was stirred at RT for 2 h. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 25 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude was purified by trituration with PE (10 mL) to afford ethyl 7-methyl-5-(methylamino)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (272 mg, 61%) as a white solid.

[00300] The suspension of ethyl 7-methyl-5-(methylamino)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (273 mg, 1.15 mmol) in MeOH/H_2O (2 mL/2mL) was treated with $LiOH.H_2O$ (97 mg, 2.31 mmol). The reaction mixture was heated to 60 °C and stirred for 5 h. The reaction was cooled and neutralized to pH 6-7 with dilute HCl. The slurry was filtered, washed with water and diethyl ether to obtain 7-methyl-5-(methylamino)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (154 mg, 65%). LC-MS m/z: 207.0 $[M+H]^+$: Purity (214 nm): >99%; t_R = 0.46 min.

Part IV – Pyrazolo[1,5-a]pyrimidine-3-carboxamide Compounds Prepared Following General Procedures

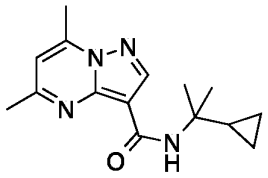
[00301] The following compounds were prepared based on the general procedures described in Part I above.

(*S*)-*N*-(1-Cyclopropylethyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



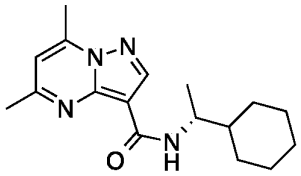
[00302] Following general procedure A, 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.15 mmol) and (*S*)-1-cyclopropylethan-1-amine afforded the title compound (19.0 mg, 49%) as a white solid. ^1H NMR (500 MHz, DMSO-d_6): δ 8.48 (s, 1H), 8.03 (d, J = 7.5 Hz, 1H), 7.13 (s, 1H), 3.64-3.59 (m, 1H), 2.74 (s, 3H), 2.63 (s, 3H), 1.25 (d, J = 6.5 Hz, 3H), 1.04-0.99 (m, 1H), 0.51-0.41 (m, 2H), 0.37-0.32 (m, 1H), 0.28-0.25 (m, 1H). LC-MS m/z: 259.2 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 9.31 min.

***N*-(2-Cyclopropylpropan-2-yl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



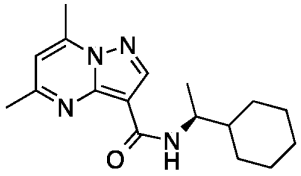
[00303] Following general procedure A, 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (25 mg, 0.13 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (8.0 mg, 22%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.13 (s, 1H), 6.68 (s, 1H), 2.78 (s, 3H), 2.62 (s, 3H), 1.44 (s, 6H), 1.39-1.33 (m, 1H), 0.49 (d, J = 6.5 Hz, 4H). LC-MS m/z: 272.1 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 9.99 min.

(*R*)-*N*-(1-Cyclohexylethyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



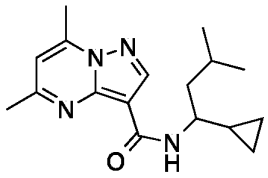
[00304] Following general procedure A, 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (38 mg, 0.20 mmol) and (*R*)-1-cyclohexylethan-1-amine afforded the title compound as a white solid (10 mg, 15%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.12 (s, 1H), 3.95-3.91 (m, 1H), 2.73 (s, 1H), 2.61 (s, 1H), 1.82-1.62 (m, 5H), 1.47-1.41 (m, 1H), 1.27-1.03 (m, 2H), 1.14 (d, J = 6.5 Hz, 3H). LC-MS m/z: 301.3 $[M+H]^+$. HPLC: Purity (214 nm): >99 %; t_R = 10.81 min.

(*S*)-*N*-(1-Cyclohexylethyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



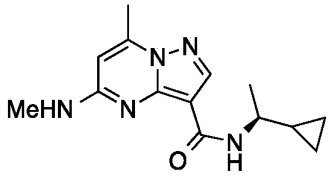
[00305] Following general procedure A, 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (25 mg, 0.13 mmol) and (*S*)-1-cyclohexylethan-1-amine afforded the title compound as a yellow solid (21.4 mg, 55%).^{1}H NMR (500 MHz, $CDCl_3$): δ 8.61 (s, 1H), 8.11 (d, J = 8.5 Hz,1H), 6.70 (s, 1H), 4.15-4.11 (m, 1H), 2.78 (s, 3H), 2.64 (s, 3H), 1.89-1.87 (m, 1H), 1.79-1.77 (m, 4H), 1.69-1.66 (m, 1H), 1.30-1.25 (m, 2H), 1.23 (d, J = 6.5 Hz, 3H), 1.19-1.10 (m, 3H). LC-MS m/z: 301.0 $[M+H]^+$. HPLC: Purity (214 nm): > 98%; t_R = 10.82 min.

N-(1-Cyclopropyl-3-methylbutyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



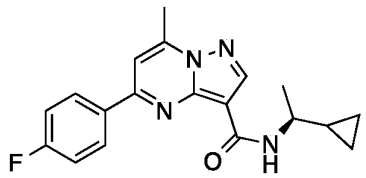
[00306] Following general procedure A, 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.21 mmol) and 1-cyclopropyl-3-methylbutan-1-amine afforded the title compound (15 mg, 23%) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.95 (d, J = 9.0 Hz, 1H), 6.68 (s, 1H), 3.85-3.81 (m, 1H), 2.79 (s, 3H), 2.65 (s, 3H), 1.84-1.78 (m, 1H), 1.64-1.52 (m, 2H), 0.96 (d, J = 6.5 Hz, 3H), 0.95 (d, J = 6.5 Hz, 3H), 0.94-0.91 (m, 1H), 0.54-0.47 (m, 2H), 0.46-0.40 (m, 1H), 0.33-0.28 (m, 1H). LC-MS m/z: 301.2 $[M+H]^+$. HPLC: Purity (214 nm): >96%; t_R = 10.70 min.

(*S*)-*N*-(1-Cyclopropylethyl)-7-methyl-5-(methylamino)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00307] Following general procedure A, 7-methyl-5-(methylamino)pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (41 mg, 0.2 mmol) and (*S*)-1-cyclopropylethan-1-amine afforded the title compound (18 mg, 33%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.36 (s, 1H), 8.17 (s, 1H), 6.04 (s, 1H), 5.59 (s, 1H), 3.79-3.75 (m, 1H), 3.08 (d, J = 5.0 Hz, 3H), 2.64 (s, 3H), 1.34 (d, J = 6.5 Hz, 3H), 0.98-0.95 (m, 1H), 0.53-0.44 (m, 3H), 0.35-0.29 (m, 1H). LC-MS m/z: 274.0 $[M+H]^+$. HPLC Purity (254 nm): >96%; t_R = 8.54 min.

(*S*)-*N*-(1-Cyclopropylethyl)-5-(4-fluorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00308] To a suspension of 60% sodium hydride (36 g, 0.905 mol) in THF (700 mL) was added 1-(4-fluorophenyl)ethan-1-one (25.0 g, 0.184 mol) at 0 °C, and the mixture was stirred at

RT for 30 min. To the mixture was added EtOAc (63.7 g, 0.724 mol) at 0 °C. The mixture was stirred at 40 °C for 3 h, and then poured into 6 N HCl (20 mL). The organic solvent was removed *in vacuo*. The residual mixture was extracted with EtOAc (20 mL x 3), washed with 6 N HCl solution (15 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo* to give 1-(4-fluorophenyl)butane-1,3-dione (20 g, 60%) as a brown oil LC-MS m/z: 180.0 $[M+H]^+$, Purity (214 nm): >90%, t_R = 1.88 min.

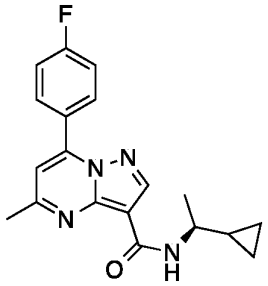
[00309] A solution of ethyl 3-amino-1*H*-pyrazole-4-carboxylate (6.0 g, 38.7 mmol) and 1-(4-fluorophenyl)butane-1,3-dione (7.62 g, 42.6 mmol) in acetic acid (10 0 mL) were heated at 110 °C overnight until the reaction was complete (LC-MS). Acetic acid was removed by blowing air with the flask being heated to 75 °C. The residue was triturated with MeOH (20 mL x 2) and filtered to afford ethyl 7-(4-fluorophenyl)-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (2.88 g, 29%) as a yellow solid. LC-MS m/z: 299.1 $[M+H]^+$. LC-MS Purity (214 nm): > 96%; t_R = 1.82 min.

[00310] The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column, eluted with PE/EA (1:0 to 3:1) to afford ethyl 5-(4-fluorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (360 mg, 4%) as a yellow solid (360 mg, 4%). LC-MS m/z: 299.1 $[M+H]^+$. LC-MS Purity (214 nm): > 66%; t_R = 1.89 min.

[00311] Following general procedure B, ethyl 5-(4-fluorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (150 mg, 0.5 mmol) afforded 5-(4-fluorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (140 mg, 99%). LC-MS m/z: 271.0 $[M+H]^+$. LC-MS Purity (214 nm): > 76%, t_R = 1.59 min.

[00312] Following general procedure A, 5-(4-fluorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (43 mg, 0.16 mmol) and (*S*)-1-cyclopropylethan-1-amine afforded the title compound (38 mg, 71%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.54 (s, 1H), 8.33-8.30 (m, 2H), 8.14 (d, J = 7.5 Hz, 1H), 7.87 (s, 1H), 7.48 (t, J = 9.0 Hz, 2H), 3.63-3.59 (m, 1H), 2.84 (s, 3H), 1.30 (d, J = 6.5 Hz, 3H), 1.12-1.08 (m, 1H), 0.54-0.49 (m, 2H), 0.39-0.32 (m, 2H). LC-MS m/z: 339.1 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 8.66 min.

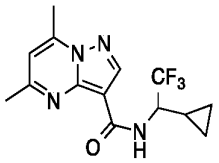
(*S*)-*N*-(1-Cyclopropylethyl)-7-(4-fluorophenyl)-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00313] Following general procedure B, ethyl 7-(4-fluorophenyl)-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (750 mg, 2.5 mmol) afforded 7-(4-fluorophenyl)-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (600 mg, 88%). LC-MS m/z: 271.0 $[M+H]^+$. LC-MS Purity (214 nm): > 99%, t_R = 1.57 min.

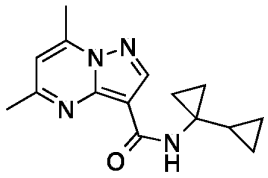
[00314] Following general procedure A, 7-(4-fluorophenyl)-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (54 mg, 0.2 mmol) and *S*)-1-cyclopropylethan-1-amine afforded the title compound (19.8 mg, 29%) as a pale white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.16 (d, J = 8.5 Hz, 1H), 8.05 (dd, J = 8.5 Hz, 5.0 Hz, 2H), 7.27 (t, J = 8.5 Hz, 2H), 6.89 (s, 1H), 3.81-3.76 (m, 1H), 2.73 (s, 3H), 1.37 (d, J = 6.5 Hz, 3H), 1.02-1.00 (m, 1H), 0.55-0.45 (m, 3H), 0.34-0.31 (m, 1H). LC-MS m/z: 339.0 $[M+H]^+$. HPLC: Purity (254 nm): >99%; t_R = 10.63 min.

***N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



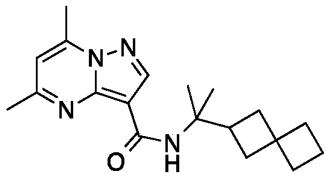
[00315] Following general procedure A, 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.21 mmol) and 1-cyclopropyl-2,2,2-trifluoroethan-1-amine afforded the title compound (30.7 mg, 47%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.57 (s, 1H), 8.44 (d, J = 9.0 Hz, 1H), 7.18 (s, 1H), 4.48-4.43 (m, 1H), 2.76 (s, 3H), 2.63 (s, 3H), 1.27-1.23 (m, 1H), 0.69-0.64 (m, 1H), 0.62-0.57 (m, 1H), 0.55-0.52 (m, 1H), 0.41-0.37 (m, 1H). LC-MS m/z: 313.1 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 8.14 min.

N-([1,1'-bi(Cyclopropan)]-1-yl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



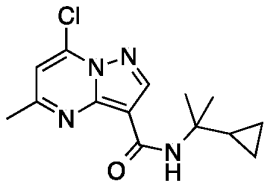
[00316] Following general procedure A, 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (37 mg, 0.19 mmol) and [1,1'-bi(cyclopropan)]-1-amine afforded the title compound (21.2 mg, 41%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.26 (s, 1H), 8.05 (s, 1H), 6.89 (s, 1H), 2.51 (s, 3H), 2.29 (s, 3H), 1.24-1.19 (m, 1H), 0.52-0.50 (m, 2H), 0.43-0.41 (m, 2H), 0.17-0.14 (m, 2H), 0.01-0.00 (m, 2H). LC-MS m/z: 270.1 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 7.45 min.

5,7-Dimethyl-*N*-(2-(spiro[3.3]heptan-2-yl)propan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00317] Following general procedure A, 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (50 mg, 0.26 mmol) and 2-(spiro[3.3]heptan-2-yl)propan-2-amine afforded the title compound (18.4 mg, 22%) as a pale yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.46 (s, 1H), 8.33 (s, 1H), 7.02 (s, 1H), 2.80 (s, 3H), 2.69 (s, 3H), 2.61-2.57 (m, 1H), 2.14 (t, J = 7.0 Hz, 2H), 2.08-1.86 (m, 8H), 1.43 (s, 6H). LC-MS m/z: 327.2 $[M+H]^+$. HPLC: Purity (214 nm): >95%; t_R = 11.86 min.

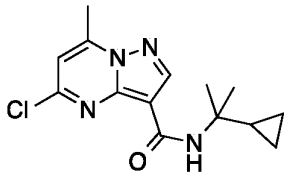
7-Chloro-*N*-(2-cyclopropylpropan-2-yl)-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00318] Following general procedure C, 7-chloro-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (100 mg, 0.47 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (40 mg, 29%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.52 (s, 1H), 7.96

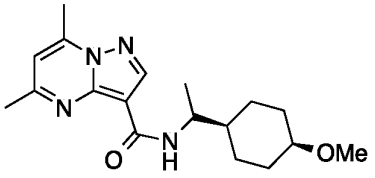
(s, 1H), 7.57 (s, 1H), 2.63 (s, 3H), 1.34 (s, 7H), 0.45-0.44 (m, 4H). LC-MS m/z: 292.7 $[M+H]^+$. HPLC Purity (214 nm): >99%; t_R = 8.25 min.

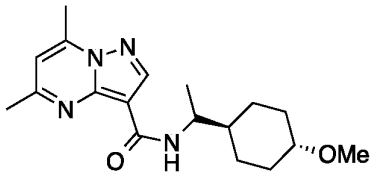
5-Chloro-*N*-(2-cyclopropylpropan-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00319] Following general procedure C, 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (100 mg, 0.47 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (60 mg, 43%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (s, 1H), 7.51 (s, 1H), 7.38(s, 1H), 2.76 (s, 3H), 1.34-1.31 (m, 7H), 0.44-0.42 (m, 4H). LC-MS m/z: 292.7 $[M+H]^+$. HPLC Purity (214 nm): >99%; t_R = 8.65 min.

***N*-((*R*)-1-((1*S*,4*S*)-4-Methoxycyclohexyl)ethyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide and *N*-((*R*)-1-((1*R*,4*R*)-4-Methoxycyclohexyl)ethyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



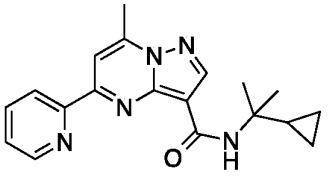


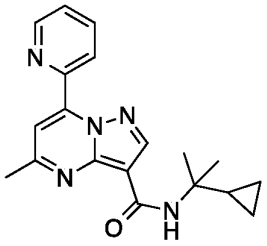
[00320] Following general procedure A, 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (50 mg, 0.26 mmol), HATU (100 mg, 0.26 mmol), and 1-(4-methoxycyclohexyl)ethan-1-amine afforded *N*-((*R*)-1-((1*S*,4*S*)-4-methoxycyclohexyl)ethyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (7.2 mg) and *N*-((*R*)-1-((1*R*,4*R*)-4-methoxycyclohexyl)ethyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (8.4 mg).

[00321] *N*-((*R*)-1-((1*S*,4*S*)-4-Methoxycyclohexyl)ethyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide: ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.46 (s, 1H), 8.43 (s, 1H), 7.02 (s, 1H), 3.37 (s, 3H), 3.22-3.17 (m, 1H), 2.80 (s, 3H), 2.67 (s, 3H), 2.20-2.18 (m, 2H), 2.00-1.98 (m, 3H), 1.48 (s, 6H), 1.31-1.21 (m, 4H). LC-MS m/z: 345.2 $[M+H]^+$. HPLC: Purity (214 nm): 99.52%; t_R = 8.08 min.

[00322] *N*-((*R*)-1-((1*R*,4*R*)-4-Methoxycyclohexyl)ethyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.44 (s, 1H), 7.02 (s, 1H), 3.51-3.50 (m, 1H), .3.35 (s, 3H), 2.80 (s, 3H), 2.69 (s, 3H), 2.10-2.07 (m, 2H), 1.99-1.96 (m, 1H), 1.87-1.66 (m, 2H), 1.54-1.48 (m, 6H), 1.48 (s, 6H), 0.87 (d, J = 7.0 Hz, 1H). LC-MS m/z: 345.2 $[M+H]^+$. HPLC: Purity (214 nm): 95.63%; t_R = 8.46 min.

_N_-(2-Cyclopropylpropan-2-yl)-7-methyl-5-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide and _N_-(2-Cyclopropylpropan-2-yl)-5-methyl-7-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide





[00323] To a solution of methyl picolinate (4.0 g, 29.20 mmol) in THF (60 mL) was added acetone (10 mL) at 0 °C. After 5 minutes, MeONa/MeOH (28%, 20 mL) was added dropwise and the mixture was stirred at RT for 2 h. The solvent was removed by concentration and the residue was acidified with 10% HCl to pH 5~6. The aqueous solution was extracted with EtOAc (100 mL x 3). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and the residue purified by silica gel chromatography (PE/EA= 10:1) to give (*Z*)-4-hydroxy-4-(pyridin-2-yl)but-3-en-2-one (3.0 g, 84%).

[00324] To a mixture of (*Z*)-4-hydroxy-4-(pyridin-2-yl)but-3-en-2-one (1.43 g, 9.20 mmol) in AcOH (20 mL) was added ethyl 3-amino-1*H*-pyrazole-4-carboxylate (1.5 g, 9.20 mmol) and the mixture was stirred at 110 °C for 2 h and then concentrated *in vacuo*. The residue was triturated in a mixed solvent of petroleum ether and EtOAc (10:1, 30 mL) and collected by filtration to give a mixture of ethyl 5-methyl-7-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate and ethyl 7-methyl-5-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (2.5 g, 87%) as a white solid. LC-MS m/z: 283.1 $[M+H]^+$. t_R = 1.74 min & 1.86 min.

[00325] Following general procedure B, the mixture of ethyl 5-methyl-7-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate and ethyl 7-methyl-5-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (collectively 1.0 g, 3.54 mmol) afforded a mixture of 5-methyl-7-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid and 7-methyl-5-(pyridin-2-

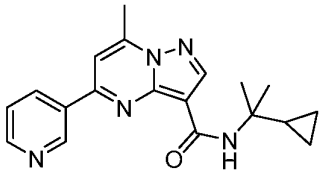
yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (800 mg, 89%) as a white solid. LC-MS m/z: 255.1 $[M+H]^+$. t_R = 1.15 min & 1.20 min.

[00326] Following general procedure A, a mixture of 5-methyl-7-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid and 7-methyl-5-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (100 mg, 0.4 mmol) and 2-cyclopropylpropan-2-amine afforded *N*-(2-cyclopropylpropan-2-yl)-7-methyl-5-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide (8.1 mg, 25.6 %) and *N*-(2-cyclopropylpropan-2-yl)-5-methyl-7-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (26.1 mg, 25.6 %) as pale white solids.

[00327] *N*-(2-Cyclopropylpropan-2-yl)-7-methyl-5-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.81 (d, J = 4.0 Hz, 1H), 8.57 (s, 1H), 8.48 (d, J = 8.0 Hz, 1H), 8.14 (d, J = 7.0 Hz, 1H), 8.13 (s, 1H), 8.10 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 7.62 (ddd, J = 8.0 Hz, 5.0 Hz, 1.0 Hz, 1H), 2.89 (s, 3H), 1.47-1.44 (m, 1H), 1.40 (s, 6H), 0.52-0.50 (m, 4H). LC-MS m/z: 336.1 $[M+H]^+$. HPLC: Purity (254 nm): 96.71%; t_R = 10.58 min.

[00328] *N*-(2-Cyclopropylpropan-2-yl)-5-methyl-7-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.93 (d, J = 8.0 Hz, 1H), 8.87 (d, J = 3.5 Hz, 1H), 8.55 (s, 1H), 8.17 (s, 1H), 8.12 (td, J = 8.0 Hz, 1.5 Hz, 1H), 7.82 (s, 1H), 7.68 (ddd, J = 8.0 Hz, 5.0 Hz, 1.0 Hz, 1H), 2.74 (s, 3H), 1.38 (s, 6H), 1.36-1.34 (m, 1H), 0.48 (d, J = 7.5 Hz, 4H). LC-MS m/z: 336.1 $[M+H]^+$. HPLC: Purity (254 nm): 98.73%; t_R = 10.77 min.

_N_-(2-Cyclopropylpropan-2-yl)-7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



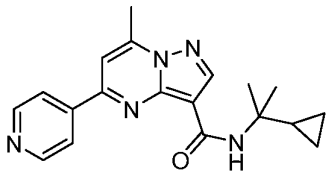
[00329] Following general procedure D, ethyl 5-chloro-7-methylpyrazolo[1,5-a]pyrimidine-3-carboxylate (500 mg, 2.1 mmol) and pyridin-3-ylboronic acid afforded ethyl 7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxylate (425 mg, 71%) as a yellow solid. LC-MS m/z: 283.1 $[M+H]^+$. Purity (214 nm): > 90%; t_R = 1.51 min.

[00330] Following general procedure B, ethyl 7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (425 mg, 1.5 mmol) afforded 7-methyl-5-(pyridin-3-

yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (362 mg, 95%). LC-MS m/z: 255.0 $[M+H]^+$, Purity (254 nm): > 95%; t_R = 1.24 min.

[00331] Following general procedure A, 7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (36 mg, 0.14 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (15 mg, 32%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.43 (s, 1H), 8.75 (d, J = 4.8 Hz, 1 H), 8.56 (d, J = 9.6 Hz, 1 H), 8.54 (s, 1 H), 8.13 (s, 1 H), 7.94 (s, 1 H), 7.64 (dd, J = 8.0 Hz, 4.0 Hz, 1 H), 2.84 (s, 3H), 1.39-1.36 (m, 1H), 1.36 (s, 6H), 0.48-0.46 (m, 4H). LC-MS m/z: 336.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.37 min.

<u>*N*-(2-Cyclopropylpropan-2-yl)-7-methyl-5-(pyridin-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide</u>

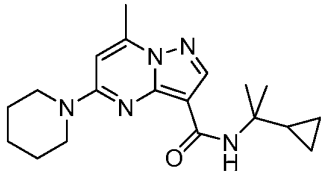


[00332] Following general procedure D, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (200 mg, 0.84 mmol) and pyridin-4-ylboronic afforded ethyl 7-methyl-5-(pyridin-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (170 mg, 72%) as a white solid. LC-MS m/z: 283.1 $[M+H]^+$.

[00333] Following general procedure B, ethyl 7-methyl-5-(pyridin-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (170 mg, 0.6 mmol) afforded 7-methyl-5-(pyridin-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (140 mg, 92%) as a white solid. LC-MS m/z: 255.1 $[M+H]^+$.

[00334] Following general procedure A, 7-methyl-5-(pyridin-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.16 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (17 mg, 31%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.85 (d, J = 6.0 Hz, 2H), 8.60 (s, 1H), 8.17 (d, J = 5.5 Hz, 2H), 8.11 (s, 1H), 8.00 (s, 1H), 2.88 (s, 3H), 1.45-1.40 (m, 1H), 1.39 (s, 6H), 0.50-0.49 (m, 4H). LC-MS m/z: 336.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.23 min.

N-(2-Cyclopropylpropan-2-yl)-7-methyl-5-(piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

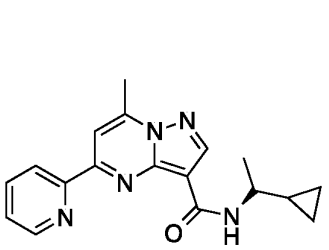


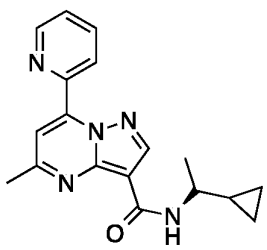
[00335] Following general procedure G, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (118 mg, 0.49 mmol) and piperidine afforded ethyl 7-methyl-5-(piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (120 mg, 85%) as a yellow solid. LC-MS m/z: 289.1 $[M+H]^+$.

[00336] Following general procedure B, ethyl 7-methyl-5-(piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (120 mg, 0.4 mmol) afforded 7-methyl-5-(piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (98 mg, 92%) as a white solid. LC-MS m/z: 261.2 $[M+H]^+$.

[00337] Following general procedure A, 7-methyl-5-(piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (35 mg, 0.13 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (12 mg, 27%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.10 (s, 1H), 7.88 (s, 1H), 6.84 (s, 1H), 3.72 (t, J = 5.0 Hz, 4H), 2.59 (s, 3H), 1.70-1.66 (m, 2H), 1.60-1.58 (m, 4H), 1.30 (s, 6H), 1.29-1.27 (m, 1H), 0.39-0.36 (m, 4H). LC-MS m/z: 342.3 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.73 min.

(*S*)-*N*-(1-Cyclopropylethyl)-7-methyl-5-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide and (*S*)-*N*-(1-Cyclopropylethyl)-5-methyl-7-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide





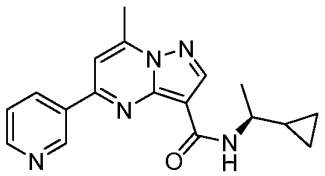
[00338] Following general procedure A, a mixture of 5-methyl-7-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid and 7-methyl-5-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-

carboxylic acid (100 mg, 0.39 mmol) and (*S*)-1-cyclopropylethan-1-amine afforded (*S*)-*N*-(1-cyclopropylethyl)-7-methyl-5-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (21.6 mg, 17%) and (*S*)-*N*-(1-cyclopropylethyl)-5-methyl-7-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (57.5 mg, 46%) as white solids.

[00339] (*S*)-*N*-(1-Cyclopropylethyl)-7-methyl-5-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide: ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.77 (d, J = 5.2 Hz, 1H), 8.60 (s, 1H), 8.51 (d, J = 7.6 Hz, 1H), 8.15 (s, 1H), 8.05 (td, J = 8.0 Hz, 1.6 Hz, 1H), 7.57 (ddd, J = 7.6 Hz, 4.8 Hz, 0.8 Hz, 1H), 3.72-3.65 (m, 1H), 2.93 (s, 3H), 1.41 (d, J = 6.8 Hz, 3H), 1.21-1.12 (m, 1H), 0.68-0.55 (m, 2H), 0.52-0.46 (m, 1H), 0.43-0.37 (m, 1H). LC-MS m/z: 322.1 $[M+H]^+$. HPLC: Purity (214 nm): 95.44%; t_R = 7.95 min.

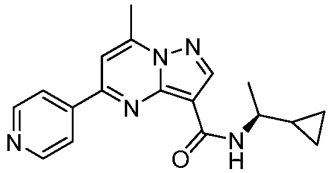
[00340] (*S*)-*N*-(1-Cyclopropylethyl)-5-methyl-7-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (d, J = 8.0 Hz, 1H), 8.87 (d, J = 4.8 Hz, 1H), 8.60 (s, 1H), 8.15 (d, J = 8.0 Hz, 1H), 8.11 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 7.68 (ddd, J = 7.6 Hz, 4.8 Hz, 0.8 Hz, 1H), 3.67-3.59 (m, 1H), 2.76 (s, 3H), 1.27 (d, J = 6.0 Hz, 3H), 1.08-1.01 (m, 1H), 0.53-0.42 (m, 2H), 0.39-0.34 (m, 1H), 0.31-0.25 (m, 1H). LC-MS m/z: 322.2 $[M+H]^+$. HPLC: Purity (254 nm): 98.89%; t_R = 8.09 min.

(*S*)-*N*-(1-Cyclopropylethyl)-7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



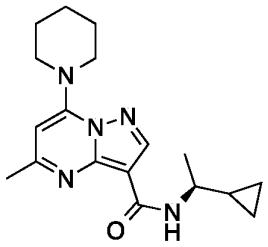
[00341] Following general procedure A, 7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (36 mg, 0.14 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (18 mg, 40%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.43 (s, 1H), 8.76 (d, J = 4.0 Hz, 1 H), 8.59-8.58 (m, 2 H), 8.11 (d, J = 6.7 Hz, 1 H), 7.96 (s, 1 H), 7.66 (dd, J = 8.0 Hz, 4.8 Hz, 1 H), 3.60 (m, J = 6.8 Hz, 1 H), 2.85 (s, 3H), 1.28 (d, J = 6.4 Hz, 3H), 1.11-1.07 (m, 1H), 0.52-0.29 (m, 4H). LC-MS m/z: 322.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 6.78 min.

(*S*)-*N*-(1-Cyclopropylethyl)-7-methyl-5-(pyridin-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



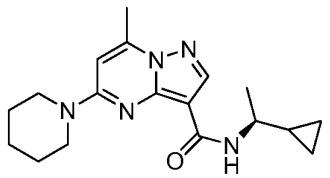
[00342] Following general procedure A, 7-methyl-5-(pyridin-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.16 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (6.7 mg, 13%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.86 (dd, J = 4.5 Hz, 1.5 Hz, 2H), 8.64 (s, 1H), 8.19 (dd, J = 4.5 Hz, 1.5 Hz, 2H), 8.12 (d, J = 4.0 Hz, 1H), 8.02 (s, 1H), 3.64-3.59 (m, 1H), 2.88 (s, 3H), 1.30 (d, J = 6.5 Hz, 3H), 1.15-1.12 (m, 1H), 0.54-0.48 (m, 2H), 0.40-0.33 (m, 2H). LC-MS m/z: 322.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 6.67 min.

(*S*)-*N*-(1-Cyclopropylethyl)-5-methyl-7-(piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



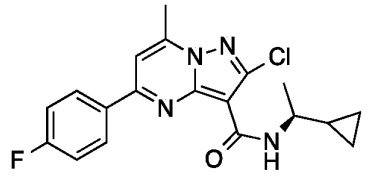
[00343] Following general procedure A, 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (50 mg, 0.19 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (13 mg, 21%) as a pale white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.38 (s, 1H), 6.40 (s, 1H), 3.83-3.82 (m, 4H), 3.72-3.68 (m, 1H), 2.58 (s, 3H), 1.82-1.78 (m, 6H), 1.36 (d, J = 7.0 Hz, 3H), 1.05-1.03 (m, 1H), 0.58-0.52 (m, 2H), 0.44-0.42 (m, 1H) ,0.32-0.30 (m, 1H). LC-MS m/z: 328.3 $[M+H]^+$. HPLC: Purity (254 nm): >99%; t_R = 10.18 min.

(*S*)-*N*-(1-Cyclopropylethyl)-7-methyl-5-(piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00344] Following general procedure A, 7-methyl-5-(piperidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (35 mg, 0.13 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (17 mg, 39%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.13 (s, 1H), 7.96 (d, J = 5.0 Hz, 1H), 6.86 (s, 1H), 3.73 (t, J = 5.0 Hz, 4H), 3.57-5.36 (m, 1H), 2.60 (s, 3H), 1.70-1.67 (m, 2H), 1.61-1.58 (m, 4H), 1.19 (d, J = 6.5 Hz, 3H), 0.95-0.94 (m, 1H), 0.46-0.39 (m, 2H) 0.30-0.23 (m, 2H). LC-MS m/z: 328.3 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.18 min.

(*S*)-2-Chloro-*N*-(1-cyclopropylethyl)-5-(4-fluorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide

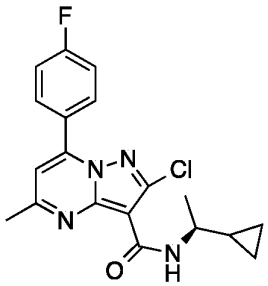


[00345] To a stirred solution of ethyl 5-amino-3-chloro-1*H*-pyrazole-4-carboxylate (200 mg, 1.05 mmol) in HOAc (5 mL) was added 1-(4-fluorophenyl)butane-1,3-dione (380 mg, 2.11 mmol) at 110 °C. The solution was stirred for approximately 4 h at this temperature, cooled and concentrated *in vacuo*. The resulting residue was dissolved in MeOH (2 mL) and purified by reverse-phase chromatography (MeCN\1% TFA) to afford ethyl 2-chloro-5-(4-fluorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (80 mg, 22%) and ethyl 2-chloro-7-(4-fluorophenyl)-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (200 mg, 57%) as white solids. **7-Me Product**: LC-MS: m/z: 333.0 $[M+H]^+$; Purity (214 nm): >92%; t_R = 1.99 min. **5-Me Product**: LC-MS: m/z: 333.0 $[M+H]^+$; Purity (214 nm): >99%; t_R = 1.91 min.

[00346] Following general procedure B, ethyl 2-chloro-7-(4-fluorophenyl)-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (80 mg, 0.24 mmol) afforded 2-chloro-7-(4-fluorophenyl)-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (60 mg, 82%) as a white solid. LC-MS: m/z: 305.0 $[M+H]^+$; Purity (214 nm): > 92%; t_R = 1.69 min.

[00347] Following general procedure A, 2-chloro-7-(4-fluorophenyl)-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.1 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (15.6 mg, 43%) as white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.34-8.30 (m, 3H), 7.97 (s, 1H), 7.49 (t, J = 8.5 Hz, 2H), 3.61-3.33 (m, 1H), 2.80 (s, 3H), 1.28 (d, J = 6.5 Hz, 3H), 1.12-1.07 (m, 1H), 0.54-0.47 (m, 2H), 0.39-0.31 (m, 2H). LC-MS m/z: 372.1 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 9.21 min.

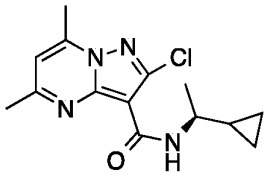
(*S*)-2-Chloro-*N*-(1-cyclopropylethyl)-7-(4-fluorophenyl)-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00348] Following general procedure B, ethyl 2-chloro-7-(4-fluorophenyl)-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (75 mg, 0.23 mmol) afforded 2-chloro-7-(4-fluorophenyl)-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (47 mg, 69%) as a white solid. LC-MS: m/z: 305.0 $[M+H]^+$; Purity (214 nm): > 92%; t_R = 1.67 min.

[00349] Following general procedure A, 2-chloro-7-(4-fluorophenyl)-5-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (37 mg, 0.12 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (26 mg, 59%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.31 (d, J = 8.0 Hz, 1H), 8.15-8.12 (m, 2H), 7.52-7.49 (m, 2H), 7.48 (s, 1H), 3.66-3.59 (m, 1H), 2.70 (s, 3H), 1.26 (d, J = 7.0 Hz, 3H), 1.05-1.07 (m, 1H), 0.50-0.44 (m, 2H), 0.38-0.25 (m, 2H). LC-MS m/z: 372.1 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 9.19 min.

(*S*)-2-Chloro-*N*-(1-cyclopropylethyl)-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide

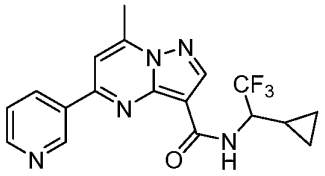


[00350] A solution of ethyl 5-amino-3-chloro-1*H*-pyrazole-4-carboxylate (80 mg, 0.84 mmol) and pentane-2,4-dione (84 mg, 0.84 mmol) in AcOH (1 ml) was stirred at 100 °C for 2 h until the reaction was complete (LC-MS). The acetic acid was removed *in vacuo* and the residue was purified by silica gel column chromatography (PE/EA: 2/1) to give ethyl 2-chloro-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 94%) as a white solid. LC-MS m/z: 253.9 $[M+H]^+$. LC-MS: Purity (214 nm): 95%; t_R = 1.66 min.

[00351] Following general procedure B, ethyl 2-chloro-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 0.4 mmol) afforded 2-chloro-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid as a white solid (70 mg, 78.7%). LC-MS m/z: 226.1 $[M+H]^+$. LCMS: Purity (214 nm): 93.51%; t_R = 0.65 min.

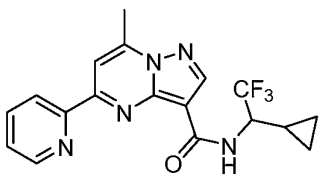
[00352] Following general procedure A, 2-chloro-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.13 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (22.6 mg, 57.9%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, *J* =7.0 Hz, 1H), 6.74 (s, 1H), 3.78-3.74 (m, 1H), 2.76 (s, 3H), 2.65 (s, 3H), 1.34 (d, *J* =6.5 Hz, 3H), 1.00-0.97 (m, 1H), 0.54-0.44 (m, 3H), 0.32-0.29 (m, 1H). LC-MS m/z: 293.1 $[M+H]^+$. LCMS: Purity (214 nm): >99%; t_R = 1.88 min.

<u>*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide</u>



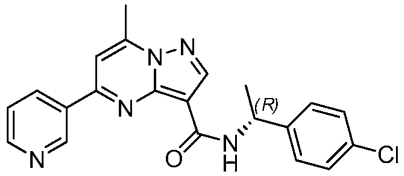
[00353] Following general procedure A, 7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.16 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine afforded the title compound (14 mg, 23%) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) *δ* 9.42 (d, *J* = 1.5 Hz, 1H), 8.77 (dd, *J* = 5.0 Hz, 1.5 Hz, 1H), 8.67 (s, 1H), 8.65 (tt, *J* = 8.5 Hz, 2.0 Hz, 1H), 7.84 (s, 1H), 7.70 (ddd, *J* = 8.0 Hz, 5.0 Hz, 0.5 Hz, 1H), 4.48-4.41 (m, 1H), 2.98 (s, 3H), 1.37-1.30 (m, 1H), 0.82-0.77 (m, 1H), 0.70-0.65 (m, 1H), 0.63-0.58 (m, 1H), 0.54-0.49 (m, 1H). LC-MS m/z: 376.2 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 9.23 min

<u>*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide</u>



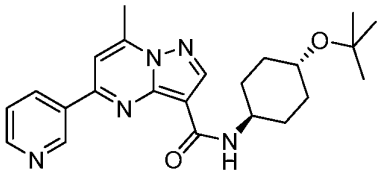
[00354] Following general procedure A, 7-methyl-5-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (50 mg, 0.20 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine afforded the title compound (36 mg, 48%) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.80 (d, J = 4.0 Hz, 1H), 8.66 (s, 1H), 8.48 (d, J = 7.5 Hz, 1H), 8.21 (s, 1H), 8.06 (td, J = 7.5 Hz, 1.5 Hz, 1H), 7.59 (ddd, J = 7.5 Hz, 5.0 Hz, 1.0 Hz, 1H), 4.49-4.42 (m, 1H), 2.97 (s, 3H), 1.41-1.34 (m, 1H), 0.83-0.78 (m, 1H), 0.71-0.66 (m, 1H), 0.64-0.59 (m, 1H), 0.57-0.52 (m, 1H). LC-MS m/z: 376.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 10.51 min.

***(R)*-*N*-(1-(4-Chlorophenyl)ethyl)-7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



[00355] Following general procedure A, 7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (25 mg, 0.18 mmol) and (*R*)-1-(4-chlorophenyl)ethanamine afforded the title compound (8.7 mg, 22%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4): δ 9.37 (dd, J = 2.5 Hz, 1.0 Hz, 1H), 8.75 (dd, J = 10.0 Hz, 2.0 Hz, 1H), 8.62 (s, 1H), 8.51 (ddd, J = 8.0 Hz, 2.5 Hz, 1.5 Hz, 1H), 7.79 (d, J = 1.0 Hz, 1H), 7.65 (ddd, J = 8.0 Hz, 5.0 Hz, 1.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 5.28 (q, J = 6.5 Hz, 1H), 2.95 (d, J = 0.5 Hz, 3H), 1.69 (d, J = 7.0 Hz, 3H). LC-MS m/z: 392.0 $[M+H]^+$. HPLC Purity (214 nm): 99%; t_R = 7.80 min.

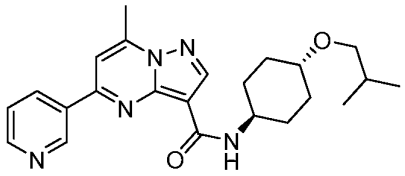
***N*-((*1R,4R*)-4-*tert*-Butoxycyclohexyl)-7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



[00356] Following general procedure A, 7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.15 mmol) and (*1R,4R*)-4-tert-butoxycyclohexanamine afforded the title compound (20 mg, 33%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (d, J = 2.0 Hz, 1H), 8.82 (dd, J = 4.5 Hz, 2.0 Hz, 1H), 8.73 (s, 1H),

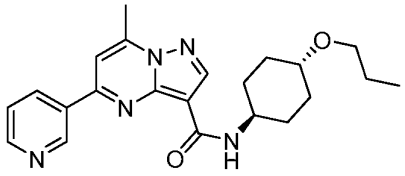
8.34 (tt, J = 7.5 Hz, 2.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.56 (dd, J = 7.5 Hz, 4.5 Hz, 1H), 7.30 (s, 1H), 4.04-3.98 (m, 1H), 3.50-3.46 (m, 1H), 2.96 (s, 3H), 2.24-2.21 (d, 2H), 1.92-1.90 (m, 2H), 1.56-1.53 (m, 2H), 1.44-1.40 (m, 2H), 1.24 (s, 9H). LC-MS m/z: 408.3 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 7.44 min.

***N-((1R,4R)*-4-Isobutoxycyclohexyl)-7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



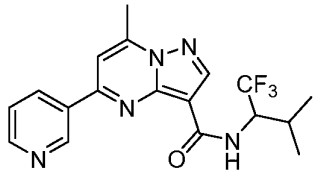
[00357] Following general procedure A, 7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.15 mmol) and (*1R,4R*)-4-isobutoxycyclohexanamine afforded the title compound (16 mg, 26%) as a yellow solid. ^{1}H NMR (500 MHz,$CDCl_3$) δ 9.36 (t, J = 1.0 Hz, 1H), 8.82 (dd, J = 4.5 Hz, 1.0 Hz, 1H), 8.74 (s, 1H), 8.35 (tt, J = 7.5 Hz, 2.0 Hz, 1H), 8.03 (d, J = 7.0 Hz, 1H), 7.55 (ddd, J = 8.0 Hz, 5.0 Hz, 0.5 Hz, 1H), 7.31 (d, J = 1.0 Hz, 1H), 4.12-4.06 (m, 1H), 3.38-3.28 (m, 1H), 3.25 (d, J = 6.0 Hz, 2H), 2.96 (d, J = 0.5 Hz, 3H), 2.26-2.23 (d, 2H), 2.12-2.08 (m, 2H), 1.54-1.50 (m, 2H), 1.44-1.40 (m, 2H), 0.94 (d, J = 6.5 Hz, 6H). LC-MS m/z: 408.3 $[M+H]^+$. HPLC: Purity (254 nm): >99%; t_R = 8.07 min.

7-Methyl-*N*-((*1R,4R*)-4-propoxycyclohexyl)-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



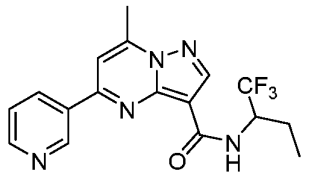
[00358] Following general procedure A, 7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (25 mg, 0.18 mmol) and (*1R,4R*)-4-propoxycyclohexanamine afforded the title compound (9 mg, 22%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4): δ 9.42 (dd, J = 2.5 Hz, 1.0 Hz, 1H), 8.77 (dd, J = 5.0 Hz, 1.5 Hz, 1H), 8.65 (ddd, J = 7.5 Hz, 2.0 Hz, 1.5 Hz, 1H), 8.63 (s, 1H), 7.80 (d, J = 0.5 Hz, 1H), 7.70 (ddd, J = 7.5 Hz, 5.0 Hz, 1.0 Hz, 1H), 4.01-3.97 (m,1H), 3.51 (t, J = 6.5 Hz, 2H), 3.45-3.41 (m, 1H), 2.95 (d, J = 0.5 Hz, 3H), 2.22-2.13 (m,4H), 1.65-1.59 (m, 2H), 1.57-1.47 (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 = 7.35 min

7-Methyl-5-(pyridin-3-yl)-*N*-(1,1,1-trifluoro-3-methylbutan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



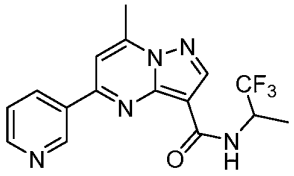
[00359] Following general procedure A, 7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.16 mmol) and 1,1,1-trifluoro-3-methylbutan-2-amine afforded the title compound (8 mg, 13%) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 9.40 (dd, J = 2.5 Hz, 0.5 Hz, 1H), 8.76 (dd, J = 5.0 Hz, 2.0 Hz, 1H), 8.69 (s, 1H), 8.63 (ddd, J = 8.0 Hz, 2.5 Hz, 2.0 Hz, 1H), 7.84 (d, J = 1.0 Hz, 1H), 7.68 (ddd, J = 8.0 Hz, 5.0 Hz, 1.0 Hz, 1H), 4.92-4.85 (m, 1H), 2.98 (d, J = 0.5 Hz, 3H), 2.424-2.37 (m, 1H), 1.17 (d, J = 6.5 Hz, 3H), 1.09 (d, J = 6.5 Hz, 3H). LC-MS m/z: 377.9 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 7.79 min.

7-Methyl-5-(pyridin-3-yl)-*N*-(1,1,1-trifluorobutan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



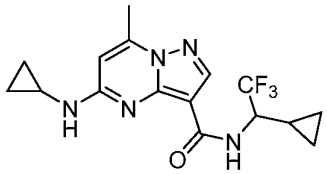
[00360] Following general procedure A, 7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (50 mg, 0.20 mmol) and 1,1,1-trifluorobutan-2-amine afforded the title compound (20 mg, 28%) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 9.40 (dd, J = 2.0 Hz, 1H), 8.76 (dd, J = 5.0 Hz, 1.5 Hz, 1H), 8.68 (s, 1H), 8.64 (ddd, J = 8.0 Hz, 2.0 Hz, 1.5 Hz, 1H), 7.84 (d, J = 1.5 Hz, 1H), 7.69 (ddd, J = 8.0 Hz, 5.0 Hz, 0.5 Hz, 1H), 4.87-4.80 (m, 1H), 2.98 (s, 3H), 2.12-2.04 (m, 1H), 1.86-1.76 (m, 1H), 1.12 (t, J = 7.5 Hz, 3H). LC-MS m/z: 364.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 9.11 min.

7-Methyl-5-(pyridin-3-yl)-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00361] Following general procedure A, 7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.16 mmol) and 1,1,1-trifluoropropan-2-amine afforded the title compound (14 mg, 26%) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 9.41 (d, J = 2.0 Hz, 1H), 8.77 (dd, J = 5.0 Hz, 1.5 Hz, 1H), 8.68 (s, 1H), 8.65 (tt, J = 8.5 Hz, 2.0 Hz, 1H), 7.84 (s, 1H), 7.70 (dd, J = 8.0 Hz, 5.0 Hz, 1H), 5.03-4.97 (m, 1H), 2.97 (s, 3H), 1.55 (d, J = 7.5 Hz, 3H). LC-MS m/z: 350.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 8.73 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(cyclopropylamino)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



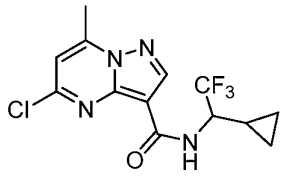
[00362] A solution of ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (98 mg, 0.41 mmol) in 5 mL of cyclopropanamine was stirred at 50 °C for 2 hr, then cooled and concentrated *in vacuo*. The resulting residue was purified by prep-TLC (PE/EA = 1/1) to afford ethyl 5-(cyclopropylamino)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (90 mg, 84%) as a yellow solid. LC-MS m/z: 261.1 $[M+H]^+$.

[00363] Following general procedure B, ethyl 5-(cyclopropylamino)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (90 mg, 0.35 mmol) afforded 5-(cyclopropylamino)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 49%) as a white solid. LC-MS m/z: 233.0 $[M+H]^+$.

[00364] Following general procedure A, 5-(cyclopropylamino)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.13 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine afforded the title compound (27 mg, 45%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.66 (s, 1H), 8.26 (s, 1H), 8.18 (s, 1H), 6.22 (s, 1H), 4.41-4.36 (m, 1H),

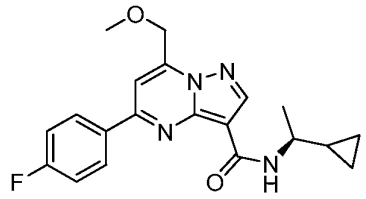
2.72-2.66 (m, 1H), 2.56 (s, 3H), 1.19-1.11 (m, 1H), 0.78 (d, J = 6.0 Hz, 2H), 0.67-0.61 (m, 1H), 0.58-0.46 (m, 4H), 0.39-0.32 (m, 1H). LC-MS m/z: 354.1 $[M+H]^+$. HPLC Purity (214 nm): 92%; t_R = 7.07 min.

5-Chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00365] Following general procedure A, 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (50 mg, 0.23 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine afforded the title compound (15.7 mg, 20%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 8.07 (d, J = 9.6 Hz, 1H), 7.44 (s, 1H), 4.42-4.32 (m, 1H), 2.78 (s, 3H), 1.26-1.20 (m, 1H), 0.69-0.65 (m, 1H), 0.60-0.54 (m, 2H), 0.38-0.33 (m, 1H). LC-MS m/z: 333.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.41 min.

(*S*)-*N*-(1-Cyclopropylethyl)-5-(4-fluorophenyl)-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00366] A mixture of ethyl 5-hydroxy-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (1.2 g, 4.8 mmol) in 15 mL of $PhPOCl_2$ was stirred at 80 °C for 4 h under N_2, cooled to RT, and poured into 250 mL of ice-water. The resulting mixture was basified to pH 8, and extracted with EA (200 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 pre-TLC plate to afford ethyl 5-chloro-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (40 mg, 3%). LC-MS m/z: 270.3 $[M+H]^+$.

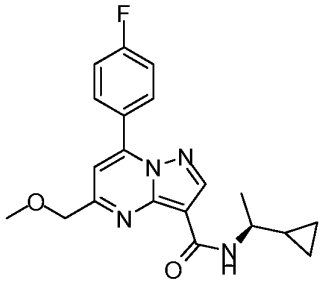
[00367] Following general procedure D, ethyl 7-chloro-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (150 mg, 0.56 mmol) and 4-fluorophenyl boronic acid afforded

ethyl 5-(4-fluorophenyl)-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (168 mg, 75%) as a yellow solid. LC-MS m/z: 330.1 $[M+H]^+$. t_R = 1.56 min.

[00368] Following general procedure B, ethyl 5-(4-fluorophenyl)-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (80 mg, 0.24 mmol) at 30 °C afforded 5-(4-fluorophenyl)-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid sodium salt (72 mg, 99%) as an orange solid. LC-MS m/z: 302.0 $[M+H]^+$. t_R = 1.76 min.

[00369] Following general procedure A, 7-(4-fluorophenyl)-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (35 mg, 0.12 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (16.4 mg, 34%) as a pale yellow solid. ^1H NMR (500 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.36 (dd, J = 9.0 Hz, 5.5 Hz, 2H), 8.14 (d, J = 7.5 Hz, 1H), 7.76 (s, 1H), 7.49 (t, J = 9.0 Hz, 2H), 5.04 (s, 2H), 3.62-3.59 (m, 1H), 3.56 (s, 3H), 1.29 (d, J = 6.5 Hz, 3H), 1.11-1.10 (m, 1H), 0.54-0.48 (m, 2H), 0.38-0.32 (m, 2H). LC-MS m/z: 369.1 $[M+H]^+$. HPLC: Purity (254 nm): 96%; t_R = 9.74 min.

(*S*)-*N*-(1-Cyclopropylethyl)-7-(4-fluorophenyl)-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00370] To a solution of methyl 4-methoxy-3-oxobutanoate (15.0 g, 100 mmol) in EtOH (20 mL) was added conc. H_2SO_4 (1 drop, cat.) at RT under a N_2 atmosphere. The mixture was heated to 80 °C, followed by the addition of $CH(OEt)_3$ (15.2 g, 100 mmol) dropwise, stirred at 80 °C for 1 h, and concentrated *in vacuo* to afford methyl 3-ethoxy-4-methoxybut-2-enoate (21 g, crude) as yellow oil. LC-MS m/z: 175.1 $[M+H]^+$. LCMS: t_R = 1.72 min.

[00371] To a solution of methyl 3-ethoxy-4-methoxybut-2-enoate (3.5 g, 18.60 mmol) in DMF (15 mL) was added ethyl 5-amino-1*H*-pyrazole-4-carboxylate (3.0g, 19.40mmol) and Cs_2CO_3 (7.3g, 22.30mmol) . The mixture was stirred at 110 °C for 4 h, and filtrated. The filtrate was purified by prep-HPLC (10 mM NH_4HCO_3, CH_3CN : H_2O = 5% - 95%) to afford give ethyl 7-hydroxy-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (3.3 g, 68%) and

ethyl 5-hydroxy-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (0.83 g, 17%) as yellow solids.

[00372] Ethyl 7-hydroxy-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate: LC-MS m/z: 252.1 $[M+H]^+$. LCMS: t_R = 1.45 min.

[00373] Ethyl 5-hydroxy-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate: LC-MS m/z: 252.1 $[M+H]^+$. LCMS: t_R = 1.37 min.

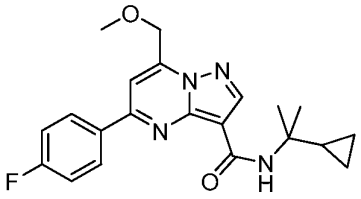
[00374] The mixture of ethyl 7-hydroxy-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (200 mg, 0.80mmol) in phenylphosphonic dichloride (2.5 mL) was stirred at 110 ^oC for 3 hours, poured into ice and extracted with EA (50 mL x 3). The organic phases were washed with $NaHCO_3$ aqueous solution (100 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford ethyl 7-chloro-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (200 mg, 94%) as a brown solid. LC-MS m/z: 270.1 $[M+H]^+$. LCMS: t_R = 1.75 min.

[00375] Following general procedure D, ethyl 7-chloro-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (200 mg, 0.74 mmol) and 4-fluorophenyl boronic acid afforded ethyl 7-(4-fluorophenyl)-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (80 mg, 33%) as a yellow solid. LC-MS m/z: 330.1 $[M+H]^+$. t_R = 1.58 min.

[00376] Following general procedure B, ethyl 7-(4-fluorophenyl)-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (80 mg, 0.24 mmol) afforded 7-(4-fluorophenyl)-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid sodium salt (72 mg, 98%) as a yellow solid. LC-MS m/z: 302.1 $[M+H]^+$. LCMS: t_R = 1.64 min.

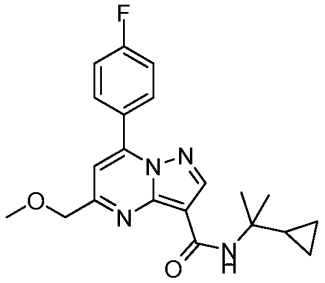
[00377] Following general procedure A, 7-(4-fluorophenyl)-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (24 mg, 0.08 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound as a yellow solid (10.3 mg, 35%). ^1H NMR (500 MHz, MeOD-d_4) δ 8.57 (s, 1H), 8.38 (dd, J = 8.5 Hz, 5.5 Hz, 2H), 8.13 (d, J = 8.0 Hz, 1H), 7.75 (s, 1H), 7.48 (t, J = 8.5 Hz, 2H), 5.04 (s, 2H), 3.62-3.59 (m, 1H), 3.56 (s, 3H), 1.29 (d, J = 6.5 Hz, 3H), 1.11-1.10 (m, 1H), 0.54-0.48 (m, 2H), 0.38-0.32 (m, 2H). LC-MS m/z: 369.1 $[M+H]^+$. HPLC: Purity (254 nm): 99%; t_R = 9.61 min.

***N*-(2-Cyclopropylpropan-2-yl)-5-(4-fluorophenyl)-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



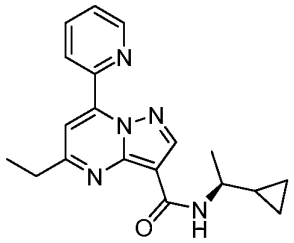
[00378] Following general procedure A, 5-(4-fluorophenyl)-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (36 mg, 0.12 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (9 mg, 20%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4): δ 8.52 (s, 1H), 8.46 (brs, 1H), 8.30 (dd, J = 9.0 Hz, 5.5 Hz, 1H), 7.71 (s, 1H), 7.33 (t, J = 9.0 Hz, 1H), 5.05 (s, 2H), 3.67 (s, 3H) 1.48 (s, 6H), 1.48-1.42 (m, 1H), 0.60-0.56 (m, 4H). LC-MS m/z: 383.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 10.29 min.

***N*-(2-Cyclopropylpropan-2-yl)-7-(4-fluorophenyl)-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



[00379] Following general procedure A, 7-(4-fluorophenyl)-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (24 mg, 0.08 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (12.7 mg, 42%) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.52 (s, 1H), 8.46 (s, 1H), 8.30 (dd, J = 8.5 Hz, 5.5 Hz, 2H), 7.72 (s, 1H), 7.35 (t, J = 8.5 Hz, 2H), 5.06 (s, 2H), 3.68 (s, 3H), 1.48 (s, 6H), 1.46-1.41 (m, 1H), 0.59-0.56 (m, 4H). LC-MS m/z: 383.1 $[M+H]^+$. HPLC: Purity (254 nm): 97%; t_R = 10.13 min.

(*S*)-*N*-(1-Cyclopropylethyl)-5-ethyl-7-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00380] Into the stirred solution of methyl 3-ethoxypent-2-enoate (10.0 g, 63.3 mmol) and ethyl 5-amino-1*H*-pyrazole-4-carboxylate (9.8 g, 63.3 mmol) in DMF (200 mL) was added Cs_2CO_3 (61.7 g, 189.9 mmol). The mixture was stirred at 100 °C for 24 h, and concentrated *in vacuo*. The residue was treated with MeOH (400 mL). The solid was filtered off, and the filtrate was concentrated *in vacuo*. The residues was purified by prep-TLC (PE : EA = 1:1) to afford ethyl 5-ethyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylate (0.8 g, 5.7%) and ethyl 7-ethyl-5-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylate (1.2 g, 8.1%) as white solids.

[00381] Ethyl 5-ethyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylate: LC-MS m/z: 236.1 $[M+H]^+$. LCMS: t_R = 0.93 min.

[00382] Ethyl 7-ethyl-5-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylate: LC-MS m/z: 236.1 $[M+H]^+$. LCMS: t_R = 1.11 min.

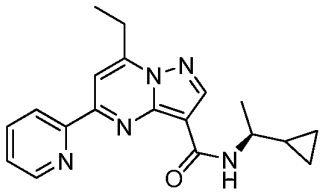
[00383] A mixture of ethyl 5-ethyl-7-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylate (0.8 g, 3.4 mmol) in phenylphosphonic dichloride (4 mL) was stirred at 100 °C for 24 h, cooled and quenched with H_2O (100 mL). The mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residues was purified by pre-TLC (PE : EA = 1 :1) to afford ethyl 7-chloro-5-ethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (450 mg, 52%) as a white solid, LC-MS m/z: 254.0 $[M+H]^+$. LCMS: t_R = 1.50 min.

[00384] Following general procedure F, ethyl 7-chloro-5-ethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (450 mg, 1.8 mmol) and 2-(tributylstannyl)pyridine afforded ethyl 5-ethyl-7-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (250 mg, 47%) as a yellow solid. LC-MS m/z: 297.1 $[M+H]^+$. LCMS: t_R = 1.26 min.

[00385] Following general procedure B, ethyl 5-ethyl-7-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (250 mg, 0.84 mmol) afforded crude 5-ethyl-7-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid sodium salt (400 mg). LC-MS m/z: 269.1 $[M+H]^+$. LCMS: t_R = 1.44 min.

[00386] Following general procedure A, 5-ethyl-7-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid sodium salt (200 mg, 0.70 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (15 mg, 6% over 2 steps) as a yellow solid ^{1}H NMR (400 MHz, MeOD-d_4): δ 8.76 (d, *J* = 4.0 Hz, 1H), 8.58 (d, *J* = 8.0 Hz, 1H), 8.49 (s, 1H), 8.04 (td, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.97 (s, 1H), 7.56 (ddd, *J* = 7.6 Hz, 4.8 Hz, 0.8 Hz, 1H), 3.74-3.67 (m, 1H), 3.21 (q, *J* = 7.2 Hz, 2H), 1.56 (t, *J* = 7.2 Hz, 3H), 1.42 (d, *J* = 6.8 Hz, 3H), 1.20-1.10 (m, 1H), 0.67-0.54 (m, 2H), 0.52-0.45 (m, 1H), 0.42-0.35 (m, 1H). LC-MS m/z: 336.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.46 min.

(*S*)-*N*-(1-Cyclopropylethyl)-7-ethyl-5-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00387] A mixture of ethyl 7-ethyl-5-hydroxypyrazolo[1,5-*a*]pyrimidine-3-carboxylate (1.2 g, 5.1 mmol) in phenylphosphonic dichloride (4 mL) was stirred at 100 °C for 24 h, cooled and quenched with H_2O (100 mL). The mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residues was purified by prep-TLC (PE : EA = 1:1) to afford ethyl 5-chloro-7-ethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (400 mg, 31%) as a white solid. LC-MS m/z: 254.0 $[M+H]^+$. LCMS: t_R = 1.51 min.

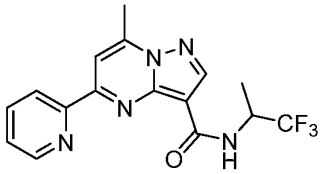
[00388] Following general procedure F, ethyl 5-chloro-7-ethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (400 mg, 1.6 mmol) and 2-(tributylstannyl)pyridine afforded ethyl 7-ethyl-5-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (200 mg, 43%) as a white solid. LC-MS m/z: 297.1 $[M+H]^+$. LCMS: t_R = 1.26 min.

[00389] Following general procedure B, ethyl 7-ethyl-5-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (200 mg, 0.67 mmol) afforded 7-ethyl-5-(pyridin-2-

yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (350 mg, contained the salts), which was used without further purification. LC-MS m/z: 269.1 $[M+H]^+$. LCMS: t_R = 1.18 min.

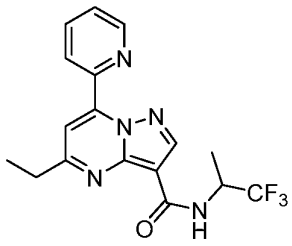
[00390] Following general procedure A, 7-ethyl-5-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid sodium salt (150 mg, 0.60 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (13 mg, 7% over 2 steps) as a white solid. ^{1}H NMR (400 MHz, MeOD-d_4): δ 8.79 (d, *J* = 4.8 Hz, 1H), 8.60 (s, 1H), 8.54 (d, *J* = 8.0 Hz, 1H), 8.17 (s, 1H), 8.07 (td, *J* = 8.0 Hz, 1.6 Hz, 1H), 7.58 (ddd, *J* = 7.6 Hz, 4.8 Hz, 0.8 Hz, 1H), 3.74-3.67 (m, 1H), 3.36 (q, *J* = 7.2 Hz, 2H), 1.55 (t, *J* = 7.2 Hz, 3H), 1.42 (d, *J* = 6.8 Hz, 3H), 1.20-1.13 (m, 1H), 0.67-0.54 (m, 2H), 0.52-0.45 (m, 1H), 0.42-0.35 (m, 1H). LC-MS m/z: 336.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.46 min.

7-Methyl-5-(pyridin-2-yl)-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



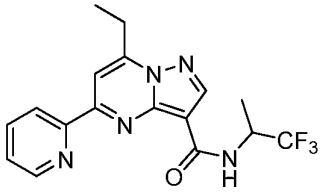
[00391] Following general procedure A, 7-methyl-5-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (35 mg, 0.14 mmol) and 1,1,1-trifluoropropan-2-amine afforded the title compound the title compound (17 mg, 35%) as a yellow solid . ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.82 (d, *J* = 4.5 Hz, 1H), 8.71 (s, 1H), 8.44 (d, *J*= 9.0 Hz, 1H), 8.42 (d, *J* = 8.0 Hz, 1H), 8.20 (s, 1H), 8.14 (td, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.64 (dd, *J* = 7.0 Hz, 5.0 Hz, 1H), 5.01-4.96 (m, 1H), 2.91 (s, 3H), 1.48 (d, *J* = 6.5 Hz, 3H). LC-MS m/z: 350.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.05 min.

5-Ethyl-7-(pyridin-2-yl)-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



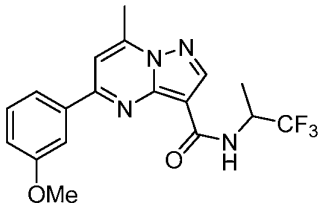
[00392] Following general procedure A, 5-ethyl-7-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid sodium salt (200 mg, 0.70 mmol) and 1,1,1-trifluoropropan-2-amine hydrochloride afforded the title compound (12 mg, 5% over 2 steps) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-d_4): δ 8.77 (d, J = 4.0 Hz, 1H), 8.54 (d, J = 8.0 Hz, 1H), 8.53 (s, 1H), 8.04 (td, J = 8.0 Hz, 1.6 Hz, 1H), 8.01 (s, 1H), 7.57 (ddd, J = 7.6 Hz, 4.8 Hz, 0.8 Hz, 1H), 5.05-4.98 (m, 1H), 3.22 (q, J = 7.6 Hz, 2H), 1.58 (t, J = 7.6 Hz, 3H), 1.54 (d, J = 6.8 Hz, 3H). LC-MS m/z: 364.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.59 min.

7-Ethyl-5-(pyridin-2-yl)-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00393] Following general procedure A, 7-ethyl-5-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid sodium salt (150 mg, 0.60 mmol) and 1,1,1-trifluoropropan-2-amine hydrochloride afforded the title compound (5 mg, 3% over 2 steps) as a white solid. ^{1}H NMR (400 MHz, MeOD-d_4): δ 8.80 (d, J = 4.4 Hz, 1H), 8.65 (s, 1H), 8.48 (d, J = 8.0 Hz, 1H), 8.20 (s, 1H), 8.07 (td, J = 8.0 Hz, 1.6 Hz, 1H), 7.59 (ddd, J = 7.6 Hz, 4.8 Hz, 0.8 Hz, 1H), 5.02-4.95 (m, 1H), 3.37 (q, J = 7.2 Hz, 2H), 1.56 (t, J = 7.2 Hz, 3H), 1.54 (d, J = 7.6 Hz, 3H). LC-MS m/z: 364.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.65 min.

5-(3-Methoxyphenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

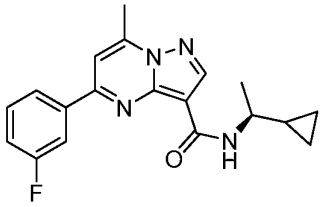


[00394] Following general procedure D, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 0.42 mmol) and 3-methoxyphenylboronic acid afforded ethyl 5-(3-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (98 mg, 75%) as a yellow solid. LC-MS m/z: 312.1 $[M+H]^+$.

[00395] Following general procedure B, ethyl 5-(3-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (90 mg, 0.29 mmol) afforded 5-(3-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (71 mg, 87%) as a white solid. LC-MS m/z: 284.1 $[M+H]^+$.

[00396] Following general procedure A, 5-(3-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.10 mmol) and 1,1,1-trifluoropropan-2-amine afforded the title compound (18 mg, 47%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.66 (s, 1H), 8.49 (d, J = 9.5 Hz, 1H), 7.97 (s, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.79 (s, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.19 (dd, J = 8.0 Hz, 2.0Hz, 1H), 5.01-4.96 (m, 1H), 3.89 (s, 3H), 2.86 (s, 3H), 1.45 (d, J = 6.5 Hz, 3H). LC-MS m/z: 379.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.58 min.

(*S*)-*N*-(1-Cyclopropylethyl)-5-(3-fluorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



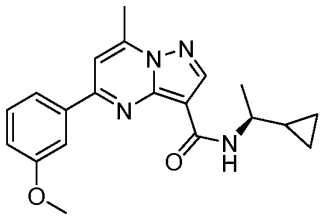
[00397] Following general procedure D, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 0.42 mmol) and 3-fluorophenylboronic acid afforded ethyl 5-(3-fluorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (90 mg, 72%) as a brown solid. LC-MS m/z: 300.1 $[M+H]^+$. Purity (214 nm): > 90%; t_R = 2.00 min.

[00398] Following general procedure B, ethyl 5-(3-fluorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (90 mg, 0.3 mmol) afforded 5-(3-fluorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (70 mg, 98%) as a brown solid. LC-MS m/z: 272.0 $[M+H]^+$. LC-MS Purity (214 nm): > 99%; t_R = 1.66 min.

[00399] Following general procedure A, 5-(3-fluorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.11 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (21 mg, 56%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.14 (t, J = 8.0 Hz, 2H), 8.09 (dt, J = 10.0 Hz, 2.5 Hz, 1H), 7.96 (s, 1H), 7.69 (ddd, J = 14.0 Hz, 8.0 Hz, 2.0 Hz, 1 H), 7.47 (td, J = 8.0 Hz, 2.5 Hz, 1H), 3.65-3.61(m, 1H), 2.86 (s, 3H),

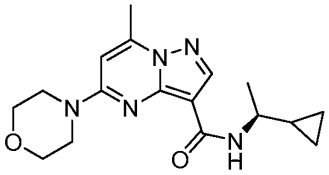
1.28 (d, J = 6.5 Hz, 3H), 1.14-1.07 (m, 1H), 0.56-0.45 (m, 2H), 0.42-0.31 (m, 2H). LC-MS m/z: 339.2 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 8.56 min.

(*S*)-*N*-(1-Cyclopropylethyl)-5-(3-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00400] Following general procedure A, 5-(3-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.10 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (10 mg, 29%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.55 (s, 1H), 8.15 (d, J = 7.5 Hz, 1H), 7.88 (s, 1H), 7.82 (d, J = 7.5 Hz, 1H), 7.78 (s, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.16 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 3.88 (s, 3H), 3.67-3.63 (m, 1H), 2.84 (s, 3H), 1.30 (d, J = 5.0 Hz, 3H), 1.08-1.05 (m, 1H), 0.53-0.47 (m, 2H), 0.41-0.38 (m, 1H), 0.34-0.30 (m, 1H). LC-MS m/z: 351.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.46 min.

(*S*)-*N*-(1-Cyclopropylethyl)-7-methyl-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

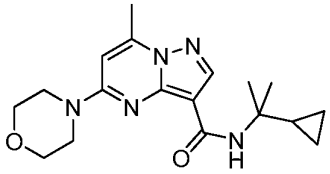


[00401] Following general procedure G, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 0.41 mmol) and morpholine afforded ethyl 7-methyl-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxylate (105 mg, 88%) as a white solid. LC-MS m/z: 291.1 $[M+H]^+$.

[00402] Following general procedure B, ethyl 7-methyl-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxylate (105 mg, 0.36 mmol) afforded 7-methyl-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (90 mg, 96%) as a white solid. LC-MS m/z: 263.0 $[M+H]^+$.

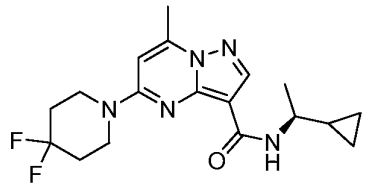
[00403] Following general procedure A, 7-methyl-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (35 mg, 0.13 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (31 mg, 70%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17 (s, 1H), 7.88 (d, J = 7.6 Hz, 1H), 6.88 (s, 1H), 3.74 (t, J = 4.0 Hz, 4H), 3.70 (t, J = 4.0 Hz, 4H), 3.54-3.48 (m, 1H), 2.62 (s, 3H), 1.20 (d, J = 6.8 Hz, 3H), 1.00-0.95 (m, 1H), 0.46-0.38 (m, 2H), 0.30-0.23 (m, 2H). LC-MS m/z: 330.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 6.68 min.

<u>*N*-(2-Cyclopropylpropan-2-yl)-7-methyl-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide</u>



[00404] Following general procedure A, 7-methyl-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (35 mg, 0.13 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (16 mg, 35%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.14 (s, 1H), 7.83 (s, 1H), 6.89 (s, 1H), 3.71 (d, J = 5.2 Hz, 8H), 2.61 (s, 3H), 1.30 (s, 6H), 1.30-1.28 (m, 1H), 0.39-0.35 (m, 4H). LC-MS m/z: 344.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.20 min.

<u>(*S*)-*N*-(1-Cyclopropylethyl)-5-(4,4-difluoropiperidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide</u>



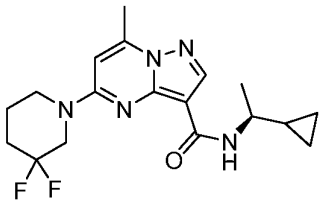
[00405] Following general procedure G, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 0.42 mmol), 4,4-difluoropiperidine hydrochloride (79 mg, 0.50 mmol) and Et_3N afforded ethyl 5-(4,4-difluoropiperidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 70%) as a yellow solid. LC-MS m/z: 325.2 $[M+H]^+$. HPLC: Purity (254 nm): > 80%; t_R = 1.41 min.

[00406] Following general procedure B, ethyl 5-(4,4-difluoropiperidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 0.31 mmol) afforded 5-(4,4-

difluoropiperidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (70 mg, 70%) as a yellow solid. LC-MS m/z: 297.1 $[M+H]^+$. Purity (254 nm): > 80%; t_R = 0.86 min.

[00407] Following general procedure A, 5-(4,4-difluoropiperidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (60 mg, 0.20 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (30 mg, 40%) as a white solid . ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.86 (d, J = 7.5 Hz, 1H), 6.99 (s, 1H), 3.87(brs, 4H), 3.54-3.49 (m, 1H), 2.62 (s, 3H), 2.15-2.06 (m, 4H), 1.20 (d, J = 6.5 Hz, 3H), 1.01-0.96 (m, 1H), 0.48-0.39 (m, 2H), 0.31-0.23 (m, 2H). LC-MS m/z: 364.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.72 min.

(*S*)-*N*-(1-Cyclopropylethyl)-5-(3,3-difluoropiperidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide

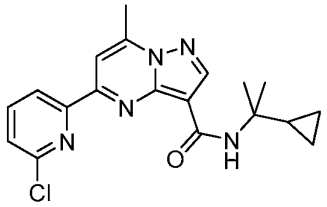


[00408] Following general procedure G, ethyl 5-chloro-7-methylpyrazolo[1,5-a]pyrimidine-3-carboxylate (100 mg, 0.42 mmol) and 3,3-difluoropiperidine hydrochloride afforded ethyl 5-(3,3-difluoropiperidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 70%) as a yellow solid. LC-MS m/z: 325.2 $[M+H]^+$. Purity (254 nm): > 80%; t_R = 1.39 min.

[00409] Following general procedure B, ethyl 5-(3,3-difluoropiperidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (90 mg, 0.28 mmol) afforded 5-(3,3-difluoropiperidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (70 mg, 85%) as a yellow solid. LC-MS m/z: 297.1 $[M+H]^+$. Purity (254 nm): > 80%; t_R = 0.86 min.

[00410] Following general procedure A, 5-(3,3-difluoropiperidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (60 mg, 0.20 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (20 mg, 25%) as a white solid . ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.00 (s, 1H), 4.18-4.10 (m, 2H), 3.80 (brs, 1H), 2.62 (s, 3H), 3.58-3.52 (m, 1H), 2.62 (s,1H), 2.20-2.12 (m, 2H), 1.79 (brs, 2H), 1.20 (d, J = 6.5 Hz, 3H), 0.99-0.94 (m, 1H), 0.49-0.39 (m, 2H), 0.33-0.24 (m, 2H). LC-MS m/z: 364.1 $[M+H]^+$, HPLC: Purity (214 nm): > 99%; t_R = 7.50 min.

5-(3-Chloro-2-pyridinyl)-*N*-(2-cyclopropylpropan-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide

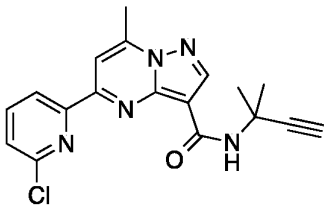


[00411] Following general procedure D, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (300 mg, 1.25 mmol) and 6-chloropyridin-2-ylboronic acid afforded ethyl 5-(6-chloropyridin-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (240 mg, 60%) as a yellow solid. LC-MS m/z: 317.2 $[M+H]^+$.

[00412] The mixture of ethyl 5-(6-chloropyridin-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (240 mg, 0.76 mmol) and $(Bu_3Sn)_2O$ (2.3 g, 3.80 mmol) in toluene (10 mL) was stirred at 110 °C for 3 days, cooled and poured into saturated $NaHCO_3$ solution (20 mL). The aqueous phase was washed with EA (5 mL x 3), acidified to pH 6 with 6N HCl 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* to afford 5-(6-chloropyridin-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (46 mg, 23%) as a yellow solid. LC-MS m/z: 289.1 $[M+H]^+$.

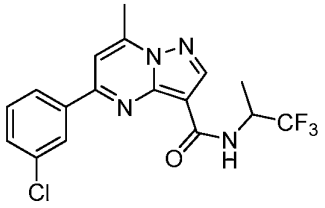
[00413] Following general procedure A, 5-(6-chloropyridin-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (50 mg, 0.14 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (15.8 mg, 25%) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4): δ 8.58 (s, 1H), 8.44 (d, J = 7.5 Hz, 1H), 8.37 (brs, 1H), 8.07 (s, 1H), 8.01 (t, J = 7.5 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 2.93 (s, 3H), 1.50 (s, 6H), 1.50-1.47 (m, 1H), 0.62-0.59 (m, 4H). LC-MS m/z: 370.1 $[M+H]^+$. HPLC Purity (214 nm): 99%; t_R = 11.43 min.

5-(6-Chloropyridin-2-yl)-7-methyl-*N*-(2-methylbut-3-yn-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00414] Following general procedure A, 5-(6-chloropyridin-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (50 mg, 0.14 mmol) and 2-methylbut-3-yn-2-amine afforded the title compound (18 mg, 30%) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4): δ 8.72 (brs, 1H), 8.62 (s, 1H), 8.51 (d, J = 8.0 Hz, 1H), 8.13 (s, 1H), 8.05 (t, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 2.97 (s, 1H), 2.96 (s, 3H), 1.88 (s, 6H). LC-MS m/z: 354.1 $[M+H]^+$. LC-MS Purity (214 nm): > 99%; t_R = 10.66 min.

5-(3-Chlorophenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

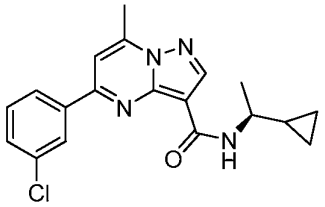


[00415] Following general procedure D, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (300 mg, 1.25 mmol) and 3-chlorophenylboronic acid afforded ethyl 5-(3-chlorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (390 mg, 98%) as a white solid. LC-MS m/z: 315.0 $[M+H]^+$. Purity (214 nm): > 72%; t_R = 2.00 min.

[00416] Following general procedure B, ethyl 5-(3-chlorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (390 mg, 1.24 mmol) afforded 5-(3-chlorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (250 mg, 70%) as a white solid. LC-MS m/z: 287.0 $[M+H]^+$. LC-MS Purity (214 nm): > 80%; t_R = 1.68 min.

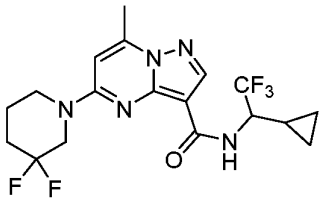
[00417] Following general procedure A, 5-(3-chlorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (60 mg, 0.21 mmol) and 1,1,1-trifluoropropan-2-amine afforded the title compound (41.8 mg, 52%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.49 (d, J = 9.0 Hz, 1H), 8.31(t, J = 2.0 Hz, 1H), 8.21 (dt, J = 7.5 Hz, 1.5 Hz, 1H), 8.03 (s, 1H), 7.70-7.65 (m, 2H), 4.97 (m, J = 8.0 Hz, 1H), 2.87 (s, 3H), 1.45 (d, J = 6.5 Hz, 3H). LC-MS m/z: 382.0 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 9.07 min.

(*S*)-5-(3-Chlorophenyl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



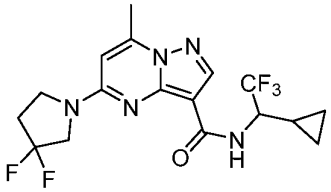
[00418] Following general procedure A, 5-(3-chlorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (60 mg, 0.21 mmol) and (S)-1-cyclopropylethanamine afforded the title compound (38.2 mg, 51%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.33 (s, 1H), 8.23 (dd, J = 8.5 Hz, 2.0 Hz, 1H), 8.15 (d, J = 7.5 Hz, 1H), 7.97 (s, 1H), 7.68-7.65 (m, 2H), 3.63 (m, J = 7.5 Hz, 1H), 2.85 (s, 3H), 1.28 (d, J = 6.5 Hz, 3H), 1.13-1.08 (m, 1H), 0.55-0.50 (m, 2H), 0.40-0.33 (m, 2H). LC-MS m/z: 354.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 9.10 min.

***N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(3,3-difluoropiperidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



[00419] Following general procedure A, 5-(3,3-difluoropiperidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.10 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine afforded the title compound as a yellow solid (17 mg, 30%). ^{1}H NMR (500 MHz, MeOD-d_4): δ 8.30 (s, 1H), 6.85 (s, 1H), 4.39 (p, J = 7.5 Hz, 1H), 4.20-4.18 (m, 1H), 4.09-4.05 (m, 1H), 3.92-3.88 (m, 1H), 3.85-3.81 (m, 1H), 2.72 (s, 3H), 2.24-2.17 (m, 2H), 1.93-1.88 (m, 2H), 1.24-1.20 (m, 1H), 0.77-0.73 (m, 1H), 0.65-0.63 (m, 1H), 0.55-0.47 (m, 2H). LC-MS m/z: 418.1 $[M+H]^+$. HPLC Purity (214 nm): 99%; t_R = 8.10 min

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(3,3-difluoropyrrolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide

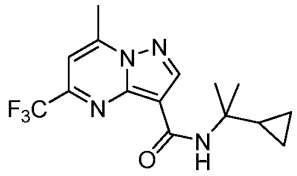


[00420] Following general procedure G, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 0.42 mmol) and 3,3-difluoropyrrolidine hydrochloride (72 mg, 0.50 mmol) afforded ethyl 5-(3,3-difluoropyrrolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (72 mg, 55%) as a yellow solid. LC-MS m/z: 311.2 $[M+H]^+$, t_R = 1.35 min.

[00421] Following general procedure B, ethyl 5-(3,3-difluoropyrrolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (50 mg, 0.16 mmol) afforded 5-(3,3-difluoropyrrolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (32 mg, 71%) as a white solid. LC-MS m/z: 283.0 $[M+H]^+$. t_R = 0.82 min.

[00422] Following general procedure A, 5-(3,3-difluoropyrrolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (32 mg, 0.11 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine afforded the tile compound (4.7 mg, 10%) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.30 (s, 1H), 6.52 (d, J = 3.0 Hz, 1H), 4.42-4.38 (m, 1H), 4.02 (t, J = 12.5 Hz, 2H), 3.89 (t, J = 7.5 Hz, 2H), 2.72 (s, 3H), 2.67-2.62 (m, 2H), 1.28-1.20 (m, 1H), 0.78-0.74 (m, 1H), 0.68-0.60 (m, 1H), 0.58-0.42 (m, 2H). LC-MS m/z: 404.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 8.13 min.

N-(2-Cyclopropylpropan-2-yl)-7-methyl-5-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



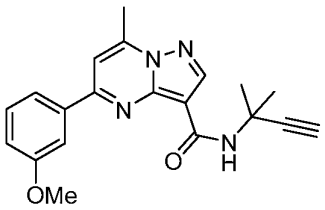
[00423] To a mixture of ethyl 5-amino-1*H*-pyrazole-4-carboxylate (1.0 g, 6.493 mmol) in AcOH (15 mL) was added 1,1,1-trifluoropentane-2,4-dione (1.0 g, 6.493 mmol) at 110 °C. The mixture was stirred for 2 hours and concentrated *in vacuo*. The residue was dissolved in EA (100 mL). The organic solution was washed with 10% $NaHCO_3$ solution (50 mL), dried over

anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford ethyl 7-methyl-5-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (1.8 g, 100%) as a yellow solid. LC-MS m/z: 274.0 $[M+H]^+$. t_R = 1.71 min.

[00424] To a mixture of ethyl 7-methyl-5-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 0.366 mmol) in toluene (10 mL) was added $(Bu_3Sn)_2O$ (440 mg, 0.732 mmol). The mixture was stirred at 120 °C for 2 days and concentrated *in vacuo*. The residue was partitioned between 10% $NaHCO_3$ solution (20 mL) and EA (30 mL x 2). The aqueous phase was acidified with 10% HCl solution to pH at 5~6, and extracted with EA (30 mL x 2). The organic phases were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford 7-methyl-5-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (75 mg, 83%) as a yellow solid. LC-MS m/z: 246.1 $[M+H]^+$. t_R = 1.53 min.

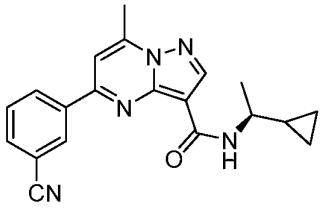
[00425] Following general procedure A, 7-methyl-5-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (75 mg, 0.31 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (35 mg, 35%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.56 (s, 1H), 8.26 (s, 1H), 7.60 (s, 1H), 2.98 (s, 3H), 1.45 (s, 6H), 1.40-1.37 (m, 1H), 0.56-0.54 (m, 4H). LC-MS m/z: 327.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.58 min.

5-(3-Methoxyphenyl)-7-methyl-*N*-(2-methylbut-3-yn-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00426] Following general procedure A, 5-(3-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.14 mmol) and 2-methylbut-3-yn-2-amine afforded the title compound (36 mg, 74%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.56 (s, 1H), 8.43 (s, 1H), 7.95 (s, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.81 (s, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.18 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 3.88 (s, 3H), 3.31 (s, 1H), 2.86 (s, 3H), 1.75 (s, 6H). LC-MS m/z: 349.2 $[M+H]^+$. LC-MS HPLC Purity (214 nm): > 99%; t_R = 8.32 min.

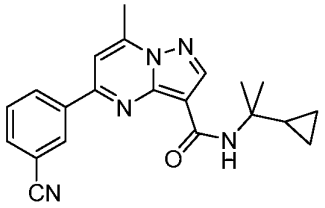
(*S*)-5-(3-Cyanophenyl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00427] Following general procedure C, 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (80 mg, 0.38 mmol) and (*S*)-1-cyclopropylethanaminehydrochloride afforded (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide as a yellow solid (30 mg, 28%). LC-MS m/z: 279.1 $[M+H]^+$. LC-MS Purity (214 nm): 99%.

[00428] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.18 mmol) and 3-cyanophenylboronic acid afforded the title compound (33.4 mg, 54%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.44 (s, 1H), 8.33 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 7.5 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.29 (s, 1H), 3.80-3.76 (m, 1H), 2.95 (s, 3H), 1.38 (d, J = 6.5 Hz, 3H), 1.08-1.04 (m, 1H), 0.63-0.57 (m, 2H), 0.50-0.48 (m, 1H), 0.41-0.37 (m, 1H). LC-MS m/z: 346.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.90 min.

5-(3-Cyanophenyl)-*N*-(2-cyclopropylpropan-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide

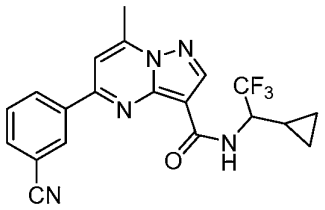


[00429] Following general procedure C, 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (80 mg, 0.38 mmol) and 2-cyclopropylpropan-2-amine afforded 5-chloro-*N*-(2-cyclopropylpropan-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (20 mg, 18%) as a yellow solid. LC-MS m/z: 293.1 $[M+H]^+$. LC-MS Purity (214 nm): 91%.

[00430] Following general procedure D, 5-chloro-*N*-(2-cyclopropylpropan-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (40 mg, 0.14 mmol) and 3-

cyanophenylboronic acid afforded the title compound (26.6 mg, 53%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.47 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 8.10 (s, 1H), 7.83 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 8.0 Hz, 1H), 7.28 (s, 1H), 2.94 (s, 3H), 1.58 (s, 6H), 1.43-1.39 (m, 1H), 0.60-0.57 (m, 2H), 0.55-0.53 (m, 2H). LC-MS m/z: 360.1 $[M+H]^+$. LC-MS HPLC Purity (214 nm): > 99%; t_R = 8.42 min.

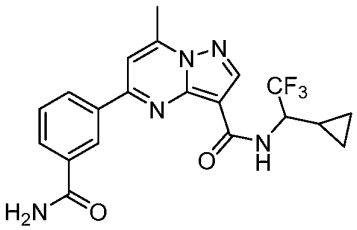
5-(3-Cyanophenyl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00431] Following general procedure C, 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (90 mg, 0.43 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (30 mg, 21%) as a yellow solid. LC-MS m/z: 333.0 $[M+H]^+$. LC-MS Purity (214 nm): 89%.

[00432] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (30 mg, 0.09 mmol) and 3-cyanophenylboronic acid afforded (10.6 mg, 29%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (s, 1H), 8.46 (d, J = 8.5 Hz, 1H), 8.37 (s, 1H), 8.33 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H), 7.33 (s, 1H), 4.53-4.48 (m, 1H), 2.96 (s, 3H), 1.25-1.20 (m, 1H), 0.77-0.72 (m, 1H), 0.64-0.52 (m, 3H). LC-MS m/z: 400.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.39 min.

5-(3-Carbamoylphenyl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide

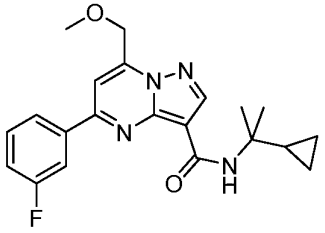


[00433] Following general procedure D, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (80 mg, 0.3 mmol) and 3-cyanophenylboronic acid afforded ethyl 5-(3-cyanophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (82 mg, 89%) as a white solid. LC-MS m/z: 307.1 $[M+H]^+$.

[00434] Following general procedure B, ethyl 5-(3-cyanophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (82 mg, 0.27 mmol) afforded 5-(3-carbamoylphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (51 mg, 64%) as a yellow solid. LC-MS m/z: 279.0 $[M+H]^+$.

[00435] Following general procedure A, 5-(3-carbamoylphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (25 mg, 0.08 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (10.6 mg, 32%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.60 (s, 1H), 8.57 (d, J = 8.5 Hz, 1H), 8.28 (d, J = 7.5 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 8.0 Hz, 1H), 7.42 (s, 1H), 4.56-4.50 (m, 1H), 3.49 (s, 2H), 2.94 (s, 3H), 1.26-1.22 (m, 1H), 0.75-0.71 (m, 1H), 0.61-0.53 (m, 3H). LC-MS m/z: 418.1 $[M+H]^+$. HPLC Purity (214nm): > 99%; t_R = 6.97 min.

***N*-(2-Cyclopropylpropan-2-yl)-5-(3-fluorophenyl)-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**

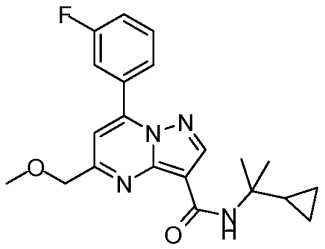


[00436] Following general procedure D, ethyl 5-chloro-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (40 mg, 0.15 mmol) and 3-fluorophenyl boronic acid afforded ethyl 5-(3-fluorophenyl)-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (33 mg, 67%) as a yellow solid. LC-MS m/z: 330.1 $[M+H]^+$. t_R = 2.07 min.

[00437] Following general procedure B, ethyl 5-(3-fluorophenyl)-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (33 mg, 0.10 mmol) afforded 5-(3-fluorophenyl)-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid sodium salt (30 mg, 92%) as a yellow solid. LC-MS m/z: 302.2 $[M+H]^+$. t_R = 1.76 min.

[00438] Following general procedure A, 5-(3-fluorophenyl)-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.10 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (1 mg, 4%) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.57 (s, 1H), 8.14 (d, J = 8.5 Hz, 1H), 8.13-8.10 (m, 2H), 7.80 (s, 1H), 7.69-7.65 (m, 1H), 7.47 (td, J = 7.5 Hz, 2.0 Hz, 1H), 5.05 (s, 2H), 3.56 (s, 3H), 1.41 (s, 6H), 1.42-1.40 (m, 1H), 0.52-0.48 (m, 4H). LC-MS m/z: 383.1 $[M+H]^+$. LC-MS Purity (214 nm): > 99%; t_R = 10.35 min.

***N*-(2-Cyclopropylpropan-2-yl)-7-(3-fluorophenyl)-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**

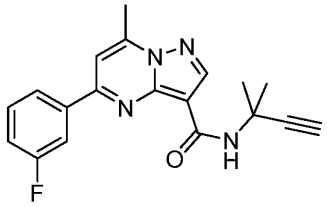


[00439] Following general procedure D, ethyl 7-chloro-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (50 mg, 0.19 mmol) and 3-fluorophenyl boronic acid afforded ethyl 7-(3-fluorophenyl)-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (44 mg, 72%) as a yellow solid. LC-MS m/z: 330.1 $[M+H]^+$. t_R = 1.96 min.

[00440] Following general procedure B, ethyl 7-(3-fluorophenyl)-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (44 mg, 0.13 mmol) afforded 7-(3-fluorophenyl)-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid sodium salt (40 mg, 95%) as a yellow solid. LC-MS m/z: 302.0 $[M+H]^+$. LCMS: t_R = 1.76 min.

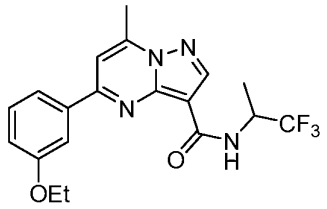
[00441] Following general procedure A, 7-(3-fluorophenyl)-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.13 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (10 mg, 20%) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.52 (s, 1H), 8.41 (s, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.99 (dd, J = 10.5 Hz, 2.5 Hz, 1H), 7.71 (s, 1H), 7.59 (ddd, J = 15.0 Hz, 7.0 Hz, 2.0 Hz, 1H), 7.33 (td, J = 8.5 Hz, 2.5 Hz, 1H), 5.04 (s, 2H), 3.67 (s, 3H), 1.49 (s, 6H), 1.45-1.37 (m, 1H), 0.63-0.55 (m, 4H). LC-MS m/z: 383.2 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 10.34 min.

5-(3-Fluorophenyl)-7-methyl-*N*-(2-methylbut-3-yn-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00442] Following general procedure A, 5-(3-fluorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.15 mmol) and 2-methylbut-3-yn-2-amine afforded the title compound (24.5 mg, 50%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.46 (s, 1H), 8.15 (d, J = 8.0 Hz, 1H), 8.09 (td, J = 12.0 Hz, 2.0 Hz, 1H), 7.98 (s, 1H), 7.71-7.66 (m, 1H), 7.46 (td, J = 8.5 Hz, 2.0 Hz, 1H), 3.35 (s, 1H), 2.86 (s, 3H), 1.75 (s, 6H). LC-MS m/z: 336.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.42 min.

5-(3-Ethoxyphenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



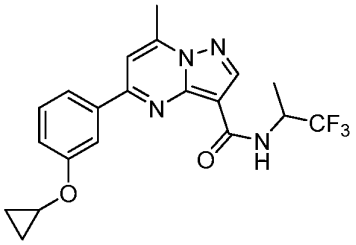
[00443] Following general procedure D, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (150 mg, 1.25 mmol) and 2-(3-ethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane afforded ethyl 5-(3-ethoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 50%) as a white solid. LC-MS m/z: 326.2 $[M+1]^+$. LC-MS Purity (214 nm): > 96%; t_R = 1.59 min.

[00444] Following general procedure B, ethyl 5-(3-ethoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 0.31 mmol) afforded 5-(3-ethoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (60 mg, 50%) as a yellow solid. LC-MS m/z: 298.1 $[M+1]^+$. LC-MS Purity (214 nm): > 98%; t_R = 0.97 min.

[00445] Following general procedure A, 5-(3-ethoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (50 mg, 0.17 mmol) and 1,1,1-trifluoropropan-2-amine hydrochloride afforded the title compound (30 mg, 45%) as a yellow solid. ^{1}H NMR (500

MHz, MeOD-d_4): δ 8.60 (s, 1H), 7.75 (d, J = 9.0 Hz, 1H), 7.73 (s, 1H), 7.70 (s, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.14 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 5.00 (p, J = 7.5 Hz, 1H), 4.17 (qd, J = 13.5 Hz, 1.5 Hz, 2H), 2.91 (s, 3H), 1.53 (d, J = 6.5 Hz, 3H), 1.46 (t, J = 7.0 Hz, 3H). LC-MS m/z: 393.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 9.09 min.

5-(3-Cyclopropoxyphenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

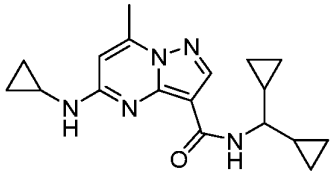


[00446] Following general procedure D, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (200 mg, 0.84 mmol) and 2-(3-cyclopropoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane afforded ethyl 5-(3-cyclopropoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (150 mg, 53%) as a yellow solid. LC-MS m/z: 338.1 $[M+H]^+$. t_R = 1.99 min.

[00447] Following general procedure B, ethyl 5-(3-cyclopropoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (150 mg, 0.44 mmol) afforded 5-(3-cyclopropoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (100 mg, 72.9%) as a tan yellow solid. LC-MS m/z: 310.1 $[M+H]^+$. LCMS: t_R = 1.83 min

[00448] Following general procedure A, 5-(3-cyclopropoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.13 mmol) and 1,1,1-trifluoropropan-2-amine hydrochloride afforded the title compound (26 mg, 50%) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.61 (s, 1H), 7.83 (s, 1H), 7.78 (d, J = 7.5 Hz, 1H), 7.69 (s, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.31 (dd, J = 8.0 Hz, 2.5 Hz, 1H), 5.00-4.97 (m, 1H), 3.93-3.91 (m, 1H), 2.92 (s, 3H), 1.52 (d, J = 6.0 Hz, 3H), 0.88-0.85 (m, 2H), 0.78-0.76 (m, 2H). LC-MS m/z: 405.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 9.18 min.

5-(Cyclopropylamino)-*N*-(dicyclopropylmethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide

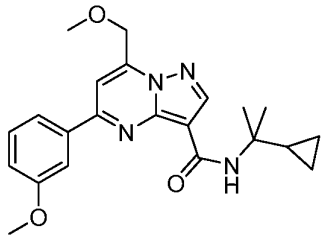


[00449] Following general procedure G, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (300 mg, 1.26 mmol) and cyclopropanamine afforded ethyl 5-(cyclopropylamino)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate as light yellow oil (215 mg, 67%). LC-MS m/z: 261.1 $[M+H]^+$. t_R = 1.59 min.

[00450] Following general procedure B, ethyl 5-(cyclopropylamino)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (215 mg, 0.83 mmol) afforded 5-(cyclopropylamino)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (146 mg, 76%) as a white solid. LC-MS m/z: 233.1 $[M+H]^+$. t_R = 0.74 min.

[00451] Following general procedure A, 5-(cyclopropylamino)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (47 mg, 0.20 mmol) and dicyclopropylmethanamine afforded the title compound (23 mg, 35%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.19 (s, 1H), 8.16 (s, 1H), 8.11 (s, 1H), 6.20 (s, 1H), 3.40 (brs, 1H), 2.76 (brs, 1H), 2.55 (s, 3H), 0.99 (d, J = 6.5 Hz, 2H), 0.81 (d, J = 5.5 Hz, 2H), 0.56 (brs, 2H), 0.47-0.42 (m, 2H), 0.39-0.34 (m, 2H), 0.33-0.25 (m, 4H). LC-MS m/z: 326.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.47 min.

***N*-(2-Cyclopropylpropan-2-yl)-7-(methoxymethyl)-5-(3-methoxyphenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



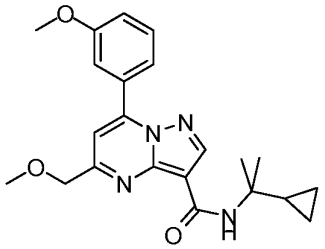
[00452] Following general procedure D, ethyl 5-chloro-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (65 mg, 0.24 mmol) and 3-methoxyphenyl boronic acid afforded 5-

(3-methoxyphenyl)-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (57 mg, 70%) as a yellow solid. LC-MS m/z: 342.1 $[M+H]^+$. t_R = 1.01 min.

[00453] Following general procedure B, ethyl 5-(3-methoxyphenyl)-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (57 mg, 0.17 mmol) at 30 °C afforded 5-(3-methoxyphenyl)-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid sodium salt (46 mg, 88%) as a red solid. LC-MS m/z: 314.1 $[M+H]^+$. LCMS: t_R = 1.65 min.

[00454] Following general procedure A, 5-(3-methoxyphenyl)-7-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (46 mg, 0.15 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (18.5 mg, 34%) as a white solid. ^1H NMR (500 MHz, DMSO-d_6): δ 8.54 (s, 1H), 8.13 (s, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.78 (d, J = 2.0 Hz, 1H), 7.74 (s, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.20 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 5.04 (s, 3H), 3.87 (s, 3H), 3.56 (s, 3H), 1.42-1.37 (m, 1H), 1.38 (s, 6H), 0.50-0.42 (m, 4H). LC-MS m/z: 395.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 10.23 min.

***N*-(2-Cyclopropylpropan-2-yl)-5-(methoxymethyl)-7-(3-methoxyphenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



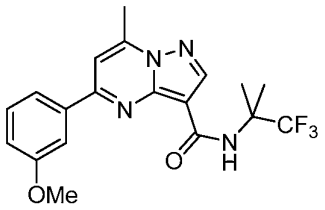
[00455] Following general procedure D, ethyl 7-chloro-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 0.37 mmol) and 3-methoxyphenyl boronic acid afforded ethyl 7-(3-methoxyphenyl)-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (44 mg, 35%) as a yellow solid. LC-MS m/z: 342.1 $[M+H]^+$. t_R = 2.05 min.

[00456] Following general procedure B, ethyl 7-(3-methoxyphenyl)-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (44 mg, 0.13 mmol) afforded 7-(3-methoxyphenyl)-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid sodium salt (30 mg, 75%) as an orange solid. LC-MS m/z: 314.1 $[M+H]^+$. LCMS: t_R = 0.95 min.

[00457] Following general procedure A, 7-(3-methoxyphenyl)-5-(methoxymethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.10 mmol) and 2-

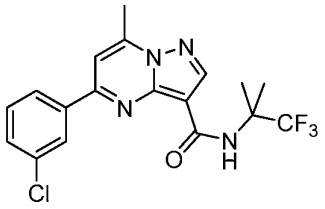
cyclopropylpropan-2-amine afforded the title compound (1.6 mg, 4%) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.39 (s, 1H), 8.37 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.58 (s, 1H), 7.37 (t, J = 8.0 Hz, 1H), 7.04 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 4.93 (s, 2H), 3.78 (s, 3H), 3.56 (s, 3H), 1.36 (s, 6H),1.33-1.30 (m,1H), 0.49-0.42 (m, 4H). LC-MS m/z: 395.2 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 10.24 min.

5-(3-Methoxyphenyl)-7-methyl-*N*-(1,1,1-trifluoro-2-methylpropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



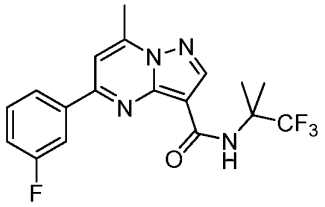
[00458] Following general procedure A, 5-(3-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.11 mmol) and 1,1,1-trifluoro-2-methylpropan-2-amine afforded the title compound (11 mg, 26%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.60 (s, 1H), 8.40 (s, 1H), 7.96 (s, 1H), 7.81 (d, J = 7.2 Hz, 1H), 7.75 (s, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.20 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 3.88 (s, 3H), 2.86 (s, 3H), 1.73 (s, 6H). LC-MS m/z: 393.1 $[M+H]^+$. LC-MS HPLC Purity (214 nm): 96%; t_R = 8.99 min.

5-(3-Chlorophenyl)-7-methyl-*N*-(1,1,1-trifluoro-2-methylpropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



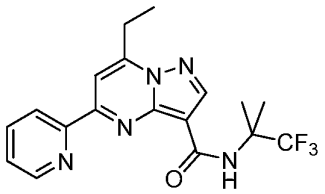
[00459] Following general procedure A, 5-(3-chlorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.11 mmol) and 1,1,1-trifluoro-2-methylpropan-2-amine afforded the title compound (9 mg, 21%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.62 (s, 1H), 8.42 (s, 1H), 8.30 (s, 1H), 8.19 (d, J = 6.8 Hz, 1H), 8.02 (s, 1H), 7.69-7.66 (m, 2H), 2.86 (s, 3H), 1.73 (s, 6H). LC-MS m/z: 397.0 $[M+H]^+$. LC-MS Purity (254 nm): 98%; t_R = 9.56 min.

5-(3-Fluorophenyl)-7-methyl-N-(1,1,1-trifluoro-2-methylpropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



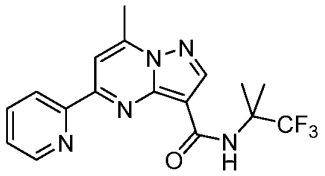
[00460] Following general procedure A, 5-(3-fluorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (24 mg, 0.09 mmol) and 1,1,1-trifluoro-2-methylpropan-2-amine afforded the title compound (2.6 mg, 8% over two steps) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.41 (s, 1H), 8.08 (d, J = 7.6 Hz, 1H), 8.03 (dt, J = 10.0 Hz, 2.4 Hz, 1H), 8.00 (s, 1H), 7.69 (ddd, J = 15.6 Hz, 7.6 Hz, 2.0 Hz, 1H), 7.48 (td, J = 8.4 Hz, 2.4 Hz, 1H), 2.86 (s, 3H), 1.72 (s, 6H). LC-MS m/z: 381.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 9.10 min.

7-Ethyl-5-(pyridin-2-yl)-*N*-(1,1,1-trifluoro-2-methylpropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



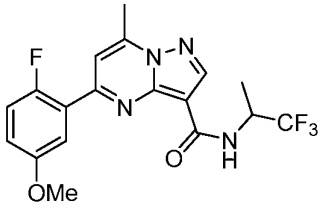
[00461] Following general procedure A, 7-ethyl-5-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (100 mg, 0.40 mmol) and 1,1,1-trifluoro-2-methylpropan-2-amine afforded the title compound (16 mg, 13%) as a white solid. ^{1}H NMR (400 MHz, MeOD-d_4): δ 8.80 (d, J = 4.4 Hz, 1H), 8.60 (s, 1H), 8.49 (d, J = 8.0 Hz, 1H), 8.19 (s, 1H), 8.05 (td, J = 8.0 Hz, 1.6 Hz, 1H), 7.59 (dd, J = 7.2 Hz, 5.6 Hz, 1H), 3.37 (q, J = 7.6 Hz, 2H), 1.82 (s, 6H), 1.55 (t, J = 7.6 Hz, 3H). LC-MS m/z: 378.1 $[M+H]^+$. HPLC Purity (214 nm): 93%; t_R = 9.35 min.

7-Methyl-5-(pyridin-2-yl)-*N*-(1,1,1-trifluoro-2-methylpropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00462] Following general procedure A, 7-methyl-5-(pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (38 mg, 0.15 mmol) and 1,1,1-trifluoro-2-methylpropan-2-amine afforded the title compound (18.0 mg, 33%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.82 (d, J = 4.5 Hz, 1H), 8.65 (s, 1H), 8.37 (d, J = 8.5 Hz, 1H), 8.37 (s, 1H), 8.19 (s, 1H), 8.14 (t, J = 8.0 Hz, 1H), 8.64 (dd, J = 7.0 Hz, 4.0 Hz, 1H), 2.90 (s, 3H), 1.75 (s, 6H). LC-MS m/z: 364.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.77 min.

5-(2-Fluoro-5-methoxyphenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

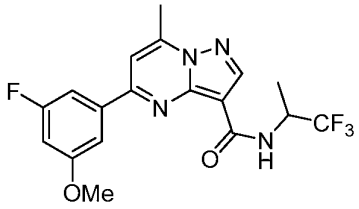


[00463] Following general procedure D, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 0.42 mmol) and 2-fluoro-5-methoxyphenylboronic acid afforded ethyl 5-(2-fluoro-5-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 72%) as a white solid. LCMS m/z: 330.0 $[M+H]^+$. Purity (254 nm): > 96%.

[00464] Following general procedure B, ethyl 5-(2-fluoro-5-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 0.30 mmol) afforded 5-(2-fluoro-5-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (80 mg, 89%) as a white solid. LC-MS m/z: 302.1 $[M+H]^+$. Purity (254 nm): > 99%.

[00465] Following general procedure A, 5-(2-fluoro-5-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.10 mmol) and 1,1,1-trifluoropropan-2-amine hydrochloride afforded the title compound (23.4 mg, 64%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.71 (s, 1H), 8.44 (d, J = 9.2 Hz, 1H), 7.74 (s, 1H), 7.58 (dd, J = 6.0 Hz, 2.8 Hz, 1H), 7.41 (dd, J = 10.8 Hz, 8.8 Hz, 1H), 7.20 (dt, J = 8.8Hz, 4.0 Hz, 1H), 5.00-4.93 (m, 1H), 3.85 (s, 3H), 2.88 (s, 3H), 1.40 (d, J = 6.8 Hz, 3H). LC-MS m/z: 397.1 $[M+H]^+$. LC-MS Purity (214 nm): > 99%; t_R = 8.71 min.

5-(3-Fluoro-5-methoxyphenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

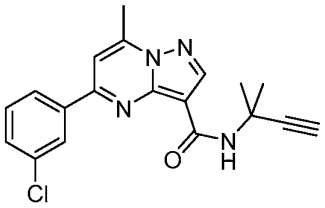


[00466] Following general procedure D, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 0.42 mmol) and 3-fluoro-5-methoxyphenylboronic acid afforded ethyl 5-(3-fluoro-5-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (130 mg, 94%) as a white solid. LCMS m/z: 330.1 $[M+H]^+$. Purity (254 nm): > 96%.

[00467] Following general procedure B, ethyl 5-(3-fluoro-5-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (85 mg, 0.26 mmol) afforded 5-(3-fluoro-5-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (48 mg, 62%) as a white solid. LC-MS m/z: 302.1 $[M+H]^+$. Purity (254 nm): > 96%.

[00468] Following general procedure A, 5-(3-fluoro-5-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (25 mg, 0.08 mmol) and 1,1,1-trifluoropropan-2-amine hydrochloride afforded the title compound (14.2 mg, 44%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (s, 1H), 8.44 (d, J = 9.2 Hz, 1H), 7.67-7.63 (m, 2H), 7.11 (dt, J = 10.8 Hz, 2.0 Hz, 1H), 5.01-4.94 (m, 1H), 3.90 (s, 3H), 2.86 (s, 3H), 1.44 (d, J = 6.8 Hz, 3H). LC-MS m/z: 397.1 $[M+H]^+$. LC-MS Purity (214 nm): > 99%; t_R = 8.81 min.

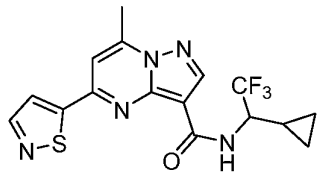
5-(3-Chlorophenyl)-7-methyl-N-(2-methylbut-3-yn-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00469] Following general procedure A, 5-(3-chlorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.10 mmol) and 2-methylbut-3-yn-2-amine afforded the title compound (15.5 mg, 44%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.59 (s, 1H), 8.45 (s, 1H), 8.35 (s, 1H), 8.26 (d, J = 5.2 Hz, 1H), 8.02 (s, 1H), 7.683 (s, 1H), 7.676

(d, J = 5.2 Hz, 1H), 3.36 (s, 1H), 2.86 (s, 3H), 1.76 (s, 6H). LC-MS m/z: 353.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.94 min.

_N_-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(isothiazol-5-yl)-7-methylpyrazolo[1,5-_a_]pyrimidine-3-carboxamide

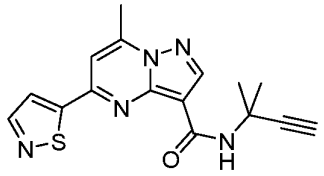


[00470] Following general procedure E, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (300 mg, 0.83 mmol) and 5-bromoisothiazole (137 mg, 0.83 mmol) afforded ethyl 5-(isothiazol-5-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (200 mg, 57%) as a yellow solid. LC-MS m/z: 289.0 $[M+H]^+$. t_R = 1.69 min.

[00471] Following general procedure B, ethyl 5-(isothiazol-5-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (200 mg, 0.69 mmol) afforded 5-(isothiazol-5-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (150 mg, 83%) as a yellow solid. LC-MS m/z: 302.1 $[M+H]^+$. t_R = 0.91 min.

[00472] Following general procedure A, 5-(isothiazol-5-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (80 mg, 0.31 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (18 mg, 25%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4): δ 8.68 (s, 1H), 8.66 (s, 1H), 8.13 (s, 1H), 7.77 (s, 1H), 4.48-4.42 (m, 1H), 2.96 (s, 3H), 1.40-1.31 (m, 1H), 0.85-0.78 (m, 1H), 0.72-0.65 (m, 1H), 0.62-0.50 (m, 2H). LC-MS m/z: 382.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 10.13 min.

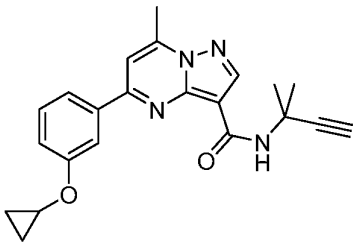
5-(Isothiazol-5-yl)-7-methyl-_N_-(2-methylbut-3-yn-2-yl)pyrazolo[1,5-_a_]pyrimidine-3-carboxamide



[00473] Following general procedure A, 5-(isothiazol-5-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (70 mg, 0.27 mmol) and 2-methylbut-3-yn-2-amine afforded the title compound (18.6 mg, 30%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4): δ 8.67

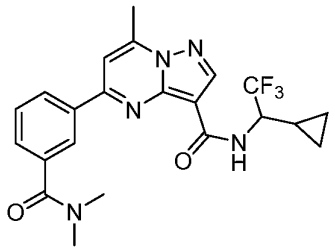
(d, J = 2.0 Hz, 1H), 8.60 (s, 1H), 8.10 (d, J = 2.0 Hz, 1H), 7.72 (s, 1H), 2.94 (s, 3H), 2.86 (s, 1H), 1.86 (s, 6H). LC-MS m/z: 326.0 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 9.40 min.

5-(3-Cyclopropoxyphenyl)-7-methyl-*N*-(2-methylbut-3-yn-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



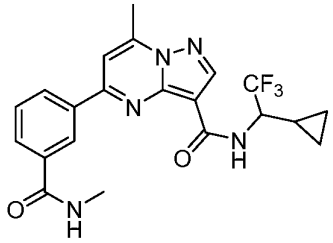
[00474] Following general procedure A, 5-(3-cyclopropoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.10 mmol) and 2-methylbut-3-yn-2-amine afforded the title compound (22.2 mg, 61%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56 (s, 1H), 8.45 (s, 1H), 7.93 (s, 1H), 7.90-7.88 (m, 2H), 7.56 (t, J = 8.0 Hz, 1H), 7.32 (dd, J = 8.0 Hz, 2.5 Hz, 1H), 4.01-3.98 (m, 1H), 3.31 (s, 1H), 2.85 (s, 3H), 1.74 (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 = 8.95 min.

***N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(3-(dimethylcarbamoyl)phenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



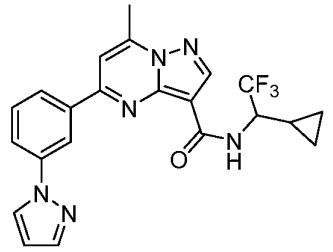
[00475] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.15 mmol) and 3-(dimethylcarbamoyl)phenylboronic acid afforded the title compound (36 mg, 45%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.68 (s, 1H), 8.58 (d, J = 9.5 Hz, 1H), 8.31 (d, J = 8.0 Hz, 1H), 8.27 (s, 1H), 8.05 (s, 1H), 7.74 (t, J = 7.5 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 4.51-4.46 (m, 1H), 3.04 (s, 3H), 2.95 (s, 3H), 2.87 (s, 3H), 1.28-1.24 (m, 1H), 0.71-0.67 (m, 1H), 0.60-0.56 (m, 2H), 0.41-0.38 (m, 1H). LC-MS m/z: 446.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.54 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(3-(methylcarbamoyl)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



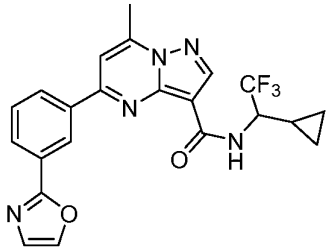
[00476] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.15 mmol) and 3-(methylcarbamoyl)phenylboronic acid afforded the title compound (13 mg, 15 %) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.68 (s, 1H), 8.64-8.61 (m, 2H), 8.37 (d, *J* = 7.5 Hz, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 8.017 (s, 1H), 7.72 (t, *J* = 7.5 Hz, 1H), 4.43-4.38 (m, 1H), 2.89 (s, 3H), 2.83 (d, *J* = 4.5 Hz, 3H), 1.39-1.35 (m, 1H), 0.72-0.68 (m, 1H), 0.63-0.59 (m, 2H), 0.41-0.38 (m, 1H). LC-MS m/z: 432.2 $[M+H]^+$. HPLC Purity (214 nm): 99%; t_R = 7.28 min.

5-(3-(1*H*-Pyrazol-1-yl)phenyl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00477] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.15 mmol) and 3-(1*H*-pyrazol-1-yl)phenylboronic acid afford the title compound (17 mg, 20%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.78 (s, 1H), 8.69 (s, 1H), 8.67-8.64 (m, 2H), 8.18 (d, *J* = 8.0 Hz, 1H), 8.09-8.08 (m, 2H), 7.78-7.75 (m, 2H), 6.62 (t, *J* = 2.5 Hz, 1H), 4.41-4.36 (m, 1H), 2.90 (s, 3H), 1.48-1.42 (m, 1H), 0.77-0.72 (m, 1H), 0.66-0.60 (m, 2H), 0.42-0.37 (m, 1H). LC-MS m/z: 441.1 $[M+H]^+$. HPLC Purity (254 nm): 99%; t_R = 8.73 min.

***N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(3-(oxazol-2-yl)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



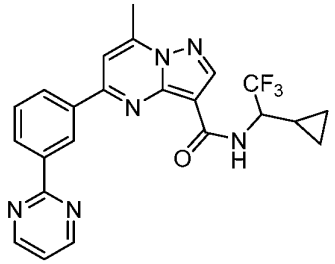
[00478] Following general procedure D, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (1.98 g, 8.27 mmol) and 3-bromophenylboronic acid afforded ethyl 5-(3-bromophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (108 mg, 4%) as a brown solid. LC-MS m/z: 360.0 $[M+H]^+$. t_R = 1.63 min.

[00479] Following general procedure B, ethyl 5-(3-bromophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (108 mg, 0.3 mmol) afforded 5-(3-bromophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (75 mg, 75%) as a light brown solid. LC-MS m/z: 332.0 $[M+H]^+$. t_R = 0.98 min.

[00480] Following general procedure A, 5-(3-bromophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (75 mg, 0.23 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded 5-(3-bromophenyl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (91 mg, 89%) as a light yellow solid. LC-MS m/z: 453.1 $[M+H]^+$. t_R = 1.70 min.

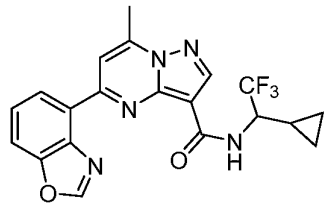
[00481] Following general procedure F, 5-(3-bromophenyl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (34 mg, 0.08 mmol) and 2-(tributylstannyl)oxazole afforded the title compound (11.2 mg, 34%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.89 (s, 1H), 8.68 (s, 1H), 8.65 (d, J = 9.6 Hz, 1H), 8.38 (d, J = 8.0 Hz, 1H), 8.27 (s, 1H), 8.20 (d, J = 8.0 Hz, 1H), 8.07 (s, 1H), 7.80 (d, J = 8.0 Hz, 1H), 7.44 (s, 1H), 4.46-4.36 (m, 1H), 2.89 (s, 3H), 1.45-1.37 (m, 1H), 0.79-0.70 (m, 1H), 0.68-0.60 (m, 2H), 0.45-0.36 (m, 1H). LC-MS m/z: 442.1 $[M+H]^+$. HPLC Purity (254 nm): > 99%; t_R = 8.88 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(3-(pyrimidin-2-yl)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



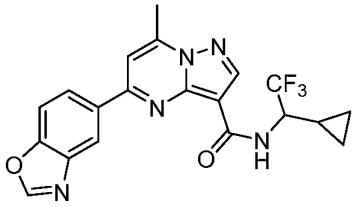
[00482] Following general procedure F, 5-(3-bromophenyl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (72 mg, 0.16 mmol) and 2-(tributylstannyl)pyrimidine afforded the title compound (2.1 mg, 3%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.40 (s, 1H), 8.90 (d, J = 4.8 Hz, 2H), 8.75 (d, J = 9.6 Hz, 1H), 8.68 (s, 1H), 8.61 (d, J = 8.0 Hz, 1H), 8.41 (d, J = 8.0 Hz, 1H), 8.06 (s, 1H), 7.79 (t, J = 8.0 Hz, 1H), 7.52 (t, J = 4.8 Hz, 1H), 4.45-4.34 (m, 1H), 2.90 (s, 3H), 1.53-1.45 (m, 1H), 0.80-0.73 (m, 1H), 0.69-0.58 (m, 2H), 0.46-0.37 (m, 1H). LC-MS m/z: 453.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 9.08 min.

5-(Benzo[*d*]oxazol-4-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



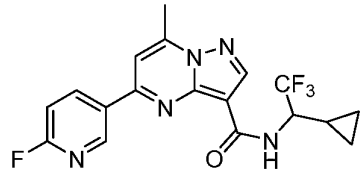
[00483] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (110 mg, 0.45 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazole afforded the title compound (1.5 mg, 1.1%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.04 (s, 1H), 8.86 (d, J = 9.5 Hz, 1H), 8.70 (s, 1H), 8.44 (s, 1H), 8.31 (d, J = 8.0 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.72 (t, J = 8.0 Hz, 1H), 4.48-4.40 (m, 1H), 2.93 (s, 3H), 1.39-1.35 (m, 1H), 0.72-0.68 (m, 1H), 0.63-0.55 (m, 2H), 0.41-0.38 (m, 1H). LC-MS m/z: 416.0 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.83 min.

5-(Benzo[*d*]oxazol-5-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



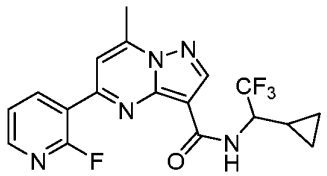
[00484] Folowing general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (210 mg, 35% purity, 0.23 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazole afforded the title compound (37 mg, 28%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.65 (s, 1H), 8.638 (s, 1H), 8.636 (s, 1H), 8.38 (d, J = 9.0 Hz, 1H), 7.92 (d, J = 9.0 Hz, 1H), 7.87 (s, 1H), 4.49-4.43 (m, 1H), 2.97 (s, 3H), 1.39-1.33 (m, 1H), 0.83-0.78 (m, 1H), 0.72-0.66 (m, 1H), 0.64-0.58 (m, 1H), 0.56-0.50 (m, 1H). LC-MS m/z: 416.1 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 9.07 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(6-fluoropyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



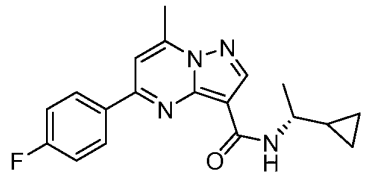
[00485] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 6-fluoropyridin-3-ylboronic acid afforded ther title compound (26 mg, 27%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.11 (d, J = 2.5 Hz, 1H), 8.76 (td, J = 8.0 Hz, 2.5 Hz, 1H), 8.70 (s, 1H), 8.48 (d, J = 9.5 Hz, 1H), 8.04 (s, 1H), 7.53 (dd, J = 9.0 Hz, 2.5 Hz, 1H), 4.46-4.40 (m, 1H), 2.88 (s, 3H), 1.34-1.29 (m, 1H), 0.71-0.67 (m, 1H), 0.62-0.57 (m, 2H), 0.38-0.36 (m, 1H). LC-MS m/z: 394.1 $[M+H]^+$. HPLC Purity (254 nm): 98%; t_R = 8.39 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(2-fluoropyridin-3-yl)-7-methylpyrazolo[1,5-a]pyrimidine-3-carboxamide



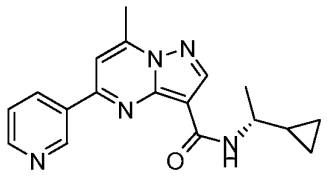
[00486] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.3 mmol) and 2-fluoropyridin-3-ylboronic acid afforded the title compound (13 mg, 11%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.74 (s, 1H), 8.60 (t, J = 8.8 Hz, 1H), 8.51-8.47 (m, 2H), 7.81 (s, 1H), 7.67 (d, J = 6.0 Hz, 1H), 4.49-4.38 (m, 1H), 2.90 (s, 3H), 1.29-1.20 (m, 1H), 0.71-0.64 (m, 1H), 0.60-0.52 (m, 2H), 0.40-0.31 (m, 1H). LC-MS m/z: 394.1 $[M+H]^+$. HPLC Purity (254 nm): > 99%; t_R = 8.26 min.

***(R)*-*N*-(1-Cyclopropylethyl)-5-(4-fluorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



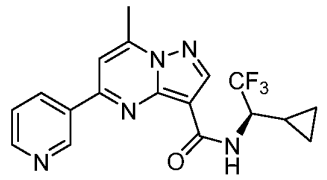
[00487] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.29 mmol) and 4-fluorophenylboronic acid afforded the title compound (42.6 mg, 43 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56 (s, 1H), 8.33 (dd, J = 8.5 Hz, 2.0 Hz, 2H), 8.16 (d, J = 7.5 Hz, 1H), 7.90 (d, J = 1.0 Hz, 1H), 7.49 (td, J = 9.0 Hz, 2.5 Hz, 2H), 3.63-3.59 (m, 1H), 2.85 (s, 3H), 1.29 (d, J = 6.5 Hz, 3H), 1.12-1.09 (m, 1H), 0.54-0.48 (m, 2H), 0.39-0.31(m, 2H). LC-MS m/z: 339.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.76 min.

(*R*)-*N*-(1-Cyclopropylethyl)-7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



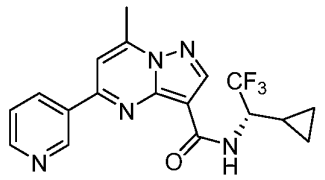
[00488] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.36 mmol), and pyridin-3-ylboronic acid afforded the title compound (31 mg, 27%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.45 (d, J = 2.5 Hz, 1H), 8.78 (dd, J = 4.0 Hz, 1.0 Hz, 1H), 8.60 (t, J = 2.0 Hz, 1H), 8.59 (s, 1H), 8.12 (d, J = 7.5 Hz, 1H), 7.98 (s, 1H), 7.67 (dd, J = 8.0 Hz, 5.0 Hz, 1H), 3.63 – 3.59 (m, 1H), 2.86 (s, 3H), 1.29 (d, J = 6.5 Hz, 3H), 1.28-1.08 (m, 1H), 0.54 -0.45 (m, 2H), 0.39-0.20 (m, 2H). LC-MS m/z: 322.2 $[M+H]^+$. HPLC: Purity (214nm): > 99%; t_R = 6.93 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



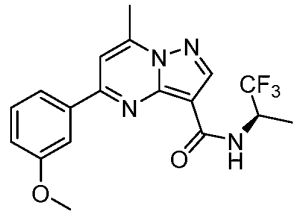
[00489] Following general procedure A, 7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (100 mg, 0.39 mmol) and (*R*)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (47 mg, 32 %) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 9.30 (d, J = 2.0 Hz, 1H), 8.65 (dd, J = 4.5 Hz, 1.0 Hz, 1H), 8.55 (s, 1H), 8.53 (d, J = 8.5 Hz, 1H), 7.72 (s, 1H), 7.58 (dd, J = 8.0 Hz, 4.5 Hz, 1H), 4.35-4.28 (m, 1H), 2.86 (s, 3H), 1.24-1.18 (m, 1H), 0.70-0.64 (m, 1H), 0.58-0.46 (m, 2H), 0.42-0.37 (m, 1H). LC-MS m/z: 376.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.69 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00490] Following general procedure A, 7-methyl-5-(pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (100 mg, 0.39 mmol) and (*S*)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (27 mg, 19%) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 9.30 (d, J = 2.0 Hz, 1H), 8.65 (dd, J = 4.5 Hz, 1.0 Hz, 1H), 8.55 (s, 1H), 8.53 (d, J = 8.5 Hz, 1H), 7.72 (s, 1H), 7.58 (dd, J = 8.0 Hz, 4.5 Hz, 1H), 4.35-4.28 (m, 1H), 2.86 (s, 3H), 1.24-1.18 (m, 1H), 0.70-0.64 (m, 1H), 0.58-0.46 (m, 2H), 0.42-0.37 (m, 1H). LC-MS m/z: 376.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.69 min.

(*R*)-5-(3-Methoxyphenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

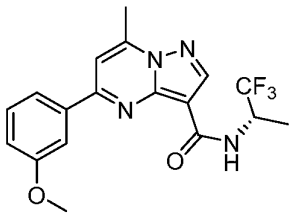


[00491] Following general procedure A, 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (422 mg, 2 mmol) and (*R*)-1,1,1-trifluoropropan-2-amine hydrochloride afforded (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (489 mg, 80 %) as a pale yellow solid. LC-MS m/z: 307.0 $[M+H]^+$. Purity (254 nm): 98.7%; t_R = 1.78 min.

[00492] Following general procedure D, (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (45 mg, 0.15 mmol) and 3-methoxyphenylboronic acid afforded the title compound (15 mg, 26 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.66 (s, 1 H), 8.49 (d, J = 9.0 Hz, 1H), 7.98 (s, 1 H), 7.83 (d, J = 7.5 Hz, 1H), 7.80 (s, 1 H), 7.55 (t, J = 8.0 Hz, 1H), 7.19 (dd, J = 8.0 Hz, 2.5 Hz, 1H), 5.01-4.96

(m, 1 H), 3.89 (s, 3H), 2.87 (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 = 8.81 min.

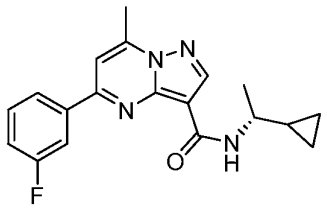
(*S*)-5-(3-Methoxyphenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00493] Following general procedure A, 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (515 mg, 2.43 mmol) and (*S*)-1,1,1-trifluoropropan-2-amine hydrochloride afforded (*S*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (371 mg, 50 %) as a white solid. LC-MS m/z: 307.0 $[M+H]^+$. t_R = 1.79 min.

[00494] Following general procedure D, (*S*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.2 mmol) and 3-methoxyphenylboronic acid afforded the title compound (53 mg, 72 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.50 (d, J = 9.5 Hz, 1H), 7.98 (s, 1H), 7.83 (d, J = 7.5 Hz, 1H), 7.80 (s, 1H), 7.55 (t, J = 8.0 Hz, 1H), 7.20 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 5.00-4.97 (m, 1H), 3.89 (s, 3H), 2.87 (s, 3H), 1.45 (d, J = 7.0 Hz, 3H). LC-MS m/z: 379.1 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 8.81 min.

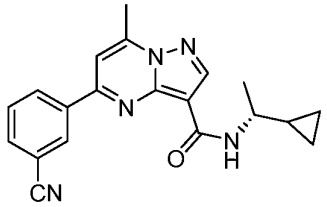
***(R)*-*N*-(1-Cyclopropylethyl)-5-(3-fluorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



[00495] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-a]pyrimidine-3-carboxamide (80 mg, 0.29 mmol) and 3-fluorophenylboronic acid afforded the title compound (53 mg, 54%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.14 (t, J = 9.0 Hz, 2H), 8.09 (dt, J = 10.5 Hz, 1.5 Hz,

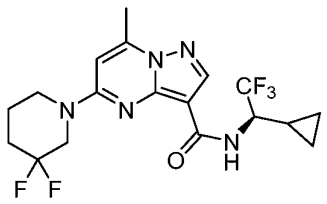
1H), 7.96 (s, 1H), 7.69 (dd, J = 14.5 Hz, 8.0Hz, 1H), 7.47 (td, J = 8.5 Hz, 2.5 Hz, 1H), 3.66-3.61 (m, 1H), 2.86 (s, 3H), 1.28 (d, J = 6.0 Hz, 3H), 1.11-1.09 (m, 1H), 0.55-0.48 (m, 2H), 0.41-0.38 (m, 1H), 0.36-0.33 (m, 1H). LC-MS m/z: 339.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.79 min.

(*R*)-5-(3-Cyanophenyl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00496] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.21 mmol) and 3-cyanophenylboronic acid afforded the title compound (44 mg, 60%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.71 (t, J = 1.5 Hz, 1H), 8.61 (s, 1H), 8.59 (dt, J = 8.0 Hz, 1.0 Hz, 1H), 8.13 (d, J = 7.5 Hz, 1H), 8.08 (dt, J = 7.5 Hz, 1.0 Hz, 1H), 8.04 (s, 1H), 7.86 (t, J = 7.5 Hz, 1H), 3.64-3.60 (m, 1H), 2.87 (s, 3H), 1.29 (d, J = 6.5 Hz, 3H), 1.16-1.11 (m, 1H), 0.55-0.50 (m, 2H), 0.41-0.34 (m, 2H). LC-MS m/z: 346.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.11 min.

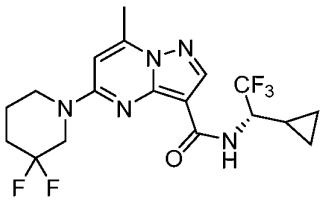
(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(3,3-difluoropiperidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00497] Following general procedure G, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (20 mg, 0.06 mmol) and 3,3-difluoropiperidine hydrochloride afforded the title compound (12 mg, 48%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.26 (s, 1H), 8.25 (d, J = 9.5 Hz, 1H), 7.05 (s, 1H), 4.45-4.40 (m, 1H), 4.16-4.10 (m, 2H), 3.82-3.77 (m, 2H), 2.63 (s, 3H), 2.20-2.11 (m, 2H), 1.81-1.74 (m,

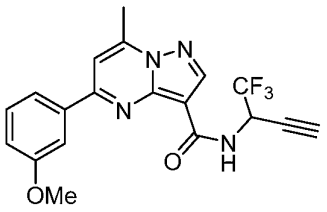
2H), 1.89-1.12 (m, 1H), 0.68-0.62 (m, 1H), 0.57-0.47 (m, 2H), 0.36-0.32 (m, 1H). LC-MS m/z: 418.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.32 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(3,3-difluoropiperidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



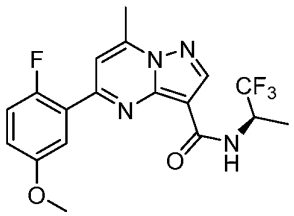
[00498] Following general procedure G, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (25 mg, 0.06 mmol) and 3,3-difluoropiperidine hydrochloride afforded the title compound (28 mg, 89%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (s, 1H), 8.25 (s, 1H), 7.05 (s, 1H), 4.43 (q, J = 8.0 Hz, 1H), 4.13 (td, J = 12.0 Hz, 2.5 Hz, 2H), 3.79 (s, 2H), 2.63 (s, 3H), 2.20-2.12 (m, 2H), 1.80-1.76 (m, 2H), 1.18-1.13 (m, 1H), 0.68-0.62 (m, 1H), 0.57-0.48 (m, 2H), 0.37-0.32 (m, 1H). LC-MS m/z: 418.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.33 min.

5-(3-Methoxyphenyl)-7-methyl-*N*-(1,1,1-trifluorobut-3-yn-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



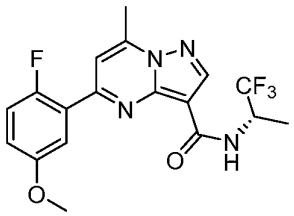
[00499] Following general procedure A, 5-(3-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.14 mmol) and 1,1,1-trifluorobut-3-yn-2-amine afforded the title compound (7.0 mg, 9%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (d, J = 11.2 Hz, 1H), 8.70 (s, 1H), 8.01 (s, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.82-7.80 (m, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.20 (dd, J = 8.0 Hz, 1.2 Hz, 1H), 6.05-5.95 (m, 1H), 3.88 (s, 3H), 3.87 (d, J = 3.0 Hz, 1H), 2.86 (s, 3H). LC-MS m/z: 389.1 $[M+H]^+$. HPLC: Purity (214 nm): 98%; t_R = 8.86 min.

(*R*)-5-(2-Fluoro-5-methoxyphenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



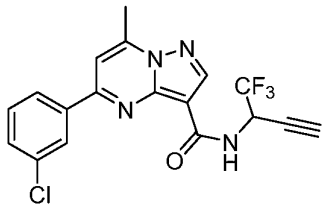
[00500] Following general procedure D, (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (62 mg, 0.2 mmol) and 2-fluoro-5-methoxyphenylboronic acid afforded the title compound (50 mg, 63 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 (s, 1 H), 8.44 (d, J = 9.5 Hz, 1H), 7.73 (s, 1 H), 7.58 (q, J = 3.0 Hz, 1H), 7.41 (dd, J = 11.5 Hz, 9.5 Hz, 1H), 7.20 (dt, J = 9.0 Hz, 3.5 Hz, 1H), 4.98-4.94 (m, 1H), 3.85 (s, 3H), 2.88 (s, 3H), 1.40 (d, J = 7.0 Hz, 3H). LC-MS m/z: 397.1 $[M+H]^+$. HPLC: Purity (214nm): > 99%; t_R = 8.93 min.

(*S*)-5-(2-Fluoro-5-methoxyphenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



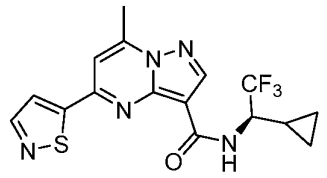
[00501] Following general procedure D, (*S*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (90 mg, 0.29 mmol) and 2-fluoro-5-methoxyphenylboronic acid afforded the title compound (67 mg, 58 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.71 (s, 1H), 8.44 (d, J = 9.5 Hz, 1H), 7.74 (s, 1H), 7.58 (q, J = 3.0 Hz, 1H), 7.41 (dd, J = 11.5 Hz, 9.5 Hz, 1H), 7.20 (dt, J = 9.0 Hz, 3.5 Hz, 1H), 5.00-4.93 (m, 1H), 3.85 (s, 3H), 2.88 (s, 3H), 1.41 (d, J = 7.5 Hz, 3H). LC-MS m/z: 397.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.96 min.

5-(3-Chlorophenyl)-7-methyl-*N*-(1,1,1-trifluorobut-3-yn-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



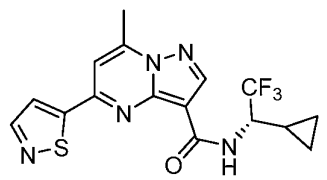
[00502] Following general procedure A, 5-(3-chlorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (100 mg, 0.35 mmol) and 1,1,1-trifluorobut-3-yn-2-amine afforded the title compound (44.3 mg, 27 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.94 (d, J = 9.0 Hz, 1H), 8.74 (s, 1H), 8.31 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H), 8.06 (s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H), 6.02-5.97 (m, 1H), 3.87 (t, J = 2.5 Hz, 1H), 2.87 (s, 3H). LC-MS m/z: 393.1 $[M+H]^+$. LC-MS Purity (214 nm): > 99%; t_R = 9.24 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(isothiazol-5-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



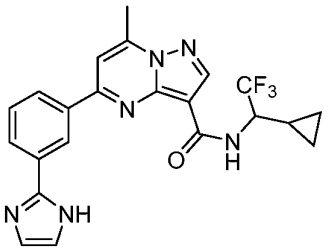
[00503] Following general procedure E*, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (75 mg, 0.226 mmol) and 5-bromoisothiazole afforded the title compound (4.3 mg, 5 %) as a light yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.81 (s, 1H), 8.71 (s, 1H), 8.28 (s, 1H), 8.26 (d, J = 10.0 Hz, 1H), 7.98 (s, 1H), 4.50-4.45 (m, 1H), 2.87 (s, 3H), 1.31-1.29 (m, 1H), 0.71-0.57 (m, 3H), 0.43-0.41 (m, 1H). LC-MS m/z: 382.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.34 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(isothiazol-5-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



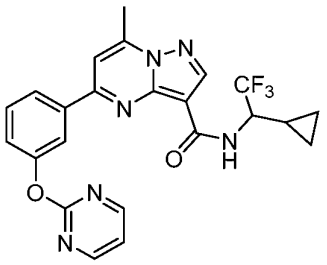
[00504] Following general procedure E*, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.30 mmol) and 5-bromoisothiazole afforded the title compound (35 mg, 31 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.81 (d, J = 1.5 Hz, 1H), 8.72 (s, 1H), 8.28 (d, J = 1.5 Hz, 1H), 8.27 (d, J = 9.5 Hz, 1H), 7.98 (s, 1H), 4.50-4.47 (m, 1H), 2.87 (s, 3H), 1.32-1.27 (m, 1H), 1.07-1.03 (m, 1H), 0.73-0.56 (m, 3H), 0.45-0.40 (m, 1H). LC-MS m/z: 382.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.33 min.

5-(3-(1*H*-Imidazol-2-yl)phenyl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00505] A mixture of 5-(3-cyanophenyl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.18 mmol), NaOMe (28 mg, 0.53 mmol) in MeOH (15 mL) was stirred at 40 °C for 16 h then 2,2-dimethoxyethanamine (21 mg, 0.21 mmol) and AcOH (420 mg, 7 mmol) were added and the mixture was stirred at 65 °C for 2 h. Then 6N HCl (1.4 mL) was added and the mixture was stirred at 80 °C for 16 h, cooled and the resulting slurry was filtered and the filtrate concentrated *in vacuo*. The residue was purified by preparative HPLC (MeCN/NH_4HCO_3) to afford the title compound (2.5 mg, 2%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.91 (s, 1H), 8.71 (d, J = 9.6 Hz, 1H), 8.68 (s, 1H), 8.19 (d, J = 7.2 Hz, 1H), 8.11 (d, J = 7.2 Hz, 1H), 7.98 (s, 1H), 7.71 (t, J = 7.2 Hz, 1H), 7.34 (s, 1H), 7.04 (s, 1H), 4.38-4.30 (m, 1H), 2.90 (s, 3H), 1.570-1.48 (m, 1H), 0.78-0.60 (m, 3H), 0.43-0.35 (m, 1H). LC-MS m/z: 441.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.53 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(3-(pyrimidin-2-yloxy)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

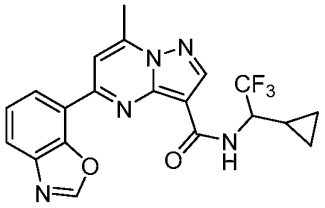


[00506] Following general procedure E*, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (572 mg, 2.39 mmol) and 2-(3-bromophenoxy)pyrimidine afforded ethyl 7-methyl-5-(3-(pyrimidin-2-yloxy)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (101 mg, 22%) as a yellow solid. LC-MS m/z: 376.1 $[M+H]^+$. LC-MS Purity (214 nm): > 96%; t_R = 1.71 min.

[00507] To a solution of ethyl 7-methyl-5-(3-(pyrimidin-2-yloxy)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (86 mg, 0.23 mmol) in toluene (2 mL) was added bis(tri-n-butyltin) oxide (273 mg, 0.46 mmol). The mixture was heated at 100 °C for 10 days, and concentrate *in vacuo*. The residue was purified by flash chromatography on silica gel (0 to 10% MeOH/EA) to afford 7-methyl-5-(3-(pyrimidin-2-yloxy)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (39 mg, 49%) as a yellow solid. LC-MS m/z: 343.1 $[M+H]^+$. LC-MS Purity (214 nm): > 93%; t_R = 1.46 min.

[00508] Following general procedure A, 7-methyl-5-(3-(pyrimidin-2-yloxy)phenyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (36 mg, 0.10 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (1.5 mg, 3%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4): δ 8.65 (d, J = 4.5 Hz, 2H), 8.62 (s, 1H), 8.17 (d, J = 8.0 Hz, 1H), 8.11 (s, 1H), 7.82 (s, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.46 (dd, J = 8.5 Hz, 2.0 Hz, 1H), 7.28 (t, J = 4.5 Hz, 1H), 4.43-4.38 (m, 1H), 2.95 (s, 3H), 1.13-1.06 (m, 1H), 0.71-0.67 (m, 1H), 0.62-0.51 (m, 2H), 0.49-0.44 (m, 1H). LC-MS m/z: 469.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.17 min.

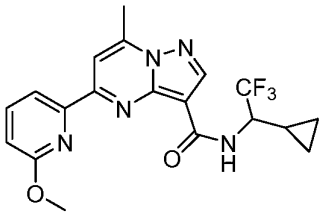
5-(Benzo[*d*]oxazol-7-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00509] A mixture of 7-bromobenzo[*d*]oxazole (500 mg, 2.53 mmol), sodium 2-ethylhexanoate (1.05 g, 6.325 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (771 mg, 3.1 mmol), and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (206 mg, 0.253 mmol) in toluene (15 mL) was stirred at 110 °C for 16 h, and concentrated *in vacuo* to afford crude 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazole (2.5 g) as a yellow oil, which was used in the next step without further purifications. LC-MS m/z: 255.1 $[M+H]^+$; t_R = 0.74 min.

[00510] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.3 mmol) and crude 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazole (800 mg) afforded the title compound (33.6 mg, 10%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.92 (s, 1H), 8.72 (s, 1H), 8.71 (d, *J* = 8.0 Hz, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 8.07 (s, 1H), 7.67 (t, *J* = 8.0 Hz, 1H), 4.48-4.43 (m, 1H), 2.92 (s, 3H), 1.34-1.32 (m, 1H) 0.72-0.70 (m, 1H), 0.62-0.58 (m, 2H), 0.38-0.36 (m, 1H). LC-MS m/z: 416.1 $[M+H]^+$. LC-MS Purity (214 nm): 98%; t_R = 8.34 min.

***N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(6-methoxypyridin-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



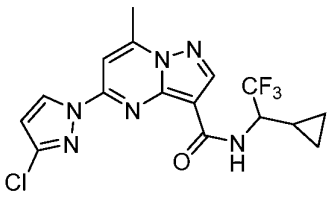
[00511] Following general procedure F, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (200 mg, 0.84 mmol) and 2-methoxy-6-(tributylstannyl)pyridine afforded ethyl

5-(6-methoxypyridin-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (220 mg, 84%) as a yellow solid. LC-MS m/z: 313.1 $[M+H]^+$. Purity (214 nm): 79.4%; t_R = 1.87 min.

[00512] Following general procedure B*, ethyl 5-(6-methoxypyridin-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (200 mg, 0.64 mmol) afforded 5-(6-methoxypyridin-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (154 mg, 84%). LC-MS m/z: 285.1 $[M+H]^+$. Purity (214 nm): 54.51%; t_R = 1.26 min.

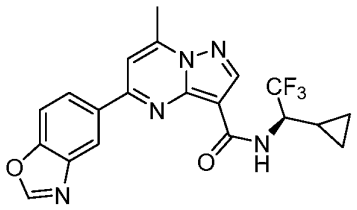
[00513] Following general procedure A, 5-(6-methoxypyridin-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (120 mg, 0.53 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (94 mg, 47%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.71 (s, 1H), 8.56 (d, J = 9.5 Hz, 1H), 8.18 (s, 1H), 8.04-8.04 (m, 2H), 7.08 (dd, J = 7.0 Hz, 2.0 Hz, 1H), 4.48-4.42 (m, 1H), 4.07 (s, 3H), 2.92 (s, 3H), 1.40-1.31 (m, 1H), 0.72-0.65 (m, 1H), 0.63-0.58 (m, 2H), 0.42-0.38 (m, 1H). LC-MS m/z: 406.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 9.46 min.

5-(3-Chloro-1*H*-pyrazol-1-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



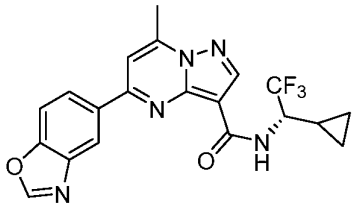
[00514] Following general procedure G, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (166 mg, 0.5 mmol) and 3-chloro-1*H*-pyrazole afforded the title compound (45 mg, 19%) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.72 (d, J = 3.0 Hz, 1H), 4.33-4.28 (m, 1H), 2.88 (s, 3H), 1.46-1.40 (m, 1H), 0.73-0.68 (m, 1H), 0.62-0.52 (m, 2H), 0.40-0.35 (m, 1H). LC-MS m/z: 399.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 9.16 min.

(*R*)-5-(Benzo[*d*]oxazol-5-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



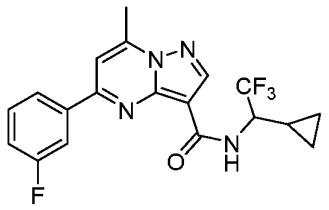
[00515] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.22 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazole afforded the title compound (63 mg, 67 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.70 (d, J = 1.6 Hz, 1H), 8.67 (s, 1H), 8.64 (d, J = 5.6 Hz, 1H), 8.36 (dd, J = 8.8 Hz, 1.6 Hz, 1H), 8.11 (s, 1H), 8.05 (d, J = 8.8 Hz, 1H), 4.52-4.46 (m, 1H), 2.88 (s, 3H), 1.33-1.27 (m, 1H), 0.73-0.67 (m, 1H), 0.63-0.56 (m, 2H), 0.45-0.40 (m, 1H). LC-MS m/z: 416.1 $[M+H]^+$. HPLC: Purity (214 nm): 97.37%; t_R = 8.33 min.

(*S*)-5-(Benzo[*d*]oxazol-5-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



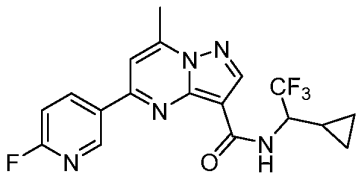
[00516] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.22 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazole afforded the title compound (63 mg, 67 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.91 (s, 1H), 8.70 (d, J = 1.5 Hz, 1H), 8.67 (s, 1H), 8.62 (d, J = 9.0 Hz, 1H), 8.36 (dd, J = 8.5 Hz, 2.0 Hz, 1H), 8.10 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 4.52-4.46 (m, 1H), 2.88 (s, 3H), 1.33-1.27 (m, 1H), 0.73-0.67 (m, 1H), 0.63-0.56 (m, 2H), 0.45-0.40 (m, 1H). LC-MS m/z: 416.1 $[M+H]^+$. HPLC: Purity (214 nm): 97.37%; t_R = 8.33 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(3-fluorophenyl)-7-methylpyrazolo[1,5-a]pyrimidine-3-carboxamide



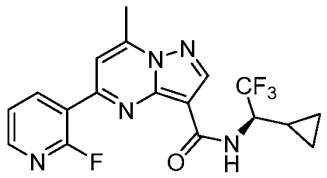
[00517] Following general procedure A, 5-(3-fluorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (55 mg, 0.20 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (5.4 mg, 7%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.69 (s, 1H), 8.56 (d, J = 9.5 Hz,, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.05 (d, J = 10.5 Hz, 1H), 8.02 (s, 1H), 7.79 (dd, J = 14.0 Hz, 8.0 Hz, 1H), 7.49 (td, J = 8.5 Hz, 2.5 Hz, 1H),4.53-4.45 (m, 1H), 2.87 (s, 3H), 1.31-1.26 (m, 1H), 0.71-0.66 (m, 1H), 0.61-0.55 (m, 2H), 0.42-0.38 (m, 1H). LC-MS m/z: 393.2 $[M+H]^+$. HPLC Purity (214 nm): 95%; t_R = 9.17 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(6-fluoropyridin-3-yl)-7-methylpyrazolo[1,5-a]pyrimidine-3-carboxamide



[00518] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 6-fluoropyridin-3-ylboronic acid afforded the title compound (25.7 mg, 27%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.11 (d, J = 2.5 Hz, 1H), 8.76 (td, J = 8.0 Hz, 2.5 Hz, 1H), 8.70 (s, 1H), 8.48 (d, J = 9.5 Hz, 1H), 8.04 (s, 1H), 7.53 (dd, J = 9.0 Hz, 2.5 Hz, 1H), 4.46-4.40 (m, 1H), 2.88 (s, 3H), 1.34-1.29 (m, 1H), 0.71-0.67 (m, 1H), 0.62-0.57 (m, 2H), 0.38-0.36 (m, 1H). LC-MS m/z: 394.1 $[M+H]^+$. HPLC Purity (254 nm): 98%; t_R = 8.39 min.

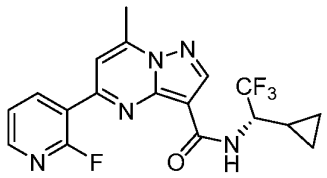
(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(2-fluoropyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00519] Following general procedure A, 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (300 mg, 1.42 mmol) and (*R*)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (300 mg, 67 %) as a white solid. LC-MS m/z: 333.1 $[M+H]^+$. HPLC: Purity (214 nm): > 95%; t_R = 1.84 min.

[00520] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 2-fluoropyridin-3-ylboronic acid afforded the title compound (15 mg, 16 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.60 (t, J = 8.0 Hz, 1H), 8.50-8.47 (m, 2H), 7.80 (s, 1H), 7.67 (t, J = 6.0 Hz, 1H), 4.46-4.40 (m, 1H), 2.89 (s, 3H), 1.27-1.19 (m, 1H), 0.70-0.64 (m, 1H), 0.60-0.52 (m, 2H), 0.39-0.33 (m, 1H). LC-MS m/z: 394.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.37 min

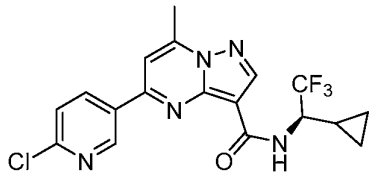
(*S*)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-5-(2-fluoropyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00521] Following general procedure A, 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (844 mg, 4.0 mmol) and (*S*)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (940 mg, 71 %) as a white solid. LC-MS m/z: 333.1 $[M+H]^+$. t_R = 1.83 min.

[00522] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (1.8 g, 5.4 mmol) and 2-fluoropyridin-3-ylboronic acid afforded the title compound (1.5 g, 69 %) as a white solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.68 (s, 1H), 8.63 (tt, J = 10.0 Hz, 2.0 Hz, 1H), 8.44 (dd, J = 2.8 Hz, 1.2 Hz, 1H), 7.71 (s, 1H), 7.59 (tt, J = 10.0 Hz, 2.0 Hz, 1H), 4.42-4.39 (m, 1H), 2.97 (s, 3H), 1.31-1.26 (m, 1H), 0.79-0.74 (m, 1H), 0.65-0.57 (m, 2H), 0.51-0.48 (m, 1H). LC-MS m/z: 394.1[M+H]$^+$. HPLC: Purity (214 nm): 99%; t_R = 8.40 min.

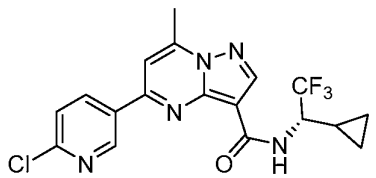
(*R*)-5-(6-Chloropyridin-3-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00523] Following general procedure A, 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (550 mg, 2.48 mmol), and (*R*)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (735 mg, 88 %) as a white solid. LC-MS m/z: 333.0 [M+H]$^+$. Purity (214 nm): > 99%; t_R = 1.86 min.

[00524] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.21 mmol) and 6-chloropyridin-3-ylboronic acid afforded the title compound (18 mg, 20 %) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.25 (d, J = 2.0 Hz, 1H), 8.71 (s, 1H), 8.61 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 8.46 (d, J = 9.5 Hz, 1H), 8.04 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 4.46-4.38 (m, 1H), 2.88 (s, 3H), 1.34-1.31 (m, 1H), 0.73-0.68 (m, 1H), 0.62-0.57 (m, 2H), 0.40-0.35 (m, 1H). LC-MS m/z: 410.1 [M+H]$^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.80 min.

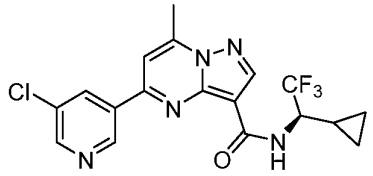
(*S*)-5-(6-Chloropyridin-3-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00525] Following general procedure A, 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (300 mg, 1.42 mmol), and (*S*)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (355 mg, 75 %) as a white solid. LC-MS m/z: 333.0 $[M+H]^+$. Purity (214 nm): > 99%; t_R = 1.86 min.

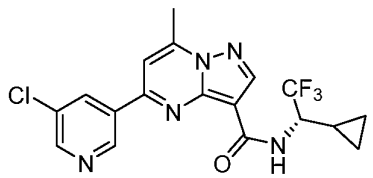
[00526] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.18 mmol) and 6-chloropyridin-3-ylboronic acid afforded the title compound (17.5 mg, 24 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.24 (d, J = 2.0 Hz, 1H), 8.71 (s, 1H), 8.61 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 8.45 (d, J = 9.5 Hz, 1H), 8.04 (s, 1H), 7.84 (d, J = 8.0 Hz, 1H), 4.46-4.38 (m, 1H), 2.88 (s, 3H), 1.34-1.31 (m, 1H), 0.72-0.67 (m, 1H), 0.61-0.59 (m, 2H), 0.40-0.36 (m, 1H). LC-MS m/z: 410.0 $[M+H]^+$. HPLC: Purity (214 nm): > 98%; t_R = 8.79 min.

(*R*)-5-(5-Chloropyridin-3-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



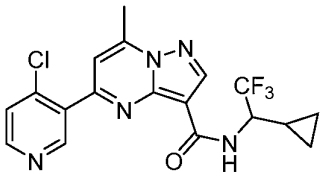
[00527] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 5-chloropyridin-3-ylboronic acid afforded the title compound (5.5 mg, 6 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.38 (d, J = 2.0Hz, 1H), 8.86 (d, J = 2.4 Hz, 1H), 8.72 (s, 1H), 8.70 (t, J = 2.0 Hz, 1H), 8.48 (d, J = 12.8 Hz, 1H), 8.12 (s, 1H), 4.50-4.46 (m, 1H), 2.88 (s, 3H), 1.32-1.26 (m, 1H), 0.72-0.67 (m, 1H), 0.61-0.56 (m, 2H), 0.43-0.37 (m, 1H). LC-MS m/z: 410.0 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.73 min.

(*S*)-5-(5-Chloropyridin-3-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



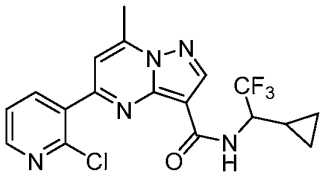
[00528] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.18 mmol) and 5-chloropyridin-3-ylboronic acid afforded the title compound (33 mg, 44 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.39 (d, J = 1.5 Hz, 1H), 8.87 (d, J = 2.0 Hz, 1H), 8.73 (s, 1H), 8.71 (s, 1H), 8.48 (d, J = 9.5 Hz, 1H), 8.12 (s, 1H), 4.53-4.44 (m, 1H), 2.89 (s, 3H), 1.33-1.26 (m, 1H), 0.74-0.67 (m, 1H), 0.62-0.57 (m, 2H), 0.45-0.39 (m, 1H). LC-MS m/z: 410.0 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.71 min.

5-(4-Chloropyridin-3-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00529] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 4-chloropyridin-3-ylboronic acid afforded the title compound (5.5 mg, 6 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.76 (s, 1H), 8.72 (d, J = 4.5 Hz, 1H), 8.40 (d, J = 9.5 Hz, 1H), 7.83 (d, J = 5.5 Hz, 1H), 7.75 (s, 1H), 4.45-4.36 (m, 1H), 2.89 (s, 3H), 1.20-1.12 (m, 1H), 0.68-0.62 (m, 1H), 0.59-0.48 (m, 2H), 0.34-0.28 (m, 1H). LC-MS m/z: 410.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.10 min.

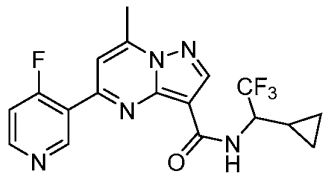
5-(2-Chloropyridin-3-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00530] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.21 mmol) and 2-chloropyridin-3-ylboronic acid afforded the title compound (12 mg, 15%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.75 (s, 1H), 8.62 (dd, J = 4.8 Hz, 1.6 Hz, 1H), 8.41 (d, J = 9.6 Hz, 1H), 8.26 (dd, J = 7.6 Hz, 1.6 Hz, 1H), 7.71 (t, J = 6.0 Hz, 1H), 4.44-4.36 (m, 1H), 2.89 (s, 3H), 1.21-1.12 (m,

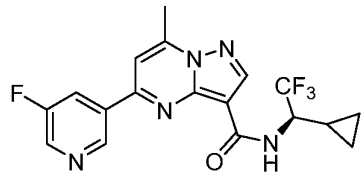
1H), 0.69-0.61 (m, 1H), 0.59-0.47 (m, 2H), 0.34-0.27 (m, 1H). LC-MS m/z: 410.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.24 min.

_N_-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(4-fluoropyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



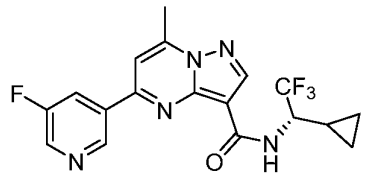
[00531] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.18 mmol) and 4-fluoropyridin-3-ylboronic acid afforded the title compound (7.7 mg, 11%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.21 (d, J = 10.8 Hz, 1H), 8.80 (dd, J = 8.0 Hz, 6.0 Hz, 1H), 8.74 (s, 1H), 8.47 (d, J = 9.6 Hz, 1H), 7.81 (s, 1H), 7.64 (dd, J = 7.6 Hz, 6.0 Hz, 1H), 4.49-4.42 (m, 1H), 2.89 (s, 3H), 1.23-1.18 (m, 1H), 0.68-0.64 (m, 1H), 0.59-0.54 (m, 2H), 0.39-0.34 (m, 1H). LC-MS m/z: 394.0 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.81 min.

(*R*)-5-(5-Fluoropyridin-3-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



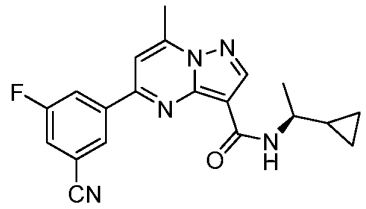
[00532] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 5-fluoropyridin-3-ylboronic acid afforded the title compound (4.2 mg, 5 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.38 (d, J = 1.6 Hz, 1H), 8.87 (d, J = 1.6 Hz, 1H), 8.72 (s, 1H), 8.70 (t, J = 2.4 Hz, 1H), 8.48 (d, J = 10.0 Hz, 1H), 8.12 (s, 1H), 4.51-4.45 (m, 1H), 2.88 (s, 3H), 1.32-1.24 (m, 1H), 0.72-0.66 (m, 1H), 0.62-0.55 (m, 2H), 0.43-0.37 (m, 1H). LC-MS m/z: 394.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.25 min.

(*S*)-5-(5-Fluoropyridin-3-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



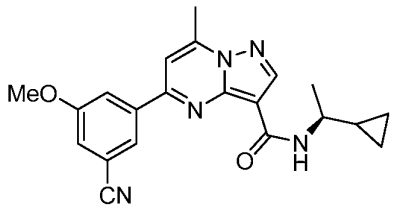
[00533] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.18 mmol) and 5-fluoropyridin-3-ylboronic acid afforded the title compound (25 mg, 35 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.32 (s, 1H), 8.84 (d, J = 2.0 Hz, 1H), 8.73 (s, 1H), 8.49-8.48 (m, 2H), 8.09 (s, 1H), 4.51-4.43 (m, 1H), 2.89 (s, 3H), 1.35-1.28 (m, 1H), 0.73-0.67 (m, 1H), 0.63-0.56 (m, 2H), 0.44-0.37 (m, 1H). LC-MS m/z: 394.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.34 min.

(*S*)-5-(3-Cyano-5-fluorophenyl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



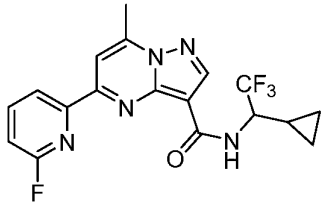
[00534] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.29 mmol) and 3-cyano-5-fluorophenylboronic acid afforded the title compound (25 mg, 25 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.61 (s, 1H), 8.46 (d, J = 9.6 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 8.07 (s, 1H), 3.66-3.60 (m, 1H), 2.87 (s, 3H), 1.28 (d, J = 6.4 Hz, 3H), 1.16-1.12 (m, 1H), 0.55-0.48 (m, 2H), 0.43-0.34 (m, 2H). LC-MS m/z: 364.1 $[M+H]^+$. HPLC: Purity (214 nm): > 98%; t_R = 8.36 min.

(*S*)-5-(3-Cyano-5-methoxyphenyl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



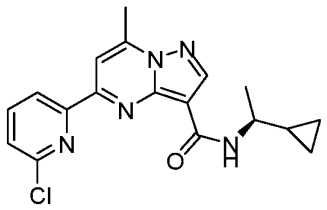
[00535] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (78 mg, 0.28 mmol) and 3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile afforded the title compound (54 mg, 51%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.60 (s, 1H), 8.27 (s, 1H), 8.11-7.98 (m, 3H), 7.69 (s, 1H), 3.95 (s, 3H), 3.64-3.60 (m, 1H), 2.85 (s, 3H), 1.29 (d, J = 6.4 Hz, 3H), 1.11-1.07 (m, 1H), 0.59-0.42 (m, 2H), 0.42-0.36 (m, 1H), 0.36-0.29 (m, 1H). LC-MS m/z: 376.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.38 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(6-fluoropyridin-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



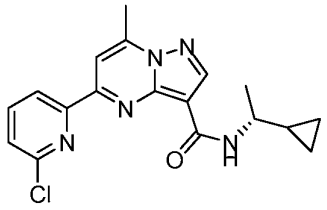
[00536] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 2-fluoro-6-(tributylstannyl)pyridine afforded the title compound (37 mg, 39%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.73 (s, 1H), 8.50 (d, J = 9.5 Hz, 1H), 8.34-8.30 (m, 2H), 8.04 (s, 1H), 7.45 (dd, J = 8.5 Hz, 4.5 Hz, 1H), 4.46-4.40 (m, 1H), 2.91 (s, 3H), 1.40-1.35 (m, 1H), 0.74-0.68 (m, 1H), 0.64-0.58 (m, 2H), 0.45-0.40 (m, 1H). LC-MS m/z: 394.1 $[M+H]^+$. HPLC Purity (214 nm): 99%; t_R = 9.00 min.

(*S*)-5-(6-Chloropyridin-2-yl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



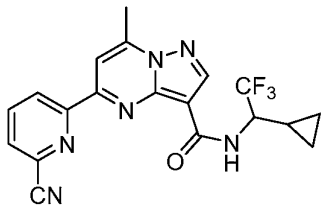
[00537] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (150 mg, 0.54 mmol) and 2-chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine afforded the title compound (73 mg, 37 %) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-d_4): δ 8.61 (s, 1H), 8.46 (d, J = 8.0 Hz, 1H), 8.11 (s, 1H), 8.05 (t, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 3.70-3.65 (m, 1H), 2.94 (s, 3H), 1.42 (d, J = 8.0 Hz, 3H), 1.19-1.14 (m, 1H), 0.66-0.58 (m, 2H), 0.50-0.46 (m, 1H), 0.41-0.36 (m, 1H). LC-MS m/z: 369.1 $[M+H]^+$. HPLC Purity (214 nm): 99%; t_R = 8.62 min.

(*R*)-5-(6-Chloropyridin-2-yl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



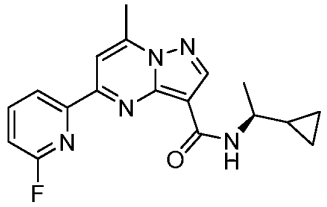
[00538] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.21 mmol) and 2-chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine afforded the title compound (31 mg, 60%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.45 (d, J = 7.5 Hz, 1H), 8.20 (t, J = 8.0 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 8.02 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 3.62-3.58 (m, 1H), 2.91 (s, 3H), 1.32 (d, J = 6.5 Hz, 3H), 1.16-1.14 (m, 1H), 0.54-0.48 (m, 2H), 0.40-0.32 (m, 2H). LC-MS m/z: 356.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 9.03 min.

5-(6-Cyanopyridin-2-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



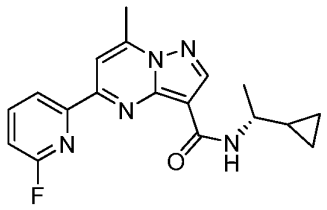
[00539] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 6-cyanopyridin-2-ylboronic acid afforded the title compound (42 mg, 44%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.74 (s, 1H), 8.65 (d, J = 8.0 Hz, 1H), 8.47 (d, J = 9.2 Hz, 1H), 8.39 (t, J = 8.0 Hz, 1H), 8.27 (d, J = 8.0 Hz, 1H), 8.14 (s, 1H), 4.41-4.37 (m, 1H), 2.92 (s, 3H), 1.40-1.36 (m, 1H), 0.72-0.67 (m, 1H), 0.64-0.57 (m, 2H), 0.40-0.37 (m, 1H). LC-MS m/z: 401.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.65 min.

(*S*)-*N*-(1-Cyclopropylethyl)-5-(6-fluoropyridin-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00540] Following general procedure F, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.28 mmol) and 2-fluoro-6-(tributylstannyl)pyridine afforded the title compound (55 mg, 56%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.62 (s, 1H), 8.40 (dd, J = 7.5 Hz, 2.0 Hz, 1H), 8.32 (dd, J = 16.0 Hz, 8.0 Hz, 1H), 8.07 (d, J = 7.5 Hz, 1H), 7.99 (s, 1H), 7.44 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 3.64-3.58 (m, 1H), 2.89 (s, 3H), 1.33 (d, J = 6.5 Hz, 3H), 1.18-1.12 (m, 1H), 0.58-0.49 (m, 2H), 0.41-0.36 (m, 1H), 0.36-0.31 (m, 1H). LC-MS m/z: 340.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.45 min.

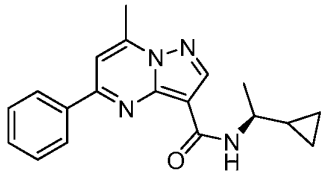
(*R*)-*N*-(1-Cyclopropylethyl)-5-(6-fluoropyridin-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00541] Following general procedure A, 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (1.0 g, 4.74 mmol) and (*R*)-1-cyclopropylethanamine afforded (*R*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (1.2 g, 90 %) as a white solid.

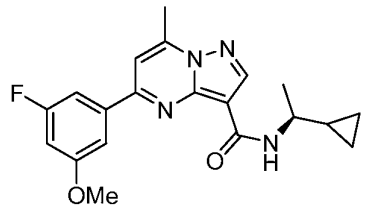
[00542] Following general procedure F, (*R*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.29 mmol), and 2-fluoro-6-(tributylstannyl)pyridine afforded the title compound (24.3 mg, 25 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.64 (s, 1H), 8.42 (dd, J = 7.6 Hz, 2.0 Hz, 1H), 8.32 (q, J = 8.0 Hz, 1H), 8.09 (d, J = 7.2 Hz, 1H), 8.01 (s, 1H), 7.45 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 3.63-3.57 (m, 1H), 2.90 (s, 3H), 1.32 (d, J = 6.4 Hz, 3H), 1.19-1.13 (m, 1H), 0.55-0.48 (m, 2H), 0.41-0.32 (m, 2H). LC-MS m/z: 340.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.51 min.

(*S*)-*N*-(1-Cyclopropylethyl)-7-methyl-5-phenylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



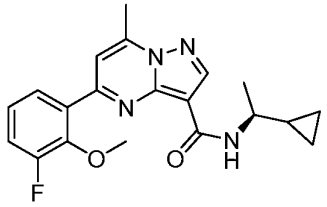
[00543] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.22 mmol) and phenylboronic acid afforded the title compound (30 mg, 57 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 8.27 (dd, J = 7.6 Hz, 2.0 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H), 7.91 (s, 1H), 7.65-7.61 (m, 3H), 3.66-3.61 (m, 1H), 2.86 (s, 3H), 1.29 (d, J = 6.4 Hz, 3H), 1.12-1.07 (m, 1H), 0.54-0.47 (m, 2H), 0.40-0.33 (m, 2H). LC-MS m/z: 321.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.66 min.

(*S*)-*N*-(1-Cyclopropylethyl)-5-(3-fluoro-5-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



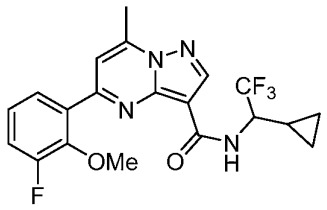
[00544] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (61 mg, 0.36 mmol) and 3-fluoro-5-methoxyphenylboronic acid afforded the title compound (80 mg, 60 %) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4): δ 8.58 (s, 1H), 7.70 (s, 1H), 7.62 (s, 1H), 7.57 (d, J = 10.0 Hz, 1H), 6.94 (dd, J = 11.0 Hz, 2.5 Hz, 1H), 3.93 (s, 3H), 3.73-3.68 (m, 1H), 2.92 (s, 3H), 1.40 (d, J = 6.5 Hz, 3H), 1.12-1.08 (m, 1H), 0.66-0.58 (m, 2H), 0.50-0.47 (m, 1H), 0.40-0.37 (m, 1H). LC-MS m/z: 369.1 $[M+H]^+$. HPLC Purity (214 nm): 99%; t_R = 8.62 min.

(*S*)-*N*-(1-Cyclopropylethyl)-5-(3-fluoro-2-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



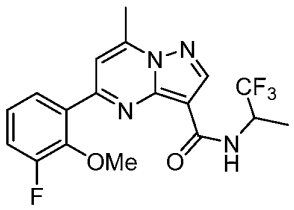
[00545] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (78 mg, 0.28 mmol) and 3-fluoro-2-methoxyphenylboronic acid afforded the title compound (55 mg, 54 %) as a grey solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.61 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.63 (s, 1H), 7.52 (ddd, J = 8.0 Hz, 3.0 Hz, 1.0 Hz, 1H), 7.37-7.32 (m, 1H), 3.91 (d, J = 1.5 Hz, 3H), 3.62-3.58 (m, 1H), 2.86 (s, 3H), 1.24 (d, J = 6.5 Hz, 3H), 1.00-0.98 (m, 1H), 0.48-0.38 (m, 2H), 0.37-0.31 (m, 1H), 0.30-0.24 (m, 1H). LC-MS m/z: 369.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.88 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(3-fluoro-2-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00546] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (72 mg, 0.22 mmol) and 3-fluoro-2-methoxyphenylboronic acid afforded the title compound (55 mg, 59 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 (s, 1H), 8.47 (d, J = 10.0 Hz, 1H), 7.67 (s, 1H), 7.66 (d, J = 10.0 Hz, 1H), 7.52 (ddd, J = 11.5 Hz, 8.0 Hz, 1.0 Hz, 1H), 7.36-7.31 (m, 1H), 4.48-4.41 (m, 1H), 3.90 (d, J = 1.0 Hz, 3H), 2.88 (s, 3H), 1.22-1.18 (m, 1H), 0.68-0.65 (m, 1H), 0.58-0.54 (m, 2H), 0.37-0.34 (m, 1H). LC-MS m/z: 423.0 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 9.32 min.

5-(3-Fluoro-2-methoxyphenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

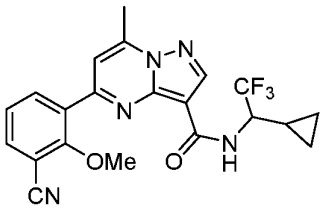


[00547] Following general procedure A, 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (1.5 g, 7.1 mmol) and 1,1,1-trifluoropropan-2-amine hydrochloride afforded 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (1.5 g, 69%) as a yellow green solid. LC-MS m/z: 307.1/309.0 $[M+H]^+$. t_R = 1.74 min.

[00548] Following general procedure D, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.15 mmol) and 3-fluoro-2-methoxyphenylboronic acid afforded the title compound (38 mg, 49 %) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.50 (d, J = 9.5 Hz, 1H), 7.65 (d, J = 7.5 Hz, 1H), 7.52 (s, 1H), 7.31-7.27 (m, 1H), 7.22-7.18 (m, 1H), 5.04-4.95 (m, 1H), 3.96 (d, J = 2.0 Hz, 3H),

2.90 (s, 3H), 1.44 (d, J = 7.0 Hz, 1H). LC-MS m/z: 397.0 $[M+H]^+$. HPLC Purity (214 nm): 99%; t_R = 8.97 min.

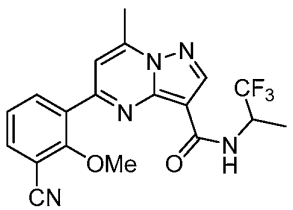
5-(3-Cyano-2-methoxyphenyl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00549] A mixture of 3-bromo-2-methoxybenzonitrile (2.12 g, 10 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (3.04 g, 12 mmol), KOAc (2.44 g, 25 mmol), $PdCl_2$(dppf)•CH_2Cl_2 (860 mg, 1 mmol) was flushed with N_2 (x3). Then 1,4-dioxane (20 mL) was added and the reaction mixture was stirred at 90 °C for 1 h, filtered and concentrated *in vacuo*. The residue was dissolved in isopropyl ether (60 mL), filtered and concentrated *in vacuo* again to afford crude 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (2 g) as a black oil.

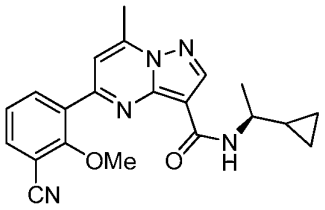
[00550] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.18 mmol) and 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile afforded the title compound (20 mg, 26 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.73 (s, 1 H), 8.43 (d, J = 9.5 Hz, 1H), 8.14 (d, J = 6.5 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.72 (s, 1 H), 7.54 (t, J = 8.0 Hz, 1H), 4.43-4.41 (m, 1H), 3.88 (s, 3H), 2.88 (s, 3H), 1.22-1.20 (m, 1H), 0.66-0.64 (m, 1H), 0.58-0.54 (m, 2H), 0.36-0.34 (m, 1H). LC-MS m/z: 430.1 $[M+H]^+$. HPLC: Purity (214 nm): 98.5 %; t_R = 8.65 min.

5-(3-Cyano-2-methoxyphenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



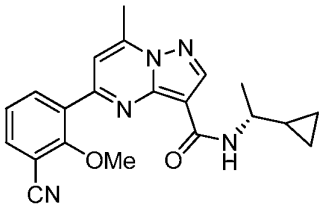
[00551] Following general procedure D, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.20 mmol) and 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile afforded the title compound (55 mg, 69 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.73 (s, 1 H), 8.37 (d, J = 9.5 Hz, 1H), 8.17 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 8.04 (dd, J = 7.5 Hz, 2.0 Hz, 1H), 7.72 (s, 1H), 7.54 (t, J = 8.0 Hz, 1H), 4.96-4.91 (m, 1H), 3.87 (s, 3H), 2.88 (s, 3H), 1.39 (d, J = 7.0 Hz, 3H). LC-MS m/z: 404.1 $[M+H]^+$. HPLC: Purity (214 nm): 98.5 %; t_R = 8.30 min.

(*S*)-5-(3-Cyano-2-methoxyphenyl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00552] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.22 mmol) and 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile afforded the title compound (8 mg, 10 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (s, 1 H), 8.21 (dd, J = 7.5 Hz, 1.5 Hz, 1H), 8.04 (dd, J = 7.5 Hz, 1.5 Hz, 2H), 7.68 (s, 1 H), 7.55 (t, J = 7.5 Hz, 1H), 3.88 (s, 3H), 3.60-3.58 (m, 1H), 2.87 (s, 3H), 1.23 (d, J = 6.5 Hz, 3H), 1.02-0.99 (m, 1H), 0.46-0.27 (m, 4H). LC-MS m/z: 376.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.14 min.

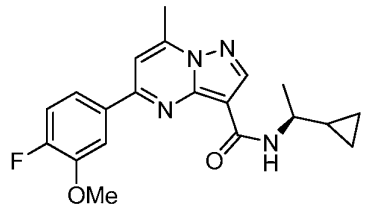
(*R*)-5-(3-Cyano-2-methoxyphenyl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00553] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (140 mg, 0.50 mmol) and 2-methoxy-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile afforded the title compound (22 mg,

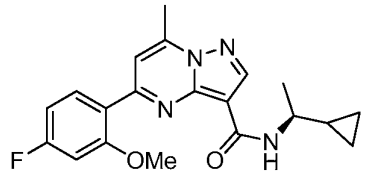
12%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.62 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 7.5 Hz, 2H), 7.67 (s, 1H), 7.55 (d, J = 8.5 Hz, 1H), 3.89 (s, 3H), 3.63-3.59 (m, 1H), 2.87 (s, 3H), 1.24 (d, J = 6.5 Hz, 3H), 1.04-1.01 (m, 1H), 0.48-0.40 (m, 2H), 0.36-0.26 (m, 2H). LC-MS m/z: 376.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.29 min.

(*S*)-*N*-(1-Cyclopropylethyl)-5-(4-fluoro-3-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00554] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (78 mg, 0.28 mmol) and 4-fluoro-3-methoxyphenylboronic acid afforded the title compound (50 mg, 48%) as a grey solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.55 (s, 1H), 8.08 (d, J = 7.6 Hz, 1H), 8.00 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.94 (s, 1H), 7.87 (ddd, J = 8.4 Hz, 4.4 Hz, 2.0 Hz, 1H), 7.42 (dd, J = 11.2 Hz, 8.8 Hz, 1H), 3.99 (s, 3H), 3.62-3.58 (m, 1H), 2.84 (s, 3H), 1.29 (d, J = 6.4 Hz, 3H), 1.11-1.00 (m, 1H), 0.51-0.40 (m, 2H), 0.40-0.30 (m, 1H), 0.30-0.21 (m, 1H). LC-MS m/z: 369.1 $[M+H]^+$. HPLC Purity (214 nm): 99%; t_R = 8.62 min.

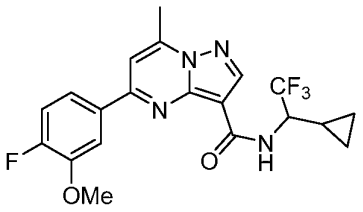
(*S*)-*N*-(1-Cyclopropylethyl)-5-(4-fluoro-2-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00555] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.18 mmol) and 4-fluoro-2-methoxyphenylboronic acid afforded the title compound (8 mg, 16 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.55 (s, 1H), 8.12 (d, J = 7.5 Hz, 1H), 7.95 (dd, J = 8.0 Hz, 6.0 Hz, 1H), 7.67 (s, 1H), 7.20 (dd, J = 11.5 Hz, 7.5 Hz, 1H), 7.05 (td, J = 8.5 Hz, 2.0 Hz, 1H), 3.95 (s, 3H), 3.65-3.58 (m, 1H), 2.83 (s, 3H), 1.24 (d, J = 6.5 Hz, 3H), 1.02-0.98 (m, 1H), 0.49-

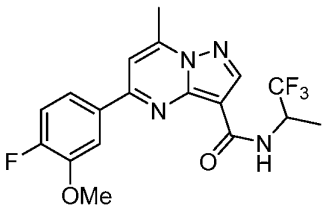
0.41 (m, 2H), 0.37-0.30 (m, 1H), 0.30-0.21 (m, 1H). LC-MS m/z: 369.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.81 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(4-fluoro-3-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



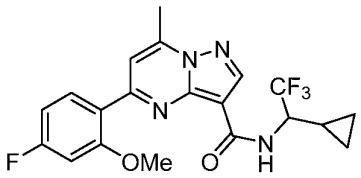
[00556] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.21 mmol) and 4-fluoro-3-methoxyphenylboronic acid afforded the title compound (55.5 mg, 62 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.66 (s, 1H), 8.51 (d, J = 9.2 Hz, 1H), 8.00 (s, 1H), 7.98 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.85 (ddd, J = 8.4 Hz, 4.0 Hz, 2.0 Hz, 1H), 7.50 (dd, J = 11.2 Hz, 8.8 Hz, 1H), 4.51-4.44 (m, 1H), 3.98 (s, 3H), 2.87 (s, 3H), 1.30-1.26 (m, 1H), 0.71-0.67 (m, 1H), 0.60-0.56 (m, 2H), 0.40-0.36 (m, 1H). LC-MS m/z: 423.2 $[M+H]^+$. HPLC Purity (254 nm): > 99%; t_R = 9.14 min.

5-(4-Fluoro-3-methoxyphenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



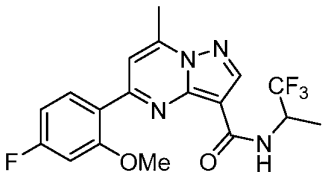
[00557] Following general procedure D, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.15 mmol) and 4-fluoro-3-methoxyphenylboronic acid afforded the title compound (38 mg, 49 %) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4): δ 8.63 (s, 1H), 7.97 (dd, J = 8.0 Hz, 2.5 Hz, 1H), 7.81 (ddd, J = 8.5 Hz, 4.0 Hz, 2.0 Hz, 1H), 7.76 (s, 1H), 7.33 (dd, J = 10.5 Hz, 8.5 Hz, 1H), 5.05-4.98 (m, 1H), 4.04 (s, 3H), 2.94 (s, 3H), 1.53 (d, J = 6.5 Hz, 2H). LC-MS m/z: 397.1 $[M+H]^+$. HPLC Purity (214 nm): 96%; t_R = 8.75 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(4-fluoro-2-methoxyphenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



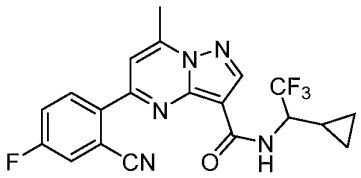
[00558] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 4-fluoro-2-methoxyphenylboronic acid afforded the title compound (44 mg, 30 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.65 (s, 1H), 8.51 (d, J = 9.6 Hz, 1H), 7.88 (dd, J = 8.4 Hz, 7.2 Hz, 1H), 7.70 (s, 1H), 7.21 (dd, J = 11.2 Hz, 2.0 Hz, 1H), 7.04 (td, J = 8.4 Hz, 2.4 Hz, 1H), 4.49-4.43 (m, 1H), 3.94 (s, 3H), 2.84 (s, 3H), 1.24-1.16 (m, 1H), 0.67-0.62 (m, 1H), 0.58-0.51 (m, 2H), 0.38-0.32 (m, 1H). LC-MS m/z: 423.1 $[M+H]^+$. HPLC Purity (254 nm): > 99%; t_R = 9.32 min.

5-(4-Fluoro-2-methoxyphenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



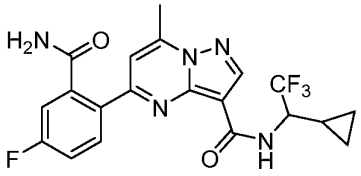
[00559] Following general procedure D, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.26 mmol) and 4-fluoro-2-methoxyphenylboronic acid afforded the title compound (50 mg, 48 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.65 (s, 1H), 8.46 (d, J = 9.5 Hz, 1H), 7.89 (dd, J = 8.5 Hz, 7.5 Hz, 1H), 7.70 (s, 1H), 7.21 (dd, J = 11.5 Hz, 2.0 Hz, 1H), 7.04 (td, J = 8.0 Hz, 2.0 Hz 1H), 4.98-4.92 (m, 1H), 3.94 (s, 3H), 2.84 (s, 3H), 1.39 (d, J = 6.5 Hz, 3H). LC-MS m/z: 397.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.91 min.

5-(2-Cyano-4-fluorophenyl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



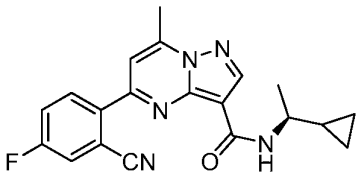
[00560] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (40 mg, 0.12 mmol) and 2-cyano-4-fluorophenylboronic acid afforded the title compound (28 mg, 55 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.74 (s, 1H), 8.27 (d, J = 9.0 Hz, 1H), 8.22-8.19 (m, 2H), 7.89 (td, J = 8.5 Hz, 3.0 Hz, 1H), 7.83 (s, 1H), 4.30-4.25 (m, 1H), 2.89 (s, 3H), 1.37-1.33 (m, 1H), 0.71-0.68 (m, 1H), 0.64-0.61 (m, 1H), 0.52-0.49 (m, 1H), 0.34-0.31 (m, 1H). LC-MS m/z: 418.1 $[M+H]^+$. HPLC: Purity (214 nm): 98%; t_R = 8.63 min.

5-(2-Carbamoyl-4-fluorophenyl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



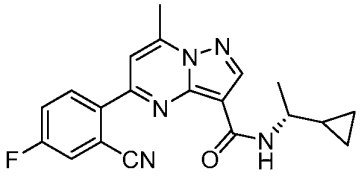
[00561] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.15 mmol), 2-cyano-4-fluorophenylboronic acid and Na_2CO_3 (0.3 mmol) afforded the title compound (44 mg, 68 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.25 (d, J = 9.2 Hz, 1H), 8.06 (s, 1H), 7.83 (dd, J = 8.8 Hz, 5.2 Hz, 1H), 7.55-7.46 (m, 3H), 7.40 (s, 1H), 4.27-4.20 (m, 1H), 2.85 (s, 3H), 1.42-1.37 (m, 1H), 0.67-0.58 (m, 3H), 0.30-0.25 (m, 1H). LC-MS m/z: 436.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.80 min.

(*S*)-5-(2-Cyano-4-fluorophenyl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



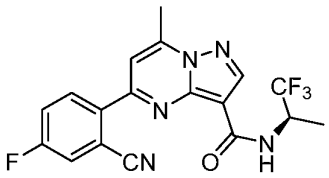
[00562] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (300 mg, 1.079 mmol) and 2-cyano-4-fluorophenylboronic acid afforded the title compound (350 mg, 90 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.65 (s, 1H), 8.23 (dd, J = 8.5 Hz, 5.5 Hz, 1H), 8.19 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 7.94 (s, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.88 (td, J = 9.0 Hz, 3.0 Hz, 1H), 7.78 (s, 1H), 3.58-3.51 (m, 1H), 2.88 (s, 3H), 1.28 (d, J = 6.5 Hz, 3H), 1.11-1.06 (m, 1H), 0.48-0.42 (m, 1H), 0.40-0.30 (m, 2H), 0.27-0.22 (m, 1H). LC-MS m/z: 364.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.14 min.

(*R*)-5-(2-Cyano-4-fluorophenyl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



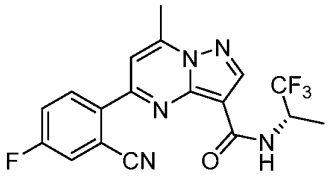
[00563] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.36 mmol) and 2-cyano-4-fluorophenylboronic acid afforded the title compound (54 mg, 42 %) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.76 (s, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.92 (dd, J = 8.5 Hz, 4.5 Hz, 1H), 7.62 (dd, J = 8.0 Hz, 2.5 Hz, 1H), 7.49 (td, J = 8.5 Hz, 2.5 Hz, 1H), 7.19 (s, 1H), 3.72-3.68 (m, 1H), 2.94 (s, 3H), 1.35 (d, J = 6.5 Hz, 3H), 1.10-1.07 (m, 1H), 0.53-0.49 (m, 1H), 0.47-0.42 (m, 2H), 0.30-0.28 (m, 1H). LC-MS m/z: 364.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.21 min.

(*R*)-5-(2-Cyano-4-fluorophenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



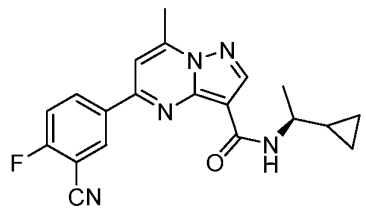
[00564] Following general procedure D, (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 2-cyano-4-fluorophenylboronic acid afforded the title compound (40 mg, 38%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): 8.75 (s, 1H), 8.23-8.20 (m, 2H), 8.12 (d, J = 9.5 Hz, 1H), 7.89 (td, J = 8.5 Hz, 2.0 Hz, 1H), 7.82 (s, 1H), 5.03-4.97 (m, 1H), 2.89 (s, 3H), 1.43 (d, J = 7.0 Hz, 3H). LC-MS m/z: 392.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.37 min.

(*S*)-5-(2-Cyano-4-fluorophenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



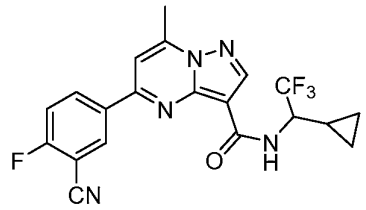
[00565] Following general procedure D, (*S*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 2-cyano-4-fluorophenylboronic acid afforded the title compound (42 mg, 42%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): 8.75 (s, 1H), 8.23-8.20 (m, 2H), 8.12 (d, J = 9.5 Hz, 1H), 7.89 (td, J = 8.5 Hz, 2.0 Hz, 1H), 7.82 (s, 1H), 5.03-4.97 (m, 1H), 2.89 (s, 3H), 1.43 (d, J = 7.0 Hz, 3H). LC-MS m/z: 392.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.38 min.

(*S*)-5-(3-Cyano-4-fluorophenyl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



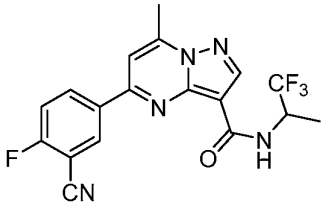
[00566] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.25 mmol) and 3-cyano-4-fluorophenylboronic acid afforded the title compound (47 mg, 40%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.84 (dd, J = 6.0 Hz, 2.0 Hz, 1H), 8.68-8.64 (m, 1H), 8.61 (s, 1H), 8.09 (d, J = 7.6 Hz, 1H), 8.02 (s, 1H), 7.82 (t, J = 9.2 Hz, 1H), 3.62-3.58 (m, 1H), 2.86 (s, 3H), 1.29 (d, J = 6.4 Hz, 3H), 1.16-1.10 (m, 1H), 0.55-0.48 (m, 2H), 0.41-0.32 (m, 2H). LC-MS m/z: 364.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.31 min.

5-(3-Cyano-4-fluorophenyl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00567] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.18 mmol) and 3-cyano-4-fluorophenylboronic acid afforded the title compound (36 mg, 47 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.77 (dd, J = 6.5 Hz, 2.0 Hz, 1H), 8.70 (s, 1H), 8.63-8.59 (m, 1H), 8.48 (d, J = 9.5 Hz, 1H), 8.05 (s, 1H), 7.86 (d, J = 9.5 Hz, 1H), 4.46-4.41 (m, 1H), 2.87 (s, 3H), 1.36-1.31 (m, 1H), 0.71-0.67 (m, 1H), 0.62-0.56 (m, 2H), 0.42-0.38 (m, 1H). LC-MS m/z: 418.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.74 min.

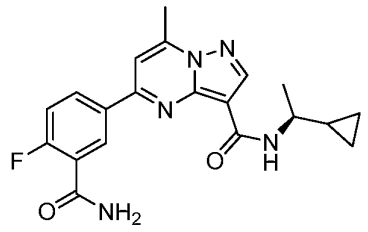
5-(3-Cyano-4-fluorophenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00568] Following general procedure D, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.20 mmol) and 3-cyano-4-fluorophenylboronic acid afforded the title compound (8 mg, 11 %) as a yellow solid. ^{1}H NMR

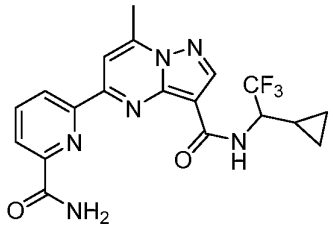
(400 MHz, DMSO-d_6): δ 8.79 (dd, J = 6.0 Hz, 2.4 Hz, 1H), 8.71 (s, 1H), 8.65-8.60 (m 1H), 8.41 (d, J = 9.2 Hz, 1H), 8.06 (s, 1H), 7.86 (t, J = 8.0 Hz, 1H), 5.00-4.94 (m, 1H), 2.87 (s, 3H), 1.46 (d, J = 6.8 Hz, 3H). LC-MS m/z: 392.0 $[M+H]^+$. HPLC: Purity (214 nm): 97%; t_R = 8.37 min.

(*S*)-5-(3-Carbamoyl-4-fluorophenyl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00569] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (110 mg, 0.35 mmol) and 3-carbamoyl-4-fluorophenylboronic acid afforded the title compound (75 mg, 55%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.62 (d, J = 6.0 Hz, 1H), 8.57 (s, 1H), 8.41 (brs, 1H), 8.21 (d, J = 7.5 Hz, 1H), 7.98 (s, 1H), 7.92 (s, 1H), 7.84 (s, 1H), 7.57 (t, J = 9.0 Hz, 1H), 3.60-3.56 (m, 1H), 2.86 (s, 3H), 1.30 (d, J = 6.0 Hz, 3H), 1.13-1.10 (m, 1H), 0.53-0.50 (m, 2H), 0.35-0.32 (m, 2H). LC-MS m/z: 382.1 $[M+H]^+$. HPLC Purity (214 nm): 99%; t_R = 6.69 min.

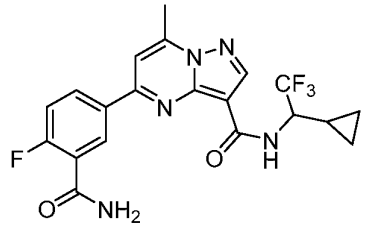
5-(6-Carbamoylpyridin-2-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00570] To a mixture of 5-(6-cyanopyridin-2-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (38 mg, 0.095 mmol) in DMSO (2 mL) was added K_2CO_3 (2 mg, 0.014 mmol) and H_2O_2 (4 mg, 0.014 mmol) at 25 °C and the mixture was stirred for 15 h, and purified by preparative HPLC (10mM NH_4HCO_3/MeCN) to afford the title compound (7.0 mg, 18 %) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.78 (s,

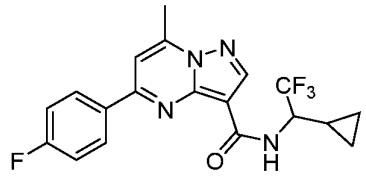
1H), 8.72 (s, 1H), 8.66 (s, 1H), 8.57 (d, J = 8.0 Hz, 1H), 8.53 (d, J = 9.5 Hz, 1H), 8.29 (t, J = 7.5 Hz, 1H), 8.23 (d, J = 7.5 Hz, 1H), 7.95 (s, 1H), 4.45-4.41 (m, 1H), 2.93 (s, 3H), 1.42-1.38 (m, 1H), 0.74-0.70 (m, 1H), 0.66-0.60 (m, 2H), 0.43-0.39 (m, 1H). LC-MS m/z: 419.0 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.40 min.

5-(3-Carbamoyl-4-fluorophenyl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00571] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.18 mmol) and 3-carbamoyl-4-fluorophenylboronic acid afforded the title compound (27.4 mg, 35 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.60-8.58 (m, 2H), 8.40-8.37 (m, 1H), 8.03 (s, 1H), 7.90 (s, 1H), 7.84 (s, 1H), 7.58 (t, J = 9.0 Hz, 1H), 4.40-4.36 (m, 1H), 2.87 (s, 3H), 1.37-1.34 (m, 1H), 0.71-0.66 (m, 1H), 0.62-0.60 (m, 2H), 0.39-0.36 (m, 1H). LC-MS m/z: 436.0 $[M+H]^+$. HPLC: Purity (214 nm): 97.8%; t_R = 7.33 min.

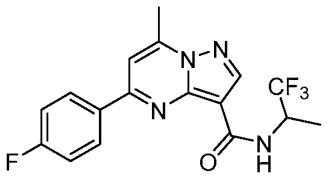
***N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(4-fluorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



[00572] Following general procedure A, 5-(4-fluorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.11 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (14 mg, 31 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.56 (d, J = 9.5 Hz, 1H), 8.30 (dd, J = 8.5 Hz, 5.0 Hz, 1H), 7.95 (s, 1H), 7.50 (t, J = 9.0 Hz, 1H), 4.48-4.42 (m, 1H), 2.51 (s, 3H), 1.34-

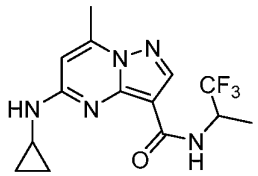
1.27 (m, 1H), 0.71-0.64 (m, 1H), 0.61-0.55 (m, 2H), 0.41-0.36 (m, 1H). LC-MS m/z: 393.0 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 9.19 min.

5-(4-Fluorophenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



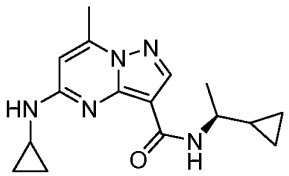
[00573] Following general procedure A, 5-(4-fluorophenyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.11 mmol) and 1,1,1-trifluoropropan-2-amine hydrochloride afforded the title compound (14 mg, 33 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.46 (d, J = 9.5 Hz, 1H), 8.30 (dd, J = 9.0 Hz, 6.0 Hz, 1H), 7.95 (s, 1H), 7.50 (t, J = 9.0 Hz, 1H), 5.00-4.94 (m, 1H), 2.86 (s, 3H), 1.46 (d, J = 6.5 Hz, 1H). LC-MS m/z: 367.1 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 8.86 min.

5-(Cyclopropylamino)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



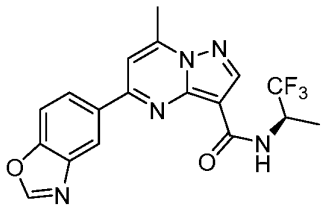
[00574] Following general procedure A, 5-(cyclopropylamino)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.13 mmol) and 1,1,1-trifluoropropan-2-amine hydrochloride afforded the title compound (24 mg, 57 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (d, J = 9.0 Hz, 1H), 8.28 (s, 1H), 8.19 (s, 1H), 6.22 (s, 1H), 4.90-4.84 (m, 1H), 2.70-2.66 (m, 1H), 2.56 (s, 3H), 1.36 (d, J = 7.0 Hz, 3H), 0.80-0.76 (m, 2H), 0.56-0.52 (m, 2H). LC-MS m/z: 328.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.44 min.

(*S*)-5-(Cyclopropylamino)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



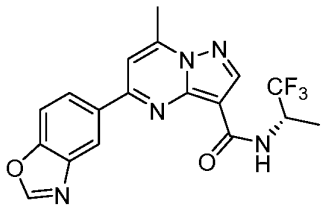
[00575] Following general procedure A, 5-(cyclopropylamino)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.13 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (13 mg, 31 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.00 (s, 1H), 7.93 (s, 1H), 7.90 (s, 1H), 5.98 (s, 1H), 3.40-3.34 (m, 1H), 2.58-2.51 (m, 1H), 2.34 (s, 3H), 1.01 (d, J = 6.5 Hz, 3H), 0.74-0.69 (m, 1H), 0.60-0.56 (m, 2H), 0.36-0.31 (m, 2H), 0.25-0.12 (m, 2H), 0.12-0.08 (m, 1H), 0.00- -0.05 (m, 1H). LC-MS m/z: 300.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.18 min.

(*R*)-5-(Benzo[*d*]oxazol-5-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



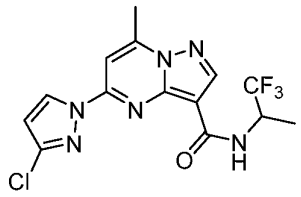
[00576] Following general procedure D, (*R*)-5-chloro-7-methyl-N-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.26 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazole afforded the title compound (88 mg, 75 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.90 (s, 1H), 8.69 (d, J = 2.0 Hz, 1H), 8.66 (s, 1H), 8.53 (d, J = 9.0 Hz, 1H), 8.35 (dd, J = 8.5 Hz, 1.5 Hz, 1H), 8.08 (s, 1H), 8.04 (d, J = 8.5 Hz, 1H), 5.00-4.96 (m, 1H), 2.88 (s, 3H), 1.48 (d, J = 7.0 Hz, 3H). LC-MS m/z: 390.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.90 min.

(*S*)-5-(Benzo[*d*]oxazol-5-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



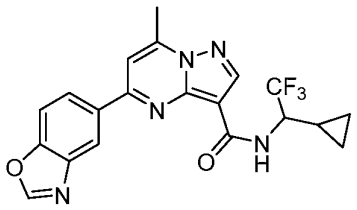
[00577] Following general procedure D, (*S*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.32 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazole afforded the title compound (18 mg, 18 %) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.64 (s, 2H), 8.63 (s, 1H), 8.38 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.86 (s, 1H), 5.02-5.49 (m, 1H), 2.97 (s, 3H), 1.57 (d, J = 7.0 Hz, 3H). LC-MS m/z: 390.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 7.90 min.

5-(3-Chloro-1*H*-pyrazol-1-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



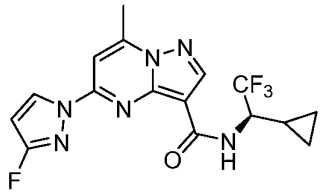
[00578] Following general procedure G, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.23 mmol) and 3-chloro-1*H*-pyrazole afforded the title compound (17 mg, 20%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.72 (d, J = 2.0 Hz, 1H), 8.66 (s, 1H), 8.02 (d, J = 9.0 Hz, 1H), 7.77 (s, 1H), 6.93 (d, J = 3.0 Hz, 1H), 4.96-4.92 (m, 1H), 2.87 (s, 3H), 1.46 (d, J = 7.0 Hz, 3H). LC-MS m/z: 373.0 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 8.79 min.

5-(Benzo[*d*]oxazol-5-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



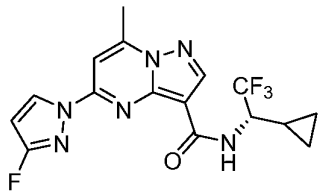
[00579] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.30 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazole afforded the title compound (45 mg, 36 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.91 (s, 1H), 8.70 (s, 1H), 8.67 (s, 1H), 8.62 (d, J = 9.0 Hz, 1H), 8.36 (d, J = 9.0 Hz, 1H), 8.10 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 4.53-4.48 (m, 1H), 2.88 (s, 3H), 1.32-1.28 (m, 1H), 0.73-0.69 (m, 1H), 0.62-0.57 (m, 2H), 0.43-0.40 (m, 1H). LC-MS m/z: 416.1 $[M+H]^+$. HPLC Purity (214 nm): 98%; t_R = 9.09 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(3-fluoro-1*H*-pyrazol-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



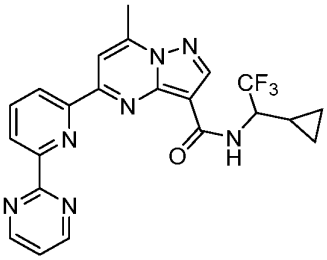
[00580] To a solution of (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) in anhydrous THF (3 mL) was added 3-fluoro-1*H*-pyrazole (25 mg, 0.288 mmol) and K_2CO_3 (100 mg, 0.72 mmol). The mixture was stirred at 70 °C for 8 h, poured into H_2O (20 mL) and extracted with EA (20 mL x 2). The organic layers were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by preparative TLC (PE/EA = 2/1) to afford the title compound (30 mg, 33 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.62 (t, J = 3.0 Hz, 1H), 8.14 (d, J = 9.5 Hz, 1H), 7.67 (s, 1H), 6.67 (q, J = 3.0 Hz, 1H), 4.33-4.27 (m, 1H), 2.86 (s, 3H), 1.47-1.23 (m, 1H), 0.73-0.56 (m, 3H), 0.39-0.36 (m, 1H). LC-MS m/z: 383.1 $[M+H]^+$. HPLC Purity (214 nm): 96.46 %; t_R = 8.82 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(3-fluoro-1*H*-pyrazol-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00581] A mixture of (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.21 mmol), 3-fluoro-1*H*-pyrazole (18 mg, 0.21 mmol), and K_2CO_3 (58 mg, 0.42 mmol) in DMF (2 mL) was stirred at 60 °C for 2 h, poured into H_2O (10 mL), and extracted with EA (30 mL x 3). The combined organic phases were washed with H_2O (50 mL) and brine (50 mL), 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 = 2/1) and preparative HPLC (10 mM NH_4HCO_3/MeCN) to afford the title compound (14 mg, 24%) as a white solid. ^{1}H NMR (400 MHz, MeOD-d_4): δ 8.59 (s, 1H), 8.55 (t, J = 2.4 Hz, 1H), 7.65 (s, 1H), 7.44 (q, J = 2.8 Hz, 1H), 4.36-4.30 (m, 1H), 2.92 (s, 3H), 1.40-1.34 (m, 1H), 0.82-0.75 (m, 1H), 0.70-0.58 (m, 2H), 0.52-0.46 (m, 1H). LC-MS m/z: 383.1 $[M+H]^+$. HPLC: Purity (214 nm): 93%; t_R = 8.83 min.

***N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(6-(pyrimidin-2-yl)pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



[00582] Following general procedure F, 2,6-dibromopyridine (2.0 g, 8.44 mmol) and 2-(tributylstannyl)pyrimidine afforded 2-(6-bromopyridin-2-yl)pyrimidine (600 mg, 40%) as a yellow solid. LC-MS m/z: 237.1 $[M+H]^+$. LC-MS Purity (214 nm): > 89 %; t_R = 1.45 min.

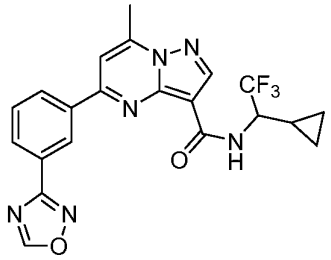
[00583] Following general procedure E*, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (200 mg, 0.83 mmol) and 2-(6-bromopyridin-2-yl)pyrimidine

afforded ethyl 7-methyl-5-(6-(pyrimidin-2-yl)pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (68 mg, 22%) as a yellow solid. LC-MS m/z: 361.1 $[M+H]^+$. LC-MS Purity (214 nm): > 96%; t_R = 1.67 min.

[00584] Following general procedure B*, ethyl 7-methyl-5-(6-(pyrimidin-2-yl)pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (60 mg, 0.16 mmol) afforded 7-methyl-5-(6-(pyrimidin-2-yl)pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (43mg, 83%) as a yellow solid. LC-MS m/z: 333.1 $[M+H]^+$. LC-MS Purity (214 nm): > 83%; t_R = 1.13 min.

[00585] Following general procedure A, 7-methyl-5-(6-(pyrimidin-2-yl)pyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.12 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (10 mg, 18%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.08 (d, *J* = 5.2 Hz, 1H), 8.74 (s, 1H), 8.60-8.54 (m, 3H), 8.32 (d, *J* = 7.6 Hz, 1H), 8.26 (s, 1H), 7.66 (t, *J* = 4.8 Hz, 1H), 4.48-4.41 (m, 1H), 2.96 (s, 3H), 1.45-1.37 (m, 1H), 0.75-0.70 (m, 1H), 0.66-0.60 (m, 2H), 0.46-0.40 (m, 1H). LC-MS m/z: 454.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.23 min.

<u>5-(3-(1,2,4-Oxadiazol-3-yl)phenyl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide</u>



[00586] To a solution of hydroxylamine hydrochloride (1.15 g, 16.5 mmol) and Na_2CO_3 (1.0 g, 9.9 mmol) in 16 mL of H_2O and 8 mL EtOH was added 3-bromobenzonitrile (1.2 g, 6.6 mmol). The reaction mixture was refluxed for 6 h, and extracted with EA (3 x 40 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford 3-bromo-*N*-hydroxybenzimidamide (800 mg, 56%) as a white solid. LC-MS m/z: 215.0 $[M+H]^+$.

[00587] To a solution of 3-bromo-*N*-hydroxybenzimidamide (1.5 g, 7.0 mmol) in triethoxymethane (5.0 mL) was added *p*-TsOH·H_2O (133 mg, 0.7 mmol). The reaction mixture was stirred at 90 °C for 16 h, and concentrated *in vacuo*. The residue was purified by flash

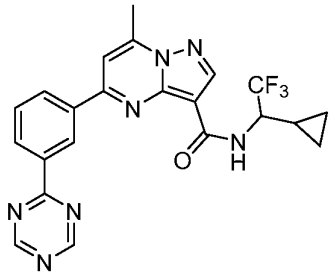
chromatography to afford 3-(3-bromophenyl)-1,2,4-oxadiazole as a white solid (900 mg, 57%). LC-MS m/z: 225.1 $[M+H]^+$.

[00588] Following general procedure D, 3-(3-bromophenyl)-1,2,4-oxadiazole (100 mg, 0.45 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) afforded 3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1,2,4-oxadiazole which was used in the next step without further purification. LC-MS m/z: 273.1 $[M+H]^+$.

[00589] Following general procedure D, 3-(3-bromophenyl)-1,2,4-oxadiazole (100 mg, 0.45 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) afforded 3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1,2,4-oxadiazole which was used in the next step without further purification. LC-MS m/z: 273.1 $[M+H]^+$.

[00590] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (66 mg, 0.19 mmol) and 3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1,2,4-oxadiazole afforded the title compound (10 mg, 20%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.88 (s, 1H), 8.82 (s, 1H), 8.72 (s, 1H), 8.64 (d, J = 9.0 Hz, 1H), 8.33 (d, J = 7.5 Hz, 1H), 8.29 (d, J = 7.5 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H), 7.44 (s, 1H), 4.45-4.42 (m, 1H), 2.96 (s, 3H), 1.36-1.30 (m, 1H), 0.76-0.73 (m, 1H), 0.65-0.52 (m, 3H). LC-MS m/z: 443.1 $[M+H]^+$. HPLC Purity (254 nm): 99%; t_R = 8.80 min.

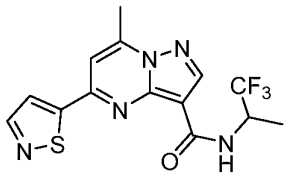
5-(3-(1,3,5-Triazin-2-yl)phenyl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00591] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (93 mg, 0.28 mmol) and 2-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1,3,5-triazine afforded the title compound (64.5 mg, 51%) as a grey solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.39 (s, 3H), 8.70 (s, 1H), 8.68 (d, J = 10.0 Hz, 1H), 8.66 (d, J = 8.0 Hz, 1H), 8.53 (d, J = 8.0 Hz, 1H), 8.07 (s, 1H), 7.87 (t, J =

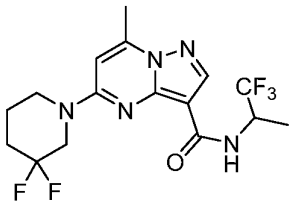
8.0 Hz, 1H), 4.46-4.37 (m, 1H), 2.91 (s, 3H), 1.49-1.43 (m, 1H), 0.82-0.76 (m, 1H), 0.70-0.61 (m, 2H), 0.46-0.40 (m, 1H). LC-MS m/z: 454.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.85 min.

5-(Isothiazol-5-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



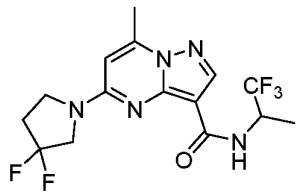
[00592] Following general procedure A, 5-(isothiazol-5-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (35 mg, 0.13 mmol) and 1,1,1-trifluoropropan-2-amine hydrochloride afforded the title compound (13.5 mg, 28%) as a white solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.67 (d, J = 2.0 Hz, 1H), 8.64 (s, 1H), 8.10 (d, J = 2.0 Hz, 1H), 7.74 (s, 1H), 5.00-4.93 (m, 1H), 2.94 (s, 3H), 1.55 (d, J = 7.2 Hz, 3H). LC-MS m/z: 356.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 9.69 min.

5-(3,3-Difluoropiperidin-1-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



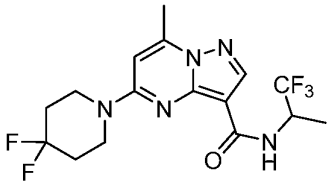
[00593] Following general procedure G, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.26 mmol) and 3,3-difluoropiperidine hydrochloride afforded the title compound (67 mg, 66%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (s, 1H), 8.23 (d, J = 9.5 Hz, 1H), 7.05 (s, 1H), 4.89-4.85 (m, 1H), 4.13 (t, J = 12.5 Hz, 2H), 3.80 (brs, 2H), 2.63 (s, 3H), 2.20-2.12 (m, 2H), 1.78 (brs, 2H), 1.36 (d, J = 7.0 Hz, 3H). LC-MS m/z: 392.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.94 min.

5-(3,3-Difluoropyrrolidin-1-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



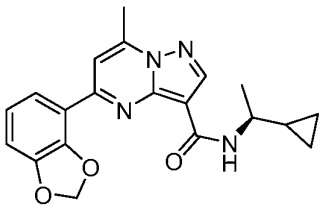
[00594] Following general procedure G, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.26 mmol) and 3,3-difluoropyrrolidine hydrochloride afforded the title compound (68 mg, 68%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (s, 2H), 6.64 (brs, 1H), 4.89-4.84 (m, 1H), 4.08-4.00 (m, 2H), 3.85-3.80 (m, 2H), 2.65 (s, 3H), 2.66-2.64 (m, 2H), 1.38 (d, J = 7.0 Hz, 3H). LC-MS m/z: 378.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.91 min.

5-(4,4-Difluoropiperidin-1-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



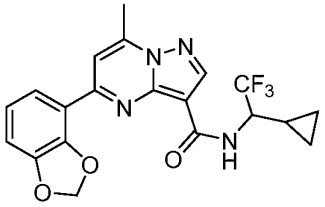
[00595] Following general procedure G, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.26 mmol) and 4,4-difluoropiperidine hydrochloride afforded the title compound (60 mg, 59%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (s, 1H), 8.22 (d, J = 9.5 Hz, 1H), 7.03 (s, 1H), 4.89-4.84 (m, 1H), 3.86 (brs, 4H), 2.63 (s, 3H), 2.13-2.06 (m, 4H), 1.37 (d, J = 7.0 Hz, 3H). LC-MS m/z: 392.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.14 min.

(*S*)-5-(Benzo[*d*][1,3]dioxol-4-yl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



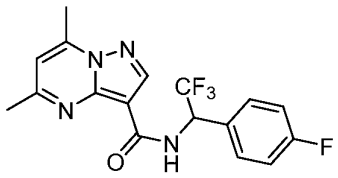
[00596] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.28 mmol) and benzo[*d*][1,3]dioxol-4-ylboronic acid afforded the title compound (77 mg, 77 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.80 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 7.0 Hz, 1H), 7.09 (t, J = 8.0 Hz, 1H), 6.26 (s, 1H), 6.25 (s, 1H), 3.65-3.61 (m, 1H), 2.85 (s, 3H), 1.28 (d, J = 6.5 Hz, 3H), 1.05-1.01 (m, 1H), 0.54-0.42 (m, 2H), 0.38-0.26 (m, 2H). LC-MS m/z: 365.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.58 min.

5-(Benzo[*d*][1,3]dioxol-4-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



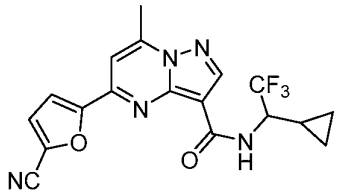
[00597] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.18 mmol) and benzo[*d*][1,3]dioxol-4-ylboronic acid afforded the title compound (29 mg, 39 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.66 (s, 1 H), 8.64 (d, J = 10.0 Hz, 1H), 7.86 (s, 1 H), 7.67 (d, J = 8.5 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.08 (t, J = 8.0 Hz, 1H), 6.26 (s, 1H), 6.20 (s, 1H), 4.47-4.42 (m, 1H), 2.87 (s, 3H), 1.25-1.22 (m, 1H), 0.72-0.68 (m, 1H), 0.60-0.56 (m, 2H), 0.38-0.35 (m, 1H). LC-MS m/z: 419.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 9.08 min.

5,7-Dimethyl-*N*-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



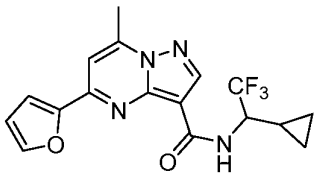
[00598] Following general procedure A, 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (50 mg, 0.52 mmol) and 2,2,2-trifluoro-1-(4-fluorophenyl)ethanamine afforded the title compound (36 mg, 38 %) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.54 (s, 1H), 7.64 (dd, J = 8.5 Hz, 5.5 Hz, 2H), 7.23 (t, J = 8.5 Hz, 2H), 7.08 (s, 1H), 5.99 (q, J = 8.0 Hz, 1H), 2.81 (s, 3H), 2.76 (s, 3H). LC-MS m/z: 367.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 9.77 min.

5-(5-Cyanofuran-2-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



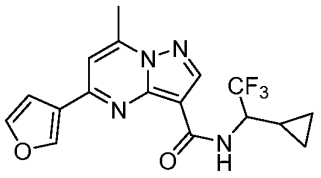
[00599] Following general procedure E*, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 5-bromofuran-2-carbonitrile afforded the title compound (3 mg, 3%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.71 (s, 1H), 8.43 (d, J = 9.5 Hz, 1H), 7.90 (d, J = 4.0 Hz, 1H), 7.84 (s, 1H), 7.68 (d, J = 4.0 Hz, 1H), 4.55-4.48 (m, 1H), 2.86 (s, 3H), 1.36-1.29 (m, 1H), 0.70-0.64 (m, 1H), 0.62-0.52 (m, 2H), 0.51-0.45 (m, 1H). LC-MS m/z: 390.0 $[M+H]^+$. HPLC Purity (214 nm): 97%; t_R = 9.17 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(furan-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



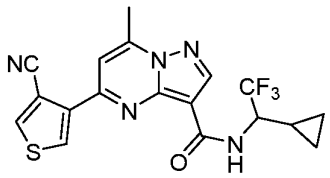
[00600] Following general procedure F, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.18 mmol) and tributyl(furan-2-yl)stannane afforded the title compound (23 mg, 30 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.61 (s, 1H), 8.52 (d, J = 9.6 Hz, 1H), 8.10 (d, J = 1.6 Hz, 1H), 7.67 (s, 1H), 7.49 (d, J = 3.2 Hz, 1H), 6.85 (dd, J = 3.2 Hz, 1.6 Hz, 1H), 4.54-4.45 (m, 1H), 2.83 (s, 3H), 1.34-1.26 (m, 1H), 0.70-0.44 (m, 4H). LC-MS m/z: 365.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.73 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(furan-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



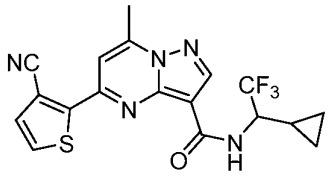
[00601] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and furan-3-ylboronic acid afforded the title compound (75 mg, 79 %) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.54 (s, 1H), 8.44 (s, 1H), 7.74 (t, J = 1.6 Hz, 1H), 7.48 (s, 1H), 7.06 (d, J = 1.6 Hz, 1H), 4.46-4.42 (m, 1H), 2.86 (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 = 10.32 min.

5-(4-Cyanothiophen-3-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



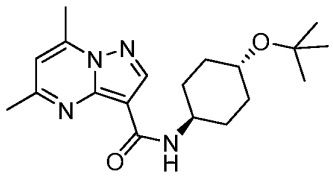
[00602] Following general procedure E*, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 4-bromothiophene-3-carbonitrile afforded the title compound (12 mg, 12%) as a white solid. ^{1}H NMR (400 MHz, MeOD-d_4): δ 8.66 (s, 1H), 8.55 (d, J = 3.0 Hz, 1H), 8.53 (d, J = 3.0 Hz, 1H), 7.68 (s, 1H), 4.16-4.12 (m, 1H), 2.94 (s, 3H), 1.68-1.65 (m, 1H), 0.80-0.76 (m, 1H), 0.63-0.58 (m, 2H), 0.39-0.34 (m, 1H). LC-MS m/z: 406.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.93 min.

5-(3-Cyanothiophen-2-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



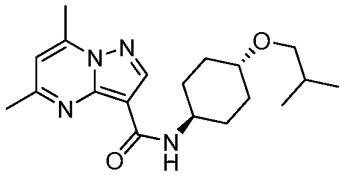
[00603] Following general procedure E*, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.301 mmol) and 2-bromothiophene-3-carbonitrile afforded the title compound (2.3 mg, 2 %) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.69 (s, 1H), 7.97 (d, J = 5.5 Hz, 1H), 7.80 (s, 1H), 7.60 (d, J = 5.0 Hz, 1H), 4.30-4.26 (m, 1H), 2.97 (s, 1H), 1.53-1.50 (m, 1H), 0.81-0.78 (m, 1H), 0.64-0.60 (m, 2H), 0.46-0.44 (m, 1H). LC-MS m/z: 406.0 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 10.13 min.

_N_-((1_R_,4_R_)-4-_tert_-butoxycyclohexyl)-5,7-dimethylpyrazolo[1,5-_a_]pyrimidine-3-carboxamide



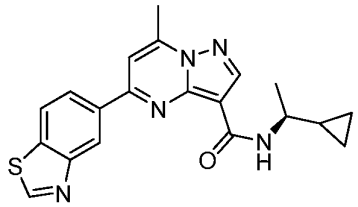
[00604] Following general procedure A, 5,7-dimethylpyrazolo[1,5-_a_]pyrimidine-3-carboxylic acid (50 mg, 0.26 mmol) and (1_R_,4_R_)-4-_tert_-butoxycyclohexanamine afforded the title compound (22 mg, 38 %) as a light brown solid. ^{1}H NMR (500 MHz, MeOD-d_4) :δ 8.48 (s, 1H), 7.01 (s, 1H), 3.90-3.88 (m, 1H), 3.63-3.60 (m, 1H), 2.78 (s, 3H), 2.67 (s, 3H), 2.13-2.10 (m, 2H), 1.93-1.91 (m, 2H), 1.52-1.46 (m, 4H), 1.24 (s, 9H). LC-MS m/z: 345.2 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 8.55 min.

_N_-((1_R_,4_R_)-4-_iso_-Butoxycyclohexyl)-5,7-dimethylpyrazolo[1,5-_a_]pyrimidine-3-carboxamide



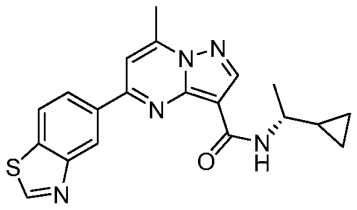
[00605] Following general procedure A, 5,7-dimethylpyrazolo[1,5-_a_]pyrimidine-3-carboxylic acid (100 mg, 0.52 mmol) and (1_R_,4_R_)-4-_iso_-butoxycyclohexanamine afforded the title compound (56 mg, 31 %) as a light brown solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.31 (s, 1H), 6.85 (s, 1H), 3.82-3.78 (m, 1H), 3.26-3.20 (m, 1H), 3.15 (d, J = 6.5 Hz, 2H), 2.64 (s, 3H), 2.53 (s, 3H), 2.02-1.94 (m, 4H), 1.72-1.66 (m, 1H), 1.38-1.30 (m, 4H), 0.81 (d, J = 6.5 Hz, 6H). LC-MS m/z: 345.2 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 9.65 min.

(_S_)-5-(Benzo[_d_]thiazol-5-yl)-_N_-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-_a_]pyrimidine-3-carboxamide



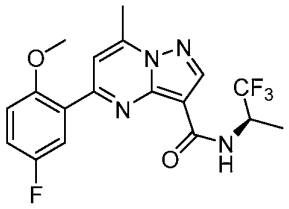
[00606] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.30 mmol) and benzo[*d*]thiazol-5-ylboronic acid afforded the title compound (72 mg, 64 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.53 (s, 1H), 8.98 (s, 1H), 8.56 (s, 1H), 8.41 (d, J = 8.5 Hz, 1H), 8.38 (d, J = 8.5 Hz, 1H), 8.26 (d, J = 6.0 Hz, 1H), 8.08 (s, 1H), 3.68-3.63 (m, 1H), 2.87 (s, 3H), 1.31 (d, J = 6.0 Hz, 3H), 1.15-1.11 (m, 1H), 0.60-0.51 (m, 2H), 0.44-0.40 (m, 1H), 0.40-0.32 (m, 1H). LC-MS m/z: 378.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.08 min.

(*R*)-5-(Benzo[*d*]thiazol-5-yl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00607] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.30 mmol) and benzo[*d*]thiazol-5-ylboronic acid afforded the title compound (38 mg, 34%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.55 (s, 1H), 9.02 (s, 1H), 8.59 (s, 1H), 8.46-8.40 (m, 2H), 8.29 (d, J = 7.6 Hz, 1H), 8.12 (s, 1H), 3.68-3.61 (m, 1H), 2.89 (s, 3H), 1.31 (d, J = 6.4 Hz, 1H), 1.17-1.10 (m, 1H), 0.60-0.52 (m, 2H), 0.46-0.32 (m, 2H). LC-MS m/z: 378.1 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 8.07 min.

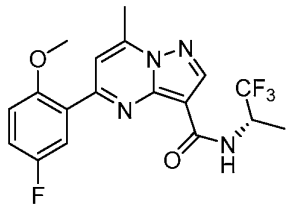
(*R*)-5-(5-Fluoro-2-methoxyphenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00608] Following general procedure D, (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.23 mmol) and 5-fluoro-2-methoxyphenylboronic acid afforded the title compound (36 mg, 39 %) as a yellow solid. ^{1}H

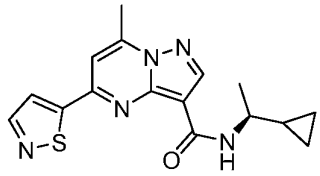
NMR (500 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.45 (d, J = 9.5 Hz, 1H), 7.79 (d, J = 1.0 Hz, 1H), 7.69 (dd, J = 9.5 Hz, 3.0 Hz, 1H), 7.43 (td, J = 9.0 Hz, 3.0 Hz, 1H), 7.30 (dd, J = 9.5 Hz, 4.5 Hz, 1H), 4.96-4.90 (m, 1H), 3.92 (s, 3H), 2.86 (s, 3H), 1.39 (d, J = 7.0 Hz, 3H). LC-MS m/z: 397.1 $[M+H]^+$. HPLC Purity (214 nm): 99.15 %; t_R = 8.83 min.

(*S*)-5-(5-Fluoro-2-methoxyphenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



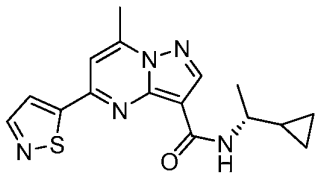
[00609] Following general procedure D, (*S*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.32 mmol) and 5-fluoro-2-methoxyphenylboronic acid afforded the title compound (18 mg, 14 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.46 (d, J = 9.2 Hz, 1H), 7.79 (s, 1H), 7.69 (dd, J = 9.6 Hz, 3.2 Hz, 1H), 7.44 (td, J = 8.0 Hz, 3.2 Hz, 1H), 7.30 (dd, J = 8.8 Hz, 4.4 Hz, 1H), 4.97-4.91 (m, 1H), 3.92 (s, 3H), 2.85 (s, 3H), 1.40 (d, J = 6.4 Hz, 3H). LC-MS m/z: 397.1 $[M+H]^+$. HPLC: Purity (254 nm): 98%; t_R = 8.84 min.

(*S*)-*N*-(1-Cyclopropylethyl)-5-(isothiazol-5-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00610] Following general procedure A, 5-(isothiazol-5-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (35 mg, 0.13 mmol) and (*S*)-1-cyclopropylethanamine afforded the title compound (18.6 mg, 42%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.66 (d, J = 2.0 Hz, 1H), 8.60 (s, 1H), 8.24 (d, J = 7.6 Hz, 1H), 8.09 (d, J = 2.0 Hz, 1H), 7.70 (s, 1H), 3.70-3.65 (m, 1H), 2.93 (s, 3H), 1.41 (d, J = 6.4 Hz, 3H), 1.13-1.10 (m, 1H), 0.66-0.58 (m, 2H), 0.49-0.44 (m, 1H), 0.39-0.35 (m, 1H). LC-MS m/z: 328.1 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 9.64 min.

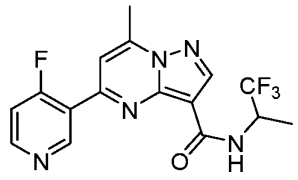
(*R*)-*N*-(1-Cyclopropylethyl)-5-(isothiazol-5-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00611] To a solution of 5-bromoisothiazole (325 mg, 2.0 mmol) in anhydrous THF (10 mL) was added n-BuLi (1.0 mL, 2.5 mmol, 2.5*M* solution in hexane) at -78°C under N_2. The mixture was stirred at -78 °C for 0.5 h, followed by the addition of Bu_3SnCl (750 mg, 2.0 mmol) at -78 °C, and stirred at -78 °C for another hour before being allowed to warm to RT. After concentration *in vacuo*, the residue was purified by preparative TLC to afford 5-(tributylstannyl)isothiazole (500 mg) as colourless oil. LC-MS m/z: 276.0 $[M+H]^+$, t_R = 2.87 min.

[00612] Following general procedure F, (*R*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (55 mg, 0.2 mmol) and 5-(tributylstannyl)isothiazole afforded the title compound (4 mg, 12%) as a yellow solid. ^1H NMR (400 MHz, MeOD-d_4) δ 8.68 (d, J = 1.2 Hz, 1H), 8.62 (s, 1H), 8.11 (s, 1H), 7.72 (s, 1H), 3.73-3.66 (m, 1H), 2.94 (s, 3H), 8.43 (d, J = 5.2 Hz, 3H), 1.16-1.12 (m, 1H), 0.67-0.58 (m, 2H), 0.51-0.46 (m, 1H), 0.41-0.36 (m, 1H). LC-MS m/z: 328.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%, t_R = 7.81 min.

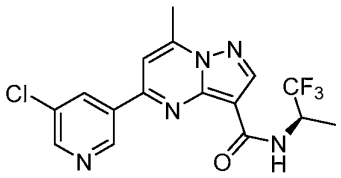
5-(4-Fluoropyridin-3-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00613] Following general procedure D, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.326 mmol) and 4-fluoropyridin-3-ylboronic acid afforded the title compound (32 mg, 27%) as a grey yellow solid. ^1H NMR (500 MHz, DMSO-d_6): δ 9.25 (d, J = 10.0 Hz, 1H), 8.80 (t, J = 7.0 Hz, 1H), 8.74 (s, 1H), 8.41 (d, J = 9.0 Hz, 1H), 7.82 (s, 1H), 7.64 (dd, J = 11.5 Hz, 6.0 Hz, 1H), 4.98-4.93 (m, 1H), 2.89 (s, 3H),

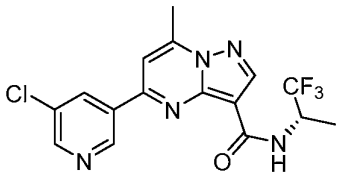
1.41 (d, J = 7.0 Hz, 1H). LC-MS m/z: 368.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.37 min.

(*R*)-5-(5-Chloropyridin-3-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



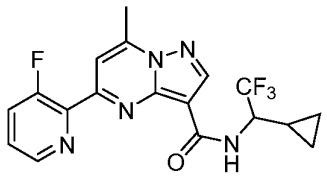
[00614] Following general procedure D, (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.23 mmol) and 5-chloropyridin-3-ylboronic acid afford the title compound (22.6 mg, 28 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.38 (d, J = 2.0 Hz, 1H), 8.86 (d, J = 2.5 Hz, 1H), 8.71 (s, 1H), 8.70 (t, J = 2.5 Hz, 1H), 8.40 (d, J = 9.0 Hz, 1H), 8.10 (s, 1H), 4.99-4.95 (m, 1H), 2.88 (s, 3H), 1.45 (d, J = 7.0 Hz, 3H). LC-MS m/z: 384.0 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.25 min.

(*S*)-5-(5-Chloropyridin-3-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



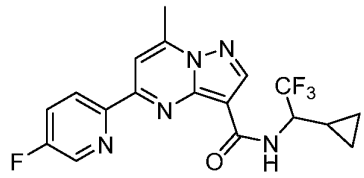
[00615] Following general procedure D, (*S*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (110 mg, 0.35 mmol) and 5-chloropyridin-3-ylboronic acid afforded the title compound (55 mg, 41 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.39 (d, J = 1.5 Hz, 1H), 8.87 (d, J = 2.0 Hz, 1H), 8.73 (s, 1H), 8.71 (t, J = 2.0 Hz, 1H), 8.40 (d, J = 9.5 Hz, 1H), 8.11 (s, 1H), 5.00-4.96 (m, 1H), 2.89 (s, 3H), 1.45 (d, J = 7.0 Hz, 3H). LC-MS m/z: 384.1 $[M+H]^+$. HPLC Purity (214 nm): 98%; t_R = 8.25 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(3-fluoropyridin-2-yl)-7-methylpyrazolo[1,5-a]pyrimidine-3-carboxamide



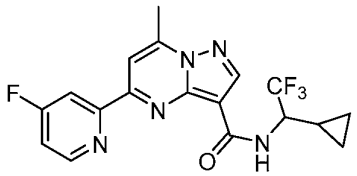
[00616] Following general procedure E*, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 2-bromo-3-fluoropyridine afforded the title compound (5.2 mg, 6 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.69 (d, J = 2.5 Hz, 1H), 8.64 (d, J = 9.5 Hz, 1H), 8.09 (s, 1H), 8.04 (dd, J = 12.5 Hz, 9.0 Hz, 1H), 7.76-7.73 (m, 1H), 4.42 (m, 1H), 2.91 (s, 3H), 1.23-1.19 (m, 1H), 0.72-0.68 (m, 1H), 0.59-0.57 (m, 2H), 0.39-0.37 (m, 1H). LC-MS m/z: 394.1 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 8.61 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(5-fluoropyridin-2-yl)-7-methylpyrazolo[1,5-a]pyrimidine-3-carboxamide



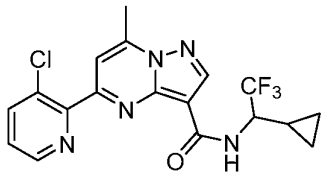
[00617] Following general procedure E*, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol), and 2-bromo-5-fluoropyridine afforded the title compound (14 mg, 15 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.83(d, J = 2.5 Hz, 1H), 8.71 (s, 1H), 8.50 (d, J = 10.5 Hz, 1H), 8.49-8.46 (m, 1H), 8.14 (s, 1H), 8.10 (td, J = 9.0 Hz, 3.0 Hz, 1H), 4.44-4.39 (m, 1H), 2.91 (s, 3H), 1.38-1.35 (m, 1H), 0.72-0.69 (m, 1H), 0.63-0.59 (m, 2H), 0.40-0.47 (m, 1H). LC-MS m/z: 394.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 9.11 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(4-fluoropyridin-2-yl)-7-methylpyrazolo[1,5-a]pyrimidine-3-carboxamide



[00618] Following general procedure E*, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 2-bromo-4-fluoropyridine afforded the title compound (4.3 mg, 2%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.87 (dd, J = 8.4 Hz, 5.2 Hz, 1H), 8.74 (s, 1H), 8.50 (d, J = 9.6 Hz, 1H), 8.20 (s, 1H), 8.18 (dd, J = 9.6 Hz, 2.4 Hz, 1H), 7.64-7.60 (m, 1H), 4.50-4.42 (m, 1H), 2.92 (s, 3H), 1.37-1.30 (m, 1H), 0.74-0.67 (m, 1H), 0.64-0.55 (m, 2H), 0.45-0.39 (m, 1H). LC-MS m/z: 394.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.94 min.

5-(3-Chloropyridin-2-yl)-N-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-a]pyrimidine-3-carboxamide

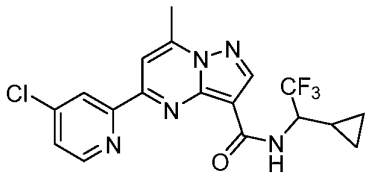


[00619] To a solution of 2-bromo-3-chloropyridine (576 mg, 3 mmol) in toluene (20 mL) under N_2 was added dropwise *n*-BuLi (2.5 M, 1.32 mL, 3.3 mmol) at -78 °C. The reaction mixture was stirred for 2 h, followed by the addition of $SnBu_3Cl$ (1.07g, 3.3 mmol). The reaction mixture was stirred 2 h at -78 °C, warmed to RT and stirred another 2 h, and then quenched with saturated NH_4Cl solution (10 mL). The mixture was extracted with EA (30 mL × 3), and the combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* to afford 3-chloro-2-(tributylstannyl)pyridine (1.0 g, 83%) as a colorless oil. LC-MS m/z: 404.1 $[M+H]^+$. t_R = 2.04 min.

[00620] Following general procedure F, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.18 mmol) and 3-chloro-2-(tributylstannyl)pyridine afforded the title compound (42 mg, 52%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.79 (d, J = 4.0 Hz, 1H), 8.74 (s, 1H), 8.48 (d J = 9.5 Hz, 1H), 8.23

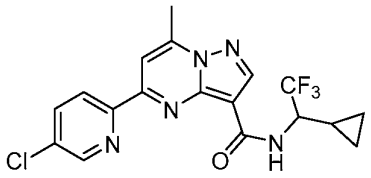
(d, J = 8.0 Hz, 1H), 7.90 (s, 1H), 7.67 (dd, J = 8.0 Hz, 4.5 Hz, 1H), 4.40-4.32 (m, 1H), 2.91 (s, 3H), 1.20-1.15 (m, 1H), 0.70-0.67 (m, 1H), 0.63-0.60 (m, 1H), 0.58-0.51 (m, 1H), 0.35-0.31 (m, 1H). LC-MS m/z: 410.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.78 min.

5-(4-Chloropyridin-2-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



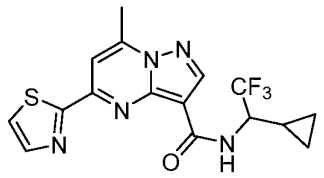
[00621] Following general procedure F, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.21 mmol) and 4-chloro-2-(tributylstannyl)pyridine afforded the title compound (22 mg, 24%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4): δ 8.75 (d, J = 5.0 Hz, 1H), 8.68 (s, 1H), 8.54 (d, J = 2.5 Hz, 1H), 8.23 (s, 1H), 8.67 (dd, J = 5.0 Hz, 2.0 Hz, 1H), 4.52-4.46 (m, 1H), 2.98 (s, 3H), 1.37-1.32 (m, 1H), 0.83-0.78 (m, 1H), 0.72-0.68 (m, 1H), 0.64-0.55 (m, 1H). LC-MS m/z: 410.0 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 9.54 min.

5-(5-Chloropyridin-2-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



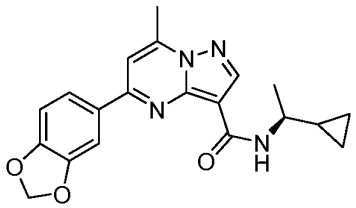
[00622] Following general procedure F, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.30 mmol) and 5-chloro-2-(tributylstannyl)pyridine afforded the title compound (36 mg, 29%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 (d, J = 2.0 Hz, 1H), 8.72 (s, 1H), 8.49 (d, J = 9.5 Hz, 1H), 8.41 (d, J = 9.0 Hz, 1H), 8.30 (dd, J = 8.5 Hz, 3.0 Hz, 1H), 8.15 (s, 1H), 4.44-4.38 (m, 1H), 2.91 (s, 3H), 1.39-1.35 (m, 1H), 0.71-0.69 (m, 1H), 0.64-0.61 (m, 2H), 0.41-0.39 (m, 1H). LC-MS m/z: 410.0 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 9.73 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(thiazol-2-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide



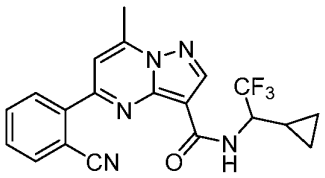
[00623] Following general procedure F, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (90 mg, 0.27 mmol) and 2-(tributylstannyl)thiazole afforded the title compound (80 mg, 70 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.72 (s, 1H), 8.36 (d, J = 9.5 Hz, 1H), 8.18 (d, J = 3.0 Hz, 1H), 8.15 (d, J = 3.0 Hz, 1H), 7.95 (s, 1H), 4.49-4.42 (m, 1H), 2.90 (s, 3H), 1.30-1.25 (m, 1H), 0.72-0.67 (m, 1H), 0.66-0.56 (m, 2H), 0.48-0.41 (m, 1H). LC-MS m/z: 382.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.55 min.

(S)-5-(Benzo[d][1,3]dioxol-5-yl)-N-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-a]pyrimidine-3-carboxamide



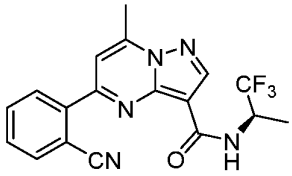
[00624] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (120 mg, 0.43 mmol) and 2-(benzo[*d*][1,3]dioxol-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane afforded the title compound (7.7 mg, 5%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-d_4): δ 8.61 (d, J = 7.2 Hz, 1H), 8.52 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.77 (s, 1H), 7.62 (s, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.10 (s, 2H), 3.73-3.66 (m, 1H), 2.88 (s, 3H), 1.38 (d, J = 6.8 Hz, 3H), 1.15-1.07 (m, 1H), 0.68-0.55 (m, 2H), 0.51-0.45 (m, 1H), 0.42-0.36 (m, 1H). LC-MS m/z: 365.1 $[M+H]^+$. HPLC Purity (214 nm): 96%; t_R = 10.21 min.

5-(2-Cyanophenyl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



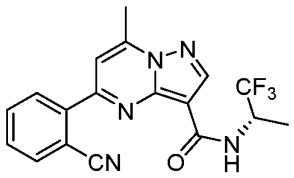
[00625] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.15 mmol), and 2-cyanophenylboronic acid afforded the title compound (14 mg, 23 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.74 (s, 1H), 8.32 (d, J = 9.5 Hz, 1H), 8.16-8.13 (m, 2H), 7.96 (d, J = 7.5 Hz, 1H), 7.83 (s, 1H), 7.80 (d, J = 7.5 Hz, 1H), 4.30-4.25 (m, 1H), 2.90 (s, 3H), 1.38-1.35 (m, 1H), 0.71-0.68 (m, 1H), 0.64-0.60 (m, 1H), 0.51-0.48 (m, 1H), 0.34-0.31 (m, 1H). LC-MS m/z: 400.1 $[M+H]^+$. HPLC Purity (214 nm): 98%; t_R = 8.46 min.

(*R*)-5-(2-cyanophenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



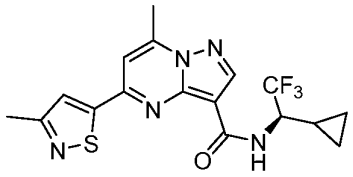
[00626] Following general procedure D, (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (62 mg, 0.2 mmol) and 2-cyanophenylboronic acid afforded the title compound (25 mg, 33%) as a pale white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.74 (s, 1H), 8.17-8.14 (m, 3H), 7.96 (t, J = 8.0 Hz, 1H), 7.82 (s, 1H), 7.80 (t, J = 8.0 Hz, 1H), 5.01-4.97 (m, 1H), 2.89 (s, 3H), 1.43 (d, J = 7.5 Hz, 3H). LC-MS m/z: 374.1 $[M+H]^+$. HPLC: Purity (214 nm): 97%; t_R = 8.09 min.

(*S*)-5-(2-Cyanophenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



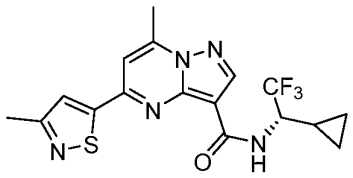
[00627] Following general procedure D, (*S*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.20 mmol) and 2-cyanophenylboronic acid afforded the title compound (18.8 mg, 26 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.17-8.14 (m, 3H), 7.96 (t, J = 8.0 Hz, 1H), 7.82 (s, 1H), 7.80 (t, J = 8.0 Hz, 1H), 5.01-4.97 (m, 1H), 2.89 (s, 3H), 1.43 (d, J = 7.5 Hz, 3H). LC-MS m/z: 374.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.11 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(3-methylisothiazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



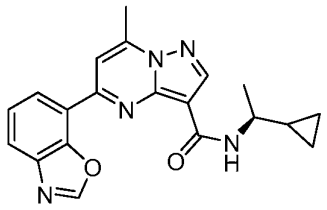
[00628] Following general procedure E*, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (99 mg, 0.30 mmol) and 5-bromo-3-methylisothiazole afforded the title compound (7.6 mg, 7%) as a light brown solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.71 (s, 1H), 8.26 (d, J = 9.5 Hz, 1H), 8.08 (s, 1H), 7.91 (s, 1H), 4.53-4.45 (m, 1H), 2.86 (s, 3H), 2.55 (s, 3H), 1.31-1.25 (m, 1H), 0.74-0.69 (m, 1H), 0.65-0.55(m, 2H), 0.45-0.40 (m, 1H). LC-MS m/z: 396.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.78 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(3-methylisothiazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



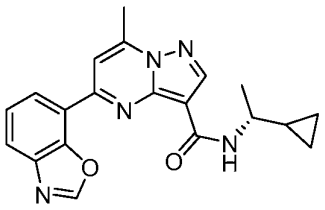
[00629] Following general procedure E*, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (101 mg, 0.30 mmol) and 5-bromo-3-methylisothiazole afforded the title compound (15 mg, 12%) as a light brown solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.71 (s, 1H), 8.26 (d, J = 9.5 Hz, 1H), 8.08 (s, 1H), 7.91 (s, 1H), 4.53-4.45 (m, 1H), 2.86 (s, 3H), 2.55 (s, 3H), 1.31-1.25 (m, 1H), 0.74-0.69 (m, 1H), 0.65-0.55(m, 2H), 0.45-0.40 (m, 1H). LC-MS m/z: 396.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.78 min.

(*S*)-5-(Benzo[*d*]oxazol-7-yl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



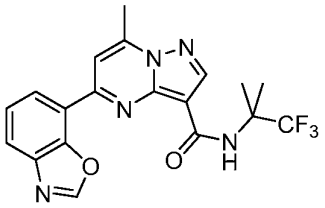
[00630] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.25 mmol) and 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazole afforded the title compound (28.3 mg, 20%) as a grey solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.98 (s, 1H), 8.61 (s, 1H), 8.28 (d, J = 7.5 Hz, 1H), 8.26 (s, 1H), 8.05 (d, J = 7.5 Hz, 1H), 7.98 (s, 1H), 7.65 (t, J = 7.5 Hz, 1H), 3.68-3.63 (m, 1H), 2.89 (s, 3H), 1.33 (d, J = 6.5 Hz, 3H), 1.12-1.08 (m, 1H), 0.52-0.49 (m, 1H), 0.48-0.40 (m, 1H), 0.40-0.32 (m, 1H), 0.32-0.28 (m, 1H). LC-MS m/z: 362.1 $[M+H]^+$. HPLC Purity (214 nm): 98%; t_R = 7.75 min.

(*R*)-5-(Benzo[*d*]oxazol-7-yl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00631] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.30 mmol) and 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazole afforded the title compound (67 mg, 62%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.62 (s, 1H), 8.28 (t, J = 7.5 Hz, 1H), 8.26 (s, 1H), 8.06 (d, J = 7.5 Hz, 1H), 8.00 (s, 1H), 7.65 (t, J = 7.5 Hz, 1H), 3.68-3.63 (m, 1H), 2.90 (s, 3H), 1.33 (d, J = 6.5 Hz, 3H), 1.12-1.08 (m, 1H), 0.52-0.49 (m, 1H), 0.48-0.40 (m, 1H), 0.40-0.32 (m, 1H), 0.32-0.28 (m, 1H). LC-MS m/z: 362.1 $[M+H]^+$. HPLC: Purity (214 nm): 98%; t_R = 7.72 min.

5-(Benzo[*d*]oxazol-7-yl)-7-methyl-*N*-(1,1,1-trifluoro-2-methylpropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

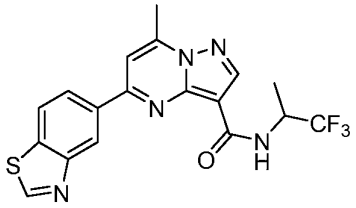


[00632] Following general procedure A, 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (500 mg, 2.37 mmol) and 1,1,1-trifluoro-2-methylpropan-2-amine hydrochloride afforded 5-chloro-7-methyl-*N*-(1,1,1-trifluoro-2-methylpropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (310 mg, 41%) as a yellow solid. LC-MS m/z: 321.1 $[M+H]^+$. Purity (214 nm): > 99%; t_R = 1.95 min.

[00633] Following general procedure D, 5-chloro-7-methyl-*N*-(1,1,1-trifluoro-2-methylpropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.25 mmol) and 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazole afforded the title compound (80 mg, 80%) as a brown solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.97 (s, 1H), 8.66 (s, 1H), 8.37

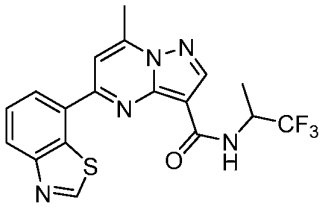
(s, 1H), 8.21 (d, J = 7.5 Hz, 1H), 8.06 (d, J = 7.5 Hz, 1H), 8.01 (s, 1H), 7.66 (t, J = 8.0 Hz, 1H), 2.92 (s, 3H), 1.73 (s, 6H). LC-MS m/z: 404.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.48 min.

5-(Benzo[*d*]thiazol-5-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



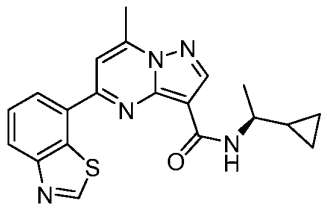
[00634] Following general procedure D, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.32 mmol) and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole afforded the title compound (55 mg, 42%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (s, 1H), 8.97 (s, 1H), 8.68 (s, 1H), 8.58 (d, J = 9.5 Hz, 1H), 8.43 (d, J = 8.5 Hz, 1H), 8.35 (dd, J = 8.5 Hz, 1.0 Hz, 1H), 8.16 (s, 1H), 5.02-4.98 (m, 1H), 2.89 (s, 3H), 1.49 (d, J = 7.0 Hz, 3H). LC-MS m/z: 406.0 $[M+H]^+$. HPLC Purity (254 nm): 98%; t_R = 8.22 min.

5-(Benzo[*d*]thiazol-7-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



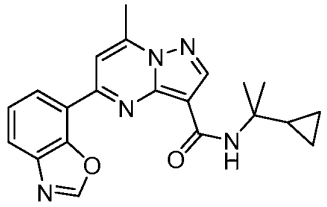
[00635] Following general procedure E*, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.26 mmol) and 7-bromobenzo[*d*]thiazole (111 mg, 0.52 mmol) afforded the title compound (19 mg, 18%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.69 (s, 1H), 8.75 (s, 1H), 8.48 (d, J = 7.5 Hz, 1H), 8.38 (d, J = 8.0 Hz, 1H), 8.19 (s, 1H), 8.15 (d, J = 10.0 Hz, 1H), 7.85 (t, J = 8.0 Hz, 1H), 5.13-5.09 (m, 1H), 2.90 (s, 3H), 1.52 (d, J = 7.5 Hz, 3H). LC-MS m/z: 406.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.38 min.

(*S*)-5-(Benzo[*d*]thiazol-7-yl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00636] Following general procedure E*, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.36 mmol) and 7-bromobenzo[*d*]thiazole afforded the title compound (24.6 mg, 18%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.72 (s, 1H), 8.64 (s, 1H), 8.47 (d, J = 7.5 Hz, 1H), 8.36 (d, J = 8.0 Hz, 1H), 8.14 (s, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.84 (t, J = 7.5 Hz, 1H), 3.65-3.61 (m, 1H), 2.89 (s, 3H), 1.38 (d, J = 6.0 Hz, 3H), 1.18-1.14 (m, 1H), 0.57-0.53 (m, 1H), 0.50-0.45 (m, 1H), 0.39-0.33 (m, 2H). LC-MS m/z: 378.1 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 8.36 min.

5-(Benzo[*d*]oxazol-7-yl)-7-methyl-*N*-(2-cyclopropylpropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

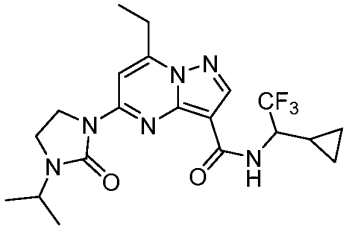


[00637] Following general procedure A, 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (500 mg, 2.37 mmo) and 2-cyclopropylpropan-2-amine afforded 5-chloro-*N*-(2-cyclopropylpropan-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (600 mg, 87%) as a yellow solid. LC-MS m/z: 293.2 $[M+H]^+$. Purity (214 nm): > 98%; t_R = 1.98 min.

[00638] Following general procedure D, 5-chloro-*N*-(2-cyclopropylpropan-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.34 mmol) and 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazole afforded the title compound (77 mg, 60%) as a grey solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.98 (s, 1H), 8.59 (s, 1H), 8.28 (d, J = 8.0 Hz, 1H), 8.15 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.97 (s, 1H), 7.65 (t, J = 8.0 Hz, 1H), 2.91

(s, 3H), 1.48-1.44 (m, 1H), 1.38 (s, 6H), 0.47-0.40 (m, 4H). LC-MS m/z: 376.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.40 min.

_N_-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-ethyl-5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

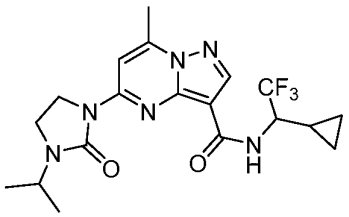


[00639] Following general procedure H, ethyl 5-chloro-7-ethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (800 mg, 3.1 mmol) and 1-*iso*-propylimidazolidin-2-one afforded ethyl 7-ethyl-5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (500 mg, 47%) as a brown solid. LC-MS m/z: 346.2 $[M+H]^+$, t_R = 1.82 min.

[00640] Following general procedure B*, ethyl 7-ethyl-5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (500 mg, 1.4 mmol) afforded 7-ethyl-5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid sodium salt (470 mg, 100%) as a yellow solid which was used directly in the next step. LC-MS m/z: 318.1 $[M+H]^+$, t_R = 1.24 min.

[00641] Following general procedure A, 7-ethyl-5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (100 mg, 0.29 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (33 mg, 26%) as a white solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.41 (s, 1H), 8.22 (s, 1H), 4.36-4.30 (m, 1H), 4.29-4.20 (m, 1H), 4.19-4.09 (m, 2H), 3.64(t, J = 8.0 Hz, 2H), 3.20 (q, J = 7.6 Hz, 2H), 1.45 (t, J = 7.6 Hz, 3H), 1.27 (d, J = 6.4 Hz, 6H), 1.29-1.26 (m, 1H), 0.77-0.74 (m, 1H), 0.66-0.55 (m, 2H), 0.48-0.45 (m, 1H). LC-MS m/z: 439.2 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 10.74 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide

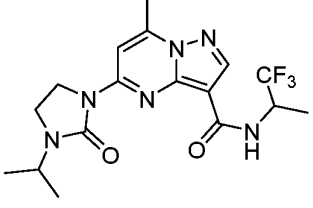


[00642] Following general procedure H, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (717 mg, 3 mmol) and 1-*iso*-propylimidazolidin-2-one afforded ethyl 5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (780 mg, 78%) as a pale solid. LC-MS m/z: 332.2 $[M+H]^+$. LCMS: Purity (214 nm): 97.9%; t_R = 1.27 min.

[00643] Following general procedure B*, ethyl 5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (331 mg, 1.0 mmol) afforded 5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (270 mg, 88%) as a solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.98 (s, 1H), 7.75 (s, 1H), 6.68 (s, 1H), 2.45 (s, 3H), 2.43 (s, 3H). LC-MS m/z: 304.1 $[M+H]^+$. LCMS: Purity (254 nm): 81.9%; t_R = 1.57 min.

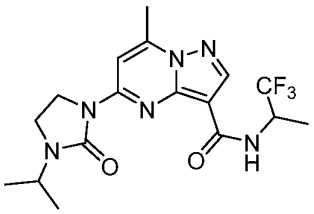
[00644] Following general procedure A, 5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (55 mg, 0.18 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (28 mg, 44%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.42 (s, 1H), 8.22 (d, J = 9.5 Hz, 1H), 8.10 (s, 1H), 4.38-4.30 (m, 1H), 4.13-4.03 (m, 2H), 4.00-3.95 (m, 1H), 3.57-3.50 (m, 2H), 2.73 (s, 3H), 1.28-1.23 (m, 1H), 1.17 (d, J = 7.0 Hz, 6H), 0.68-0.64 (m, 1H), 0.57-0.54 (m, 2H), 0.35-0.32 (m, 1H). LC-MS m/z: 425.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.85 min.

7-Ethyl-5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



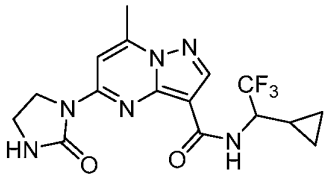
[00645] Following general procedure A, 7-ethyl-5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (100 mg, 0.29 mmol) and 1,1,1-trifluoropropan-2-amine hydrochloride afforded the title compound (20 mg, 17%) as a white solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.42 (s, 1H), 8.21 (s, 1H), 4.93-4.90 (m, 1H), 4.25-4.12 (m, 3H), 3.65 (t, J = 8.0 Hz, 2H), 3.20 (q, J = 7.2 Hz, 2H), 1.49 (d, J = 7.2 Hz, 3H), 1.46 (d, J = 7.2 Hz, 3H), 3.65 (d, J = 6.8 Hz, 6H). LC-MS m/z: 413.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.90 min.

5-(3-*iso*-Propyl-2-oxoimidazolidin-1-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00646] Following general procedure A, 5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (50 mg, 0.15 mmol) and 1,1,1-trifluoropropan-2-amine hydrochloride afforded the title compound (15.6 mg, 24%) as a white solid. ^{1}H NMR (500MHz, DMSO-d_6), δ 8.43 (s, 1H), 8.13 (d, J = 9.5 Hz, 1H), 8.09 (s, 1H), 4.93-4.86 (m, 1H), 4.13-4.06 (m, 2H), 3.99-3.93 (m, 1H), 3.58-3.50 (m, 2H), 2.73 (s, 3H), 1.40 (d, J = 7.0 Hz, 3H), 1.17 (d, J = 6.5 Hz, 6H). LC-MS m/z: 399.1 $[M+H]^+$. HPLC : Purity (214 nm): 98%; t_R = 8.13min.

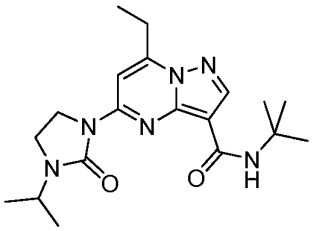
***N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(2-oxoimidazolidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



[00647] Following general procedure H, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.30 mmol) and imidazolidin-2-one afforded the title compound (15 mg, 13%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.43 (s, 1H), 8.23 (d, J = 10.0 Hz, 1H), 8.11 (s, 1H), 7.88 (s, 1H), 4.39-4.32 (m, 1H), 4.18-4.10

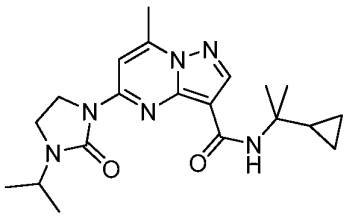
(m, 1H), 4.08-4.02 (m, 1H), 3.54-3.50 (m, 2H), 2.74 (s, 3H), 1.26-1.21 (m, 1H), 0.68-0.64 (m, 1H), 0.59-0.54 (m, 2H), 0.39-0.34 (m, 1H). LC-MS m/z: 383.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.63 min.

N-tert-Butyl-7-ethyl-5-(3-_iso_-propyl-2-oxoimidazolidin-1-yl)pyrazolo[1,5-_a_]pyrimidine-3-carboxamide



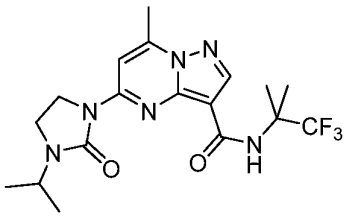
[00648] Following general procedure A, 7-ethyl-5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (100 mg, 0.29 mmol) and 2-methylpropan-2-amine afforded the title compound (32 mg, 28%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.34 (s, 1H), 8.16 (s, 1H), 4.28-4.20 (m, 1H), 4.14 (t, J = 8.0 Hz, 2H), 3.69 (t, J = 8.0 Hz, 2H), 3.17 (q, J = 7.6 Hz, 2H), 1.51 (s, 9H), 1.44 (t, J = 7.2 Hz, 3H), 1.26 (d, J = 8.0 Hz, 6H). LC-MS m/z: 373.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%, t_R = 8.80 min.

_N_-(2-Cyclopropylpropan-2-yl)-5-(3-_iso_-propyl-2-oxoimidazolidin-1-yl)-7-methylpyrazolo[1,5-_a_]pyrimidine-3-carboxamide



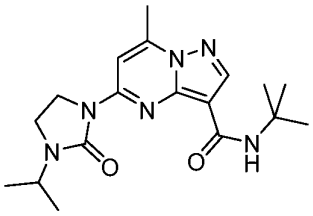
[00649] Following general procedure A, 5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (50 mg, 0.16 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (1.5 mg, 3%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4): δ 8.35 (s, 1H), 8.11 (s, 1H), 4.25-4.22 (m,1H), 4.12 (t, J = 7.5 Hz, 2H), 3.61 (t, J = 8.0 Hz, 2H), 2.75 (s, 3H), 1.42 (s, 6H), 1.44-1.41 (m, 1H), 1.27 (d, J = 6.5 Hz, 6H), 0.50-0.49 (m, 4H). LC-MS m/z: 385.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.74 min.

5-(3-*iso*-Propyl-2-oxoimidazolidin-1-yl)-7-methyl-*N*-(1,1,1-trifluoro-2-methylpropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



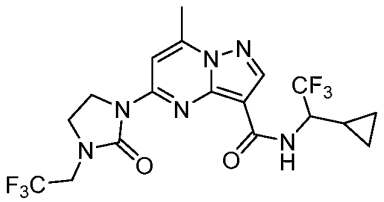
[00650] Following general procedure A, 5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (50 mg, 0.16 mmol) and 1,1,1-trifluoro-2-methylpropan-2-amine hydrochloride afforded the title compound (32 mg, 47%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.37 (s, 1H), 8.10 (s, 1H), 7.99 (s, 1H), 4.13-4.08 (m, 1H), 4.01 (t, J = 7.5 Hz, 2H), 3.55 (t, J = 8.0 Hz, 2H), 2.73 (s, 3H), 1.67 (s, 6H), 1.16 (d, J = 10.0 Hz, 6H). LC-MS m/z: 413.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.89 min.

***N-tert*-Butyl-5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



[00651] Following general procedure A, 5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.14 mmol) and 2-methylpropan-2-amine afforded the title compound (28 mg, 59%) as a white solid. ^{1}H NMR (400 MHz, MeOD-d_4): δ 8.33 (s, 1H), 8.08 (s, 1H), 8.03 (s, 1H), 4.27-4.21 (m, 1H), 4.07 (t, J = 8.0 Hz, 2H), 3.61 (t, J = 8.0 Hz, 2H), 2.73 (d, J = 0.4 Hz, 3H), 1.52 (s, 9H), 1.27 (d, J = 6.8 Hz, 6H). LC-MS m/z: 359.1 $[M+H]^+$, 381.2$[M+Na]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.32 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(2-oxo-3-(2,2,2-trifluoroethyl)imidazolidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

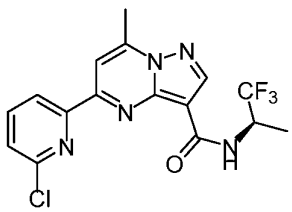


[00652] To a solution of 2,2,2-trifluoroethanamine (6.0 g, 60.6 mmol) in MeCN (30 mL) was added 1-chloro-2-isocyanatoethane (7.0 g, 66.7 mmol). The reaction mixture was stirred at RT for 4 h, and filtered to collect 1-(2-chloroethyl)-3-(2,2,2-trifluoroethyl)urea (2.6 g, 22%) as a white solid. LC-MS m/z: 191.1 $[M+H]^+$.

[00653] To a solution of 1-(2-chloroethyl)-3-(2,2,2-trifluoroethyl)urea (1.3 g, 6.4 mmol) in THF (4 mL) was added NaH (305 mg, 7.6 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 16 h, and quenched with saturated NH_4Cl (20 mL). The mixture was extracted with EA (10 mL x 3), and the combined organic layers were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford 1-(2,2,2-trifluoroethyl)imidazolidin-2-one (500 mg, 47%) as a white solid. LC-MS m/z: 169.2 $[M+H]^+$.

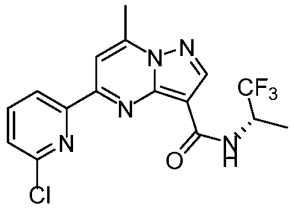
[00654] Following general procedure H, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 1-(2,2,2-trifluoroethyl)imidazolidin-2-one afforded the title compound (50 mg, 40%) as an off white solid. ^1H NMR (400 MHz, DMSO-d_6): δ 8.47 (s, 1H), 8.18 (d, J = 9.6 Hz, 1H), 8.05 (s, 1H), 4.34-4.28 (m, 1H), 4.19-4.02 (m, 3H), 3.72 (t, J = 8.0 Hz, 2H), 2.76 (s, 3H), 1.30-1.23 (m, 1H), 0.69-0.65 (m, 1H), 0.59-0.55 (m, 2H), 0.35-0.30 (m, 1H). LC-MS m/z: 465.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.76 min.

(*R*)-5-(6-Chloropyridin-2-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



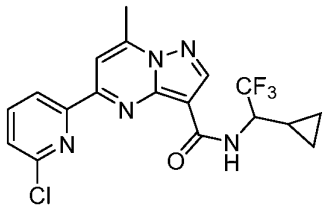
[00655] Following general procedure D, (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (62 mg, 0.2 mmol) and 2-chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine afforded the title compound (28 mg, 37 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.40-8.38 (m, 1H), 8.20 (t, J = 8.0 Hz, 1H), 8.05 (s, 1 H), 7.61 (dd, J = 8.0 Hz, 1.0 Hz, 1H), 5.01-4.96 (m, 1H), 2.92 (s, 3H), 1.49 (d, J = 7.5 Hz, 3H). LC-MS m/z: 384.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 9.13 min.

(*S*)-5-(6-Chloropyridin-2-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00656] Following general procedure D, (*S*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (90 mg, 0.29 mmol) and 2-chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine afforded the title compound (9.2 mg, 8 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.40-8.38 (m, 1H), 8.20 (t, J = 8.0 Hz, 1H), 8.05 (s, 1 H), 7.61 (dd, J = 8.0 Hz, 1.0 Hz, 1H), 5.01-4.96 (m, 1H), 2.92 (s, 3H), 1.49 (d, J = 7.5 Hz, 3H). LC-MS m/z: 384.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 9.13 min.

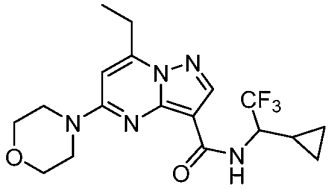
5-(6-Chloropyridin-2-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00657] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 2-chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine afforded the title compound (29 mg, 30%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.74 (s, 1H), 8.50 (d, J = 9.5 Hz, 1H), 8.39 (d, J = 7.5 Hz, 1H), 8.21 (d, J = 8.0 Hz, 1H), 8.08 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 4.44-4.40 (m,

1H), 2.93 (s, 3H), 1.40-1.36 (m, 1H), 0.72-0.67 (m, 1H), 0.65-0.58 (m, 2H), 0.43-0.38 (m, 1H). LC-MS m/z: 410.0 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 10.05 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-ethyl-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxamide

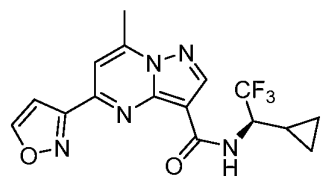


[00658] Into the stirred solution of ethyl 5-chloro-7-ethylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (0.2 g, 0.8 mmol) and Cs_2CO_3 (1.3 g, 4.0 mmol) in DMF was added morpholine (87 mg, 1.0 mmol). The mixture was stirred at 100 °C for 24 h, and concentrated *in vacuo*. The residue was purified by preparative TLC (PE: EA = 1:1) to afford ethyl 7-ethyl-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 38%) as a brown solid. LC-MS m/z: 259.1 $[M+H]^+$, t_R = 1.21 min.

[00659] Following general procedure B*, ethyl 7-ethyl-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 0.39 mmol) afforded 7-ethyl-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid sodium salt (117 mg, 100%) as a yellow solid which was used directly in the next step. LC-MS m/z: 277.2 $[M+H]^+$, t_R = 1.07 min.

[00660] Following general procedure A, 7-ethyl-5-morpholinopyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (117 mg, 0.39 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (21 mg, 13%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.27 (s, 1H), 6.68 (s, 1H), 4.38-4.35 (m, 1H), 3.84-3.76 (m, 8H), 3.14-3.08 (m, 2H), 1.42 (t, J = 8.0 Hz, 3H), 1.22-1.19 (m, 1H), 0.74-0.72 (m, 1H), 0.63-0.59 (m, 1H), 0.52-0.43 (m, 2H). LC-MS m/z: 397.8 $[M+H]^+$. HPLC Purity (254 nm): > 99%, t_R = 8.19 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(isoxazol-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00661] A mixture of tributyl(vinyl)stannane (1.142 g, 3.6 mmol), ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (717 mg, 3 mmol), and $Pd(PPh_3)_4$ (347 mg, 0.3 mmol) in dioxane (5 mL) was heated at 100 °C under nitrogen atmosphere for 2 hours, cooled to room temperature and concentrated *in vacuo* after the addition of hydroquinone (10 mg). The resulting residue was purified by silica gel column chromatography (PE/EA: 1/1) to afford ethyl 7-methyl-5-vinylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (478 mg, 69%) as a solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (s, 1H), 7.01 (s, 1H), 6.94 (dd, J = 17.5 Hz, 11.0 Hz 1H), 6.38 (d, J = 17.5 Hz, 1H), 5.79 (d, J = 11.0 Hz, 1H), 4.42 (q, J = 7.0 Hz, 2H), 2.83 (s, 3H), 1.43 (t, J = 7.0 Hz, 3H). LC-MS m/z: 232.1 $[M+H]^+$. LCMS: Purity (214 nm): 98.3 %; t_R = 1.72 min.

[00662] To a solution of ethyl 7-methyl-5-vinylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (167 mg, 0.72 mmol) and OsO_4 (2 mg, 0.007 mmol) in THF/H_2O (10 mL/ 3 mL) was added $NaIO_4$ (616 mg, 2.89 mmol). The resulting mixture was stirred at RT for 12 h, and diluted with H_2O (50 mL). The mixture was extracted with EA (20 mL× 3), and the organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford ethyl 5-formyl-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (150 mg), which was used directly in the next step. LC-MS m/z: 234.1 $[M+H]^+$. LCMS: Purity (254nm): 30%; t_R = 1.65 min.

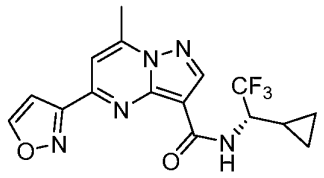
[00663] To a solution of ethyl 5-formyl-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (150 mg) in MeOH (5 mL) were added hydroxylammonium chloride (108 mg, 1.45 mmol) and Et_3N (219 mg, 2.17 mmol). The mixture was stirred at RT for 2 h, and concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography (PE/EA: 1/2) to afford ethyl 5-((hydroxyimino)methyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 55% two steps) as a yellow solid. LC-MS m/z: 271.0 $[M+Na]^+$. LCMS: Purity (254nm): 78%; t_R = 1.08 min.

[00664] To a solution of ethyl 5-((hydroxyimino)methyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 0.40 mmol) and ethynyltrimethylsilane (78 mg, 0.8 mmol) in MeCN (5 mL) was added CrO_2 (332 mg, 4.0 mmol). The reaction mixture was stirred at 80 °C for 2 h, and filtered through Celite. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (PE/EA: 5/1) to afford ethyl 7-methyl-5-(5-(trimethylsilyl)isoxazol-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (63 mg, 45%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.71 (s, 1H), 7.83 (s, 1H), 7.29 (s,

1H), 4.32 (q, J = 7.0 Hz, 2H), 2.87 (s, 3H), 1.36 (t, J = 7.0 Hz, 3H), 0.41 (s, 9H). LC-MS m/z: 345.1 $[M+H]^+$. LCMS: Purity (254nm): 88 %; t_R = 2.14 min.

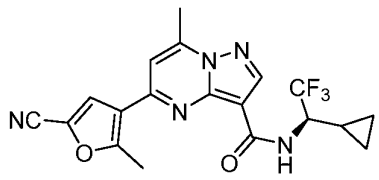
[00665] Following general procedure A, 5-(isoxazol-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.16 mmol) and (*R*)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (5.8 mg, 11%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.25 (d, J = 1.5 Hz, 1H), 8.74 (s, 1H), 8.39 (d, J = 10.0 Hz, 1H), 7.88 (s, 1H), 7.13 (d, J = 2.0 Hz, 1H), 4.45-4.40 (m, 1H), 2.90 (s, 3H), 1.38-1.35 (m, 1H), 0.70-0.67 (m, 1H), 0.60-0.58 (m, 2H), 0.42-0.39 (m, 1H). LC-MS m/z: 366.1 $[M+H]^+$. HPLC: Purity (214nm): > 99%; t_R = 8.34 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(isoxazol-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00666] Following general procedure A, 5-(isoxazol-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.16 mmol) and (*S*)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (10 mg, 18%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.25 (d, J = 1.5 Hz, 1H), 8.74 (s, 1H), 8.39 (d, J = 10.0 Hz, 1H), 7.88 (s, 1H), 7.13 (d, J = 2.0 Hz, 1H), 4.45-4.40 (m, 1H), 2.90 (s, 3H), 1.38-1.35 (m, 1H), 0.70-0.67 (m, 1H), 0.60-0.58 (m, 2H), 0.42-0.39 (m, 1H). LC-MS m/z: 366.1 $[M+H]^+$. HPLC: Purity (214nm): > 99%; t_R = 8.62 min.

(*R*)-5-(5-Cyano-2-methylfuran-3-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide

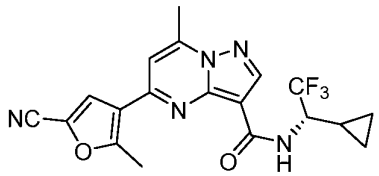


[00667] The solution of methyl 5-methylfuran-2-carboxylate (1.5 g, 10.71 mmol) and $AlCl_3$ (2.14 g, 16.07 mmol) in 20 mL of chloroform was stirred at 0 °C for 30 minutes and then Br_2

(0.77 mL) was added at 0 °C. The reaction mixture was stirred at 0 °C for 12 hours, poured into ice cubes (100 g) and extracted with DCM (50 mL x 3). The organic layers were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford methyl 4-bromo-5-methylfuran-2-carboxylate (2.0 g, 86%).

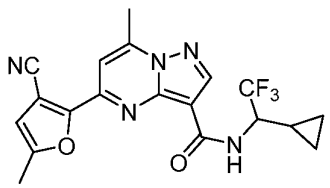
[00668] Following general procedure E*, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.18 mmol) and 4-bromo-5-methylfuran-2-carbonitrile afforded the title compound (3.5 mg, 5 %) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4): δ 8.62 (s, 1H), 7.94 (s, 1H), 7.47 (s, 1H), 4.32-4.27 (m, 1H), 2.91 (s, 3H), 2.89 (s, 3H), 1.28-1.24 (m, 1H), 0.84-0.80 (m, 1H), 0.68-0.62 (m, 2H), 0.47-0.43 (m, 1H). LC-MS m/z: 404.1 $[M+H]^+$. HPLC Purity (214nm): > 99%; t_R = 9.06 min.

(*S*)-5-(5-Cyano-2-methylfuran-3-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00669] Following general procedure E*, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 4-bromo-5-methylfuran-2-carbonitrile afforded the title compound (12 mg, 13 %) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4): δ 8.62 (s, 1H), 8.43 (d, J = 9.5 Hz, 1H), 7.95 (s, 1H), 7.48 (s, 1H), 4.33-4.28 (m, 1H), 2.91 (s, 3H), 2.89 (s, 3H), 1.28-1.23 (m, 1H), 0.85-0.80 (m, 1H), 0.65-0.62 (m, 2H), 0.47-0.43 (m, 1H). LC-MS m/z: 404.1 $[M+H]^+$. HPLC Purity (214 nm): 94.6%; t_R = 9.05 min.

5-(3-Cyano-5-methylfuran-2-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



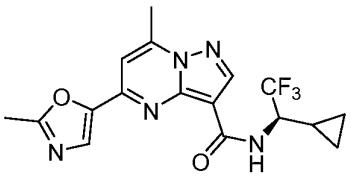
[00670] Following general procedure A, 5-methylfuran-3-carboxylic acid (1.26 g, 10 mmol) and NH_4Cl afforded 5-methylfuran-3-carboxamide (700 mg, 56%) as a white solid. LC-MS m/z: 126.1 $[M+H]^+$. LCMS: Purity (214 nm): 85.2%; t_R = 1.28 min.

[00671] To a solution of 5-methylfuran-3-carboxamide (400 mg, 2.10 mmol), and Et_3N (1.7 g, 16.8 mmol) in DCM (20 mL) under N_2 was added $POCl_3$ (964 mg, 6.3 mmol) dropwise at 0°C. The mixture was stired at RTfor 2 h, concentrated *in vacuo* and the residue was dissolved with EA (20 mL) and washed with saturated $NaHCO_3$ solution (20 mL). The combined organic layers were dried (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 5-methylfuran-3-carbonitrile (270 mg, 75%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (s, 1H), 6.20 (s, 1H), 2.33 (s, 3H). LCMS: Purity (254 nm): 95%; t_R = 1.68 min.

[00672] To a solution of 5-methylfuran-3-carbonitrile (321 mg, 3 mmol) in THF (10 mL) under N_2 was dropwise added *n*-BuLi (1.14 mL, 2.5 M in heptanes, 2.85 mmol) at -78 °C.. The reaction mixture was stirred at -78 °C for 0.5 h, followed by the addition of Bu_3SnCl (1.2 g, 3.6 mmol). The reaction mixture was stirred at -78 °C for 2 h, allowed to stir at RT for another 2 h, and quenched with NH_4Cl (10 mL). The reaction mixture was extracted with EA (50 mL × 3) and the combined organic layers were washed with brine (30 mL), dried (Na_2SO_4) and filtered. The filtrate was concentrated *in vacuo* to afford 5-methyl-2-(tributylstannyl)furan-3-carbonitrile (1.25 g, crude), which was used in the next step without purifications. LC-MS m/z: 420.1 $[M+H]^+$. LCMS: t_R = 2.17 min.

[00673] Following general procedure F, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.30 mmol) and 5-methyl-2-(tributylstannyl)furan-3-carbonitrile afforded the title compound (90 mg, 75 %) as a yellow solid. ^1H NMR (500 MHz, DMSO-d_6) δ 8.73 (s, 1H), 7.99 (d, J = 9.5 Hz, 1H), 7.68 (s, 1H), 6.97 (s, 1H), 4.19-4.16 (m, 1 H), 2.88 (s, 3H), 2.45 (s, 3H), 1.60-1.53 (m, 1H), 0.71-0.63 (m, 2H), 0.54-0.53 (m, 1H), 0.26-0.24 (m, 1H). LC-MS m/z: 404.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 9.16 min.

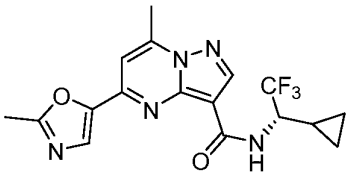
(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(2-methyloxazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00674] To a solution of 2-methyloxazole (1.0 g, 12.0 mmol) in Et_2O (20 mL) was added *n*-BuLi (6.24 mL, 2.5*M*, 15.6 mmol) dropwise at -78 °C. After stirring for 2 h, a solution of Bu_3SnCl (3.59 g, 11.0 mmol) in Et_2O (10 mL) was added dropwise at -78 °C. The reaction was allowed to warm to RT and stirred overnight. Then the reaction was quenched with saturated NH_4Cl (25 mL) and then extracted with Et_2O (50 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford 2-methyl-5-(tributylstannyl)oxazole (3.5 g, 77 %) as a yellow oil, which was used directly in the next step.

[00675] Following general procedure A, 7-methyl-5-(2-methyloxazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.12 mmol) and (*R*)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (15 mg, 32 %) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-d_4): δ 8.56 (s, 1H), 7.90 (s, 1H), 7.53 (s, 1H), 4.52-4.48 (m, 1H), 2.90 (s, 3H), 2.63 (s, 3H), 1.36-1.30 (m, 1H), 0.77-0.73 (m, 1H), 0.69-0.65 (m, 1H), 0.61-0.53 (m, 2H). LC-MS m/z: 380.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.78 min.

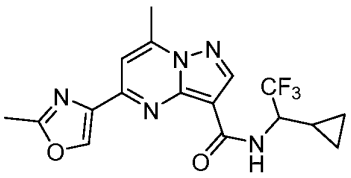
(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(2-methyloxazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00676] Following general procedure A, 7-methyl-5-(2-methyloxazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.12 mmol) and (*S*)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (21 mg, 46%) as a yellow solid. ^{1}H NMR (400 MHz, MeOD-d_4): δ 8.56 (s, 1H), 7.90 (s, 1H), 7.53 (s, 1H), 4.52-4.48 (m, 1H),

2.90 (s, 3H), 2.63 (s, 3H), 1.36-1.30 (m, 1H), 0.77-0.73 (m, 1H), 0.69-0.65 (m, 1H), 0.61-0.53 (m, 2H). LC-MS m/z: 380.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.78 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(2-methyloxazol-4-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide



[00677] To a stirred solution of ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (1.0 g, 3.6 mmol) and tributyl(1-ethoxyvinyl)stannane (2.1 g, 5.4 mmol) in dioxane (10 mL) was added $Pd(PPh_3)_2Cl_2$ (253 mg, 0.36 mmol). The reaction mixture was stirred for 3 h at 110 °C under N_2. The product was purified by silica gel column chromatography (PE/EA = 3/1) to afford ethyl 5-(1-ethoxyvinyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (891 mg, 90 %) as a white solid. LC-MS m/z: 276.1 $[M+H]^+$.

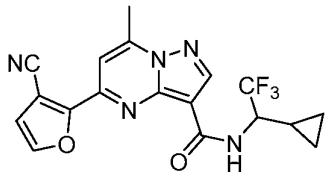
[00678] To a stirred solution of ethyl 5-(1-ethoxyvinyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (880 mg, 3.2 mmol) in THF/H_2O (10 mL/1 mL) was added NBS (627 mg, 3.5 mmol). The reaction mixture was stirred for 3 h at RT, and filtered to remove the solid. The cake was washed with CH_3CN (10 mL), and the filtrated was concentrated *in vacuo* to afford ethyl 5-(2-bromoacetyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (800 mg, 77 %) as a yellow solid. LC-MS m/z: 328.0 $[M+H]^+$.

[00679] A solution of ethyl 5-(2-bromoacetyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (800 mg, 2.5 mmol) and acetamide (1.5 g, 25 mmol) in DMF (5 mL) was stirred for 4 h at 110 °C. The product was purified by silica gel column chromatography (PE/EA = 3/1) to afford ethyl 7-methyl-5-(2-methyloxazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (140 mg, 20 %) as a yellow solid. LC-MS m/z: 287.1 $[M+H]^+$.

[00680] Following general procedure B*, ethyl 7-methyl-5-(2-methyloxazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (140 mg, 0.49 mmol) afforded 7-methyl-5-(2-methyloxazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (115 mg, 91 %) as a yellow solid. LC-MS m/z: 259.1 $[M+H]^+$.

[00681] Following general procedure A, 7-methyl-5-(2-methyloxazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.16 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (14 mg, 23 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.74 (s, 1H), 8.64 (s, 1H), 8.43 (d, J = 9.5 Hz, 1H), 7.68 (s, 1H), 4.40-4.34 (m, 1H), 2.85 (s, 3H), 2.55 (s, 3H), 1.46-1.41 (m, 1H), 0.70-0.60 (m, 1H), 0.59-0.56 (m, 2H), 0.45-0.42 (m, 1H). LC-MS m/z: 380.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.40 min.

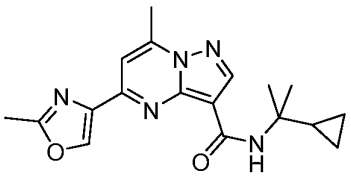
5-(3-Cyanofuran-2-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00682] To an ice cold solution of 2,2,6,6-tetramethylpiperidine (1.9 g, 13.5 mmol) in THF (15 mL) was added BuLi (2.5*M* in hexanes, 4.8 mL, 12.0 mmol) slowly. The solution was stirred at 0 °C for 30 min, 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 min and the mixture was stirred for 2 h at -78 °C. A solution of $SnBu_3Cl$ in THF (5 mL, 18 mmol) was added dropwise over 30 min and the mixture was stirred overnight with the temperature rising to RT during that time. 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 a colorless oil. LC-MS m/z: no MS signal. t_R = 2.65 min.

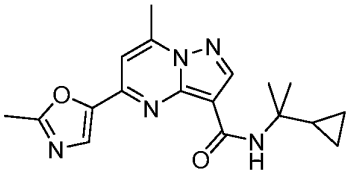
[00683] Following general procedure F, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (111 mg, 0.33 mmol) and 2-(tributylstannyl)furan-3-carbonitrile afforded the title compound (34 mg, 26%) as a light yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.31 (d, J = 1.5 Hz, 1H), 7.98 (d, J = 11.5 Hz, 1H), 7.73 (s, 1H), 7.34 (d, J = 2.0 Hz, 1H), 4.23-4.12 (m, 1H), 2.88 (s, 3H), 1.61-1.52 (m, 1H), 0.75-0.63 (m, 2H), 0.56-0.49 (m, 1H), 0.28-0.22 (m, 1H). LC-MS m/z: 390.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99 %; t_R = 8.49 min.

***N*-(2-Cyclopropylpropan-2-yl)-7-methyl-5-(2-methyloxazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



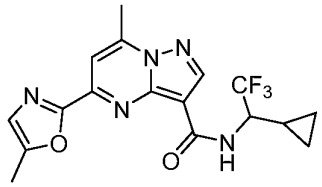
[00684] Following general procedure A, 7-methyl-5-(2-methyloxazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.16 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (19 mg, 35 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.64 (s, 1H), 8.51 (s, 1H), 7.98 (s, 1H), 7.61 (s, 1H), 2.83 (s, 3H), 2.54 (s, 3H), 1.44-1.42 (m, 1H), 1.37 (s, 6H), 0.48-0.46 (m, 4H). LC-MS m/z: 340.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.39 min.

***N*-(2-Cyclopropylpropan-2-yl)-7-methyl-5-(2-methyloxazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



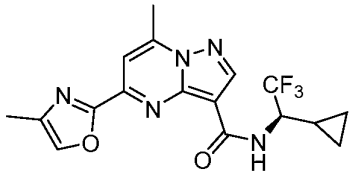
[00685] Following general procedure A, 7-methyl-5-(2-methyloxazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (127 mg, 0.49 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (20 mg, 15 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.50 (s, 1H), 8.000 (s, 1H), 7.997 (d, J = 2.4 Hz, 1H), 7.59 (s, 1H), 2.80 (s, 3H), 2.56 (s, 3H), 1.37 (s, 6H), 1.36-1.33 (m, 1H), 0.49 (d, J = 6.8 Hz, 4H). LC-MS m/z: 340.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.80 min.

***N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(5-methyloxazol-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



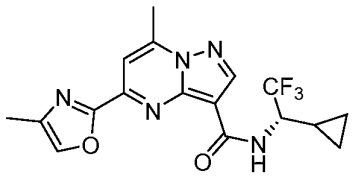
[00686] To a solution of 5-methyloxazole (160 mg, 2.0 mmol) in THF (10 mL) was added *n*-BuLi (2.5 mmol, 1.0 mL, 2.5 M) at -78 °C under N_2 and the mixture was stirred for 20 min, followed by the addition of $ZnCl_2$ (2.0 mmol, 2 mL ether solution, 1M). The solution was then stirred at -78 °C under N_2 for another 30 min, warmed to RT and 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (166 mg, 0.5 mmol) and $Pd(PPh_3)_2Cl_2$ (70 mg, 0.1 mmol) were added. The mixture was stirred at 60 °C under N_2 for 5 h, concentrated *in vacuo* and purified by preparative HPLC (10 mM NH_4HCO_3/MeCN)) to afford the title compound (24 mg, 13 %) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4): δ 8.66 (s, 1H), 7.78 (s, 1H), 7.18 (d, J = 0.8 Hz, 1H), 4.56-4.51 (m, 1H), 2.94 (s, 3H), 2.52 (d, J = 0.8 Hz, 3H), 1.40-1.35 (m, 1H), 0.77-0.71 (m, 1H), 0.70-0.64 (m, 2H), 0.52-0.52 (m, 1H). LC-MS m/z: 380.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.48 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(4-methyloxazol-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



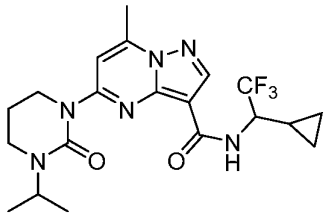
[00687] To a solution of 4-methyloxazole (160 mg, 2.0 mmol) in anhydrous THF (10 mL) was added BuLi (2.5 mmol, 1.0 mL, 2.5*M* solution in hexane) dropwise at -78 °C under N_2. The mixture was stirred at -78 °C for 0.5 h, followed by the dropwise addition of $ZnCl_2$ (2.5 mmol, 2.5 mL, 1*M* solution in ether) at -78 °C. After stirring at -78 °C for 2 h, the reaction mixture was allowed to warm to RT, and to this was added (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (330 mg, 1.0 mmol), and $Pd(PPh_3)_2Cl_2$ (30 mg, 0.05 mmol). The resulting mixture was stirred at 70 °C under N_2 for 24 h, and concentrated *in vacuo*. The residue was purified by preparative HPLC (10mM NH_3/MeCN) to afford the title compound (5 mg, 3 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.46 (d, J = 10.0 Hz, 1H), 8.23 (d, J = 1.2 Hz, 1H), 7.88 (s, 1H), 4.61-4.52 (m, 1H), 2.87 (s, 3H), 2.52 (s, 3H), 1.28-1.18 (m, 1H), 0.70-0.48 (m, 4H). LC-MS m/z: 380.1 $[M+H]^+$. HPLC: Purity (214 nm): 92%, t_R = 8.40 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(4-methyloxazol-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00688] To a solution of 4-methyloxazole (85 mg, 1.0 mmol) in THF (5 mL) was added dropwise n-BuLi (2.5*M* in n-hexane, 0.44 mL, 1.1 mmol) at -78 °C. The resulting solution was stirred for 0.5 h at –78 °C, followed by the addition of $ZnCl_2$ (1.0*M* in Et_2O, 4.4 mL, 4.4 mmol), and warmed to RT. To the reaction mixture were added (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (99 mg, 0.30 mmol) and $Pd(PPh_3)_2Cl_2$ (25 mg, 0.03 mmol). The mixture then stirred for 2 h at 60 °C, quenched with saturated NH_4Cl solution (50 mL) and extracted with EA (30 mL x 3). The organic layers were washed with H_2O (50 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (10/1 of EA/MeOH) to afford the title compound (9 mg, 8 %) as a white solid. ^1H NMR (500 MHz, DMSO-d_6): δ 8.72 (s, 1H), 8.46 (d, J = 9.5 Hz, 1H), 8.23 (d, J = 1.0 Hz, 1H), 7.88 (s, 1H), 4.60-4.53 (m, 1H), 2.88 (s, 3H), 2.25 (d, J = 0.5 Hz, 3H), 1.26-1.21 (m, 1H), 0.69-0.52 (m, 4H). LC-MS m/z: 380.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.47 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(3-*iso*-propyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide

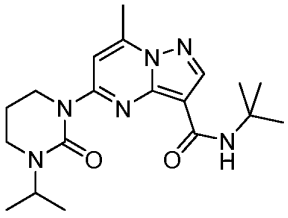


[00689] Following general procedure H ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (1.7g, 7.04 mmol) and 1-*iso*-propyltetrahydropyrimidin-2(1*H*)-one afforded ethyl 5-(3-*iso*-propyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (600 mg, 25%) as a grey oil. LC-MS m/z: 346.2 $[M+H]^+$, t_R = 1.74 min.

[00690] Following general procedure B*, ethyl 5-(3-*iso*-propyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (600 mg, 1.74 mmol) afforded 5-(3-*iso*-propyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid sodium salt (590 mg, 99%) as a light green solid which was used directly in the next step. LC-MS m/z: 318.1$[M+H]^+$, t_R = 1.19 min.

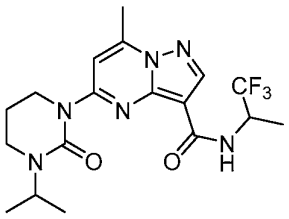
[00691] Following general procedure A, 5-(3-*iso*-propyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid sodium salt (200 mg, 0.59 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (42 mg, 16%) as a pink solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.45 (s, 1H), 8.23 (d, J = 10.0 Hz, 1H), 8.80 (s, 1H), 4.65-4.60 (m, 1H), 4.39-4.34 (m, 1H), 3.98-3.91 (m, 2H), 3.29 (t, J = 6.0 Hz, 2H), 2.72 (s, 3H), 2.07-2.02 (m, 2H), 1.23-1.21 (m, 1H), 1.14 (d, J = 6.5 Hz, 6H), 0.69-0.65 (m, 1H), 0.58-0.55 (m, 2H), 0.37-0.33 (m, 1H). LC-MS m/z: 438.8 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.72min.

***N*-*tert*-Butyl-5-(3-*iso*-propyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



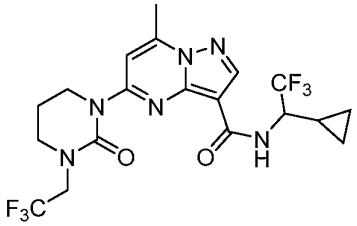
[00692] Following general procedure A, 5-(3-*iso*-propyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (63 mg, 0.11 mmol) and 2-methylpropan-2-amine afforded the title compound (3.0 mg, 4%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.33 (s, 1H), 7.79 (s, 1H), 7.75 (d, J = 0.5 Hz, 1H), 4.65-4.61 (m, 1H), 3.96 (t, J = 6.0 Hz, 2H), 3.28 (t, J = 6.0 Hz, 2H), 2.70 (s, 3H), 2.06-2.02 (m, 1H), 1.42 (s, 9H), 1.15 (d, J = 7.0 Hz, 6H). LC-MS m/z: 372.9 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.20 min.

5-(3-*iso*-Propyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00693] Following general procedure A, 5-(3-*iso*-propyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.09 mmol) and 1,1,1-trifluoropropan-2-amine hydrochloride afforded the title compound (7.2 mg, 19%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.45 (s, 1H), 8.15 (d, J = 9.0 Hz, 1H), 7.79 (s, 1H), 4.93-4.87 (m, 1H), 4.65-4.60 (m, 1H), 4.01-3.97 (m, 1H), 3.93-3.88 (m, 1H), 3.29 (t, J = 6.0 Hz, 2H). LC-MS m/z: 413.2 $[M+H]^+$. HPLC Purity (214 nm): 99%; t_R = 8.30 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(2-oxo-3-(2,2,2-trifluoroethyl)tetrahydropyrimidin-1(2*H*)-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

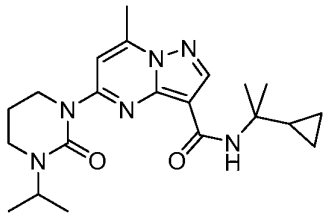


[00694] To a solution of 2,2,2-trifluoroethanamine (1.5 g, 15 mmol) in MeCN (10 mL) was added 1-chloro-3-isocyanatopropane (2.2 g, 18 mmol). The reaction mixture was stirred at RT for 4 h, and filtered to afford 1-(3-chloropropyl)-3-(2,2,2-trifluoroethyl)urea (1.3 g, 39%) as a white solid.

[00695] To a solution of 1-(3-chloropropyl)-3-(2,2,2-trifluoroethyl)urea (1.3 g, 5.9 mmol) in THF (4 mL) was added NaH (477 mg, 11.9 mmol) at 0 °C. The reaction mixture was warmed to RT and stirred for 16 h, and quenched with saturated NH_4Cl (20 mL). The mixture was extracted with EA (10 mL x 3), and the combined organic layers were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford 1-(2,2,2-trifluoroethyl)tetrahydropyrimidin-2(1*H*)-one (600 mg, 56%) as a white solid.

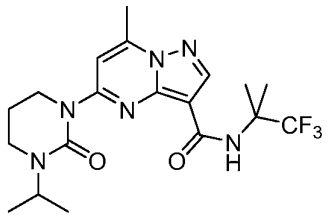
[00696] Following general procedure H, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.18 mmol) and 1-(2,2,2-trifluoroethyl)tetrahydropyrimidin-2(1*H*)-one afforded the title compound (60 mg, 27%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.11 (d, *J* = 10.0 Hz, 1H), 7.80 (d, *J* = 1.0 Hz, 1H), 4.50-4.44 (m, 1H), 4.18-4.05 (m, 4H), 3.64-3.61 (m, 2H), 2.78 (s, 3H), 2.26-2.19 (m, 2H), 1.12-1.10 (m, 1H), 0.71-0.69 (m, 1H), 0.56-0.52 (m, 3H). LC-MS m/z: 478.7 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.62 min.

<u>*N*-(2-Cyclopropylpropan-2-yl)-5-(3-*iso*-propyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide</u>



[00697] Following general procedure A, 5-(3-*iso*-propyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.09 mmol) and 2-cyclopropylpropan-2-amine afforded the title compound (11.5 mg, 32%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.32 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.75 (s, 1H), 4.62-4.58 (m, 1H), 3.97 (t, *J* = 6.0 Hz, 2H), 3.28 (t, *J* = 6.0 Hz, 2H), 2.69 (s, 3H), 2.06-2.00 (m, 2H), 1.39-1.33 (m, 1H), 1.32 (s, 6H), 1.14 (d, *J* = 6.8 Hz, 6H), 0.42-0.37 (m, 4H). LC-MS m/z: 399.2 $[M+H]^+$. HPLC Purity (214 nm): 99%; t_R = 8.53 min.

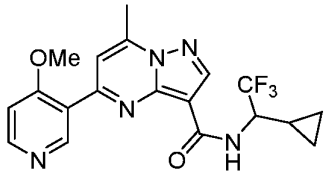
<u>5-(3-*Iso*-propyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)-7-methyl-*N*-(1,1,1-trifluoro-2-methylpropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide</u>



[00698] Following general procedure A, 5-(3-*iso*-propyl-2-oxotetrahydropyrimidin-1(2*H*)-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.09 mmol) and 1,1,1-trifluoro-2-methylpropan-2-amine hydrochloride afforded the title compound (4.5 mg, 12%) as

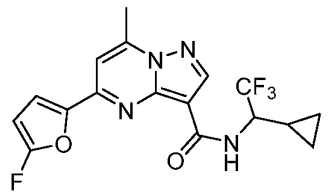
a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.38 (s, 1H), 8.00 (s, 1H), 7.77 (s, 1H), 4.63-4.60 (m, 2H), 3.92 (t, J = 5.5 Hz, 2H), 3.30-3.27 (m, 2H), 2.70 (s, 3H), 2.06-2.01 (m, 2H), 1.66 (s, 6H), 1.14 (d, J = 7.0 Hz, 6H). LC-MS m/z: 427.1 $[M+H]^+$. HPLC Purity (214 nm): 97%; t_R = 8.73 min.

_N_-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(4-methoxypyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00699] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.30 mmol) and 4-methoxypyridin-3-ylboronic acid afforded the title compound (29 mg, 24 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.87 (s, 1H), 8.68 (s, 1H), 8.61 (d, J = 6.0 Hz, 1H), 8.46 (d, J = 9.5 Hz, 1H), 7.73 (d, J = 1.0 Hz, 1H), 7.33 (d, J = 6.0 Hz, 1H), 4.52-4.47 (m, 1H), 4.00 (s, 3H), 2.86 (d, J = 0.5 Hz, 3H), 1.20-1.16 (m, 1H), 0.68-0.65(m, 1H), 0.57-0.54 (m, 2H), 0.38-0.34 (m, 1H). LC-MS m/z: 406.0 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.57 min.

_N_-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(5-fluorofuran-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide

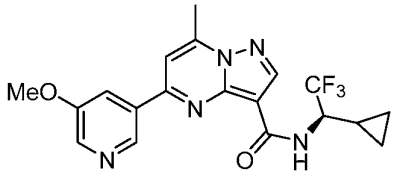


[00700] A mixture of 5-bromofuran-2-carboxylic acid (3 g, 15.8 mmol) and sodium bicarbonate (3.3 g, 39.5 mmol) was stirred in 135 mL of pentane/water (2/5) at room temperature for 30 minutes, followed by the addition of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octanebis-tetrafluoroborate (5.6 g, 15.8 mmol). The mixture was stirred for another hour at room temperature, and separated to afford the pentane solution of 5-bromo-2-fluorofuran, which was dried ($MgSO_4$), diluted with 20 mL of anhydrous THF, and cooled to -78 °C under nitrogen. To this was added n-butyllithium (2.6*M*, 3.2 mL, 7.9 mmol). The

mixture was stirred at-78 °C for 30 minutes, followed by the addition of tri-n-butylstannyl chloride (2.6 g, 7.9 mmol). The mixture was then allowed to stir at room temperature for another 20 minutes, quenched with saturated NH_4Cl (100 mL), and separated. The organic phase was dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated *in vacuo* to afford tributyl(5-fluorofuran-2-yl)stannane (3.0 g) as a brown oil, which was used for the next step without further purification.

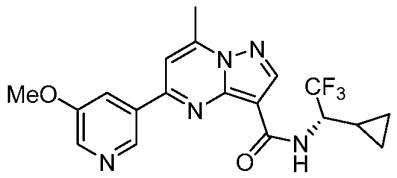
[00701] Following general procedure F, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.33 mmol) and tributyl(5-fluorofuran-2-yl)stannane afforded the title compound (58.3 mg, 49 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.46 (d, J = 9.6 Hz, 1H), 7.61 (s, 1H), 7.56(t, J = 3.6 Hz, 1H), 6.24 (dd, J = 6.8 Hz, 3.6 Hz, 1H), 4.57-4.46 (m, 1H), 2.81 (s, 3H), 1.31-1.26 (m, 1H), 0.70-0.41 (m, 4H). LC-MS m/z: 383.1 $[M+H]^+$. HPLC: Purity (214 nm): 98%; t_R = 9.02 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(5-methoxypyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



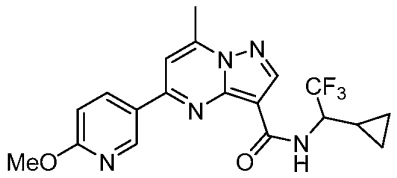
[00702] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.15 mmmol) and 3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine afforded the title compound (18 mg, 29 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.03 (d, J = 1.5 Hz, 1H), 8.70 (s, 1H), 8.51 (d, J = 2.5 Hz, 1H), 8.50 (d, J = 9.5 Hz, 1H), 8.11 (dd, J = 2.5 Hz, 2.0 Hz, 1H), 8.08 (s, 1H), 4.50-4.48 (m, 1H), 3.96 (s, 3H), 2.88 (s, 3H), 1.29-1.22 (m, 1H), 0.70-0.67 (m, 1H), 0.60-0.56 (m, 2H), 0.40-0.38 (m, 1H). LC-MS m/z: 406.1 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 7.99 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(5-methoxypyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



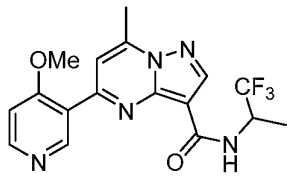
[00703] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.15 mmmol) and 3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine afforded the title compound (16 mg, 26 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.03 (d, J = 1.5 Hz, 1H), 8.70 (s, 1H), 8.51 (d, J = 2.5 Hz, 1H), 8.50 (d, J = 9.5 Hz, 1H), 8.11 (dd, J = 2.5 Hz, 2.0 Hz, 1H), 8.08 (s, 1H), 4.50-4.48 (m, 1H), 3.96 (s, 3H), 2.88 (s, 3H), 1.29-1.22 (m, 1H), 0.70-0.67 (m, 1H), 0.60-0.56 (m, 2H), 0.40-0.38 (m, 1H). LC-MS m/z: 406.1 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 8.00 min.

***N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(6-methoxypyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



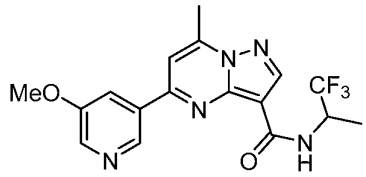
[00704] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 6-methoxypyridin-3-ylboronic acid afforded the title compound (74 mg, 76 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.07 (d, J = 2.5 Hz, 1H), 8.64 (s, 1H), 8.52 (d, J = 9.5 Hz, 1H), 8.49 (dd, J = 8.5 Hz, 3.0 Hz, 1H), 7.95 (s, 1H), 7.09 (d, J = 9.0 Hz, 1H), 4.46-4.43 (m, 1H), 3.98 (s, 3H), 2.85 (s, 3H), 1.31-1.28 (m, 1H), 0.70-0.68 (m, 1H), 0.60-0.58 (m, 2H), 0.40-0.37 (m, 1H). LC-MS m/z: 406.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.87 min.

5-(4-Methoxypyridin-3-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



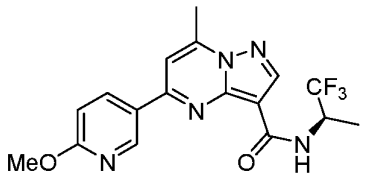
[00705] Following general procedure D, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.33 mmol) and 4-methoxypyridin-3-ylboronic acid afforded the title compound (42.5 mg, 34 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.88 (s, 1H), 8.68 (s, 1H), 8.61 (d, J = 6.0 Hz, 1H), 8.42 (d, J = 9.0 Hz, 1H), 7.73 (s, 1H), 7.32 (d, J = 5.5 Hz, 1H), 4.97-4.92 (m, 1H), 4.00 (s, 3H), 2.86 (s, 3H), 1.39 (d, J = 7.0 Hz, 3H). LC-MS m/z: 380.1 $[M+H]^+$. HPLC Purity (214nm): > 99%; t_R = 7.12 min.

5-(5-Methoxypyridin-3-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



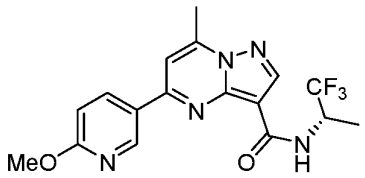
[00706] Following general procedure D, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (90 mg, 0.29 mmol) and 3-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine afforded the title compound (64 mg, 65 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.69 (s, 1H), 8.50 (d, J = 3.0 Hz, 1H), 8.41 (d, J = 9.0 Hz, 1H), 8.12 (s, 1H), 8.07 (s, 1H), 5.01-4.95 (m, 1H), 3.96 (s, 3H), 2.88 (s, 3H), 1.45 (d, J = 7.0 Hz, 3H). LC-MS m/z: 380.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.61 min.

(*R*)-5-(6-Methoxypyridin-3-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



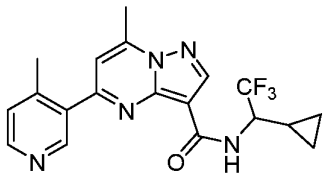
[00707] Following general procedure D, (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.23 mmol) and 6-methoxypyridin-3-ylboronic acid afforded the title compound (43 mg, 49 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.05 (d, J = 2.0 Hz, 1H), 8.63 (s, 1H), 8.46 (dd, J = 9.0 Hz, 2.5 Hz, 1H), 8.41 (d, J = 9.5 Hz, 1H), 7.91 (s, 1H), 7.07 (d, J = 8.5 Hz, 1H), 4.99-4.94 (m,1H), 3.97 (s, 3H), 2.84 (s, 3H), 1.46 (d, J = 6.5 Hz, 3H). LC-MS m/z: 380.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.40 min.

(*S*)-5-(6-Methoxypyridin-3-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



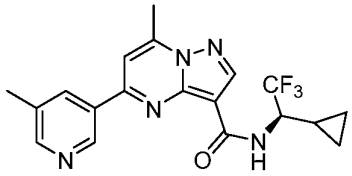
[00708] Following general procedure D, (*S*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (110 mg, 0.35 mmol) and 6-methoxypyridin-3-ylboronic acid afforded the title compound (55 mg, 40 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.07 (d, J = 2.0 Hz, 1H), 8.64 (s, 1H), 8.49 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 8.42 (d, J = 9.5 Hz, 1H), 7.94 (s, 1H), 7.10 (d, J = 8.5 Hz, 1H), 5.00-4.94 (m, 1H), 3.98 (s, 3H), 2.85 (s, 3H), 1.46 (d, J = 6.5 Hz, 3H). LC-MS m/z: 380.1 $[M+H]^+$. HPLC: Purity (214 nm): 99.39%; t_R = 8.93 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(4-methylpyridin-3-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide



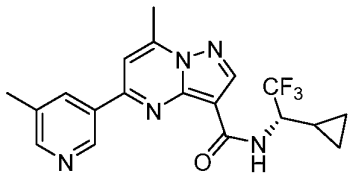
[00709] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 4-methylpyridin-3-ylboronic acid afforded the title compound (3.6 mg, 4 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.80 (s, 1H), 8.72 (s, 1H), 8.59 (d, J = 5.0 Hz, 1H), 8.34 (d, J = 9.0 Hz, 1H), 7.66 (s, 1H), 7.47 (d, J = 5.0 Hz, 1H), 4.41-4.38 (m, 1H), 2.88 (s, 3H), 2.57 (s, 3H), 1.17-1.15 (m, 1H), 0.66-0.51 (m, 3H), 0.32-0.29 (m, 1H). LC-MS m/z: 390.1 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 7.78 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(5-methylpyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



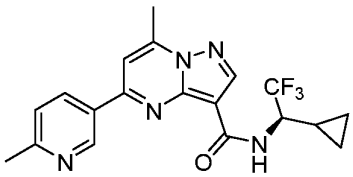
[00710] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (75 mg, 0.23 mmol) and 5-methylpyridin-3-ylboronic acid afforded the title compound (25 mg, 28 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.23 (d, J = 2.0 Hz, 1H), 8.68 (s, 1H), 8.64 (d, J = 1.0 Hz, 1H), 8.54 (d, J = 9.5 Hz, 1H), 8.40 (s, 1H), 8.03 (s, 1H), 4.55-4.51 (m, 1H), 2.88 (s, 3H), 2.43 (s, 3H), 1.31-1.26 (m, 1H), 0.71-0.67 (m, 1H), 0.62-0.55 (m, 2H), 0.43-0.40 (m, 1H). LC-MS m/z: 390.1 $[M+H]^+$. HPLC: Purity (214 nm): > 98%; t_R = 8.11 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(5-methylpyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00711] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (67 mg, 0.20 mmol) and 5-methylpyridin-3-ylboronic acid afforded the title compound (35 mg, 45 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (d, J = 2.0 Hz, 1H), 8.69(s, 1H), 8.64 (d, J = 1.2 Hz, 1H), 8.55 (d, J = 9.6 Hz, 1H), 8.41 (s, 1H), 8.04 (s, 1H), 4.52 (q, J = 8.0 Hz, 1H), 2.88 (s, 3H), 2.43 (s, 3H), 1.31-1.27 (m, 1H), 0.71-0.67 (m, 1H), 0.61-0.57 (m, 2H), 0.43-0.39 (m, 1H). LC-MS m/z: 390.1 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 8.12 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(6-methylpyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



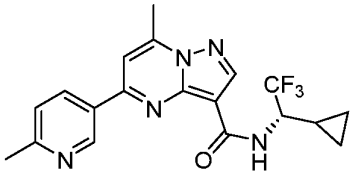
[00712] Following general procedure D, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (239 mg, 1.0 mmol) and 6-methylpyridin-3-ylboronic acid afforded ethyl 7-methyl-5-(6-methylpyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (150 mg, 50 %) as a yellow solid. LC-MS m/z: 297.1 $[M+H]^+$. t_R = 1.65 min.

[00713] Following general procedure B*, ethyl 7-methyl-5-(6-methylpyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (150 mg, 0.506) afforded 7-methyl-5-(6-methylpyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (110 mg, 81 %) as a yellow solid. LC-MS m/z: 269.1 $[M+H]^+$. t_R = 1.14 min.

[00714] Following general procedure A, 7-methyl-5-(6-methylpyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (60 mg, 0.22 mmol) and (*R*)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the ttile compound (44 mg, 38 %) as a white solid.

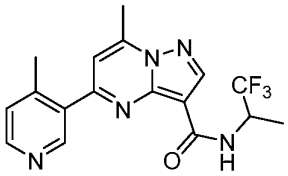
^{1}H NMR (500 MHz, DMSO-d_6) δ 9.30 (d, J = 2.5 Hz, 1H), 8.67 (s, 1H), 8.53 (d, J = 9.5 Hz, 1H), 8.46 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 8.00 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 4.56-4.40 (m, 1H), 2.87 (s, 3H), 2.59 (s, 3H), 1.36-1.23 (m, 1H), 0.77-0.54 (m, 3H), 0.42-0.35 (m, 1H). LC-MS m/z: 390.2 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.05 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(6-methylpyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



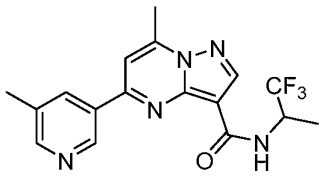
[00715] Following general procedure A, 7-methyl-5-(6-methylpyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (55 mg, 0.205 mmol) and (*S*)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (24 mg, 30 %) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 9.28 (d, J = 2.5 Hz, 1H), 8.65 (s, 1H), 8.52 (dd, J = 8.5 Hz, 2.0 Hz, 1H), 7.81 (d, J = 0.5 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 4.46-4.42 (m, 1H), 2.96 (s, 3H), 2.67 (s, 3H), 1.35-1.31 (m, 1H), 0.81-0.76 (m, 1H), 0.72-0.62 (m, 1H), 0.61-0.58 (m, 1H), 0.52-0.49 (m, 4H). LC-MS m/z: 390.1 $[M+H]^+$. HPLC: Purity (214 nm): 97.01%; t_R = 8.05 min.

7-Methyl-5-(4-methylpyridin-3-yl)-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



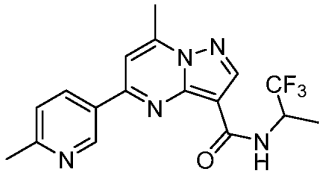
[00716] Following general procedure D, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.26 mmol) and 4-methylpyridin-3-ylboronic acid afforded the title compound (18.2 mg, 19 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.81 (s, 1H), 8.72 (s, 1H), 8.59 (d, J = 5.0 Hz, 1H), 8.24 (d, J = 9.5 Hz, 1H), 7.67 (s, 1H), 7.48 (d, J = 5.0 Hz, 1H), 4.98-4.94 (m, 1H), 2.87 (s, 3H), 2.56 (s, 3H), 1.36 (d, J = 7.0 Hz, 3H). LC-MS m/z: 364.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.35 min

7-Methyl-5-(5-methylpyridin-3-yl)-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



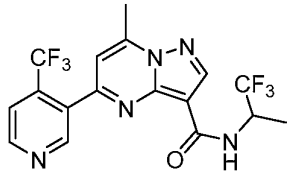
[00717] Following general procedure D, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.26 mmol) and 5-methylpyridin-3-ylboronic afforded the title compound (11.2 mg, 12 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.24 (d, J = 2.0 Hz, 1H), 8.69 (s, 1H), 8.64 (s, 1H), 8.49 (d, J = 9.0 Hz, 1H), 8.42 (s, 1H), 8.04 (s, 1H), 5.02-4.95 (m, 1H), 2.88 (s, 3H), 2.44 (s, 3H), 1.46 (d, J = 7.0 Hz, 3H). LC-MS m/z: 364.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.67 min.

7-Methyl-5-(6-methylpyridin-3-yl)-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



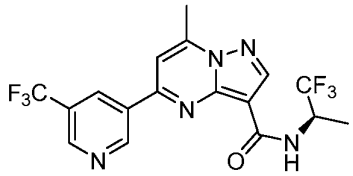
[00718] Following general procedure D, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.327 mmol) and 6-methylpyridin-3-ylboronic acid afforded the title compound (8.2 mg, 7 %) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 9.27 (d, J = 2.0 Hz, 1H), 8.64 (s, 1H), 8.52 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 7.79 (s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 5.00-4.97 (m, 1H), 2.95 (s, 3H), 2.67 (s, 3H), 1.54 (d, J = 7.0 Hz, 3H). LC-MS m/z: 364.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 6.46 min.

7-Methyl-5-(4-(trifluoromethyl)pyridin-3-yl)-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



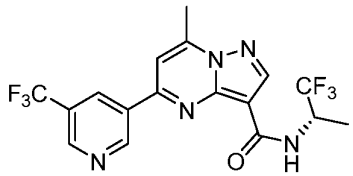
[00719] Following general procedure E*, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (90 mg, 0.29 mmol) and 3-bromo-4-(trifluoromethyl)pyridine afforded the title compound (10 mg, 8 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.10 (s, 1H), 9.07 (d, J = 5.0 Hz, 1H), 8.78 (s, 1H), 8.05 (d, J = 5.0 Hz, 1H), 7.99 (d, J = 9.0 Hz, 1H), 7.72 (s, 1H), 5.01-4.94 (m, 1H), 2.91 (s, 3H), 1.31 (d, J = 7.0 Hz, 3H). LC-MS m/z: 418.0 $[M+H]^+$. HPLC: Purity (214 nm): 98%; t_R = 7.79 min.

(*R*)-7-Methyl-5-(5-(trifluoromethyl)pyridin-3-yl)-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00720] Following general procedure D, (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.23 mmol) and 5-(trifluoromethyl)pyridin-3-ylboronic acid afforded the title compound (59 mg, 61 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (d, J = 1.6 Hz, 1H), 9.21 (d, J = 3.2 Hz, 1H), 8.95 (s, 1H), 8.73 (s, 1H), 8.42 (d, J = 9.2 Hz, 1H), 8.21 (s, 1H), 5.02-4.96 (m, 1H), 2.90 (s, 3H), 1.44 (d, J = 7.2 Hz, 3H). LC-MS m/z: 418.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.49 min.

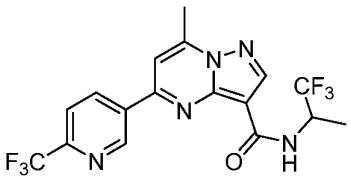
(*S*)-7-Methyl-5-(5-(trifluoromethyl)pyridin-3-yl)-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00721] Following general procedure D, (*S*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.23 mmol) and 5-(trifluoromethyl)pyridin-3-ylboronic acid afforded the title compound (33.4 mg, 34 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.72 (d, J = 1.6 Hz, 1H), 9.21 (d, J = 3.2 Hz, 1H), 8.95 (s, 1H), 8.73 (s, 1H), 8.42 (d, J = 9.2 Hz, 1H), 8.21 (s, 1H), 5.02-4.96 (m, 1H), 2.90

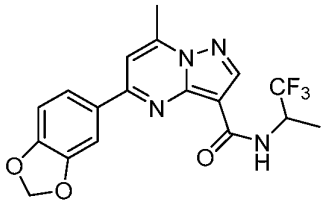
(s, 3H), 1.44 (d, J = 7.2 Hz, 3H). LC-MS m/z: 418.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.48 min.

7-Methyl-5-(6-(trifluoromethyl)pyridin-3-yl)-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



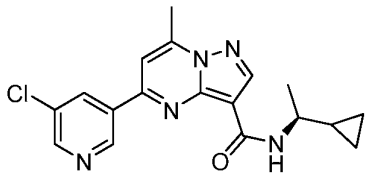
[00722] Following general procedure D, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.26 mmol) and 6-(trifluoromethyl)pyridin-3-ylboronic acid afforded the title compound (18 mg, 19 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.57 (s, 1H), 8.85 (dd, J = 8.5 Hz, 1.5 Hz, 1H), 8.75 (s, 1H), 8.36 (d, J = 9.0 Hz, 1H), 8.23 (d, J = 8.0 Hz, 1H), 8.12 (s, 1H), 5.02-4.94 (m, 1H), 2.90 (s, 3H), 1.47 (d, J = 7.0 Hz, 3H). LC-MS m/z: 418.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.66 min.

5-(Benzo[*d*][1,3]dioxol-5-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



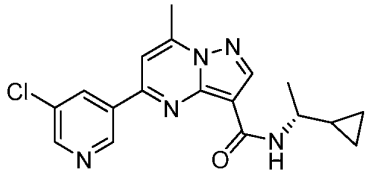
[00723] Following general procedure D, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (140 mg, 0.46 mmol) and 2-(benzo[*d*][1,3]dioxol-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane afforded the title compound (35 mg, 19 %) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.58 (s, 1H), 7.82 (dd, J = 8.0 Hz, 1.5 Hz 1H), 7.20 (d, J = 1.5 Hz, 1H), 7.66 (s, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.12 (s, 1H), 4.99-4.96 (m, 1H), 2.90 (s, 3H), 1.54 (d, J = 7.0 Hz, 3H). LC-MS m/z: 393.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 8.49 min.

(*S*)-5-(5-Chloropyridin-3-yl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



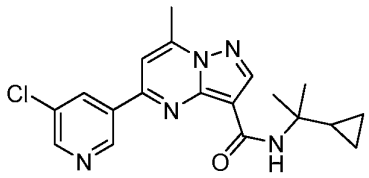
[00724] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (150 mg, 0.54 mmol) and 5-chloropyridin-3-ylboronic acid afforded the title compound (37 mg, 19 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.41 (s, 1H), 8.85 (s, 1H), 8.72 (s, 1H), 8.62 (s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 8.06 (s, 1H), 3.65-3.60 (m, 1H), 2.86 (s, 3H), 1.28 (d, J = 6.5 Hz, 3H), 1.14-1.10 (m, 1H), 0.56-0.46 (m, 2H), 0.42-0.32 (m, 2H). LC-MS m/z: 356.1 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 8.16 min.

(*R*)-5-(5-Chloropyridin-3-yl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



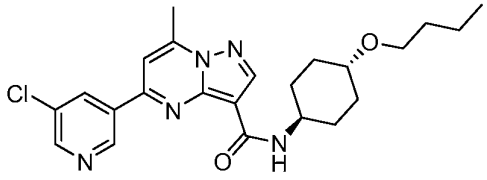
[00725] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.25 mmol) and 5-chloropyridin-3-ylboronic acid afforded the title compound (21 mg, 22%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (d, J = 1.6 Hz, 1H), 8.85 (d, J = 2.0 Hz, 1H), 8.73 (s, 1H) 8.62 (s, 1H), 8.09 (s, 1H), 8.08 (d, J = 7.6 Hz, 1H), 4.66-4.58 (m, 1H), 2.87 (s, 3H), 1.28 (d, J = 6.4 Hz, 3H), 1.16-1.07 (m, 1H), 0.58-0.46 (m, 2H), 0.44-0.29 (m, 2H). LC-MS m/z: 356.1 $[M+H]^+$. HPLC: Purity (214 nm): 95%; t_R = 8.21 min.

5-(5-Chloropyridin-3-yl)-*N*-(2-cyclopropylpropan-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00726] Following general procedure D, 5-chloro-*N*-(2-cyclopropylpropan-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (150 mg, 0.54 mmol) and 5-chloropyridin-3-ylboronic acid afforded the title compound (37 mg, 19 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.39 (d, J = 2.0 Hz, 1H), 8.84 (d, J = 2.5 Hz, 1H), 8.69 (t, J = 2.0 Hz, 1H), 8.58 (s, 1H), 8.07 (s, 1H), 8.04 (s, 1H), 2.86 (s, 3H), 1.40-1.38 (m, 1H), 1.38 (s, 6H), 0.53-0.48 (m, 4H).

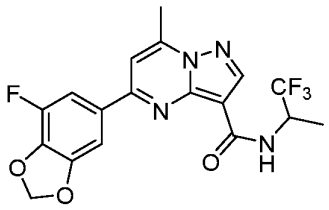
***N*-((1*R*,4*R*)-4-Butoxycyclohexyl)-5-(5-chloropyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide**



[00727] Following general procedure A, 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (600 mg, 2.84 mg) and (1*R*,4*R*)-4-butoxycyclohexanamine afforded *N*-((1*R*,4*R*)-4-butoxycyclohexyl)-5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (820 mg, 80 %) as a yellow solid. LC-MS m/z: 365.2 $[M+H]^+$. Purity (214 nm): 63.1%; t_R = 1.96 min.

[00728] Following general procedure D, *N*-((1*R*,4*R*)-4-butoxycyclohexyl)-5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (150 mg, 0.41 mmol) and 5-chloropyridin-3-ylboronic acid afforded the title compound (35 mg, 19 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.36 (s, 1H), 8.85 (s, 1H), 8.69 (s, 1H), 8.62 (s, 1H), 8.03 (s, 1H), 7.99 (d, J = 6.5 Hz, 1H), 3.85-3.83 (m, 1H), 3.44-3.41 (m, 1H), 3.41 (t, J = 6.0 Hz, 2H), 2.85 (s, 3H), 2.02-1.97 (m, 4H), 1.48-1.32 (m, 8H), 0.89 (t, J = 6.0 Hz, 3H). LC-MS m/z: 442.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 9.42 min.

5-(7-Fluorobenzo[*d*][1,3]dioxol-5-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00729] To a solution of 3-fluoro-2-hydroxybenzaldehyde (5 g, 35.6 mmol) in MeCN (40 mL) was added NBS (6.008 g, 36 mmol) and $CH_3CO_2NH_4$ (270 mg, 3.56 mmol) at RT and the mixture was stirred at RT for 2 h, poured into H_2O (30 mL) and extracted with EA (20 mL × 2). The organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and the residue purified by silica gel column chromatography (PE/EA = 8/1 to 4/1) to afford 5-bromo-3-fluoro-2-hydroxybenzaldehyde (6.6 g, 85 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.24 (s, 1H), 10.22 (s, 1H), 7.84 (dd, J = 10.4 Hz, 2.4 Hz, 1H), 7.59 (dd, J = 2.4 Hz, 1.6 Hz, 1H). LC-MS: t_R = 1.284 min.

[00730] To a solution of 5-bromo-3-fluoro-2-hydroxybenzaldehyde (6.6 g, 30.13 mmol) in THF (43 mL) was added dropwise aqueous NaOH solution (0.05*N*, 119 mL, 6 mmol) at 0 °C, followed by the addition of 30% H_2O_2 solution (16.5 mL). The mixture was stirred for 2 h at RT, followed by the addition of a second portion of 30% H_2O_2 solution (16.5 mL). After stirring for 4 h, it was cooled to 0 °C and aq. NaOH solution (2*N*, 18.5 mL) was added until pH 10~11 was reached, and then the mixture was stirred for 0.5 hour and quenched with conc. HCl at 0 °C to pH 2~3. It was extracted with DCM (40 mL x 3), and the organic phases were washed with brine (50 mL x 2), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford 5-bromo-3-fluorobenzene-1,2-diol (5.1 g, 82 %) as a yellow oil. LC-MS m/z: 205 $[M-H]^-$. t_R = 1.469 min.

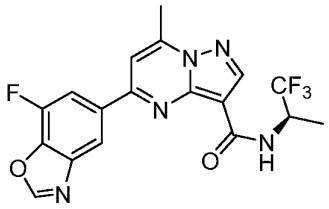
[00731] To a solution of 5-bromo-3-fluorobenzene-1,2-diol (5.0 g, 18.5 mmol) and $BrClCH_2$ (3.6 g, 27.75 mmol) in anhydrous DMF (100 mL) was added Cs_2CO_3 (12.1 g, 37 mmol). The mixture was stirred at 60°C for 3 h, poured into H_2O (200 mL), and extracted with EA (80 mL x 3). The combined extracts were washed with brine (100 mL), 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 = 50/1 to 10/1) to afford 6-bromo-4-

fluorobenzo[*d*][1,3]dioxole (1.8 g, 43%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 6.13 (s, 1H), 6.08 (s, 1H), 5.26 (s, 2H). LC-MS m/z: t_R = 1.89 min.

[00732] To a solution of 6-bromo-4-fluorobenzo[*d*][1,3]dioxole (1.6 g, 7.3 mmol) in dioxane (20 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.04 g, 8.03 mmol), AcOK (1.43 g, 14.6 mmol) and Pd(dppf)Cl_2•DCM (534 mg, 0.73 mmol) under N_2. The mixture was stirred at 110 °C for 14 h, poured into H_2O (60 mL) and extracted with EA (50 mL x 2). 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 = 30/1 to 10/1) to afford 2-(7-fluorobenzo[*d*][1,3]dioxol-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.6 g, 82 %) as yellow oil. LC-MS: t_R = 2.03 min.

[00733] Following general procedure D, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.37 mmol) and 2-(7-fluorobenzo[*d*][1,3]dioxol-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane afforded the title compound (5.8 mg, 4 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.44 (d, *J* = 9.0 Hz, 1H), 7.94 (s, 1H), 7.82 (dd, *J* = 11.5 Hz, 1.0 Hz, 1H), 7.70 (d, *J* = 1.0 Hz, 1H), 6.29 (s, 2H), 5.00-4.92 (m, 1H), 2.83 (s, 3H), 1.44 (d, *J* = 7.0 Hz, 3H). LC-MS m/z: 411.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.71 min.

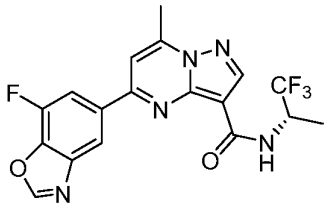
(*R*)-5-(7-Fluorobenzo[*d*]oxazol-5-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00734] To a mixture of 2-amino-4-bromo-6-fluorophenol (500 mg, 2.4 mmol) in methyl orthoformate (5 mL) was added *p*-TsOH·H_2O (41.6 mg, 0.24 mmol). The mixture was stirred for 2 hours at 85 °C under N_2, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE/EA = 20/1~10/1) to afford 5-bromo-7-fluorobenzo[*d*]oxazole (370 mg, 67 %) as a yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.93(s, 1H), 7.96(s, 1H), 8.78(d, *J* = 10.0 Hz, 1H).

[00735] A mixture of 5-bromo-7-fluorobenzo[*d*]oxazole (90 mg, 0.41 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (157 mg, 0.62 mmol), $Pd(PPh_3)_2Cl_2$ (33 mg, 0.04 mmol) and KOAc (81 mg, 0.83 mmol) in 1,4-dioxane (5 mL) was stirred for 2 h at 90 °C under N_2, and then cooled to RT. To this mixture was added (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (78 mg, 0.25 mmol), Na_2CO_3 (88 mg, 0.83 mmol) and H_2O (1 mL) and stirred for 3 h at 90 °C under N_2. The mixture was diluted with H_2O (10 mL), extracted with EA (15 mL x 3), washed with brine (10 mL), 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 = 10:1~1:1) and preparative HPLC ($MeCN/NH_4HCO_3$) to afford the title compound (25 mg, 38%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6): δ 9.02 (s, 1H), 8.68 (s, 1H), 8.60 (d, J = 1.6 Hz, 1H), 8.49 (d, J = 9.6 Hz, 1H), 8.27 (d, J = 12.4 Hz, 1H), 8.14 (s, 1H), 5.00~4.98 (m, 1H), 2.87 (s, 3H), 1.47 (d, J = 7.2 Hz, 3H). LC-MS m/z: 408.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.34 min.

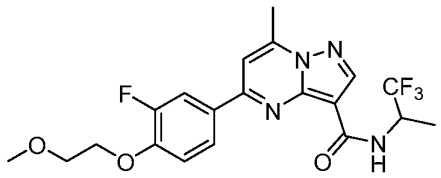
(*S*)-5-(7-Fluorobenzo[*d*]oxazol-5-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00736] A mixture of 5-bromo-7-fluorobenzo[*d*]oxazole (90 mg, 0.41 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (157 mg, 0.62 mmol), $Pd(PPh_3)_2Cl_2$ (33 mg, 0.04 mmol) and KOAc (81 mg, 0.83 mmol) in 1,4-dioxane (5 mL) was stirred for 2 h at 90 °C under N_2, and then cooled to RT. To this mixture were added (*S*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (78 mg, 0.25 mmol), Na_2CO_3 (88 mg, 0.83 mmol) and water (1 mL) and stirred for 3 h at 90 °C under N_2. The mixture was diluted with H_2O (10 mL), extracted with EA (15 mL x 3), washed with brine (10 mL), 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 = 10:1~1:1) and preparative HPLC ($MeCN/NH_4HCO_3$) to afford the title compound (50 mg, 75%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6): δ 9.02 (s, 1H), 8.68 (s, 1H), 8.60 (d, J = 1.6 Hz, 1H), 8.49 (d, J =

9.6 Hz, 1H), 8.27 (d, J = 12.4 Hz, 1H), 8.14 (s, 1H), 5.00~4.98 (m, 1H), 2.87 (s, 3H), 1.47 (d, J = 7.2 Hz, 3H). LC-MS m/z: 408.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.34 min.

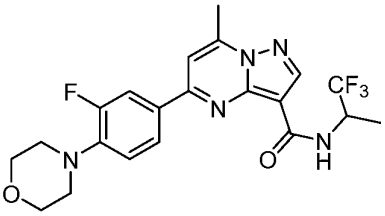
5-(3-Fluoro-4-(2-methoxyethoxy)phenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00737] Following general procedure D, 4-bromo-2-fluoro-1-(2-methoxyethoxy)benzene (4.0 g, 16.0 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) afforded 2-(3-fluoro-4-(2-methoxyethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4.0 g, 83 %) as a yellow solid. LC-MS m/z: 314.3 $[M+H]^+$. Purity (214 nm): 73%; t_R = 1.98 min.

[00738] Following general procedure D, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (174 mg, 0.81 mmol) and 2-(3-fluoro-4-(2-methoxyethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane afforded the title compound (96 mg, 43 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.62 (s, 1H), 8.47 (d, J = 9.2 Hz, 1H), 8.08 (d, J = 10.8 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.93 (s, 1H), 7.44 (t, J = 8.8 Hz, 1H), 5.01-4.96 (m, 1H), 4.32 (t, J = 3.6 Hz, 2H), 3.73 (t, J = 3.6 Hz, 2H), 2.84 (s, 3H), 1.46 (d, J = 6.8 Hz, 3H). LC-MS m/z: 441.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.58 min.

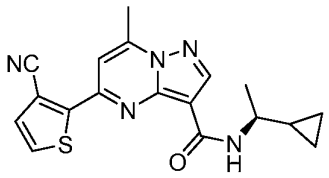
5-(3-Fluoro-4-morpholinophenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00739] Following general procedure D, 5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.23 mmol) and 3-fluoro-4-morpholinophenylboronic acid afforded the title compound (48 mg, 47 %) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.59 (s, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.96 (dd, J = 14.5 Hz, 1.5

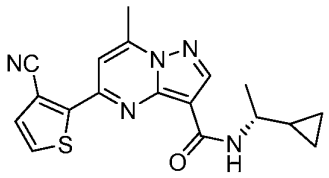
Hz, 1H), 7.70 (s, 1H), 7.21 (t, J = 8.0 Hz, 1H), 4.99-4.95 (m, 1H), 3.89 (t, J = 5.0 Hz, 4H), 3.26 (dd, J = 9.5 Hz, 4.5 Hz, 4H), 2.91 (s, 3H) 1.54 (d, J = 6.5 Hz, 3H). LC-MS m/z: 452.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.72 min.

(*S*)-5-(3-Cyanothiophen-2-yl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



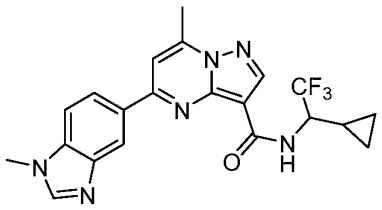
[00740] Following general procedure E*, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.29 mmol) and 2-bromothiophene-3-carbonitrile afforded the title compound (5.5 mg, 5 %) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.64 (s, 1H), 8.13 (d, J = 5.2 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 4.4 Hz, 1H), 7.70 (s, 1H), 3.55-3.53 (m, 1H), 2.87 (s, 3H), 1.30 (d, J = 6.4 Hz, 3H), 1.20-1.11 (m, 1H), 0.49-0.48 (m, 1H), 0.43-0.41 (m, 1H), 0.31-0.23 (m, 2H). LC-MS m/z: 352.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.17 min.

(*R*)-5-(3-Cyanothiophen-2-yl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00741] Following general procedure E*, (*R*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (160 mg, 0.58 mmol) and 2-bromothiophene-3-carbonitrile afforded the title compound (53 mg, 26 %) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.62 (s, 1H), 8.24 (d, J = 6.5 Hz, 1H), 7.93 (d, J = 5.0 Hz, 1H), 7.66 (s, 1H), 7.58 (d, J = 5.0 Hz, 1H), 3.63-3.58 (m, 1H), 2.93 (s, 3H), 1.43 (d, J = 7.0 Hz, 3H), 1.27-1.24 (m, 1H), 0.60-0.56 (m, 1H), 0.52-0.47 (m, 1H), 0.44-0.41 (m, 1H), 0.33-0.28 (m, 1H). LC-MS m/z: 352.0 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.51 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(1-methyl-1*H*-benzo[*d*]imidazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00742] A mixture of 4-bromo-1-fluoro-2-nitrobenzene (2.0 g, 9.1 mmol) in CH_3NH_2/MeOH (10 mL) was heated at 80 °C for 2 h in a sealed tube, poured into H_2O (60 mL) and extracted with EA (40 mL x 2). The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford 4-bromo-*N*-methyl-2-nitroaniline (2.1 g, 100 %) as a yellow solid. LC-MS m/z: 232.9 $[M+H]^+$. t_R = 1.90 min.

[00743] To a solution of 4-bromo-*N*-methyl-2-nitroaniline (2.1 g, 9 mmol) in MeOH (50 mL) was added Fe powder (2.5 g, 45 mmol) and NH_4Cl (4.8 g, 90 mmol). The mixture was stirred at 80 °C for 4 h, poured into H_2O (60 mL) and extracted with EA (40 mL x 2). The organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford 4-bromo-N^1-methylbenzene-1,2-diamine (2.0 g, 99 %) as a yellow solid. LC-MS m/z: 203.1 $[M+H]^+$. t_R = 1.64 min.

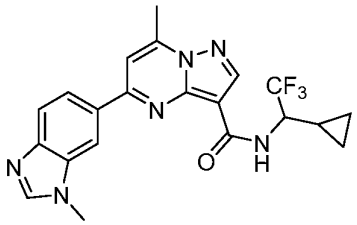
[00744] To a solution of 4-bromo-N^1-methylbenzene-1,2-diamine (1.7 g, 8 mmol) in triethyl orthoformate (10 mL) was added PTSA•H_2O (152 mg, 0.8 mmol). The mixture was stirred at 85 °C for 2 h, poured into H_2O (50 mL) and extracted with EA (40 mL x 2). The organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography (PE/EA = 50/1 to 10/1) to afford 5-bromo-1-methyl-1*H*-benzo[*d*]imidazole (1.5 g, 89 %) as a yellow solid. LC-MS m/z: 211.1 $[M+H]^+$. t_R = 1.90 min.

[00745] To a solution of 5-bromo-1-methyl-1*H*-benzo[*d*]imidazole (1.0 g, 4.74 mmol) in dioxane (10 mL) were added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.5 g, 5.68 mmol), sodium 2-ethylhexanoate (1.968 g, 11.86 mmol) and Pd(dppf)Cl_2•DCM (247 mg, 0.474 mmol) under N_2. The mixture was stirred at 110 °C for 4 h, poured into H_2O (60 mL) and extracted with EA (50 mL x 2). The organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and purified by silica gel column chromatography (PE/EA = 1/1) to

afford 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazole (1.0 g, 82 %) as a yellow solid. LC-MS m/z: 259.1 $[M+H]^+$. t_R = 1.67 min.

[00746] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (150 mg, 0.45 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazole afforded the title compound (19 mg, 10 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.72 (d, *J* = 9.5 Hz, 1H), 8.62 (s, 1H), 8.61 (d, *J* = 9.0 Hz, 1H), 8.34 (s, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 8.08 (s, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 4.55-4.51 (m, 1H), 3.92 (s, 3H), 2.86 (s, 3H), 1.31-1.27 (m, 1H), 0.72-0.62 (m, 1H), 0.61-0.58 (m, 2H), 0.44-0.40 (m, 1H). LC-MS m/z: 429.1 $[M+H]^+$. HPLC Purity (214 nm): 93.56 %; t_R = 7.55 min.

<u>*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide</u>



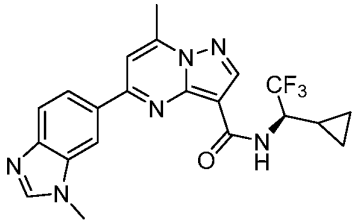
[00747] A mixture of 4-bromo-2-fluoro-1-nitrobenzene (4.0 g, 18.26 mmol) in 30 mL $MeNH_2$/MeOH was stirred at 80 °C for 15 h, and poured into H_2O (100 mL). The mixture was extracted with EA (30 mL x 3), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford 5-bromo-*N*-methyl-2-nitroaniline (3.8 g, 90 %) as a yellow solid. LC-MS m/z: 232.9 $[M+H]^+$. Purity (214 nm): 88.0%; t_R = 1.89 min.

[00748] To a mixture of 5-bromo-*N*-methyl-2-nitroaniline (3.6 g, 16 mmol) in 100 mL of MeOH were added Fe powder (4.38 g, 78 mmol) and NH_4Cl (16.53 g, 311.8 mmol) at RT and the mixture was stirred at 75 °C for 15 h, cooled and filtered. The filtrate was concentrated *in vacuo*, and the residue was washed with H_2O (50 mL). The aqueous phase was extracted with EA (30 mL x 3), and the organic phases were dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford 5-bromo-N^1-methylbenzene-1,2-diamine as a black solid (3.1 g, 90 %). LC-MS m/z: 201.1 $[M+H]^+$. Purity (214 nm): 73%; t_R = 1.66 min.

[00749] To a mixture of 5-bromo-N^1-methylbenzene-1,2-diamine (2.0 g, 10.0 mmol) in 15 mL of trimethoxymethane was added *p*-TsOH•H_2O (0.172 g, 0.02 mmol) at RT and the mixture was stirred at 105 °C for 1 h, cooled and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (20.0 g, PE/EA: 10/1-5/1) to afford 6-bromo-1-methyl-1*H*-benzo[*d*]imidazole as a yellow solid (1.6 g, 76 %). LC-MS m/z: 213.0 $[M+H]^+$. Purity (214 nm): 99%; t_R = 1.57 min.

[00750] Following general procedure E*, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (160 mg, 0.48 mmol) and 6-bromo-1-methyl-1*H*-benzo[*d*]imidazole afforded the title compound (22 mg, 11 %) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.70 (d, *J* = 9.0 Hz, 1H), 8.64 (s, 1H), 8.50 (s, 1H), 8.39 (s, 1H), 8.16 (dd, *J* = 8.5 Hz, 1.5 Hz, 1H), 8.07 (s, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 4.56-4.52 (m, 1H), 3.94 (s, 3H), 2.89 (s, 3H), 1.36-1.32 (m, 1H), 0.73-0.68 (m, 1H), 0.64-0.56 (m, 2H), 0.46-0.42 (m, 1H). LC-MS m/z: 429.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.44 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

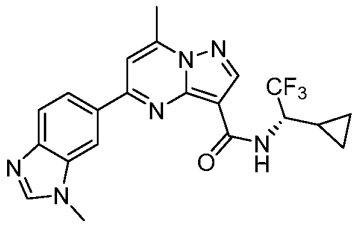


[00751] Following general procedure D, 6-bromo-1-methyl-1*H*-benzo[*d*]imidazole (500 mg, 2.38 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) afforded 1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazole (300 mg, 49 %) as a yellow solid. LC-MS m/z: 441.0 $[M+H]^+$; Purity (214 nm): 86.74%; t_R = 1.68 min.

[00752] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazole afforded the title compound (45 mg, 46%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.70 (d, *J* = 9.6 Hz, 1H), 8.63 (s, 1H), 8.49 (d, *J* = 1.2 Hz, 1H), 8.38 (s, 1H), 8.15 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 8.06 (s, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 4.54-4.48 (m, 1H), 3.93 (s, 3H), 2.87 (s, 3H), 1.35-

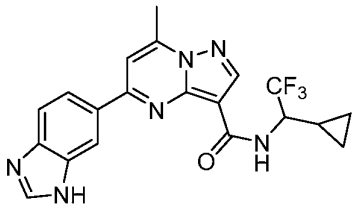
1.30 (m, 1H), 0.72-0.65 (m, 1H), 0.63-0.55 (m, 2H), 0.44-0.40 (m, 1H). LC-MS m/z: 429.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.42 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(1-methyl-1*H*-benzo[*d*]imidazol-6-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00753] Following general procedure E, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.33 mmol) and 6-bromo-1-methyl-1*H*-benzo[*d*]imidazole afforded the title compound (6 mg, 5 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.70 (d, *J* = 9.5 Hz, 1H), 8.64 (s, 1H), 8.50 (d, *J* = 1.5 Hz, 1H), 8.40 (s, 1H), 8.16 (dd, *J* = 8.5 Hz, 1.5 Hz, 1H), 8.07 (s, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 4.54-4.48 (m, 1H), 3.93 (s, 3H), 2.87 (s, 3H), 1.35-1.30 (m, 1H), 0.72-0.65 (m, 1H), 0.63-0.55 (m, 2H), 0.44-0.40 (m, 1H). LC-MS m/z: 429.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.46 min.

5-(1*H*-Benzo[*d*]imidazol-6-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



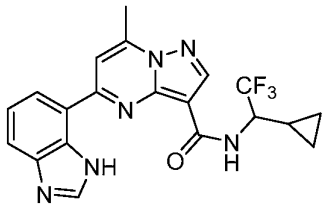
[00754] A mixture of 6-bromo-1*H*-benzo[*d*]imidazole (1 g, 5.08 mmol), Boc_2O (1.56 g, 4.22 mmol), and DIPEA (1.54 g, 15.23 mmol) in DCM (20 mL) was stirred at 20 °C for 16 h under N_2, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (EA:PE; 0 to 10%) to afford *tert*-butyl 6-bromo-1*H*-benzo[*d*]imidazole-1-carboxylate (1.4 g, 92 %) as a yellow solid. LC-MS m/z: 241.0 $[M-56]^+$. LC-MS Purity (214 nm): > 98 %; t_R = 1.98 min.

[00755] The mixture of *tert*-butyl 6-bromo-1*H*-benzo[*d*]imidazole-1-carboxylate (1.4 g, 4.74 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.44 g, 5.65 mmol),

Pd(dppf)Cl_2•DCM (383 mg, 0.47 mmol), and CH_3COOK (1.16 g, 11.78 mmol) in 1,4-dioxane (10 mL) was stirred at 70 °C for 16 h under N_2. The mixture was filtered and the organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give crude *tert*-butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazole-1-carboxylate, which was used in the next step directly (4 g). LC-MS m/z: 289.1 $[M-56]^+$. LC-MS Purity (214 nm): > 47%; t_R = 2.07 min.

[00756] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.30 mmol) and *tert*-butyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazole-1-carboxylate afforded the title compound (6 mg, 5 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.79 (s, 1H), 8.70 (d, *J* = 9.5 Hz, 1H), 8.61 (s, 1H), 8.47 (s, 1H), 8.12 (d, *J* = 9 Hz, 1H), 8.03 (s, 1H), 7.76 (s, 1H), 4.50-4.45 (m,1H), 2.97 (s, 3H), 1.32-1.28 (m, 1H), 0.73-0.68 (m, 1H), 0.64-0.60 (m, 2H), 0.45-0.40 (m, 1H). LC-MS m/z: 415.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.03 min.

5-(1*H*-Benzo[*d*]imidazol-7-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



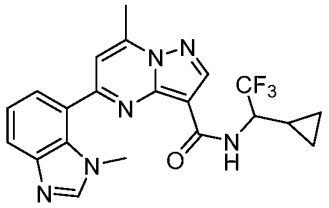
[00757] The mixture of 7-bromo-1*H*-benzo[*d*]imidazole (1 g, 5.08 mmol), Boc_2O (1.56 g, 4.22 mmol), and DIPEA (1.54 g, 15.23 mmol) in DCM (20 mL) was stirred at 20 °C for 16 h under N_2, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (EA:PE; 0 to 10%) to afford *tert*-butyl 7-bromo-1*H*-benzo[*d*]imidazole-1-carboxylate (1.2 g, 79 %) as a yellow solid. LC-MS m/z: 241.0 $[M-56]^+$. LC-MS Purity (214 nm): > 98 %; t_R = 1.93 min.

[00758] The mixture of *tert*-butyl 7-bromo-1*H*-benzo[*d*]imidazole-1-carboxylate (1.2 g, 4.04 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (1.23 g, 4.85 mmol), Pd(dppf)Cl_2•DCM (329 mg, 0.40 mmol), and CH_3COOK (0.99 g, 10.10 mmol) in 1,4-dioxane (10 mL) was stirred at 70 °C for 16 h under N_2. The mixture was filtered and the organic layers

were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give crude *tert*-butyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazole-1-carboxylate, which was used in the next step directly (3 g). LC-MS m/z: 289.1 $[M-56]^+$. LC-MS Purity (214 nm): > 42%; t_R = 2.07 min.

[00759] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.30 mmol) and *tert*-butyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazole-1-carboxylate afforded the title compound (6 mg, 5 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.89 (s, 1H), 8.82 (d, *J* = 9.5 Hz, 1H), 8.70 (s, 1H), 8.48 (s, 1H), 8.16 (d, *J* = 5.5 Hz, 1H), 7.84 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 4.50-4.42 (m, 1H), 2.90 (s, 3H), 1.34-1.27 (m, 1H), 0.72-0.67 (m, 1H), 0.60-0.58 (m, 2H), 0.44-0.38 (m, 1H). LC-MS m/z: 415.1 $[M+H]^+$. HPLC Purity (214 nm): 99%; t_R = 7.54 min.

<u>*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(1-methyl-1*H*-benzo[*d*]imidazol-7-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide</u>



[00760] A mixture of 1-bromo-2-fluoro-3-nitrobenzene (2.19 g, 10.0 mmol) in $MeNH_2$ (MeOH solution, 40 mL) was stirred at reflux for 3 h, poured into saturated $NaHCO_3$ aqueous solution (100 mL), and extracted with EA (80 mL x 3). The combined organic phases were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford 2-bromo-*N*-methyl-6-nitroaniline (1.9 g, 82.6% yield) as a red oil. LC-MS m/z: 231.0 $[M+H]^+$. t_R = 1.82 min.

[00761] A mixture of 2-bromo-*N*-methyl-6-nitroaniline (1.9 g, 8.26 mmol), Fe powder (2.8 g), and NH_4Cl (8.84 g, 165.2 mmol) in MeOH (100 mL) was stirred at reflux for 8 h, and filtered. The filtrate was concentrated *in vacuo*, and the residue was dissolved in saturated $NaHCO_3$ solution (200 mL). The mixture was extracted with EA (150 mL x 3). The combined extracts were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford a mixture of 6-bromo-N^1-methylbenzene-1,2-diamine and 7-bromo-1-methyl-1*H*-

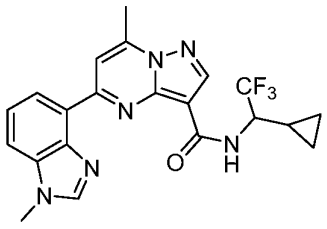
benzo[*d*]imidazole (1.8 g) as a green oil. LC-MS m/z: 211.0 $[M+H]^+$. t_R = 1.56 min. 201.0 $[M+H]^+$. t_R = 1.64 min.

[00762] A mixture of 6-bromo-N^1-methylbenzene-1,2-diamine and 7-bromo-1-methyl-1*H*-benzo[*d*]imidazole (1.8 g, crude), trimethoxymethane (10 mL) and 4-methylbenzenesulfonic acid (172 mg, 1.0 mmol) was stirred at 85 °C for 1 h, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EA/PE = 4/1) to afford 7-bromo-1-methyl-1*H*-benzo[*d*]imidazole (1.6 g, 92% yield over 2 steps) as a green solid. LC-MS m/z: 213.1 $[M+H]^+$. t_R = 1.58 min.

[00763] Following general procedure D, 7-bromo-1-methyl-1*H*-benzo[*d*]imidazole (105 mg, 0.5 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) afforded crude 1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazole (650 mg) as a black oil, which was used in the next step without further purification. LC-MS m/z: 259.2 $[M+H]^+$. t_R = 1.74 min.

[00764] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.21 mmol) and 1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-benzo[*d*]imidazole afforded the title compound (68 mg, 59 %) as a grey solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.74 (s, 1H), 8.34 (d, J = 9.5 Hz, 1H), 8.33 (s, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.70 (s, 1H), 7.54 (d, J = 7.5 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 4.38-4.33 (m, 1H), 3.67 (s, 3H), 2.90 (s, 3H), 1.05-1.00 (m, 1H), 0.63-0.44 (m, 3H), 0.26-0.21 (m, 1H). LC-MS m/z: 429.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.43 min.

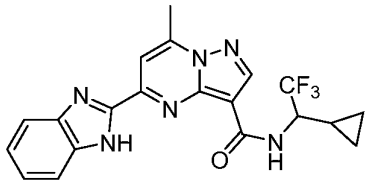
<u>*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(1-methyl-1*H*-benzo[*d*]imidazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide</u>



[00765] Following general procedure E*, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.30 mmol) and 4-bromo-1-methyl-

1*H*-benzo[*d*]imidazole afforded the title compound (60 mg, 29 %) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (d, *J* = 10.0 Hz, 1H), 8.75 (s, 1H), 8.70 (s, 1H), 8.30 (d, *J* = 7.5 Hz, 1H), 8.05 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 4.60-4.56 (m, 1H), 3.97 (s, 3H), 2.97 (s, 3H), 1.28-1.25 (m, 1H), 0.74-0.70 (m, 1H), 0.63-0.56 (m, 3H). LC-MS m/z: 429.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.27 min.

5-(1*H*-Benzo[*d*]imidazol-2-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide

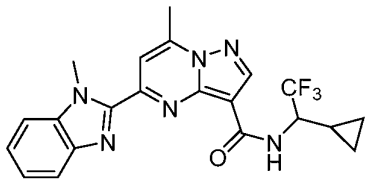


[00766] To a mixture of ethyl 5-formyl-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (235 mg, 1.01 mmol) and benzene-1,2-diamine (109 mg, 1.01 mmol) in MeCN (6 mL) were added 30% (*w/w)* H_2O_2 (241 mg, 7.09 mmol), and 37% (*w/w)* HCl (130 mg, 3.61 mmol). The mixture was stirred at RT for 2 h, diluted with H_2O (100 mL) 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*, and the residue was purified by silica gel column chromatography (40 g, eluting with PE/EA = 1/0 to 1/4) to afford ethyl 5-(1*H*-benzo[*d*]imidazol-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate as a grey solid (102 mg, 31%). LC-MS m/z: 322.1 $[M+H]^+$. t_R = 1.71 min.

[00767] Following general procedure B*, ethyl 5-(1*H*-benzo[*d*]imidazol-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (97 mg, 0.3 mmol) afforded 5-(1*H*-benzo[*d*]imidazol-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (86 mg, 92 %) as a light yellow solid. LC-MS m/z: 294.1 $[M+H]^+$. t_R = 1.25 min.

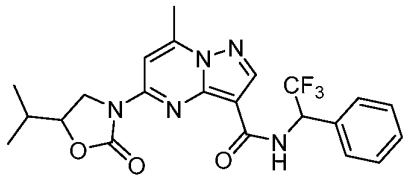
[00768] Following general procedure A, 5-(1*H*-benzo[*d*]imidazol-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (81 mg, 0.28 mmol) and 1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (20 mg, 18 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.43 (s, 1H), 8.75 (s, 1H), 8.41 (d, *J* = 9.0 Hz, 1H), 8.12 (s, 1H), 7.86-7.68 (m, 2H), 7.42-7.29 (m, 2H), 4.26-4.17 (m, 1H), 2.91 (s, 3H), 1.71-1.63 (m, 1H), 0.81-0.76 (m, 1H), 0.70-0.59 (m, 2H), 0.43-0.38 (m, 1H). LC-MS m/z: 415.1 $[M+H]^+$. HPLC: Purity (214 nm): 97%; t_R = 8.15 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(1-methyl-1*H*-benzo[*d*]imidazol-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00769] Following general procedure E*, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.178 mmol) and 2-bromo-1-methyl-1*H*-benzo[*d*]imidazole afforded the title compound (19 mg, 25 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.28 (d, J = 9.0 Hz, 1H), 8.18 (s, 1H), 7.81 (d, J = 7.5 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 4.39 (s, 3H), 4.33-4.27 (m, 1H), 2.91 (s, 3H), 1.30-1.25 (m, 1H), 0.76-0.67 (m, 2H), 0.62-0.57 (m, 1H), 0.39-0.32 (m, 1H). LC-MS m/z: 429.1 $[M+H]^+$. HPLC Purity (214 nm): 93.8 %; t_R = 8.79 min.

5-(5-*i*-Propyl-2-oxooxazolidin-3-yl)-7-methyl-*N*-(2,2,2-trifluoro-1-phenylethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

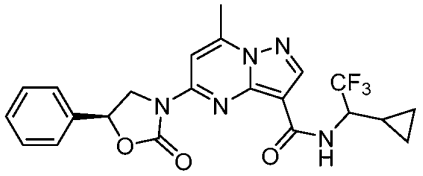


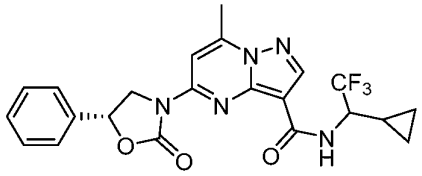
[00770] Following general procedure A, 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (400 mg, 1.89 mmol) and 2,2,2-trifluoro-1-phenylethanamine afforded 5-chloro-7-methyl-*N*-(2,2,2-trifluoro-1-phenylethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (558 mg, 80 %) as a white solid. LC-MS m/z: 369.0 $[M+H]^+$. LCMS: t_R = 1.92 min.

[00771] Following general procedure H, 5-chloro-7-methyl-*N*-(2,2,2-trifluoro-1-phenylethyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (200 mg, 0.54 mmol) and 5-*iso*-propyloxazolidin-2-one afforded the title compound (15 mg, 6 %) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.50 (s, 1H), 8.09 (dd, J = 5.5 Hz, 1.0 Hz, 1H), 7.60-7.54 (m, 2H), 7.49-7.44 (m, 3H), 6.00-5.98 (m, 1H), 4.60-4.55 (m, 1H), 4.50-4.44 (m, 1H), 4.09 (dd, J = 10.0 Hz, 8.0 Hz, 1H), 2.84 (s, 3H), 2.11-2.03 (m, 1H), 1.12 (dd, J = 6.5 Hz, 6.0 Hz, 3H), 1.04 (dd, J

= 6.5 Hz, 2.5 Hz, 3H). LC-MS m/z: 462.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 9.12 min.

<u>*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-((*S*)-2-oxo-5-phenyloxazolidin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide & *N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-((*R*)-2-oxo-5-phenyloxazolidin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide</u>





[00772] The solution of 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (200 mg, 0.6 mmol), 2-amino-1-phenylethanol (495 mg, 3.61 mmol) and TEA (60 mg, 0.60 mmol) in MeCN (2 mL) was stirred at 80 °C for 2 h, and cooled. The solution was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (EA) to afford *N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-5-(2-hydroxy-2-phenylethylamino)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (250 mg, 96 %) as a white solid. LC-MS m/z: 434.1 $[M+H]^+$. Purity (214 nm): >97%; t_R = 1.71 min.

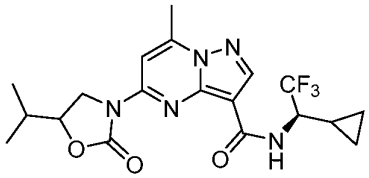
[00773] A solution of *N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-5-(2-hydroxy-2-phenylethylamino)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (200 mg, 0.46 mmol), CDI (1.12 g, 6.32 mmol) and TEA (93 mg, 0.92 mmol) in THF (8 mL) was stirred at 70 °C for 16 hours, and cooled. The solution was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (50% EA in PE) and triturated with Et_2O to afford *N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-((*S*)-2-oxo-5-phenyloxazolidin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (48 mg, 23 %) as a white solid and *N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-((*R*)-2-oxo-5-phenyloxazolidin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (56 mg, 26 %) as a white solid.

[00774] *N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-((*S*)-2-oxo-5-phenyloxazolidin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.05 (d, J = 9.5 Hz, 1H), 7.97 (s, 1H), 7.56-7.55 (m, 2H), 7.49-7.42 (m, 3H), 5.92 (t, J = 8.0 Hz, 1H), 4.68 (t, J = 9.0 Hz, 1H), 4.37-4.33 (m, 1H), 4.24-4.20 (m, 1H), 2.82 (s, 3H), 1.19-1.12 (m,

1H), 0.62-0.57 (m, 1H), 0.52-0.47 (m, 1H), 0.41-0.32 (m, 1H), 0.31-0.27 (m, 1H). LC-MS m/z: 460.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.76 min.

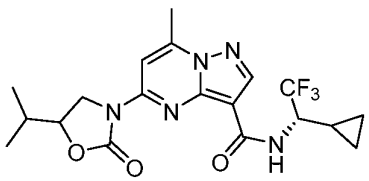
[00775] *N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-((*R*)-2-oxo-5-phenyloxazolidin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.12 (d, J = 9.0 Hz, 1H), 7.98 (s, 1H), 7.56-7.55 (m, 2H), 7.50-7.43 (m, 3H), 5.90 (t, J = 8.5 Hz, 1H), 4.78 (t, J = 10.0 Hz, 1H), 4.34-4.31 (m, 1H), 4.14-4.11 (m, 1H), 2.82 (s, 3H), 1.25-1.17 (m, 1H), 0.67-0.62 (m, 1H), 0.56-0.52 (m, 2H), 0.36-0.32 (m, 1H). LC-MS m/z: 460.1 $[M+H]^+$. HPLC: Purity (214 nm): > 97%; t_R = 8.72 min.

<u>*N*-((*R*)-1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(5-*iso*-propyl-2-oxooxazolidin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide</u>



[00776] Following general procedure H, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.21 mmol) and 5-*iso*-propyloxazolidin-2-one afforded the title compound (13 mg, 14 %) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.51 (s, 1H), 8.07 (d, J = 6.5 Hz, 1H), 4.56-4.52 (m, 1H), 4.47-4.37 (m, 2H), 4.09-4.01 (m, 1H), 2.86 (s, 3H), 1.27-1.25 (m, 1H), 1.12 (dd, J = 6.5 Hz, 3.0 Hz, 3H), 1.04 (dd, J = 6.5 Hz, 2.0 Hz, 3H), 0.78-0.75 (m, 1H), 0.65-0.60 (m, 1H), 0.59-0.50 (m, 2H). LC-MS m/z: 426.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 8.91 min.

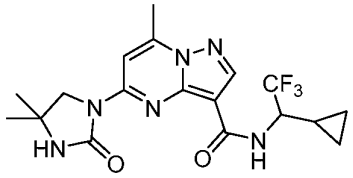
<u>*N*-((*S*)-1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(5-*iso*-propyl-2-oxooxazolidin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide</u>



[00777] Following general procedure H, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.21 mmol) and 5-*iso*-propyloxazolidin-2-one afforded the title compound (5.6 mg, 6 %) as a white solid. ^{1}H NMR

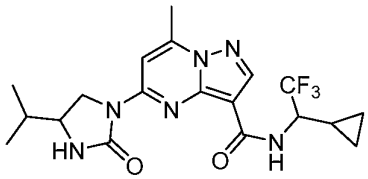
(500 MHz, MeOD-d_4) δ 8.51 (s, 1H), 8.07 (d, J = 6.5 Hz, 1H), 4.56-4.52 (m, 1H), 4.47-4.37 (m, 2H), 4.09-4.01 (m, 1H), 2.86 (s, 3H), 1.27-1.25 (m, 1H), 1.12 (dd, J = 6.5 Hz, 3.0 Hz, 3H), 1.04 (dd, J = 6.5 Hz, 2.0 Hz, 3H), 0.78-0.75 (m, 1H), 0.65-0.60 (m, 1H), 0.59-0.50 (m, 2H). LC-MS m/z: 426.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 8.91 min.

<u>*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(4,4-dimethyl-2-oxoimidazolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide</u>



[00778] Following general procedure H, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.30 mmol) and 4,4-dimethylimidazolidin-2-one afforded the title compound (32 mg, 26 %) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.43 (s, 1H), 8.16 (s, 1H), 4.42-4.39 (m, 1H), 3.97 (d, J = 10.5 Hz, 1H), 3.92 (d, J = 10.5 Hz, 1H), 2.80 (s, 3H), 1.443 (s, 3H), 1.435 (s, 3H), 1.29-1.25 (m, 1H), 0.79-0.75 (m, 1H), 0.67-0.63 (m, 1H), 0.59-0.54 (m, 1H), 0.53-0.49 (m, 1H). LC-MS m/z: 411.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.70 min.

<u>*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(4-*iso*-propyl-2-oxoimidazolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide</u>



[00779] To a mixture of 2-amino-3-methylbutanoic acid (15 g, 128 mmol), and $NaBH_4$ (19.5 g, 512 mmol) in THF (200 mL) was added I_2 (32 g, 128 mmol, dissolved in 100 mL of THF) dropwise at 0 °C. The reaction mixture was stirred at 65 °C for 16 h, quenched with MeOH (100 mL) and concentrated *in vacuo*. The white residue was dissolved in 225 mL of 20% aqueous KOH and stirred for 3 h at RT, extracted with EA (100 mL x 3), and the organic phases dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to

afford 2-amino-3-methylbutan-1-ol (7 g, 50 %) as an oil. LC-MS m/z: 118.1 $[M+H]^+$. Purity (214 nm): 90%; t_R = 0.34 min.

[00780] To a mixture of 2-amino-3-methylbutan-1-ol (7 g, 60 mmol), and Na_2CO_3 (22 g, 180 mmol) in H_2O (100 mL) was added benzyl chloroformate (12 g, 66 mmol). The mixture was stirred at RT for 16 h, and extracted with EA (50 mL x 3) and dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (EA:PE = 1:3) to afford benzyl 1-hydroxy-3-methylbutan-2-ylcarbamate (9 g, 65 %) as a white solid. LC-MS m/z: 238.1 $[M+H]^+$. Purity (214 nm): 90%; t_R = 1.62 min.

[00781] To a mixture of benzyl 1-hydroxy-3-methylbutan-2-ylcarbamate (1 g, 4.2 mmol), and Et_3N (850 mg, 8.4 mmol) in toluene (15 mL) was added MsCl (480 mg, 4.2 mmol). The mixture was stirred at RT for 15 minutes, followed by the addition of a solution of NaN_3 (2.7 g, 42 mmol) in 20 mL of water, and Bu_4NBr (680 mg, 2.1 mmol). The resulting mixture was stirred at 90 °C for 16 h, extracted with DCM (30 mL × 3), dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford benzyl 1-azido-3-methylbutan-2-ylcarbamate (1.1 g, 90%) as a white oil, which was used directly in the next step. LC-MS m/z: 263.1 $[M+H]^+$. Purity (214 nm): 90%; t_R = 1.86 min.

[00782] A mixture of benzyl 1-azido-3-methylbutan-2-ylcarbamate (1.1 g, 4.2 mmol), triphenylphosphine (1.6 g, 6.3 mmol), and H_2O (1 g, 42 mmol) in THF (20 mL) was stirred at RT for 16 h, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EA:PE = 1:3) to afford benzyl 1-amino-3-methylbutan-2-ylcarbamate (900 mg, 90%) as a white solid. LC-MS m/z: 237.1 $[M+H]^+$. Purity (214 nm): 90%; t_R = 1.50 min.

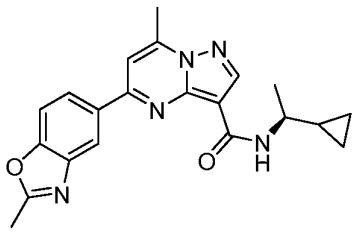
[00783] A mixture of benzyl 1-amino-3-methylbutan-2-ylcarbamate (100 mg, 0.42 mol), 10% Pd/C (100 mg, 0.47 mmol), and 4*M* HCl/dioxane (2 mL) in MeOH (10 mL) was stirred for 3 h at 30 °C under H_2, and filtered. The filtrate was concentrated *in vacuo* to afford 3-methylbutane-1,2-diamine (40 mg, crude) as a colorless oil.

[00784] A mixture of 3-methylbutane-1,2-diamine (40 mg, crude), CDI (129 mg, 0.78 mmol), Et_3N (88 mg, 0.87 mmol) in DCM (10 mL) was stirred for 18 h at 30 °C, and concentrated *in vacuo*. The residue was dissolved in H_2O (5 mL), which was adjusted to pH = 6~7, and extracted with DCM (20 mL x 3). The organic phases were dried over anhydrous

Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford 4-*iso*-propylimidazolidin-2-one (23 mg, crude) as a light yellow solid.

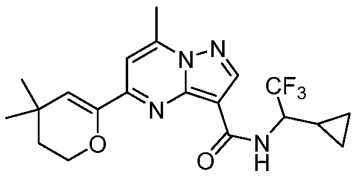
[00785] Following general procedure H, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (59.7 mg, 0.18 mmol) and 4-*iso*-propylimidazolidin-2-one afforded the title compound (8 mg, 4% over three steps) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.43 (s, 1H), 8.24 (dd, J = 23.5 Hz, 8.0 Hz, 1H), 8.18 (d, J = 5.0 Hz, 1H), 8.08 (s, 1H), 4.48-4.42 (m, 1H), 4.18 (dd, J = 10.5 Hz, 9.0 Hz, 1H), 4.09 (t, J = 10.0 Hz, 1H), 3.75 (dd, J = 9.5 Hz, 6.5 Hz, 1H), 3.68 (dd, J = 11.0 Hz, 6.5 Hz, 1H), 3.57-3.32 (m, 1H), 2.73 (s, 3H), 1.73-1.67 (m, 1H), 1.21-1.16 (m, 1H), 0.91 (dd, J = 7.0 Hz, 1.5 Hz, 3H), 0.87 (dd, J = 6.5 Hz, 4.0 Hz, 3H), 0.67-0.62 (m, 1H). 0.56-0.49 (m, 2H), 0.40-0.35 (m, 1H). LC-MS m/z: 425.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.14 min.

(*S*)-*N*-(1-Cyclopropylethyl)-7-methyl-5-(2-methylbenzo[*d*]oxazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00786] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.29 mmol) and 2-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]oxazole afforded the title compound (3.1 mg, 3 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.57 (d, J = 1.5 Hz, 1H), 8.55 (s, 1H), 8.30 (dd, J = 8.5 Hz, 1.5 Hz, 1H), 8.22 (d, J = 7.5 Hz, 1H), 8.00 (s, 1H), 7.91 (d, J = 8.5 Hz, 1H), 3.67-3.63 (m, 1H), 2.86 (s, 3H), 2.68 (s, 3H), 1.30 (d, J = 6.5 Hz, 3H), 1.13-1.09 (m, 1H), 0.57-0.50 (m, 2H), 0.42-0.39 (m, 1H), 0.37-0.34 (m, 1H). LC-MS m/z: 376.1 $[M+H]^+$. HPLC Purity (214 nm): 97.4%; t_R = 8.09 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(4,4-dimethyl-3,4-dihydro-2*H*-pyran-6-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00787] To a stirred solution of 4,4-dimethyltetrahydro-2*H*-pyran-2-one (4.3 g, 33.5 mmol) in DCM (150 ml) at -78 °C, was added a solution of DIBAL-H (36.9 ml, 36.9 mmol) in toluene over 1 h. The resulting solution was stirred for an additional 30 min, quenched with MeOH (25 ml) and allowed to warm slowly to RT overnight. The resulting suspension was diluted with 30% aqueous solution of sodium potassium tartrate (200 ml) and stirred for 30 min, the organic layer was separated and washed with 30% aqueous sodium potassium tartrate (100 mL x 2). The combined aqueous layers were then extracted with DCM (100 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to give crude 4,4-dimethyltetrahydro-2*H*-pyran-2-ol (4.3 g, 100%) as a clear liquid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.20 (d, J = 6.0 Hz, 1H), 4.72-4.68 (m,1H), 3.75-3.70 (m, 1H), 3.51 (td, J = 10.8 Hz, 2.8 Hz, 1H), 1.39-1.36 (m, 1H), 1.31-1.24 (m, 1H), 1.18-1.09 (m, 2H), 0.94 (s, 6H).

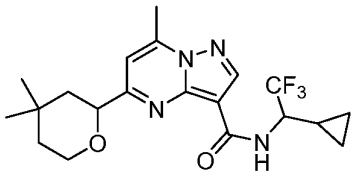
[00788] 4,4-Dimethyltetrahydro-2*H*-pyran-2-ol (0.62 g, 4.76 mmol) was added dropwise to a solution of *p*-TsOH (80 mg) in quinoline (5 mL) preheated to 190 °C attached to a short-path distillation apparatus equipped with a dry ice/acetone filled cold trap. After the addition was complete the temperature was raised to 220 °C, and the distillation was carried out to afford 4,4-dimethyl-3,4-dihydro-2*H*-pyran (220 mg, 40%) as a clear liquid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.25 (d, J = 6.4 Hz, 1H), 4.50 (d, J = 6.4 Hz, 1H), 3.89 (t, J = 5.2 Hz, 2H), 1.58 (t, J = 5.2 Hz, 2H), 0.99 (s, 6H).

[00789] To a solution of 4,4-dimethyl-3,4-dihydro-2*H*-pyran (1.0 g, 8.93 mmol) in hexane (40 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.27 g, 8.93 mmol), $[Ir(OMe)(cod)]_2$ (298 mg, 0.45 mmol) and 4,4'-di-*tert*-butyl-2,2'bipyridyl (238 mg, 0.89 mmol). The mixture was stirred for 20 h at reflux under N_2, cooled to RT and concentrated to give a residue which was purified by silica gel column chromatography (PE:EA = 5:1) to afford 2-(4,4-dimethyl-3,4-dihydro-2*H*-pyran-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

(900 mg, 42%) as a colorless oil. LC-MS m/z: 239.2 $[M+H]^+$. Purity (214 nm): 26%; t_R = 1.67 min.

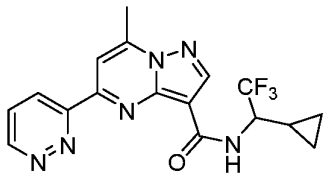
[00790] Following general procedure D, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (348 mg, 1.05 mmol) and 2-(4,4-dimethyl-3,4-dihydro-2*H*-pyran-6-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane afforded the title compound (170 mg, 39%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.59 (d, J = 9.6 Hz, 1H), 7.21 (s, 1H), 6.12 (s, 1H), 4.63-4.57 (m, 1H), 4.24 (dd, J = 6.0 Hz, 4.0 Hz, 2H), 2.84 (s, 3H), 1.79 (t, J = 4.8 Hz, 2H), 1.26-1.19 (m, 1H), 1.15 (s, 6H), 0.70-0.65 (m, 1H), 0.61-0.49 (m, 3H). LC-MS m/z: 409.0 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 10.15 min.

<u>*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(4,4-dimethyltetrahydro-2*H*-pyran-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide</u>



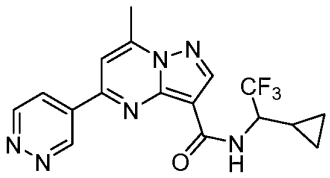
[00791] To a stirred solution of *N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-5-(4,4-dimethyl-3,4-dihydro-2*H*-pyran-6-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.20 mmol) in THF (20 mL) at RT was added 5% Pd/C (10 mg) under a H_2 atmosphere and the mixture was stirred at RT for 2 h. The crude reaction mixture was eluted through a short plug of celite (EA followed by DCM) and the organic layer was concentrated *in vacuo* to provide a residue which was purified by preparative HPLC to afford the title compound (47 mg, 60%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.62 (s, 1H), 8.47 (d, J = 10.0 Hz, 1H), 7.34 (s, 1H), 4.72 (dd, J = 12.0 Hz, 2.5 Hz, 1H), 4.59-4.53 (m,1H), 3.98-3.95 (m,1H), 3.83-3.80 (m,1H), 2.81 (s, 3H), 1.79-1.76 (m,1H),1.50-1.34 (m, 3H),1.21-1.20 (m, 1H), 1.13 (s, 3H), 0.97 (s, 3H),0.65-0.64 (m, 1H), 0.58-0.57 (m, 1H), 0.49-0.48 (m, 1H), 0.43-0.41 (m, 1H). LC-MS m/z: 411.1 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 10.12 min.

_N_-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(pyridazin-3-yl)pyrazolo[1,5-_a_]pyrimidine-3-carboxamide



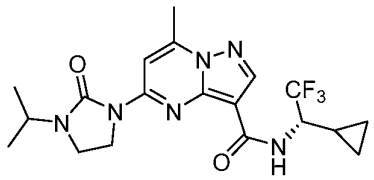
[00792] Following general procedure F, 5-chloro-_N_-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-_a_]pyrimidine-3-carboxamide (100 mg, 0.3 mmol) and 3-(tributylstannyl)pyridazine afforded the title compound (10 mg, 9%) as a light yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.99 (dd, J = 2.5 Hz, 1.5 Hz, 1H), 9.57 (dd, J = 5.5 Hz, 1.5 Hz, 1H), 8.78 (s, 1H), 8.46 (d, J = 9.5 Hz, 1H), 8.39 (dd, J = 5.5 Hz, 3.0 Hz, 1H), 8.16 (s, 1H), 4.45-4.40 (m, 1H), 2.92 (s, 3H), 1.39-1.35 (m, 1H), 0.73-0.70 (m, 1H), 0.63-0.59 (m, 2H), 0.41-0.39 (m, 1H). LC-MS m/z: 377.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 6.92 min.

_N_-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(pyridazin-4-yl)pyrazolo[1,5-_a_]pyrimidine-3-carboxamide



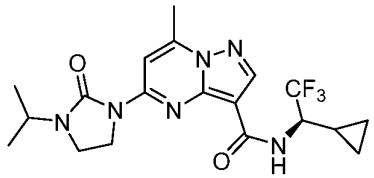
[00793] Following general procedure F, 5-chloro-_N_-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-_a_]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 4-(tributylstannyl)pyridazine afforded the title compound (33 mg, 37 %) as a grey solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.99 (s, 1H), 9.57 (d, J = 5.5 Hz, 1H), 8.78 (s, 1H), 8.46 (d, J = 9.5 Hz, 1H), 8.39 (dd, J = 5.5 Hz, 3.0 Hz, 1H), 8.17 (s, 1H), 4.45-4.40 (m, 1H), 2.91 (s, 3H), 1.39-1.34 (m, 1H), 0.74-0.71 (m, 1H), 0.64-0.57 (m, 2H), 0.40-0.37 (m, 1H). LC-MS m/z: 377.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 6.92 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



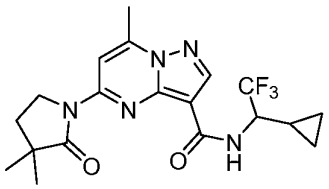
[00794] Following general procedure A, 5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (65 mg, 0.21 mmol) and (*S*)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (12.4 mg, 14 %) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.51 (s, 1H), 8.17 (d, *J* = 9.5 Hz, 1H), 8.15 (s, 1H), 4.52-4.47 (m, 1H), 4.33-4.27 (m, 1H), 4.12-4.06 (m, 2H), 3.57 (t, *J* = 7.0 Hz, 2H), 2.78 (s, 3H), 1.25 (d, *J* = 7.0 Hz, 6H), 1.14-1.10 (m, 1H), 0.71-0.67 (m, 1H), 0.57-0.50 (m, 3H). LC-MS m/z: 425.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.60 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



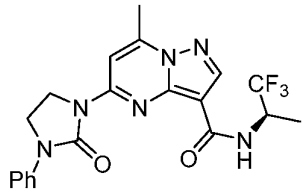
[00795] Following general procedure A, 5-(3-*iso*-propyl-2-oxoimidazolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (65 mg, 0.21 mmol) and (*R*)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (5.6 mg, 6 %) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.50 (s, 1H), 8.17 (d, *J* = 9.5Hz, 1H), 8.15 (s, 1H), 4.52-4.47 (m, 1H), 4.33-4.27 (m, 1H), 4.12-4.06 (m, 2H), 3.57 (t, *J* = 7.0 Hz, 2H), 2.78 (s, 3H), 1.25 (d, *J* = 7.0Hz, 6H), 1.14-1.10 (m, 1H), 0.71-0.67 (m, 1H), 0.57-0.50 (m, 3H). LC-MS m/z: 425.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.60 min.

N-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(3,3-dimethyl-2-oxopyrrolidin-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



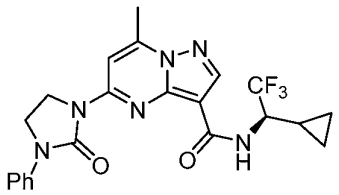
[00796] Following general procedure H, 5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.30 mmol) and 3,3-dimethylpyrrolidin-2-one afforded the title compound (20 mg, 16 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.53 (s, 1H), 8.19 (d, J = 9.0 Hz, 1H), 8.18 (s, 1H), 4.38-4.31 (m, 1H), 4.11-4.01 (m, 1H), 3.41-3.31 (m, 1H), 2.78 (s, 3H), 2.04 (t, J = 7.0 Hz, 2H), 1.30-1.24 (m, 1H), 1.24 (s, 6H), 0.71-0.65 (m, 1H), 0.68-0.55 (m, 2H), 0.42-0.32 (m, 1H). LC-MS m/z: 410.2 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.94 min.

(*R*)-7-Methyl-5-(2-oxo-3-phenylimidazolidin-1-yl)-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



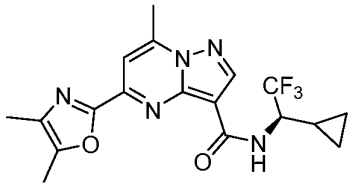
[00797] Following general procedure H, (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.326 mmol) and 1-phenylimidazolidin-2-one afforded the title compound (18.3 mg, 13%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.49 (s, 1H), 8.17 (s, 1H), 8.12 (d, J = 9.0 Hz, 1H), 7.69 (d, J = 7.5 Hz, 2H), 7.44 (t, J = 8.0 Hz, 2H), 7.17 (t, J = 7.5 Hz, 1H), 4.94-4.92 (m, 1H), 4.26-4.07 (m, 4H), 2.79 (s, 3H), 1.44 (d, J = 6.5 Hz, 3H). LC-MS m/z: 433.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 8.75 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(2-oxo-3-phenylimidazolidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



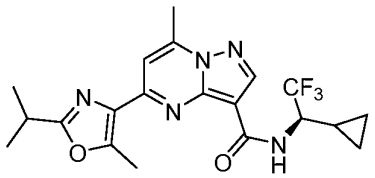
[00798] Following general procedure H, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (94 mg, 0.28 mmol) and 1-phenylimidazolidin-2-one afforded the title compound (30 mg, 23%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.20 (d, J = 0.8 Hz, 1H), 8.15 (d, J = 6.0 Hz, 1H), 7.62 (dd, J = 8.8 Hz, 1.2 Hz, 2H), 7.44 (td, J = 8.4 Hz, 2.0 Hz, 2H), 7.21 (t, J = 7.6 Hz, 1H), 4.51-4.49 (m, 1H), 4.28-4.23 (m, 2H), 4.13-4.08 (m, 2H), 2.82 (s, 3H), 1.15-1.13 (m, 1H), 0.73-0.70 (m, 1H), 0.58-0.52 (m, 3H). LC-MS m/z: 459.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 9.22 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(4,5-dimethyloxazol-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00799] To a stirred solution of 4,5-dimethyloxazole (150 mg, 1.55 mmol) in anhydrous THF (10 mL) was added n-BuLi (0.62 mL, 1.55 mmol) dropwise at -78 °C. The mixture was stirred for 30 minutes and then 1*M* $ZnCl_2$ (3.87 mL, 3.87 mol) was added at -78 °C, stirred an additional 30 minutes and warmed to RT. (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (90 mg, 0.27 mmol) was added followed by $Pd(PPh_3)_2Cl_2$ (18.9 mg, 0.027) and the mixture was stirred at 60 °C for 3 h under N_2 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EA/PE = 80%) to afford the title compound (18 mg, 17 %) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 8.51 (d, J = 9.6 Hz, 1H), 7.82 (s, 1H), 4.64-4.60 (m, 1H), 2.86 (s, 3H), 2.43 (s, 3H), 2.19 (s, 3H), 1.27-1.23 (m, 1H), 0.68-0.58 (m, 3H), 0.54-0.48 (m, 1H). LC-MS m/z: 394.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 11.36 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(2-*iso*-propyl-5-methyloxazol-4-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00800] To a stirred solution of ethyl 5-formyl-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (0.3 g, 1.29 mmol) in THF (3 mL) was added EtMgBr$_2$ (1.42 mL, 1.42 mmol) at -78 °C and the solution was stirred at -78 °C for 1.5 h and then quenched with saturated NH_4Cl (10 mL). The mixture was extracted with EA (20 mL) the organic layer was washed with H_2O (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* and purified by silica gel chromatography (PE/EA = 2:3) to afford ethyl 5-(1-hydroxypropyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (70 mg, 20%) as a yellow oil. LC-MS m/z: 264.2 $[M+H]^+$. Purity (214 nm): 93%; t_R = 1.09 min.

[00801] To a stirred solution of ethyl 5-(1-hydroxypropyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (70 mg, 0.27 mmol) in DCM (3 mL) was added Dess-Martin reagent (223 mg, 0.54 mmol) at 0 °C under N_2 and the solution was stirred at RT overnight. The reaction was quenched with saturated $NaHCO_3$ (10 mL), extracted with DCM (20 mL), washed with H_2O (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* and purified by silica gel chromatography (PE/EA = 2:1) to give ethyl 7-methyl-5-propionylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (50 mg, 72%) as a yellow solid. LC-MS m/z: 262.1 $[M+H]^+$. Purity (254 nm): 96%; t_R = 1.88 min.

[00802] To a solution of ethyl 7-methyl-5-propionylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (70 mg, 0.27 mmol) in MeOH (5 mL) was added $HONH_2$•HCl (186 mg, 2.68 mmol) and TEA (183 mg, 1.34 mmol) and the mixture was stirred at RT for 3 h. Then it was poured into H_2O (20 mL) and extracted with EA (15mL x 2). The combined extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated to give ethyl 5-(1-(hydroxyimino)propyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (70 mg, 95%) as a white solid. LC-MS (m/z): 277.2 $[M+H]^+$, Purity (214 nm): 95%, t_R = 1.24 min.

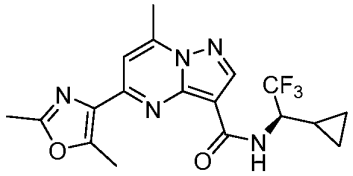
[00803] To a solution of ethyl 5-(1-(hydroxyimino)propyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 0.36 mmol) and DMAP (3.0 mg, 0.023 mmol) in 1,2-

dichlorobenzene (1 mL) at 0 °C was added dropwise *iso*-butyryl chloride (385 mg, 3.6 mmol). The reaction mixture was heated at 180 °C for 1 h under microwave conditions, cooled, concentrated and then purified by silica gel chromatography (EA) to give ethyl 5-(2-*iso*-propyl-5-methyloxazol-4-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (70 mg, 59%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.61 (s, 1H), 7.64 (s, 1H), 4.30 (q, J = 7.0 Hz, 2H), 2.89 (s, 3H), 2.81 (s, 3H), 2.48 (s, 3H), 1.34 (t, J = 7.0 Hz, 3H). LC-MS (m/z): 300.1 $[M+H]^+$, t_R = 1.32 min.

[00804] Following general procedure B*, ethyl 5-(2-*iso*-propyl-5-methyloxazol-4-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (70 mg, 0.21 mmol) afforded 5-(2-*iso*-propyl-5-methyloxazol-4-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (69 mg, 100%). LC-MS (m/z): 301.1 $[M+H]^+$, Purity (214 nm): 79%, t_R = 1.17 min.

[00805] Following general procedure A, 5-(2-*iso*-propyl-5-methyloxazol-4-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (70 mg, 0.21 mmol) and (*R*)-1-cyclopropyl-2,2,2-trifluoroethan-1-amine afforded the title compound (29 mg, 33%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.18 (d, J = 9.5 Hz, 1H), 7.67 (s, 1H), 4.34-4.28 (m, 1H), 3.18-3.12 (m, 1H), 2.85 (s, 3H), 2.79 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 1.23-1.15 (m, 1H), 0.75-0.55 (m, 3H), 0.35-0.3 (m, 1H). LC-MS m/z: 422.2 $[M+H]^+$. HPLC Purity (214 nm): >99%; t_R = 10.16 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(2,5-dimethyloxazol-4-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



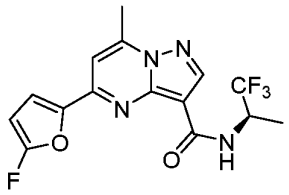
[00806] To a solution of ethyl 5-(1-(hydroxyimino)propyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (70 mg, 0.25 mmol) and DMAP (2.0 mg, 0.016 mmol) in 1,2-dichlorobenzene (0.5 mL) at 0 °C was added dropwise acetyl chloride (40 mg, 0.51 mmol). The reaction mixture was heated at 180 °C for 45 min under microwave conditions, cooled, concentrated and then purified by silica gel chromatography (PE/EA = 1:5) to give ethyl 5-(2,5-dimethyloxazol-4-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (30 mg, 40%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.61 (s, 1H), 7.64 (s, 1H), 4.30 (q, J = 7.0 Hz,

2H), 2.89 (s, 3H), 2.81 (s, 3H), 2.48 (s, 3H), 1.34 (t, J = 7.0 Hz, 3H). LC-MS (m/z): 300.1 $[M+H]^+$, t_R = 1.32 min.

[00807] Following general procedure B*, ethyl 5-(2,5-dimethyloxazol-4-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (30 mg, 0.1 mmol) afforded crude 5-(2,5-dimethyloxazol-4-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 100%) as a brown solid. LC-MS (m/z): 273.1 $[M+H]^+$, Purity (214 nm): 74%, t_R = 1.04 min.

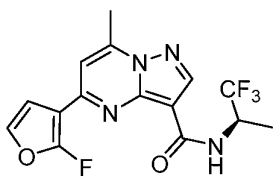
[00808] Following general procedure A, 5-(2,5-dimethyloxazol-4-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.1 mmol) and (*R*)-1-cyclopropyl-2,2,2-trifluoroethan-1-amine afforded the title compound (6.4 mg, 16%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.18 (d, J = 9.5 Hz, 1H), 7.69 (s, 1H), 4.33-4.26 (m, 1H), 2.84 (s, 3H), 2.78 (s, 3H), 2.49 (s, 3H), 1.20-1.16 (m, 1H), 0.77-0.62 (m, 2H), 0.60-0.55 (m, 1H), 0.35-0.25 (m, 1H). LC-MS m/z: 394.0 $[M+H]^+$. HPLC Purity (214 nm): >99%; t_R = 8.88 min.

(*R*)-5-(5-Fluorofuran-2-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00809] Following general procedure F, (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.16 mmol) and tributyl(5-fluorofuran-2-yl)stannane afforded the title compound (37 mg, 64%) as a white solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.55 (s, 1H), 7.42 (s, 1H), 7.39 (d, J = 4.5 Hz, 1H), 5.98 (dd, J = 8.5 Hz, 4.5 Hz, 1H), 4.95-4.93 (m, 1H), 2.86 (s, 3H), 1.52 (d, J = 8.5 Hz, 3H). LC-MS m/z: 357.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 8.62 min.

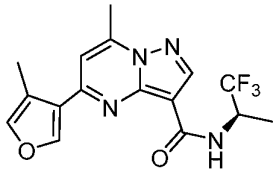
(*R*)-5-(2-Fluorofuran-3-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00810] A mixture of 3-bromofuran-2-carboxylic acid (300 mg, 1.57 mmol) and $NaHCO_3$ (316 mg, 3.76 mmol) was stirred in 3.5 mL of pentane/water (2/5) at RT for 5 minutes, followed by the addition of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octanebis-tetrafluoroborate (668 mg, 1. 88 mmol). The mixture was stirred for 1 hour at RT, and separated to afford the pentane solution of 3-bromo-2-fluorofuran, which was dried ($MgSO_4$), diluted with 3 mL of anhydrous Et_2O, and cooled to -78 °C under N_2. To this was added n-BuLi (1.6*M*, 0.25 mL, 0.39 mmol) and the mixture was stirred at -78 °C for 10 minutes, followed by the addition of *n*-Bu_3SnCl (127 mg, 0. 39 mmol). The mixture was then allowed to stir at RT for another 20 minutes, quenched with saturated NH_4Cl (50 mL), and separated. The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford tributyl(2-fluorofuran-3-yl)stannane (155 mg) as a brown oil which was used directly in the next step.

[00811] Following general procedure F, (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.15 mmol) and tributyl(2-fluorofuran-3-yl)stannane afforded the title compound (6.8 mg, 13%) as a yellow solid. ^1H NMR (500 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.41 (d, J = 9.0 Hz, 1H), 7.57 (d, J = 2.5 Hz, 1H), 7.56 (s, 1H), 7.21 (t, J = 2.5 Hz, 1H), 4.98-4.92 (m, 1H), 2.82 (s, 3H), 1.42 (d, J = 7.5 Hz, 3H). LC-MS m/z: 357.0 $[M+H]^+$. HPLC: Purity (214 nm): 97%; t_R = 8.52 min.

(*R*)-7-Methyl-5-(4-methylfuran-3-yl)-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

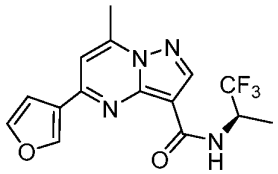


[00812] A mixture of (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (700 mg, 2.29 mmol), $Pd(PPh_3)_2Cl_2$ (160 mg, 0.23 mmol) and Sn_2Bu_6 (2.6 g, 4.58 mmol) in dioxane (40 mL) was stirred at 80 °C for 16 h under N_2. The reaction mixture was filtered and concentrated *in vacuo* and purified by silica gel chromatography (PE:EA = 4:1) to afford (*R*)-7-methyl-5-(tributylstannyl)-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (400 mg, 32%) as a white solid. LC-MS m/z: 562.0 $[M+H]^+$, Purity (214 nm): 95%; t_R = 2.22 min.

[00813] Following general procedure F, (*R*)-7-methyl-5-(tributylstannyl)-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (400 mg, 0.71mmol) and 3,4-dibromofuran afforded (*R*)-5-(4-bromofuran-3-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 34%) as a white solid. LC-MS m/z: 417.0 $[M+H]^+$, Purity (214 nm): 95%; t_R = 1.47 min.

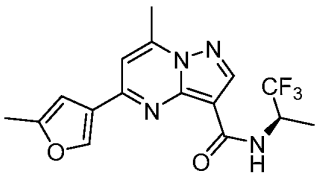
[00814] A mixture of (*R*)-5-(4-bromofuran-3-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.24 mmol), $(P(o\text{-}Tol)_3)_2PdCl_2$ (17 mg, 0.024 mmol), $SnMe_4$ (86 mg, 0.48 mmol) in dioxane (3 mL)/ DMF (1 mL) was stirred at 120 °C under N_2 and microwave for 30 min. The reaction mixture was filtered and concentrated *in vacuo* to give a residue which was purified by preparative HPLC to afford the title compound (5 mg, 6%) as a white solid. ^1H NMR (500 MHz, DMSO-d_6) δ 8.65 (d, J = 1.5 Hz, 1H), 8.59 (s, 1H), 8.04 (d, J = 9.0 Hz, 1H), 7.72 (s, 1H), 7.63 (s, 1H), 4.07-4.00 (m, 1H), 2.78 (s, 3H), 2.40 (s, 3H), 1.40 (d, J = 7.5 Hz, 3H). LC-MS m/z: 353.0 $[M+H]^+$, HPLC : Purity (214 nm): >99%; t_R = 8.74 min.

(*R*)-5-(Furan-3-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



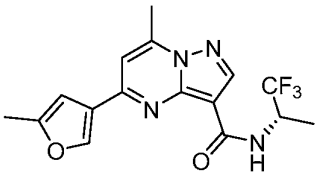
[00815] Following general procedure E*, (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.30 mmol) and 3-bromofuran afforded the title compound (5 mg, 5%) as a white solid. ^1H NMR (500 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.59 (s, 1H), 8.41 (d, J = 9.5 Hz, 1H), 7.95 (d, J = 1.5 Hz, 1H), 7.67 (s, 1H), 7.06 (d, J = 1.0 Hz, 1H), 4.99-4.9 (m, 1H), 2.80 (s, 3H), 1.46 (d, J = 6.5 Hz, 3H). LC-MS m/z: 339.0 $[M+H]^+$, HPLC: Purity (214 nm): >99%; t_R = 8.28 min.

(*R*)-7-Methyl-5-(5-methylfuran-3-yl)-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



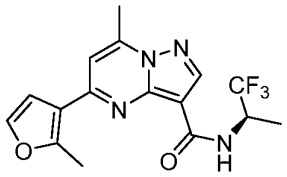
[00816] Following general procedure E*, (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (120 mg, 0.40 mmol) and 4-bromo-2-methylfuran afforded the title compound (5.7 mg, 4%) as a grey solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.51 (s, 1H), 8.41 (d, J = 9.5 Hz, 1H), 7.61 (s, 1H), 6.65 (s, 1H), 4.96-4.92 (m, 1H), 2.78 (s, 3H), 2.38 (s, 3H), 1.46 (d, J = 7.0 Hz, 3H). LC-MS m/z: 353.1 $[M+H]^+$. HPLC: Purity (214 nm): 97%; t_R = 8.77 min.

(*S*)-7-Methyl-5-(5-methylfuran-3-yl)-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



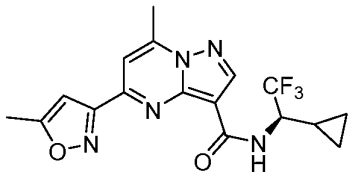
[00817] Following general procedure E*, (*S*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (110 mg, 0.36 mmol) and 4-bromo-2-methylfuran afforded the title compound (10.4 mg, 8%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.51 (s, 1H), 8.41 (d, J = 10.0 Hz, 1H), 7.61 (s, 1H), 6.65 (s, 1H), 4.99-4.90 (m, 1H), 2.78 (s, 3H), 2.38 (s, 3H), 1.46 (d, J = 7.0 Hz, 3H). LC-MS m/z: 353.2 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 8.81 min.

(*R*)-7-Methyl-5-(2-methylfuran-3-yl)-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00818] Following general procedure D, (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (40 mg, 0.130 mmol) and 4,4,5,5-tetramethyl-2-(2-methylfuran-3-yl)-1,3,2-dioxaborolane afforded the title compound (10 mg, 17 %) as a white solid. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.61 (s, 1H), 8.11 (d, J = 9.6 Hz, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.58 (s, 1H), 7.14 (d, J = 1.6 Hz, 1H), 5.02-4.97 (m, 1H), 2.81 (s, 3H), 2.75 (s 3H), 1.42 (d, J = 6.8 Hz, 3H). LC-MS m/z: 353.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.61 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(5-methylisoxazol-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00819] A mixture of ethyl 5-formyl-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (300 mg, 1.28 mmol) and 1-(tritylphosphanylidene)propan-2-one (389 mg, 1.28 mmol) in THF (20 mL) was heated at reflux for 0.5 h. The reaction was concentrated and then triturated with Et_2O (20 ml) to afford ethyl (*E*)-7-methyl-5-(3-oxobut-1-en-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (295 mg, 85%) as a white solid. LC-MS m/z: 274.1$[M+H]^+$. Purity (214 nm): 96%; t_R = 1.13 min.

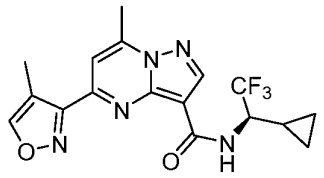
[00820] To a solution of *N*-hydroxy-4-methylbenzenesulfonamide (500 mg, 2.59 mmol) in 1.8 mL of MeOH/H_2O (6/1) was added in portions K_2CO_3 (408 mg, 2.96 mmol) followed by the addition of ethyl (*E*)-7-methyl-5-(3-oxobut-1-en-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 0.37 mmol) in MeOH (3 mL) and the reaction mixture was stirred for 3 h at 40 °C. Additional K_2CO_3 (200 mg) was added and the mixture was stirred for 8 h at 60 °C. The reaction mixture was diluted with EA (80 mL), washed with H_2O (15 mL) and brine (15 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel chromatography (PE:EA = 1:1) to afford ethyl 7-methyl-5-(5-methylisoxazol-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (86 mg, 86%) as a yellow solid. LC-MS m/z: 273.1$[M+H]^+$. Purity (214 nm): 65%; t_R = 1.19 min.

[00821] Following general procedure B*, ethyl 7-methyl-5-(5-methylisoxazol-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (86 mg, 0.32 mmol) afforded 7-methyl-5-(5-

methylisoxazol-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (72 mg, 90%) as a yellow solid. LC-MS m/z: 259.1 $[M+H]^+$. LCMS: Purity (214 nm): 95%; $t_R = 0.75$ min.

[00822] Following general procedure A, 7-methyl-5-(5-methylisoxazol-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (65 mg, 0.25 mmol) and (*R*)-1-cyclopropyl-2,2,2-trifluoroethan-1-amine afforded the title compound (39 mg, 41%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.39 (d, $J = 10.0$ Hz, 1H), 7.83 (s, 1H), 6.78 (s, 1H), 4.29-4.37 (m, 1H), 2.88 (s, 3H), 2.57 (s, 3H), 1.38-1.35 (m, 1H), 0.70-0.68 (m, 1H), 0.61-0.58 (m, 2H), 0.40-0.37 (m, 1H). LC-MS m/z: 380.1 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 8.93 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(4-methylisoxazol-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



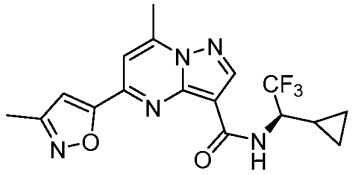
[00823] A mixture of ethyl 5-formyl-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (320 mg, 1.37 mmol) and 2-(tritylphosphanylidene)propanal (436 mg, 1.37 mmol) in THF (20 mL) was heated at reflux for 0.5 h. The reaction was concentrated and then triturated with Et_2O (20 mL) to afford ethyl (*E*)-7-methyl-5-(2-methyl-3-oxoprop-1-en-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (310 mg, 83%) as a yellow solid. LC-MS m/z: 274.1$[M+H]^+$. Purity (214 nm): 96%; $t_R = 1.77$ min.

[00824] To a solution of *N*-hydroxy-4-methylbenzenesulfonamide (277 mg, 1.48 mmol) in 1.8 mL of MeOH/H_2O (6/1) was added in portions K_2CO_3 (255 mg, 1.48 mmol) followed by the addition of ethyl (*E*)-7-methyl-5-(2-methyl-3-oxoprop-1-en-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 0.37 mmol) in MeOH (5 mL) and the reaction mixture was stirred for 18 h at RT. Additional K_2CO_3 (100 mg) was added and the mixture was stirred for 4 h at 60 °C. The reaction mixture was diluted with EA (80 mL), washed with H_2O (15 mL) and brine (15 mL) and dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel chromatography (PE:EA = 1:1) to afford ethyl 7-methyl-5-(4-methylisoxazol-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (62 mg, 61%) as a yellow solid. LC-MS m/z: 273.0$[M+H]^+$. Purity (214 nm): 83%; $t_R = 1.72$ min.

[00825] Following general procedure B*, ethyl 7-methyl-5-(4-methylisoxazol-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (62 mg, 0.23 mmol) afforded 7-methyl-5-(4-methylisoxazol-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (25 mg, 42%) as a yellow solid. LC-MS m/z: 259.0$[M+H]^+$. LCMS: Purity (214 nm): 80%; t_R = 1.17 min.

[00826] Following general procedure A, 7-methyl-5-(4-methylisoxazol-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (25 mg, 0.10 mmol) and (*R*)-1-cyclopropyl-2,2,2-trifluoroethan-1-amine afforded the title compound (14.0 mg, 27%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.01 (s, 1H), 8.74 (s, 1H), 8.15 (d, J = 9.5 Hz, 1H), 7.84 (s, 1H), 4.31-4.28 (m, 1H), 2.88 (s, 3H), 2.41 (s, 3H), 1.18-1.15 (m, 1H), 0.73-0.66 (m, 2H), 0.58-0.55 (m, 1H), 0.33-0.31 (m, 1H). LC-MS m/z: 380.1 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 8.83 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(3-methylisoxazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00827] A suspension of ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (480 mg, 2 mmol), ethynyltrimethylsilane (392 mg, 2 mmol), $Pd(PPh_3)Cl_2$ (140 mg, 0.2 mmol), CuI (38 mg, 0.2 mmol), and Et_3N (404 mg, 4 mmol) in THF (5 mL) was stirred at RT for 0.5 hour under N_2 atmosphere, and then at 50 °C for 2 h. The reaction mixture was cooled to RT, quenched with saturated NH_4Cl (20 mL), and extracted with EA (30 mL× 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 (PE/EA: 2/1) to afford ethyl 7-methyl-5-((trimethylsilyl)ethynyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (540 mg, 89 %) as a pale yellow solid. LC-MS m/z: 302.1 $[M+H]^+$. LCMS: Purity (214 nm): 95.6%; t_R = 1.56 min.

[00828] To a solution of ethyl 7-methyl-5-((trimethylsilyl)ethynyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (150 mg, 0.5 mmol) in MeOH (10 mL) was added KF (58 mg, 1 mmol). The reaction mixture was stirred at RT for 10 minutes, and concentrated *in vacuo* after the addition of silica gel. The residue was purified by silica gel column chromatography

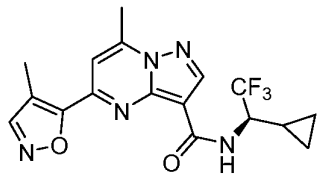
(PE/EA: 1/2) to afford ethyl 5-ethynyl-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (89 mg, 79 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.69 (s, 1H), 7.40 (s, 1H), 4.84 (s, 1H), 4.31 (q, J = 7.0 Hz, 2H), 2.76 (s, 3H), 1.32 (t, J = 7.0 Hz, 3H). LC-MS m/z: 230.1 $[M+H]^+$. LCMS: Purity (254nm): 99%; t_R = 1.15 min.

[00829] To a solution of ethyl 5-ethynyl-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (46 mg, 0.2 mmol), and acetaldehyde oxime (89 mg, 1.5 mmol) in MeOH/H_2O (5/1, 2 mL) was added bis-[(trifluoroacetoxy) iodo]benzene (130 mg, 0.3 mmol). The reaction mixture was stirred at RT for 12 h, concentrated *in vacuo* and purified by silica gel column chromatography (PE/EA: 2/1) to afford ethyl 7-methyl-5-(3-methylisoxazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (50 mg, 84 %) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 7.49 (s, 1H), 7.10 (s, 1H), 4.44 (q, J = 7.2 Hz, 2H), 2.92 (s, 3H), 2.43 (s, 3H), 1.46 (t, J = 6.8 Hz, 3H). LC-MS m/z: 287.1 $[M+Na]^+$. LCMS: Purity (214 nm): 79%; t_R = 1.68 min.

[00830] Following general procedure B*, ethyl 7-methyl-5-(3-methylisoxazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (40 mg, 0.17 mmol) afforded 7-methyl-5-(3-methylisoxazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 80 %) as a yellow solid. LC-MS m/z: 258.1 $[M+H]^+$. LCMS: Purity (254 nm): 75%; t_R = 0.99 min.

[00831] Following general procedure A, 7-methyl-5-(3-methylisoxazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (40 mg, 0.16 mmol) and (*R*)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (10 mg, 17 %) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.74 (s, 1H), 8.38 (d, J = 9.5 Hz, 1H), 8.84 (s, 1H), 7.25 (s, 1H), 7.14 (d, J = 1.5 Hz, 1H), 4.47-4.44 (m, 1H), 2.88 (s, 3H), 2.40 (s, 3H), 1.36-1.32 (m, 1H), 0.70-0.67 (m, 1H), 0.62-0.56 (m, 2H), 0.45-0.40 (m, 1H). LC-MS m/z: 380.1 $[M+H]^+$. HPLC: Purity (214 nm): 97.9%; t_R = 8.49 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(4-methylisoxazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide

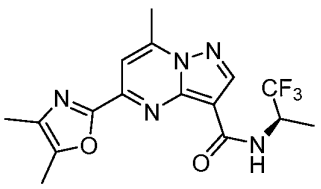


[00832] A mixture of (*E*)-7-methyl-5-(2-methyl-3-oxoprop-1-en-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (782 mg, 2.86 mmol), $HONH_2$ hydrochloride (296 mg, 4.29 mmol) and KOAc (420 mg, 4.29 mmol) in MeOH (10 mL) was stirred at RT overnight. The mixture was filtered to afford ethyl 5-((1*E*,3*Z*)-3-(hydroxyimino)-2-methylprop-1-en-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (608 mg, 73%) as a yellow solid which was used directly in the next step. LC-MS m/z: 289.1$[M+H]^+$. Purity (214 nm): 84%; t_R = 1.15 min.

[00833] A mixture of ethyl 5-((1*E*,3*Z*)-3-(hydroxyimino)-2-methylprop-1-en-1-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (500 mg, 1.74 mmol) and MnO_2 (1.5 g, 17.4 mmol) in $CHCl_3$ (30 mL) was stirred at 65 °C overnight. Then the mixture was filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (PE:EA = 1:1) to afford ethyl 7-methyl-5-(4-methylisoxazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (120 mg, 24%) as a yellow solid. LC-MS m/z: 287.1$[M+H]^+$. Purity (214 nm): 80%; t_R = 1.28 min.

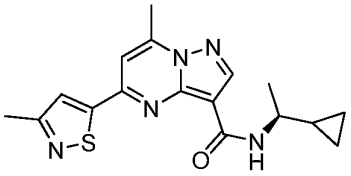
[00834] To a stirred solution of (*R*)-1-cyclopropyl-2,2,2-trifluoroethan-1-amine hydrochloride (293 mg, 1.67 mmol) in toluene (2 mL) was added $AlMe_3$ (0.98 mL, 1.96 mmol) at 0 °C and the solution was stirred at RT for 1 h. Then a solution of ethyl 7-methyl-5-(4-methylisoxazol-5-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (40 mg, 0.14 mmol) in THF (2 mL) was added and the reaction was stirred at 110 °C for 40 min. Saturated NH_4Cl (10 mL) solution was added and the mixture was extracted with EA (20 mL), washed with H_2O (5 mL) and brine (5 mL), concentrated *in vacuo* and purified by silica gel chromatography (PE:EA = 2:3) and preparative HPLC to afford the title compound (12.7 mg, 23%) as a white solid. ^1H NMR (500 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.75 (s, 1H), 8.16 (d, J = 9.5 Hz, 1H), 7.80 (s, 1H), 4.35-4.30 (m, 1H), 2.90 (s, 3H), 2.51 (s, 3H), 1.19-1.17 (m, 1H), 0.73-0.68 (m,1H), 0.67-0.66 (m, 1H), 0.59-0.56 (m, 1H), 0.34-0.33 (m, 1H). LC-MS m/z: 379.8 $[M+H]^+$. HPLC: Purity (214 nm): 95%; t_R = 8.65 min.

(*R*)-5-(4,5-Dimethyloxazol-2-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



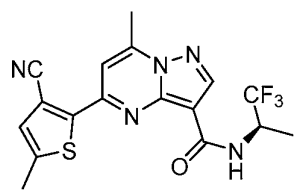
[00835] To a mixture of 4,5-dimethyloxazole (92 mg, 0.66 mmol) in THF (5 mL) was added n-BuLi (0.3 mL, 0.80 mmol) at -78 °C, and the mixture was stirred at -78 °C for 30 minutes followed by the addition of $ZnCl_2$ (1.8 mL, 2.0 mmol). The resulting mixture was stirred at -78 °C for 30 minutes, followed by the addition of (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.33 mmol), and $Pd(PPh_3)_2Cl_2$ (28 mg, 0.03 mmol), and stirred at 65 °C for 16 h under N_2. The reaction mixture was filtered and filtrate was concentrated *in vacuo*, and the residue was purified by preparative HPLC ($MeCN/NH_4HCO_3$) to afford the title compound (7 mg, 5 %) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 8.52 (d, J = 8.8 Hz, 1H), 7.81 (s, 1H), 4.97-4.91 (m, 1H), 2.86 (s, 3H), 2.41 (s, 3H), 2.19 (s, 3H), 1.43 (d, J = 7.2 Hz, 3H). LC-MS m/z: 368.1 $[M+H]^+$. HPLC: Purity (214 nm): 99%; t_R = 8.36 min.

(*S*)-*N*-(1-Cyclopropylethyl)-7-methyl-5-(3-methylisothiazol-5-yl)pyrazolo[1,5-a]pyrimidine-3-carboxamide



[00836] Following general procedure E*, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (130 mg, 0.47 mmol) and 5-bromo-3-methylisothiazole afforded the title compound (31 mg, 19 %) as a light yellow solid. ^1H NMR (500 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.06 (s, 1H), 7.87 (d, J = 9.5 Hz, 1H), 7.86 (s, 1H), 3.67-3.60 (m, 1H), 2.85 (s, 3H), 2.54 (s, 3H), 1.30 (d, J = 7.0 Hz, 3H), 1.11-1.04 (m, 1H), 0.57-0.47 (m, 2H), 0.41-0.36 (m, 1H), 0.34-0.29 (m, 1H). LC-MS m/z: 342.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.14 min.

(*R*)-5-(3-Cyano-5-methylthiophen-2-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00837] Following general procedure B*, methyl 5-methylthiophene-3-carboxylate (5.0 g, 32.0 mmol) afforded 5-methylthiophene-3-carboxylic acid as a white solid (4.2 g, 92%), which was used directly in the next step. LC-MS m/z: no signal; t_R = 0.75 min.

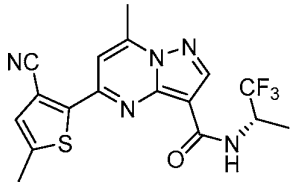
[00838] To a solution of 5-methylthiophene-3-carboxylic acid (1.42 g, 10.0 mmol) in HOAc (15 mL) was added a solution of Br_2 (1.6 g, 10.0 mmol) in HOAc (10 mL) dropwise. The reaction was stirred at RT for 1 h, and quenched with water (100 mL). The resulting precipitate was filtered and dried *in vacuo* to afford 2-bromo-5-methylthiophene-3-carboxylic acid (2.0 g, 90%) as a white solid. LC-MS m/z: no signal; t_R = 1.15 min.

[00839] Following general procedure A, 2-bromo-5-methylthiophene-3-carboxylic acid (2.0 g, 9.05 mmol), and NH_4Cl afforded 2-bromo-5-methylthiophene-3-carboxamide as a grey solid (1.2 g, 59%). LC-MS m/z: 220.1 $[M+H]^+$. t_R = 1.45 min.

[00840] A mixture of 2-bromo-5-methylthiophene-3-carboxamide (1.17 g, 5.3 mmol), TFAA (1.45 g, 6.9 mmol) and TEA (1.34 g, 13.25 mmol) in DCM (15 mL) was stirred at RT for 1 h, and partitioned between CH_2Cl_2 (50 mL) and saturated $NaHCO_3$ (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford 2-bromo-5-methylthiophene-3-carbonitrile (1.25 g, 100%) as a brown solid. LC-MS m/z: no signal; t_R = 1.80 min.

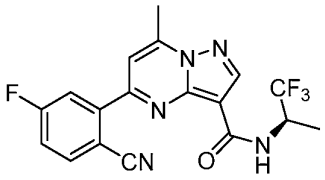
[00841] Following general procedure E*, (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.23 mmol) and 2-bromo-5-methylthiophene-3-carbonitrile afforded the title compound (10 mg, 10%) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.72 (s, 1H), 7.98 (d, *J* = 9.6 Hz, 1H), 7.66 (s, 1H), 7.49 (s, 1H), 5.04-4.99 (m, 1H), 2.87 (s, 3H), 2.59 (s, 3H), 1.46 (d, *J* = 7.2 Hz, 3H). LC-MS m/z: 394.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.94 min.

(*S*)-5-(3-Cyano-5-methylthiophen-2-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



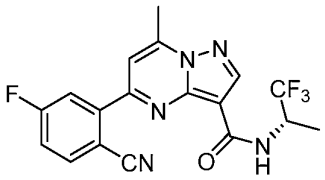
[00842] Following general procedure E*, (*S*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (113 mg, 0.37 mmol) and 2-bromo-5-methylthiophene-3-carbonitrile afforded the title compound (35 mg, 28%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.72 (s, 1H), 7.98 (d, J = 9.0 Hz, 1H), 7.65 (s, 1H), 7.49 (d, J = 1.0 Hz, 1H), 5.05-4.98 (m, 1H), 2.87 (s, 3H), 2.59 (d, J = 1.0 Hz, 3H), 1.46 (d, J = 7.0 Hz, 3H). LC-MS m/z: 394.1 $[M+H]^+$. HPLC: Purity (214 nm): 97%; t_R = 8.92 min.

(*R*)-5-(2-Cyano-5-fluorophenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00843] Following general procedure D, (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.26 mmol) and 4-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile afforded the title compound (33 mg, 32 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.77 (s, 1H), 8.26 (dd, J = 8.5 Hz, 5.5 Hz, 1H), 8.11 (d, J =9.5 Hz, 1H), 8.08 (dd, J = 9.5 Hz, 2.5 Hz, 1H), 7.88 (s, 1H), 7.70 (td, J = 8.0 Hz, 2.5 Hz, 1H), 5.03-4.98 (m, 1H), 2.89 (s, 3H), 1.44 (d, J = 7.0 Hz, 3H). LC-MS m/z: 392.0 $[M+H]^+$. HPLC Purity (214nm): > 99%; t_R = 8.33 min.

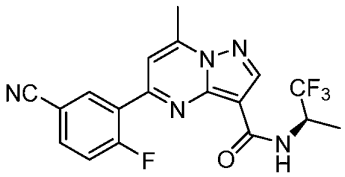
(*S*)-5-(2-Cyano-5-fluorophenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00844] Following general procedure D, (*S*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.26 mmol) and 4-fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile afforded the title compound (37 mg, 37 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.77 (s, 1H), 8.26 (dd, J = 8.5 Hz, 5.5 Hz, 1H), 8.11 (d, J =9.5 Hz, 1H), 8.08 (dd, J = 9.5 Hz, 2.5 Hz, 1H), 7.88 (s, 1H), 7.70 (td, J = 8.0

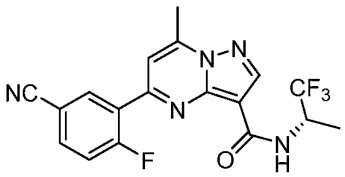
Hz, 2.5 Hz, 1H), 5.03-4.98 (m, 1H), 2.89 (s, 3H), 1.44 (d, J = 7.0 Hz, 3H). LC-MS m/z: 392.0 $[M+H]^+$. HPLC Purity (214nm): > 99%; t_R = 8.33 min.

(*R*)-5-(5-Cyano-2-fluorophenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



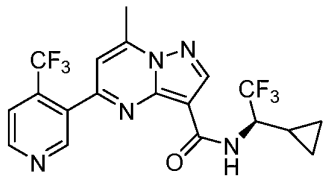
[00845] Following general procedure D, (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.26 mmol) and 4-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile afforded the title compound (35.4 mg, 35%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.74 (s, 1H), 8.58 (dd, J = 7.5 Hz, 2.0 Hz, 1H), 8.42 (d, J = 9.5 Hz, 1H), 8.18 (ddd, J = 9.0 Hz, 4.5 Hz, 2.0 Hz, 1H), 7.82 (s, 1H), 7.75 (dd, J = 11.0 Hz, 8.5 Hz, 1H), 5.00-4.92 (m, 1H), 2.89 (s, 3H), 1.41 (d, J = 7.0 Hz, 3H). LC-MS m/z: 392.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.30 min.

(*S*)-5-(5-Cyano-2-fluorophenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



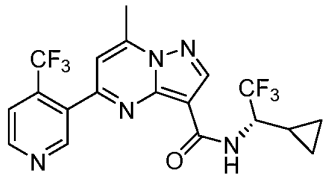
[00846] Following general procedure D, (*S*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.26 mmol) and 4-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile afforded the title compound (41 mg, 40%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.74 (s, 1H), 8.58 (dd, J = 7.5 Hz, 2.0 Hz, 1H), 8.42 (d, J = 9.5 Hz, 1H), 8.18 (ddd, J = 9.0 Hz, 4.5 Hz, 2.0 Hz, 1H), 7.82 (s, 1H), 7.75 (dd, J = 11.0 Hz, 8.5 Hz, 1H), 5.00-4.92 (m, 1H), 2.89 (s, 3H), 1.41 (d, J = 7.0 Hz, 3H). LC-MS m/z: 392.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.26 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(4-(trifluoromethyl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



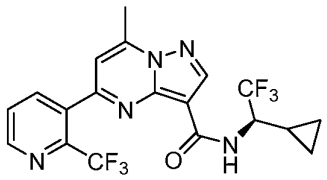
[00847] Following general procedure E*, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 3-bromo-4-(trifluoromethyl)pyridine afforded the title compound (5.7 mg, 5 %) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4): δ 8.85 (s, 1H), 8.82 (d, J = 5.0 Hz, 1H), 8.52 (s, 1H), 8.19 (d, J = 9.5 Hz, 1H), 7.78 (d, J = 5.5 Hz, 1H), 7.30 (s, 1H), 4.10-4.05 (m, 1H), 2.78 (s, 3H), 0.97-0.91 (m, 1H), 0.57-0.51 (m, 1H), 0.39-0.33 (m, 2H), 0.21-0.16 (m, 1H). LC-MS m/z: 444.1 $[M+H]^+$. HPLC Purity (214 nm): 96.4%; t_R = 8.44 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(4-(trifluoromethyl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



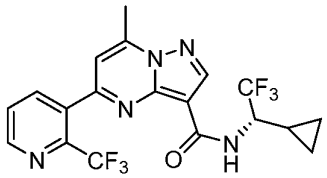
[00848] Following general procedure E*, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 3-bromo-4-(trifluoromethyl)pyridine afforded the title compound (2.1 mg, 2 %) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4): δ 8.85 (s, 1H), 8.82 (d, J = 5.0 Hz, 1H), 8.52 (s, 1H), 8.19 (d, J = 9.5 Hz, 1H), 7.78 (d, J = 5.5 Hz, 1H), 7.30 (s, 1H), 4.10-4.05 (m, 1H), 2.78 (s, 3H), 0.97-0.91 (m, 1H), 0.57-0.51 (m, 1H), 0.39-0.33 (m, 2H), 0.21-0.16 (m, 1H). LC-MS m/z: 444.1 $[M+H]^+$. HPLC Purity (214 nm): 96.4%; t_R = 8.44 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(2-(trifluoromethyl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



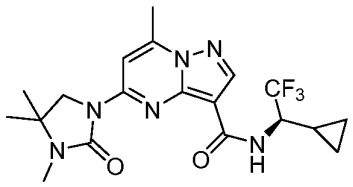
[00849] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.150 mmol) and 2-(trifluoromethyl) pyridin-3-ylboronic acid afforded the title compound (22 mg, 33%) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.72 (d, J = 8.0 Hz, 1H), 8.70 (s, 1H), 8.32 (t, J = 8.0 Hz, 1H), 8.23 (d, J = 0.5 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 4.45-4.42 (m, 1H), 3.00 (d, J = 0.5 Hz, 3H), 1.41-1.37 (m, 1H), 0.84-0.80 (m, 1H), 0.70-0.61 (m, 2H), 0.57-0.51 (m, 1H). LC-MS m/z: 444.1 $[M+H]^+$. HPLC: Purity (214 nm): 98.97%; t_R = 9.70 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(2-(trifluoromethyl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



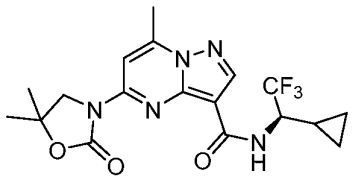
[00850] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.150 mmol) and 2-(trifluoromethyl) pyridin-3-ylboronic acid afforded the title compound (21 mg, 31%) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.72 (d, J = 8.0 Hz, 1H), 8.70 (s, 1H), 8.32 (t, J = 8.0 Hz, 1H), 8.23 (d, J = 0.5 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 4.45-4.42 (m, 1H), 3.00 (d, J = 0.5 Hz, 3H), 1.41-1.37 (m, 1H), 0.84-0.80 (m, 1H), 0.70-0.61 (m, 2H), 0.57-0.51 (m, 1H). LC-MS m/z: 444.1 $[M+H]^+$. HPLC: Purity (214 nm): 98.97%; t_R = 9.70 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(3,4,4-trimethyl-2-oxoimidazolidin-1-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



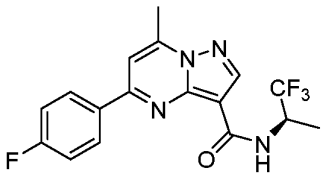
[00851] Following general procedure H, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (33 mg, 0.1 mmol) and 1,5,5-trimethylimidazolidin-2-one afforded the title compound (8.9 mg, 21%) as a pale white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 (s, 1H), 8.21 (d, J = 10.0 Hz, 1H), 8.08 (s, 1H), 4.39-4.35 (m, 1H), 3.85 (d, J = 10.8 Hz, 1H), 3.75 (d, J = 10.8 Hz, 1H), 2.78 (s, 3H), 2.74 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H), 1.28-1.24 (m, 1H), 0.69-0.65 (m, 1H), 0.59-0.55 (m, 2H), 0.38-0.36 (m, 1H). LC-MS m/z: 425.1 $[M+H]^+$. HPLC: Purity (214 nm): 97.06%; t_R = 8.44 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(5,5-dimethyl-2-oxooxazolidin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



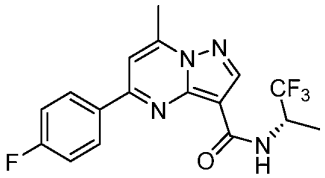
[00852] Following general procedure H, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (73 mg, 0.219 mmol) and 5,5-dimethyloxazolidin-2-one afforded the title compound (22 mg, 25 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.54 (s, 1H), 8.13 (d, J = 9.5 Hz, 1H), 7.94 (s, 1H), 4.36-4.31 (m, 1H), 4.08 (d, J = 10.0 Hz, 1H), 3.98 (d, J = 10.0 Hz, 1H), 2.80 (s, 3H), 1.54 (s, 6H), 1.31-1.28 (m, 1H), 0.70-0.66 (m, 1H), 0.61-0.55 (m, 2H), 0.38-0.34 (m, 1H). LC-MS m/z: 412.2 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 8.42 min.

(*R*)-5-(4-Fluorophenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



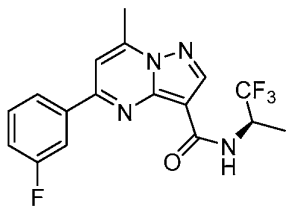
[00853] Following general procedure D, (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.16 mmol) and 4-fluorophenylboronic acid afforded the title compound (18 mg, 30%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.46 (d, J = 9.2 Hz, 1H), 8.30 (dd, J = 8.8 Hz, 5.2Hz, 1H), 7.96 (s, 1H), 7.50 (t, J = 8.8 Hz, 1H), 5.01-4.94 (m, 1H), 2.86 (s, 3H), 1.46 (d, J = 6.8 Hz, 3H). LC-MS m/z: 367.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.98 min.

(*S*)-5-(4-Fluorophenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



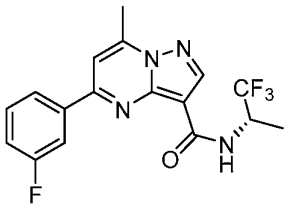
[00854] Following general procedure D, (*S*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.21 mmol) and 4-fluorophenylboronic acid afforded the title compound (61 mg, 70%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.46 (d, J = 9.2 Hz, 1H), 8.30 (dd, J = 8.8 Hz, 5.2 Hz, 1H), 7.96 (s, 1H), 7.50 (t, J = 8.8 Hz, 1H), 5.01-4.94 (m, 1H), 2.86 (s, 3H), 1.46 (d, J = 6.8 Hz, 3H). LC-MS m/z: 367.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.98 min.

(*R*)-5-(3-Fluorophenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



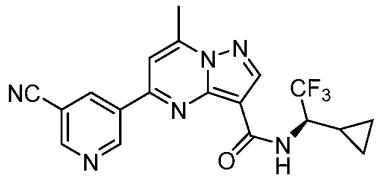
[00855] Following general procedure D, (*R*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.16 mmol) and 3-fluorophenylboronic acid afforded the title compound (28 mg, 47%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.48 (d, J = 10.0 Hz, 1H), 8.10 (d, J = 8.5 Hz, 1H), 8.06 (dt, J = 10.0 Hz, 1.5 Hz, 1H), 8.01 (s, 1H), 7.72-7.67 (m, 1H), 7.48 (td, J = 8.5 Hz, 2.5 Hz, 1H), 5.01-4.94 (m, 1H), 2.87 (s, 3H), 1.46 (d, J = 6.8 Hz, 3H). LC-MS m/z: 367.1 $[M+H]^+$. HPLC: Purity (214 nm): 95%; t_R = 8.96 min.

(*S*)-5-(3-Fluorophenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00856] Following general procedure D, (*S*)-5-chloro-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.21 mmol) and 3-fluorophenylboronic acid afforded the title compound (36 mg, 40%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.48 (d, J = 9.2 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 8.06 (dt, J = 10.8 Hz, 1.2 Hz, 1H), 8.01 (s, 1H), 7.72-7.67 (m, 1H), 7.48 (td, J = 8.4 Hz, 2.4 Hz, 1H), 5.01-4.94 (m, 1H), 2.87 (s, 3H), 1.46 (d, J = 6.8 Hz, 3H). LC-MS m/z: 367.1 $[M+H]^+$. HPLC: Purity (214 nm): 95%; t_R = 8.96 min.

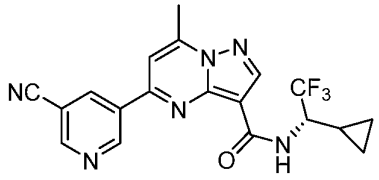
(*R*)-5-(5-Cyanopyridin-3-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00857] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.18 mmol) and 5-cyanopyridin-3-ylboronic acid afforded the title compound (24 mg, 33%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (d, J = 2.0 Hz, 1H), 9.24 (d, J = 2.0 Hz, 1H), 9.06 (t, J =

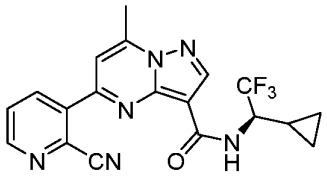
2.4 Hz, 1H), 8.74 (s, 1H), 8.46 (d, J = 9.6 Hz, 1H), 8.12 (s, 1H), 4.47-4.43 (m, 1H), 2.89 (s, 3H), 1.36-1.30 (m, 1H), 0.73-0.67 (m, 1H), 0.62-0.55 (m, 2H), 0.42-0.38 (m, 1H). LC-MS m/z: 401.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.03 min.

(*S*)-5-(5-Cyanopyridin-3-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



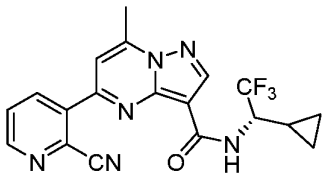
[00858] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 5-cyanopyridin-3-ylboronic acid afforded the title compound (12 mg, 13%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): 9.56 (d, J = 2.0 Hz, 1H), 8.81 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 8.76 (s, 1H), 8.46 (d, J = 9.5 Hz, 1H), 8.37 (d, J = 8.5 Hz, 1H), 8.13 (s, 1H), 4.45-4.40 (m, 1H), 2.91 (s, 3H), 1.35-1.30 (m, 1H), 0.72-0.67 (m, 1H), 0.65-0.56 (m, 2H), 0.42-0.35 (m, 1H). LC-MS m/z: 401.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.29 min.

(*R*)-5-(2-Cyanopyridin-3-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



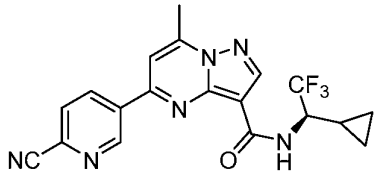
[00859] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.18 mmol) and 2-cyanopyridin-3-ylboronic acid afforded the title compound (2 mg, 3.0 %) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4): δ 8.90 (dd, J = 5.0 Hz, 2.0 Hz, 1H), 8.74 (s, 1H), 8.54 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 7.91 (dd, J = 8.0 Hz, 4.5 Hz, 1H), 7.70 (d, J = 0.5 Hz, 1H), 4.27-4.20 (m, 1H), 3.00 (s, 3H), 1.47-1.42 (m, 1H), 0.82-0.76 (m, 1H), 0.63-0.58 (m, 2H), 0.46-0.41 (m, 1H). LC-MS m/z: 401.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.97 min.

(*S*)-5-(2-Cyanopyridin-3-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



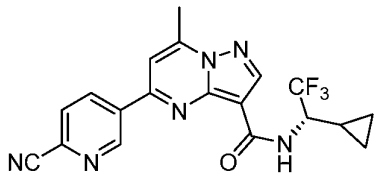
[00860] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.18 mmol) and 2-cyanopyridin-3-ylboronic acid afforded the title compound (2 mg, 3 %) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4): δ 8.90 (dd, J = 5.0 Hz, 2.0 Hz, 1H), 8.74 (s, 1H), 8.54 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 7.91 (dd, J = 8.0 Hz, 4.5 Hz, 1H), 7.70 (d, J = 0.5 Hz, 1H), 4.27-4.20 (m, 1H), 3.00 (s, 3H), 1.47-1.42 (m, 1H), 0.82-0.76 (m, 1H), 0.63-0.58 (m, 2H), 0.46-0.41 (m, 1H). LC-MS m/z: 401.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.97 min.

(*R*)-5-(6-Cyanopyridin-3-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



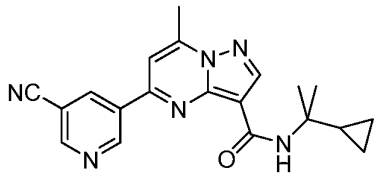
[00861] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 6-cyanopyridin-3-ylboronic acid afforded the title compound (12.2 mg, 13 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.37 (d, J = 1.5 Hz, 1H), 9.62 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 9.57 (s, 1H), 9.26 (d, J = 9.5 Hz, 1H), 9.17 (d, J = 8.5 Hz, 1H), 8.94 (s, 1H), 5.24-5.20 (m, 1H), 3.72 (s, 3H), 2.15-2.13 (m, 1H), 1.53-1.50 (m, 1H), 1.43-1.38 (m, 2H), 1.20-1.18 (m, 1H). LC-MS m/z: 401.1 $[M+H]^+$. HPLC: Purity (254 nm): > 99%; t_R = 8.28 min.

(*S*)-5-(6-Cyanopyridin-3-yl)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



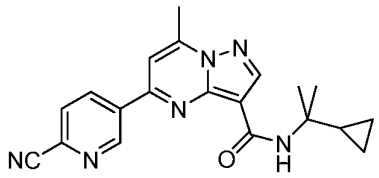
[00862] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.15 mmol) and 6-cyanopyridin-3-ylboronic acid afforded the title compound (16 mg, 27 %) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 9.54 (d, J = 1.5 Hz, 1H), 8.76 (dd, J = 8.5 Hz, 2.5 Hz, 1H), 8.70 (s, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.89 (s, 1H), 4.43-4.39 (m, 1H), 2.99 (s, 3H), 1.35-1.33 (m, 1H), 0.82-0.77 (m, 1H), 0.68-0.61(m, 2H), 0.51-0.48 (m, 1H). LC-MS m/z: 401.1 $[M+H]^+$. HPLC: Purity (254 nm): 99.48%; t_R = 8.30 min.

5-(5-Cyanopyridin-3-yl)-*N*-(2-cyclopropylpropan-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



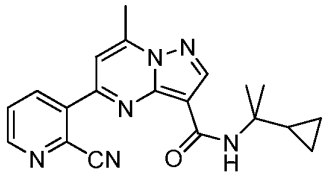
[00863] Following general procedure D, 5-chloro-*N*-(2-cyclopropylpropan-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.17 mmol) and 5-cyanopyridin-3-ylboronic acid afforded the title compound (9 mg, 8%) as a yellow solid. ^{1}H NMR (500 MHz, DSMO-d_6): δ 9.68 (d, J = 2.0 Hz, 1H), 9.23 (d, J = 2.0 Hz, 1H), 9.06 (t, J = 2.0 Hz, 1H), 8.61 (s, 1H), 8.07 (s, 1H), 8.06 (s, 1H), 2.87 (s,3H), 1.43-1.39 (m, 1H), 1.38 (s, 6H), 0.51-0.50 (m, 4H). LC-MS m/z: 362.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 7.93 min.

5-(6-Cyanopyridin-3-yl)-*N*-(2-cyclopropylpropan-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



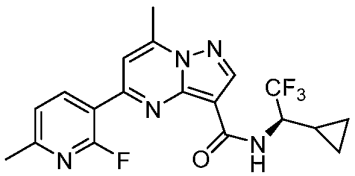
[00864] Following general procedure D, 5-chloro-*N*-(2-cyclopropylpropan-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.17 mmol) and 6-cyanopyridin-3-ylboronic acid afforded the title compound (8 mg, 8%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.56 (d, J = 1.5 Hz, 1H), 8.79 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 8.60 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 8.05 (s, 1H), 8.04 (s, 1H), 2.87 (s,3H), 1.43-1.40 (m, 1H), 1.37 (s, 6H), 0.49-0.48 (m, 4H). LC-MS m/z: 362.1 $[M+H]^+$. HPLC Purity (214 nm): 97%; t_R = 8.26 min.

5-(2-Cyanopyridin-3-yl)-*N*-(2-cyclopropylpropan-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



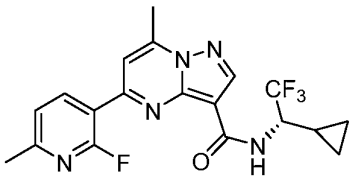
[00865] Using general procedure D, 5-chloro-*N*-(2-cyclopropylpropan-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.24 mmol) and 2-cyanopyridin-3-ylboronic acid afforded the title compound (10 mg, 9%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.93 (dd, J = 5.0 Hz 1.5Hz, 1H), 8.66 (s, 1H), 8.51 (dd, J = 8.0 Hz, 1.0 Hz, 1H), 7.99 (dd, J = 8.0 Hz, 4.5 Hz, 1H), 7.97 (s, 1H), 7.76 (s, 1H), 3.34 (s, 3H), 2.89 (s, 3H), 1.50-1.44 (m, 1H), 0.42-0.37 (m, 2H), 0.36-0.31 (m, 2H). LC-MS m/z: 361.1 $[M+H]^+$. HPLC Purity (214 nm): 98%; t_R = 8.26 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(2-fluoro-6-methylpyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



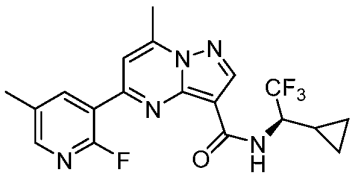
[00866] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.18 mmol) and 2-fluoro-6-methylpyridin-3-ylboronic acid afforded the title compound (35 mg, 48 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.71 (s, 1H), 8.48-8.53 (m, 2H), 7.77 (s, 1H), 7.53 (dd, J = 7.5 Hz, 1.0 Hz, 1H), 4.46-4.40 (m, 1H), 2.88 (s, 3H), 2.55 (s, 3H), 1.26-1.22 (m, 1H), 0.72-0.66 (m, 1H), 0.60-0.55 (m, 2H), 0.39-0.35 (m, 1H). LC-MS m/z: 408.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.83 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(2-fluoro-6-methylpyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



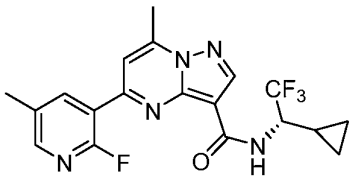
[00867] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 2-fluoro-6-methylpyridin-3-ylboronic acid afforded the title compound (45 mg, 46 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.71 (s, 1H), 8.48-8.53 (m, 2H), 7.77 (s, 1H), 7.53 (dd, J = 7.5 Hz, 1.0 Hz, 1H), 4.46-4.40 (m, 1H), 2.88 (s, 3H), 2.55 (s, 3H), 1.26-1.22 (m, 1H), 0.72-0.66 (m, 1H), 0.60-0.55 (m, 2H), 0.39-0.35 (m, 1H). LC-MS m/z: 408.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.86 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(2-fluoro-5-methylpyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



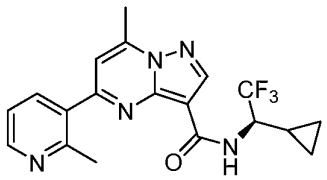
[00868] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (60 mg, 0.18 mmol) and 2-fluoro-5-methylpyridin-3-ylboronic acid afforded the title compound (43 mg, 58 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.51 (d, J = 9.5 Hz, 1H), 8.44 (dd, J = 9.5 Hz, 2.0 Hz, 1H), 8.29 (s, 1H), 7.79 (s, 1H), 4.50-4.46 (m, 1H), 2.89 (s, 3H), 2.41 (s, 3H), 1.26-1.22 (m, 1H), 0.69-0.66 (m, 1H), 0.58-0.55 (m, 2H), 0.40-0.36 (m,1H). LC-MS m/z: 408.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.87 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(2-fluoro-5-methylpyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



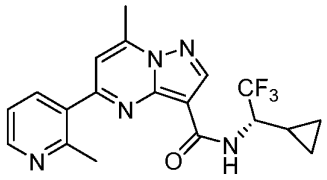
[00869] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.15 mmol) and 2-fluoro-5-methylpyridin-3-ylboronic acid afforded the title compound (45 mg, 73 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.51 (d, J = 9.5 Hz, 1H), 8.44 (dd, J = 9.5 Hz, 2.0 Hz, 1H), 8.29 (s, 1H), 7.79 (s, 1H), 4.50-4.46 (m, 1H), 2.89 (s, 3H), 2.41 (s, 3H), 1.26-1.22 (m, 1H), 0.69-0.66 (m, 1H), 0.58-0.55 (m, 2H), 0.40-0.36 (m,1H). LC-MS m/z: 408.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.87 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(2-methylpyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



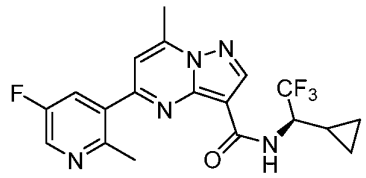
[00870] Following general procedure D, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 2-methylpyridin-3-ylboronic acid afforded the title compound (36 mg, 39%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.71(s, 1H), 8.63 (dd, J = 5.0 Hz, 1.5 Hz, 1H), 8.34 (d, J = 9.5 Hz, 1H), 8.03 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 7.61 (s, 1H), 7.46 (dd, J = 8.0 Hz, 5.0 Hz, 1H), 4.41-4.37 (m, 1H), 2.87 (s, 3H), 2.71 (s, 3H), 1.17-1.14 (m, 1H), 0.66-0.63 (m, 1H), 0.57-0.50 (m, 2H), 0.31-0.28 (m, 1H). LC-MS m/z: 390.1 $[M+H]^+$. HPLC: Purity (214 nm): 98%; t_R = 7.75 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(2-methylpyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00871] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.15 mmol) and 2-methylpyridin-3-ylboronic acid afforded the title compound (23 mg, 40 %) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (s, 1H), 8.67(dd, J = 5.0 Hz, 1.5 Hz, 1H), 8.33 (d, J = 9.5 Hz, 1H), 7.86 (dd, J = 8.0 Hz, 1.5 Hz, 1H), 7.33 (dd, J = 8.0 Hz, 5.0 Hz, 1H), 7.05 (d, J = 1.5 Hz, 1H), 4.41-4.36 (m, 1H), 2.93 (s, 3H), 2.77 (s, 3H), 1.16-1.09 (m, 1H), 0.72-0.66 (m, 1H), 0.57-0.49 (m, 2H), 0.46-0.41 (m, 1H). LC-MS m/z: 390.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 7.72 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(5-fluoro-2-methylpyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00872] To a solution of n-BuLi/THF (1.45 mL, 2.5 mol/L) in THF (5 mL) was added a solution of 3-bromo-2-chloro-5-fluoropyridine (630 mg, 3.0 mmol) in THF (5 mL) dropwise at -78 °C. The reaction mixture was stirred at -78 °C for another 30 minutes, followed by the addition of $B(OiPr)_3$ (677 mg, 3.6 mmol) in THF (2 mL). The mixture was stirred at -78 °C for another 2 h, and quenched with 5% NaOH aqueous solution (10 mL). The mixture was acidified to pH 1~2 with dilute aqueous HCl solution, and extracted with EA (60 mL x 3). The combined organic phases were dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* to afford 2-chloro-5-fluoropyridin-3-ylboronic acid (1.5 g, crude) as grey oil, which was used in the next step without further purifications. LC-MS m/z: 176.1 $[M+H]^+$. t_R = 0.64 min.

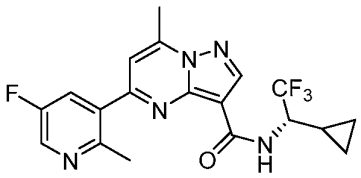
[00873] Following general procedure D, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (800 mg, 3.34 mmol) and 2-chloro-5-fluoropyridin-3-ylboronic acid afforded ethyl 5-(2-chloro-5-fluoropyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (260 mg, 23%) as a grey solid. LC-MS m/z: 335.1 $[M+H]^+$. t_R = 1.75 min.

[00874] A solution of ethyl 5-(2-chloro-5-fluoropyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (180 mg, 0.53 mmol) and 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (203 mg, 1.61 mmol), K_2CO_3 (190 mg, 1.38mmol), and bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine) dichloropalladium (II) (75 mg, 0.106 mmol) in DMF (10 mL) was stirred at 90 °C for 16 hours under N_2, poured into H_2O (30 mL), and extracted with EA (80 mL x 3). The combined organic phases were dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (PE/EA = 9/1) to afford ethyl 5-(5-fluoro-2-methylpyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (146 mg, 88%) as a red solid. LC-MS m/z: 315.1 $[M+H]^+$. t_R = 1.67 min.

[00875] Following general procedure B*, ethyl 5-(5-fluoro-2-methylpyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (144 mg, 0.45 mmol) afforded 5-(5-fluoro-2-methylpyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (72 mg, 56%) as a grey solid. LC-MS m/z: 287.1 $[M+H]^+$. t_R = 1.11 min.

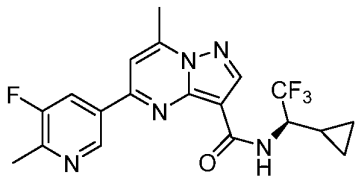
[00876] Following general procedure A, 5-(5-fluoro-2-methylpyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (20 mg, 0.07 mmol) and (*R*)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (6.4 mg, 22 %) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.74 (s, 1H), 8.67 (d, J = 3.0 Hz, 1H), 8.31 (d, J = 9.5 Hz, 1H), 8.03 (dd, J = 9.5 Hz, 3.0 Hz, 1H), 7.67 (s, 1H), 4.44-4.35 (m, 1H), 2.88 (s, 3H), 2.70 (s, 3H), 1.21-1.14 (m, 1H), 0.68-0.64 (m, 1H), 0.60-0.49 (m, 2H), 0.33-0.28 (m, 1H). LC-MS m/z: 408.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.36 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(5-fluoro-2-methylpyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00877] Following general procedure A, 5-(5-fluoro-2-methylpyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (20 mg, 0.07 mmol) and (*S*)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (6.4 mg, 22 %) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.74 (s, 1H), 8.67 (d, J = 3.0 Hz, 1H), 8.31 (d, J = 9.5 Hz, 1H), 8.03 (dd, J = 9.5 Hz, 3.0 Hz, 1H), 7.67 (s, 1H), 4.44-4.35 (m, 1H), 2.88 (s, 3H), 2.70 (s, 3H), 1.21-1.14 (m, 1H), 0.68-0.64 (m, 1H), 0.60-0.49 (m, 2H), 0.33-0.28 (m, 1H). LC-MS m/z: 408.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.36 min.

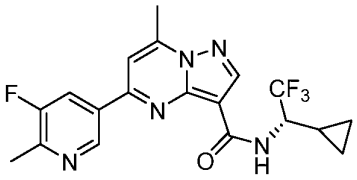
(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(5-fluoro-6-methylpyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00878] A solution of 5-bromo-2-methylpyridin-3-amine (2 g, 10.69 mmol) and $NOBF_4$ (1.5 g, 12.83 mmol) in DCM (20 mL) was stirred at 20 °C for 16 h, and quenched with saturated $NaHCO_3$ (10 mL) to pH = 8. The mixture was diluted with DCM (20 mL) and washed with H_2O (10 mL x 3). The organic phase was dried over anhydrous Na_2SO_4, filtered, concentrated *in vacuo*, and the residue was purified by silica gel flash chromatography (EA:PE; 0 to 5%) to afford 5-bromo-3-fluoro-2-methylpyridine (500 mg, 40 %) as a yellow solid. LC-MS m/z: 191.1 $[M+H]^+$. LC-MS Purity (214 nm): > 88%; t_R = 1.24 min.

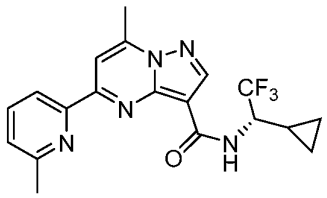
[00879] Following general procedure E*, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 5-bromo-3-fluoro-2-methylpyridine afforded the title compound (17 mg, 17 %) as a yellow solid. ^1H NMR (500 MHz, DMSO-d_6): δ 9.18 (s, 1H), 8.70 (s, 1H), 8.48 (d, *J* = 10.0 Hz, 1H), 8.38 (dd, *J* = 10.5 Hz, 1.5 Hz, 1H), 8.05 (s, 1H), 4.50-4.43 (m, 1H), 2.87 (s, 3H), 2.57 (d, *J* = 3.0 Hz, 3H), 1.31-1.25 (m, 1H), 0.72-0.66 (m, 1H), 0.61-0.55 (m, 2H), 0.41-0.37 (m, 1H). LC-MS m/z: 408.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.66 min.

<u>(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(5-fluoro-6-methylpyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide</u>



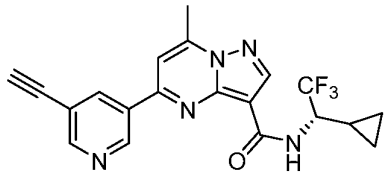
[00880] Following general procedure E*, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (80 mg, 0.24 mmol) and 5-bromo-3-fluoro-2-methylpyridine afforded the title compound (8.8 mg, 9 %) as a yellow solid. ^1H NMR (500 MHz, MeOD-d_4): δ 9.14 (s, 1H), 8.66 (s, 1H), 8.34 (dd, *J* = 10.5 Hz, 2.0 Hz, 1H), 7.83 (s, 1H), 4.46-4.43 (m, 1H), 2.96 (s, 3H), 2.64 (d, *J* = 3.0 Hz, 3H),1.34-1.30 (m, 1H), 0.81-0.78 (m, 1H), 0.69-0.60 (m, 2H), 0.59-0.50 (m, 1H). LC-MS m/z: 408.1 $[M+H]^+$. HPLC Purity (214 nm): > 99%; t_R = 8.70 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(6-methylpyridin-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00881] Following general procedure F, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.15 mmol) and 2-methyl-6-(tributylstannyl)pyridine afforded the title compound (38 mg, 65 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.69 (s, 1H), 8.56 (d, J = 10.0 Hz, 1H), 8.22 (d, J = 7.5 Hz ,1H), 8.16 (d, J = 1.0 Hz, 1H), 8.00 (t, J = 7.5 Hz, 1H), 7.50 (d, J = 7.5 Hz ,1H), 4.48~4.44 (m, 1H), 2.91 (s, 3H), 1.36-1.32 (m, 1H), 0.72-0.66 (m, 1H), 0.63-0.57 (m, 2H), 0.45-0.39 (m, 1H). LC-MS m/z: 390.1 $[M+H]^+$. HPLC: Purity (214 nm): 98.31%; t_R = 9.53 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(5-ethynylpyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00882] Following general procedure D, ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (721 mg, 2.97 mmmol) and 5-bromopyridin-3-ylboronic acid afforded ethyl 5-(5-bromopyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (200 mg, 22 %) as a yellow solid. LC-MS m/z: 361.0 $[M+H]^+$. t_R = 6.92 min.

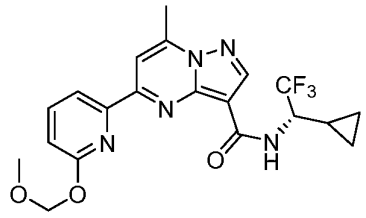
[00883] To a solution of ethyl 5-(5-bromopyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (150 mg, 0.41 mmol) in CH_3CN (5 mL) was added ethynyltrimethylsilane (61 mg, 0.62 mmol), Et_3N (84 mg, 0.83 mmol), $Pd(PPh_3)_2Cl_2$ (29 mg, 0.04 mmol), CuI (4.5 mg, 0.04 mmol) and PPh_3 (33 mg, 0.3 mmol). The mixture was stirred for 18 h at 80 °C under N_2, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (PE:EA=10:1~2:1) to afford ethyl 7-methyl-5-(5-((trimethylsilyl)ethynyl)pyridin-3-

yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (100 mg, 63 %) as a yellow solid. LC-MS m/z: 390.0 $[M+H]^+$, t_R = 1.60 min

[00884] To a solution of ethyl 7-methyl-5-(5-((trimethylsilyl)ethynyl)pyridin-3-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (150 mg, 0.39 mmol) in THF/MeOH/H_2O (6 mL, 2/2/2) was added LiOH•$2H_2O$ (71 mg, 1.19 mmol). The mixture was stirred for 18 h at 30 °C, and extracted with DCM (20 mL x 3). The organic phases were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford 5-(5-ethynylpyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (100 mg, 91 %) as a yellow solid. LC-MS m/z: 279.1 $[M+H]^+$, t_R = 1.01 min.

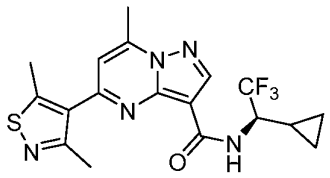
[00885] Following general procedure A, 5-(5-ethynylpyridin-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (100 mg, 0.36 mmol) and (*S*)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (60 mg, 42 %) as a white solid. ^1H NMR (500 MHz, DMSO-d_6): δ 9.42 (d, J = 2.0 Hz, 1H), 8.88 (d, J = 1.5 Hz, 1H), 8.71 (s, 1H), 8.69 (t, J = 2.0 Hz, 1H), 8.49 (d, J = 9.0 Hz, 1H), 8.11 (s, 1H), 4.61 (s, 1H), 4.51-4.46 (m, 1H), 2.88 (s, 3H), 1.29-1.25 (m, 1H), 0.71-0.67 (m, 1H), 0.60-0.57 (m, 2H), 0.42-0.39 (m, 1H). LC-MS m/z: 400.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.36 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(6-(methoxymethoxy)pyridin-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



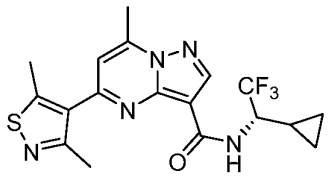
[00886] Following general procedure E*, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.15 mmol) and 2-bromo-6-(methoxymethoxy)pyridine (69 mg, 0.32 mmol) afforded the title compound (18 mg, 27%) as a white solid. ^1H NMR (500 MHz, MeOD-d_4) δ 8.65 (s,1H), 8.15-8.12 (m, 2H), 7.97 (t, J = 7.5 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 5.73 (s, 2H), 4.47-4.44 (m,1H), 3.58 (s,3H), 2.96 (s, 3H), 1.38-1.33 (m,1H), 0.81-0.77 (m,1H), 0.70-0.65 (m,1H), 0.63-0.58 (m, 1H), 0.56-0.51 (m, 1H). LC-MS m/z: 436.1 $[M+H]^+$, HPLC: Purity (214 nm): >99%; t_R = 9.30 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(3,5-dimethylisothiazol-4-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



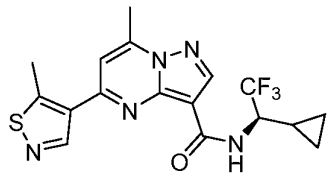
[00887] Following general procedure F, (*R*)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(tributylstannyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.12 mmol) and 4-iodo-3,5-dimethylisothiazole afforded the title compound (7.0 mg, 14 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 (s, 1H), 8.28 (d, J = 9.5 Hz, 1H), 7.49 (s, 1H), 4.36-4.31 (m, 1H), 2.86 (s, 3H), 2.68 (s, 3H), 2.55 (s, 3H), 1.20-1.15 (m, 1H), 0.69-0.65 (m, 1H), 0.61-0.57(m, 1H), 0.54-0.50 (m, 1H), 0.31-0.26 (m, 1H). LC-MS m/z: 410.1 [M+H]+. HPLC: Purity (214 nm): >99 %; t_R = 9.90 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(3,5-dimethylisothiazol-4-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



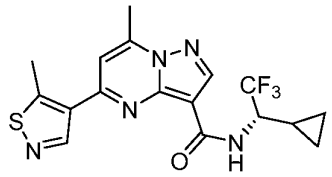
[00888] Following general procedure F, (*S*)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(tributylstannyl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide (70 mg, 0.12 mmol) and 4-iodo-3,5-dimethylisothiazole afforded the title compound (4.0 mg, 10 %) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 (s, 1H), 8.28 (d, J = 9.5 Hz, 1H), 7.49 (s, 1H), 4.36-4.31 (m, 1H), 2.86 (s, 3H), 2.68 (s, 3H), 2.55 (s, 3H), 1.20-1.15 (m, 1H), 0.69-0.65 (m, 1H), 0.61-0.57(m, 1H), 0.54-0.50 (m, 1H), 0.31-0.26 (m, 1H). LC-MS m/z: 410.1 [M+H]+. HPLC: Purity (214 nm): >99 %; t_R = 9.90 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(5-methylisothiazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



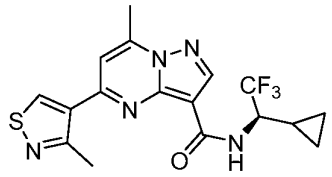
[00889] Following general procedure E*, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.30 mmol) and 4-bromo-5-methylisothiazole afforded the title compound (18 mg, 20%) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 9.01 (s, 1H), 8.63 (s, 1H), 7.61 (s, 1H), 4.34-4.28 (m, 1H), 2.98 (s, 3H), 2.92 (s, 3H), 1.26-1.21 (m, 1H), 0.81-0.77 (m, 1H), 0.66-0.56 (m, 2H), 0.45-0.41(m, 1H). LC-MS m/z: 396.0 $[M+H]^+$. HPLC: Purity (214 nm): >99 %; t_R = 8.80 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(5-methylisothiazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



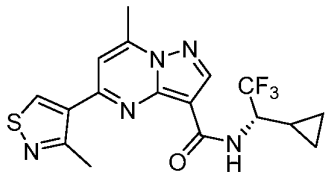
[00890] Following general procedure E*, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.30 mmol) and 4-bromo-5-methylisothiazole afforded the title compound (1.8 mg, 2.0%) as a white solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 9.01 (s, 1H), 8.63 (s, 1H), 7.61 (s, 1H), 4.34-4.28 (m, 1H), 2.98 (s, 3H), 2.92 (s, 3H), 1.26-1.21 (m, 1H), 0.81-0.77 (m, 1H), 0.66-0.56 (m, 2H), 0.45-0.41(m, 1H). LC-MS m/z: 396.0 $[M+H]^+$. HPLC: Purity (214 nm): >99 %; t_R = 8.80 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(3-methylisothiazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



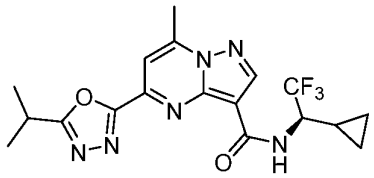
[00891] Following general procedure E*, (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (110 mg, 0.33 mmol) and 4-bromo-3-methylisothiazole afforded the title compound (35 mg, 26 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.78 (s, 1H), 8.67 (s, 1H), 8.25 (d, J = 9.5 Hz, 1H), 7.76 (s, 1H), 4.32-4.28 (m, 1H), 2.85 (s, 3H), 2.84 (s, 3H), 1.23-1.18 (m, 1H), 0.74-0.62 (m, 2H), 0.61-0.56 (m, 1H), 0.34-0.28 (m, 1H). LC-MS m/z: 396.0 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.54 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-7-methyl-5-(3-methylisothiazol-4-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00892] Following general procedure E*, (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (110 mg, 0.33 mmol) and 4-bromo-3-methylisothiazole afforded the title compound (75 mg, 58 %) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.78 (s, 1H), 8.67 (s, 1H), 8.25 (d, J = 9.5 Hz, 1H), 7.76 (s, 1H), 4.32-4.28 (m, 1H), 2.85 (s, 3H), 2.84 (s, 3H), 1.23-1.18 (m, 1H), 0.74-0.62 (m, 2H), 0.61-0.56 (m, 1H), 0.34-0.28 (m, 1H). LC-MS m/z: 396.0 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 8.54 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(5-*iso*-propyl-1,3,4-oxadiazol-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00893] A mixture of (*R*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.30 mmol), $Pd(PPh_3)_2Cl_2$•CH_2Cl_2 (25 mg, 0.03 mmol) and Et_3N (100 mg, 0.9 mmol) in MeOH (10 mL) was stirred at 65 °C for 6 h under 10 atm of CO. The reaction mixture was filtered and concentrated *in vacuo* to give crude (*R*)-3-((1-cyclopropyl-2,2,2-trifluoroethyl)carbamoyl)-7-methylpyrazolo[1,5-

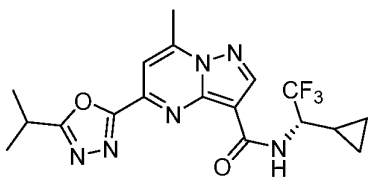
a]pyrimidine-5-carboxylic acid (100 mg, 93%) as a yellow solid. LC-MS m/z: 343.1 $[M+H]^+$, Purity (214 nm): 90%; t_R = 1.23 min.

[00894] A mixture of (*R*)-3-((1-cyclopropyl-2,2,2-trifluoroethyl)carbamoyl)-7-methylpyrazolo [1,5-*a*]pyrimidine-5-carboxylic acid (100 mg, 0.30 mmol) and thionyl chloride (100 mg, 0.9 mmol) in MeOH (10 mL) was stirred at 65 °C for 1 h. The reaction mixture was concentrated *in vacuo* and purified by silica gel chromatography (EA) to give methyl (*R*)-3-((1-cyclopropyl-2,2,2-trifluoroethyl)carbamoyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-5-carboxylate (70 mg, 67%) as a yellow solid. LC-MS m/z: 357.1 $[M+H]^+$, Purity (214 nm): 93%; t_R = 1.76 min.

[00895] A mixture of methyl (*R*)-3-((1-cyclopropyl-2,2,2-trifluoroethyl)carbamoyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-5-carboxylate (55 mg, 0.15 mmol) and hydrazine hydrate (55 mg, 1.5 mmol) in EtOH (10 mL) was stirred at RT for 1 h. The reaction mixture was concentrated *in vacuo* to give crude (*R*)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-5-(hydrazinecarbonyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 97%) as a yellow solid. LC-MS m/z: 357.1 $[M+H]^+$, Purity (214 nm): 90%; t_R = 1.46 min.

[00896] A mixture of (*R*)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-5-(hydrazinecarbonyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (50 mg, 0.14 mmol), 1,1,1-trimethoxy-2-methylpropane (50 mg, 0.28 mmol) in HOAc (5 mL) was stirred at RT for 4 h. Then EA (50 mL) was added and washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the title compound (10 mg, 15%) as a white solid. ^1H NMR (500 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.41 (d, J = 9.5 Hz, 1H), 8.00 (s, 1H), 4.65-4.60 (m, 1H), 3.42-3.36 (m, 1H), 2.92 (s, 3H), 3.41 (d, J = 7.0 Hz, 6H), 1.26-1.20 (m, 1H), 0.69-0.65 (m, 1H), 0.62-0.57 (m, 1H) 0.53-0.49 (m, 2H). LC-MS m/z: 409.1 $[M+H]^+$, HPLC : Purity (214 nm): >99%; t_R = 8.52 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(5-*iso*-propyl-1,3,4-oxadiazol-2-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



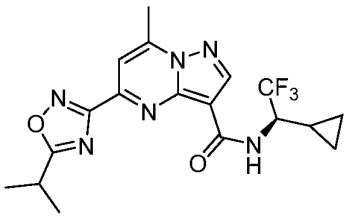
[00897] A mixture of (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (150 mg, 0.45 mmol), $Pd(PPh_3)_2Cl_2 \cdot CH_2Cl_2$ (37 mg, 0.05 mmol), Et_3N (138 mg, 1.35 mmol) in MeOH (10 mL) was stirred at 65 °C for 6 h under 10 atm of CO. The reaction mixture was filtered and concentrated *in vacuo* to give crude (*S*)-3-((1-cyclopropyl-2,2,2-trifluoroethyl)carbamoyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-5-carboxylic acid (150 mg, 93%) as a yellow solid. LC-MS m/z: 343.1 $[M+H]^+$, Purity (214 nm): 95%; t_R = 1.23 min.

[00898] A mixture of (*S*)-3-((1-cyclopropyl-2,2,2-trifluoroethyl)carbamoyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-5-carboxylic acid (150 mg, 0.45 mmol) and thionyl chloride (145 mg, 0.9 mmol) in MeOH (10 mL) was stirred at 65 °C for 1 h. The reaction mixture was concentrated *in vacuo* and purified by silica gel chromatography (EA) to give methyl (*S*)-3-((1-cyclopropyl-2,2,2-trifluoroethyl)carbamoyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-5-carboxylate (120 mg, 75%) as a white solid. LC-MS m/z: 357.1 $[M+H]^+$, Purity (214 nm): 92%; t_R = 1.76 min.

[00899] A mixture of methyl (*S*)-3-((1-cyclopropyl-2,2,2-trifluoroethyl)carbamoyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-5-carboxylate (120 mg, 0.34 mmol) and hydrazine hydrate (120 mg, 3.40 mmol) in EtOH (10 mL) was stirred at RT for 1 h. The reaction mixture was concentrated *in vacuo* to give crude (*S*)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-5-(hydrazinecarbonyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 80%) as a yellow solid. LC-MS m/z: 357.1 $[M+H]^+$, Purity (214 nm): 97%, t_R = 1.46 min.

[00900] A mixture of (*S*)-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-5-(hydrazinecarbonyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.28 mmol), 1,1,1-trimethoxy-2-methylpropane (100 mg, 0.56 mmol) in HOAc (5 mL) was stirred at RT for 16 h. Then EA (50 mL) was added and washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo.* The residue was purified by preparative HPLC to give the title compound (10 mg, 8.0%) as a white solid. ^1H NMR (500 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.41 (d, J = 9.5 Hz, 1H), 8.00 (s, 1H), 4.65-4.60 (m, 1H), 3.42-3.36 (m, 1H), 2.92 (s, 3H), 3.41 (d, J = 7.0 Hz, 6H), 1.27-1.21 (m, 1H), 0.70-0.64 (m, 1H), 0.61-0.56 (m, 1H) 0.54-0.49 (m, 2H). LC-MS m/z: 409.1 $[M+H]^+$, HPLC : Purity (214 nm): >99%; t_R = 8.52 min.

(*R*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(5-*iso*-propyl-1,2,4-oxadiazol-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00901] A mixture of ethyl 5-chloro-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (2 g, 8.34 mmol), $Pd_2(dba)_3$ (480 mg, 0.834 mmol), dppf (924 mg, 1.67 mmol), and $Zn(CN)_2$ (1.96 g, 16.73 mmol) was purged with N_2, followed by the addition of DMF (25 mL). The suspension was purged with N_2, heated at 90 °C for 4 h and then cooled to RT and filtered. The filtrate was diluted with water (100 mL), and extracted with EA (80 mL x 3). The organic phases were washed with H_2O (50 mL x 3), brine (100 mL), dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel chromatography (PE/EA = 6/4, v/v) to afford ethyl 5-cyano-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (1.50 g, 78 %) as a white solid. LC-MS m/z: 231.1 [M+H].

[00902] A mixture of ethyl 5-cyano-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (500 mg, 2.17 mmol), hydroxylamine hydrochloride (308 mg, 4.34 mmol), and Et_3N (657 mg, 6.51 mmol) in 10 mL of DMF was stirred at 90 °C for 17 h and diluted with water (40 mL). The suspension was filtered to afford ethyl 5-(*N*-hydroxycarbamimidoyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (524 mg, 91 %) as a white solid. LC-MS m/z: 264.1 $[M+H]^+$.

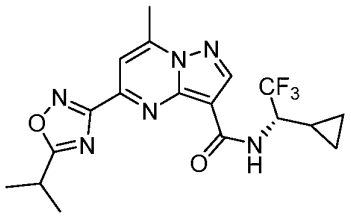
[00903] A mixture of ethyl 5-(*N*-hydroxycarbamimidoyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (514 g, 1.95 mmol), *iso*-butyric anhydride (926 mg, 5.86 mmol) in 15 mL of DCM was stirred at RT for 1 hour, and concentrated *in vacuo*. The residue was diluted with 15 mL of DMSO and heated at 90 °C for 24 h. The reaction mixture was diluted with H_2O (80 mL), and the suspension was filtered to afford ethyl 5-(5-*iso*-propyl-1,2,4-oxadiazol-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (390 mg, 96 %) as a white solid. LC-MS m/z: 316.1 $[M+H]^+$.

[00904] Following general procedure B*, ethyl 5-(5-*iso*-propyl-1,2,4-oxadiazol-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (580 mg, 1.84 mmol) afforded 5-(5-*iso*-propyl-

1,2,4-oxadiazol-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (529 mg, 100%) as a brown solid. LC-MS m/z: 288.1 $[M+H]^+$.

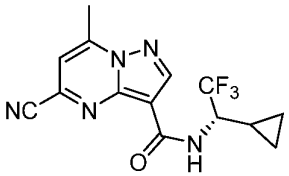
[00905] Following general procedure A, 5-(5-*iso*-propyl-1,2,4-oxadiazol-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (110 mg, 0.38 mmol) and (*R*)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (39 mg, 25 %) as a gray solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.52 (d, J = 10.0 Hz, 1H), 7.89 (s, 1H), 4.67-4.61 (m, 1H), 3.48-3.40 (m, 1H), 2.92 (s, 3H), 1.43 (d, J = 7.0 Hz, 6H), 1.25-1.21 (m, 1H), 0.66-0.56 (m, 3H), 0.50-0.46 (m, 1H). LC-MS m/z: 409.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 9.26 min.

(*S*)-*N*-(1-Cyclopropyl-2,2,2-trifluoroethyl)-5-(5-*iso*-propyl-1,2,4-oxadiazol-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00906] Following general procedure A, 5-(5-*iso*-propyl-1,2,4-oxadiazol-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.10 mmol) and (*S*)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride afforded the title compound (4.7 mg, 11 %) as a gray solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.70 (s, 1H), 7.85 (s, 1H), 4.55-4.49 (m,1H), 3.44-3.39 (m, 1H), 2.96 (s, 3H), 1.51 (d, J = 7.0 Hz, 6H), 1.38-1.32 (m, 1H), 0.74-0.60 (m, 3H), 0.54-0.51 (m, 1H). LC-MS m/z: 409.1 $[M+H]^+$. HPLC: Purity (214 nm): > 99%; t_R = 9.26 min.

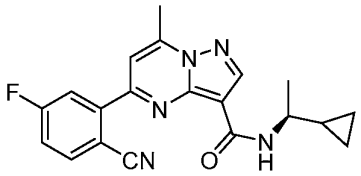
(*S*)-5-Cyano-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00907] To a solution of (*S*)-5-chloro-*N*-(1-cyclopropyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (150 mg, 0.45 mmol) in 3 mL dioxane were

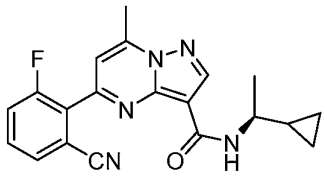
added $Zn(CN)_2$ (158 mg, 1.355 mmol) and $Pd(PPh_3)_4$ (52 mg, 0.045 mmol) at RT under N_2 atmosphere. The mixture was stirred at 110 °C for 15 h, then cooled and concentrated and purified by silica gel chromatography (EA: PE = 1:1) to give the title compound (7 mg, 4.8%) as a yellow solid. ^{1}H NMR (500 MHz, MeOD-d_4) δ 8.81 (s, 1H), 7.60 (s, 1H), 4.38-4.34 (m, 1H), 2.96 (s, 3H), 1.35-1.31 (m, 1H), 0.81-0.78 (m, 1H), 0.70-0.67 (m, 1H), 0.62-0.59 (m, 1H), 0.50-0.48 (m, 1H). LC-MS m/z: 339.1 $[M+H]^+$. HPLC: Purity (214 nm): 100%; t_R = 8.68 min.

(*S*)-5-(2-Cyano-5-fluorophenyl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-a]pyrimidine-3-carboxamide



[00908] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide and (2-cyano-5-fluorophenyl)boronic acid afforded the title compound (55 mg, 60%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.25 (dd, J = 8.5 Hz, 5.5 Hz, 1H), 8.10 (dd, J = 10.0 Hz, 2.5 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.85 (s, 1H), 7.69 (td, J = 8.5 Hz, J = 2.5 Hz, 1H), 3.55-3.52 (m, 1H), 2.89 (s, 3H), 1.29 (d, J = 6.5 Hz, 1H), 1.12-1.09 (m, 1H), 0.47-0.44 (m, 1H), 0.38-0.32 (m, 1H), 0.32-0.25 (m, 1H). LC-MS m/z: 364.1 $[M+H]^+$. HPLC: Purity (214 nm): 96%; t_R = 8.20 min.

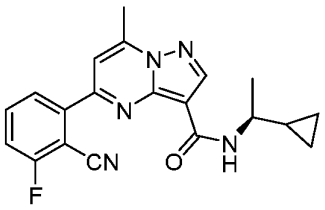
(*S*)-5-(2-Cyano-6-fluorophenyl)-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-a]pyrimidine-3-carboxamide



[00909] Following general procedure E*, (S)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide and 2-bromo-3-fluorobenzonitrile afforded the title compound (22 mg, 21%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.03 (d, J = 7.5 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.91-7.82 (m, 2H), 7.63 (d, J = 3.0 Hz, 1H), 3.60-3.55 (m, 1H), 2.90 (s, 3H), 1.24 (d, J = 6.5 Hz, 3H), 1.03-0.99 (m, 1H), 0.45-0.41 (m,

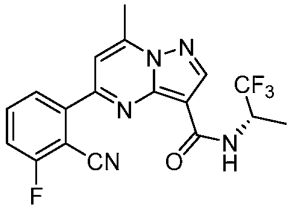
1H), 0.37-0.31 (m,2H), 0.26-0.24 (m, 1H). LC-MS m/z: 364.2 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 8.05 min.

(*S*)-5-(2-Cyano-3-fluorophenyl)-N-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-a]pyrimidine-3-carboxamide



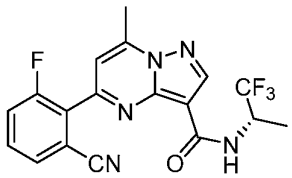
[00910] Following general procedure D, (*S*)-5-chloro-*N*-(1-cyclopropylethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide and (2-cyano-3-fluorophenyl)boronic acid afforded the title compound (46 mg, 49%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.04-8.03 (m, 2H), 7.98 (d, J = 8.5 Hz, 1H), 7.83 (s, 1H), 7.83-7.79 (m, 1H), 3.55-3.54 (m, 1H), 2.89 (s, 3H), 1.29 (d, J = 6.5 Hz, 1H), 1.11-1.09 (m, 1H), 0.47-0.46 (m, 1H), 0.37-0.32 (m, 2H), 0.26-0.24 (m, 1H). LC-MS m/z: 364.1 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 8.12 min.

(*S*)-5-(2-Cyano-3-fluorophenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



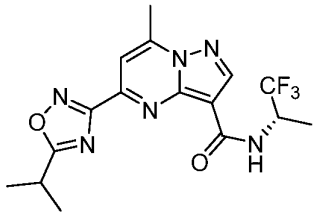
[00911] Following general procedure D, (*S*)-5-chloro-*N*-(1-methyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (79 mg, 0.26 mmol) and (2-cyano-3-fluorophenyl)boronic acid afforded the title compound (65 mg, 64%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.08 (d, J = 9.5 Hz, 1H), 8.05-8.01 (m, 2H), 7.86 (s, 1H), 7.82-7.78 (m, 1H), 5.01-4.99 (m, 1H), 2.91 (s, 3H), 1.44 (d, J = 7.0 Hz, 3H). LC-MS m/z: 392.0 $[M+H]^+$. HPLC: Purity (214 nm): 97%; t_R = 8.26 min.

(*S*)-5-(2-Cyano-6-fluorophenyl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



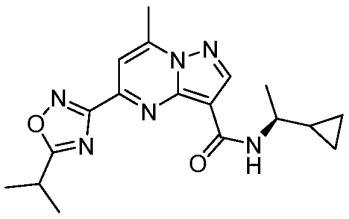
[00912] Following general procedure E*, (*S*)-5-chloro-*N*-(1-methyl-2,2,2-trifluoroethyl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (100 mg, 0.32 mmol) and 2-bromo-3-fluorobenzonitrile afforded the title compound (64 mg, 41%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.13 (d, J = 9.5 Hz, 1H), 8.03 (d, J = 7.5 Hz, 1H), 7.92-7.83 (m, 2H), 7.68 (d, J = 3.0 Hz, 1H), 4.98-4.94 (m, 1H), 2.91 (s, 3H), 1.39 (d, J = 6.5 Hz, 3H). LC-MS m/z: 392.1 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 8.22 min.

(*S*)-5-(5-*iso*-Propyl-1,2,4-oxadiazol-3-yl)-7-methyl-*N*-(1,1,1-trifluoropropan-2-yl)pyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00913] Following general procedure A, 5-(5-*iso*-propyl-1,2,4-oxadiazol-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.10 mmol) and (*S*)-1,1,1-trifluoropropan-2-amine (22 mg, 0.15 mmol) afforded the title compound (6.5 mg, 15%) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.54 (d, J = 9.0 Hz, 1H), 7.88 (d, J = 1.0 Hz, 1H), 4.95 (q, J = 8.0 Hz, 1H), 3.47-3.41 (m, 1H), 2.92 (s, 3H), 1.43 (d, J = 7.0 Hz, 9H). LC-MS m/z: 383.1 $[M+H]^+$. HPLC: Purity (214 nm): >99%; t_R = 8.83 min.

(*S*)-*N*-(1-Cyclopropylethyl)-5-(5-*iso*-propyl-1,2,4-oxadiazol-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide



[00914] Following general procedure A, 5-(5-*iso*-propyl-1,2,4-oxadiazol-3-yl)-7-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid (30 mg, 0.10 mmol) and (*S*)-1-cyclopropylethan-1-amine afforded the title compound (8.8 mg, 23%) as a red solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.14 (d, J = 7.5 Hz, 1H), 7.84 (s, 1H), 3.77-3.73 (m, 1H), 3.47-3.41 (m, 1H), 2.91 (s, 3H), 1.43 (d, J = 7.0 Hz, 6H), 1.26 (d, J = 6.5 Hz, 3H), 1.03-0.98 (m, 1H), 0.50-0.42 (m, 3H), 0.29-0.27 (m, 1H). LC-MS m/z: 355.2 $[M+H]^+$. HPLC: Purity (254 nm): 96%; t_R = 8.73 min.

EXAMPLE 2 – BIOLOGICAL ACTIVITY EVALUATION

[00915] The ability of exemplary compounds to activate glucocerebrosidase (Gcase) was measured. Experimental procedures and results are provided below.

Part I: Assay Procedure

[00916] 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.

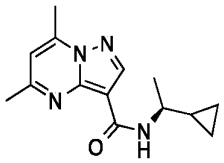
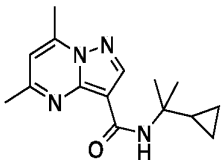
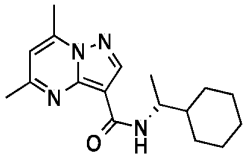
[00917] Test compounds were diluted to the desired concentrations with dimethylsulfoxide (DMSO) from 10 mM stocks, and 0.41 µL of the DMSO compound mixture was added to 100 µL of micellar solution containing 10 nM GCase and 100 nM saposin C (Enzo ALX-201-262-C050). Pre-incubation was allowed to occur for 30 minutes at room temperature, after which the reaction was initiated by combining 25 µL of substrate solution with 25 µL of

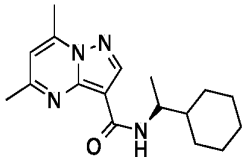
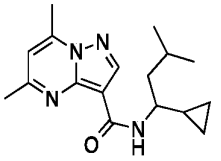
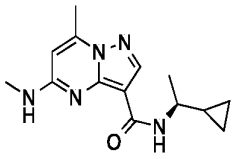
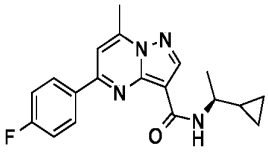
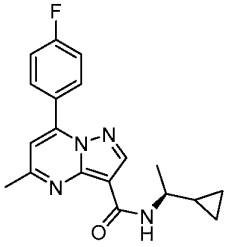
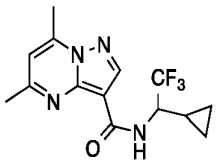
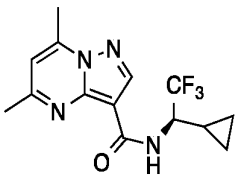
compound/GCase/saposin mixture. The reaction proceeded for 15 minutes at room temperature and was stopped by adding 150 μL of 1M glycine, pH 12.5. The endpoint of the reaction was monitored by measuring fluorescence intensity (excitation: 365 nm; emission: 440 nm) on a SpectraMax i3 instrument (Molecular 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.

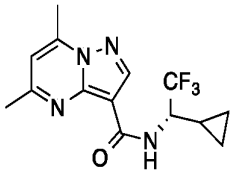
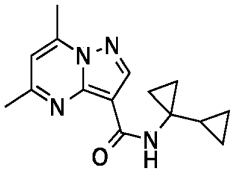
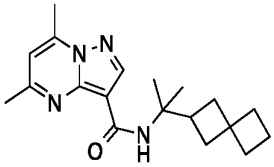
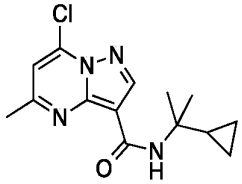
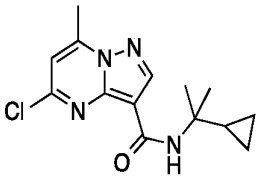
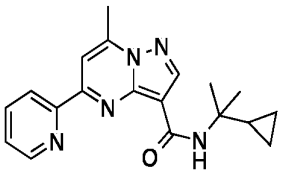
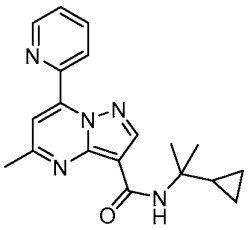
Part II: Results

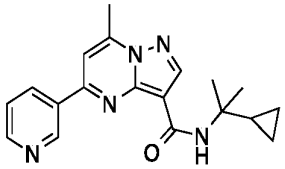
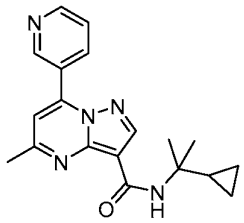
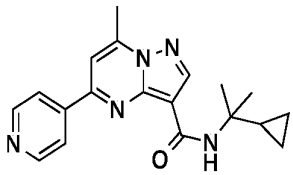
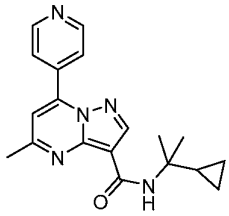
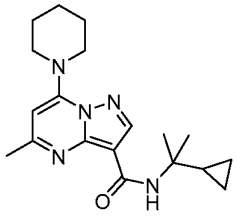
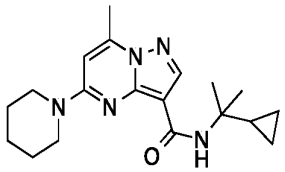
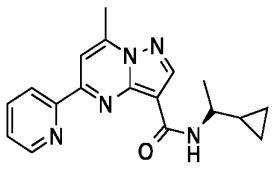
[00918] Gcase activation values for tested compounds are provided in Tables 3A, 3B, and 4 below, along with cLogP, PSA, and compound solubility in water. For experiments in which the test compound was used at a concentration of 1.0 μM, the symbol "+" indicates less than 30% Gcase activation; the symbol "++" 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.

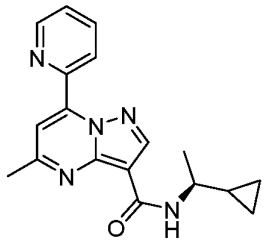
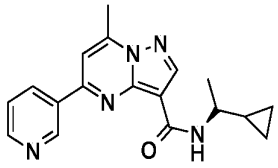
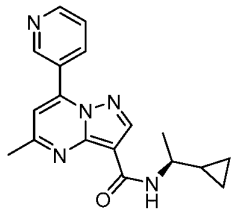
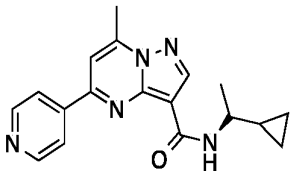
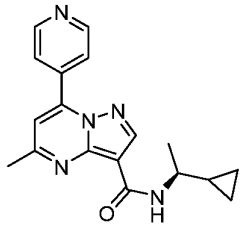
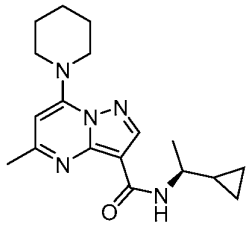
TABLE 3A.

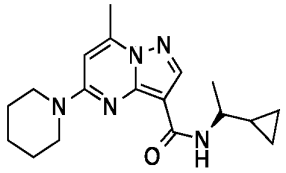
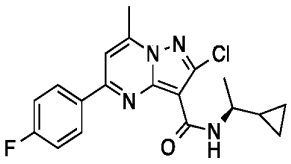
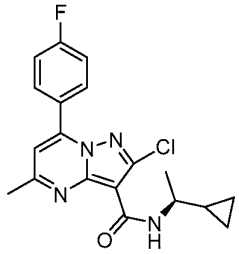
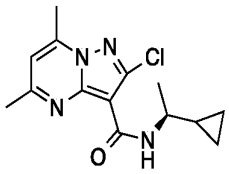
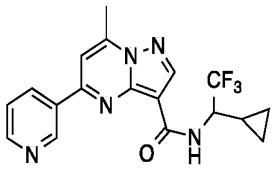
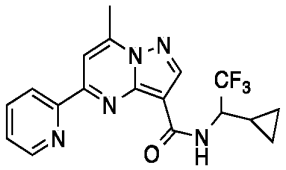
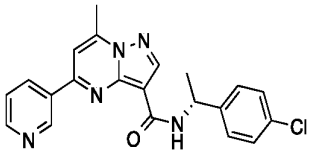
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-1		2.0	57.1	27.0	++	*
III-2		2.4	57.1	27.4	+++	**
III-3		3.6	57.1	8.7	+++	***

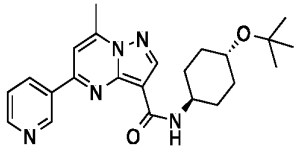
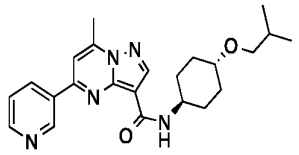
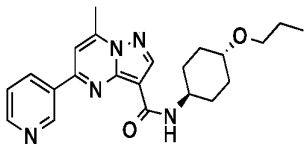
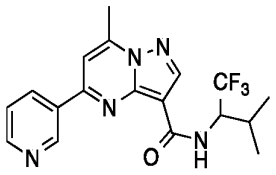
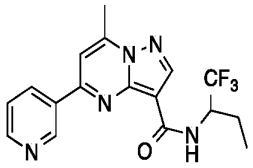
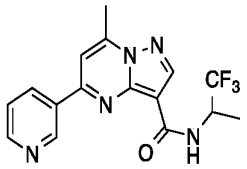
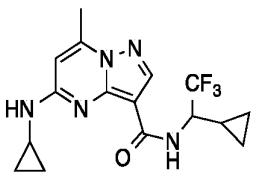
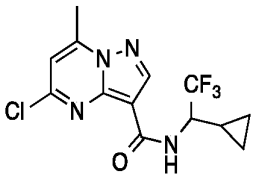
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-4		3.6	57.1	16.1	+++	***
III-5		3.4	57.1	25.7	+++	***
III-6		2.0	69.1	23.8	++	*
III-7		3.7	57.1	1.6	+++	**
III-8		3.7	57.1	0.5	+	*
III-9		2.2	57.1	18.0	+++	**
III-10		2.2	57.1	15.3	+++	**

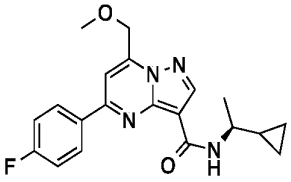
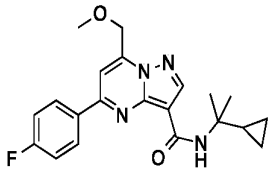
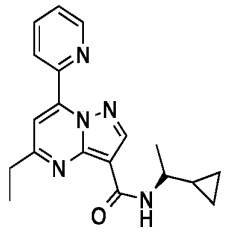
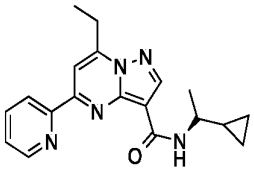
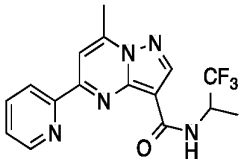
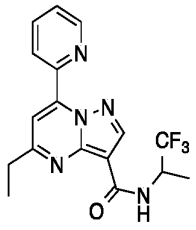
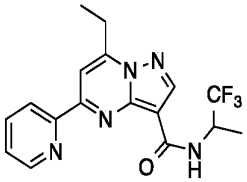
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-11		2.2	57.1	13.4	+++	**
III-12		1.9	57.1	38.4	+	*
III-13		3.8	57.1	0.3	+++	***
III-14		4.3	57.1	10.7	++	**
III-15		2.6	57.1	14.1	+++	***
III-16		2.5	69.4	1.1	+++	**
III-17		2.7	69.4	2.2	+	*

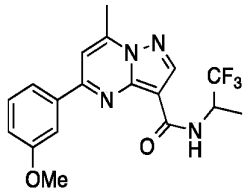
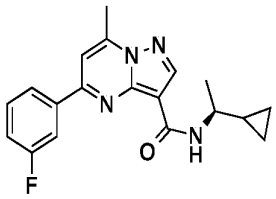
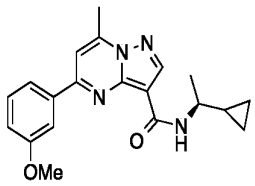
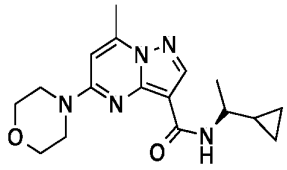
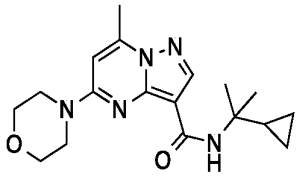
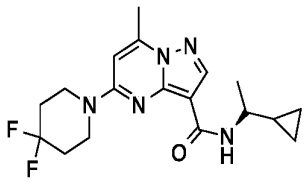
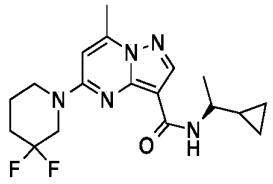
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-18		2.5	69.4	17.4	+++	**
III-19		2.5	69.4	5.3	+	*
III-20		2.5	69.4	6.3	+++	*
III-21		2.5	69.4	10.0	+	*
III-22		3.3	60.3	0.5	++	*
III-23		3.3	60.3	6.8	+++	***
III-24		2.3	69.4	8.1	+++	**

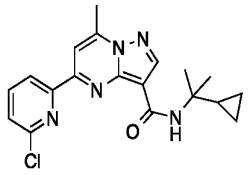
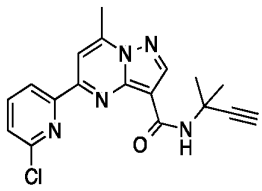
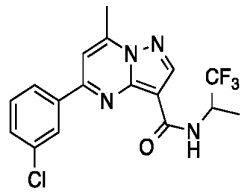
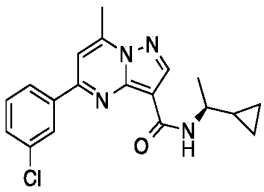
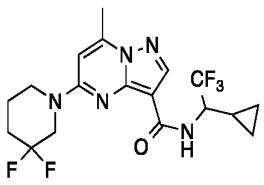
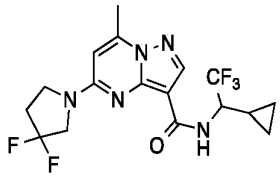
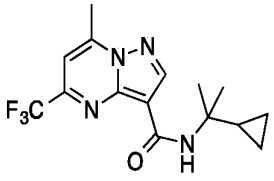
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-25		2.3	69.4	22.5	+	*
III-26		2.1	69.4	26.0	++	*
III-27		2.1	69.4	18.0	+	*
III-28		2.1	69.4	27.6	++	*
III-29		2.1	69.4	18.9	+	*
III-30		2.9	60.3	4.7	+	*

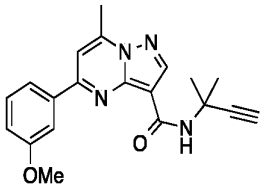
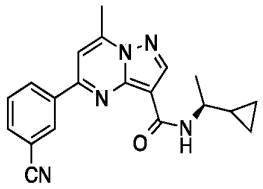
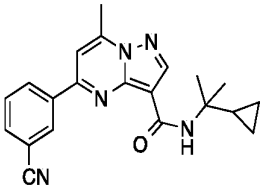
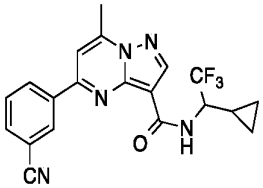
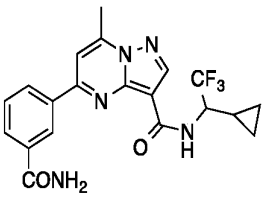
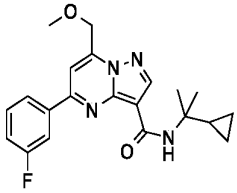
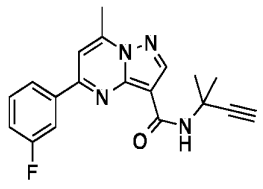
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-31		2.9	60.3	43.5	+++	***
III-32		3.6	57.1	0.1	+++	**
III-33		3.6	57.1	0.5	++	*
III-34		1.7	57.1	10.3	+	*
III-35		2.4	69.4	6.5	+++	**
III-36		2.4	69.4	0.4	+++	***
III-37		3.8	69.4	2.1	+++	**

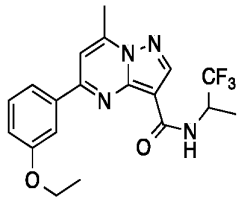
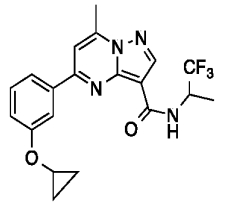
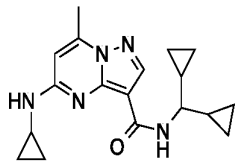
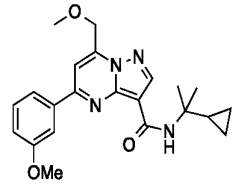
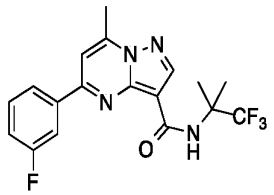
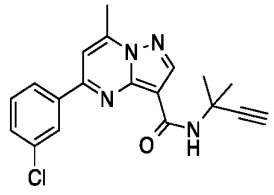
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-38		2.6	78.7	18.2	+	*
III-39		2.8	78.7	4.4	+++	**
III-40		2.4	78.7	20.0	+	*
III-41		2.9	69.4	1.9	+++	**
III-42		2.5	69.4	15.1	+++	*
III-43		1.9	69.4	12.1	++	*
III-44		2.8	69.1	3.0	+++	***
III-45		2.4	57.1	10.2	+++	***

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-46		3.0	66.3	3.4	++	*
III-47		3.4	66.3	0.3	+++	**
III-48		2.9	69.4	19.8	++	*
III-49		2.9	69.4	2.5	+++	*
III-50		2.1	69.4	1.6	+++	**
III-51		2.7	69.4	14.1	+	*
III-52		2.7	69.4	2.4	+++	*

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-55		3.4	66.3	1.7	+++	***
III-56		3.7	57.1	1.1	+++	***
III-57		3.6	66.3	2.7	+++	***
III-58		1.5	69.5	20.1	+	*
III-59		1.9	69.5	10.3	++	*
III-60		2.2	60.3	4.4	++	*
III-61		3.1	60.3	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-62		3.5	69.4	1.2	+++	***
III-63		3.1	69.4	0.2	++	**
III-64		4.1	57.1	6.2	+++	***
III-65		4.3	57.1	0.9	+++	***
III-66		3.4	60.3	0.3	+++	***
III-67		2.8	60.3	1.9	+++	***
III-68		2.8	57.1	11.9	+	*

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-69		3.6	66.3	0.5	+++	***
III-70		3.0	80.9	2.1	+++	***
III-71		3.4	80.7	0.5	+++	***
III-72		3.3	80.9	0.1	+++	***
III-73		2.4	100.2	0.4	+++	***
III-74		3.4	66.3	0.8	+++	**
III-75		3.7	57.1	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-76		3.9	66.3	0.2	+++	***
III-77		4.0	66.3	0.3	+++	***
III-78		3.0	69.1	5.6	+++	***
III-79		3.3	75.5	0.5	+++	***
III-80		3.8	57.1	0.2	+++	**
III-81		4.3	57.1	1.5	+++	***

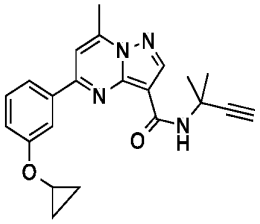
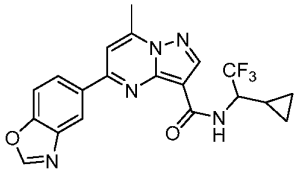
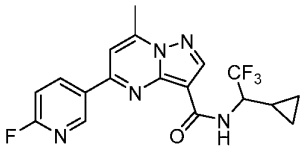
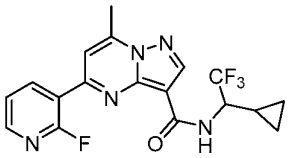
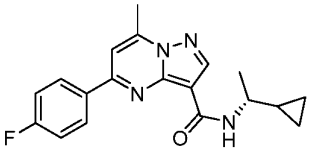
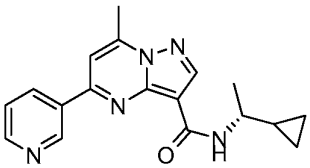
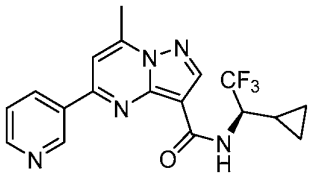
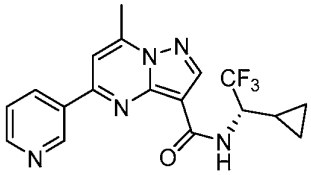
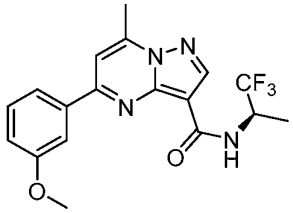
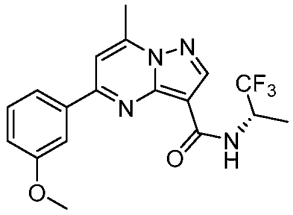
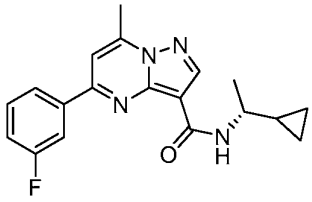
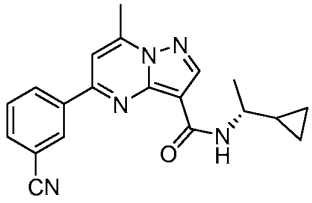
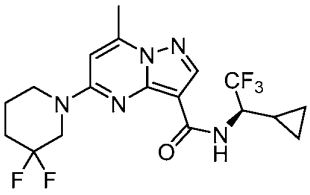
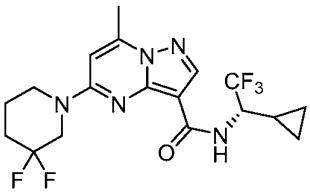
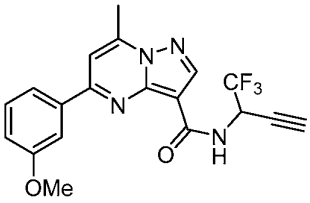
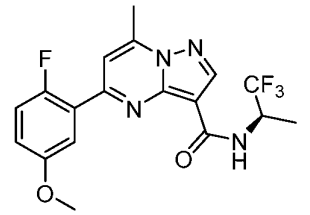
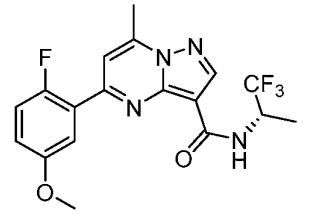
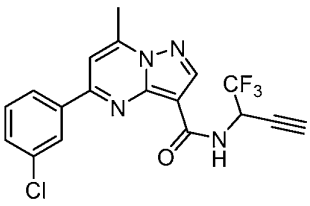
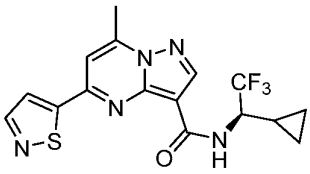
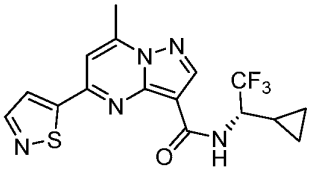
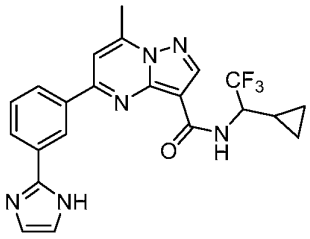
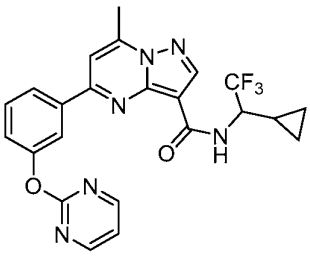
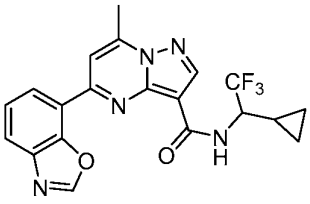
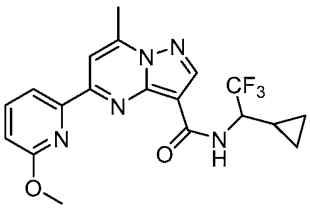
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-82		4.2	66.3	1.5	+++	***
III-83		NA	78.7	0.3	+++	***
III-84		3.7	69.4	0.8	+++	***
III-85		3.6	69.4	1.0	+++	***

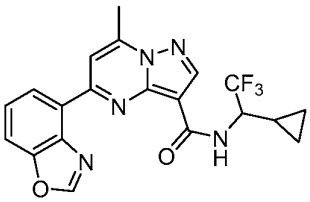
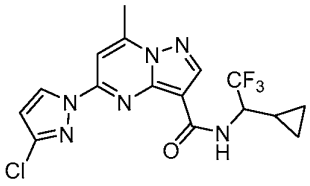
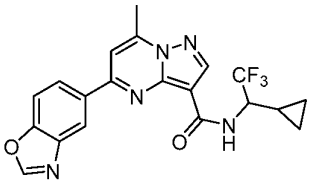
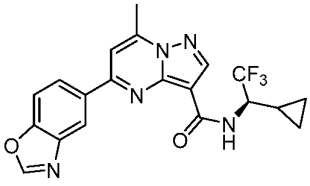
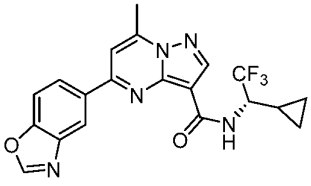
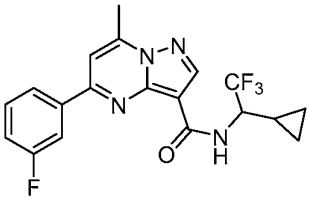
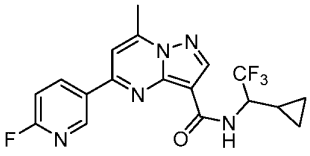
TABLE 3B.

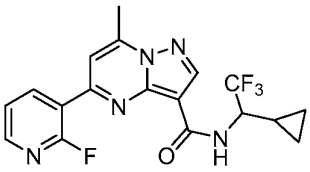
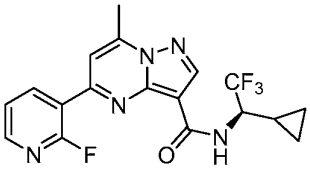
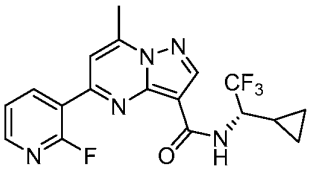
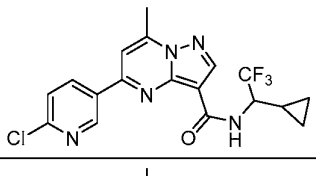
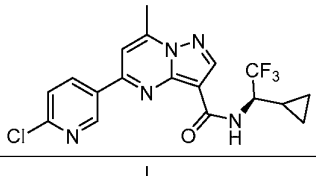
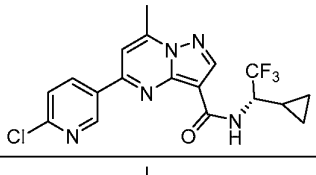
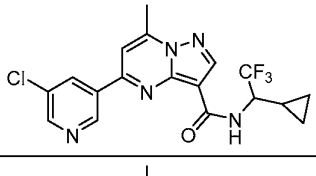
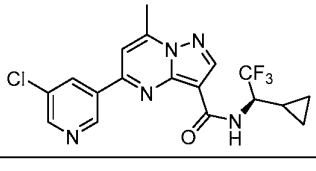
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-86		N/A	N/A	2.8	+++	**
III-87		N/A	N/A	N/A	+	*

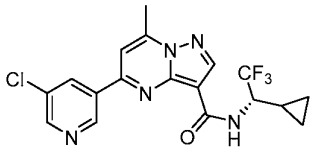
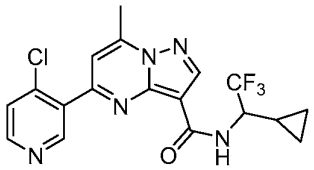
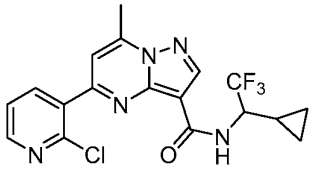
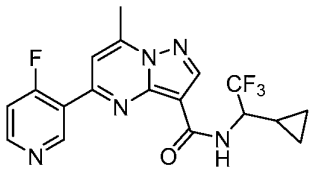
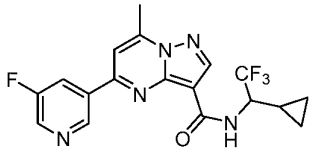
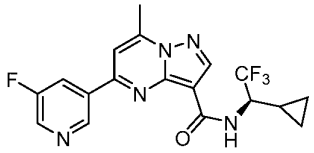
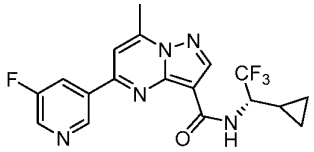
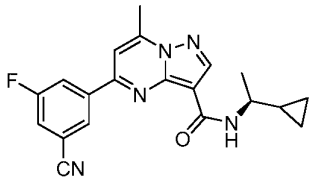
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-88		2.4	69.4	14.8	+++	***
III-89		2.4	69.4	10.4	+++	**
III-90		N/A	N/A	2.0	+++	***
III-91		N/A	N/A	1.7	+++	***
III-92		N/A	N/A	0.2	+++	***
III-93		N/A	N/A	N/A	+++	**

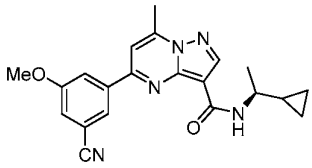
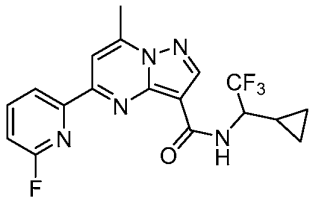
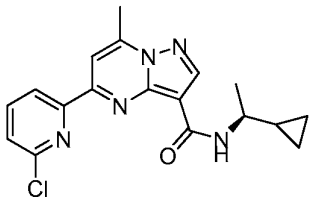
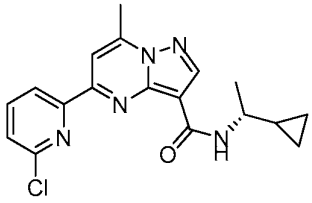
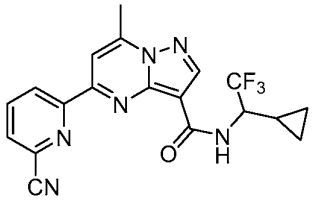
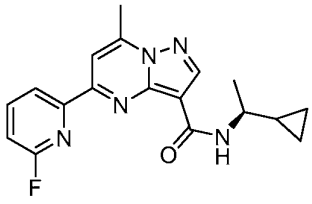
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-94		N/A	N/A	0.6	+++	***
III-95		N/A	N/A	1.0	+++	***
III-96		3.6	66.3	2.0	+++	***
III-97		N/A	N/A	0.2	+++	**
III-98		N/A	N/A	0.3	+++	***
III-99		4.3	57.1	0.2	++	***

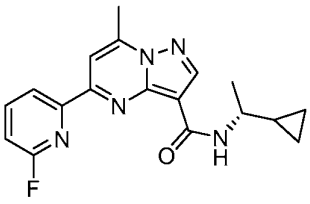
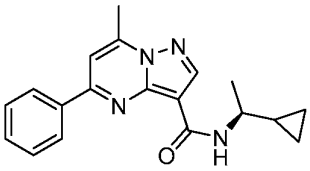
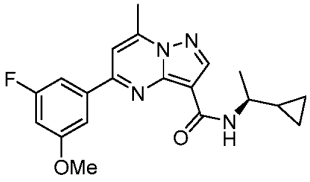
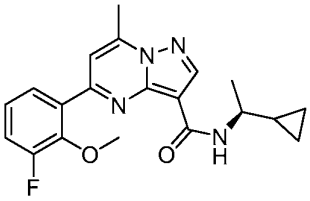
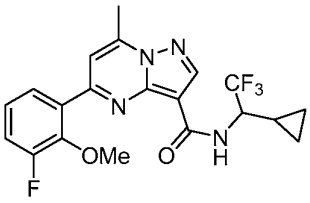
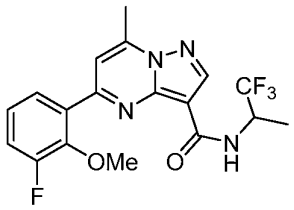
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-100		N/A	N/A	0.9	+++	***
III-101		N/A	N/A	1.3	+++	***
III-102		3.9	72.7	0.4	+	*
III-103		3.5	91.0	0.8	+++	*
III-104		3.1	78.7	0.02	+++	***
III-105		3.5	78.7	0.08	+++	***

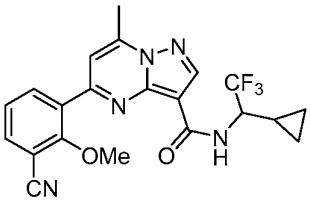
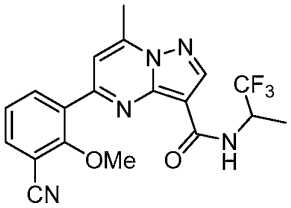
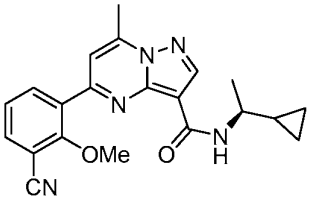
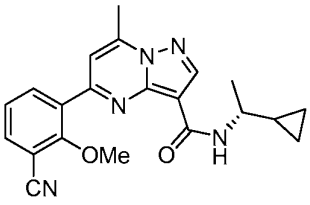
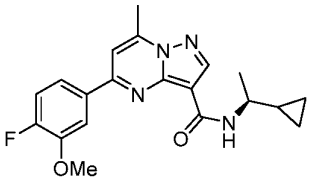
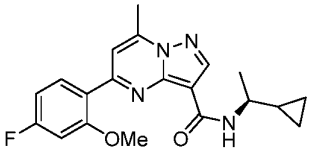
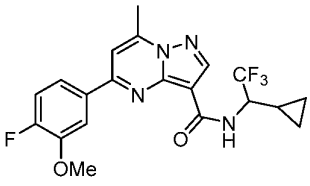
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-106		3.1	78..7	0.1	++	***
III-107		2.8	72.7	0.1	+++	***
III-108		2.8	78.7	0.3	+++	***
III-109		N/A	N/A	0.5	+++	***
III-110		N/A	N/A	0.4	+++	***
III-111		4.0	57.1	0.07	+++	***
III-112		2.6	69.4	0.8	+++	***

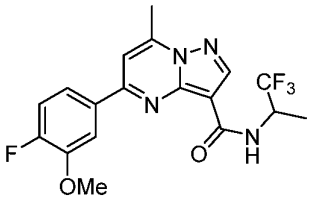
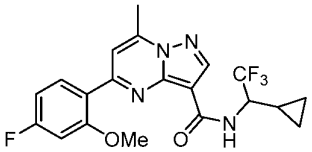
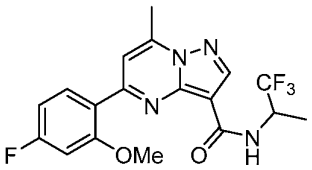
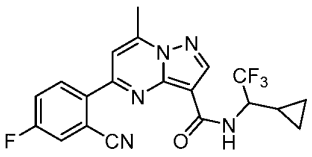
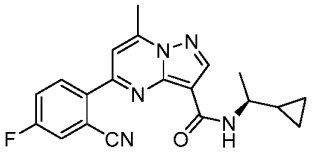
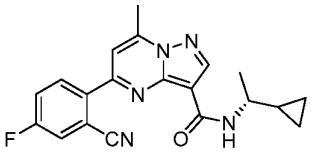
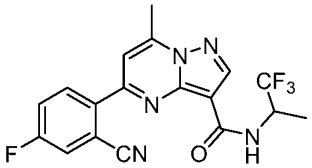
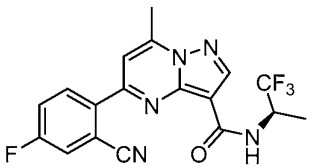
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-113		2.6	69.4	1.0	+++	***
III-114		2.6	69.4	2.1	+++	***
III-115		2.6	69.4	1.9	+++	***
III-116		3.1	69.4	1.0	+++	***
III-117		N/A	N/A	0.8	+++	***
III-118		N/A	N/A	0.4	+++	***
III-119		3.1	69.4	0.08	+++	***
III-120		3.1	69.4	0.7	+++	***

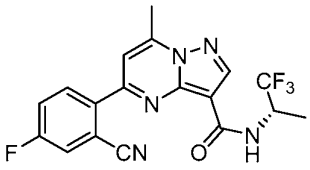
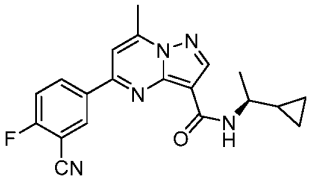
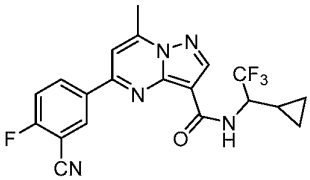
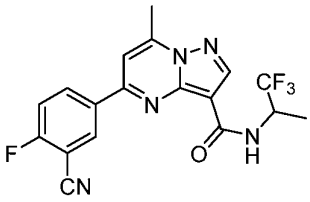
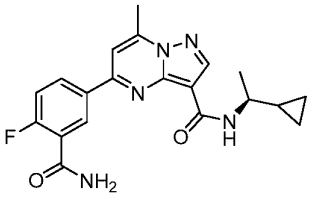
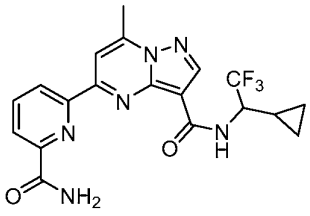
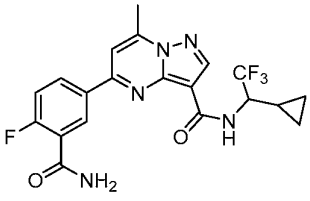
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-121		3.1	69.4	0.7	+++	***
III-122		2.9	69.4	2.1	+++	***
III-123		2.9	69.4	2.1	+++	**
III-124		2.6	69.4	1.9	+++	***
III-125		2.6	69.4	3.4	+++	***
III-126		2.6	69.4	1.8	+++	***
III-127		2.6	69.4	2.5	+++	***
III-128		3.1	80.9	3.0	+++	***

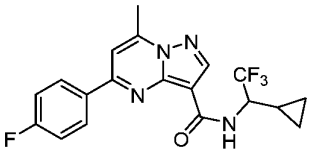
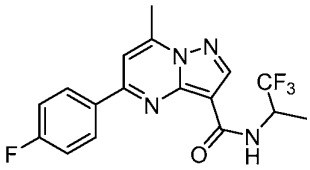
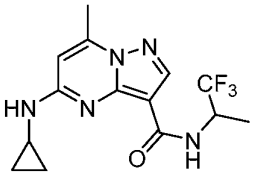
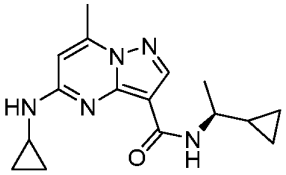
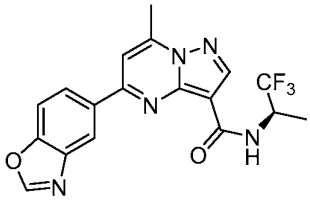
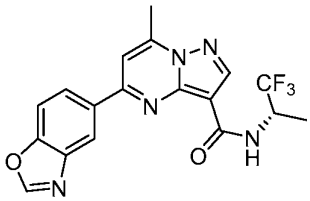
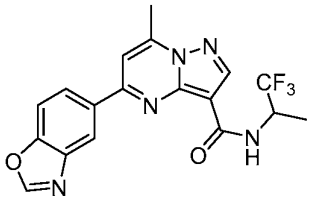
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-129		3.3	90.1	0.02	+++	***
III-130		2.8	69.4	0.2	+++	***
III-131		3.1	69.4	0.6	+++	***
III-132		N/A	N/A	N/A	+++	**
III-133		2.4	93.2	0.2	+++	**
III-134		2.5	69.4	0.8	+++	**

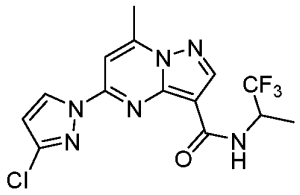
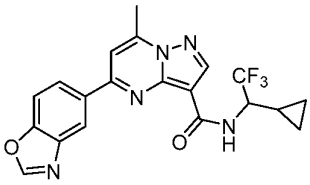
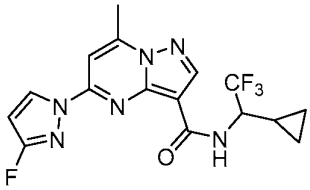
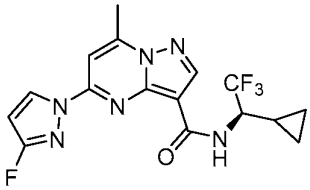
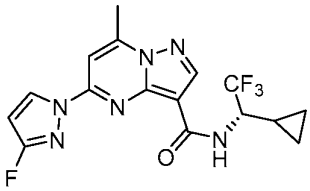
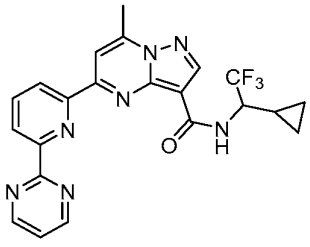
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-135		N/A	N/A	1.5	+++	**
III-136		3.6	57.1	5.1	+++	***
III-137		3.8	66.3	0.8	+++	***
III-138		3.0	66.3	2.5	+++	**
III-139		3.3	66.3	0.1	+++	**
III-140		2.8	66.3	1.1	+++	**

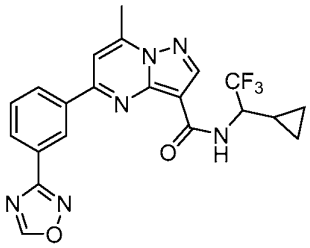
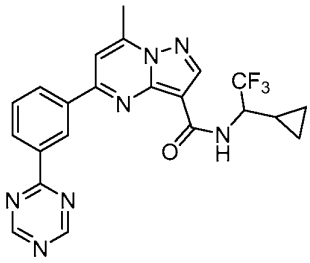
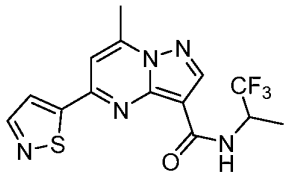
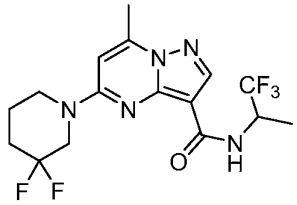
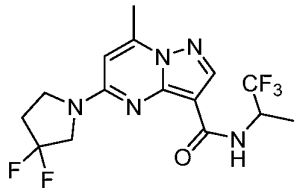
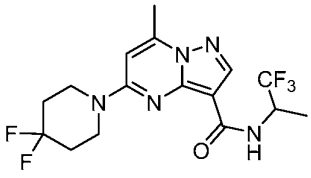
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-141		3.0	90.1	1.1	+++	*
III-142		2.5	90.1	2.2	+	*
III-143		2.7	90.1	17.4	+	*
III-144		N/A	N/A	N/A	+	*
III-145		3.6	66.3	0.2	+++	***
III-146		3.2	66.3	0.9	+++	***
III-147		3.9	66.3	0.4	+++	***

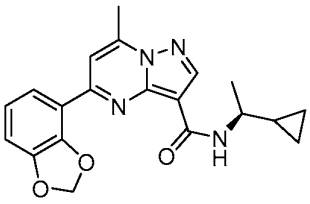
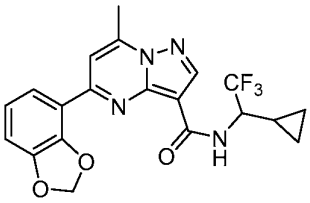
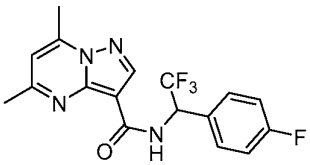
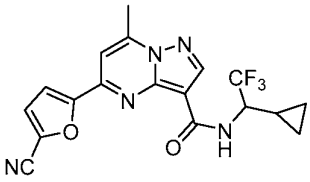
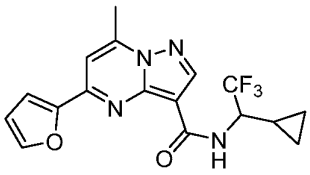
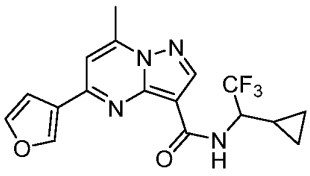
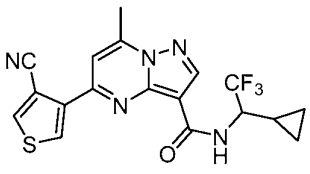
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-148		3.4	66.3	1.2	+++	**
III-149		3.5	66.3	1.1	+++	***
III-150		3.1	66.3	0.7	+++	***
III-151		3.4	80.9	0.1	+++	***
III-152		3.1	80.9	0.5	+++	***
III-153		N/A	N/A	4.5	+++	**
III-154		3.0	80.9	0.7	+++	***
III-155		N/A	N/A	N/A	++	*

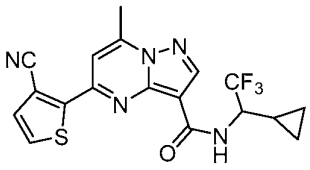
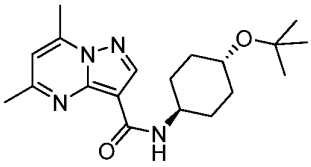
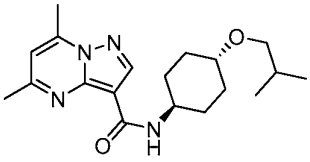
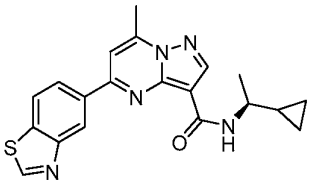
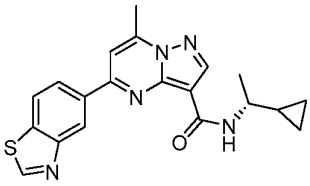
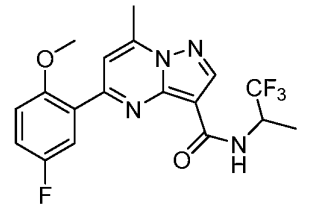
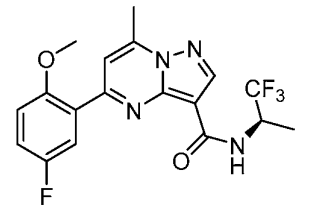
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-156		N/A	N/A	0.3	+++	***
III-157		3.1	80.9	2.9	+++	***
III-158		3.4	89	0.3	+++	***
III-159		3.0	80.9	3.8	+++	**
III-160		2.0	100.0	1.1	+++	**
III-161		2.1	112.5	1.0	+++	*
III-162		2.3	100.0	1.0	+++	***

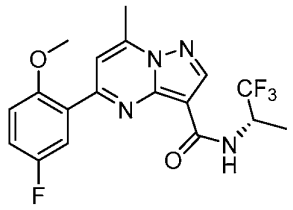
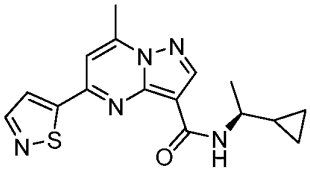
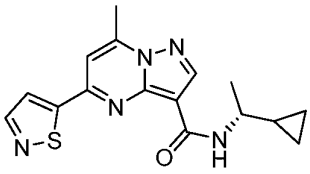
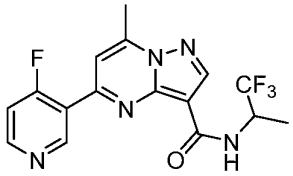
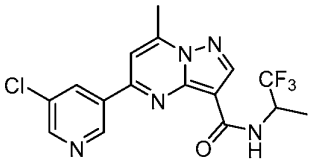
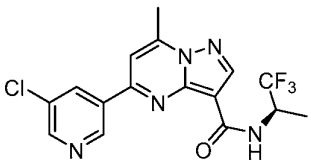
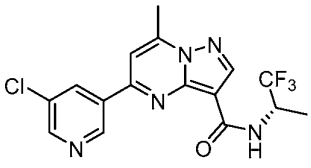
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-163		4.0	57.1	0.4	+++	***
III-164		3.5	57.1	1.1	+++	***
III-165		2.4	69.1	4.0	+++	**
III-166		2.6	69.1	10.9	+++	**
III-167		2.6	78.7	0.7	+++	***
III-168		2.6	78.7	0.3	+++	***
III-169		2.6	78.7	1.6	+++	***

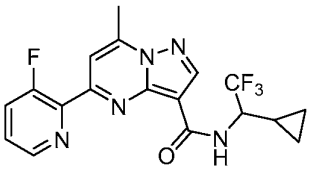
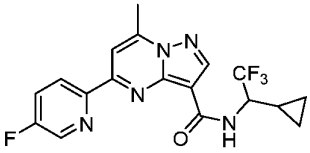
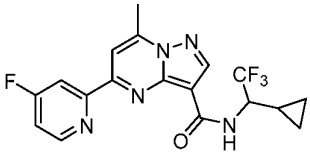
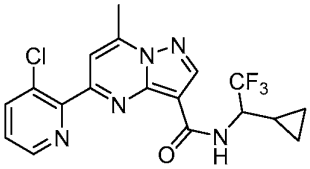
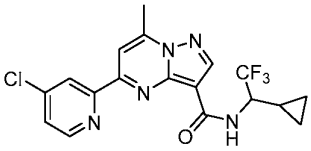
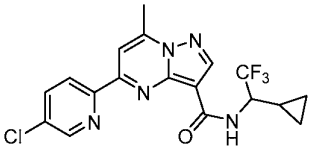
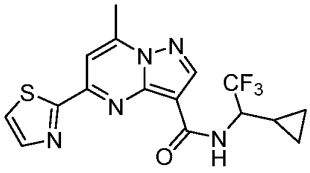
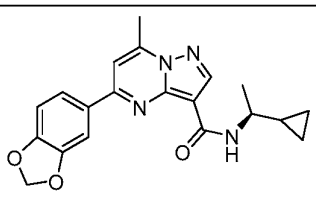
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-170		2.3	72.7	0.5	++	**
III-171		3.1	78.7	0.4	+++	***
III-172		2.2	72.7	0.5	+++	***
III-173		N/A	N/A	1.4	+++	***
III-174		N/A	N/A	N/A	+++	***
III-175		2.5	94.1	1.0	+	*

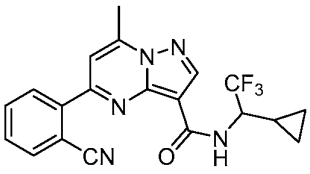
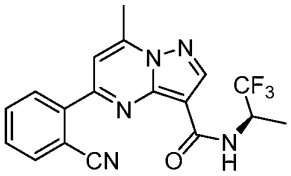
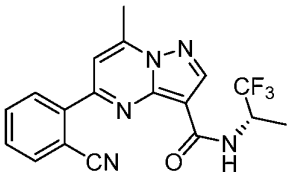
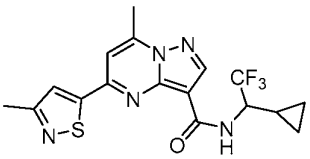
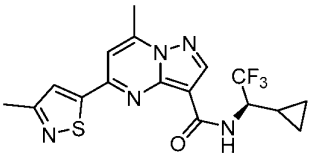
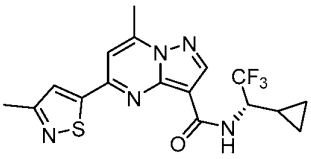
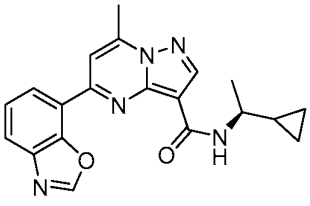
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-176		3.3	91.0	0.2	+++	***
III-177		2.5	94.1	0.2	+++	***
III-178		2.4	69.4	0.7	+++	**
III-179		3.0	60.3	1.1	+++	***
III-180		2.4	60.3	4.8	+++	**
III-181		2.1	60.3	4.5	+++	*

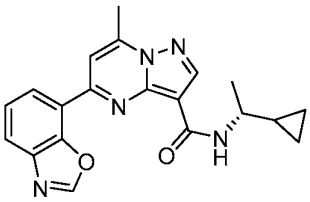
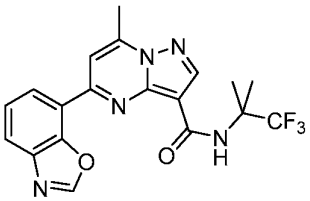
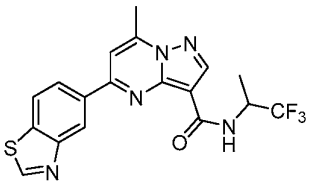
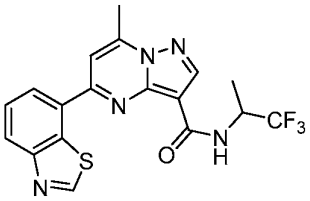
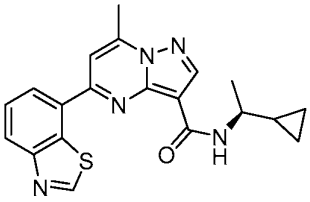
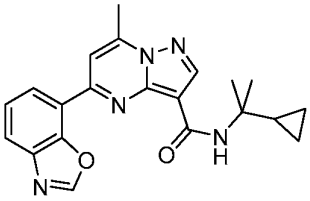
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-182		3.6	75.5	0.2	++	***
III-183		3.9	75.5	0.5	+++	***
III-184		3.6	57.1	1.1	+++	***
III-185		2.6	90.1	6.3	+++	***
III-186		3.2	66.3	0.6	+++	***
III-187		3.0	66.3	0.5	+++	***
III-188		3.0	80.9	0.3	+++	***

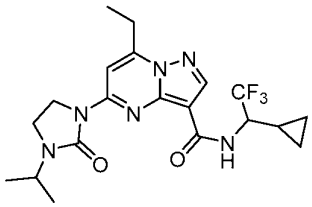
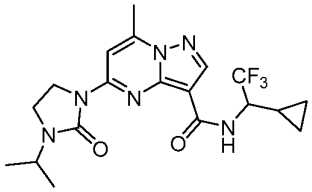
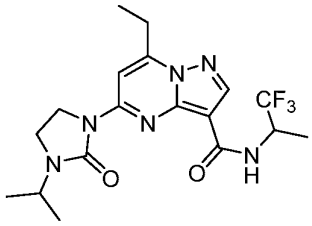
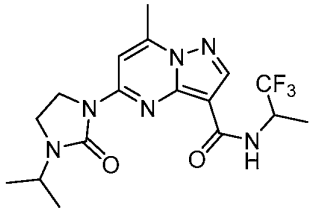
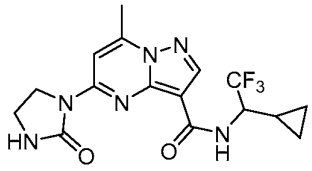
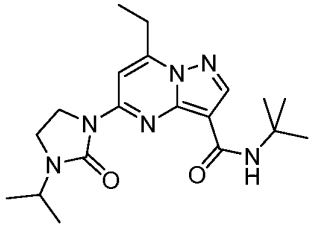
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-189		3.2	80.9	5.1	+++	***
III-190		2.4	66.3	8.9	+	*
III-191		2.7	66.3	26.3	+++	*
III-192		3.5	69.4	0.2	+++	***
III-193		N/A	N/A	N/A	+++	***
III-194		3.0	66.7	0.4	+++	***
III-195		N/A	N/A	0.01	+++	***

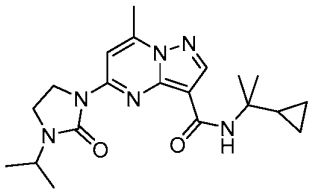
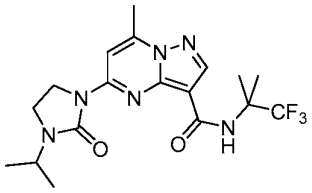
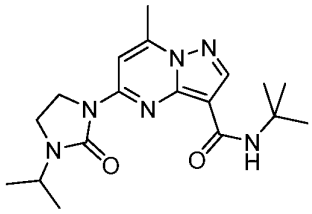
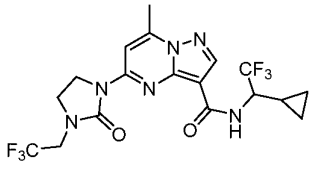
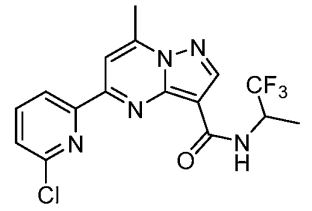
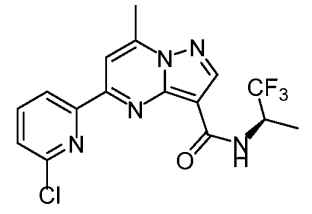
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-196		N/A	N/A	N/A	+++	***
III-197		2.5	69.4	6.5	+++	***
III-198		N/A	N/A	N/A	+++	*
III-199		2.1	69.4	7.8	++	*
III-200		2.7	69.4	1.0	+++	***
III-201		N/A	N/A	3.1	+++	***
III-202		N/A	N/A	2.5	+++	***

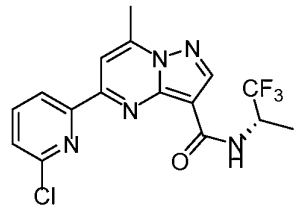
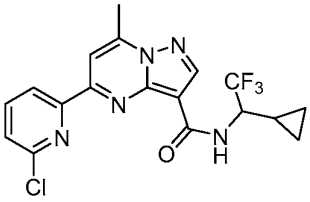
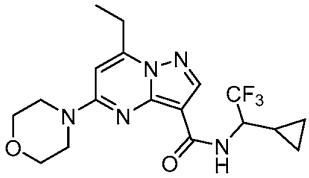
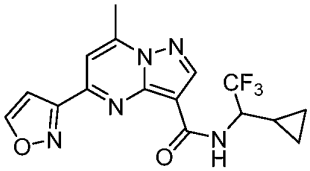
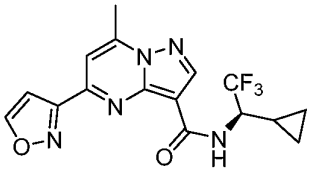
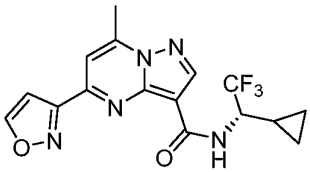
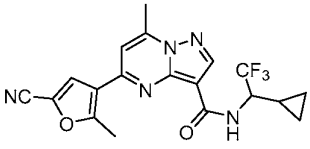
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-203		2.8	69.4	0.07	+++	***
III-204		2.8	69.4	0.1	+++	***
III-205		2.8	69.4	0.1	+++	***
III-206		3.1	69.4	2.1	+++	***
III-207		3.4	69.4	0.6	+++	***
III-208		3.4	69.4	0.04	+	**
III-209		2.4	69.4	1.2	+++	***
III-210		3.6	75.5	2.4	+++	***

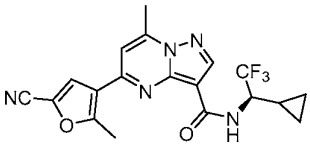
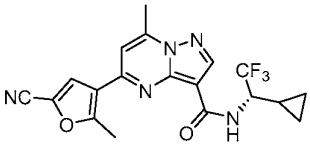
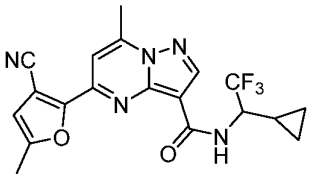
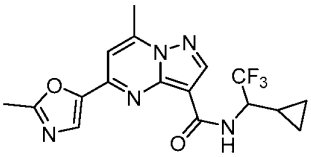
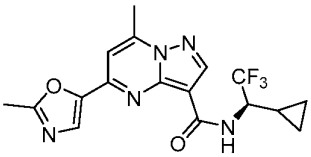
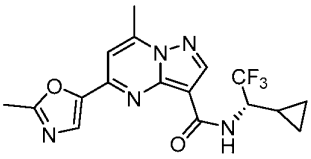
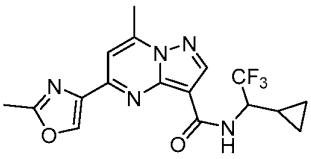
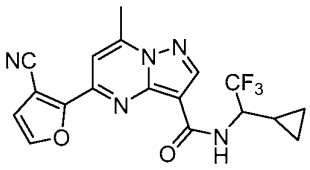
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-211		3.3	80.9	0.2	+++	***
III-212		3.3	80.9	0.7	++	*
III-213		3.3	80.9	0.6	+++	***
III-214		3.3	69.4	2.3	+++	***
III-215		N/A	N/A	0.3	+++	***
III-216		N/A	N/A	0.9	+++	***
III-217		2.8	78.7	3.2	+++	**

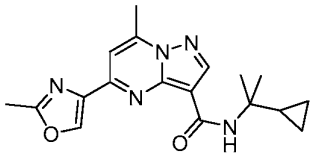
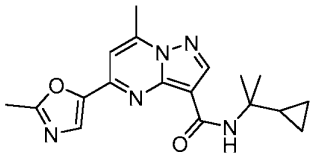
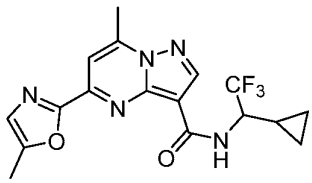
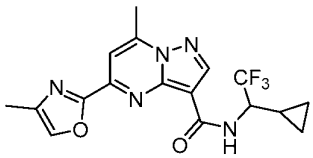
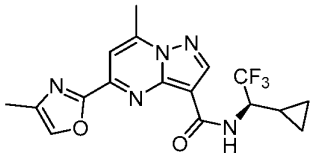
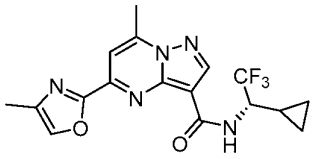
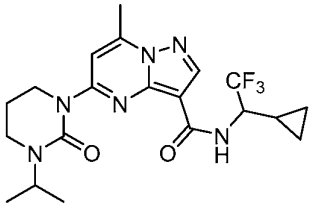
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-218		N/A	N/A	N/A	++	*
III-219		3.0	78.7	2.7	++	**
III-220		3.3	69.4	0.1	+++	***
III-221		3.3	69.4	0.2	+++	***
III-222		3.5	69.4	0.6	+++	***
III-223		3.2	78.7	0.2	+++	***

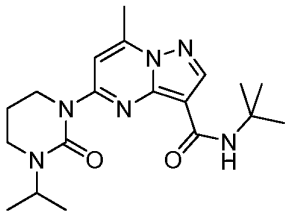
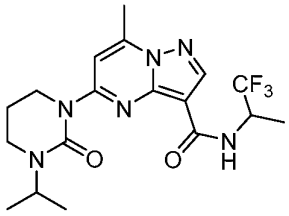
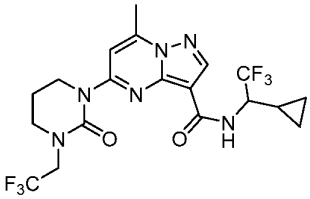
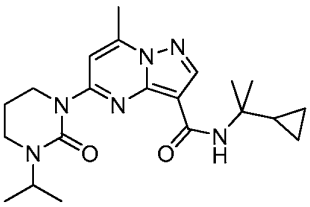
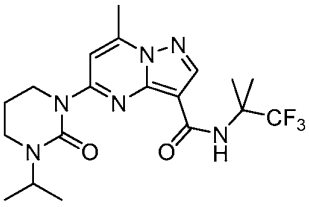
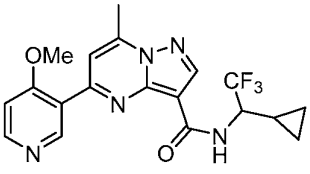
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-224		2.6	80.6	1.2	+++	**
III-225		2.1	80.6	19.3	+++	**
III-226		2.2	80.6	5.9	++	*
III-227		1.6	80.6	9.4	+	*
III-228		2.1	89.4	2.4	+++	*
III-229		2.3	80.6	13.5	++	*

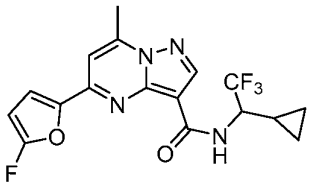
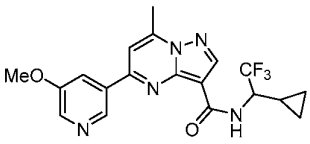
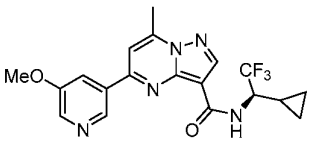
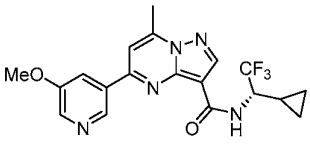
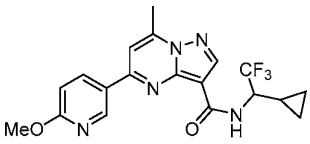
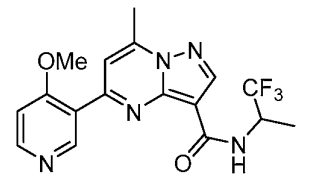
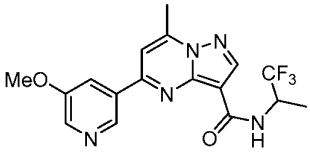
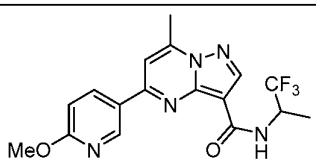
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-230		2.2	80.6	2.6	++	*
III-231		2.0	80.6	3.0	++	*
III-232		1.8	80.6	23.7	+	*
III-233		1.5	80.6	0.7	+++	**
III-234		2.9	69.4	0.2	+++	***
III-235		N/A	N/A	6.4	+++	**

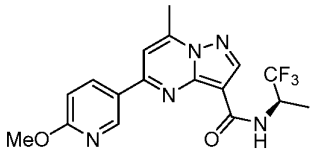
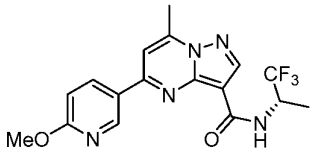
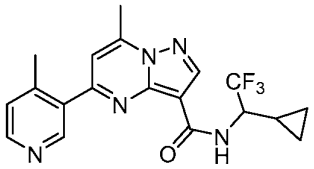
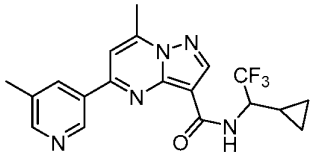
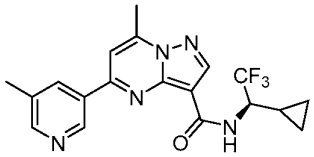
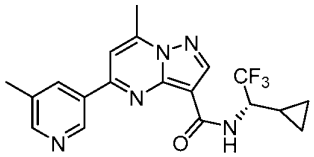
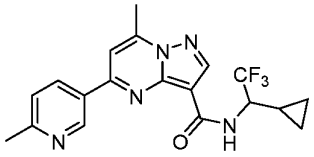
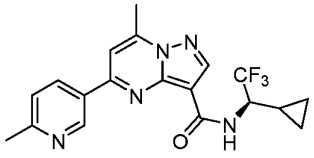
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-236		N/A	N/A	5.9	+++	***
III-237		3.4	69.4	0.05	+++	***
III-238		2.3	69.5	13.5	+++	*
III-239		2.1	78.7	0.8	+++	**
III-240		N/A	N/A	N/A	+++	***
III-241		N/A	N/A	N/A	+++	***
III-242		2.6	90.1	3.2	+++	***

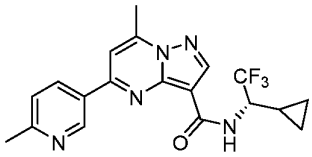
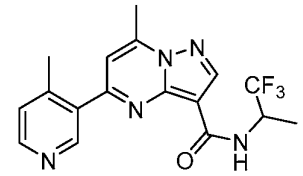
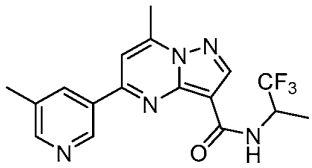
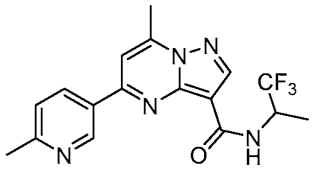
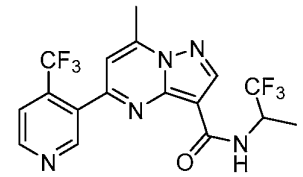
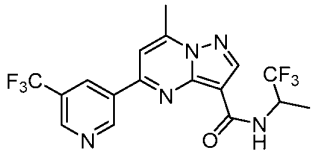
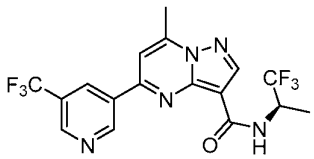
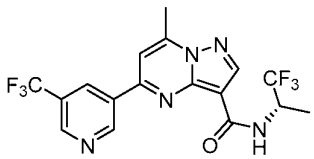
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-243		N/A	N/A	N/A	+++	***
III-244		N/A	N/A	N/A	+++	***
III-245		3.1	90.1	0.008	+	*
III-246		2.0	78.7	3.1	+++	**
III-247		N/A	N/A	0.6	+++	***
III-248		N/A	N/A	0.7	+++	***
III-249		2.0	78.7	0.6	+++	**
III-250		2.6	90.1	0.4	+++	***

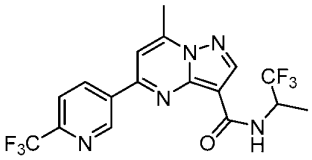
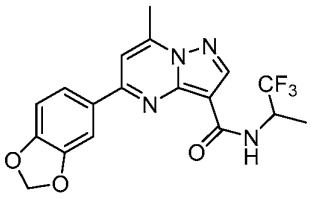
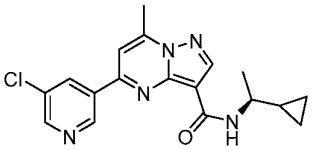
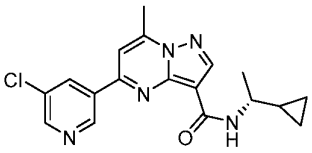
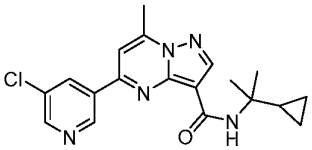
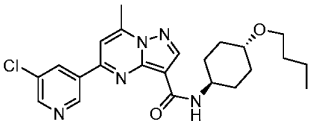
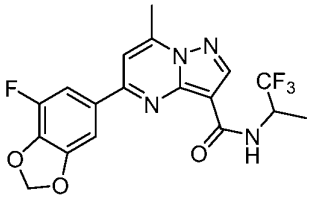
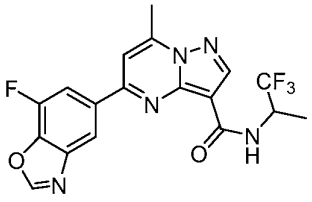
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-251		2.2	78.7	3.9	+++	**
III-252		2.2	78.7	11.0	+++	*
III-253		2.0	78.7	0.7	+++	***
III-254		2.0	78.7	0.6	+++	***
III-255		N/A	N/A	1.6	+++	**
III-256		N/A	N/A	0.5	+++	***
III-257		2.6	80.6	11.6	++	**

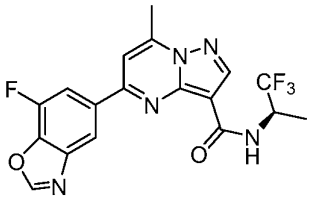
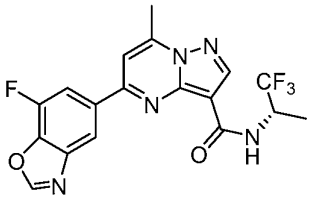
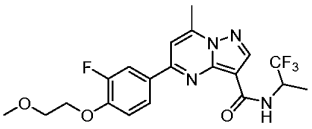
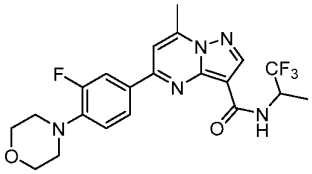
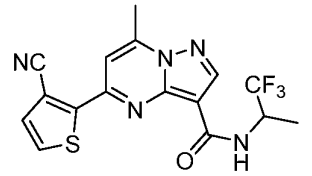
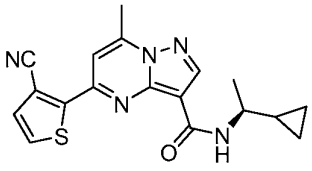
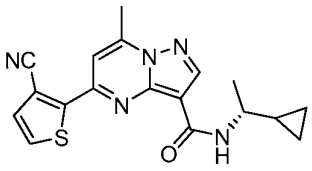
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-258		2.3	80.6	26.4	+	*
III-259		2.2	80.6	25.8	+	*
III-260		2.1	80.6	21.0	++	*
III-261		2.8	80.6	23.0	+	*
III-262		2.5	80.6	19.0	+	*
III-263		2.2	78.7	8.9	++	*

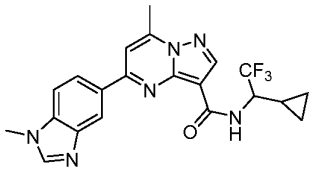
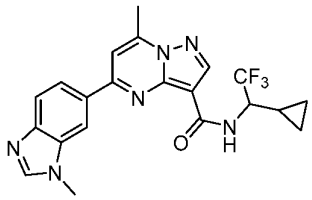
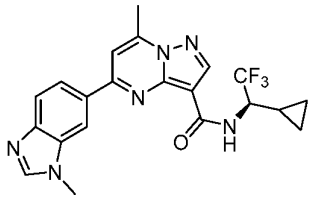
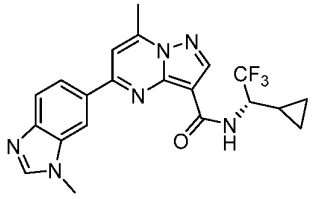
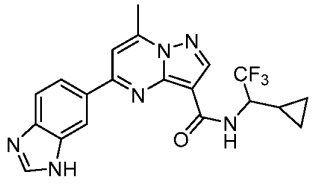
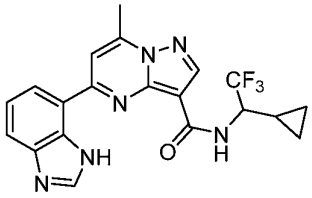
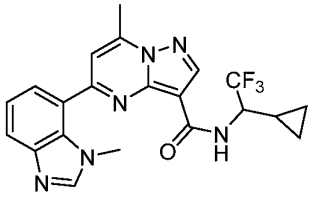
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-264		3.3	66.3	0.4	+++	***
III-265		2.8	78.7	1.3	+++	***
III-266		N/A	N/A	N/A	+++	***
III-267		N/A	N/A	N/A	+++	***
III-268		3.2	78.7	1.2	+++	***
III-269		1.8	78.7	12.7	+	*
III-270		2.4	78.7	4.9	+++	**
III-271		2.8	78.7	2.3	+++	***

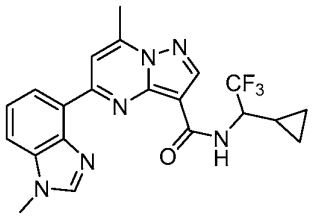
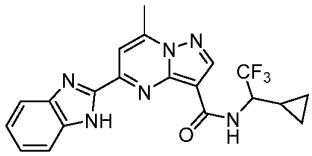
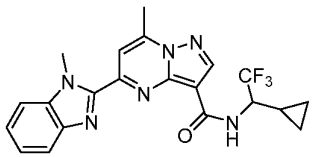
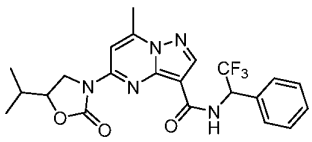
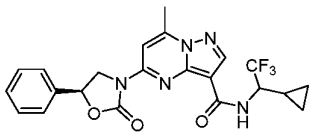
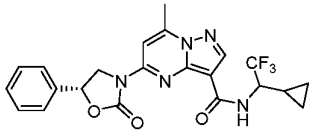
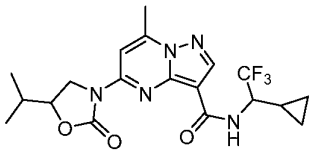
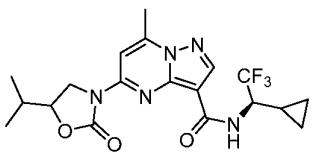
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-272		N/A	N/A	3.1	+++	**
III-273		N/A	N/A	3.4	+++	***
III-274		2.1	69.4	2.3	+++	*
III-275		2.9	69.4	2.6	+++	***
III-276		N/A	N/A	1.8	+++	***
III-277		N/A	N/A	5.3	+++	***
III-278		2.9	69.4	0.5	+++	***
III-279		N/A	N/A	1.5	+++	**

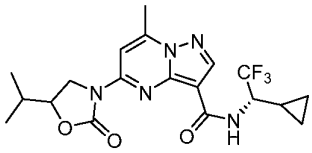
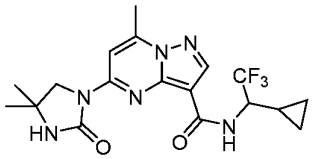
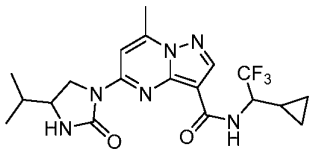
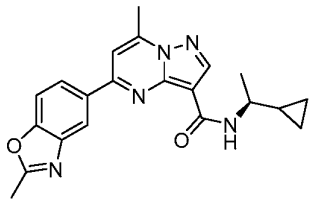
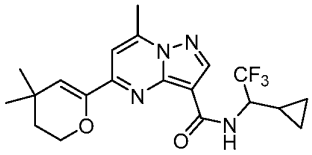
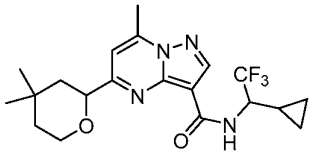
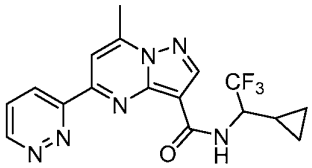
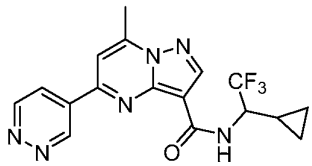
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-280		N/A	N/A	1.3	+++	***
III-281		2.1	69.4	12.5	+	*
III-282		2.4	69.4	6.2	+++	**
III-283		2.4	69.4	12.7	++	*
III-284		2.9	69.4	13.2	+++	**
III-285		2.9	69.4	1.2	+++	***
III-286		N/A	N/A	2.1	+++	***
III-287		N/A	N/A	2.4	+++	***

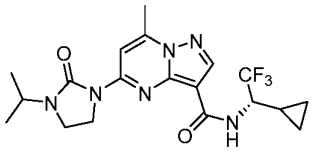
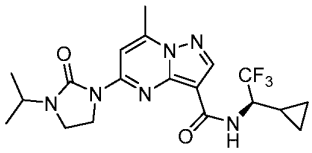
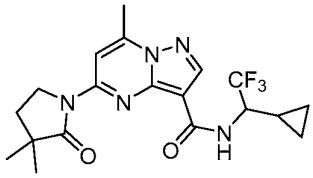
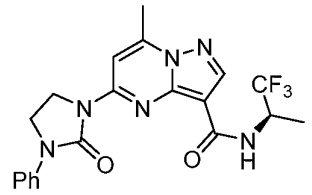
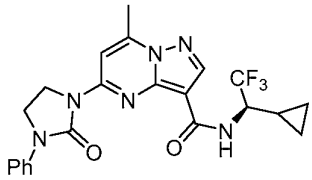
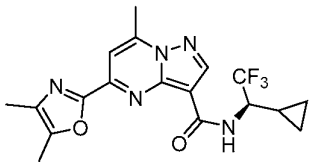
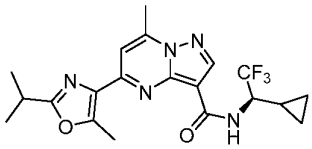
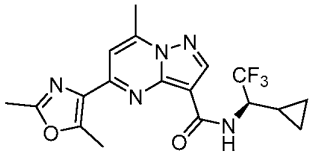
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-288		2.9	69.4	1.4	+++	**
III-289		3.4	75.5	0.8	+++	***
III-290		2.9	69.4	2.1	+++	***
III-291		N/A	N/A	N/A	+++	***
III-292		3.3	69.4	0.3	+++	***
III-293		3.7	78.7	0.3	+++	***
III-294		3.6	75.5	0.6	+++	***
III-295		2.9	78.7	3.4	+++	***

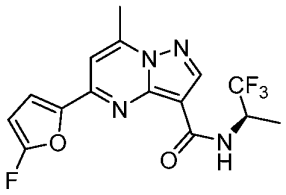
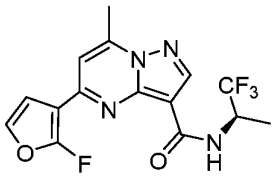
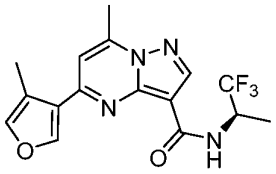
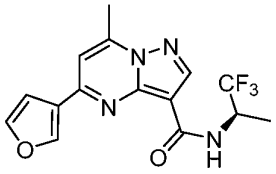
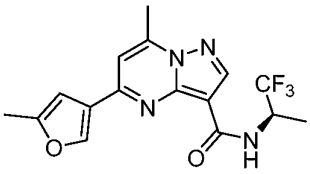
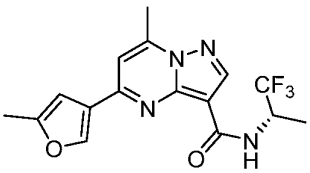
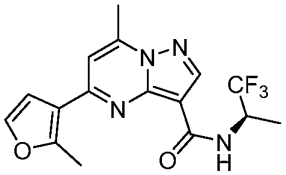
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-296		2.9	78.7	N/A	+++	***
III-297		2.9	78.7	N/A	+++	***
III-298		3.3	75.5	1.5	+++	***
III-299		3.2	69.5	0.5	+++	***
III-300		2.8	80.9	1.4	+++	***
III-301		3.0	80.9	1.1	+++	***
III-302		N/A	N/A	0.5	+++	***

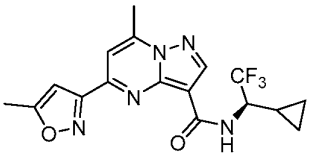
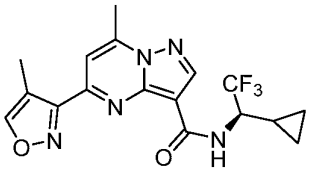
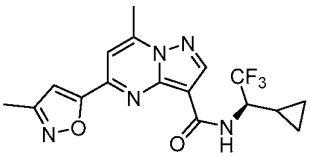
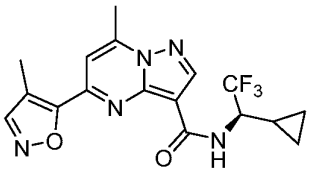
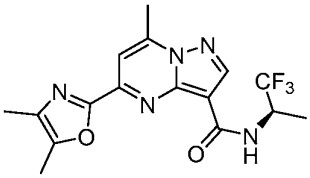
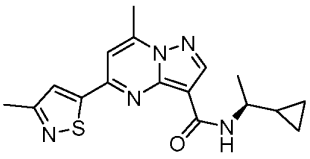
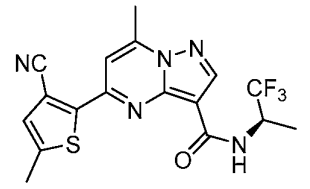
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-303		3.3	72.7	3.2	+	**
III-304		3.3	72.7	0.4	+++	**
III-305		N/A	N/A	N/A	+++	***
III-306		N/A	N/A	N/A	+++	***
III-307		3.2	81.5	0.3	++	***
III-308		3.2	81.5	4.6	+++	*
III-309		3.3	72.7	31.4	+	*

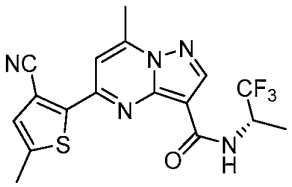
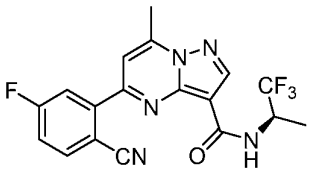
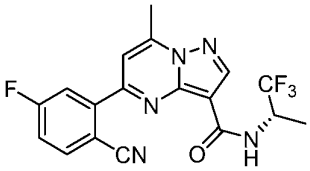
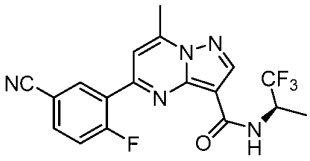
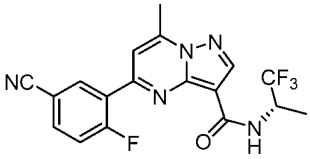
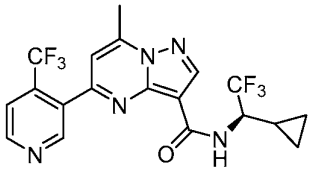
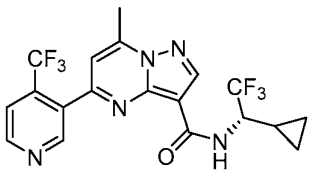
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-310		3.3	72.7	0.3	+++	**
III-311		3.6	81.5	0.6	++	*
III-312		3.5	72.7	0.3	++	**
III-313		3.4	86.6	0.1	+++	***
III-314		2.3	86.6	0.2	+++	***
III-315		2.3	86.6	0.1	+++	***
III-316		2.2	86.6	1.3	+++	**
III-317		2.2	86.6	N/A	+++	**

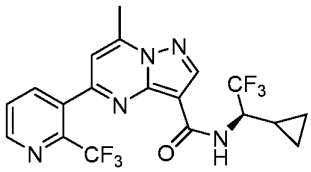
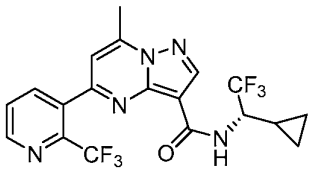
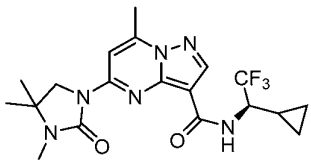
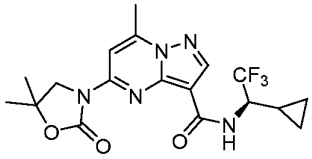
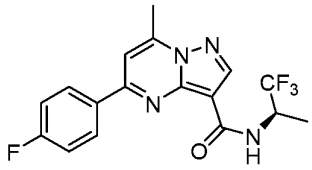
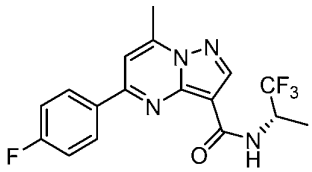
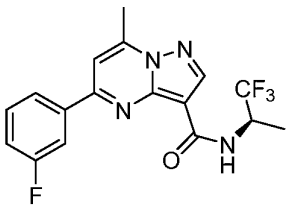
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-318		2.2	86.6	N/A	+++	**
III-319		3.1	89.4	1.3	+++	**
III-320		3.5	89.4	N/A	+++	***
III-321		3.1	78.7	1.9	+++	***
III-322		3.1	66.3	N/A	+++	***
III-323		3.1	66.3	N/A	+++	**
III-324		1.4	81.8	N/A	+	*
III-325		1.2	81.8	14.6	+	*

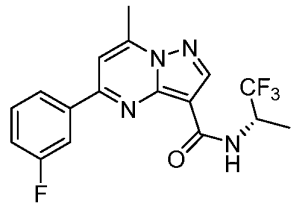
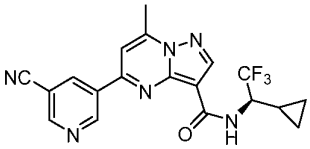
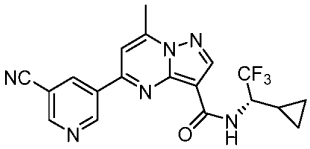
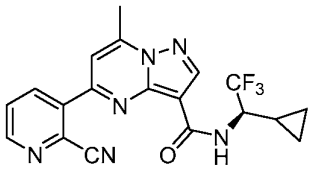
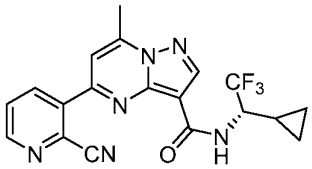
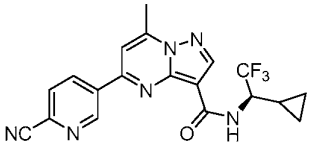
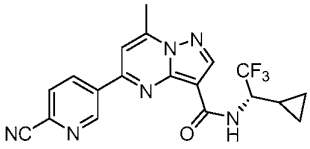
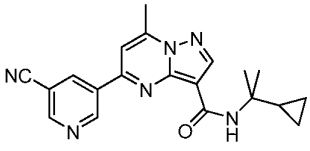
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-326		2.1	80.6	21.0	+++	*
III-327		2.1	80.6	32.8	+++	**
III-328		2.7	77.4	3.3	+++	**
III-329		2.3	80.6	N/A	+	*
III-330		2.7	80.6	N/A	++	**
III-331		2.3	78.7	1.0	+++	***
III-332		2.5	78.7	N/A	+++	***
III-333		2.0	78.7	N/A	+++	***

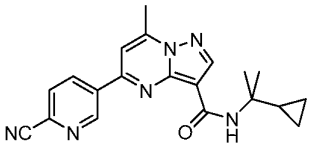
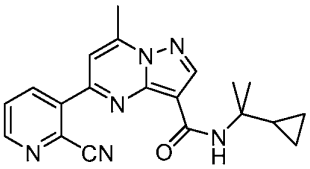
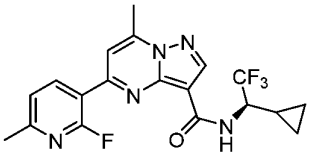
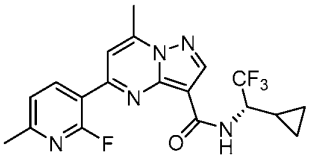
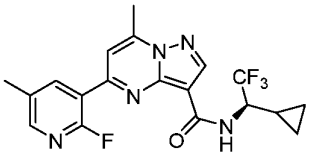
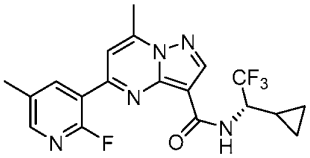
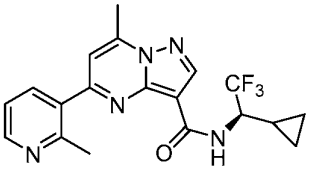
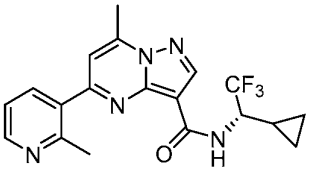
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-334		2.9	66.3	2.0	+++	***
III-335		2.7	66.3	N/A	+++	***
III-336		2.8	66.3	N/A	+++	***
III-337		2.6	66.3	N/A	+++	***
III-338		3.1	66.3	0.2	+++	***
III-339		3.1	66.3	N/A	+++	***
III-340		3.1	66.3	N/A	+++	***

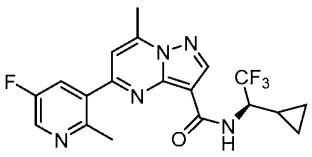
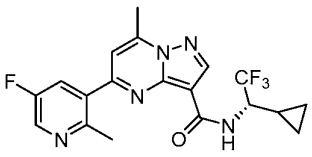
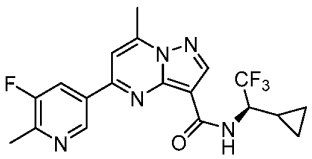
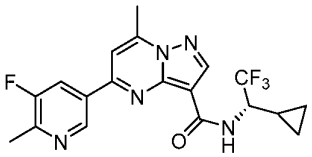
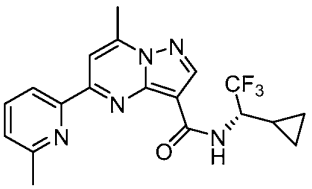
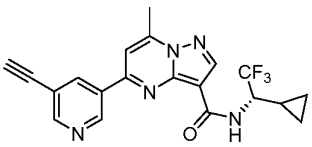
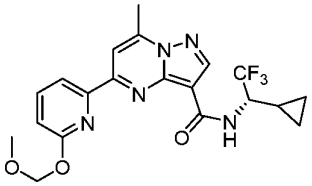
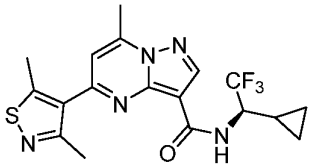
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-341		2.4	78.7	N/A	+++	***
III-342		2.1	78.7	N/A	+++	***
III-343		2.4	78.7	1.5	+++	***
III-344		2.1	78.7	N/A	+++	***
III-345		1.8	78.5	1.0	+++	**
III-346		3.0	69.4	18.8	+++	**
III-347		3.3	80.9	N/A	+++	***

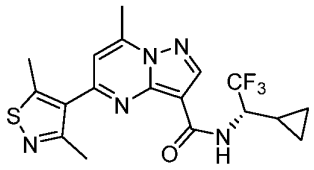
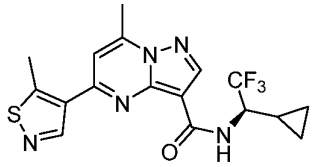
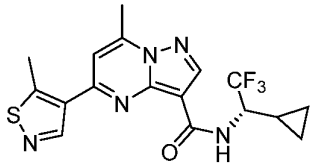
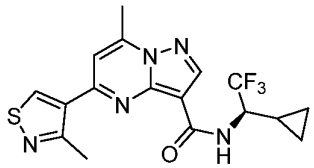
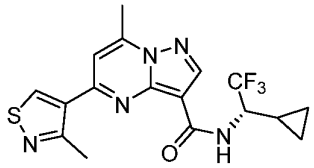
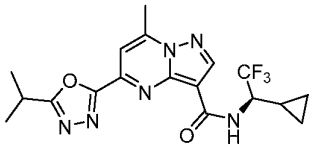
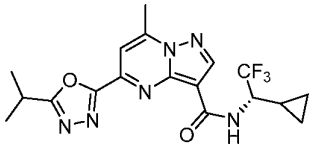
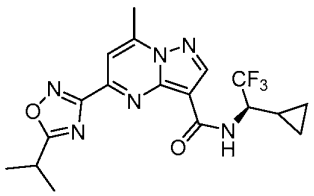
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-348		3.3	80.9	N/A	+++	***
III-349		3.0	80.9	0.1	++	***
III-350		3.0	80.9	0.3	+++	***
III-351		3.0	90.9	N/A	+++	**
III-352		3.0	90.9	N/A	+++	**
III-353		3.4	69.4	8.3	+++	***
III-354		3.4	69.4	13.5	+++	***

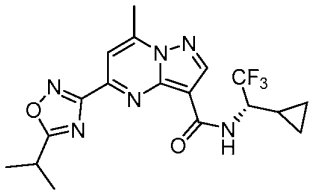
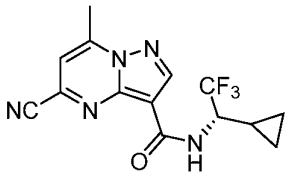
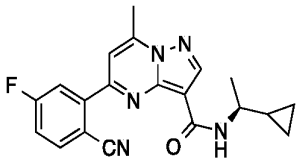
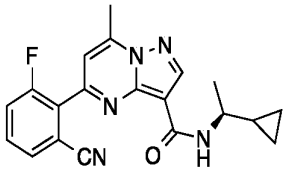
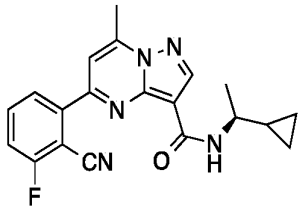
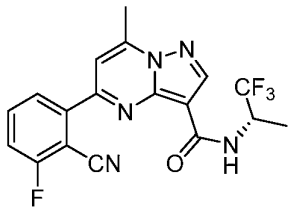
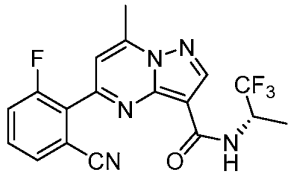
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-355		3.4	69.4	0.1	+++	***
III-356		3.4	69.4	N/A	+++	***
III-357		2.3	80.6	N/A	+++	**
III-358		1.8	86.6	N/A	++	*
III-359		3.5	57.1	0.7	+++	**
III-360		3.5	57.1	0.7	+++	***
III-361		3.5	57.1	0.7	+++	***

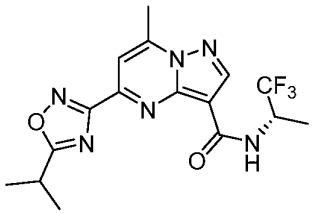
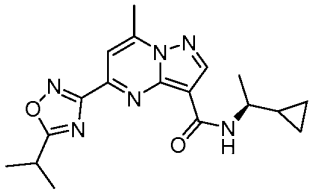
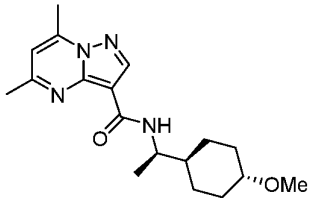
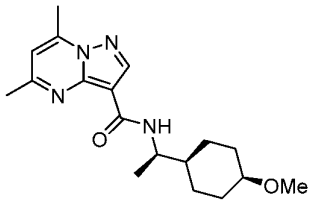
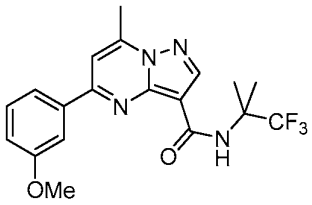
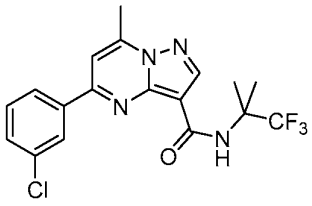
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-362		3.5	57.1	0.6	+++	***
III-363		2.0	93.2	1.7	+++	***
III-364		2.0	93.2	N/A	+++	**
III-365		2.2	93.2	1.8	+++	**
III-366		2.2	93.2	1.1	+++	***
III-367		2.2	93.2	0.4	+++	**
III-368		2.2	93.2	N/A	+++	**
III-369		2.1	93.2	N/A	+++	**

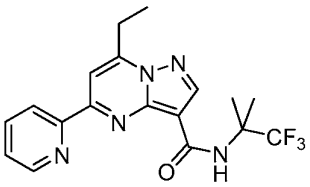
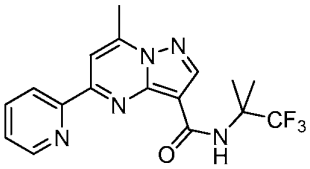
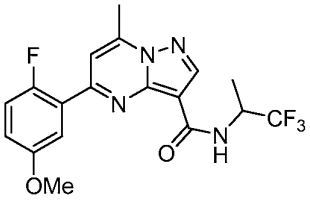
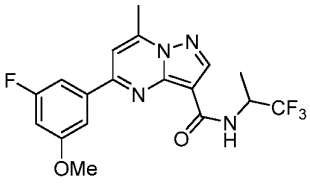
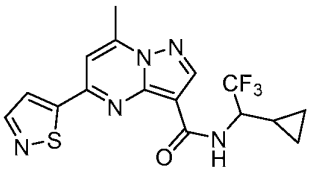
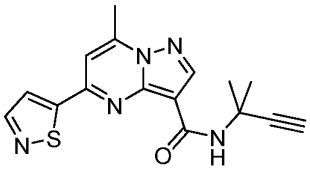
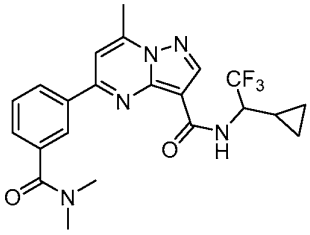
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-370		2.3	93.2	N/A	+++	*
III-371		2.3	93.2	N/A	+++	*
III-372		3.1	69.4	1.7	+++	***
III-373		3.1	69.4	N/A	+++	***
III-374		3.1	69.4	1.1	+++	***
III-375		3.1	69.4	N/A	+++	***
III-376		2.6	69.4	N/A	+	*
III-377		2.6	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
III-378		2.8	69.4	N/A	+++	**
III-379		2.8	69.4	N/A	+++	**
III-380		3.1	69.4	0.3	+++	***
III-381		3.1	69.4	N/A	+++	***
III-382		3.1	69.4	N/A	+++	***
III-383		2.6	69.4	0.2	+++	***
III-384		2.9	87.9	0.1	+++	**
III-385		3.0	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
III-386		3.0	69.4	N/A	+	*
III-387		2.8	69.4	N/A	+++	***
III-388		2.8	69.4	N/A	+++	***
III-389		2.8	69.4	N/A	+++	***
III-390		2.8	69.4	N/A	+++	***
III-391		2.5	91.0	0.3	+++	**
III-392		2.5	91.0	0.4	+++	**
III-393		2.6	91.0	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
III-394		2.6	91.0	0.7	+++	***
III-395		1.5	80.9	N/A	++	*
III-396		3.1	80.9	0.3	+++	***
III-397		3.1	80.9	N/A	+++	**
III-398		3.1	80.9	0.2	+++	***
III-399		3.0	80.9	0.1	+++	***
III-400		3.0	80.9	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
III-401		2.2	91.0	N/A	+++	***
III-402		2.3	91.0	N/A	+++	***
III-403		2.7	66.3	21.4	++	*
III-404		2.7	66.3	15.1	+++	*
III-405		3.7	66.3	1.5	+++	***
III-406		4.3	57.1	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-407		3.0	69.4	0.09	+	*
III-408		2.5	69.4	0.4	+++	**
III-409		3.6	66.3	0.9	+++	***
III-410		3.6	66.3	0.06	+++	***
III-411		2.8	69.4	0.7	+++	***
III-412		2.6	69.4	3.7	+++	*
III-413		2.3	77.4	6.0	+++	*

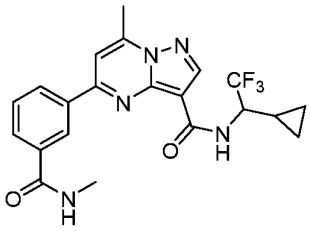
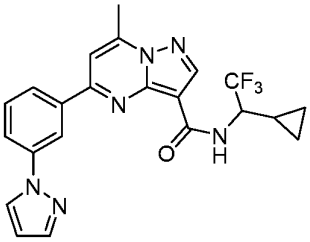
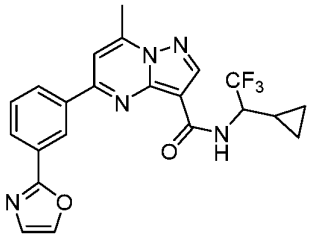
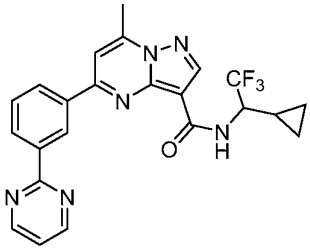
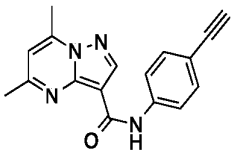
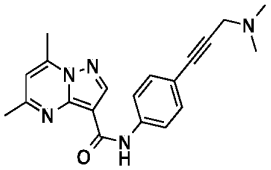
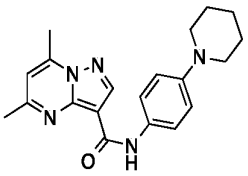
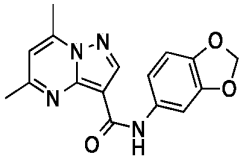
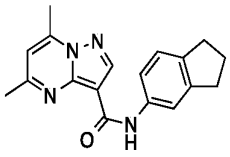
Compound No.	Compound Structure	cLogP	PSA	Compound Solubility in Water (μg/mL)	Percent Gcase Activation	
					1 μM Test Compound	0.1 μM Test Compound
III-414		2.7	86.2	1.6	+++	*
III-415		3.9	72.7	1.2	++	***
III-416		3.6	78.7	0.3	+++	***
III-417		3.5	81.8	0.04	+++	***

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		2.2	57.1	<1.5	++	**
IV-2		2.5	60.3	5.1	+	*
IV-3		3.0	60.3	<1.5	+	*
IV-4		1.7	75.5	0.6	++	*
IV-5		3.1	57.1	0.5	+++	**

INCORPORATION BY REFERENCE

[00919] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

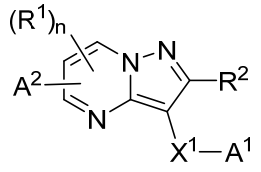
EQUIVALENTS

[00920] 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 represents independently for each occurrence C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, cyclopropyl, cyano, chloro, or fluoro;

R^2 is hydrogen;

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^7 represents independently for each occurrence halogen, hydroxyl, cyano, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{1-4} haloalkoxyl, C_{3-6} cycloalkyl, -O-(C_{3-6} cycloalkyl), -O-(C_{1-6} alkylene)-C_{1-6} alkoxyl, -(C_{1-6} alkylene)-CN, -N(R^4)$_2$, -C(O)N(R^4)$_2$, or heteroaryl;

R^8 is a bond or C_{1-6} alkylene;

R^9 is hydrogen or C_{1-6} alkyl;

X^1-A^1 is one of the following:

- X^1 is -C(O)N(H)(C_{1-6} haloalkylene)-ψ, where ψ is a bond to A^1; wherein A^1 is one of the following:
  - (i) 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; or
  - (ii) C_{1-8} alkyl; or
- X^1 is -C(O)N(H)C(C_{1-6} alkyl)$_2$-R^8-ψ or -C(O)N(H)C(C_{1-6} alkyl)(R^9)-R^8-ψ, where ψ is a bond to A^1, and A^1 is a 3-5 membered saturated carbocyclyl substituted by 0, 1, or 2 occurrences of Y^1 and 0, 1, 2, or 3 occurrences of Y^2;

A^2 is one of the following:

- phenyl substituted by 1, 2, or 3 occurrences of R^7; or
- a cyclic group selected from a 3-12 membered heterocyclyl, 4-12 membered oxoheterocyclyl, or 4-10 membered cycloalkyl; each of which is optionally substituted by 1, 2, or 3 occurrences of R^7;

Y^1 represents, independently for each occurrence, -O-(C_{1-7} alkyl);

Y^2 represents, independently for each occurrence, C_{1-6} alkyl, C_{3-6} cycloalkyl, halogen, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, or hydroxyl; and

n is 1;

wherein A^2 is located at the 5-position of the pyrazolo[1,5-a]pyrimidinyl, and the R^1 group is located at the 7-position of the pyrazolo[1,5-a]pyrimidinyl.

2. The compound of claim 1, wherein X^1 is -C(O)N(H)C(H)(CF_3)-ψ.

3. The compound of claim 1, wherein X^1 is -C(O)N(H)C(H)(CF_3)-ψ, and A^1 is C_{1-8} alkyl.

4. The compound of claim 1, wherein X^1 is -C(O)N(H)(C(H)(CH_3))-ψ.

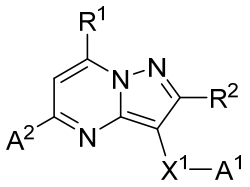
5. The compound of claim 1, wherein A^1 is (i) 3-5 membered saturated carbocyclyl, or (ii) a 6-14 membered saturated spirocyclic carbocyclyl, each optionally substituted with 1 or 2 C_{1-4} alkyl groups.

6. The compound of claim 1, wherein A^2 is phenyl 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)$_2$.

7. The compound of claim 3, wherein A^2 is phenyl substituted by C_{1-4} alkoxyl, cyano, or halogen.

8. The compound of claim 2, 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)$_2$.

9. A compound represented by Formula I-A:



(I-A)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is methyl;

R^2 is hydrogen;

X^1 is -C(O)N(H)C(H)(CF_3)-ψ, -C(O)N(H)($C(CH_3)_2$)-ψ, or -C(O)N(H)(C(H)(CH_3))-ψ, where ψ is a bond to A^1;

A^1 is cyclopropyl; and

A^2 is a cyclic group selected from:

- phenyl 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; and
- 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.

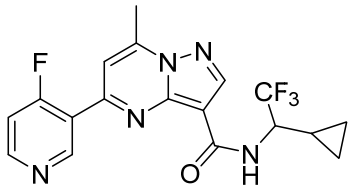
10. The compound of claim 9, wherein A^2 is phenyl substituted by 1, 2, or 3 substituents independently selected from the group consisting of C_{1-4} haloalkyl, C_{1-4} alkoxyl, C_{3-5} cycloalkyl, cyano, and halogen.

11. The compound of claim 9, 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, and hydroxyl.

12. The compound of claim 10, wherein X^1 is -C(O)N(H)(C(H)(CH_3))-ψ.

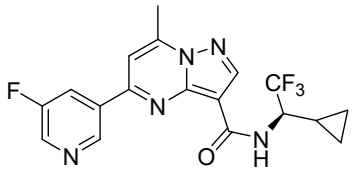
13. The compound of claim 11, wherein X^1 is -C(O)N(H)C(H)(CF_3)-ψ.

14. The compound of claim 9, wherein the compound is



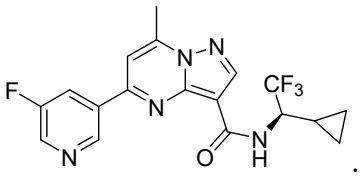
or a pharmaceutically acceptable salt thereof.

15. The compound of claim 9, wherein the compound is



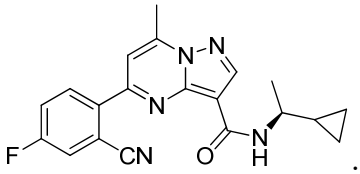
or a pharmaceutically acceptable salt thereof.

16. The compound of claim 15, wherein the compound is



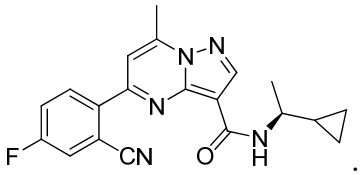
.

17. A compound having the following formula or a pharmaceutically acceptable salt thereof:



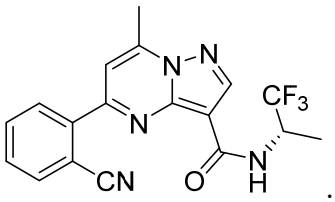
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18. The compound of claim 17, wherein the compound is



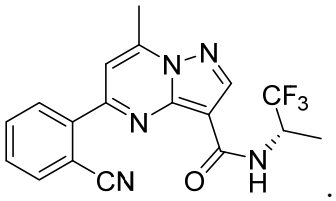
.

19. A compound having the following formula or a pharmaceutically acceptable salt thereof:



.

20. The compound of claim 19, wherein the compound is



21. A pharmaceutical composition, comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

22. A pharmaceutical composition, comprising a compound of claim 9 and a pharmaceutically acceptable carrier.

23. A pharmaceutical composition, comprising a compound of claim 14 and a pharmaceutically acceptable carrier.

24. A pharmaceutical composition, comprising a compound of claim 15 and a pharmaceutically acceptable carrier.

25. A pharmaceutical composition, comprising a compound of claim 16 and a pharmaceutically acceptable carrier.

26. A pharmaceutical composition, comprising a compound of claim 17 and a pharmaceutically acceptable carrier.

27. A pharmaceutical composition, comprising a compound of claim 18 and a pharmaceutically acceptable carrier.

28. A pharmaceutical composition, comprising a compound of claim 19 and a pharmaceutically acceptable carrier.

29. A pharmaceutical composition, comprising a compound of claim 20 and a pharmaceutically acceptable carrier.

30. A compound of claim 1 for use in 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.

31. Use of a compound of claim 1 in the manufacture of a medicament for 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.