

HETEROCYCLIC COMPOUNDS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This PCT application claims the priority benefit of U.S. Provisional Application No. 63/501,005, filed May 9, 2023, which is incorporated herein by reference in its entirety.

REFERENCE TO SEQUENCE LISTING SUBMITTED ELECTRONICALLY
VIA EFS-WEB

[0002] The content of the electronically submitted sequence listing (Name: 5411_003PC01_Seqlisting_ST26; Size: 29,305 bytes; and Date of Creation: May 8, 2024) submitted in this application is incorporated herein by reference in its entirety.

FIELD OF THE DISCLOSURE

[0003] The present disclosure relates to compounds that can promote remyelination. Specifically, the disclosure relates to PDGFR α inhibitors and the use of such inhibitors to treat diseases associated with impaired myelination (*e.g.*, multiple sclerosis).

BACKGROUND OF THE DISCLOSURE

[0004] Proper myelination by oligodendrocytes is essential for central nervous system (CNS) development and function. Gacem *et al.*, *Life* 11(4): 327 (Apr. 2021). Myelin maintains axon potential conduction velocity of neural signals and provides metabolic support to axons, supporting their survival. During normal development, oligodendrocyte progenitor cells (OPCs) undergo morphological and molecular changes as they differentiate into oligodendrocytes that can myelinate axons. Accordingly, any abnormal developmental processes or pathogenic immune activation and failure of oligodendrocytes to myelinate axons or loss of myelin can lead to neurodegenerative diseases such as multiple sclerosis.

[0005] Multiple sclerosis (MS) is generally characterized by inflammation and demyelination of neuronal axons. Patients with early MS often suffer from isolated immune attacks with effective remyelination and recovery between attacks. However, as the disease progresses, MS patients have a reduced ability to effectively remyelinate resulting in

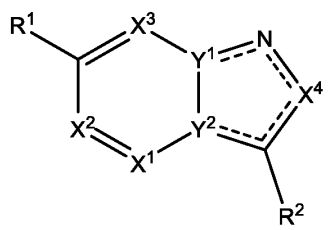
permanent neurological disability. Current treatments for MS and other neurodegenerative diseases largely focus on reducing the immune attack on myelin but do not restore myelin on the damaged neuronal axons.

[0006] Therefore, there remains a need for a new and more effective treatment of such demyelinating diseases, particularly treatments that can induce the remyelination of demyelinated, vulnerable neuronal axons.

BRIEF SUMMARY OF THE DISCLOSURE

[0007] The present disclosure describes the discovery that compounds that inhibit PDGFR α can promote remyelination. Compounds and methods of the present disclosure are therefore useful for treating diseases associated with demyelination (*e.g.*, hypomyelination).

[0008] Provided herein is a compound of Formula I:



[0009] or a pharmaceutically acceptable salt or solvate thereof, wherein:

===== indicates a single bond or a double bond such that all valences are satisfied;

X¹, X², X³, and X⁴ are selected from N and CR^a, with the proviso that not more than two of X¹, X², X³, and X⁴ are N;

one of Y¹ and Y² is N and the other of Y¹ and Y² is C;

each R^a is independently selected from H, halo, C₁-C₄alkyl, and C₁-C₄alkoxy;

R¹ is selected from C₁-C₄alkyl, C₃-C₈cycloalkyl, 3-8 membered heterocyclyl, heteroaryl, aryl, and C₁-C₈alkoxy, all of which can be optionally substituted with one, two, three, four, five, or six substituents selected from halo, hydroxy, oxo, C₁-C₄alkyl, aminoC₁-C₄alkyl, hydroxyC₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₄alkoxyC₁-C₄alkyl, 3-8 membered heterocyclyl, and 3-8 membered heterocyclylC₁-C₄alkyl, with the proviso that the number of substituents does not exceed the number of substitutable positions;

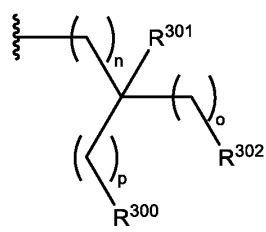
R² is selected from cycloalkyl, cycloalkenyl, alkyl, oxoalkylamino, aminoalkylamino, amino, heterocyclyl, heteroaryl, aminoheterocyclyl, heterocyclylamino,

and aminoalkylamino, all of which can be optionally substituted with one or more substituents selected from D, halo, hydroxy, oxo, and C₁-C₄alkyl;

R² is substituted by one, two, or three R³;

R³ is selected from aryl, heteroaryl, -C(O)R³¹, -C(O)OR³¹, -C(O)NR³¹R³², -S(O)₂NR³¹R³², -S(O)(NR³³)R³¹, -S(O)₂R³¹, -S(O)(NR³³)NR³¹R³², -C(S)NR³¹R³², C₃-C₈cycloalkyl, 3-8 membered heterocyclyl, and C₁-C₄alkyl, all of which can be optionally substituted with one, two, three, four, or five R³⁰;

each R³⁰ is independently selected from D, halo, aryl, -OR³⁰⁰, -NR³⁰⁰R³⁰³, -S(O)_rR³⁰⁰, -C(O)R³⁰⁰, -C(=CR³⁴R³⁵)R³⁰⁰, and



r is selected from 0, 1, and 2;

each R³⁰⁰ is independently selected from C₁-C₆alkyl, C₃-C₇cycloalkyl, aryl, heteroaryl, 3-8 membered heterocyclyl, and 3-8 membered heterocyclylaryl, all of which can be optionally substituted with one, two, three, four, or five substituents selected from D, halo, hydroxy, amino, alkylamino, cyano, C₁-C₄alkyl, C₁-C₄haloalkyl, and C₁-C₄alkoxy;

each R³⁰¹ is independently selected from H, halo, and C₁-C₄alkyl;

each R³⁰² is independently selected from H, F, hydroxyl, amino, alkylamino, oxo, and C₁-C₄alkoxy;

each R³⁰³ is independently selected from H and C₁-C₄alkyl;

n, o, and p are each independently selected from 0, 1, 2, 3, and 4;

each R³¹ is independently selected from C₁-C₈alkyl, arylC₁-C₄alkyl, heteroarylC₁-C₄alkyl, heterocyclyl, heterocyclylC₁-C₄alkyl, cycloalkyl, and cycloalkylC₁-C₄alkyl, all of which can be optionally substituted with one, two, three, four, or five substituents selected from D, halo, cyano, hydroxy, amino, -OCF₃, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, hydroxyc₁-C₄alkyl, -S(O)₂NR³⁰⁴R³⁰⁵, -C(O)OR³⁰⁴R³⁰⁵, -C(O)NR³⁰⁴R³⁰⁵, and -NR³⁰⁴C(O)R³⁰⁵;

each R³⁰⁴ and R³⁰⁵ is independently selected from H and C₁-C₄alkyl;

each R³² is independently selected from H and C₁-C₄alkyl; or

R^{31} and R^{32} together with the atom to which they are connected to form a 5-8 membered heterocycyl, optionally substituted with one, two, three, four, or five substituents selected from D, halo, cyano, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, and $-C(O)NR^{34}R^{35}$; and

each R^{34} and R^{35} is independently selected from H, C_1 - C_4 alkyl, and C_1 - C_4 haloalkyl; and

each R^{33} is independently selected from H, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, and $-C(O)R^{34}$; or

R^{31} and R^{33} together with the atoms to which they are connected form a 4-8 membered heterocycyl.

[0010] In some aspects, Y^1 is N and Y^2 is C.

[0011] In some aspects, Y^1 is C and Y^2 is N.

[0012] In some aspects, X^1 is N, X^2 is CR^a , X^3 is CR^a , and X^4 is CR^a .

[0013] In some aspects, X^1 is CR^a , X^2 is N, X^3 is CR^a , and X^4 is CR^a .

[0014] In some aspects, X^1 is CR^a , X^2 is CR^a , X^3 is N, and X^4 is CR^a .

[0015] In some aspects, X^1 is CR^a , X^2 is CR^a , X^3 is CR^a , and X^4 is N.

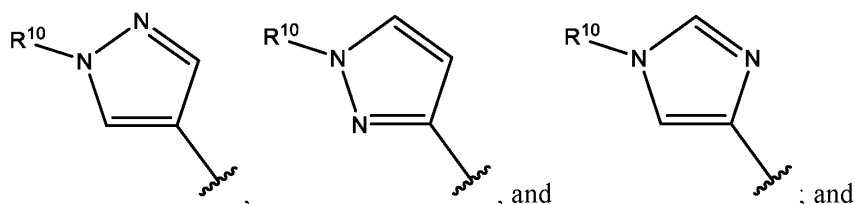
[0016] In some aspects, X^1 is CR^a , X^2 is CR^a , X^3 is CR^a , and X^4 is CR^a .

[0017] In some aspects, R^1 is 5- or 6-membered heteroaryl optionally substituted with C_1 - C_4 alkyl or oxo.

[0018] In some aspects, R^2 is substituted with one R^3 .

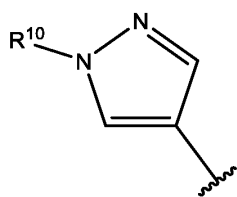
[0019] In some aspects, R^1 is an optionally substituted pyrazolyl.

[0020] In some aspects, R^1 is selected from:



[0021] R^{10} is selected from H, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, amino C_1 - C_4 alkyl, hydroxy C_1 - C_4 alkyl, and C_1 - C_4 alkylsulfonyl, wherein the C_1 - C_4 alkyl, C_1 - C_4 alkoxy, amino C_1 - C_4 alkyl, hydroxy C_1 - C_4 alkyl, and C_1 - C_4 alkylsulfonyl can be optionally substituted by one or more substituents selected from hydroxyl, C_1 - C_4 alkoxy, $NR^{10a}R^{10b}$, halo, and deuterium, wherein R^{10a} and R^{10b} are selected from hydrogen and C_1 - C_4 alkyl, or wherein R^{10a} and R^{10b} taken together with the nitrogen atom to which they are attached form a 4- to 8-membered ring.

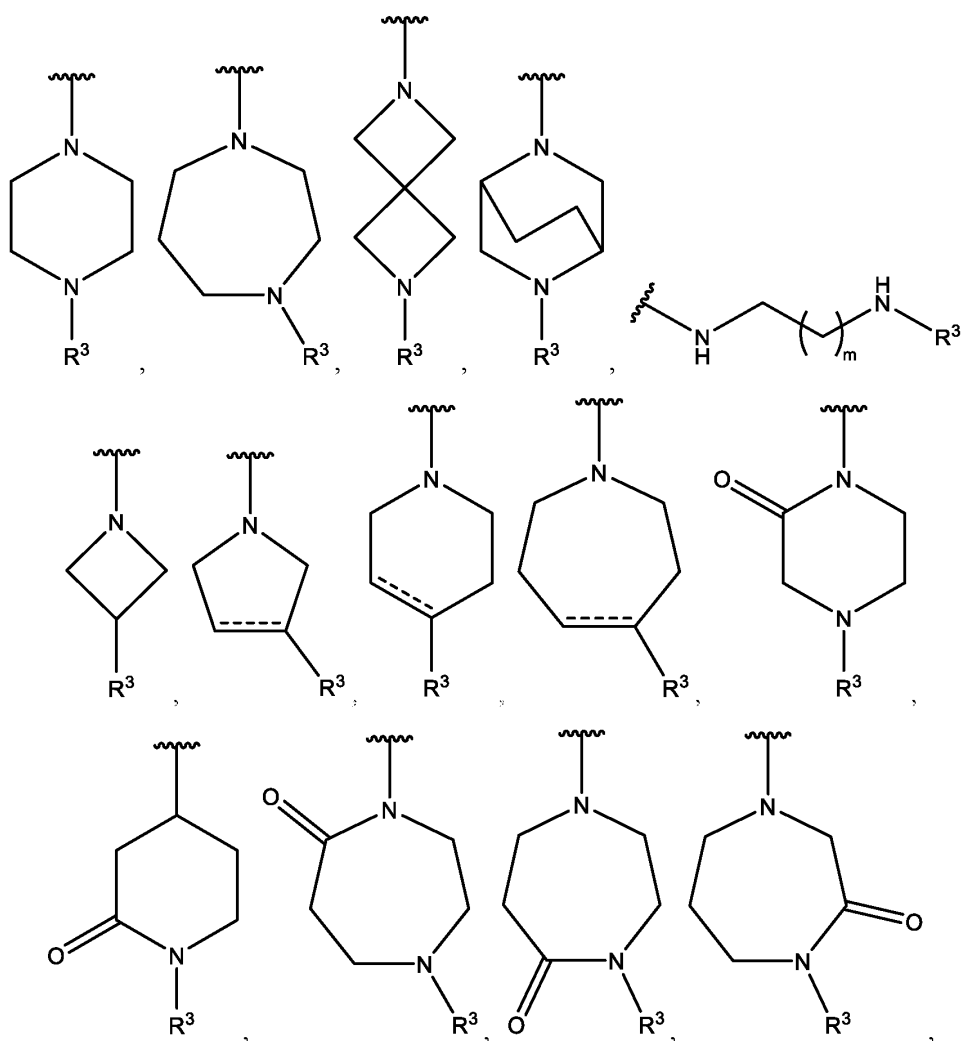
[0022] In some aspects, R^1 is

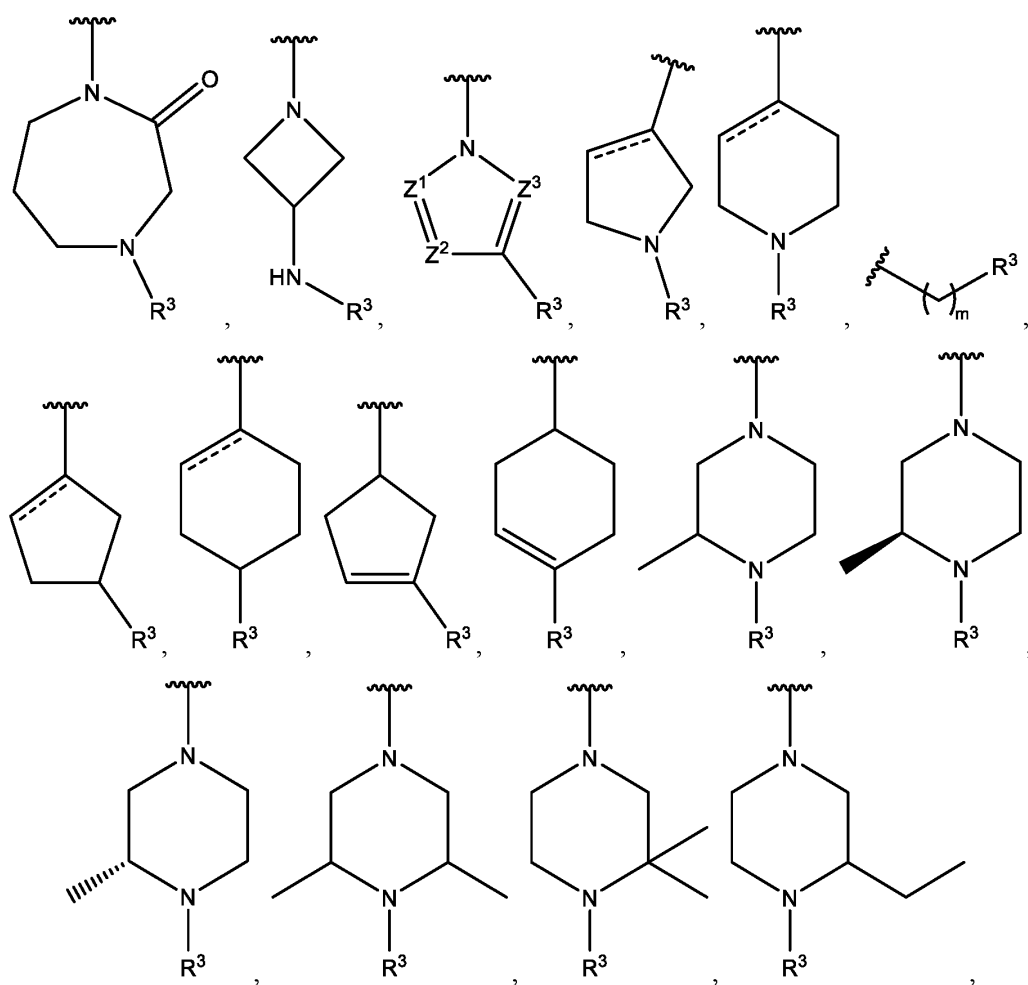


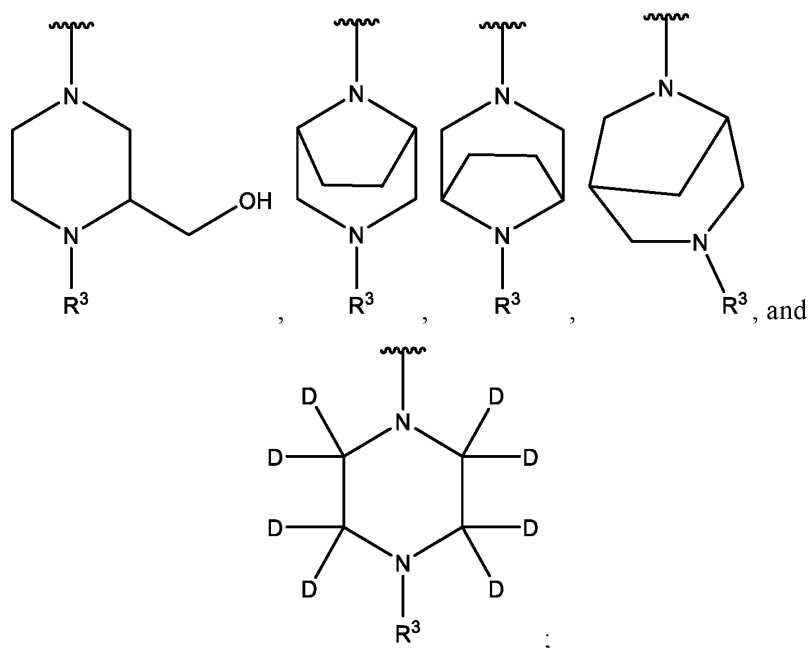
[0023] In some aspects, R^{10} is CH_3 .

[0024] In some aspects, R^2 is heterocyclyl.

[0025] In some aspects, R^2 is selected from:





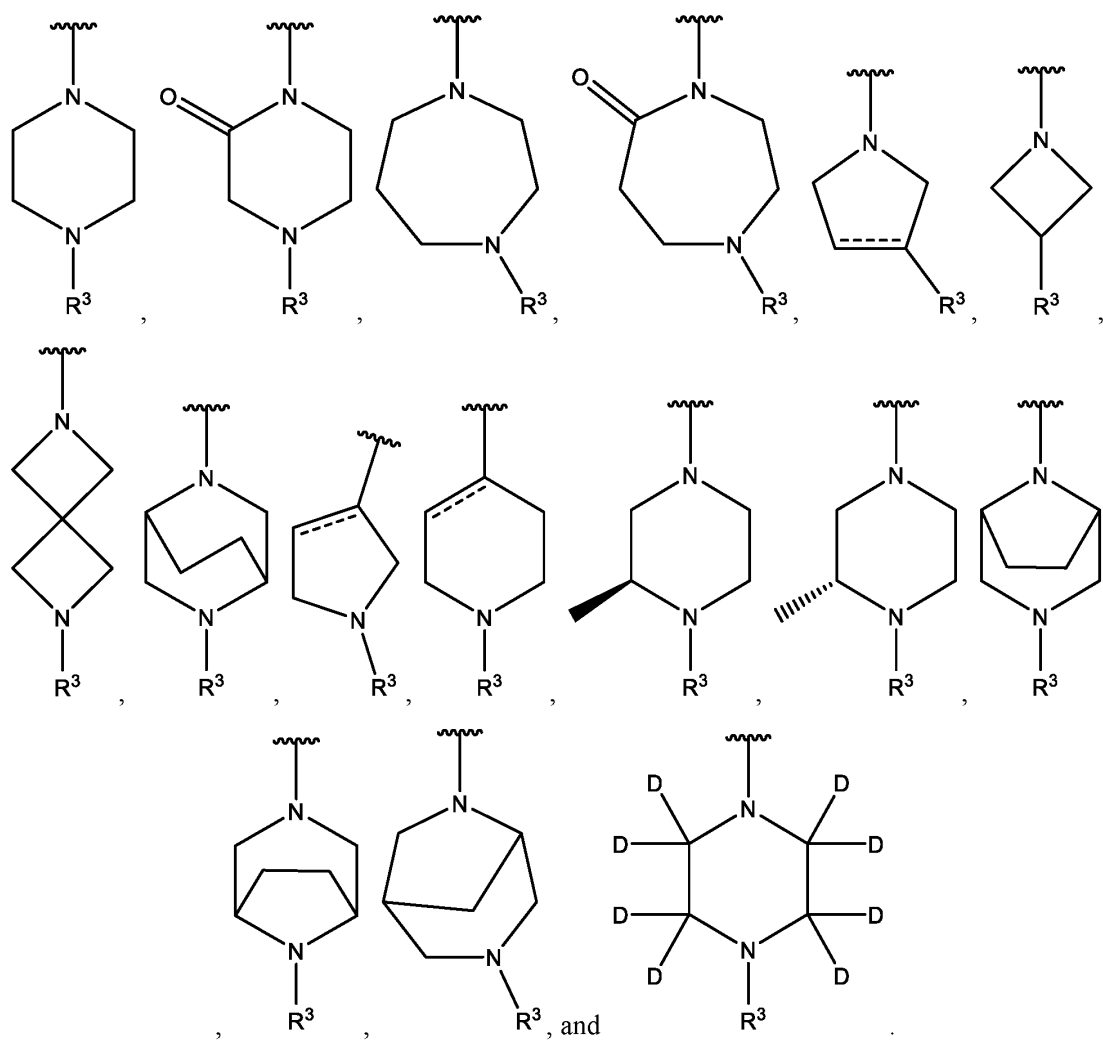


[0026] ===== indicates a single bond or a double bond such that all valences are satisfied;

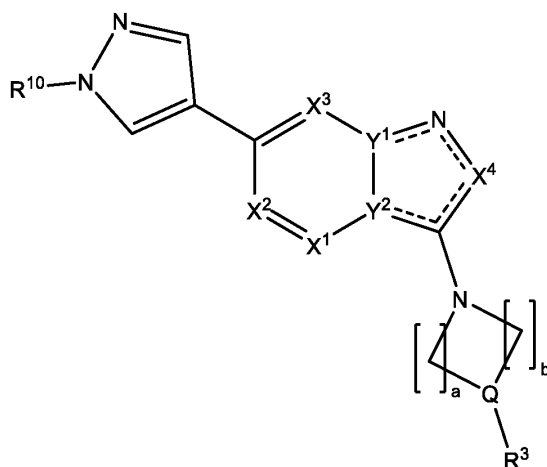
[0027] m is selected from 0, 1, 2, 3, 4, 5, and 6; and

[0028] Z^1 , Z^2 , and Z^3 are selected from N and CR^a .

[0029] In some aspects, R^2 is selected from:



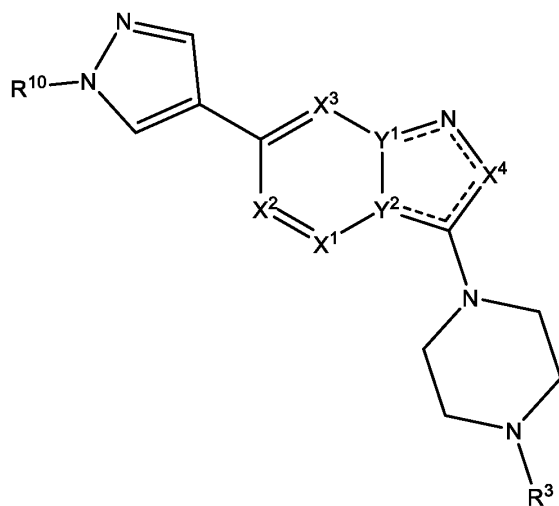
[0030] In some aspects, the compound, or a pharmaceutically acceptable salt or solvate thereof, has Formula Ia:



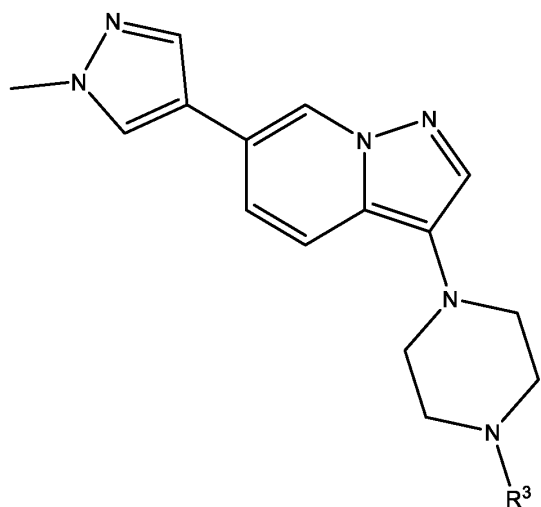
[0031] wherein a and b are each independently selected from 1, 2, and 3; and

[0032] Q is selected from -CH- and -N-, with the proviso that if Q is -N-, a and b are not 1.

[0033] In some aspects, the compound, or a pharmaceutically acceptable salt or solvate thereof, has Formula II:

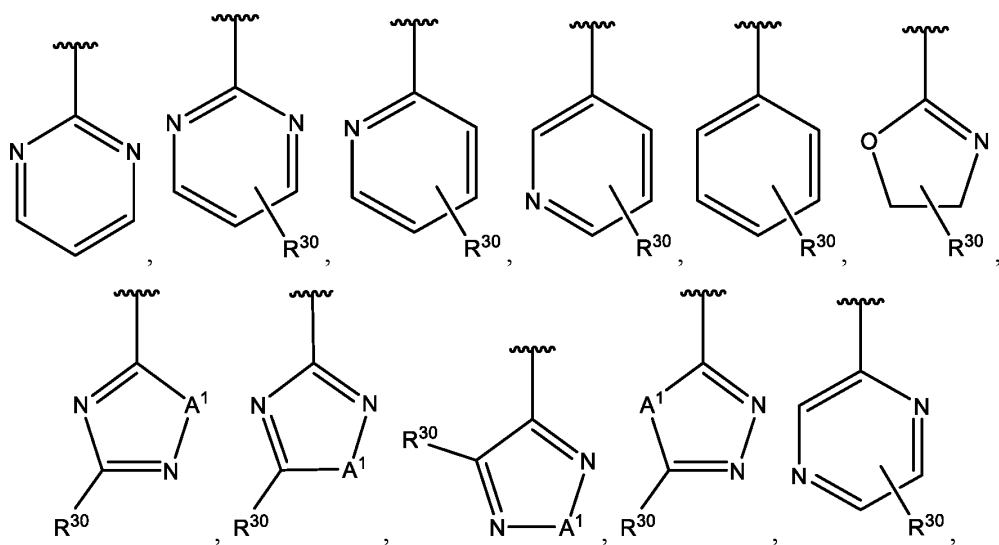


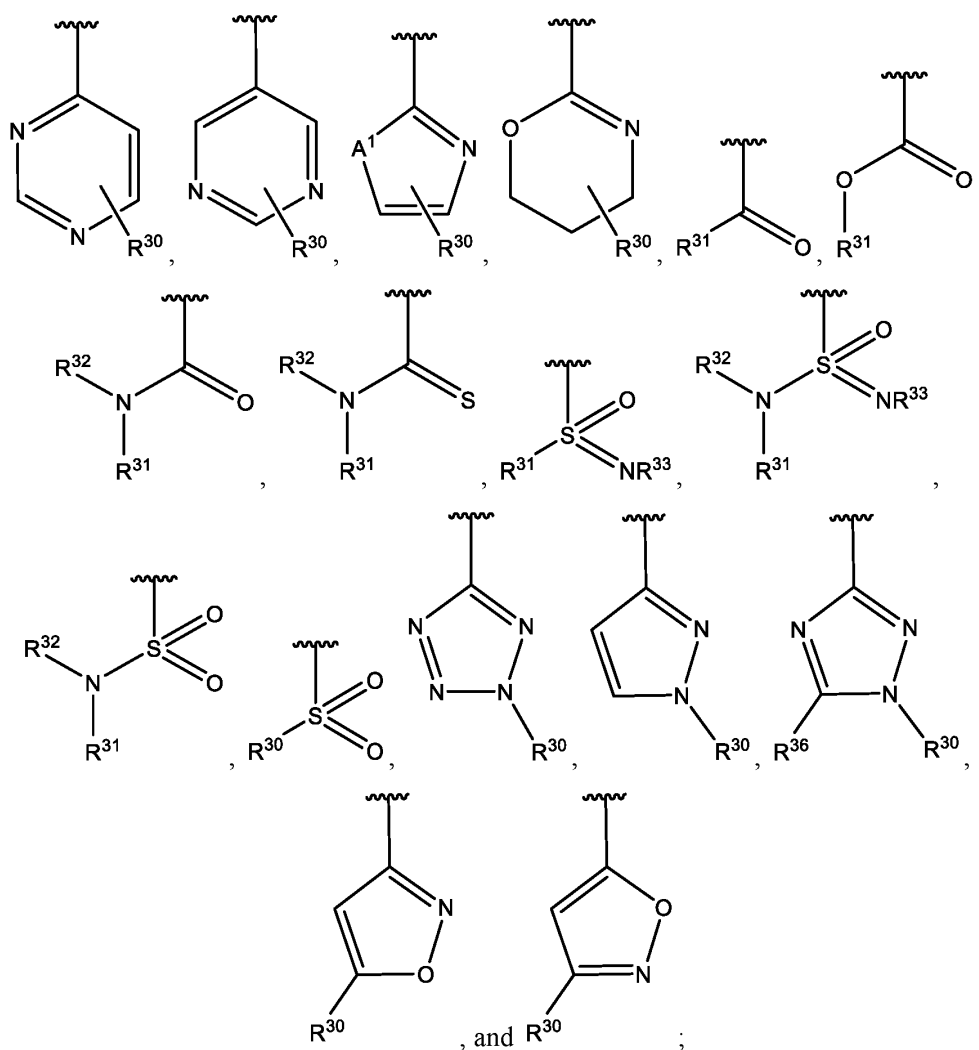
[0034] In some aspects, the compound, or a pharmaceutically acceptable salt or solvate thereof, has Formula IIa:



[0035] In some aspects, R^3 is heteroaryl optionally substituted with one, two, three, four, or five R^{30} .

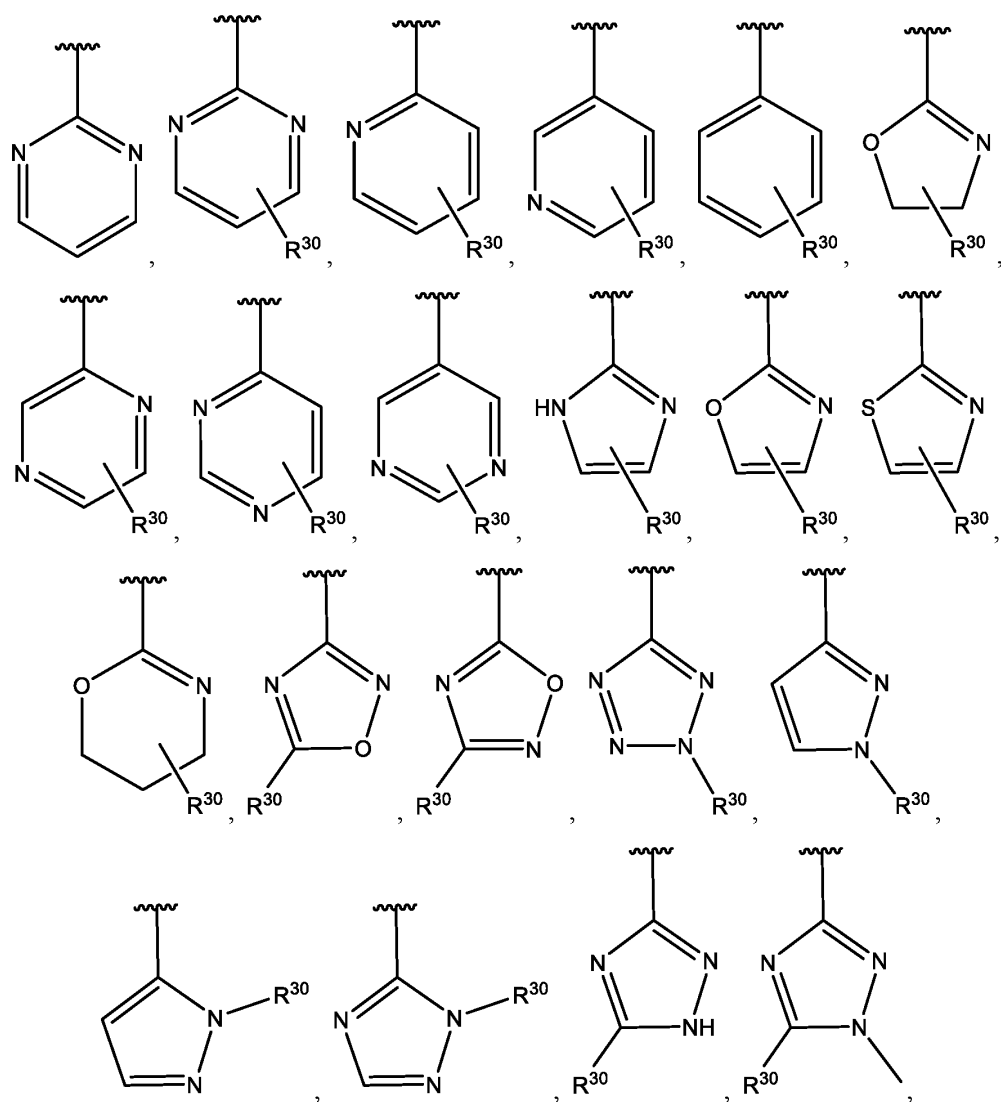
[0036] In some aspects, R^3 is selected from:

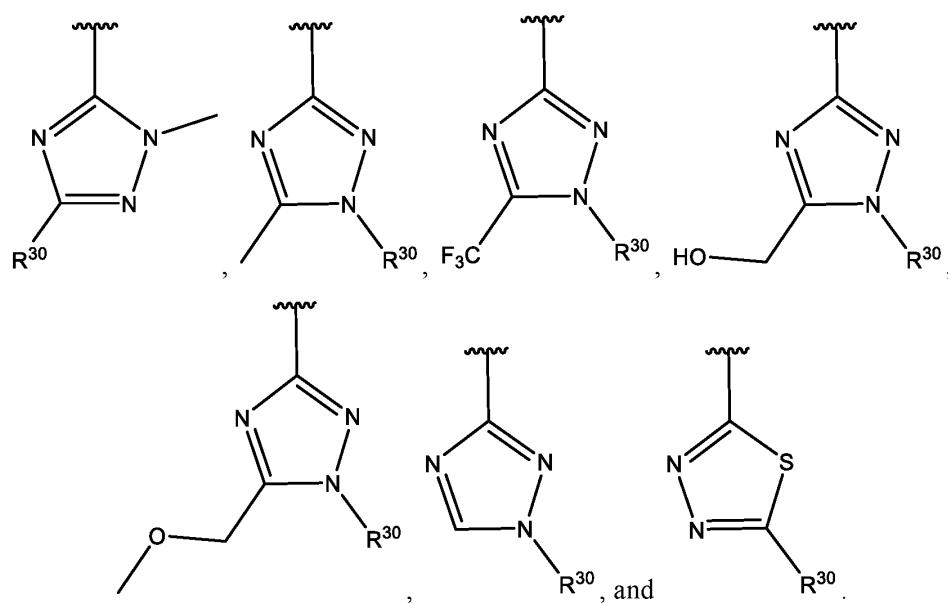




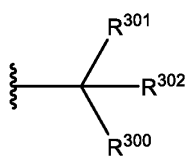
[0037] wherein A¹ is selected from O, S, and NR³⁷, R³⁶ is selected from hydrogen, optionally substituted C₁-C₆alkyl, and optionally substituted C₁-C₆alkylaryl, and R³⁷ is selected from hydrogen and C₁-C₆alkyl.

[0038] In some aspects, R³ is selected from:

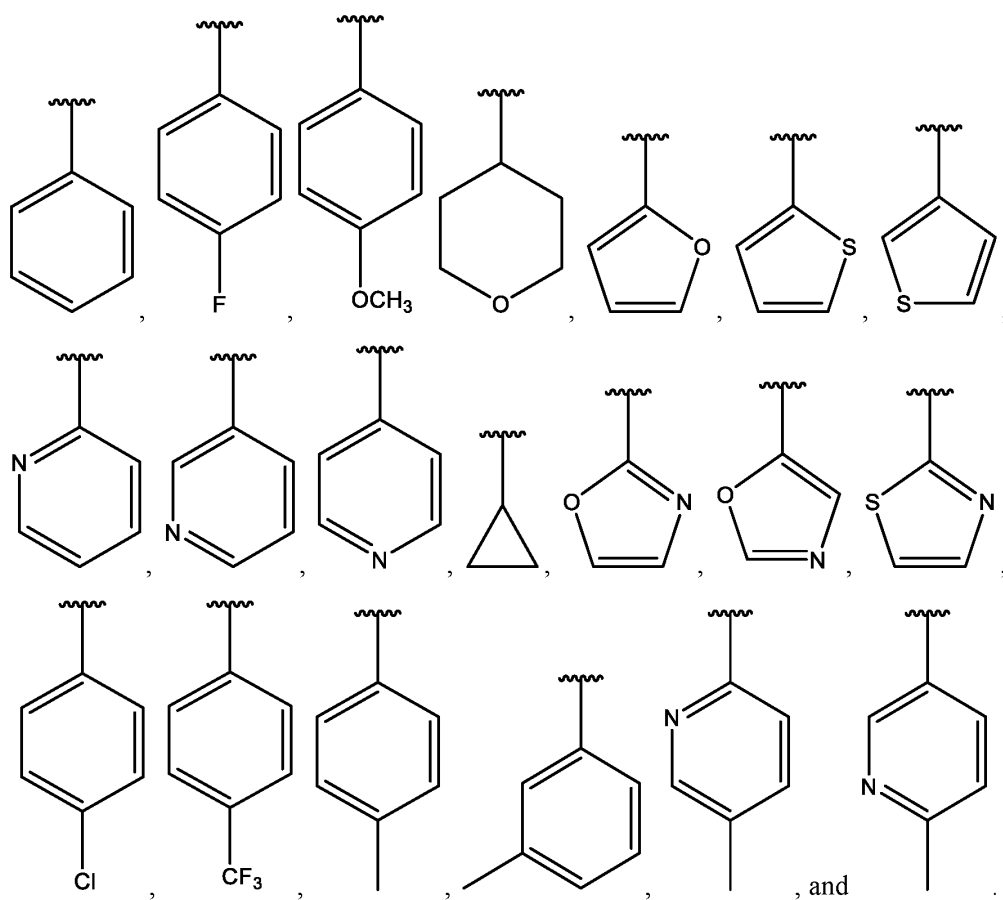




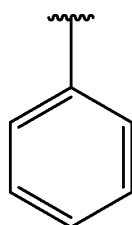
[0039] In some aspects, R^{30} is:



[0040] In some aspects, R^{300} is selected from:

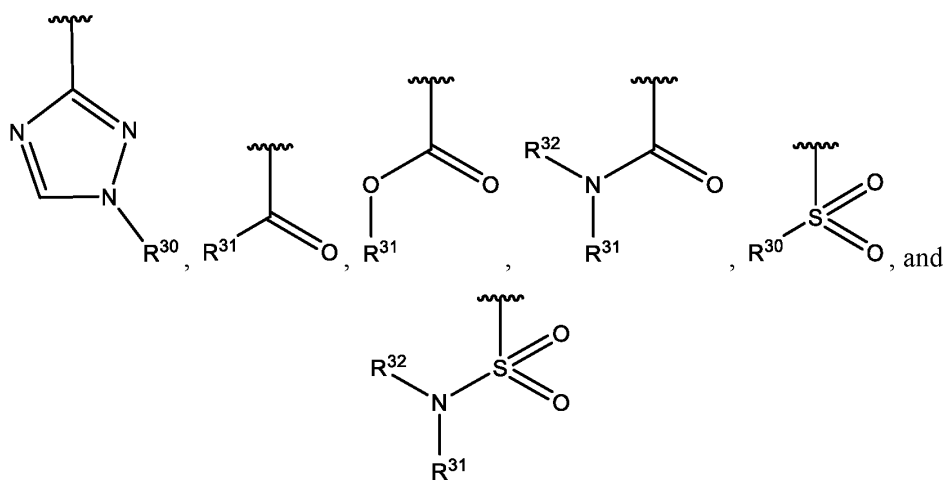


[0041] In some aspects, R^{300} is:

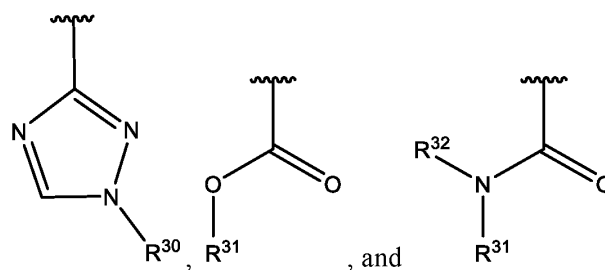


[0042] In some aspects, R^{301} is H and R^{302} is -OH or CH_3 .

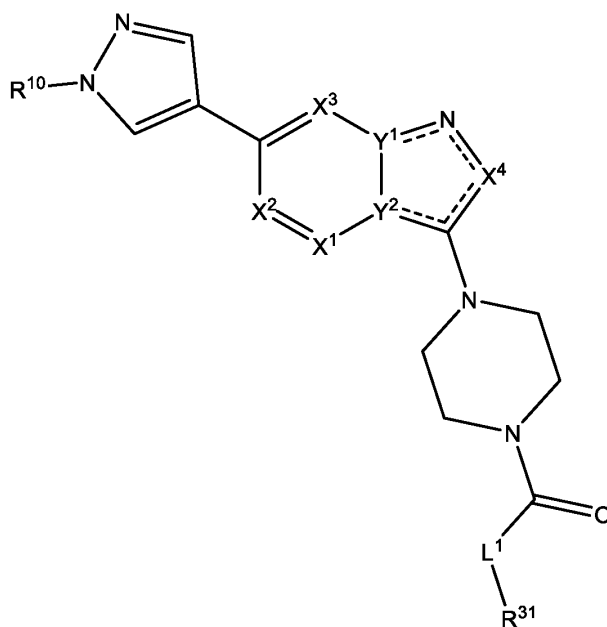
[0043] In some aspects, R^3 is selected from:



[0044] In some aspects, R^3 is selected from:

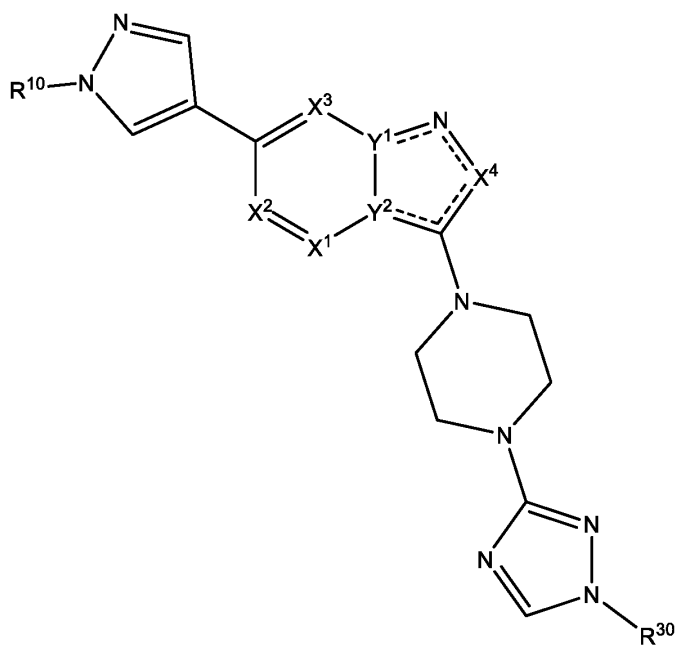


[0045] In some aspects, the compound, or a pharmaceutically acceptable salt or solvate thereof, has Formula IV:

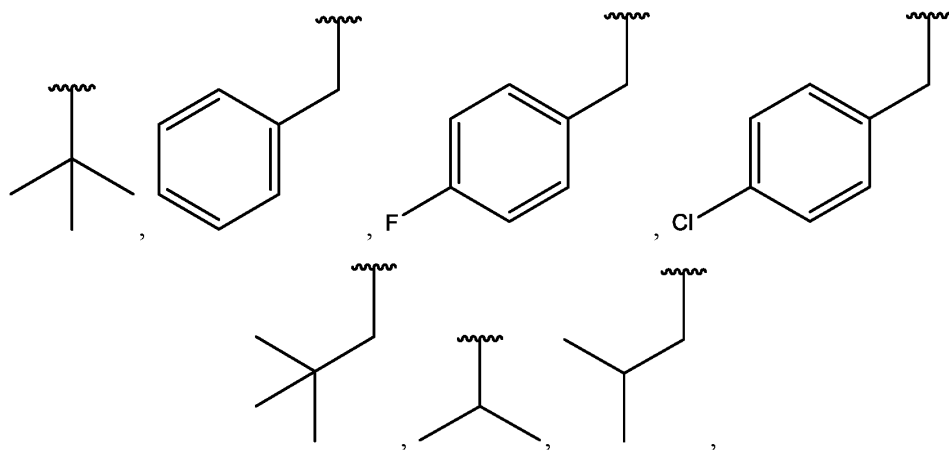


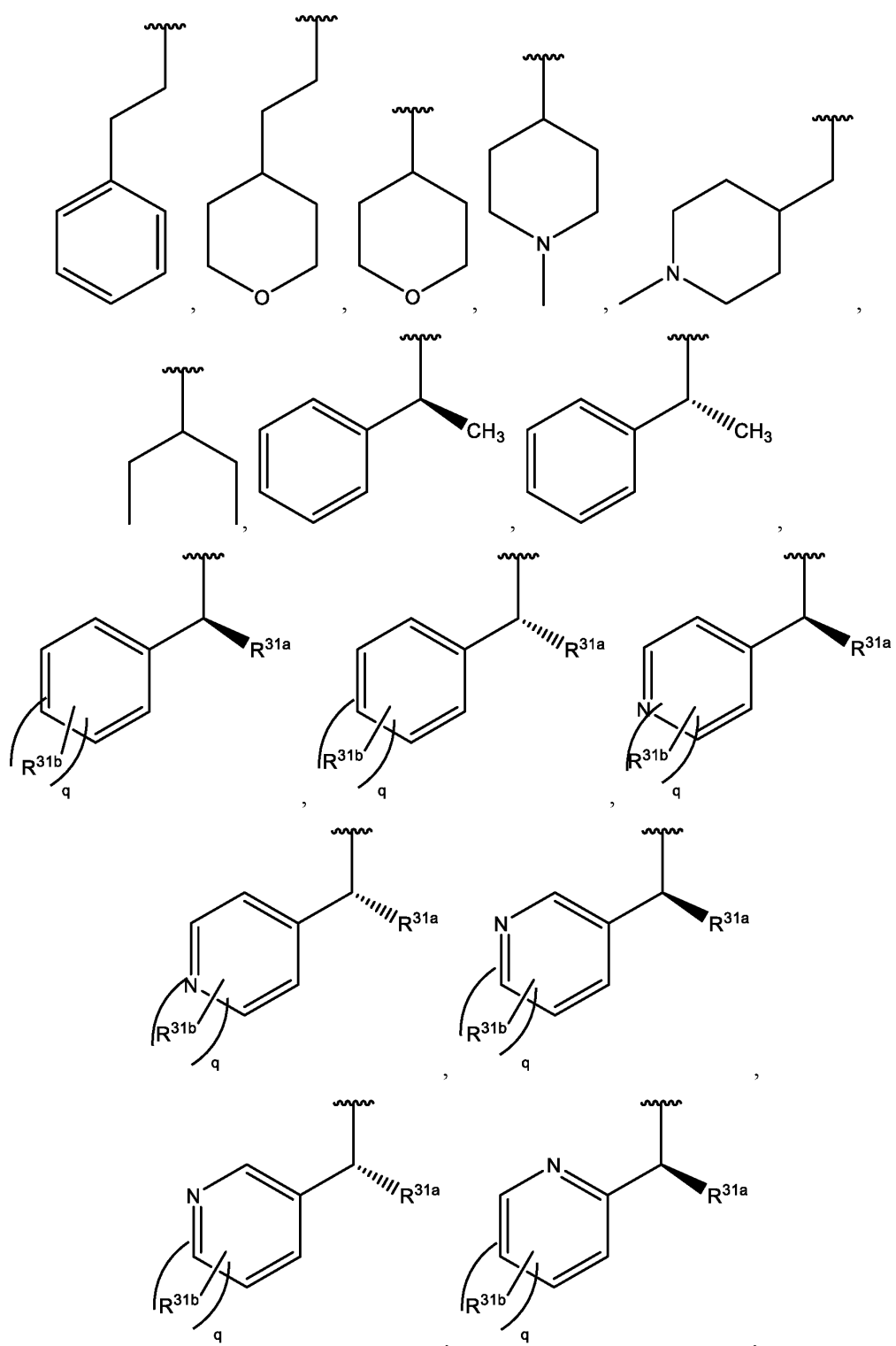
wherein L^1 is NH or O.

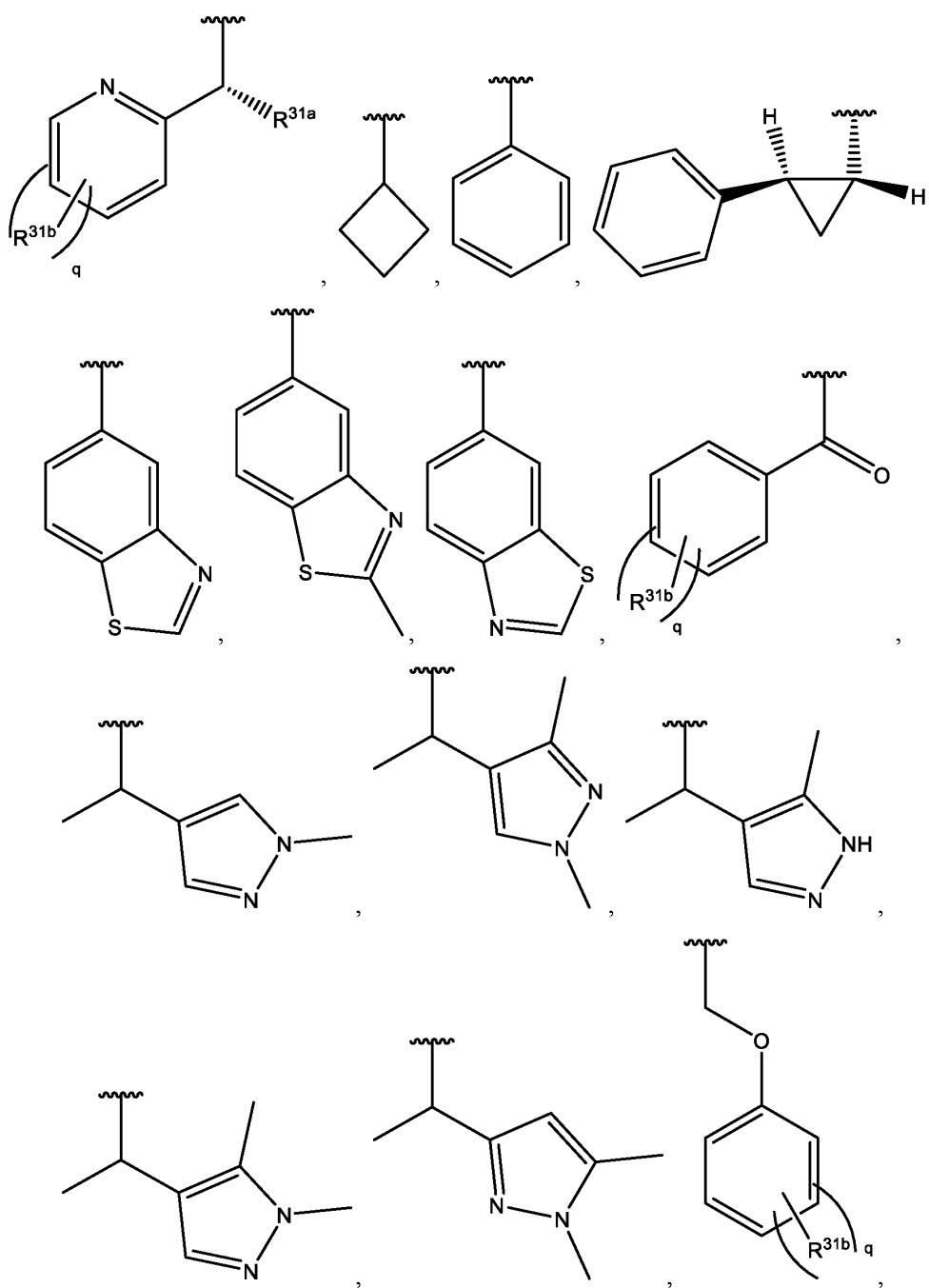
[0046] In some aspects, the compound, or a pharmaceutically acceptable salt or solvate thereof, has Formula V:



[0047] In some aspects, R^{31} is selected from:







[0048] wherein R^{31a} is selected from H, D, alkylamino, optionally substituted C₁-C₄alkyl, C₁-C₄alkoxy, amino, and C₁-C₄haloalkyl,

- [0049] each R^{31b} is independently selected from H, D, halo, hydroxy, amino, cyano, alkylamino, optionally substituted C₁-C₄alkyl, C₁-C₄haloalkyl, optionally substituted C₁-C₄alkoxy, and C₃-C₆cycloalkyl, and q is 1, 2, or 3.
- [0050] In some aspects, the compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, is selected from any one of the compounds of Table 1.
- [0051] In some aspects, the compound of Formula I can exhibit one or more of the following properties: (i) promote the differentiation of an OPC into an oligodendrocyte, (ii) promote the expression of a protein associated with oligodendrocyte differentiation and/or myelination (*e.g.*, G-protein coupled receptor 17 (GPR17), myelin basic protein (MBP), ASPA, GST-pi, CC1, myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, proteolipid protein 1 (PLP1), or a combination thereof), (iii) promote the myelination of an axon, (iv) promote the remyelination of a demyelinated axon, (v) inhibit PDGFR α kinase activity, (vi) achieve a brain to plasma ratio of greater than 0.1 when systemically administered to a subject, and (vii) any combination thereof.
- [0052] In some aspects, the compound of Formula I can inhibit PDGFR α kinase activity.
- [0053] In some aspects, the compound of Formula I can inhibit PDGFR α kinase activity with an IC₅₀ of less than 500 nM, less than 400 nM, less than 300 nM, less than 200 nM, less than 100 nM, less than 75 nM, less than 50 nM, less than 40 nM, less than 30 nM, less than 20 nM, less than 10 nM, less than 5 nM, less than 2.5 nM, less than 1 nM, less than 0.5 nM, or less than 0.2 nM.
- [0054] In some aspects, the IC₅₀ of the PDGFR α inhibitor of Formula I is determined using an enzymatic PDGFR α kinase assay (*e.g.*, Promega kinase assay described in Example 131).
- [0055] In some aspects, the enzymatic PDGFR α kinase assay comprises 20 ng of purified PDGFR α protein, 150 μ M of ATP and 1 μ g of substrate, Poly (Glu4Tyr1) in a volume of 15 μ l.
- [0056] In some aspects, the compound of Formula I can inhibit PDGFR α kinase activity with an IC₅₀ of from about 500 nM to about 0.001 nM, from about 400 nM to about 0.001 nM, from about 300 nM to about 0.001 nM, from about 200 nM to about 0.001 nM, from about 100 nM to about 0.001 nM, from about 75 nM to about 0.001 nM, from about 50 nM to about 0.001 nM, from about 40 nM to about 0.001 nM, from about 30 nM to about 0.001

nM, from about 20 nM to about 0.001 nM, from about 10 nM to about 0.001 nM, from about 5 nM to about 0.001 nM, from about 2.5 nM to about 0.001 nM, from about 1 nM to about 0.001 nM, from about 0.5 nM to about 0.001 nM, or from about 0.2 nM to about 0.001 nM.

- [0057] In some aspects, the disclosure provides a compound that can inhibit a PDGFR α activity of a cell and can further exhibit one or more of the following properties: (i) promote the differentiation of an OPC into an oligodendrocyte, (ii) promote the expression of a protein associated with oligodendrocyte differentiation and/or myelination (*e.g.*, G-protein coupled receptor 17 (GPR17), myelin basic protein (MBP), ASPA, GST-pi, CC1, myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, proteolipid protein 1 (PLP1), or a combination thereof), (iii) promote the myelination of an axon, (iv) promote the remyelination of a demyelinated axon, (v) inhibit PDGFR α kinase activity, (vi) achieve a brain to plasma ratio of greater than 0.1 when systemically administered to a subject, or (vii) any combination thereof.
- [0058] In some aspects, the compound can inhibit PDGFR α kinase activity with an IC₅₀ of less than 500 nM, less than 400 nM, less than 300 nM, less than 200 nM, less than 100 nM, less than 75 nM, less than less than 50 nM, less than 40 nM, less than 30 nM, less than 20 nM, less than 10 nM, less than 5 nM, or less than 2 nM.
- [0059] In some aspects, the IC₅₀ of the PDGFR α inhibitor is determined using an enzymatic PDGFR α kinase assay (*e.g.*, Promega™ kinase assay described in Example 131).
- [0060] In some aspects, the enzymatic PDGFR α kinase assay comprises 20 ng of purified PDGFR α protein, 150 μ M of ATP and 1 μ g of substrate, Poly (Glu4Tyr1) in a volume of 15 μ l.
- [0061] The disclosure also provides a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.
- [0062] The disclosure also provides a kit comprising a compound disclosed herein, or a pharmaceutically acceptable salt or solvate thereof, or a composition disclosed herein, and instructions for use.
- [0063] The disclosure also provides a method of producing a PDGFR α inhibitor comprising synthesizing a compound disclosed herein.

- [0064] The disclosure also provides a compound disclosed herein, or a pharmaceutical composition disclosed herein, for use as a medicament.
- [0065] The disclosure also provides a compound disclosed herein, or a pharmaceutical composition disclosed herein, for use in therapy.
- [0066] The disclosure also provides a method of treating a demyelinating disease in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a compound disclosed herein or a pharmaceutical composition disclosed herein.
- [0067] The disclosure also provides a method of improving a subject's performance in a test for assessing one or more symptoms associated with a demyelinating disease, comprising administering to the subject a therapeutically effective amount of a compound disclosed herein or a pharmaceutical composition disclosed herein, wherein after the administration, the subject's performance in the test is improved as compared to a reference subject (*e.g.*, the subject prior to the administration).
- [0068] In some aspects, the test is selected from one or more of a visual evoked potential (VEP) test, a multifocal visual evoked potential (mfVEP) test, a low contrast visual acuity (LC-VA) test, a magnetic resonance imaging (MRI) (*e.g.*, magnetization transfer ratio (MTR), myelin water fraction (MWF), quantitative susceptibility mapping (QSM), and T2 imaging), an electromyography (EMG), a nerve conduction velocity (NCV) test, an Extended Disability Status Scale (EDSS), a timed walk test (*e.g.*, timed 25-foot walk), a Nine-Hole Peg Test (9HPT), an ocular coherence tomograph (OCT), a quality of life measure test (*e.g.*, Multiple Sclerosis Quality of Life-54 and Vision-Related Quality of Life), cognitive assessment (*e.g.*, Symbol-Digit Modalities Test or Montreal Cognitive Assessment), or combinations thereof.
- [0069] In some aspects, the demyelinating disease comprises one or more of an acute disseminated encephalomyelitis (ADEM), acute hemorrhagic leukoencephalitis, acute transverse myelitis, adrenoleukodystrophy, adrenomyeloneuropathy, Alexander disease, Alzheimer's disease, aminoacidurias, amyotrophic lateral sclerosis, anti-MAG peripheral neuropathy, anti-MOG associated spectrum, Balo concentric sclerosis, brain injury, CAMFAK syndrome, Canavan disease, carbon monoxide toxicity, central pontine myelinolysis, cerebral hypoxia, cerebral ischemia, Charcot-Marie-Tooth disease, chronic inflammatory demyelinating polyneuropathy, chronic traumatic encephalopathy, clinically isolated syndrome (CIS), congenital cataract, copper deficiency associated condition,

delayed post-hypoxic leukoencephalopathy, diffuse cerebral sclerosis of Schilder, diffuse myelinoclastic sclerosis, extrapontine myelinolysis Gaucher disease, Guillain–Barré syndrome, hereditary neuropathy, hereditary neuropathy with liability to pressure palsy, HTLV-1-associated myelopathy, Hurler syndrome, hypomyelination, hypoxic brain injury, Krabbe disease, Leber hereditary optic atrophy and related mitochondrial disorders, leukodystrophic disorders, Marchiafava-Bignami disease, metachromatic leukodystrophy, multiple sclerosis (*e.g.*, primary progressive multiple sclerosis (PPMS), relapsing-remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), progressive relapsing multiple sclerosis, Marburg multiple sclerosis, tumefactive multiple sclerosis, and optic-spinal multiple sclerosis), multiple system atrophy, myelinoclastic disorders, myelopathy, nerve injury, neuromyelitis optica (NMO), Niemann-Pick disease, optic neuropathy, optic neuritis (*e.g.*, acute optic neuritis and chronic relapsing inflammatory optic neuritis (CRION)), osmotic demyelination syndrome, Parkinson’s disease, Pelizaeus-Merzbacher disease, peripheral neuropathy, phenylketonuria, progressive inflammatory neuropathy, progressive multifocal leukoencephalopathy, progressive subcortical ischemic demyelination, reperfusion injury, Schilder disease, solitary sclerosis, spinal cord injury, subacute sclerosing panencephalitis, Tabes dorsalis, Tay-Sachs disease, transverse myelitis, traumatic brain injury, tropical spastic paraparesis, vitamin B12 deficiency, and cerebral palsy.

- [0070] In some aspects, the demyelinating disease is characterized by demyelination of one or more cells within the CNS of the subject.
- [0071] In some aspects, the demyelinating disease is multiple sclerosis.
- [0072] In some aspects, the multiple sclerosis comprises a clinically isolated syndrome (“CIS”), relapsing-remitting MS (“RRMS”), secondary progressive MS (“SPMS”), primary progressive MS (“PPMS”), optic neuritis or transverse myelitis.
- [0073] In some aspects, the demyelinating disease is an optic neuritis.
- [0074] In some aspects, treating the demyelinating disease comprises reducing one or more symptoms associated with the demyelinating disease.
- [0075] In some aspects, the one or more symptoms comprise one or more of fatigue, dizziness, malaise, elevated fever and high body temperature, extreme sensitivity to cold in the hands and feet, weakness and stiffness in muscles and joints, weight changes, digestive or gastrointestinal problems, low blood pressure, high blood pressure, irritability, anxiety,

depression, impaired vision (*e.g.*, blurred vision, double vision, reduction in low contrast visual acuity (LC-VA)), ataxia, clonus, spasms, dysarthria, weakness, clumsiness, hand paralysis, hemiparesis, genital anesthesia, sexual dysfunction, incoordination, paresthesias, ocular paralysis, impaired muscle coordination, loss of sensation, tingling, numbness, pain, neurological symptoms, impaired cognition, unsteady gait, balance problems, dizziness, spastic paraparesis, incontinence, hearing problems, speech problems, loss of olfaction, and agusia.

[0076] The disclosure also provides a method of promoting the myelination of an axon in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound disclosed herein or a pharmaceutical composition disclosed herein.

[0077] In some aspects, promoting the myelination of an axon results in an increase in the expression of one or more of the following markers within the subject: myelin basic protein (MBP) Myelin Oligodendrocyte Glycoprotein (MOG), Oligodendrocyte Specific Protein/Claudin-11, CNPase, proteolipid protein 1 (PLP1), or any combination thereof.

[0078] In some aspects, the myelination of an axon can be determined by visualizing and/or quantifying the expression of one or more of the following markers: myelin basic protein (MBP) Myelin Oligodendrocyte Glycoprotein (MOG), Oligodendrocyte Specific Protein/Claudin-11, CNPase, proteolipid protein 1 (PLP1), or any combination thereof.

[0079] The disclosure also provides method of promoting the remyelination of a demyelinated axon in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound disclosed herein or a pharmaceutical composition disclosed herein.

[0080] In some aspects, promoting the remyelination of a demyelinated axon results in an increase in the expression of one or more of the following markers within the subject: myelin basic protein (MBP) Myelin Oligodendrocyte Glycoprotein (MOG), Oligodendrocyte Specific Protein/Claudin-11, CNPase, proteolipid protein 1 (PLP1), or any combination thereof.

[0081] In some aspects, the remyelination of a demyelinated axon can be determined by visualizing and/or quantifying the expression of one or more of the following markers: myelin basic protein (MBP), Myelin Oligodendrocyte Glycoprotein (MOG), Oligodendrocyte Specific Protein/Claudin-11, CNPase, proteolipid protein 1 (PLP1), or any combination thereof.

- [0082]** The disclosure also provides a method of reducing the demyelination of a myelinated neuronal axon in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound disclosed herein or a pharmaceutical composition disclosed herein.
- [0083]** In some aspects, reducing the demyelination of a myelinated neuronal axon results in an increase in the expression of one or more of the following markers: myelin basic protein (MBP) Myelin Oligodendrocyte Glycoprotein (MOG), Oligodendrocyte Specific Protein/Claudin-11, CNPase, proteolipid protein 1 (PLP1), or any combination thereof.
- [0084]** In some aspects, the reduction in the demyelination of a myelinated neuronal axon can be determined by visualizing and/or quantifying the expression of one or more of the following markers: myelin basic protein (MBP) Myelin Oligodendrocyte Glycoprotein (MOG), Oligodendrocyte Specific Protein/Claudin-11, CNPase, proteolipid protein 1 (PLP1), or any combination thereof.
- [0085]** The present disclosure also provides a method of activating an oligodendrocyte progenitor cell (OPC) within the central nervous system (CNS) of a subject in need thereof, the method comprising administering to the subject an effective amount of a compound disclosed herein or a pharmaceutical composition disclosed herein.
- [0086]** In some aspects, the subject has, or is at risk of developing a demyelinating disease, for example a disease disclosed herein.
- [0087]** In some aspects, the method is a method of treating or preventing a demyelinating disease, for example a disease disclosed herein.
- [0088]** In some aspects, the compound or the pharmaceutical composition is administered to the subject once.
- [0089]** In some aspects, the compound or the pharmaceutical composition is administered to the subject more than once using intermittent dosing.
- [0090]** In some aspects, the intermittent dosing comprises administering the compound or pharmaceutical composition to the subject every other day, every three days, every four days, every five days, every six days, once a week, every eight days, every nine days, every 10 days, every 11 days, every 12 days, every 13 days, once every two weeks, once every three weeks, once a month, once every two months, once every three months, once every four months, once every five months, once every six months, or once every twelve months.

- [0091] In some aspects, the intermittent dosing comprises administering to the subject a first dose and a second dose of the compound or pharmaceutical composition, wherein the second dose is administered at least one day, at least two days, at least three days, at least four days, at least five days, at least six days, at least seven days, at least eight days, at least nine days, at least 10 days, at least 11 days, at least 12 days, at least 13 days, at least two weeks, at least three weeks, at least one month, at least two months, at least three months, at least four months, at least five months, at least six months, or at least 12 months after administering the first dose.
- [0092] In some aspects, the second dose is administered to the subject one day, two days, three days, four days, five days, six days, seven days, eight days, nine days, 10 days, 11 days, 12 days, 13 days, two weeks, three weeks, one month, two months, three months, four months, five months, six months, or 12 months after administering the first dose.
- [0093] In some aspects, after the administration, the compound or the pharmaceutical composition can achieve a brain to plasma ratio of greater than 0.1, greater than 0.2, greater than 0.3, greater than 0.4, greater than 0.5, greater than 0.6, greater than 0.7, greater than 0.8, greater than 0.9, greater than 1.0, greater than 1.1, greater than 1.2, greater than 1.3, greater than 1.4, greater than 1.5, greater than 1.6, greater than 1.7, greater than 1.8, greater than 1.9, or greater than 2.0. In some aspects, the brain to plasma ratio may be assessed in preclinical species using bioanalytical gas or liquid chromatography and mass spectrometry methods.
- [0094] In some aspects, the method further comprises administering to the subject an additional therapeutic agent.
- [0095] In some aspects, the additional therapeutic agent comprises a standard care of treatment.
- [0096] In some aspects, the additional therapeutic agent comprises an immunomodulatory agent.
- [0097] In some aspects, the additional therapeutic agent is selected from interferon beta-1b, interferon beta-1a, peginterferon beta-1a, alemtuzumab, natalizumab, ocrelizumab, ofatumumab, ublituximab-xiiy, glatiramer acetate, teriflunomide, dimethyl fumarate, monomethyl fumarate, diroximel fumarate, fingolimod hydrochloride, siponimod fumaric acid, ozanimod hydrochloride, ponesimod, cladribine, mitoxantrone, a BTK inhibitor (e.g.,

masitinib, evobrutinib, or tolebrutinib), a statin (e.g., simvastatin), or a pharmaceutically acceptable salt thereof.

[0098] In some aspects, the additional therapeutic agent is administered to the subject prior to, concurrently, or after the administration of the compound or the pharmaceutical composition.

[0099] The disclosure also provides a method of inducing the differentiation of an oligodendrocyte progenitor cell (OPC) into an oligodendrocyte, the method comprising contacting the OPC with an effective amount of a compound disclosed herein or a pharmaceutical composition disclosed herein.

[0100] In some aspects, inducing the differentiation of the OPC into an oligodendrocyte results in an increase in the expression of the following markers in the subject: GPR17, MBP, ASPA, GST-pi, CC1, myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, proteolipid protein 1 (PLP1), or a combination thereof.

[0101] In some aspects, the differentiation of the OPC into an oligodendrocyte is measured by determining the expression of GPR17, MBP, ASPA, GST-pi, CC1, myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, proteolipid protein 1 (PLP1), or a combination thereof.

[0102] The disclosure also provides a method of inhibiting PDGFR α activity in a cell, the method comprising contacting the cell with an effective amount of a compound disclosed herein or a pharmaceutical composition disclosed herein.

[0103] In some aspects, the inhibition of the PDGFR α activity is measured by one or more of the following: an *in vitro* OPC differentiation assay (e.g., as described in Example 132), a cuprizone model for demyelination, an *in vivo* OPC differentiation assay (e.g., as described in Example 134), an enzymatic PDGFR α kinase assay (e.g., as described in Example 131), or any combination thereof.

[0104] In some aspects, the contacting occurs *ex vivo* or *in vivo*.

[0105] In some aspects, the method is a method of treating by a therapy.

[0106] The disclosure also provides a method of treating a PDGF-associated tumor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound disclosed herein or a pharmaceutical composition disclosed herein, wherein after the administration, PDGFR α activity is reduced in the subject.

[0107] In some aspects, the PDGF-associated tumor comprises an oligodendroglioma.

[0108] In some aspects, the method is a method of treatment by therapy.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0109] The present disclosure describes compounds that can induce the differentiation of OPCs into cells that have features of mature oligodendrocytes, including morphological characteristics and the protein expression patterns associated with myelination, and can also affect remyelination. Accordingly, as described herein, the compounds of the present disclosure can be useful in treating various diseases, such as those associated with demyelination. Additional aspects of the present disclosure are provided throughout the present application.

[0110] Before the present disclosure is described in greater detail, it is to be understood that this disclosure is not limited to the particular compositions or process steps described, which can, of course, vary. As will be apparent to those of skill in the art upon reading this disclosure, each of the individual aspects described and illustrated herein has discrete components and features, which can be readily separated from, or combined with, the features of any of the other several aspects without departing from the scope or spirit of the present disclosure. Any recited method can be carried out in the order of events recited or in any other order which is logically possible.

[0111] The headings provided herein are not limitations of the various aspects of the disclosure, which can be defined by reference to the specification as a whole. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only, and is not intended to be limiting, since the scope of the present disclosure will be limited only by the appended claims.

I. Terms

[0112] In order that the present disclosure can be more readily understood, certain terms are first defined. As used in this application, except as otherwise expressly provided herein, each of the following terms shall have the meaning set forth below. Additional definitions are set forth throughout the application.

[0113] The term “a” or “an” entity refers to one or more of that entity; for example, “a nucleotide sequence,” is understood to represent one or more nucleotide sequences. As

such, the terms “a” (or “an”), “one or more,” and “at least one” can be used interchangeably herein.

[0114] Furthermore, “**and/or**” where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term “and/or” as used in a phrase such as “A and/or B” herein is intended to include “A and B,” “A or B,” “A” (alone), and “B” (alone). Likewise, the term “and/or” as used in a phrase such as “A, B, and/or C” is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0115] It is understood that wherever aspects are described herein with the language “**comprising**,” otherwise analogous aspects described in terms of “**consisting of**” and/or “**consisting essentially of**” are also provided.

[0116] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 5th ed., 2013, Academic Press; and the Oxford Dictionary of Biochemistry and Molecular Biology, 2nd ed., 2008, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure.

[0117] Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range. Where a range of values is recited, it is to be understood that each intervening integer value, and each fraction thereof, between the recited upper and lower limits of that range is also specifically disclosed, along with each subrange between such values. The upper and lower limits of any range can independently be included in or excluded from the range, and each range where either, neither or both limits are included is also encompassed within the disclosure. Thus, ranges recited herein are understood to be shorthand for all of the values within the range, inclusive of the recited endpoints. For example, a range of 1 to 10 is understood to include any number, combination of numbers, or sub-range from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

[0118] Where a value is explicitly recited (*e.g.*, 10), it is to be understood that values that are about the same quantity or amount as the recited value (*e.g.*, $\pm 10\%$) are also within the

scope of the disclosure. Where a combination is disclosed, each subcombination of the elements of that combination is also specifically disclosed and is within the scope of the disclosure. Conversely, where different elements or groups of elements are individually disclosed, combinations thereof are also disclosed. Where any element of a disclosure is disclosed as having a plurality of alternatives, examples of that disclosure in which each alternative is excluded singly or in any combination with the other alternatives are also hereby disclosed; more than one element of a disclosure can have such exclusions, and all combinations of elements having such exclusions are hereby disclosed.

- [0119] The term “**halo**” as used herein by itself or as part of another group refers to Cl, F, Br, or I.
- [0120] The term “**nitro**” as used herein by itself or as part of another group refers to NO₂.
- [0121] The term “**cyano**” as used herein by itself or as part of another group refers to CN.
- [0122] The term “**hydroxy**” as herein used by itself or as part of another group refers to OH.
- [0123] The term “**alkyl**” as used herein by itself or as part of another group refers to a straight- or branched-chain aliphatic hydrocarbon containing one to twelve carbon atoms, *i.e.*, a C₁-C₁₂alkyl, or the number of carbon atoms designated, *e.g.*, a C₁alkyl such as methyl, a C₂alkyl such as ethyl, etc. In some aspects, the alkyl is a C₁-C₁₀alkyl. In some aspects, the alkyl is a C₁-C₆alkyl. In some aspects, the alkyl is a C₁-C₄alkyl. In some aspects, the alkyl is a C₁-C₃alkyl, *i.e.*, methyl, ethyl, propyl, or isopropyl. Non limiting exemplary C₁-C₁₂ alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, *tert*-butyl, *iso*-butyl, 3-pentyl, hexyl, heptyl, octyl, nonyl, and decyl. In some aspects, one or more of the hydrogen atoms of the alkyl group are replaced by deuterium atoms, *i.e.*, the alkyl group is isotopically-labeled with deuterium. A non-limiting exemplary deuterated alkyl group is -CD₃.
- [0124] The term “**haloalkyl**” as used herein by itself or as part of another group refers to an alkyl group wherein one or more hydrogen atoms of the alkyl group are replaced by halo atoms. In some aspects, the haloalkyl group is a -CF₃ group.
- [0125] The term “**alkoxy**” as used herein by itself or as part of another group refers to an alkyl group attached to a terminal oxygen atom. In some aspects, the alkyl is a C₁-C₈alkyl and resulting alkoxy is thus referred to as a “C₁-C₈alkoxy.” In some aspects, the alkyl is a

C₁-C₄alkyl group. Non-limiting exemplary alkoxy groups include methoxy, ethoxy, and *tert*-butoxy.

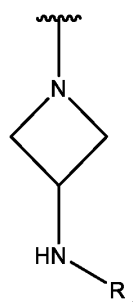
- [0126] The term “**alkoxyalkyl**” as used herein by itself or as part of another group refers to an alkyl group substituted with an alkoxy group. In some aspects, the alkyl is a C₁-C₄ alkyl and the alkoxy is a C₁-C₄ alkoxy and the resulting alkoxyalkyl is thus referred to as a “C₁-C₄alkoxyC₁-C₄alkyl”.
- [0127] The term “**amino**” as used herein by itself or as part of another group refers to -NH₂, which may be optionally substituted with one or two alkyl, two alkyl linked to form a ring, haloalkyl, (hydroxy)alkyl, (alkoxy)alkyl, (amino)alkyl, heteroalkyl, optionally substituted cycloalkyl, optionally substituted heterocyclo, optionally substituted aryl, optionally substituted heteroaryl, (aryl)alkyl, (cycloalkyl)alkyl, (heterocyclo)alkyl, or (heteroaryl)alkyl.
- [0128] The term “**heterocyclamino**” as used herein by itself or as part of another group refers to an amino group substituted with a heterocyclyl group.
- [0129] The term “**aminoalkyl**” as used herein by itself or as part of another group refers to an alkyl group substituted with an amino group. In some aspects, the alkyl is a C₁-C₄alkyl and the resulting aminoalkyl is thus referred to as an “aminoC₁-C₄alkyl”.
- [0130] The term “**hydroxyalkyl**” as used herein by itself or as part of another group refers to an alkyl group substituted with a hydroxy group. In some aspects, the alkyl is a C₁-C₄alkyl and the resulting hydroxyalkyl is thus referred to as a “hydroxyC₁-C₄alkyl”.
- [0131] The term “**aminoalkylamino**” as used herein by itself or as part of another group refers to an amino group substituted with an aminoalkyl group. In some aspects, the aminoalkylamino group is -NHCH₂CH₂NH₂.
- [0132] The term “**oxo**” as used herein refers to an oxygen atom that is connected to a carbon atom by a double bond, *i.e.* to form a keto group.
- [0133] The term “**cycloalkyl**” as used herein by itself or as part of another group refers to saturated and partially unsaturated, *e.g.*, containing one or two double bonds, monocyclic, bicyclic, or tricyclic aliphatic hydrocarbons containing three to twelve carbon atoms, *i.e.*, a C₃-C₁₂cycloalkyl, or the number of carbons designated, *e.g.*, a C₃cycloalkyl such as cyclopropyl, a C₄cycloalkyl such as cyclobutyl, etc. In some aspects, the cycloalkyl is bicyclic, *i.e.*, it has two rings. In some aspects, the cycloalkyl is monocyclic, *i.e.*, it has one ring. In some aspects, the cycloalkyl is a C₃-C₈cycloalkyl. In some aspects, the cycloalkyl

is a C₃₋₆cycloalkyl, *i.e.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some aspects, the cycloalkyl is a C₅cycloalkyl, *i.e.*, cyclopentyl or cyclopentenyl. In some aspects, the cycloalkyl is a C₆cycloalkyl, *i.e.*, cyclohexyl or cyclohexenyl. A cycloalkyl group containing one or two double bonds may also be referred to as a “cycloalkenyl” group.

- [0134] The term “**heterocyclyl**” as used herein by itself or as part of another group refers to saturated and partially unsaturated, *e.g.*, containing one or two double bonds, monocyclic, bicyclic, or tricyclic groups containing three to fourteen ring members, *i.e.*, a 3- to 14-membered heterocyclyl, comprising one, two, three, or four heteroatoms. Each heteroatom is independently oxygen, sulfur, or nitrogen. The term heterocyclyl includes groups wherein one or more -CH₂- groups is replaced with one or more -C(=O)- groups, including cyclic ureido groups such as imidazolidinyl-2-one, cyclic amide groups such as piperidin-2-one or piperazin-2-one, and cyclic carbamate groups such as oxazolidinyl-2-one.
- [0135] The term “**heterocyclylaryl**” as used herein by itself or as part of another group refers to an aryl group that is substituted with a heterocyclyl group.
- [0136] The term “**arylC₁-C₄alkyl**” as used herein by itself or as part of another group refers to a C₁-C₄alkyl group substituted with an aryl group.
- [0137] The term “**heteroarylC₁-C₄alkyl**” as used herein by itself or as part of another group refers to a C₁-C₄alkyl group substituted with a heteroaryl group.
- [0138] The term “**heterocyclylC₁-C₄alkyl**” as used herein by itself or as part of another group refers to a C₁-C₄alkyl group substituted with a heterocyclyl group.
- [0139] The term “**cycloalkylC₁-C₄alkyl**” as used herein by itself or as part of another group refers to a C₁-C₄alkyl group substituted with a cycloalkyl group.
- [0140] The term “**alkylsulfonyl**” as used herein by itself or as part of another group refers to a sulfonyl group, *i.e.*, -SO₂-, substituted by an alkyl group. A non-limiting exemplary alkylsulfonyl group is -SO₂CH₃.
- [0141] The term “**aryl**” as used herein by itself or as part of another group refers to an aromatic ring system having six to fourteen carbon atoms, *i.e.*, C₆-C₁₄ aryl. Non-limiting exemplary aryl groups include phenyl (abbreviated as “Ph”), naphthyl, phenanthryl, anthracyl, indenyl, azulenyl, biphenyl, biphenylenyl, and fluorenyl groups. In some aspects, the aryl group is phenyl.

[0142] The term “**heteroaryl**” as used herein by itself or as part of another group refers to monocyclic and bicyclic aromatic ring systems having five to fourteen ring members, *i.e.*, a 5- to 14-membered heteroaryl, comprising one, two, three, or four heteroatoms. Each heteroatom is independently oxygen, sulfur, or nitrogen. In some aspects, the heteroaryl has three heteroatoms. In some aspects, the heteroaryl has two heteroatoms. In some aspects, the heteroaryl has one heteroatom. In some aspects, the heteroaryl is a 5- to 10-membered heteroaryl. In some aspects, the heteroaryl has 5 ring atoms, *e.g.*, thienyl, a 5-membered heteroaryl having four carbon atoms and one sulfur atom. In some aspects, the heteroaryl has 6 ring atoms, *e.g.*, pyridyl, a 6-membered heteroaryl having five carbon atoms and one nitrogen atom. Non-limiting exemplary heteroaryl groups include thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, benzofuryl, pyranlyl, isobenzofuranyl, benzoxazolyl, chromenyl, xanthenyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, cinnolyl, quinazolinyl, pteridinyl, 4*aH*-carbazolyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, thiazolyl, isothiazolyl, phenothiazolyl, isoxazolyl, furazanyl, and phenoxazinyl. The term heteroaryl also includes N-oxides. A non-limiting exemplary N-oxide is pyridyl N-oxide.

[0143] The term “**aminoheterocyclyl**” as used herein by itself or as part of another group refers to a heterocyclyl group substituted with an optionally substituted amino group. Non-limiting exemplary aminoheterocyclyl groups include:



[0144] The chemical terms used herein may be combined to describe larger substituents. For a monovalent substituent, the substituent that is recited last in the combined term is the substituent that contains the attachment point. For example, an “arylC₁-C₄alkyl” group contains an attachment point on the alkyl group, whereas an “C₁-C₄alkylaryl” group contains an attachment point on the aryl group.

[0145] The present disclosure encompasses any of the disclosed compounds being isotopically-labelled (*i.e.*, radiolabeled) by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^1H , ^2H (or deuterium (D)), ^3H , ^{11}C , ^{12}C , ^{13}C , ^{14}C , ^{14}N , ^{15}N , ^{18}O , ^{17}O , ^{16}O , ^{31}P , ^{32}P , ^{32}S , ^{33}S , ^{34}S , ^{35}S , ^{36}S , ^{18}F , ^{19}F , ^{35}Cl , ^{37}Cl , and ^{36}Cl , respectively, *e.g.*, ^3H , ^{11}C , and ^{14}C . In some aspects, provided is a composition wherein substantially all of the atoms at a position within the disclosed compound are replaced by an atom having a different atomic mass or mass number. In some aspects, provided is a composition wherein a portion of the atoms at a position within the disclosed compound are replaced, *i.e.*, the disclosed compound is enriched at a position with an atom having a different atomic mass or mass number. Isotopically-labelled disclosed compounds can be prepared by methods known in the art. The present disclosure also encompasses any of the disclosed compounds wherein a quaternary carbon atom is replaced with a silicon atom.

[0146] As noted above, the compounds disclosed herein contain one or more asymmetric carbon atoms and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms. The present disclosure encompasses the use of all such possible forms, as well as their racemic and resolved forms and mixtures thereof. The individual enantiomers can be separated according to methods known in the art in view of the present disclosure. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that they include both E and Z geometric isomers. All tautomers are also encompassed by the present disclosure.

[0147] As used herein, the term “**stereoisomers**” is a general term for all isomers of individual molecules that differ only in the orientation of their atoms in space. It includes enantiomers and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereomers).

[0148] The term “**chiral center**” or “**asymmetric carbon atom**” refers to a carbon atom to which four different groups are attached.

[0149] The terms “**enantiomer**” and “**enantiomeric**” refer to a molecule that cannot be superimposed on its mirror image and hence is optically active wherein the enantiomer

rotates the plane of polarized light in one direction and its mirror image compound rotates the plane of polarized light in the opposite direction.

[0150] The term “**racemic**” refers to a mixture of equal parts of enantiomers and which mixture is optically inactive. In some aspects, the compounds disclosed are racemic.

[0151] The term “**absolute configuration**” refers to the spatial arrangement of the atoms of a chiral molecular entity (or group) and its stereochemical description, *e.g.*, R or S.

[0152] The stereochemical terms and conventions used in the specification are meant to be consistent with those described in *Pure & Appl. Chem* 68:2193 (1996), unless otherwise indicated.

[0153] The term “**enantiomeric excess**” or “**ee**” refers to a measure for how much of one enantiomer is present compared to the other. For a mixture of *R* and *S* enantiomers, the percent enantiomeric excess is defined as $|R - S| * 100$, where *R* and *S* are the respective mole or weight fractions of enantiomers in a mixture such that $R + S = 1$. With knowledge of the optical rotation of a chiral substance, the percent enantiomeric excess is defined as $([\alpha]_{\text{obs}}/[\alpha]_{\text{max}}) * 100$, where $[\alpha]_{\text{obs}}$ is the optical rotation of the mixture of enantiomers and $[\alpha]_{\text{max}}$ is the optical rotation of the pure enantiomer. Determination of enantiomeric excess is possible using a variety of analytical techniques, including NMR spectroscopy, chiral column chromatography or optical polarimetry.

[0154] The terms “**administration**,” “**administering**,” and grammatical variants thereof, refer to introducing a composition, such as a PDGFR α inhibitor of the present disclosure, into a subject via a pharmaceutically acceptable route. Any suitable route of administration can be used in administering the PDGFR α inhibitors described herein to a subject. Non-limiting examples of such routes of administration are provided elsewhere in the present disclosure.

[0155] The term “**central nervous system**” or “**CNS**” refers to a complex of nerve tissues that control the various activities of the body (*e.g.*, voluntary and involuntary movements) and the mind (*e.g.*, thoughts, perceptions, and emotions). The CNS generally consists of the brain and the spinal cord.

[0156] As used herein, the term “**demyelinating disease**” refers to any disorder of the nervous system in which there is reduced myelination, including disorders in which insufficient or dysfunctional myelin (*e.g.*, hypomyelination) is generated during development or disorders in which the myelin sheath of neurons is damaged. “**Myelin**” and

“**Myelin sheath**” refer to the specialized membrane formed by oligodendrocytes that insulates the axons of neurons. The insulation provided by the myelin sheath helps to increase the rate of transmission of nerve signals along the axon, thereby promoting timely and energetically efficient neuronal signaling. Myelin also provides metabolic support of the axons, maintaining their health and survival. In some aspects, the neuronal axon of a subject suffering from or at risk of developing a demyelinating disease is completely demyelinated. In some aspects, the neuronal axon of a subject suffering from or at risk of developing a demyelinating disease is partially demyelinated (*e.g.*, at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 95% compared to a reference neuronal axon that is fully myelinated). Accordingly, unless indicated otherwise, the term “**demyelination**” comprises any of the following: complete hypomyelination, complete demyelination, partial hypomyelination, partial demyelination, and combinations thereof. In some aspects, because of the partial and/or complete demyelination, the demyelinating diseases described herein are associated with impaired conduction of nerve signals or axonal or neuronal survival, which can, in turn, cause deficiencies in sensation, movement, cognition, or other functions depending on which neurons are affected. Non-limiting examples of demyelinating diseases are provided elsewhere in the present disclosure. In general, the term “**under myelination**” refers to a cell, tissue, or subject that lacks normal levels of myelination (*e.g.*, level of myelination observed in a corresponding cell, tissue, or subject who does not have a demyelinating disease), regardless of etiology.

[0157] As used herein, the term “**hypomyelination**” refers to a deficiency in myelin for any reason (*e.g.*, body is unable to produce myelin at normal levels). Unless indicated otherwise, hypomyelination includes demyelination (related to myelin destruction) and dysmyelination (related to abnormal myelin deposition). Accordingly, hypomyelination includes diseases in which insufficient myelin is generated during development as well as diseases associated with demyelination and/or dysmyelination. In some aspects, compared to a reference (*e.g.*, corresponding tissue, *e.g.*, brain, of a subject who does not suffer from a demyelinating disease), there is hypomyelination of all (*i.e.*, “**complete hypomyelination**”) or a portion of the nervous system (*i.e.*, “**partial hypomyelination**”), for example the brain (*e.g.*, hypomyelination in white matter and/or gray matter), of at least

5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 95%.

[0158] As used herein, the term “**neuron**” includes electrically excitable cells that process and transmit information through electrical and chemical signals. Neurons are major components of the brain and spinal cord of the CNS, and of the ganglia of the peripheral nervous system (PNS) and can connect to each other to form neural networks. A typical neuron is composed of a cell body (soma), dendrites, and an axon. The “**soma**” (the cell body) of a neuron contains the nucleus. The “**dendrites**” of a neuron are cellular extensions generally having many branches, where the majority of input to the neuron occurs. The “**axon**” (also referred to herein as “**neuronal axon**”) extends from the soma and carries nerve signals away from the soma and certain types of information back to the soma.

[0159] As used herein, the term “**oligodendrocyte progenitor cells**” or “**OPCs**” (also known in the art as “**oligodendrocyte precursor cells**,” “**polydendrocytes**,” “**NG2 cells**,” and “**O-2A cells**”) refer to a subtype of glial cells in the central nervous system. They are precursors to “**oligodendrocytes**,” (also known as “**oligodendroglia**”) which are responsible for generating the myelin sheath that wraps around axons, providing insulation, aiding electrical conduction, and providing metabolic support. Nerve impulses can travel up to 200 times faster along a myelinated axon compared to an unmyelinated axon. OPCs and immature oligodendrocytes are generally positive for the following markers: A2B5, neuron-glia antigen 2 (NG2), and PDGFR α . Other suitable markers that can be used are known in the art.

[0160] As used herein, the term “**remyelination**” (or derivatives thereof) refers to generation of new myelin sheaths around demyelinated (*e.g.*, including hypomyelinated) axons. The remyelination process involves the differentiation of OPCs into oligodendrocytes that generate functional myelin sheaths around demyelinated axons. Remyelination of the axons can restore action potential conduction properties to axons, and thereby, promote and/or improve neurological function. Further, remyelination can provide metabolic support to axons, preventing their damage or loss. In the context of the present application, unless otherwise specified, “remyelination” refers to any aspect of a process that can result in remyelination. For example, in some aspects, “remyelination” comprises the migration or colonization of OPCs to sites of demyelinated axons. In some aspects, “remyelination” comprises the differentiation of OPCs into oligodendrocytes. In some

aspects, “remyelination” comprises the generation of myelin sheaths by oligodendrocytes around demyelinated axons. In some aspects, the term “remyelination” comprises any combination of the following: (i) migration or colonization of OPCs to sites of demyelinated axons; (ii) differentiation of OPCs into oligodendrocytes; and (iii) generation of myelin sheaths by oligodendrocytes around demyelinated (*e.g.*, including hypomyelinated) axons.

[0161] As used herein, the term “**restore**” (and derivatives thereof) comprises both complete restoration and partial restoration. For example, in some aspects, remyelinating a demyelinated axon restores conduction properties to the axon, such that the conduction properties are the same as those of the axon prior to the demyelination (*i.e.*, complete restoration). In some aspects, remyelinating a demyelinated axon restores conduction properties to the axon, where the conduction properties are improved but not the same as those of the axon prior to the demyelination (*i.e.*, partial restoration). In some aspects, remyelination provides metabolic support to axons, preventing their damage or loss. In some aspects, remyelination provides partial metabolic support to axons, delaying their damage or loss.

[0162] As used herein, the term “**promoting**” refers to the ability of an agent (*e.g.*, PDGFR α inhibitor described herein) to induce or increase a particular result (*e.g.*, remyelination of a demyelinated axon). In some aspects, the term comprises both inducing and increasing a particular result.

[0163] As used herein, the term “**subject**” refers to any animal subject including a human, a laboratory animal (*e.g.*, a non-human primate, rat, and mouse), livestock (*e.g.*, cow, sheep, goat, pig, turkey, and chicken), and household pets (*e.g.*, dog, cat, and rodent).

[0164] The terms “**treat**,” “**treating**,” and “**treatment**,” as used herein, refer to any type of intervention or process performed on, or administering an active agent (*e.g.*, PDGFR α inhibitor described herein) to, the subject with the objective of reversing, alleviating, ameliorating, inhibiting, or slowing down; or preventing the progression, development, severity or recurrence of a symptom, complication, condition or one or more biochemical indicia associated with a disease, or enhancing overall survival. As described herein, in some aspects, treatment can be of a subject having a disease (*e.g.*, exhibiting one or more symptoms associated with the disease). In some aspects, treatment can be of a subject with some degree of demyelination but not yet exhibiting any symptoms associated with the

disease. In the context of such subjects, administering a PDGFR α inhibitor of the present disclosure can help delay or prevent the onset of symptoms associated with the disease.

[0165] The term “**effective dose**” or “**effective amount**” is defined as an amount sufficient to achieve or at least partially achieve a desired effect (*e.g.*, induce remyelination of a demyelinated neuronal axon). A “**therapeutically effective amount**” or “**therapeutically effective dosage**” of a therapeutic agent (*e.g.*, PDGFR α inhibitor) is any amount of the therapeutic agent that, when used alone or in combination with another therapeutic agent, promotes disease regression as evidenced by a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, a prevention of impairment or disability due to the disease affliction, or a reduction in disease progression. A therapeutically effective amount or dosage of a therapeutic agent includes a “**prophylactically effective amount**” or a “**prophylactically effective dosage**,” which is any amount of the therapeutic agent that, when administered alone or in combination with another therapeutic agent to a subject at risk of developing a disease or of suffering a recurrence of disease, inhibits the development or recurrence of the disease. The ability of a therapeutic agent to promote disease reversal or inhibit the development, progression or recurrence of the disease can be evaluated using a variety of methods known to the skilled practitioner, such as in human subjects during clinical trials, in animal model systems predictive of efficacy in humans, or by assaying the activity of the agent in *in vitro* assays.

[0166] As used herein, the term “**dosing interval**” refers to the amount of time that elapses between multiple (*e.g.*, 2 or more) doses of a PDGFR α inhibitor described herein. Not to be bound by any one theory, in some aspects, a PDGFR α inhibitor provided herein exerts its therapeutic effect by inducing the differentiation of oligodendrocyte progenitor cells (OPCs) into oligodendrocytes. Accordingly, in some aspects, for a PDGFR α inhibitor to have a therapeutic effect in a subject (*e.g.*, by inducing OPC differentiation), it is necessary that the subject has a pool of OPCs which a PDGFR α inhibitor described herein can act upon. As demonstrated herein, administering a PDGFR α inhibitor too frequently to a subject can be counterproductive in treating a demyelinating disease because the OPC population would not have sufficient time to repopulate the brain. Accordingly, in some aspects, a dosing interval that is suitable for the present disclosure is the amount of time required for a subject’s OPC population to have sufficiently recovered after the administration of an initial dose of a PDGFR α inhibitor provided herein, or a period longer

than that, such that the administration of a second (or additional dose) of the PDGFR α inhibitor would have a therapeutic effect (*e.g.*, such as those described herein, *e.g.*, increases the number of differentiated oligodendrocytes) in the subject. As is apparent from the present disclosure, in some aspects, a PDGFR α inhibitor described herein is administered to a subject at a dosing interval, wherein the dosing interval is the amount of time required, after the administration of an initial dose of the PDGFR α inhibitor, for the subject's OPC population (*e.g.*, in size) to be at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 100% to that of a reference OPC population (*e.g.*, the subject's OPC population prior to the initial administration of the PDGFR α inhibitor). In some aspects, an OPC population may be measured by quantifying the density of NG2+ (neuron-glia antigen 2/chondroitin sulfate proteoglycan-4) or PDGFR α + cells in mice, rats, pigs, dogs, non-human primates or other species using immunohistochemistry or fluorescence-activated cell sorting. Repopulation may be calculated as the OPC cell density at a given time after dosing relative to the OPC population in an untreated reference animal.

[0167] In some aspects, a suitable dosing interval for the present disclosure comprises the amount of time required, after an initial dose of the PDGFR α inhibitor, for the plasma level of the PDGFR α inhibitor to reach less than 50%, less than 40%, less than 30%, less than 20%, less than 10%, or less than 5%, as compared to a reference (*e.g.*, plasma level of the PDGFR α inhibitor in a corresponding subject immediately after, *e.g.*, about 4 hours after, the administration of the initial dose of the PDGFR α inhibitor), a suitable dosing interval is the time between administering the first dose of the PDGFR α inhibitor and the subject's plasma level of the PDGFR α inhibitor reaching a reduced level as compared to the reference. In some aspects, the additional dose of the PDGFR α inhibitor is administered to the subject when the subject's plasma level has decreased by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or about 100% as compared to the reference. In some aspects, the brain to plasma ratio may be assessed in preclinical species using bioanalytical gas or liquid chromatography and mass spectrometry methods.

[0168] As used herein, the terms “**binds**,” “**recognizes**,” “**targets**” are analogous terms and refer to molecules (*e.g.*, PDGFR α inhibitors described herein) that can bind and/or target a particular region of a protein (*e.g.*, PDGFR α), as such binding and/or targeting is

understood by one skilled in the art. For instance, as described herein, in some aspects, a PDGFR α inhibitor is a small molecule that can target and inhibit the kinase portion of PDGFR α (*e.g.*, by binding to the ATP binding site, by allosterically interfering with PDGFR α kinase activity, or both), and thereby, inhibit its activity. Unless indicated otherwise, the above terms (*i.e.*, binds, recognizes, and targets) are used interchangeably and comprises any binding or targeting of PDGFR α , such that its activity is reduced and/or inhibited (*e.g.*, binding of a small molecule to an ATP binding site of PDGFR α , binding of a small molecule to a substrate binding site of PDGFR α , allosterically interfering with PDGFR α kinase activity, or a combination thereof).

[0169] “**Potency**” is an expression of the activity of a therapeutic agent in terms of the amount or concentration of the therapeutic agent that achieves a desired effect. Accordingly, functional assays, such as those described herein, can be used to identify compounds useful for the present disclosure.

[0170] Molecules (*e.g.*, PDGFR α inhibitors, such as those described herein) that “**compete with another protein or compound for binding to a target**” refers to molecules that inhibit (partially or completely) the binding of the other protein (*e.g.*, naturally existing PDGFR α ligand) to the target (*e.g.*, PDGFR α). Whether two compounds compete with each other for binding to a target, *i.e.*, whether and to what extent a PDGFR α inhibitor described herein inhibits the binding of the naturally existing ligand to a PDGFR α , can be determined using known competition experiments. In some aspects, a PDGFR α inhibitor described herein competes with, and inhibits the binding of the naturally existing ligand to PDGFR α by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100%. Competition assays can be conducted as described herein or, for example, in Ed Harlow and David Lane, Cold Spring Harb. Protoc.; 2006; doi: 10.1101/pdb.prot4277 or in Chapter 11 of “Using Antibodies” by Ed Harlow and David Lane, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, USA 1999.

[0171] Additional non-limiting examples of other competitive binding assays that can be used with the present disclosure include: solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (*see* Stahli *et al.*, *Methods in Enzymology* 9:242 (1983)); solid phase direct biotin-avidin EIA (*see* Kirkland *et al.*, *J. Immunol.* 137:3614 (1986)); solid phase direct labeled

assay, solid phase direct labeled sandwich assay (*see* Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Press, Second Edition (2014)); solid phase direct label RIA using 1-125 label (*see* Morel *et al.*, *Mol. Immunol.* 25(1):7 (1988)); solid phase direct biotin-avidin EIA (Cheung *et al.*, *Virology* 176:546 (1990)); and direct labeled RIA. (Moldenhauer *et al.*, *Scand. J. Immunol.* 32:77 (1990)).

[0172] As further described elsewhere in the present disclosure, in some aspects, the antagonistic activity of a PDGFR α inhibitor described herein does not depend on interfering with the binding of another protein or compound to PDGFR α . Another non-limiting example includes small molecules that can bind to PDGFR α and inhibit (partially or completely) binding of ATP or substrate, or otherwise inhibit PDGFR α activity. In some aspects, a PDGFR α inhibitor described herein can inhibit or reduce PDGFR α activity via allosteric inhibition. In some aspects, a PDGFR α inhibitor can reduce protein levels of PDGFR α by reducing synthesis or enhancing degradation. While exemplary mechanisms of actions are provided, it will be apparent from the present disclosure that the PDGFR α inhibitors described herein are not intended to be limited to such mechanisms.

[0173] As used herein, the terms “**ug**” and “**uM**” are used interchangeably with “**μg**” and “**μM**,” respectively.

[0174] Various aspects described herein are described in further detail in the following subsections. The various aspects and embodiments of the present disclosure can optionally be combined. For instance, in some embodiments any of the disclosed compounds can be used in any of the disclosed methods and uses.

II. PDGFR α Inhibitors

[0175] Disclosed herein are compounds that can inhibit PDGFR α activity and/or elicit one or more activities associated with inhibition of the receptor. PDGFR α can bind with high affinity to several PDGF isoforms (*i.e.*, PDGF-A, PDGF-B, PDGF-C, and PDGF-D). As used herein, references to inhibition of PDGFR α binding to its ligand refer to inhibition of binding of one or more of the PDGF isoforms that bind to PDGFR α . In some embodiments, the binding of all isoforms of PDGF that bind to PDGFR α is inhibited. The binding of the platelet-derived growth factor (PDGF) isoforms to PDGFR α affects various cell signaling pathways, such as those involved in cell proliferation and differentiation. Accordingly, PDGFR α activity is critical for both the proper development and long-term maintenance of

certain tissues and organs. For example, animals globally lacking a functional *PDGFRA* gene die at birth or soon thereafter due to various developmental defects (*e.g.*, cardiac malformations). Bax *et al.*, *Dev. Dyn.* 239(8): 2307-2317 (Aug. 2010). Conditional PDGFR α knockout in OPCs during animal development results in severe hypomyelination and the animals die soon after birth. Hamashima *et al.*, *Neuroscience* 436: 11-26 (Jun. 2020)

[0176] In humans, the gene encoding PDGFR α (*i.e.*, *PDGFRA*) is located on chromosome 4 (for example, nucleotides 54,229,127-54,298,245 of GenBank Accession Number NC_000004.12; plus strand orientation). In addition to those provided above, other synonyms of PDGFR α are known and include: “PDGFR α ,” “PDGFR2,” “alpha-type platelet-derived growth factor receptor,” “platelet-derived growth factor receptor A,” “platelet-derived growth factor receptor alpha,” “platelet-derived growth factor receptor 2,” “CD140a,” and “CD140 antigen-like family member A.” As used herein, the term “**PDGFR α** ” includes any variants or isoforms of PDGFR α that are naturally expressed by cells.

[0177] Despite its importance in various biological processes, the present disclosure describes the discovery that inhibiting or reducing PDGFR α activity, for example, with one or more of the compounds described herein, can have certain biological effects that can be useful for treating demyelinating diseases, such as those described herein. As demonstrated herein, in some aspects, inhibiting or reducing PDGFR α activity with the PDGFR α inhibitors described herein can promote oligodendrocyte differentiation and induce myelin formation. In some aspects, the PDGFR α inhibitors of the present disclosure are capable of (and in some embodiments used for) promoting remyelination of demyelinated neuronal axons, which can be useful in the treatment of various demyelinating diseases (*e.g.*, multiple sclerosis). As used herein, the terms “**PDGFR α inhibitors**” and “**PDGFR α antagonists**” are used interchangeably and refer to any compound that is capable of (and in some embodiments used for) reducing and/or inhibiting PDGFR α activity (*e.g.*, by any of the exemplary mechanisms or methods described herein). In some aspects, a PDGFR α inhibitor provided herein can inhibit a tyrosine kinase activity of a PDGFR α . In some aspects, a PDGFR α inhibitor provided herein can inhibit any other activity of a PDGFR α . Where the term “**capable of**” is used herein to describe certain features of a PDGFR α inhibitor, the term means that the PDGFR α inhibitor can (*i.e.*, has the ability to) exhibit such features, *e.g.*, under appropriate conditions. Unless indicated otherwise, the term does

not mean that the PDGFR α inhibitor always exhibits such features, *e.g.*, when administered to a subject with impaired oligodendrocyte progenitor cell population. The term “**capable of**” and “**can**” are used interchangeably in the present application.

[0178] In some aspects, a PDGFR α inhibitor inhibits the kinase activity of PDGFR α . As used herein, unless indicated otherwise, the term “**inhibit**” (and derivatives thereof) comprises both complete inhibition and partial inhibition (*e.g.*, reduced kinase activity). Accordingly, in some aspects, when an OPC (expressing PDGFR α) interacts with a PDGFR α inhibitor described herein, the PDGFR α kinase activity is reduced by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% or more (for example, at least 50% or more), compared to PDGFR α kinase activity in a corresponding OPC that was not contacted with the PDGFR α inhibitor described herein (*e.g.*, contacted with a vehicle control). In some aspects, the kinase activity is completely inhibited. As is apparent from the present disclosure, the inhibition (partial or complete) of PDGFR α kinase activity in an OPC can promote the differentiation of the OPC into a myelinating oligodendrocyte. Inhibition of PDGFR α kinase activity can be assayed using methods known in the art. In some aspects, the inhibition of PDGFR α kinase activity can be determined using the *in vitro* differentiation assay described in Example 132 of the present application. In some aspects, the inhibition of PDGFR α kinase activity can be assessed using a cuprizone model for demyelination, such as that described in Torkildsen *et al.*, *Acta Neurol Scand Suppl* 188:72-6 (2008). In some aspects, the inhibition of PDGFR α kinase activity is determined using an enzymatic PDGFR α kinase assay, such as that described in Example 131 of the present disclosure. In some aspects, the inhibition of PDGFR α kinase activity can be determined using an *in vivo* OPC differentiation assay, such as that described in Example 134.

[0179] As described herein, in some aspects, a PDGFR α inhibitor useful for the present disclosure comprises one or more of the following properties: (1) capable of (and in some embodiments used for) promoting (*e.g.*, inducing and/or enhancing) the differentiation of an OPC into an oligodendrocyte (*in vitro*, *in vivo*, or both); (2) capable of (and in some embodiments used for) promoting (*e.g.*, inducing and/or enhancing) the expression of a protein associated with oligodendrocyte differentiation and/or myelination (*e.g.*, G-protein coupled receptor 17 (GPR17), myelin basic protein (MBP), ASPA, GST-pi, CC1, myelin

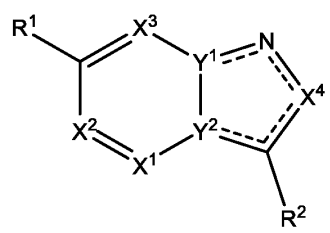
oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, proteolipid protein 1 (PLP1), or a combination thereof); (3) capable of (and in some embodiments used for) promoting (*e.g.*, inducing and/or enhancing) the myelination of a neuronal axon; (4) capable of (and in some embodiments used for) promoting (*e.g.*, inducing and/or enhancing) the remyelination of a demyelinated neuronal axon; (5) capable of (and in some embodiments used for) inhibiting a PDGFR α kinase activity (*e.g.*, IC₅₀ of less than 10,000 nM, as measured using a Promega kinase assay; (*e.g.*, described in Example 131); (6) capable of (and in some embodiments used for) penetrating the brain (*e.g.*, following systemic administration) at a sufficient level to support activity in the CNS; and (7) any combination thereof. Non-limiting examples of additional properties are provided elsewhere in the present disclosure.

[0180] In addition to the properties described above, a PDGFR α inhibitor described herein can comprise one or more additional features that are not present in other inhibitors known in the art. As is apparent from the present disclosure, such additional features can be useful in various clinical settings, *e.g.*, to treat a demyelinating disease, such as those described herein.

[0181] As described elsewhere in the present disclosure, some exemplary PDGFR α inhibitors of the present disclosure are capable of have greater therapeutic effect than inhibitors known in the art, *e.g.*, when an inhibitor known in the art and an exemplary inhibitor provided herein are assayed against a vehicle control. For example, in some aspects, a PDGFR α inhibitor can have greater potency compared to inhibitors known in the art. In some aspects, a PDGFR α inhibitor can better penetrate the CNS (*e.g.*, can more effectively pass across the blood-brain barrier). Accordingly, in some aspects, PDGFR α inhibitors described herein are more effective at promoting OPC differentiation as compared to inhibitors known in the art. For example, in some aspects, a PDGFR α inhibitor of the present disclosure can achieve greater than 2-fold increase in GPR17 expression compared to a vehicle control at a dose of less than 50 mg/kg, as measured using an *in vivo* GPR17 assay (such as that described in Example 134). In some aspects, a PDGFR α inhibitor of the present disclosure can achieve greater than 2-fold increase in GPR17 expression compared to the vehicle control at a dose of less than 40 mg/kg, less than 30 mg/kg, less than 20 mg/kg, less than 10 mg/kg, less than 5 mg/kg, less than 4 mg/kg, less than 3 mg/kg, less than 2 mg/kg, or less than 1 mg/kg, as measured using an *in vivo* GPR17

assay (such as that described in Example 134). As described elsewhere in the present disclosure, GPR17 expression is a suitable marker for OPC differentiation. Additionally, in some aspects, any of the other proteins associated with oligodendrocyte differentiation and/or myelination can be used instead of GPR17 or in combination with GPR17. Non-limiting examples of such proteins include: MBP, ASPA, GST-pi, CC1, MOG, oligodendrocyte-specific protein/claudin-11, CNPase, proteolipid protein 1 (PLP1), or a combination thereof.

[0182] In some aspects, the PDGFR α inhibitor is a compound of Formula I:



[0183] or a pharmaceutically acceptable salt or solvate thereof, wherein:

----- indicates a single bond or a double bond such that all valences are satisfied;

X¹, X², X³, and X⁴ are selected from N and CR^a, with the proviso that not more than two of X¹, X², X³, and X⁴ are N;

one of Y¹ and Y² is N and the other of Y¹ and Y² is C;

each R^a is independently selected from H, halo, C₁-C₄alkyl, and C₁-C₄alkoxy;

R¹ is selected from C₁-C₄alkyl, C₃-C₈cycloalkyl, 3-8 membered heterocyclyl, heteroaryl, aryl, and C₁-C₈alkoxy, all of which can be optionally substituted with one, two, three, four, five, or six substituents selected from halo, hydroxy, oxo, C₁-C₄alkyl, aminoC₁-C₄alkyl, hydroxyC₁-C₄alkyl, C₁-C₄alkoxy, C₁-C₄alkoxyC₁-C₄alkyl, 3-8 membered heterocyclyl, and 3-8 membered heterocyclylC₁-C₄alkyl, with the proviso that the number of substituents does not exceed the number of substitutable positions;

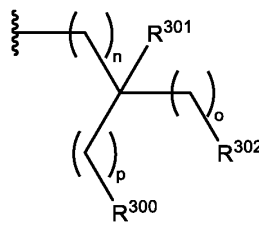
R² is selected from cycloalkyl, cycloalkenyl, alkyl, aminoalkylamino, amino, heterocyclyl, heteroaryl, aminoheterocyclyl, heterocyclylamino, and aminoalkylamino, all of which can be optionally substituted with one or more substituents selected from D, halo, oxo, and C₁-C₄alkyl;

R² is substituted with one, two, or three R³;

R³ is selected from aryl, heteroaryl, -C(O)R³¹, -C(O)OR³¹, -C(O)NR³¹R³², -S(O)₂NR³¹R³², -S(O)₂R³¹, -S(O)(NR³³)R³¹, -S(O)(NR³³)NR³¹R³², -C(S)NR³¹R³², C₃-

C₈cycloalkyl, 3-8 membered heterocyclyl, and C₁-C₄alkyl, all of which can be optionally substituted with one, two, three, four, or five R³⁰;

each R³⁰ is independently selected from D, halo, aryl, -OR³⁰⁰, -NR³⁰⁰R³⁰¹,



-S(O)_rR³⁰⁰, -C(O)R³⁰⁰, -C(=CR³⁴R³⁵)R³⁰⁰, and

r is selected from 0, 1, and 2;

each R³⁰⁰ is independently selected from C₁-C₆alkyl, C₃-C₇cycloalkyl, aryl, heteroaryl, 3-8 membered heterocyclyl, and 3-8 membered heterocyclylaryl, all of which can be optionally substituted with one, two, three, four, or five substituents selected from D, halo, hydroxy, amino, alkylamino, cyano, C₁-C₄alkyl, C₁-C₄haloalkyl, and C₁-C₄alkoxy;

each R³⁰¹ is independently selected from H, halo, and C₁-C₄alkyl;

each R³⁰² is independently selected from H, F, hydroxy, amino, alkylamino, oxo, and C₁-C₄alkoxy;

each R³⁰³ is independently selected from H and C₁-C₄alkyl;

n, o, and p are each independently selected from 0, 1, 2, 3, and 4;

each R³¹ is independently selected from C₁-C₈alkyl, arylC₁-C₄alkyl, heteroarylC₁-C₄alkyl, heterocyclyl, heterocyclylC₁-C₄alkyl, cycloalkyl, and cycloalkylC₁-C₄alkyl, all of which can be optionally substituted with one, two, three, four, or five substituents selected from D, halo, cyano, hydroxy, amino, -OCF₃, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, hydroxyC₁-C₄alkyl, -S(O)₂NR³⁰⁴R³⁰⁵, -C(O)OR³⁰⁴R³⁰⁵, -C(O)NR³⁰⁴R³⁰⁵, and -NR³⁰⁴C(O)R³⁰⁵;

each R³⁰⁴ and R³⁰⁵ is independently selected from H and C₁-C₄ alkyl;

each R³² is independently selected from H and C₁-C₄alkyl; or

R³¹ and R³² together with the atom to which they are connected form a 5-8 membered heterocycl, optionally substituted with one, two, three, four, or five substituents selected from D, halo, cyano, C₁-C₄alkyl, and C₁-C₄haloalkyl, and -C(O)NR³⁴R³⁵;

each R³⁴ and R³⁵ is independently selected from H, C₁-C₄alkyl, and C₁-C₄haloalkyl;

and

each R^{33} is independently selected from H, C₁-C₄alkyl, C₁-C₄haloalkyl, and $-C(O)R^{34}$, or

R^{31} and R^{33} together with the atoms to which they are connected form a 4-8 membered heterocycyl.

[0184] In some aspects, Y^1 is N and Y^2 is C.

[0185] In some aspects, Y^1 is C and Y^2 is N.

[0186] In some aspects, X^1 is N, X^2 is CR^a, X^3 is CR^a, and X^4 is CR^a.

[0187] In some aspects, X^1 is CR^a, X^2 is N, X^3 is CR^a, and X^4 is CR^a.

[0188] In some aspects, X^1 is CR^a, X^2 is CR^a, X^3 is N, and X^4 is CR^a.

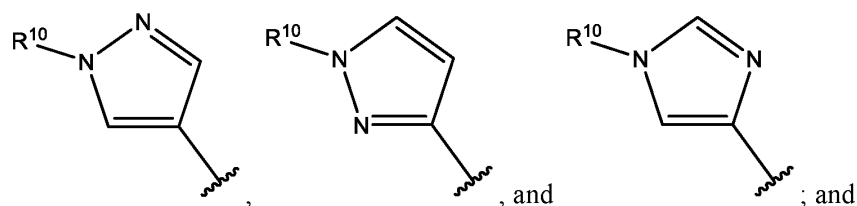
[0189] In some aspects, X^1 is CR^a, X^2 is CR^a, X^3 is CR^a, and X^4 is N.

[0190] In some aspects, X^1 is CR^a, X^2 is CR^a, X^3 is CR^a, and X^4 is CR^a.

[0191] In some aspects, R^1 is 5- or 6-membered heteroaryl.

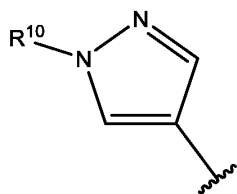
[0192] In some aspects, R^1 is an optionally substituted pyrazolyl.

[0193] In some aspects, R^1 is selected from:



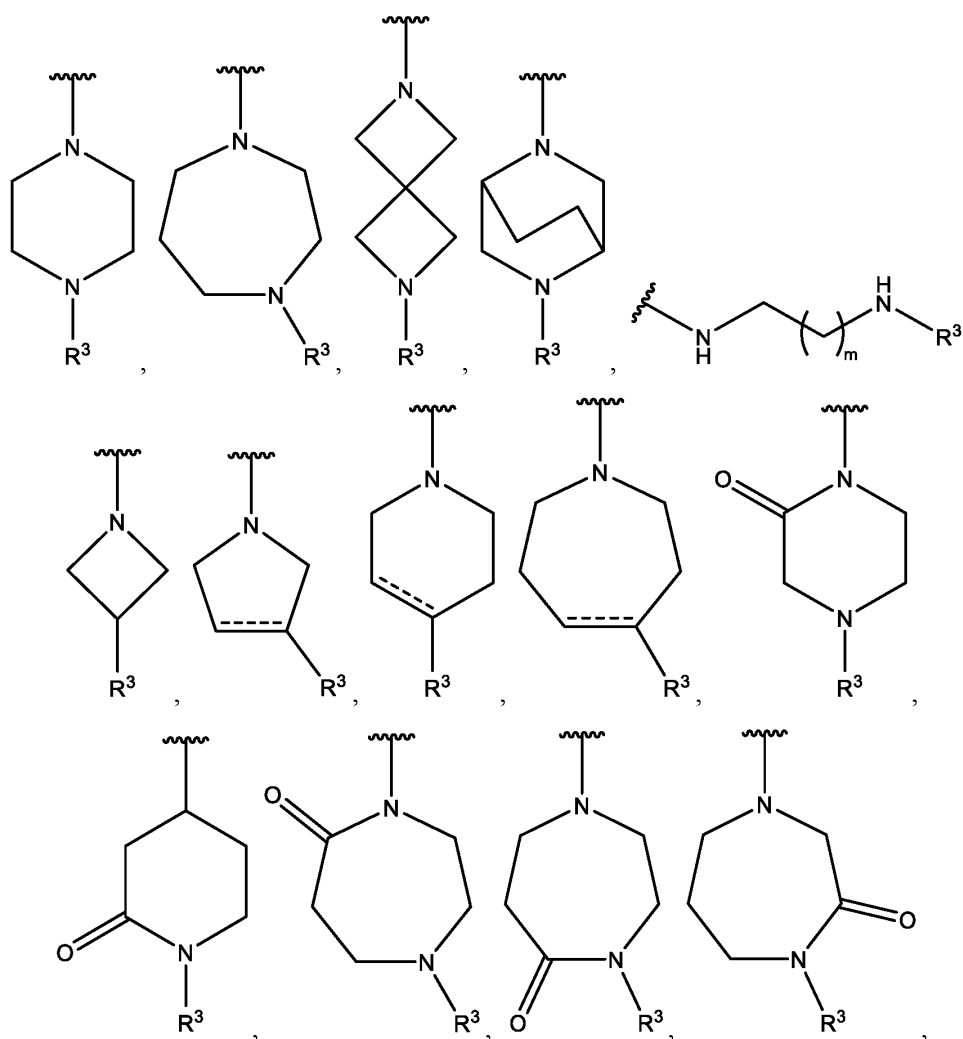
R^{10} is selected from H, C₁-C₄alkyl, C₁-C₄alkoxy, aminoC₁-C₄alkyl, hydroxyC₁-C₄alkyl, and C₁-C₄alkylsulfonyl, wherein the C₁-C₄alkyl, C₁-C₄alkoxy, aminoC₁-C₄alkyl, hydroxyC₁-C₄alkyl, and C₁-C₄alkylsulfonyl can be optionally substituted by one or more substituents selected from hydroxyl, C₁-C₄alkoxy, NR^{10a}R^{10b}, halo, and deuterium, wherein R^{10a} and R^{10b} are selected from hydrogen and C₁-C₄alkyl, or wherein R^{10a} and R^{10b} taken together with the nitrogen atom to which they are attached form a 4- to 8-membered ring.

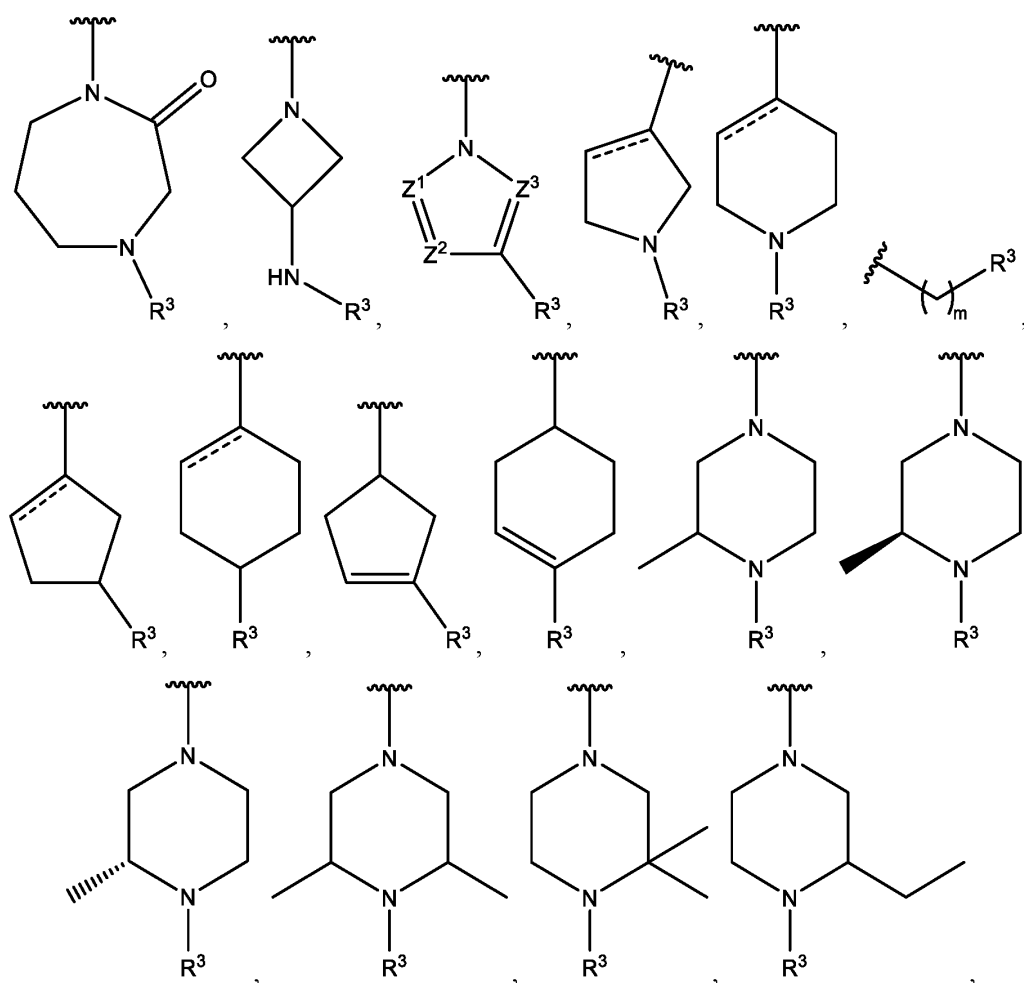
[0194] In some aspects, R^1 is

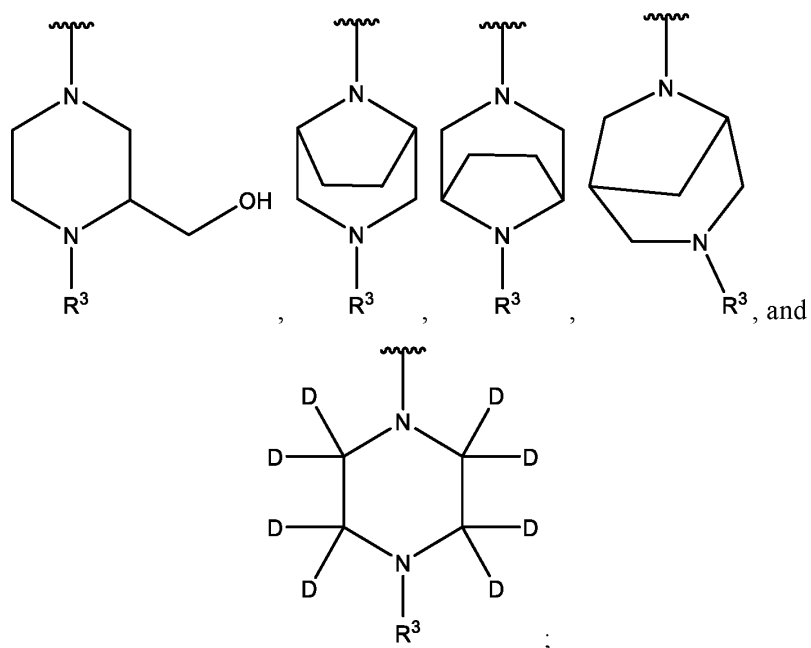


[0195] In some aspects, R^{10} is CH₃.

- [0196] In some aspects, R^2 is selected from cycloalkyl, cycloalkenyl, alkyl, oxoalkylamino, aminoalkylamino, amino, heterocyclyl, heteroaryl, aminoheterocyclyl, heterocyclylamino, and aminoalkylamino, all of which can be optionally substituted with six or more substituents selected from D, halo, hydroxy, oxo, and C_1 - C_4 alkyl.
- [0197] In some aspects, R^2 is heterocyclyl optionally substituted with C_1 - C_4 alkyl or oxo.
- [0198] In some aspects, R^2 is substituted with one R^3 .
- [0199] In some aspects, R^2 is selected from:







----- indicates a single bond or a double bond such that all valences are satisfied;

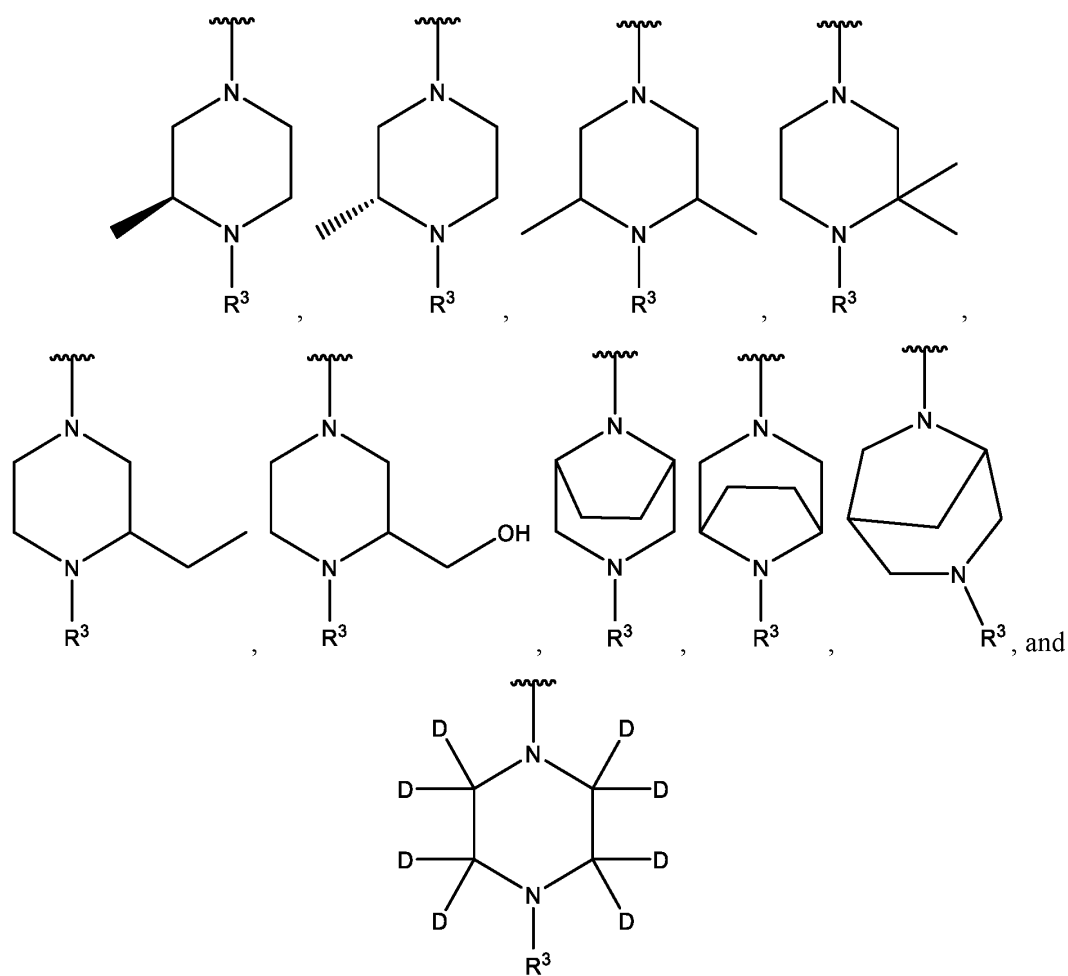
m is selected from 0, 1, 2, 3, 4, 5, and 6; and

Z^1 , Z^2 , and Z^3 are selected from N and CR^a .

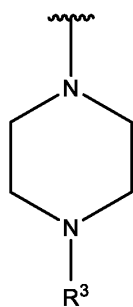
[0200]

In some aspects, R^2 is selected from:

In some aspects, R^2 is selected from the group consisting of:



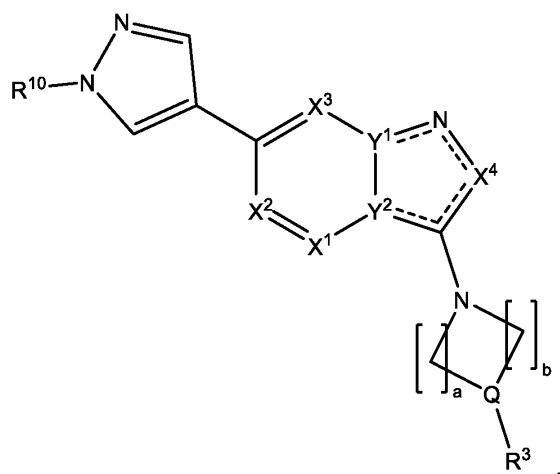
[0202] In some aspects, R^2 is:



[0203] In some aspects, R^3 is selected from aryl, heteroaryl, $-C(O)R^{31}$, $-C(O)OR^{31}$, $-C(O)NR^{31}R^{32}$, $-S(O)_2NR^{31}R^{32}$, cycloalkyl, and alkyl, all of which can be optionally substituted with one, two, three, four, or five R^{30} .

[0204] In some aspects, R^3 is selected from heteroaryl optionally substituted with one, two, three, four, or five R^{30} and $-C(O)OR^{31}$.

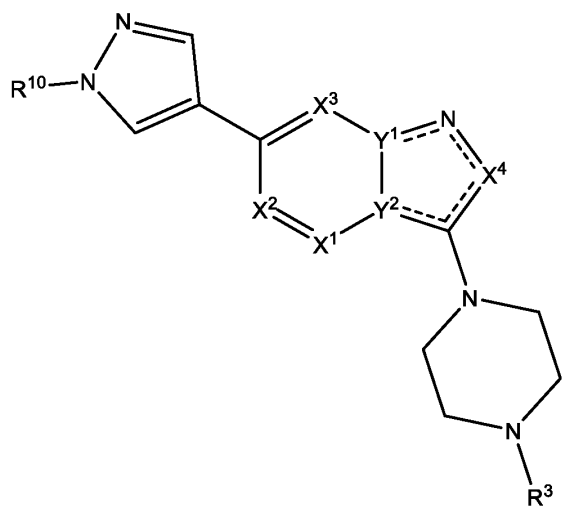
[0205] In some aspects, the PDGFR α inhibitor is a compound of Formula Ia:



[0206] or a pharmaceutically acceptable salt or solvate thereof, wherein a and b are each independently selected from 1, 2, and 3; and

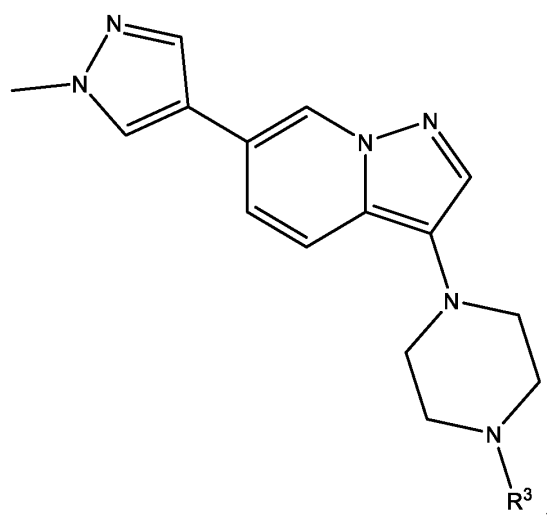
Q is selected from $-CH-$ and $-N-$, with the proviso that if Q is $-N-$, a and b are not 1.

[0207] In some aspects, the PDGFR α inhibitor is a compound of Formula II:



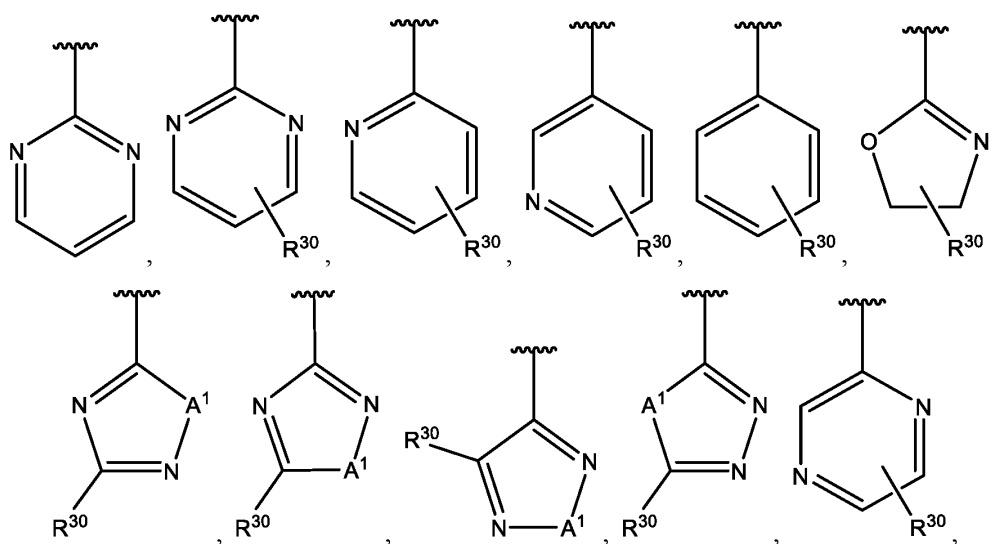
or a pharmaceutically acceptable salt or solvate thereof.

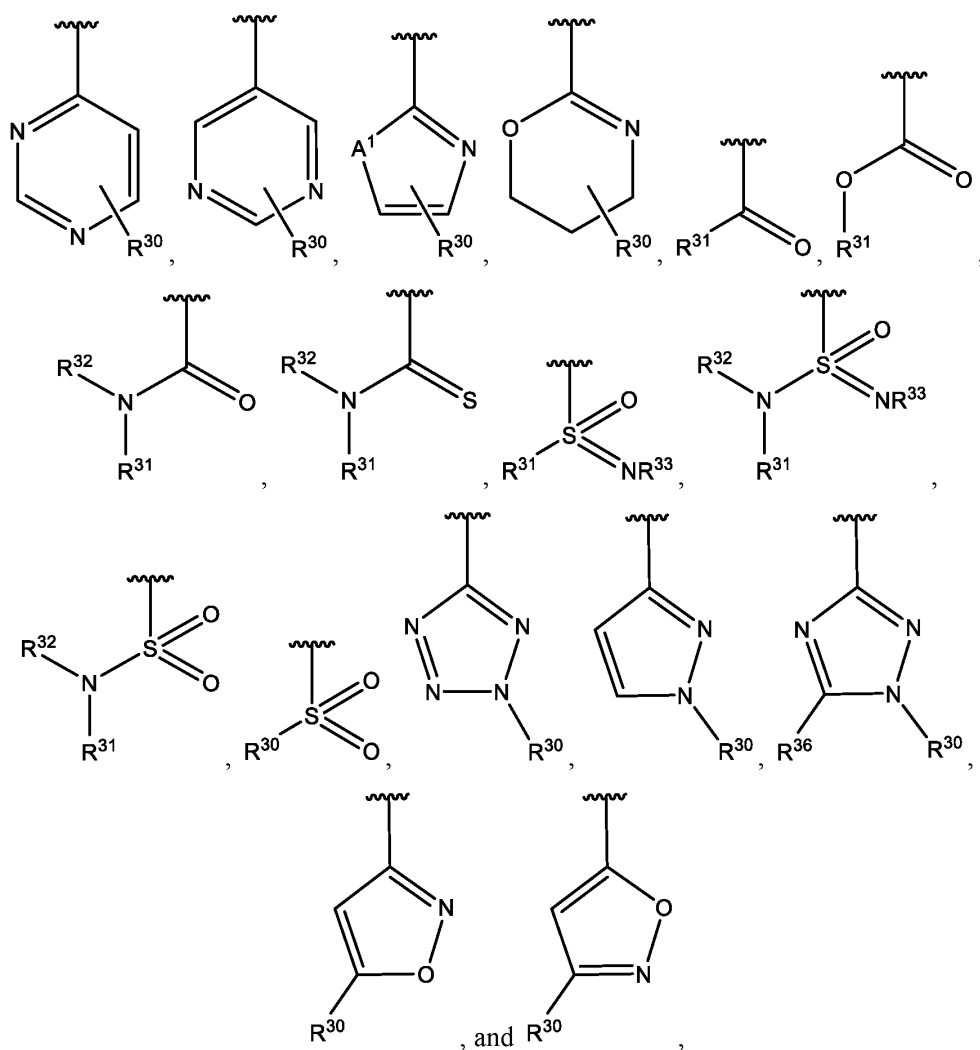
[0208] In some aspects, the PDGFR α inhibitor is a compound of Formula IIa:



or a pharmaceutically acceptable salt or solvate thereof.

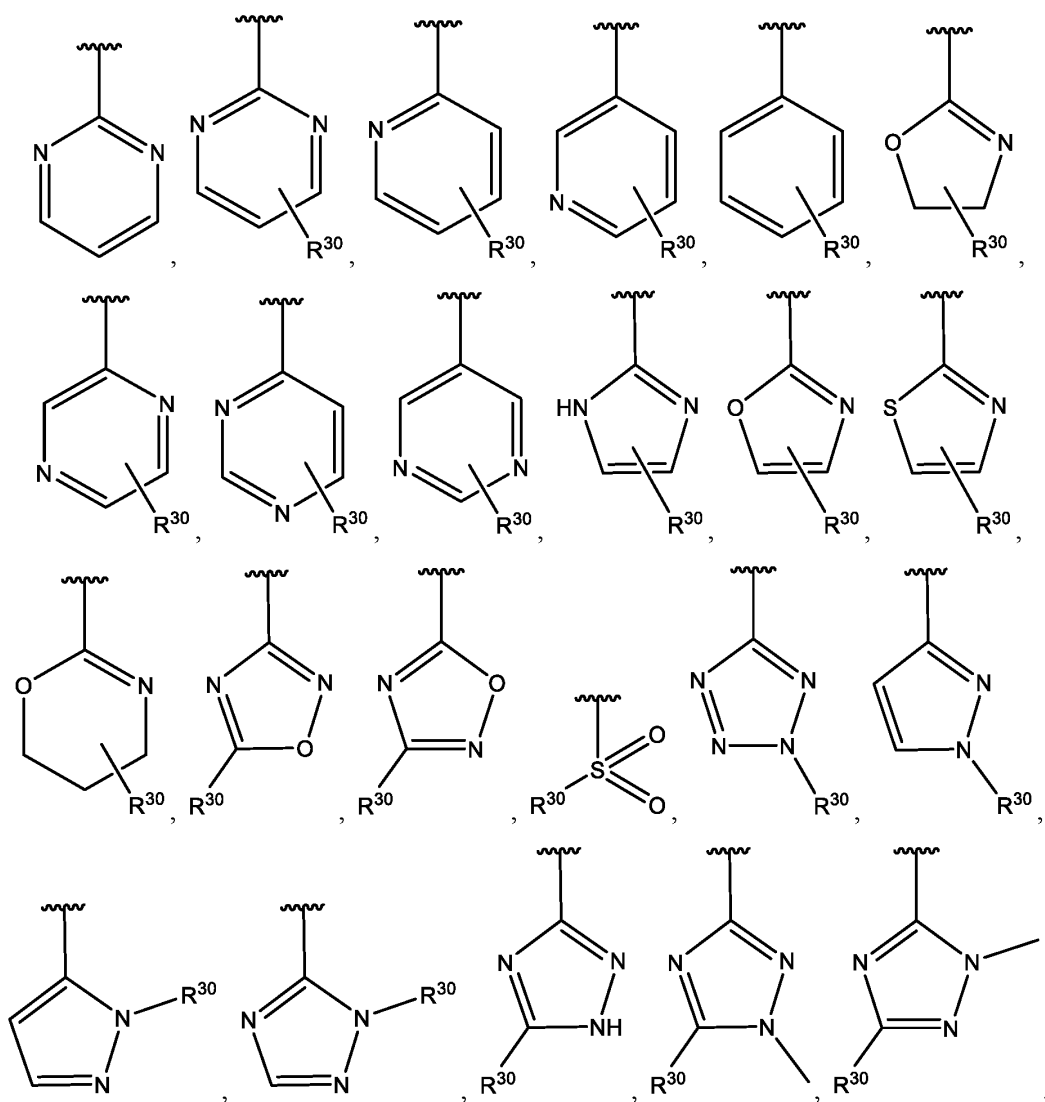
[0209] In some aspects, R^3 is selected from:

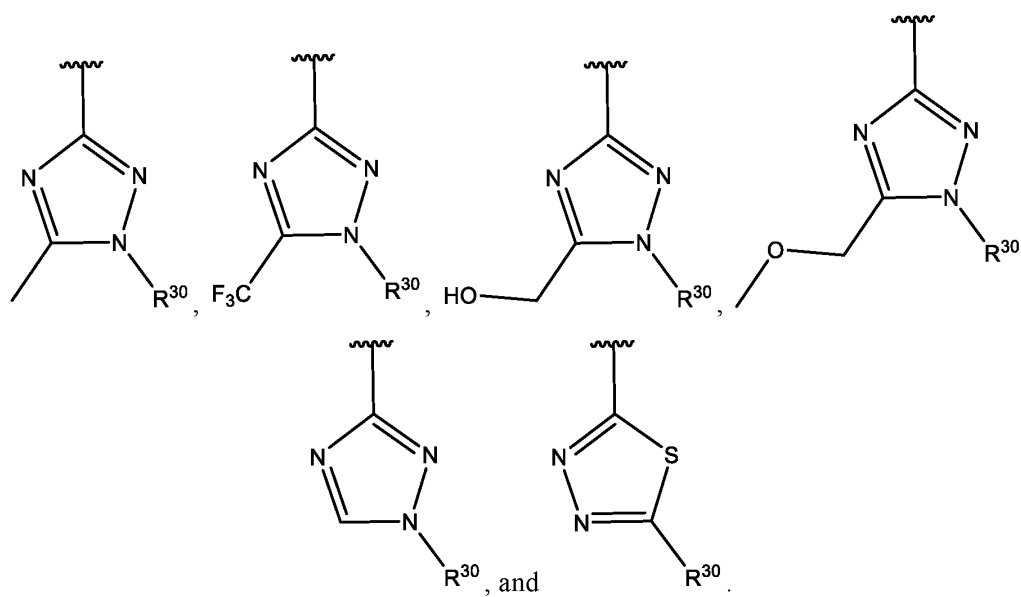




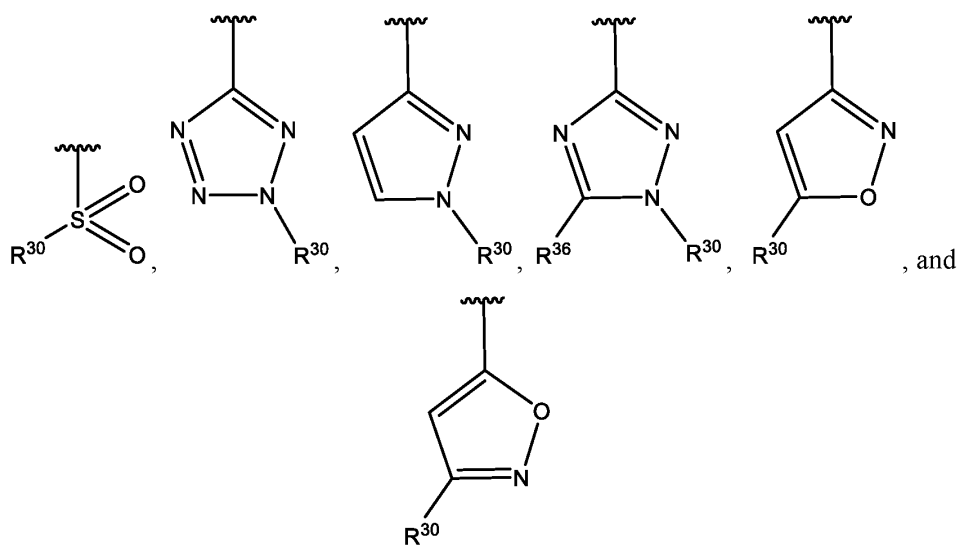
wherein A^1 is selected from O, S, and NR^{37} , R^{36} is selected from hydrogen, optionally substituted C_1 - C_6 alkyl, and optionally substituted C_1 - C_6 alkylaryl, and R^{37} is selected from hydrogen and C_1 - C_6 alkyl.

[0210] In some aspects, R^3 is selected from:



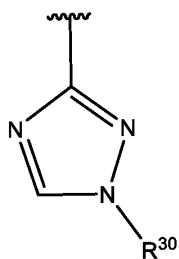


[0211] In some aspects, R^3 is selected from:

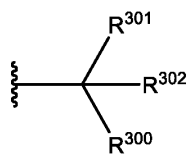


[0212] In some aspects, R³ is heteroaryl.

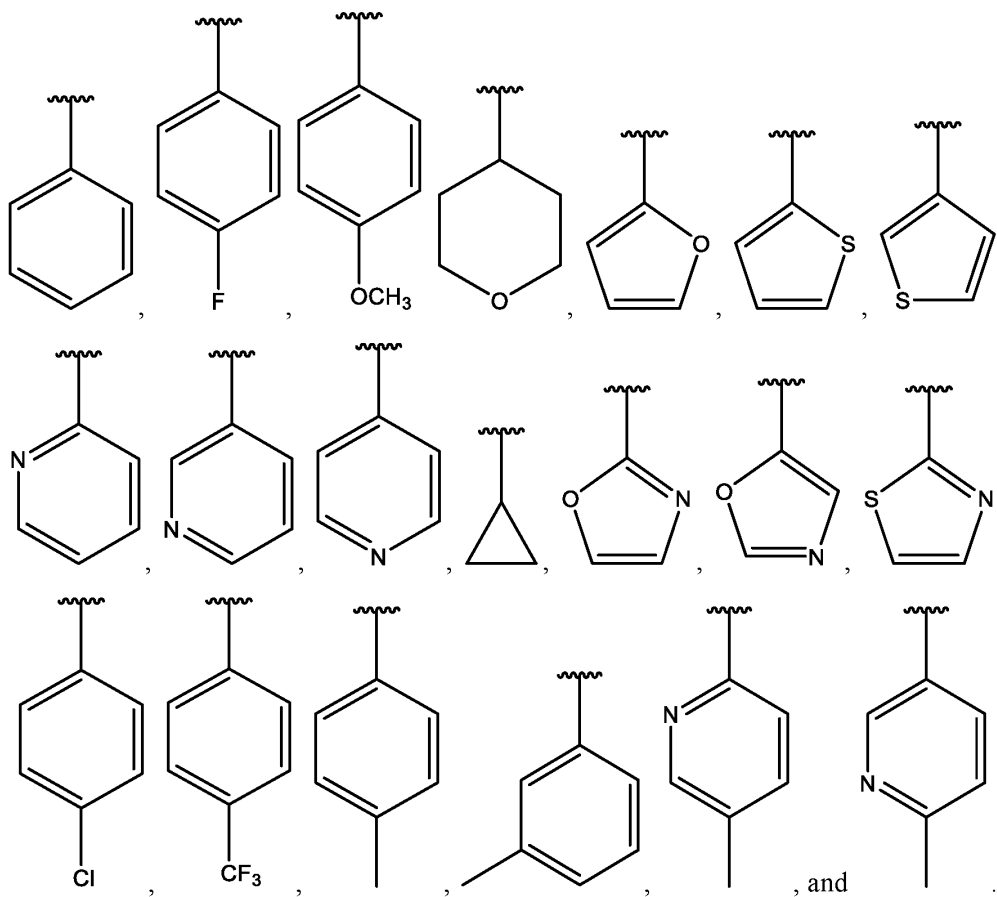
[0213] In some aspects, $\mathbb{R}^3$ is:



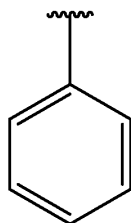
[0214] In some aspects, R^{30} is:



[0215] In some aspects, R^{300} is selected from:



[0216] In some aspects, R^{300} is:



[0217] In some aspects, R³⁰¹ is selected from H and CH₃.

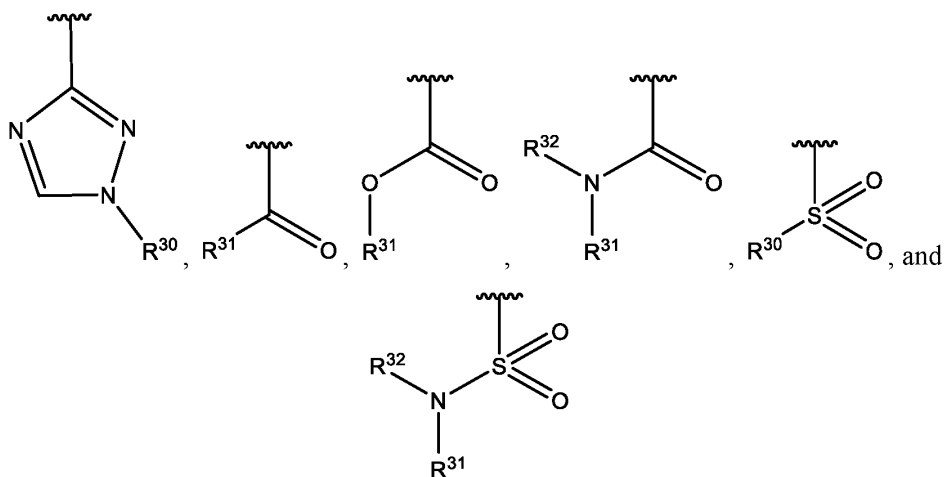
[0218] In some aspects, R³⁰¹ is H.

[0219] In some aspects, R^{302} is H.

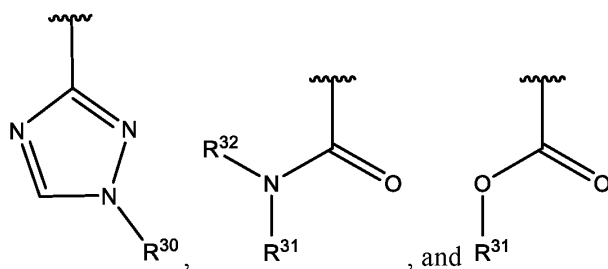
[0220] In some aspects, R^{301} and R^{302} are H.

[0221] In some aspects, R^{30} is benzyl.

[0222] In some aspects, R^3 is selected from:

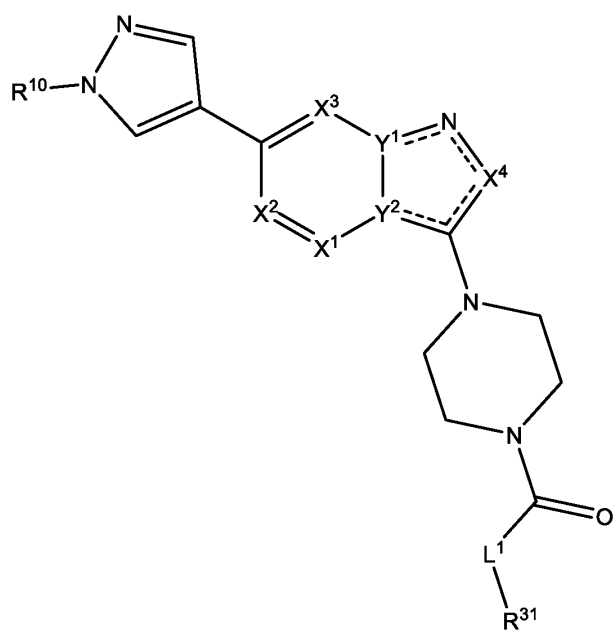


[0223] In some aspects, R^3 is selected from:



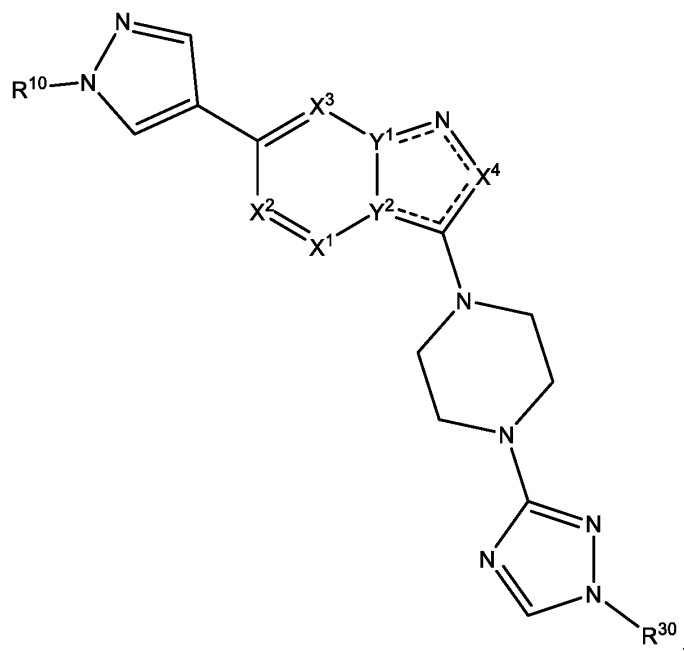
[0224] In some aspects, R^{32} is H.

[0225] In some aspects, the PDGFR α inhibitor is a compound of Formula IV:



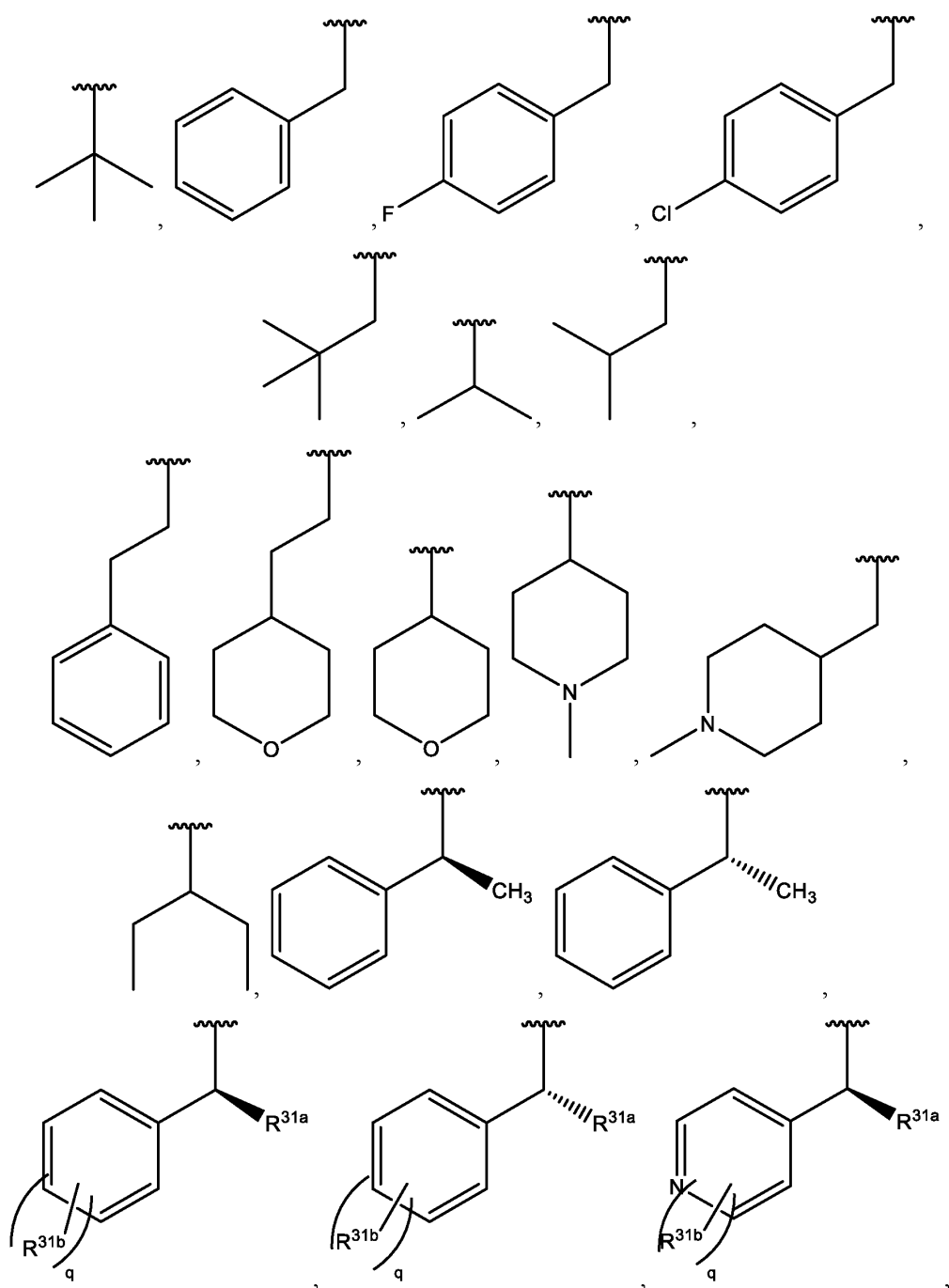
or a pharmaceutically acceptable salt or solvate thereof, wherein L^1 is a NH or O.

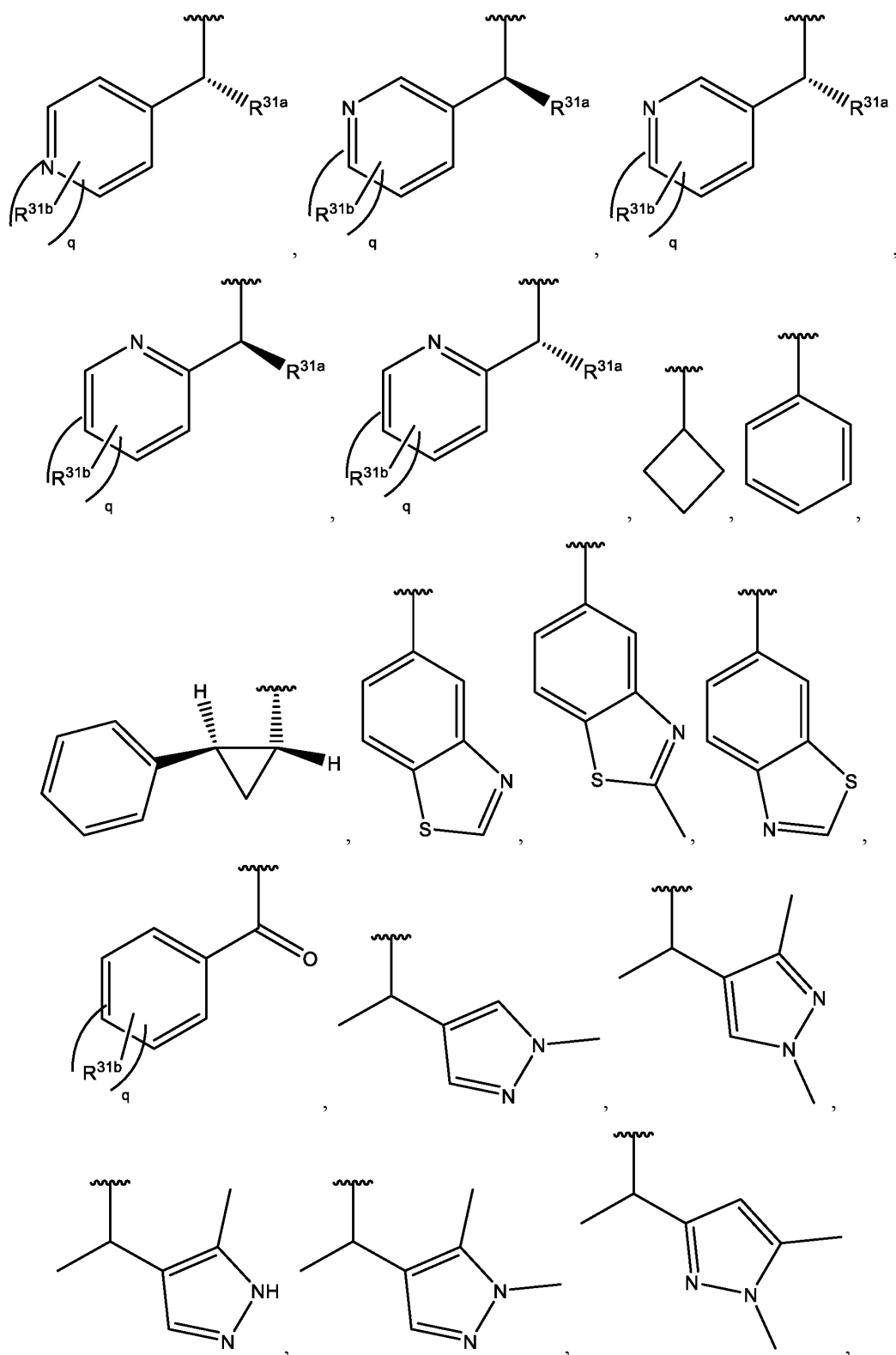
[0226] In some aspects, the PDGFR α inhibitor is a compound of Formula V:



or a pharmaceutically acceptable salt or solvate thereof.

[0227] In some aspects, R^{31} is selected from:



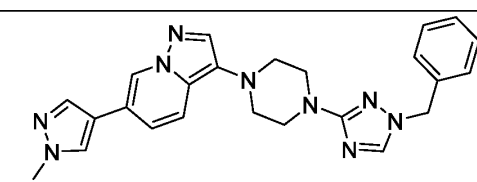
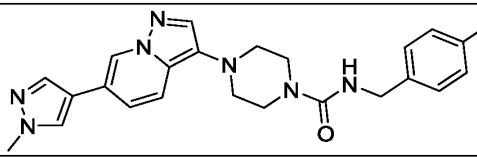
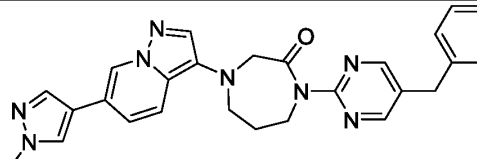
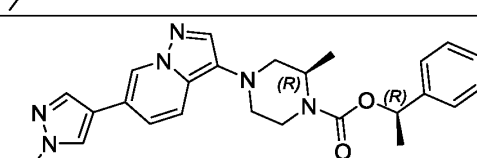
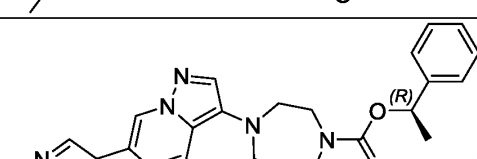
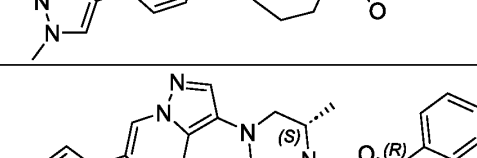


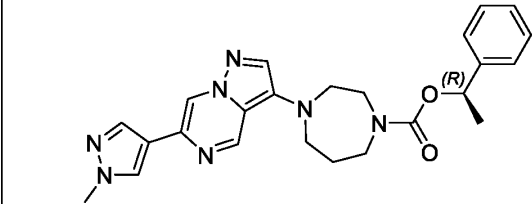
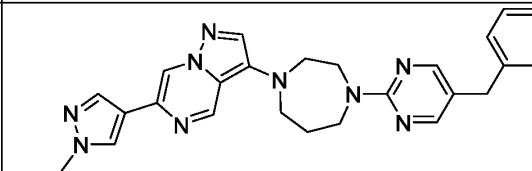
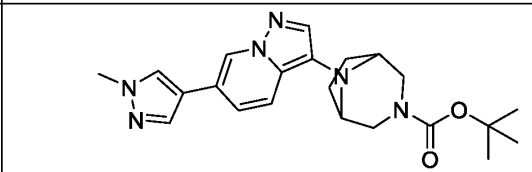
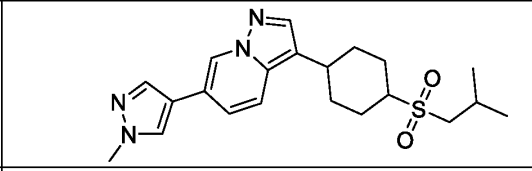
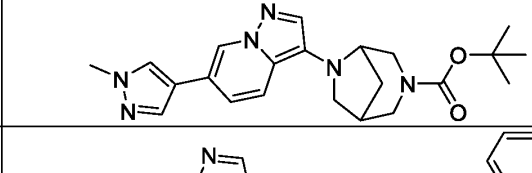
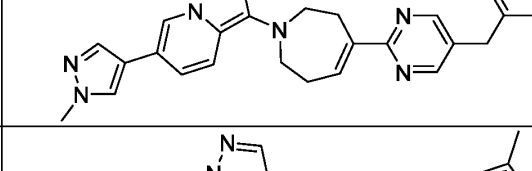
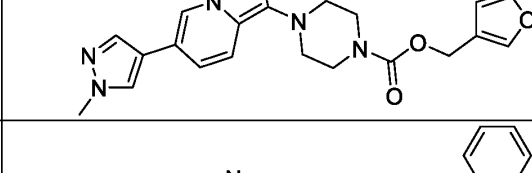
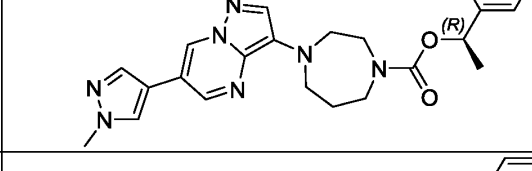
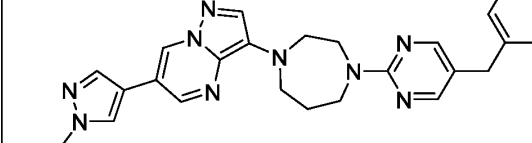
wherein R^{31a} is selected from H, D, alkylamino, optionally substituted C₁-C₄alkyl, C₁-C₄alkoxy, amino, and C₁-C₄haloalkyl;

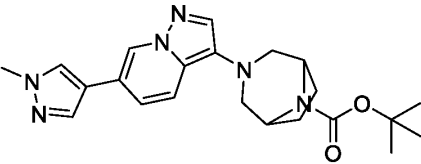
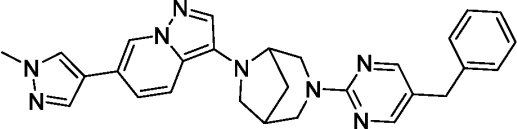
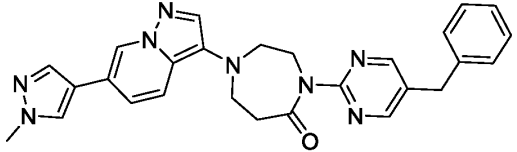
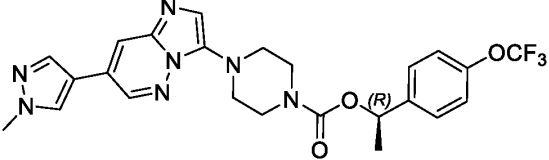
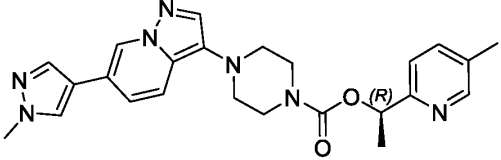
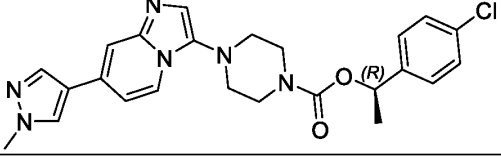
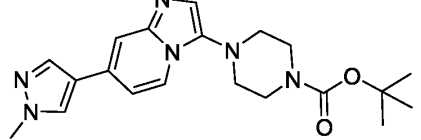
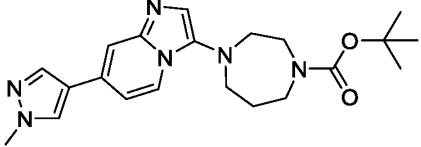
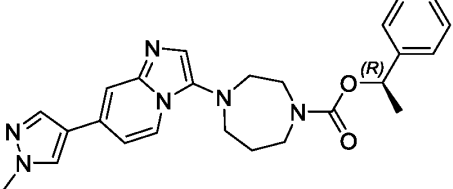
each R^{31b} is independently selected from H, D, halo, hydroxy, amino, cyano, alkylamino, optionally substituted C₁-C₄alkyl, C₁-C₄haloalkyl, optionally substituted C₁-C₄alkoxy, and C₃-C₆cycloalkyl, and q is 1, 2, or 3.

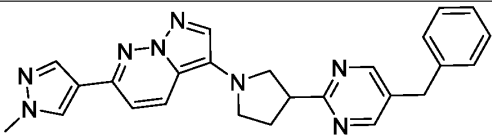
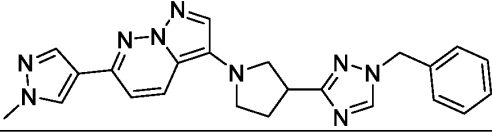
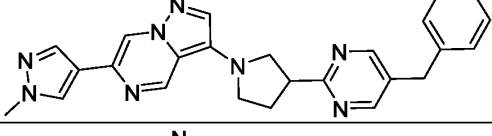
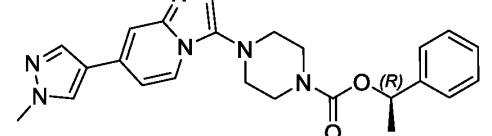
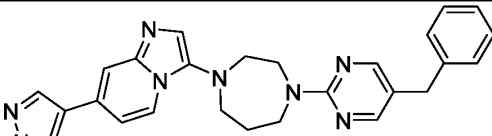
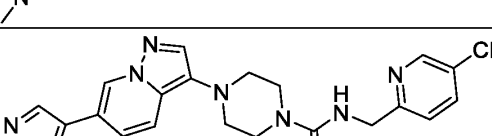
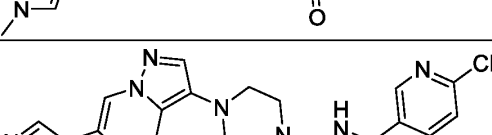
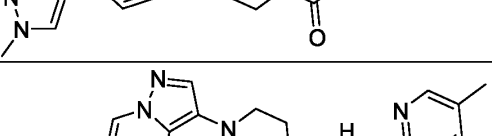
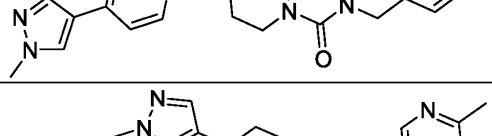
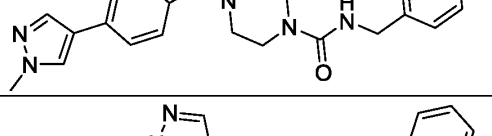
[0228] Table 1 (below) provides the structure of exemplary compounds that are useful for the present disclosure (*e.g.*, can target and inhibit kinase activity associated with PDGFR α expressed on OPCs).

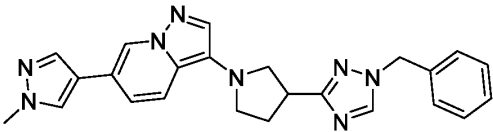
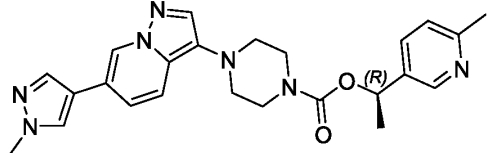
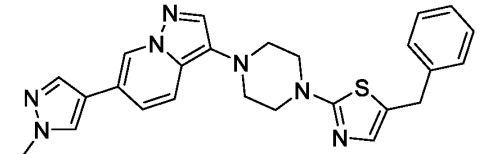
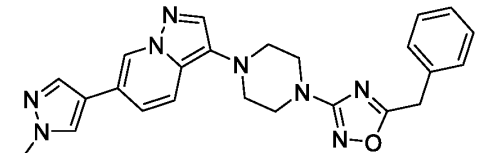
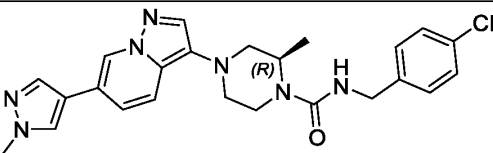
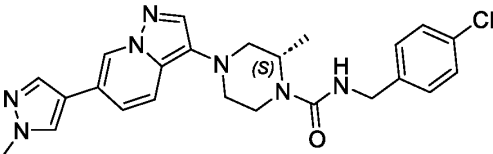
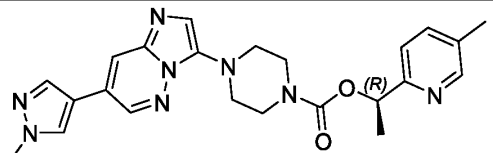
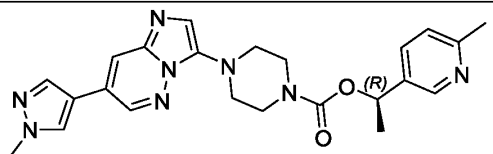
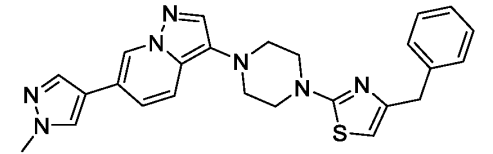
Table 1. Exemplary Compounds With PDGFR α Inhibitory Activity

Cmpd. No.	Structure
156	
275	
326	
327	
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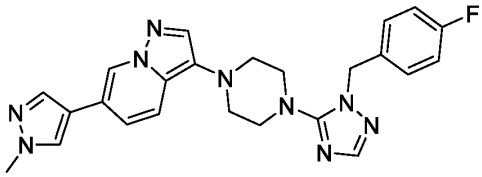
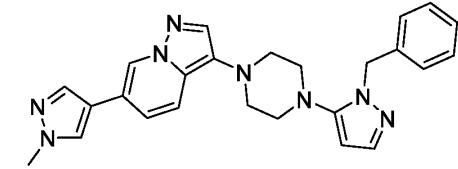
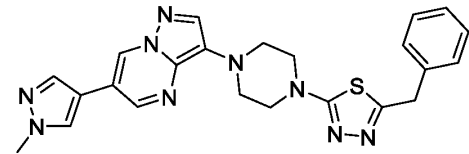
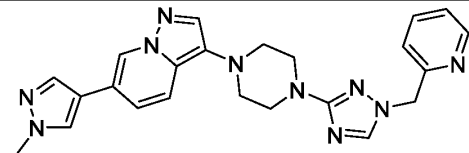
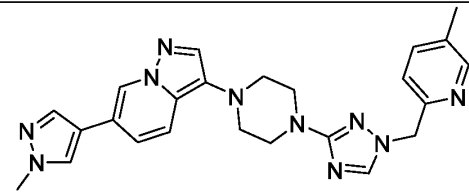
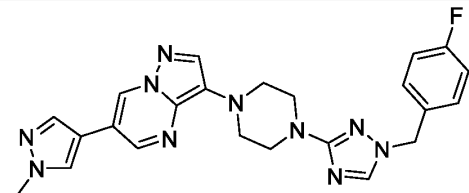
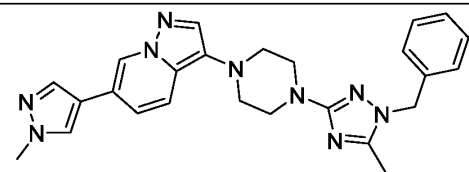
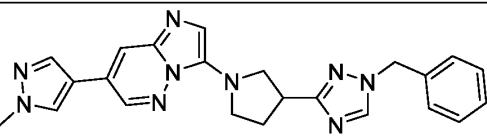
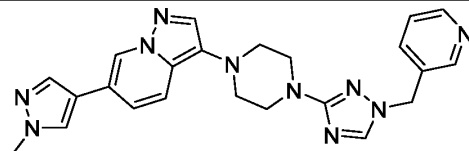
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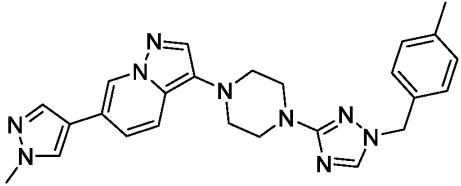
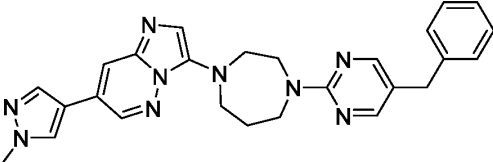
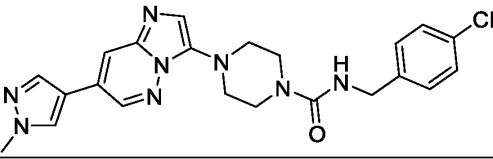
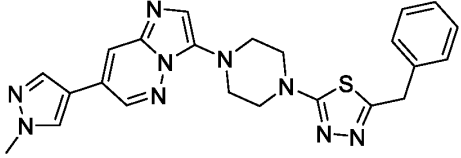
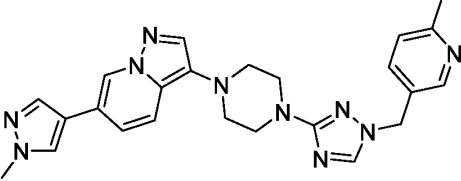
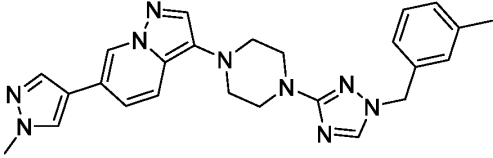
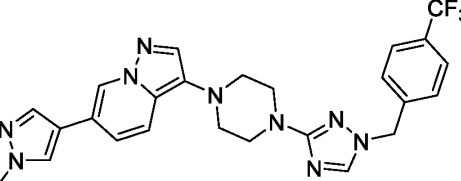
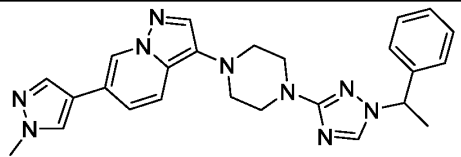
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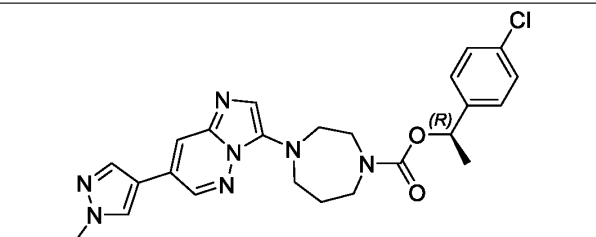
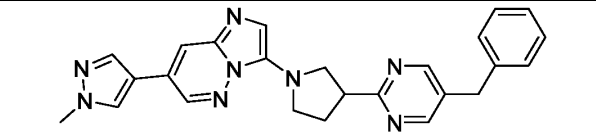
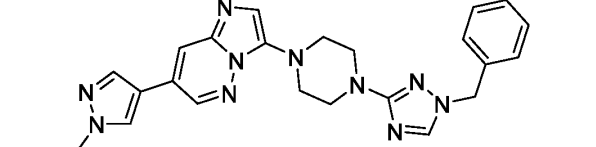
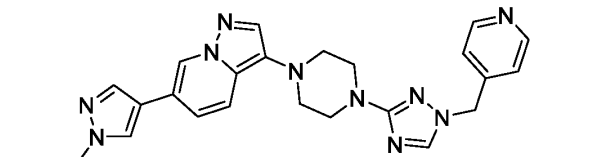
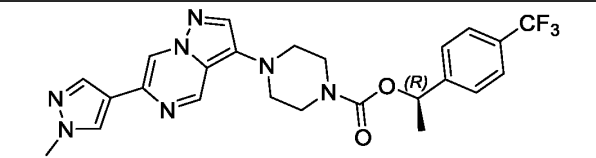
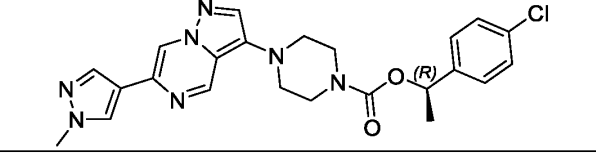
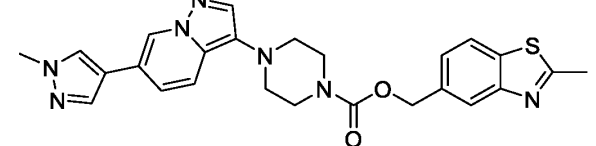
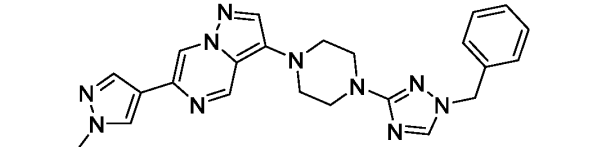
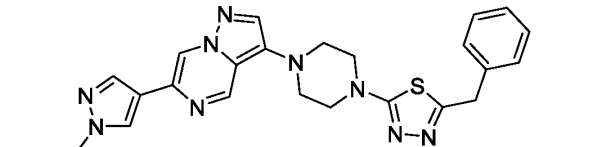
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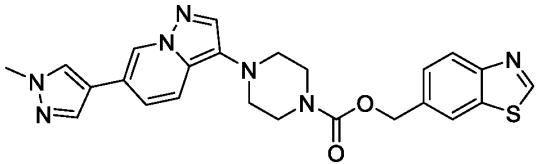
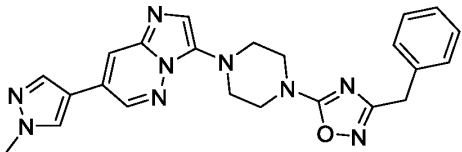
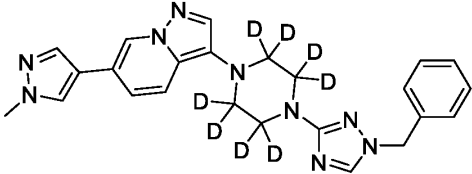
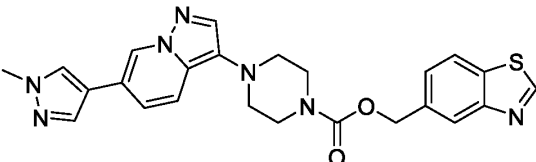
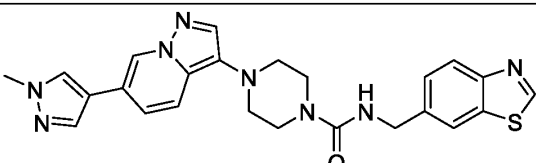
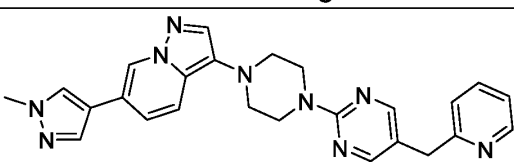
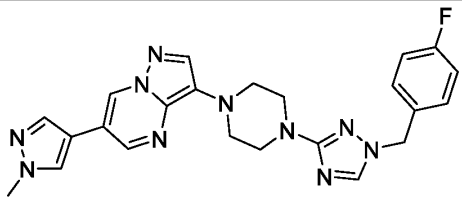
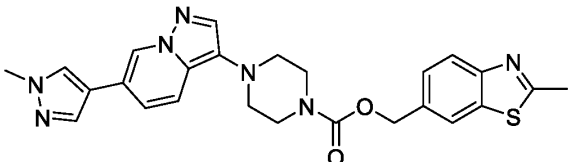
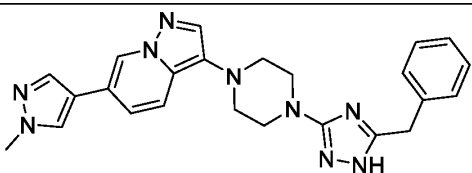
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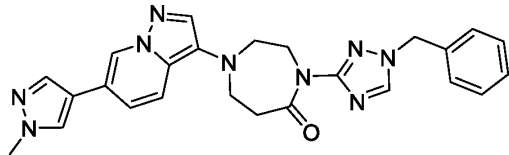
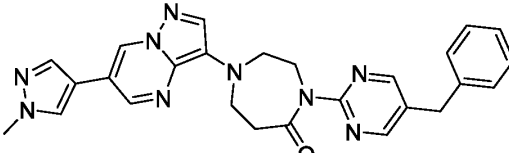
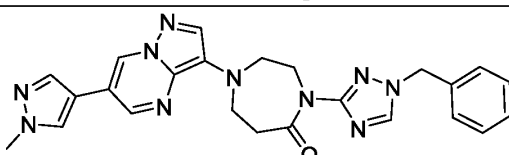
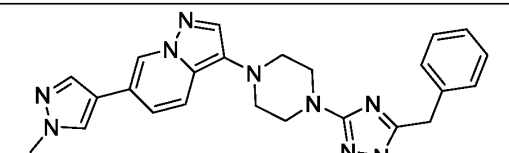
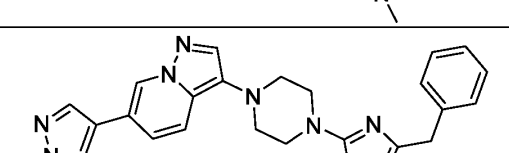
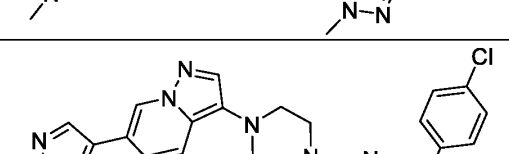
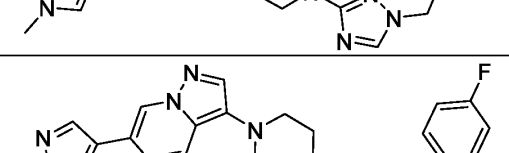
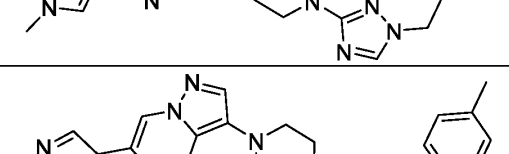
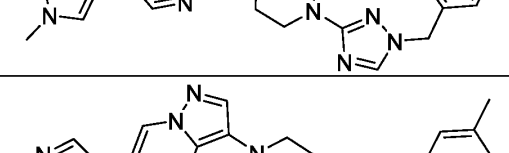
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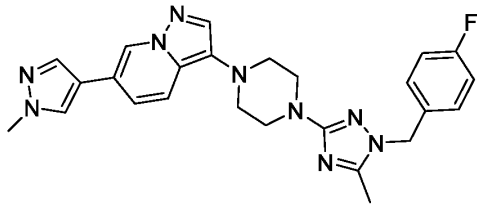
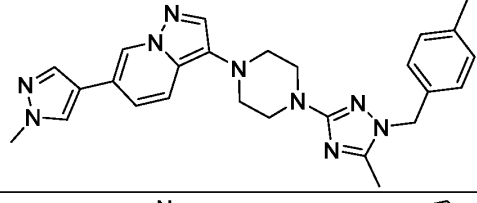
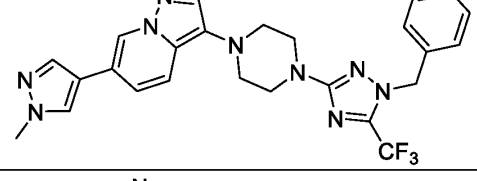
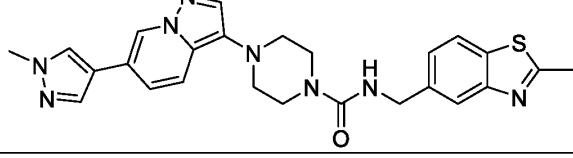
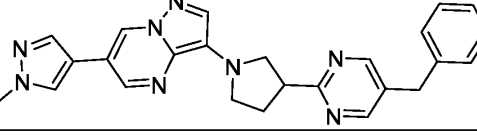
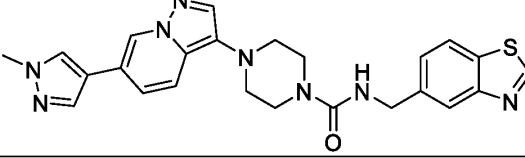
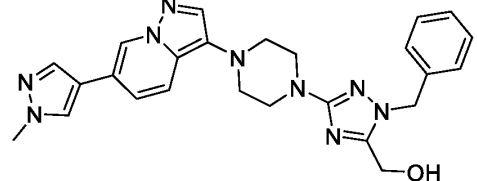
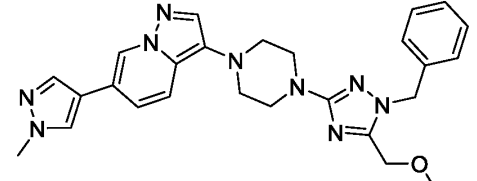
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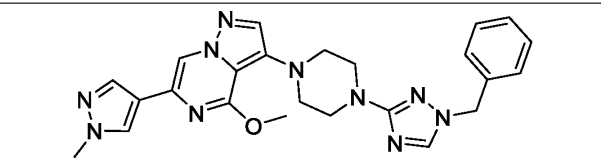
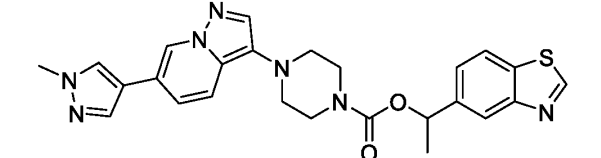
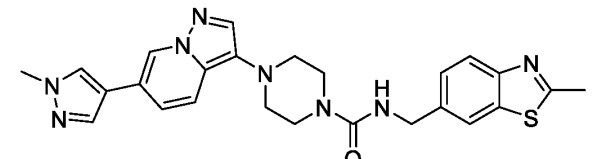
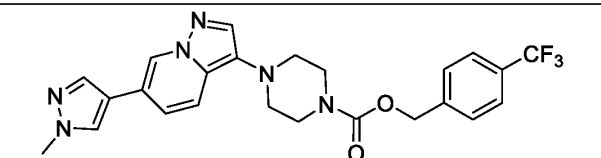
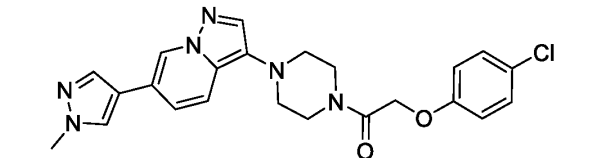
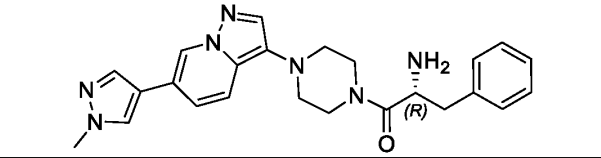
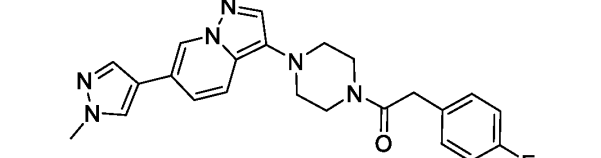
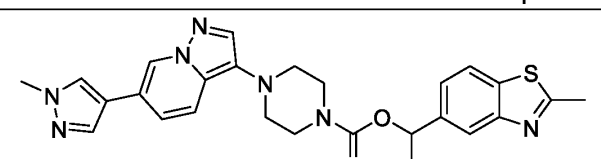
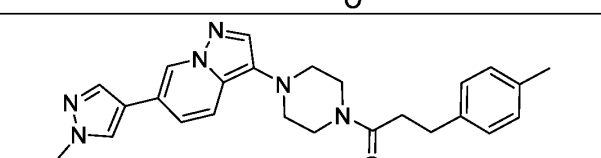
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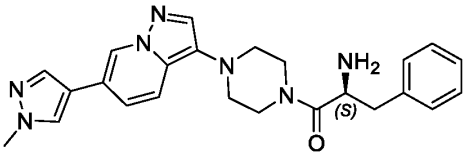
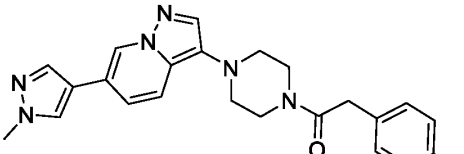
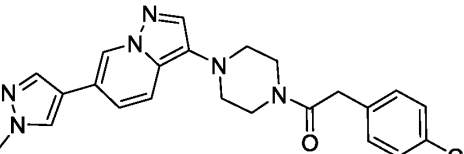
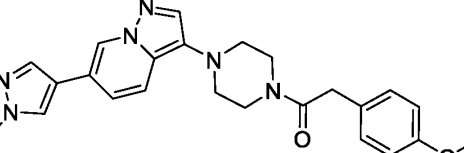
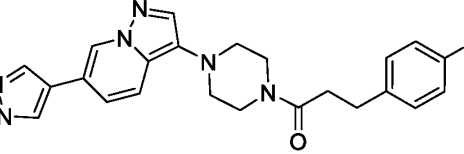
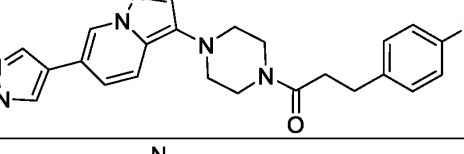
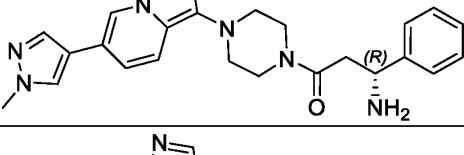
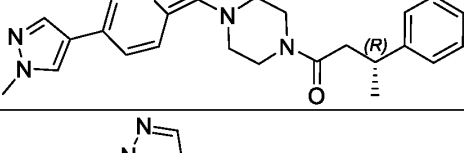
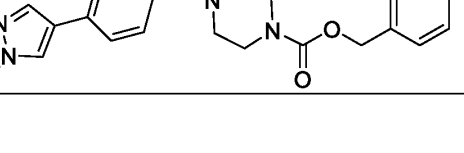
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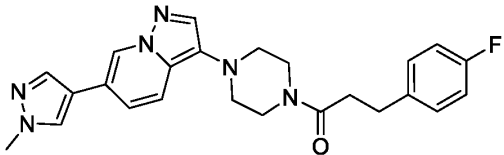
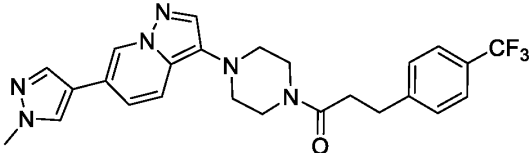
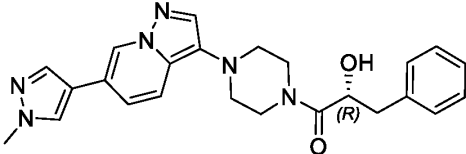
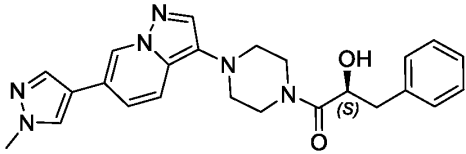
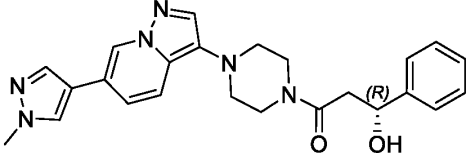
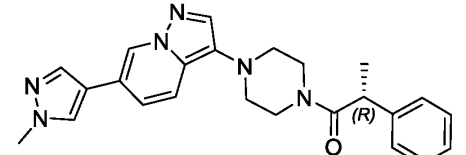
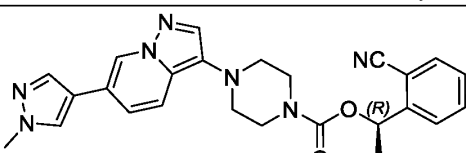
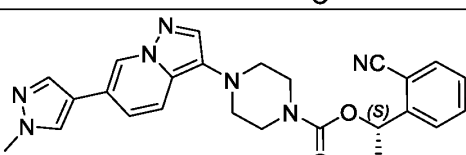
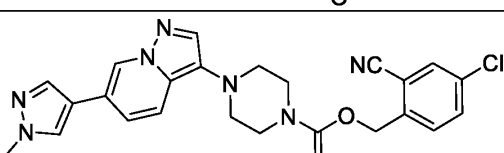
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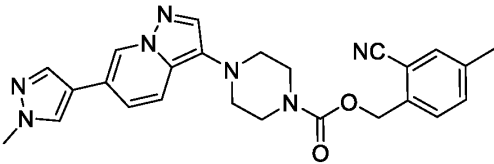
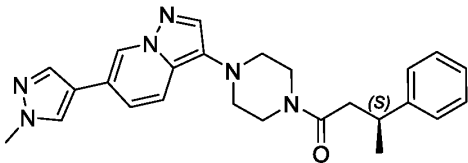
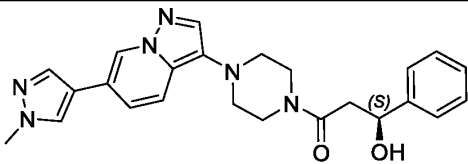
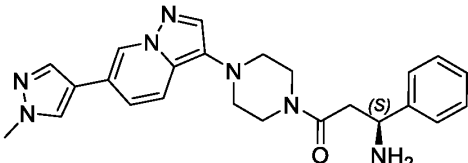
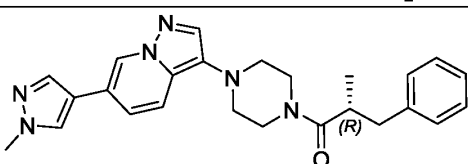
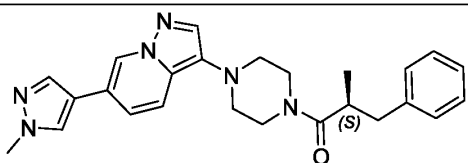
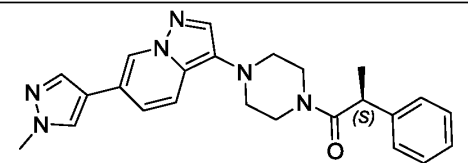
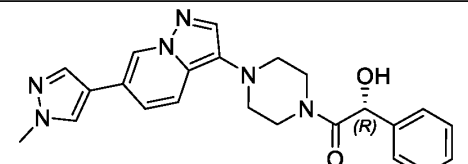
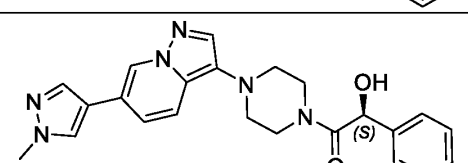
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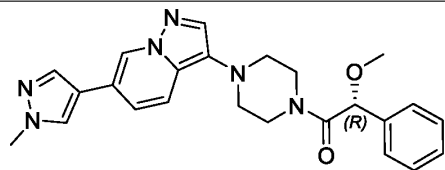
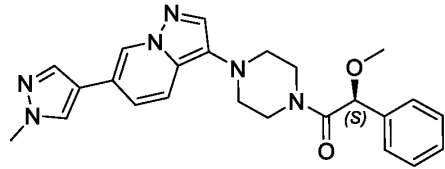
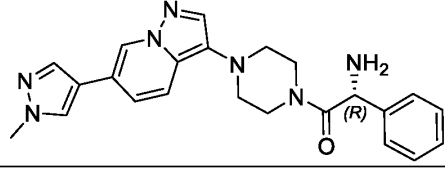
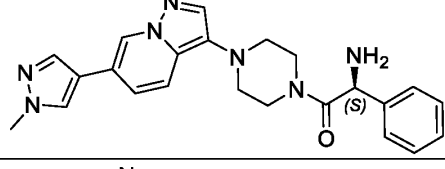
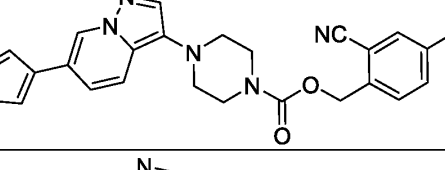
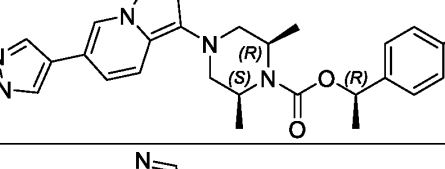
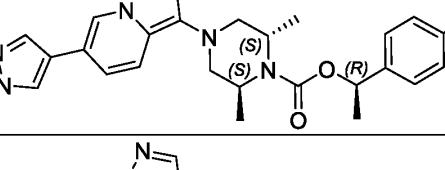
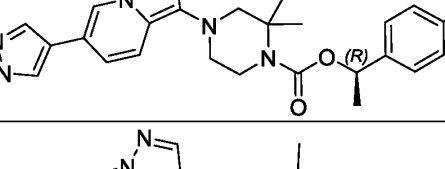
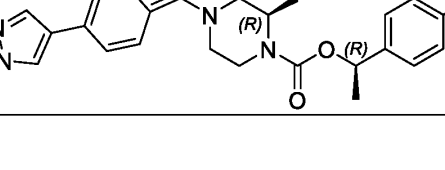
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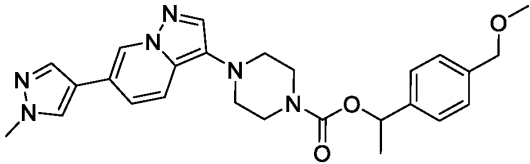
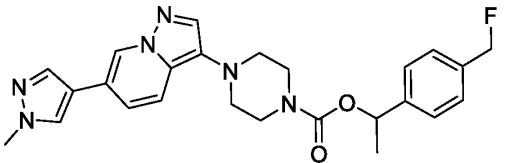
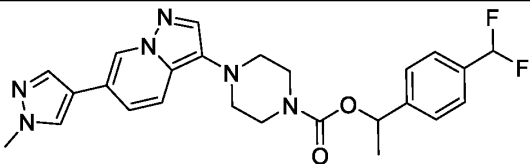
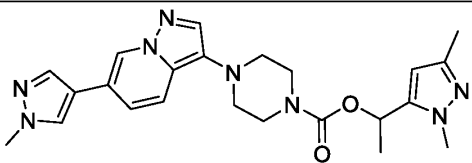
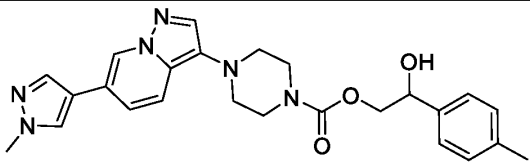
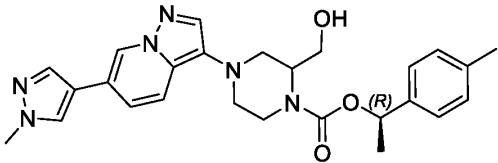
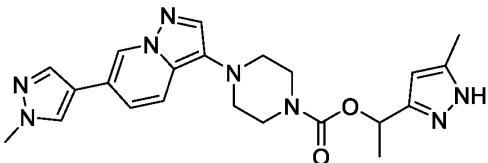
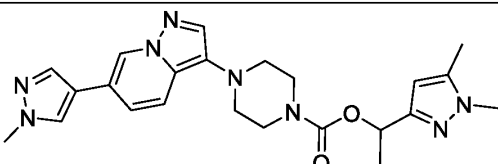
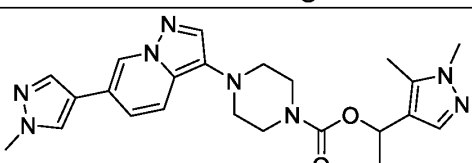
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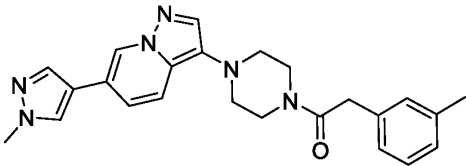
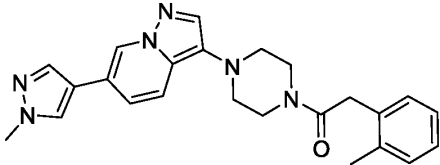
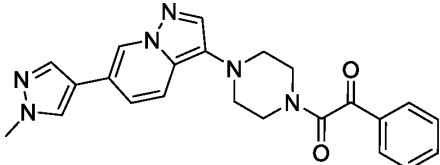
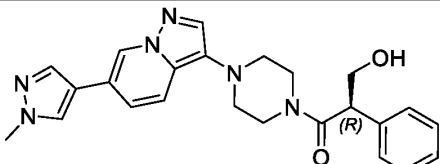
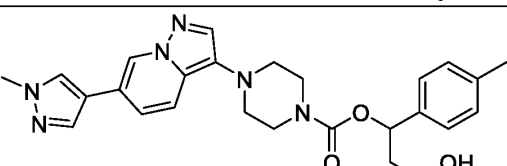
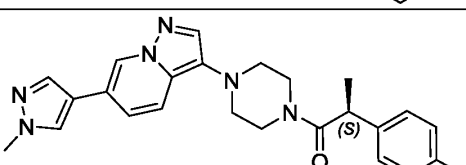
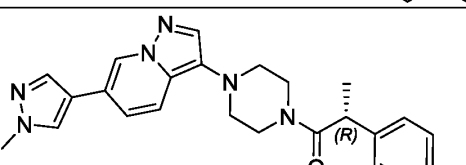
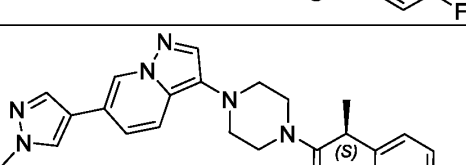
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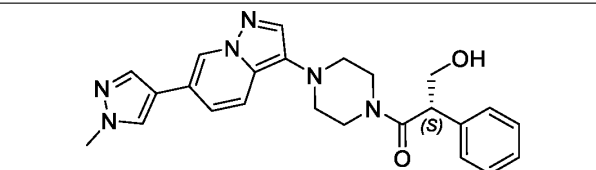
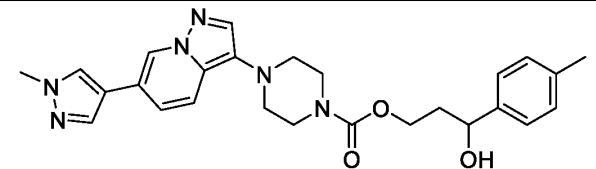
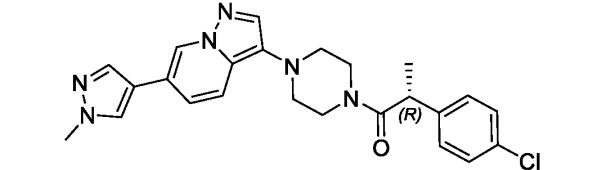
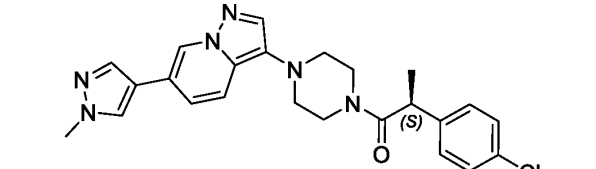
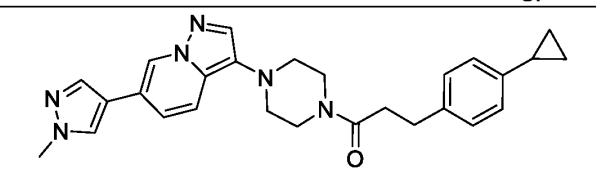
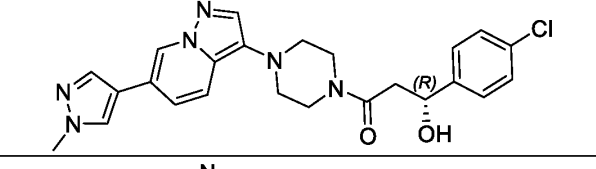
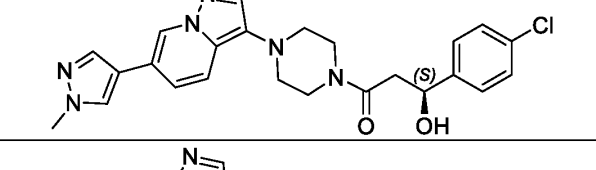
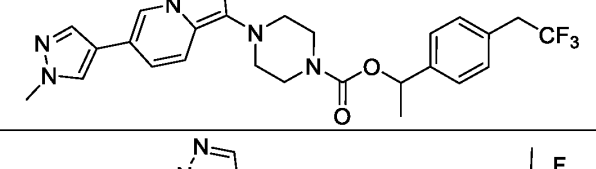
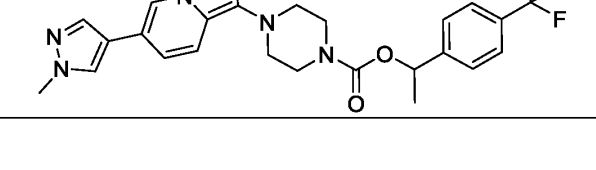
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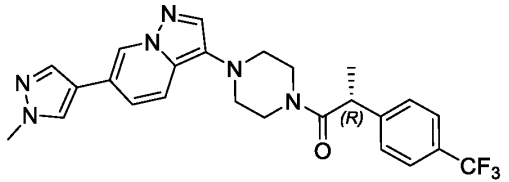
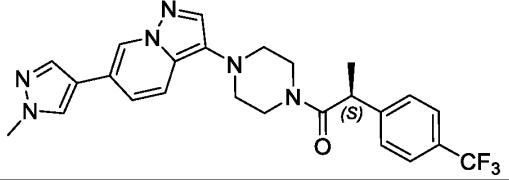
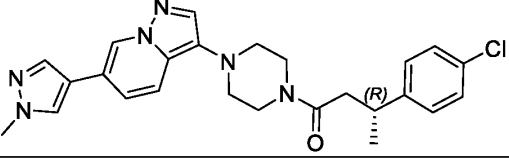
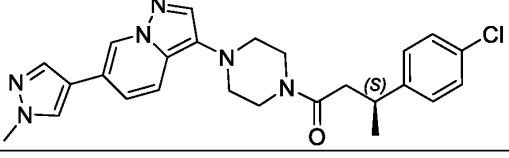
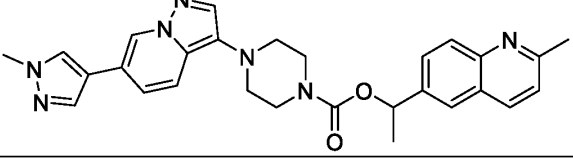
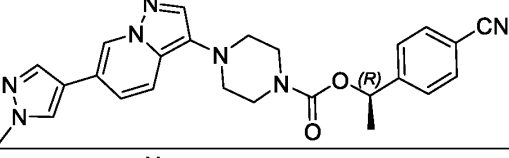
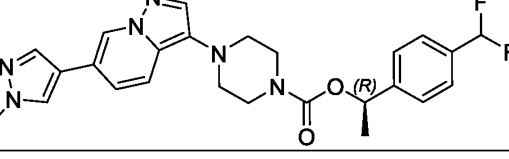
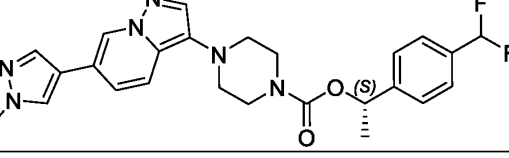
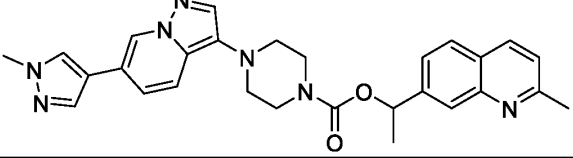
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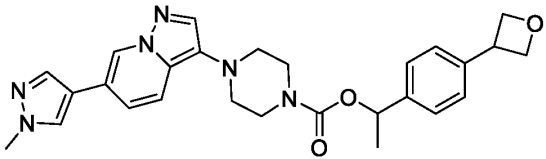
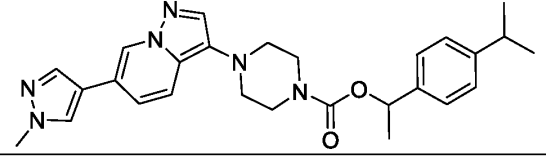
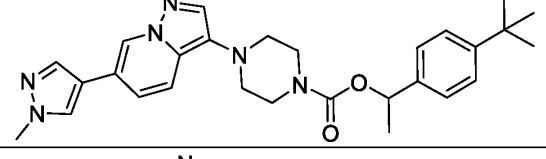
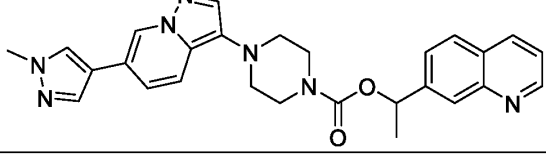
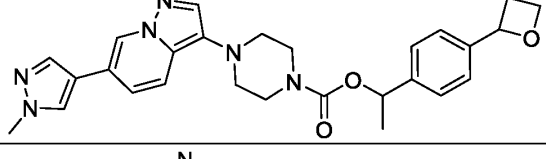
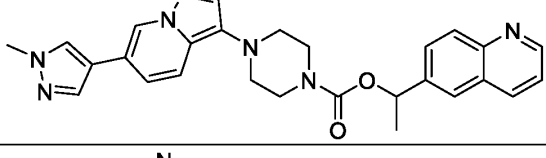
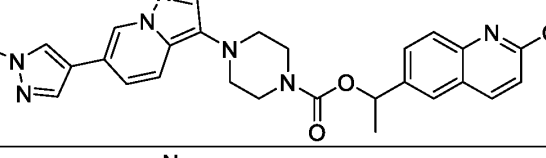
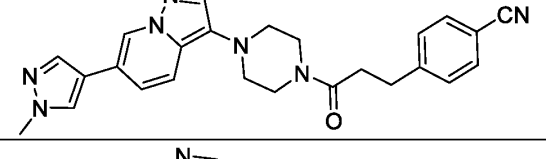
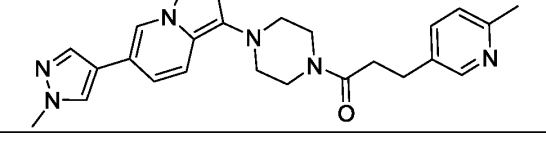
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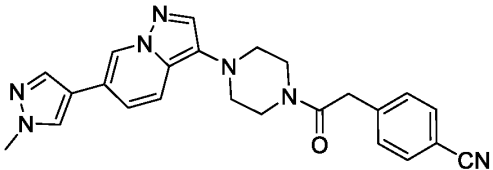
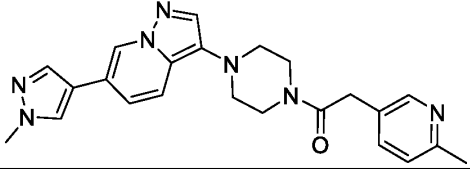
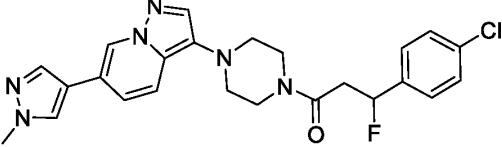
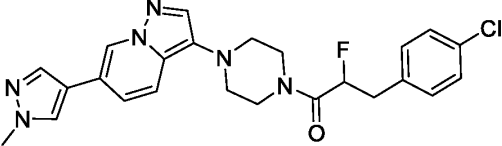
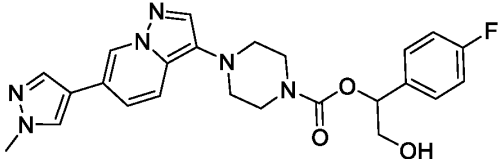
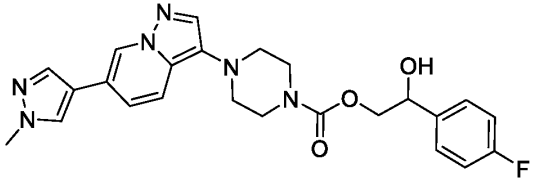
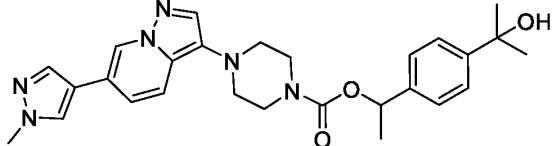
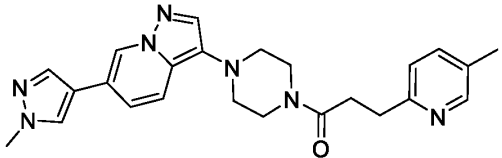
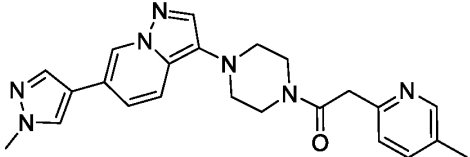
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[0229] In some aspects, the exemplary compounds of the present invention do not include compounds 156, 250 and 275. In some aspects, the exemplary compounds of the present invention do not include the compounds described in Table 1 on pp. 117-170 of International Appl. No. PCT/US2022/079480, which is herein incorporated by reference in its entirety.

[0230] In some aspects, the PDGFR α inhibitor is a compound described in Table 1 on pp. 117-170 of International Appl. No. PCT/US2022/079480.

[0231] In some aspects, the PDGFR α inhibitor is not a compound described in Table 1 on pp. 117-170 of International Appl. No. PCT/US2022/079480.

III. *Pharmaceutical Compositions*

[0232] Provided herein are compositions comprising a PDGFR α inhibitor of the present disclosure having the desired degree of purity, and a pharmaceutically acceptable carrier or excipient, in a form suitable for administration to a subject. In some aspects, the PDGFR α inhibitor has a purity of about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, or greater than about 99%. Pharmaceutically acceptable excipients or carriers can be determined in part by the particular composition being administered, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of pharmaceutical compositions (*See, e.g.*, Remington, 23rd Edition, The Science and Practice of Pharmacy, editor: A. Adejare, 2020, Adademic Press.). The pharmaceutical compositions are generally formulated sterile and in full compliance with all Good Manufacturing Practice (GMP) regulations of the U.S. Food and Drug Administration.

[0233] In some aspects, a pharmaceutical composition comprises a PDGFR α inhibitor described herein, and a pharmaceutically acceptable carrier. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum

albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.*, Zn-protein complexes); and/or non-ionic surfactants such as TWEEN[®], PLURONICS[®], or polyethylene glycol (PEG).

[0234] In some aspects, a pharmaceutical composition disclosed herein comprises one or more additional components selected from: a bulking agent, stabilizing agent, surfactant, buffering agent, or combinations thereof.

[0235] Buffering agents useful for the current disclosure can be a weak acid or base used to maintain the acidity (pH) of a solution near a chosen value after the addition of another acid or base. Suitable buffering agents can maximize the stability of the pharmaceutical compositions by maintaining pH control of the composition. Suitable buffering agents can also ensure physiological compatibility or optimize solubility. Rheology, viscosity and other properties can also be dependent on the pH of the composition. Common buffering agents include, but are not limited to, a Tris buffer, a Tris-Cl buffer, a histidine buffer, a TAE buffer, a HEPES buffer, a TBE buffer, a sodium phosphate buffer, a MES buffer, an ammonium sulfate buffer, a potassium phosphate buffer, a potassium thiocyanate buffer, a succinate buffer, a tartrate buffer, a DIPS buffer, a HEPPSO buffer, a POPS buffer, a PIPES buffer, a PBS buffer, a MOPS buffer, an acetate buffer, a phosphate buffer, a cacodylate buffer, a glycine buffer, a sulfate buffer, an imidazole buffer, a guanidine hydrochloride buffer, a phosphate-citrate buffer, a borate buffer, a malonate buffer, a 3-picoline buffer, a 2-picoline buffer, a 4-picoline buffer, a 3,5-lutidine buffer, a 3,4-lutidine buffer, a 2,4-lutidine buffer, a Aces, a diethylmalonate buffer, a N-methylimidazole buffer, a 1,2-dimethylimidazole buffer, a TAPS buffer, a bis- Tris buffer, a L-arginine buffer, a lactate buffer, a glycolate buffer, or combinations thereof.

[0236] In some aspects, a pharmaceutical composition disclosed herein further comprises a bulking agent. Bulking agents can be added to a pharmaceutical product in order to add volume and mass to the product, thereby facilitating precise metering and handling thereof. Bulking agents that can be used with the present disclosure include, but are not limited to, sodium chloride (NaCl), mannitol, glycine, alanine, or combinations thereof.

- [0237] In some aspects, a pharmaceutical composition disclosed herein can also comprise a stabilizing agent. Non-limiting examples of stabilizing agents that can be used with the present disclosure include: sucrose, trehalose, raffinose, arginine, or combinations thereof.
- [0238] In some aspects, a pharmaceutical composition disclosed herein comprises a surfactant. In some aspects, the surfactant can be selected from the following: alkyl ethoxylate, nonylphenol ethoxylate, amine ethoxylate, polyethylene oxide, polypropylene oxide, fatty alcohols such as cetyl alcohol or oleyl alcohol, cocamide MEA, cocamide DEA, polysorbates, dodecyl dimethylamine oxide, or combinations thereof. In some aspects, the surfactant is polysorbate 20 or polysorbate 80.
- [0239] In some aspects, a pharmaceutical composition disclosed herein (*e.g.*, comprising a PDGFR α inhibitor) further comprises an amino acid. In some aspects, the amino acid is selected from arginine, glutamate, glycine, histidine, or combinations thereof. In some aspects, the composition further comprises a sugar alcohol. Non-limiting examples of sugar alcohol includes: sorbitol, xylitol, maltitol, mannitol, or combinations thereof.
- [0240] A pharmaceutical composition disclosed herein (*e.g.*, comprising a PDGFR α inhibitor) can be formulated for any route of administration to a subject. Specific examples of routes of administration include intramuscularly, cutaneously, subcutaneously, ophthalmic, intravenously, intraperitoneally, intradermally, intraorbitally, intracerebrally, intracranially, intraspinally, intraventricularly, intrathecally, intracapsularly, orally, pulmonarily, intranasally, intra-arterially, intralymphatically, periocularly, topically, transdermally, rectally, vaginally, or intratumorally, or via intratympanic injection. Parenteral administration, characterized by, *e.g.*, cutaneous, subcutaneous, intramuscular, or intravenous injection, is also contemplated herein.
- [0241] Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. The injectables, solutions and emulsions also contain one or more excipients. Suitable excipients are, for example, water, saline, dextrose, glycerol, or ethanol. In addition, if desired, the pharmaceutical compositions to be administered can also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, and cyclodextrins.

- [0242]** Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents, and other pharmaceutically acceptable substances. Examples of aqueous vehicles include sodium chloride injection, Ringer's injection, isotonic dextrose injection, sterile water injection, dextrose, and lactated Ringer's injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations can be added to parenteral preparations packaged in multiple-dose containers which include, for example, phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride, and benzethonium chloride. Isotonic agents include sodium chloride, and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (TWEEN® 80). Sequestering or chelating agent of metal ions includes EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol, and propylene glycol for water miscible vehicles; and sodium hydroxide, hydrochloric acid, citric acid, or lactic acid for pH adjustment.
- [0243]** Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use, and sterile emulsions. The solutions can be either aqueous or nonaqueous.
- [0244]** If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol, and mixtures thereof.
- [0245]** Topical mixtures comprising a compound described herein are prepared as described for the local and systemic administration. The resulting mixture can be a solution, suspension, emulsions, or the like and can be formulated as creams, gels, ointments,

emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches, or any other formulations suitable for topical administration.

[0246] A therapeutic agent described herein (*e.g.*, PDGFR α inhibitor) can be formulated as an aerosol for topical application, such as by inhalation (*see, e.g.*, U.S. Patent Nos. 4,044,126; 4,414,209; and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflations, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation can have diameters of less than about 50 microns, *e.g.*, less than about 10 microns. In some aspects, the particle diameters can have diameters of less than about 50 microns, *e.g.*, less than about 10 microns, as measured by dynamic light scattering (DLS) or static image analysis using microscopy.

[0247] A therapeutic agent disclosed herein (*e.g.*, PDGFR α inhibitor) can be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies.

[0248] Transdermal patches, including iontophoretic and electrophoretic devices, are well known to those of skill in the art, and can be used to administer a therapeutic agent (*e.g.*, those disclosed herein). For example, such patches are disclosed in U.S. Patent Nos. 6,267,983; 6,261,595; 6,256,533; 6,167,301; 6,024,975; 6,010,715; 5,985,317; 5,983,134; 5,948,433; and 5,860,957.

[0249] In some aspects, a pharmaceutical composition comprising a therapeutic agent described herein (*e.g.*, PDGFR α inhibitor) is a lyophilized powder, which can be reconstituted for administration as solutions, emulsions, and other mixtures. It can also be reconstituted and formulated as a solid or a gel. The lyophilized powder is prepared by dissolving a compound as described herein, or a pharmaceutically acceptable derivative thereof, in a suitable solvent. In some aspects, the lyophilized powder is sterile. The solvent can contain an excipient, which improves the stability or other pharmacological component

of the powder or reconstituted solution that is prepared from the powder. Excipients that can be used include, but are not limited to, dextrose, sorbitol, fructose, corn syrup, xylitol, glycerin, glucose, sucrose, or other suitable agent. The solvent can also contain a buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, in some aspects, about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. In some aspects, the resulting solution can be apportioned into vials for lyophilization. Each vial can contain a single dosage or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4°C to room temperature.

[0250] Reconstitution of a lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, the lyophilized powder is added to sterile water or other suitable carrier. The precise amount depends upon the selected compound. Such an amount can be empirically determined.

[0251] Pharmaceutical compositions provided herein (*e.g.*, comprising a PDGFR α inhibitor) can also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated. Many such targeting methods are known to those of skill in the art. All such targeting methods are contemplated herein for use in the instant compositions. For non-limiting examples of targeting methods, *see, e.g.*, U.S. Patent Nos. 6,316,652; 6,274,552; 6,271,359; 6,253,872; 6,139,865; 6,131,570; 6,120,751; 6,071,495; 6,060,082; 6,048,736; 6,039,975; 6,004,534; 5,985,307; 5,972,366; 5,900,252; 5,840,674; 5,759,542; and 5,709,874.

[0252] The pharmaceutical compositions to be used for *in vivo* administration can be sterile. This can be accomplished, for example, by filtration through, *e.g.*, a sterile filtration membrane.

IV. Kits

[0253] Also provided herein are kits comprising one or more PDGFR α inhibitors described herein. In some aspects, provided herein is a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions described herein, such as one or more PDGFR α inhibitors provided herein, and optionally, an instruction for use. In some aspects, the kits contain a pharmaceutical

composition described herein (*e.g.*, a PDGFR α inhibitor) and any prophylactic or therapeutic agent, such as those described herein.

V. Methods of the Disclosure

[0254] As demonstrated herein, PDGFR α inhibitors of the present disclosure are useful in reducing or inhibiting PDGFR α activity, which, in some aspects, can promote the myelination of an axon and/or remyelination of a demyelinated neuronal axon.

[0255] In some aspects, the present disclosure relates to methods of inhibiting or reducing PDGFR α activity in a cell or tissue, *e.g.*, of a subject in need thereof, comprising contacting the cell or tissue with a PDGFR α inhibitor described herein. In some aspects, after the contacting, PDGFR α kinase activity in the cell or tissue is inhibited by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% compared to a reference (*e.g.*, PDGFR α activity in the cell prior to the contacting and/or PDGFR α activity in a corresponding cell that was not contacted with the PDGFR α inhibitor). The PDGFR α activity status of a cell can be determined using any suitable method known in the art. In some aspects, PDGFR α activity can be determined by measuring the corresponding gene expression level, *e.g.*, by qRT-PCR. In some aspects, PDGFR α activity can be determined by measuring the PDGFR α protein level, *e.g.*, by immunoblotting. In some aspects, the PDGFR α activity can be determined by measuring receptor phosphorylation, *e.g.*, by western blotting. An exemplary method of assaying such an activity, a purified protein enzyme assay, is provided in Example 131 (also referred to herein as the "Promega Assay"). In some aspects, the enzymatic PDGFR α kinase assay comprises 20 ng of purified PDGFR α protein, 150 μ M of ATP and 1 μ g of substrate, Poly (Glu4Tyr1) in a volume of 15 μ l. The potency of a compound can be determined using such assays. In general, compounds most useful in the methods of the present disclosure have an IC₅₀ below 10,000 nM (*e.g.*, less than 9,000 nM, less than 8,000 nM, less than 7,000 nM, less than 6,000 nM, less than 5,000 nM, less than 4,000 nM, less than 3,000 nM, less than 2,000 nM, less than 1,000 nM, less than 900 nM, less than 800 nM, less than 700 nM, less than 600 nM, less than 500 nM, less than 400 nM, less than 300 nM, less than 200 nM, less than 100 nM, less than 50 nM, less than 25 nM, less than 10 nM, less than 5 nM, less than 2.5 nM, less than 1 nM, less than 0.5 nM, or less

than 0.2 nM, for instance, less than 500 nM) in such an assay. As described herein, in some aspects, the cell is an oligodendrocyte progenitor cell (OPC).

[0256] As both described and demonstrated herein, inhibiting or reducing PDGFR α activity can promote the myelination of a neuron (*e.g.*, an axon of a neuron), *e.g.*, by promoting the differentiation of an OPC into an oligodendrocyte that, in turn, myelinates the axon. Similarly, inhibiting or reducing PDGFR α activity can also promote the remyelination of a demyelinated neuronal axon. And, as will be apparent to those skilled in the art, in some aspects, remyelination can repair damage to demyelinated (*e.g.*, hypomyelinated) axons, and thereby, aid in recovering axonal signalling or reducing axonal injury or loss.

[0257] Accordingly, in some aspects, provided herein is a method of promoting the myelination of an axon, *e.g.*, in a subject in need thereof (*e.g.*, subject suffering from or at risk of developing a demyelinating disease), the method comprising contacting an OPC with an effective amount of a PDGFR α inhibitor described herein, wherein the contacting results in the OPC to differentiate into an oligodendrocyte, and wherein the oligodendrocyte is capable of (and in some embodiments used for) promoting the myelination of the axon. In some aspects, after the contacting, the number of neurons with axons that are myelinated is increased by at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 30-fold, at least 35-fold, at least 40-fold, at least 45-fold, or at least 50-fold compared to a reference (*e.g.*, the number of neurons with myelinated axons in the subject prior to the administration and/or the number of neurons with myelinated axons in a corresponding subject that did not receive the administration of the PDGFR α inhibitor). The increase in the number of neurons with axons that are myelinated can be determined using any suitable methods known in the art or described herein. In some aspects, the increase in the number of neurons with axons that are myelinated can be determined by visualizing and/or quantifying the expression of a marker associated with myelinated neurons. For example, in some aspects, the marker associated with myelinated neurons comprises myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, proteolipid protein 1 (PLP1), or a combination thereof.

[0258] In some aspects, also provided herein is a method of promoting remyelination of an axon of a neuron (*e.g.*, demyelinated neuronal axon in a subject in need thereof), comprising contacting an OPC with an effective amount of any of the PDGFR α inhibitors described herein, wherein the contacting results in the OPC to differentiate into an oligodendrocyte, and wherein the oligodendrocyte is capable of (and in some embodiments used for) promoting the remyelination of the demyelinated neuronal axon. In some aspects, after the contacting, the number of demyelinated axons that are myelinated is increased by at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 30-fold, at least 35-fold, at least 40-fold, at least 45-fold, or at least 50-fold compared to a reference (*e.g.*, the number of demyelinated neuronal axons in the subject prior to the administration and/or the amount of demyelinated neuronal axons in a corresponding subject that did not receive the administration of the PDGFR α inhibitor). The increase in the number of demyelinated axons that are myelinated can be determined using any suitable methods known in the art or described herein. In some aspects, the increase in the number of demyelinated axons that are myelinated can be determined by visualizing and/or quantifying the expression of a marker associated with myelinated neurons. For example, in some aspects, the marker associated with myelinated neurons comprises myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, proteolipid protein 1 (PLP1), or a combination thereof.

[0259] In some aspects, also provided herein is a method of increasing remyelination in a subject (*e.g.*, increasing remyelination of a demyelinated neuronal axon in a subject in need thereof), comprising contacting an OPC with an effective amount of any of the PDGFR α inhibitors described herein, wherein the contacting results in the OPC to differentiate into an oligodendrocyte, and wherein the oligodendrocyte is capable of (and in some embodiments used for) increasing remyelination in the subject. In some aspects, after the contacting, the remyelination is increased by at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 30-fold, at least 35-fold, at least 40-fold, at least 45-fold, or at least 50-fold compared to a reference (*e.g.*, the number of demyelinated neuronal axons in the subject prior to the administration and/or the amount of demyelinated neuronal axons in a corresponding subject that did not receive the

administration of the PDGFR α inhibitor). The increase in the number of demyelinated axons that are myelinated can be determined using any suitable methods known in the art or described herein. In some aspects, the increase in the number of demyelinated axons that are myelinated can be determined by visualizing and/or quantifying the expression of a marker associated with myelinated neurons. For example, in some aspects, the marker associated with myelinated neurons comprises myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, proteolipid protein 1 (PLP1), or a combination thereof.

[0260] In some aspects, provided herein is a method of reducing the demyelination of a myelinated axon (*e.g.*, reducing the rate at which the myelinated axons become demyelinated) in a subject in need thereof, comprising contacting an OPC with an effective amount of any of the PDGFR α inhibitors described herein, wherein the contacting results in the OPC to differentiate into an oligodendrocyte, and wherein the oligodendrocyte is capable of (and in some embodiments used for) reducing the demyelination of the myelinated axon. In some aspects, after the contacting, demyelination of a myelinated axon in the subject is reduced by at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 30-fold, at least 35-fold, at least 40-fold, at least 45-fold, or at least 50-fold compared to a reference (*e.g.*, demyelination of a myelinated axon in a corresponding subject that did not receive an administration of the PDGFR α inhibitor). The decrease in the number of neurons with axons that are demyelinated can be determined using any suitable methods known in the art or described herein. In some aspects, the decrease in the number of neurons with axons that are demyelinated can be determined by visualizing and/or quantifying the expression of a marker associated with myelinated neurons. For example, in some aspects, the marker associated with myelinated neurons comprises myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, proteolipid protein 1 (PLP1), or a combination thereof.

[0261] In some aspects, provided herein is a method of decreasing the rate of demyelination (*e.g.*, decreasing the rate at which myelinated axons in a subject become demyelinated) in a subject in need thereof, comprising contacting an OPC with an effective amount of any of the PDGFR α inhibitors described herein, wherein the contacting results in the OPC to

differentiate into an oligodendrocyte, and wherein the oligodendrocyte is capable of (and in some embodiments used for) reducing the rate of demyelination in the subject. In some aspects, after the contacting, the rate of demyelination in the subject is decreasing by at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 30-fold, at least 35-fold, at least 40-fold, at least 45-fold, or at least 50-fold compared to a reference (*e.g.*, the rate of demyelination in a corresponding subject that did not receive an administration of the PDGFR α inhibitor). The decrease in the number of neurons with axons that are demyelinated can be determined using any suitable methods known in the art or described herein. In some aspects, the decrease in the number of neurons with axons that are demyelinated can be determined by visualizing and/or quantifying the expression of a marker associated with myelinated neurons. For example, in some aspects, the marker associated with myelinated neurons comprises myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, proteolipid protein 1 (PLP1), or a combination thereof.

[0262] In any of the methods provided herein, in some aspects, the contacting can occur *ex vivo* (*e.g.*, OPCs of a subject can be isolated and contacted with a PDGFR α inhibitor *in vitro* to assess the therapeutic efficacy of the inhibitor). In some aspects, the contacting occurs *in vivo* (*e.g.*, in a subject in need thereof). Where the contacting occurs *in vivo*, the methods can further comprise administering to the subject an effective amount of any of the PDGFR α inhibitors described herein.

[0263] Not to be bound by any one theory, in some aspects, after administration to a subject, a PDGFR α inhibitor described herein is capable of (and in some embodiments used for) migrating into the CNS of the subject (*e.g.*, by crossing the blood-brain barrier) and interacting with the nervous system cells present within the CNS. For instance, as described and demonstrated herein, PDGFR α inhibitors of the present disclosure are capable of (and in some embodiments used for) targeting PDGFR α expressed on an OPC, and thereby inhibit or reduce the PDGFR α activity of the OPC. In some aspects, this results in the activation of the OPC and the subsequent differentiation of the OPC into an oligodendrocyte. Accordingly, in some aspects, provided herein is a method of activating an OPC within the CNS of a subject in need thereof, the method comprising administering to the subject any of the PDGFR α inhibitors described herein.

[0264] As described herein, the myelin sheath which surrounds the neuronal axons can affect various functions of neurons. For example, in some aspects, by increasing the myelination of neuronal axons, PDGFR α inhibitors described herein can increase the rate of transmission of electrical impulses (*i.e.*, nerve signals or action potentials) along the axon of a neuron. Accordingly, in some aspects, the present disclosure provides a method of increasing electrical impulse transmission along the axon of a neuron, comprising contacting an OPC with an effective amount of any of the PDGFR α inhibitors described herein, wherein the contacting results in the OPC to differentiate into an oligodendrocyte, and wherein the oligodendrocyte is capable of (and in some embodiments used for) myelinating the axon of the neuron, and thereby increase the electrical impulse transmission. In some aspects, after contacting the OPC, the electrical impulse transmission along the axon of the neuron is increased by at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 30-fold, at least 35-fold, at least 40-fold, at least 45-fold, or at least 50-fold compared to a reference (*e.g.*, electrical impulse transmission across the axon prior to or in the absence of contact with the PDGFR α inhibitors). Action potential conduction velocities can be measured as compound action potentials across the corpus callosum *in vitro* or by auditory or visual evoked potential recording *in vivo*. In some aspects, remyelination may overcome conduction block, allowing axonal signals that would be prematurely terminated to be transmitted. Remyelination can enhance axonal health and prevent axonal degradation in a diseased state. Non-limiting examples of methods useful for measuring such properties of a neuronal axon are described in, *e.g.*, Li *et al.*, *PLoS One* 11(11): e0165637 (Nov. 2016); Maheras *et al.*, *Sci Rep* 8(1): 3798 (Feb. 2018); and Alqudah *et al.*, *Audiol Neurotol* 23(1): 20-31 (2018).

[0265] As is apparent from the present disclosure, the PDGFR α inhibitors described herein can be useful in the treatment of a demyelinating disease, *e.g.*, by inducing the differentiation of an OPC into an oligodendrocyte, thereby promoting the remyelination of neuronal axons. Accordingly, in some aspects, the present disclosure is directed to a method of treating a demyelinating disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a PDGFR α inhibitor described herein. References to a method of treating a demyelinating disease as described herein also refer

to the agents and compositions as described herein for use in treating a demyelinating disease.

[0266] The PDGFR α inhibitors provided herein can be used to treat a wide range of demyelinating diseases (including those that are associated with demyelination and/or hypomyelination). In some aspects, the demyelinating disease that can be treated with the present disclosure comprise those that are characterized by demyelination of one or more cells within the CNS. Non-limiting examples of demyelinating disease that can be treated with the present disclosure include one or more of: acute disseminated encephalomyelitis (ADEM), acute hemorrhagic leukoencephalitis, acute optic neuritis, acute transverse myelitis, adrenoleukodystrophy, adrenomyeloneuropathy, Alexander disease, Alzheimer's disease, aminoacidurias, amyotrophic lateral sclerosis, anti-MAG peripheral neuropathy, anti-MOG associated spectrum, Balo concentric sclerosis, brain injury, CAMFAK Syndrome, Canavan disease, carbon monoxide toxicity, central pontine myelinolysis, cerebral hypoxia, cerebral ischemia, Charcot–Marie–Tooth disease, chronic inflammatory demyelinating polyneuropathy, chronic relapsing inflammatory optic neuritis (CRION), chronic traumatic encephalopathy, clinically isolated syndrome (CIS), congenital cataract, copper deficiency associated condition, delayed post-hypoxic leukoencephalopathy, diffuse cerebral sclerosis of Schilder, diffuse myelinoclastic sclerosis, extrapontine myelinolysis Gaucher disease, Guillain–Barré syndrome, hereditary neuropathy, hereditary neuropathy with liability to pressure palsy, HTLV-1-associated myelopathy, Hurler syndrome, hypomyelination, hypoxic brain injury, Krabbe disease, Leber hereditary optic atrophy and related mitochondrial disorders, leukodystrophic disorders, Marburg multiple sclerosis, Marchiafava-Bignami disease, metachromatic leukodystrophy, multiple sclerosis, multiple system atrophy, myelinoclastic disorders, myelopathy, nerve injury, neuromyelitis optica (NMO), Niemann-Pick disease, optic neuropathy, optic-spinal multiple sclerosis, osmotic demyelination syndrome, Parkinson's disease, Pelizaeus-Merzbacher disease, periventricular leukomalacia, peripheral neuropathy, phenylketonuria, primary progressive multiple sclerosis (PPMS), progressive inflammatory neuropathy, progressive multifocal leukoencephalopathy, progressive subcortical ischemic demyelination, progressive-onset multiple sclerosis, relapsing-onset multiple sclerosis, relapsing-remitting multiple sclerosis (RRMS), reperfusion injury, Schilder disease, secondary progressive multiple sclerosis (SPMS), solitary sclerosis,

spinal cord injury, subacute sclerosing panencephalitis, Tabes dorsalis, Tay-Sachs disease, transverse myelitis, traumatic brain injury, tropical spastic paraparesis, tumefactive multiple sclerosis, vitamin B12 deficiency, and cerebral palsy. In some aspects, a disease that can be treated with the present disclosure comprises a tumor associated with abnormal (*e.g.*, increased) PDGF or PDGFR α activity. Such a tumor is referred to herein as "**PDGF-associated tumor**." Accordingly, in some aspects, provided herein is a method of treating a PDGF-associated tumor in a subject in need thereof, comprising administering to the subject any of the PDGFR α inhibitor described herein. A non-limiting example of a PDGF-associated tumor comprises oligodendroglioma.

[0267] In some aspects, the demyelinating disease that can be treated with a PDGFR α inhibitor described herein comprises multiple sclerosis. As used herein, the term "**multiple sclerosis**" (MS) refers to a chronic and often disabling disease of the central nervous system characterized by the progressive destruction of the myelin sheath. Multiple sclerosis is generally diagnosed as one of four internationally recognized categories or stages of MS: (1) primary progressive multiple sclerosis (PPMS), (2) relapsing-remitting multiple sclerosis (RRMS), (3) secondary progressive multiple sclerosis (SPMS), and (4) progressive relapsing multiple sclerosis. Standards for diagnosis are known to those of skill in the art and exemplary diagnostic criteria are described in, *e.g.*, "Merck Manual, Professional Version" (www.merckmanuals.com/professional/neurologic-disorders/demyelinating-disorders/multiple-sclerosis-ms). Unless indicated otherwise, the term "multiple sclerosis" encompasses all of the different categories of MS. Accordingly, in some aspects, the PDGFR α inhibitors of the present disclosure can be used to treat all types of MS.

[0268] In some aspects, a PDGFR α inhibitor of the present disclosure can be used to treat clinically isolated syndrome (CIS). In some aspects, a PDGFR α inhibitor of the present disclosure can be used to treat radiologically isolated syndrome (RIS).

[0269] In some aspects, provided herein is a method of treating a relapsing form of multiple sclerosis in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of any of the PDGFR α inhibitors provided herein.

[0270] In some aspects, the demyelinating disease that can be treated with the present disclosure is an optic neuritis. Accordingly, in some aspects, a PDGFR α inhibitor is used to ameliorate optic neuritis, *e.g.*, optic neuritis that is due to multiple sclerosis.

[0271] As is apparent from the present disclosure, by promoting the myelination of an axon and/or the remyelination of a demyelinated axon, PDGFR α inhibitors of the present disclosure can help restore nervous system cell function and thereby, reduce and/or alleviate one or more symptoms associated with a demyelinating disease. Accordingly, in some aspects, treating a demyelinating disease comprises reducing one or more symptoms associated with the demyelinating disease. Non-limiting examples of such symptoms include one or more of: fatigue, dizziness, malaise, elevated fever and high body temperature, extreme sensitivity to cold in the hands and feet, weakness and stiffness in muscles and joints, weight changes, digestive or gastrointestinal problems, low blood pressure, high blood pressure, irritability, anxiety, depression, blurred vision, double vision, ataxia, clonus, spasms, dysarthria, weakness, clumsiness, hand paralysis, hemiparesis, genital anesthesia, sexual dysfunction, incoordination, paresthesias, ocular paralysis, impaired muscle coordination, loss of sensation, tingling, numbness, pain, impaired vision, neurological symptoms, unsteady gait, balance problems, dizziness, spastic paraparesis, incontinence, hearing problems, speech problems, loss of olfaction, and agusia.

[0272] Moreover, PDGFR α inhibitors described herein can also be used to prevent or delay the onset of one or more symptoms associated with a demyelinating disease. With many demyelinating diseases, particularly during the early stages, a subject may not exhibit any apparent symptoms of the disease. For instance, in some aspects, the damage to the myelin sheaths may not be as severe, such that the oligodendrocytes present within the CNS of the subject can adequately repair any damages. However, as is the case with most demyelinating diseases (*e.g.*, multiple sclerosis), the damage to the myelin sheaths can become more severe, resulting in the manifestation of one or more symptoms of the disease. In some aspects, by administering a PDGFR α inhibitor described herein to the subject when the damage to the myelin sheath is still minor, the manifestation of the one or more symptoms of the disease can be prevented or delayed. In some aspects, compared to a reference subject (*e.g.*, corresponding subject that did not receive an administration of the PDGFR α inhibitor), the manifestation of the one or more symptoms of the disease is delayed by at least 1.1-fold, at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least 25-fold, at least 30-fold, at least 35-fold, at least 40-fold, at least 45-fold, or at least 50-fold. In some aspects, compared to the reference subject, the subject

treated with a PDGFR α inhibitor described herein exhibits less number of symptoms and/or the symptoms are reduced in severity.

[0273] Whether a subject exhibits one or more symptoms associated with a demyelinating disease can be assessed using any suitable approaches known in the art. In some aspects, whether a subject exhibits the one or more symptoms associated with a demyelinating disease can be determined by assessing the subject's performance in one or more of the following tests: a visual evoked potential (VEP) test, a multifocal visual evoked potential (mfVEP) test, a low contrast visual acuity (LCVA) test, a magnetic resonance imaging (MRI) (*e.g.*, magnetization transfer ratio (MTR), myelin water fraction (MWF), quantitative susceptibility mapping (QSM), and T2 imaging), an electromyography (EMG), a nerve conduction velocity (NCV) test, an Extended Disability Status Scale (EDSS), a timed walk test (*e.g.*, timed 25-foot walk), a Nine-Hole Peg Test (9HPT), an ocular coherence tomograph (OCT), a quality of life measure test (*e.g.*, Multiple Sclerosis Quality of Life-54 and Vision-Related Quality of Life), cognitive assessment (*e.g.*, Symbol-Digit Modalities Test or Montreal Cognitive Assessment), or combinations thereof. In some aspects, whether a subject exhibits one or more symptoms associated with a demyelinating disease is determined by assessing the subject's performance in a LC-VA test. In some aspects, whether a subject exhibits one or more symptoms associated with a demyelinating disease is determined by assessing the subject's performance in a cognitive assessment.

[0274] In some aspects, an improved performance as compared to a reference performance (*e.g.*, a corresponding subject's performance in the test where the reference subject was not treated with a PDGFR α inhibitor described herein and/or the subject's performance prior to the treatment with a PDGFR α inhibitor) indicates that the one or more symptoms associated with a demyelinating disease is reduced or alleviated in the subject. In some aspects, a comparable or reduced performance as compared to a reference performance (*e.g.*, a corresponding subject's performance in the test where the subject was not treated with a PDGFR α inhibitor described herein and/or the subject's performance prior to the treatment with a PDGFR α inhibitor) indicates that the one or more symptoms associated with a demyelinating disease is maintained or has worsened in the subject.

[0275] Accordingly, some aspects of the present disclosure are directed to methods of treating a demyelinating disease in a subject in need thereof, comprising assessing the subject's performance in a test for assessing one or more symptoms associated with a

demyelinating disease, wherein the subject received a treatment comprising a PDGFR α inhibitor described herein prior to the assessment. In some aspects, if the subject's performance in the test is improved as compared to a reference performance (*e.g.*, a corresponding subject's performance in the test where the reference subject was not treated with a PDGFR α inhibitor described herein and/or the subject's performance prior to the treatment with a PDGFR α inhibitor), the treatment comprising a PDGFR α inhibitor can be maintained in the subject (*e.g.*, the subject receives one or more additional administration of the PDGFR α inhibitor at the same dose and/or dosing interval). In some aspects, where the subject exhibits improved performance, the treatment comprising a PDGFR α inhibitor is reduced (*e.g.*, the subject receives one or more additional administration of the PDGFR α inhibitor but at a lower dose and/or longer dosing interval) or stopped. In some aspects, if the subject's performance is comparable or reduced as compared to a reference performance, (*e.g.*, a corresponding subject's performance in the test where the subject was not treated with a PDGFR α inhibitor described herein and/or the subject's performance prior to the treatment with a PDGFR α inhibitor), the treatment comprising a PDGFR α inhibitor is adjusted such that the subject receives one or more administrations of the PDGFR α inhibitor at a higher dose and/or shorter dosing interval.

[0276] Some aspects of the present disclosure are directed to methods of improving a subject's performance in a test for assessing one or more symptoms associated with a demyelinating disease, comprising administering to the subject any of the PDGFR α inhibitors described herein. In some aspects, after the administration, the subject's performance in the test is increased as compared to a reference performance (*e.g.*, a corresponding subject's performance in the test where the reference subject was not treated with a PDGFR α inhibitor described herein and/or the subject's performance prior to the treatment with a PDGFR α inhibitor). In some aspects, the test is one or more of a visual evoked potential (VEP) test, a multifocal visual evoked potential (mfVEP) test, a low contrast visual acuity (LC-VA) test, a magnetic resonance imaging (MRI) (*e.g.*, magnetization transfer ratio (MTR), myelin water fraction (MWF), quantitative susceptibility mapping (QSM), and T2 imaging), an electromyography (EMG), a nerve conduction velocity (NCV) test, an Extended Disability Status Scale (EDSS), a timed walk test (*e.g.*, timed 25-foot walk), a Nine-Hole Peg Test (9HPT), an ocular coherence tomograph (OCT), a quality of life measure test (*e.g.*, Multiple Sclerosis Quality of Life-

54 and Vision-Related Quality of Life), cognitive assessment (*e.g.*, Symbol-Digit Modalities Test or Montreal Cognitive Assessment), or combinations thereof. In some aspects, the test is a LCVA test. In some aspects, the test is a cognitive assessment.

[0277] As is apparent from the present disclosure, the introduction of a PDGFR α inhibitor into a subject can be done by any suitable route, including, but not limited to, intratumorally, orally, pulmonarily, intranasally, parenterally (intravenously, intra-arterially, intramuscularly, intraperitoneally, or subcutaneously), rectally, vaginally, intralymphatically, intrathecally, periocularly, cutaneously, intradermally, intraorbitally, intracerebrally, intracranially, intraspinally, intraventricularly, intracapsularly, or topically. Administration includes self-administration and the administration by another. A suitable route of administration allows the PDGFR α inhibitors described herein to perform its intended function (*e.g.*, inhibit PDGFR α activity and induce OPC differentiation). In some aspects, a suitable route of administration includes that which would allow a PDGFR α inhibitor to reach the CNS or any other sites where OPCs are present. Non-limiting examples of such routes include intranasal delivery, intrathecal administration, intracranial administration, and combinations thereof. In some aspects, a PDGFR α inhibitor described herein is administered orally. In some aspects, a PDGFR α inhibitor of the present disclosure is administered intravenously. In some aspects, a PDGFR α inhibitor can be administered both orally and intravenously.

[0278] In any of the methods provided herein where a PDGFR α inhibitor is administered to a subject, the PDGFR α inhibitor can be administered to the subject using any suitable dosing schedule. In some aspects, the PDGFR α inhibitor is administered to the subject once. In some aspects, multiple doses of the PDGFR α inhibitor are administered to the subject. In some aspects, a PDGFR α inhibitor described herein is administered to a subject according to an intermittent dosing schedule. As used herein, the term "**intermittent dosing schedule**" (and any variants thereof) refers to a dosing schedule in which the therapeutic agent (*e.g.*, PDGFR α inhibitor) is administered non-continuously (*i.e.*, an intervening period exists between doses). An intermittent dosing schedule useful for the present disclosure can encompass any discontinuous administration regimen that provides a therapeutically effective amount of a PDGFR α inhibitor to a subject in need thereof. Intermittent dosing regimens can use equivalent, lower, or higher doses of a PDGFR α inhibitor than would be used in continuous dosing regimens. Advantages of intermittent

dose administration include, but are not limited to, improved safety, decreased toxicity (*e.g.*, decreased weight loss), acceptable levels of ADME criteria, acceptable levels of undesirable effects on organ systems such as heart, pulmonary, hepatic, reproductive (for example, ovarian or testicular) or gastrointestinal, increased exposure, increased efficacy, and/or increased subject compliance. These advantages can be realized when the PDGFR α inhibitor is administered as a single agent and/or when administered in combination with one or more additional therapeutic agents, *e.g.*, standard of care. When administered in combination with one or more additional therapeutic agents, in some aspects, the dosing regimen for the PDGFR α inhibitor (*e.g.*, intermittent dosing) and the additional therapeutic agents are independent of each other. For example, in some aspects, the PDGFR α inhibitor is administered using a first dosing regimen and the additional therapeutic agent is administered using a second dosing regimen, wherein the first and second dosing regimens are different.

[0279] In some aspects, the intermittent dosing schedule comprises administering the PDGFR α inhibitor to the subject every other day. In some aspects, the PDGFR α inhibitor is administered to the subject one time per day. In some aspects, the PDGFR α inhibitor is administered to the subject two times per day. In some aspects, the PDGFR α inhibitor is administered to the subject three times per day. In some aspects, the PDGFR α inhibitor is administered to the subject four times per day. In some aspects, the PDGFR α inhibitor is administered to the subject every three days. In some aspects, the PDGFR α inhibitor is administered to the subject every four days. In some aspects, the PDGFR α inhibitor is administered to the subject every five days. In some aspects, the PDGFR α inhibitor is administered to the subject every six days. In some aspects, the PDGFR α inhibitor is administered to the subject once a week. In some aspects, the PDGFR α inhibitor is administered to the subject once every eight days. In some aspects, the PDGFR α inhibitor is administered to the subject once every nine days. In some aspects, the PDGFR α inhibitor is administered to the subject every 10 days. In some aspects, the PDGFR α inhibitor is administered to the subject every 11 days. In some aspects, the PDGFR α inhibitor is administered to the subject every 12 days. In some aspects, the PDGFR α inhibitor is administered to the subject every 13 days. In some aspects, the PDGFR α inhibitor is administered to the subject once every two weeks. In some aspects, the PDGFR α inhibitor is administered to the subject once every three weeks. In some aspects, the PDGFR α

inhibitor is administered to the subject once a month. In some aspects, the PDGFR α inhibitor is administered to the subject once every five weeks. In some aspects, the PDGFR α inhibitor is administered to the subject once every six weeks. In some aspects, the PDGFR α inhibitor is administered to the subject once every seven weeks. In some aspects, the PDGFR α inhibitor is administered to the subject once every two months. In some aspects, the PDGFR α inhibitor is administered to the subject once every nine weeks. In some aspects, the PDGFR α inhibitor is administered to the subject once every 10 weeks. In some aspects, the PDGFR α inhibitor is administered to the subject once every 11 weeks. In some aspects, the PDGFR α inhibitor is administered to the subject once every three months. In some aspects, the PDGFR α inhibitor is administered to the subject once every four months. In some aspects, the PDGFR α inhibitor is administered to the subject once every five months. In some aspects, the PDGFR α inhibitor is administered to the subject once every six months. In some aspects, the PDGFR α inhibitor is administered to the subject once every twelve months.

[0280] In some aspects, the intermittent dosing schedule comprises administering to the subject a first dose and a second dose of a PDGFR α inhibitor, wherein the second dose is administered at least one day after administering the first dose. In some aspects, the second dose is administered at least two days after administering the first dose. In some aspects, the second dose is administered at least three days after administering the first dose. In some aspects, the second dose is administered at least four days after administering the first dose. In some aspects, the second dose is administered at least five days after administering the first dose. In some aspects, the second dose is administered at least six days after administering the first dose. In some aspects, the second dose is administered at least seven days after administering the first dose. In some aspects, the second dose is administered at least eight days after administering the first dose. In some aspects, the second dose is administered at least nine days after administering the first dose. In some aspects, the second dose is administered at least 10 days after administering the first dose. In some aspects, the second dose is administered at least 11 days after administering the first dose. In some aspects, the second dose is administered at least 12 days after administering the first dose. In some aspects, the second dose is administered at least 13 days after administering the first dose. In some aspects, the second dose is administered at least two weeks after administering the first dose. In some aspects, the second dose is administered

at least three weeks after administering the first dose. In some aspects, the second dose is administered at least one month after administering the first dose. In some aspects, the second dose is administered at least two months after administering the first dose. In some aspects, the second dose is administered at least three months after administering the first dose. In some aspects, the second dose is administered at least four months after administering the first dose. In some aspects, the second dose is administered at least five months after administering the first dose. In some aspects, the second dose is administered at least six months after administering the first dose. In some aspects, the second dose is administered at least 12 months after administering the first dose.

[0281] In some aspects, the intermittent dosing schedule comprises administering to the subject a first set of doses and a second set of doses of a PDGFR α inhibitor, wherein the second set of doses is administered at least one day after administering the first set of doses. In some aspects, the first set of doses can be, e.g., one, two, three, or four doses per day, administered over a period of, e.g., one, two, three, or four days. In some aspects, the second set of doses can be, e.g., one, two, three, or four doses per day, administered over a period of, e.g., one, two, three, or four days.

[0282] In some aspects, the second set of doses is administered at least two days after administering the first set of doses. In some aspects, the second set of doses is administered at least three days after administering the first set of doses. In some aspects, the second set of doses is administered at least four days after administering the first set of doses. In some aspects, the second set of doses is administered at least five days after administering the first set of doses. In some aspects, the second set of doses is administered at least six days after administering the first set of doses. In some aspects, the second set of doses is administered at least seven days after administering the first set of doses. In some aspects, the second set of doses is administered at least eight days after administering the first set of doses. In some aspects, the second set of doses is administered at least nine days after administering the first set of doses. In some aspects, the second set of doses is administered at least 10 days after administering the first set of doses. In some aspects, the second set of doses is administered at least 11 days after administering the first set of doses. In some aspects, the second set of doses is administered at least 12 days after administering the first set of doses. In some aspects, the second set of doses is administered at least 13 days after administering the first set of doses. In some aspects, the second set of doses is administered

at least two weeks after administering the first set of doses. In some aspects, the second set of doses is administered at least three weeks after administering the first set of doses. In some aspects, the second set of doses is administered at least one month after administering the first set of doses. In some aspects, the second set of doses is administered at least two months after administering the first set of doses. In some aspects, the second set of doses is administered at least three months after administering the first set of doses. In some aspects, the second set of doses is administered at least four months after administering the first set of doses. In some aspects, the second set of doses is administered at least five months after administering the first set of doses. In some aspects, the second set of doses is administered at least six months after administering the first set of doses. In some aspects, the second set of doses is administered at least 12 months after administering the first set of doses.

[0283] Not to be bound by any one theory, in some aspects, the use of an intermittent dosing schedule allows the OPC population of the treated subject (*i.e.*, subject who previously received an administration of the PDGFR α inhibitor) to sufficiently recover prior to the next dose of the PDGFR α inhibitor. As described herein, OPCs are capable of self-renewal and therefore, under a steady-state condition (*i.e.*, no inhibition of PDGFR α activity), the OPC population of a subject is continuously replenished and maintained. As described and demonstrated herein, when a PDGFR α inhibitor described herein is administered to a subject, the PDGFR α inhibitor induces the differentiation of the OPCs within the subject into oligodendrocytes. In some aspects, this can result in a decrease of the OPC population within the subject, and therefore, an immediate or rapid subsequent administration of a PDGFR α inhibitor would have diminished therapeutic activity (*e.g.*, reduced further generation of oligodendrocytes). Accordingly, in some aspects, an intermittent dosing schedule useful for the present disclosure comprises administering a first dose of a PDGFR α inhibitor and a second dose of a PDGFR α inhibitor, wherein the second dose of the PDGFR α inhibitor is administered to the subject after the OPC population of the subject has sufficiently recovered from the effects of the first dose of the PDGFR α inhibitor. When referring to an OPC population (*e.g.*, of a subject treated with a PDGFR α inhibitor), the expression "**sufficiently recovered**" means that the number of OPCs within the subject has increased, such that an additional administration of the PDGFR α inhibitor is capable of resulting in additional generation of oligodendrocytes. In some aspects, an OPC population has sufficiently recovered is comparable to that of a reference subject, wherein the reference

subject comprises (i) the subject prior to the initial administration of the PDGFR α inhibitor, (ii) a corresponding, normal healthy subject (*i.e.*, does not suffer from a demyelinating disease) who has not received an administration of the PDGFR α inhibitor, or (iii) both (i) and (ii). In some aspects, the number of OPCs within an OPC population that has sufficiently recovered is at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% of the number of OPCs within the OPC population of the reference subject.

[0284] Accordingly, where a method provided herein comprises administering a first dose and a second dose of a PDGFR α inhibitor to a subject (*e.g.*, to treat a demyelinating disease), in some aspects, a first dose of the PDGFR α inhibitor is administered to a subject and then the subject's OPC population is assessed, wherein if the subject's OPC population has sufficiently recovered as compared to a reference subject (*e.g.*, as described above), a second dose of the PDGFR α inhibitor is administered to the subject. In some aspects, a second dose of the PDGFR α inhibitor is administered to the subject if the size of the subject's OPC population (*e.g.*, number of OPCs within the OPC population) is at least at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% of the size of the reference subject's OPC population. In some aspects, where an additional dose of the PDGFR α inhibitor is administered to the subject, the additional dose is administered to the subject at the same dosing interval as that used for the first and second doses of the PDGFR α inhibitor. In some aspects, where an additional dose of the PDGFR α inhibitor is administered to the subject, the method comprises assessing the subject's OPC population again after the second administration, wherein if the subject's OPC population has sufficiently recovered as compared to a reference subject (*e.g.*, as described above), the additional dose of the PDGFR α inhibitor is administered to the subject. In some aspects, the additional dose of the PDGFR α inhibitor is administered to the subject if the size of the subject's OPC population (*e.g.*, number of OPCs within the OPC population) is at least at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or 100% of the size of the reference subject's OPC population. As further described elsewhere in the present disclosure, in some aspects, the amount of time required for the subject's OPC population to have sufficiently recovered after an initial administration of a PDGFR α inhibitor is the dosing interval of the PDGFR α inhibitor.

[0285] Whether a subject's OPC population has sufficiently recovered (and thus, determine a dosing interval for a PDGFR α inhibitor) can be determined using any suitable method known in the art. For example, in some aspects, a cuprizone animal model can be used. As demonstrated herein, in some aspects, a dosing interval suitable for a PDGFR α inhibitor described herein can be determined by administering a first dose and second dose of the PDGFR α inhibitor to the cuprizone animal model, and then assessing the number of newly generated oligodendrocytes present within the brain of the animals (*e.g.*, by quantifying the number of GPR17+ cells within the brain). If the number of newly generated oligodendrocytes within the brain is the same or increased compared to a reference (*e.g.*, the number of newly generated oligodendrocytes present within the brain of corresponding animal that received a single administration of the PDGFR α inhibitor), then a suitable dosing interval is the time between the administration of the first dose and the second dose of the PDGFR α inhibitor or any time longer than that. If the number of newly generated oligodendrocytes within the brain is reduced compared to a reference (*e.g.*, the number of newly generated oligodendrocytes present within the brain of corresponding animal that received a single administration of the PDGFR α inhibitor), then a suitable dosing interval is longer than the time between the administration of the first dose and the second dose of the PDGFR α inhibitor.

[0286] In some aspects, a suitable dosing interval for a PDGFR α inhibitor is directly related to the plasma level of the PDGFR α inhibitor. Accordingly, in some aspects, a method of determining a suitable dosing interval for a PDGFR α inhibitor comprises administering a first dose of the PDGFR α inhibitor to a subject and determining the plasma level of the PDGFR α inhibitor in the subject. In some aspects, where the plasma level of the PDGFR α inhibitor is comparable to that of a reference (*e.g.*, a subject who has not previously received a dose of the PDGFR α inhibitor and/or a subject who has previously received a dose of the PDGFR α inhibitor but the subject's OPC population has sufficiently recovered as described herein), a suitable dosing interval is the time between administering the first dose of the PDGFR α inhibitor and the subject's plasma level of the PDGFR α inhibitor being comparable to that of the reference. In some aspects, where the plasma level of the PDGFR α inhibitor is reduced as compared to a reference (*e.g.*, plasma level of the PDGFR α inhibitor in the subject immediately after, *e.g.*, about 4 hours after, the administration of the initial dose of the PDGFR α inhibitor), a suitable dosing interval is the time between administering

the first dose of the PDGFR α inhibitor and the subject's plasma level of the PDGFR α inhibitor reaching a reduced level as compared to the reference. In some aspects, the additional dose of the PDGFR α inhibitor is administered to the subject when the subject's plasma level has decreased by at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or about 100% as compared to the reference. In some aspects, the brain to plasma ratio may be assessed in preclinical species using bioanalytical gas or liquid chromatography and mass spectrometry methods.

[0287] In some aspects, the plasma level of the PDGFR α inhibitor is related to the half-life of the PDGFR α inhibitor. In some aspects, an intermittent dosing schedule useful for the present disclosure comprises administering two or more doses of a PDGFR α inhibitor at a dosing interval that is longer than the half-life of the PDGFR α inhibitor. In some aspects, the dosing interval is at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 100% longer than the half-life of the PDGFR α inhibitor. In some aspects, the dosing interval is at least 1.5-fold, at least 2-fold, at least 3-fold, at least 4-fold, at least 5-fold, at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, at least 10-fold, at least 15-fold, at least 20-fold, at least about 30-fold, at least 40-fold, or at least 50-fold longer than the half-life of the PDGFR α inhibitor. In some aspects, compared to the half-life of the PDGFR α inhibitor, the dosing interval is at least one day, at least two days, at least three days, at least four days, at least five days, at least six days, at least one week, at least two weeks, at least three weeks, at least one month, at least two months, or at least three months longer.

[0288] In some aspects, the methods described herein (*e.g.*, treating a demyelinating disease) can comprise administering an additional therapeutic agent to the subject. For examples, in some aspects, the PDGFR α inhibitors described herein are used in conjunction with an immunomodulatory drug. In some aspects, the PDGFR α inhibitors are used alone in the methods provided herein.

[0289] As described herein, "**immunomodulatory drug**" refers to a therapeutic agent that works by modulating (*e.g.*, increasing and/or decreasing) one or more aspects of an immune response. In some aspects, an immunomodulatory drug useful for the present disclosure is capable of reducing or alleviating the proinflammatory nature of a demyelinating disease (*e.g.*, multiple sclerosis). For instance, in some aspects, the immunomodulatory drug could block the production of proinflammatory mediators, promote the production of anti-

inflammatory cytokines (*e.g.*, IL-10 or TGF- β), promote the production of regulatory T cells (T_{regs}), influence B cells, prevent the entry of immune cells into the brain, or any combination thereof. Non-limiting examples of immunomodulatory drugs that are useful for the present disclosure include: interferon beta-1b (BETASERON[®], EXTAVIA[®]), interferon beta-1a (AVONEX[®], REBIF[®]), peginterferon beta-1a (PLEGRIDY[®]), alemtuzumab (LEMTRADA[®]), natalizumab (TYSABRI[®]), ocrelizumab (OCREVUS[®]), ofatumumab (KESIMPTA[®]), glatiramer acetate (COPAXONE[®], GLATOPA[®]), teriflunomide (AUBAGIO[®]), dimethyl fumarate (TECFIDERA[®]), monomethyl fumarate (BAFIERTAM[®]), diroximel fumarate (Vumerity[®]), and combinations thereof.

[0290] Where an additional therapeutic agent (*e.g.*, immunomodulatory drug) is administered to a subject, in some aspects, the additional therapeutic agent is administered to the subject prior to the administration of a PDGFR α inhibitor. Accordingly, in some aspects, any of the methods provided herein (*e.g.*, method of treating a demyelinating disease) comprise administering to the subject a PDGFR α inhibitor, wherein the subject had previously received an additional therapeutic agent (*e.g.*, immunomodulatory drug). In some aspects, the additional therapeutic agent is administered after the administration of a PDGFR α inhibitor. In some aspects, the additional therapeutic agent is administered concurrently with the administration of a PDGFR α inhibitor.

[0291] In some aspects, to improve delivery to the CNS, a PDGFR α inhibitor described herein can be administered to a subject in combination with an agent that assists the delivery of the inhibitor to the CNS (*e.g.*, allows the inhibitor to cross the blood-brain barrier). In some aspects, a PDGFR α inhibitor described herein is administered to a subject in combination with a peptide blood-brain barrier (BBB) shuttle, wherein the peptide BBB shuttle enhances the ability of the PDGFR α inhibitor to cross the blood-brain barrier and reach the CNS. Non-limiting examples of such peptide BBB shuttles are provided in Table 2 (below). *See, e.g.*, Oller-Salvia *et al.*, *Chem Soc Rev* 45: 4690-4707 (2016), and Jafari *et al.*, *Expert Opinion on Drug Delivery* 16:583-605 (2019).

TABLE 2: Peptide BBB Shuttle

SEQ ID NO	Peptide	Sequence
1	Angiopep-2	TFFYGGSRGKRNNFKTEEY-OH

2	ApoB (3371–3409)	SSVIDALQYKLEGTTTRLTRK- RGLKLATALSLSNKFVEGS
3	ApoE (159–167) ₂	(LRKLRKRLL) ₂
4	Peptide-22	Ac-C(&)MPRLRGC(&)-NH ₂
5	THR	THRPPMWSPVWP-NH ₂
6	THR retro-enantio	pwvpswmprrht-NH ₂
7	CRT	C(&)RTIGPSVC(&)
8	Leptin30	YQQILTSMPSRNVIQISND-LENLRDLLHVL
9	RVG29	YTIWMPENPRPGTPCDIFT-NSRGKRASNG-OH
10	^D CDX	GreirtGraerwsekf-OH
11	Apamin	C(& ₁)NC(& ₂)KAPETALC(& ₁)-AR-RC(& ₂)QQH-NH ₂
12	MiniAp-4	[Dap](&)KAPETALD(&)
13	GSH	γ-L-glutamyl-CG-OH
14	G23	HLNILSTLWKYRC
15	g7	GFtGFLS(O-β-Glc)-NH ₂
16	TGN	TGNYKALHPHNG
17	TAT (47–57)	YGRKKRRQRRR-NH ₂
18	SynB1	RGGRLSYSRRRFSTSTGR
19	Diketopiperazines	&(N-MePhe)-(N-MePhe)Diketo-piperazines
20	PhPro	(Phenylproline) ₄ -NH ₂

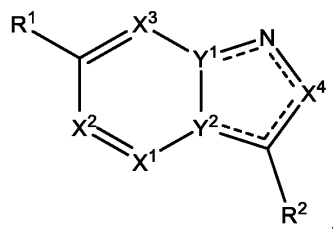
Nomenclature for cyclic peptides (&) is adapted to the 3-letter amino acid code from the one described by Spengler *et al. Pept. Res.*, 2005, **65**, 550–555

[Dap] stands for diaminopropionic acid.

VI. Enumerated Clauses

[0292] The present disclosure also provides the following enumerated clauses:

[0293] Clause 1. A compound of Formula I:



- [0294] or a pharmaceutically acceptable salt or solvate thereof, wherein:
- [0295] ----- indicates a single bond or a double bond such that all valences are satisfied;
- [0296] X^1 , X^2 , X^3 , and X^4 are selected from N and CR^a , with the proviso that not more than two of X^1 , X^2 , X^3 , and X^4 are N;
- [0297] one of Y^1 and Y^2 is N and the other of Y^1 and Y^2 is C;
- [0298] each R^a is independently selected from H, halo, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy;
- [0299] R^1 is selected from C_1 - C_4 alkyl, C_3 - C_8 cycloalkyl, 3-8 membered heterocyclyl, heteroaryl, aryl, and C_1 - C_8 alkoxy, all of which can be optionally substituted with one, two, three, four, five, or six substituents selected from halo, hydroxy, oxo, C_1 - C_4 alkyl, amino C_1 - C_4 alkyl, hydroxy C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 alkoxy C_1 - C_4 alkyl, 3-8 membered heterocyclyl, and 3-8 membered heterocyclyl C_1 - C_4 alkyl, with the proviso that the number of substituents does not exceed the number of substitutable positions;
- [0300] R^2 is selected from cycloalkyl, cycloalkenyl, alkyl, oxoalkylamino, aminoalkylamino, amino, heterocyclyl, heteroaryl, aminoheterocyclyl, heterocyclylamino, and aminoalkylamino, all of which can be optionally substituted with one or more substituents selected from D, halo, hydroxy, oxo, and C_1 - C_4 alkyl;
- [0301] R^2 is substituted with one, two, or three R^3 ;
- [0302] R^3 is selected from aryl, heteroaryl, $-C(O)R^{31}$, $-C(O)OR^{31}$, $-C(O)NR^{31}R^{32}$, $-S(O)_2NR^{31}R^{32}$, $-S(O)(NR^{33})R^{31}$, $-S(O)_2R^{31}$, $-S(O)(NR^{33})NR^{31}R^{32}$, $-C(S)NR^{31}R^{32}$, C_3 - C_8 cycloalkyl, 3-8 membered heterocyclyl, and C_1 - C_4 alkyl, all of which can be optionally substituted with one, two, three, four, or five R^{30} ;
- [0303] each R^{30} is independently selected from D, halo, aryl, $-OR^{300}$, $-NR^{300}R^{303}$, $-S(O)_rR^{300}$, $-C(O)R^{300}$, $-C(=CR^{34}R^{35})R^{300}$, and
- ;
- [0304] r is selected from 0, 1, and 2;
- [0305] each R^{300} is independently selected from C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, aryl, heteroaryl, 3-8 membered heterocyclyl, and 3-8 membered heterocyclylaryl, all of which

- can be optionally substituted with one, two, three, four, or five substituents selected from D, halo, hydroxy, amino, alkylamino, cyano, C₁-C₄alkyl, C₁-C₄haloalkyl, and C₁-C₄alkoxy;
- [0306] each R³⁰¹ is independently selected from H, halo, and C₁-C₄alkyl;
- [0307] each R³⁰² is independently selected from H, F, hydroxyl, amino, alkylamino, oxo, and C₁-C₄alkoxy;
- [0308] each R³⁰³ is independently selected from H and C₁-C₄alkyl;
- [0309] n, o, and p are each independently selected from 0, 1, 2, 3, and 4;
- [0310] each R³¹ is independently selected from C₁-C₈alkyl, arylC₁-C₄alkyl, heteroarylC₁-C₄alkyl, heterocyclyl, heterocyclylC₁-C₄alkyl, cycloalkyl, and cycloalkylC₁-C₄alkyl, all of which can be optionally substituted with one, two, three, four, or five substituents selected from D, halo, cyano, hydroxy, amino, -OCF₃, C₁-C₄alkyl, C₁-C₄haloalkyl, C₁-C₄alkoxy, hydroxycycloalkyl, -S(O)₂NR³⁰⁴R³⁰⁵, -C(O)OR³⁰⁴R³⁰⁵, -C(O)NR³⁰⁴R³⁰⁵, and -NR³⁰⁴C(O)R³⁰⁵;
- [0311] each R³⁰⁴ and R³⁰⁵ is independently selected from H and C₁-C₄alkyl;
- [0312] each R³² is independently selected from H and C₁-C₄alkyl; or
- [0313] R³¹ and R³² together with the atom to which they are connected to form a 5-8 membered heterocycl, optionally substituted with one, two, three, four, or five substituents selected from D, halo, cyano, C₁-C₄alkyl, C₁-C₄haloalkyl, and -C(O)NR³⁴R³⁵; and
- [0314] each R³⁴ and R³⁵ is independently selected from H, C₁-C₄alkyl, and C₁-C₄haloalkyl; and
- [0315] each R³³ is independently selected from H, C₁-C₄alkyl, C₁-C₄haloalkyl, and -C(O)R³⁴; or
- [0316] R³¹ and R³³ together with the atoms to which they are connected form a 4-8 membered heterocycl.
- [0317] Clause 2. The compound of clause 1, or a pharmaceutically acceptable salt or solvate thereof, wherein Y¹ is N and Y² is C.
- [0318] Clause 3. The compound of clause 1, or a pharmaceutically acceptable salt or solvate thereof, wherein Y¹ is C and Y² is N.
- [0319] Clause 4. The compound of any one of clauses 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, wherein X¹ is N, X² is CR^a, X³ is CR^a, and X⁴ is CR^a.
- [0320] Clause 5. The compound of any one of clauses 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, wherein X¹ is CR^a, X² is N, X³ is CR^a, and X⁴ is CR^a.

[0321] Clause 6. The compound of any one of clauses 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is CR^a , X^2 is CR^a , X^3 is N, and X^4 is CR^a .

[0322] Clause 7. The compound of any one of clauses 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is CR^a , X^2 is CR^a , X^3 is CR^a , and X^4 is N.

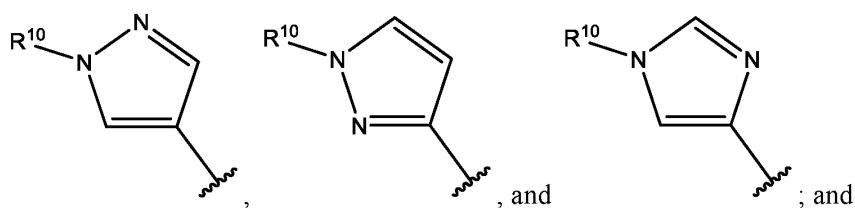
[0323] Clause 8. The compound of any one of clauses 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is CR^a , X^2 is CR^a , X^3 is CR^a , and X^4 is CR^a .

[0324] Clause 9. The compound of any one of clauses 1 to 8, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is 5- or 6-membered heteroaryl.

[0325] Clause 10. The compound of any one of clauses 1 to 9, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is an optionally substituted pyrazolyl.

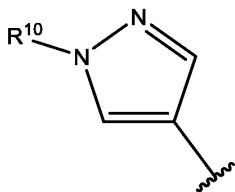
[0326] Clause 11. The compound of any one of clauses 1 to 10, or a pharmaceutically acceptable salt or solvate thereof, wherein:

[0327] R^1 is selected from:



[0328] R^{10} is selected from H, C₁-C₄alkyl, C₁-C₄alkoxy, aminoC₁-C₄alkyl, hydroxyC₁-C₄alkyl, and C₁-C₄alkylsulfonyl, wherein the C₁-C₄alkyl, C₁-C₄alkoxy, aminoC₁-C₄alkyl, hydroxyC₁-C₄alkyl, and C₁-C₄alkylsulfonyl can be optionally substituted by one or more substituents selected from hydroxyl, C₁-C₄alkoxy, $NR^{10a}R^{10b}$, halo, and deuterium, wherein R^{10a} and R^{10b} are selected from hydrogen and C₁-C₄alkyl, or wherein R^{10a} and R^{10b} taken together with the nitrogen atom to which they are attached form a 4- to 8-membered ring.

[0329] Clause 12. The compound of clause 11, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is

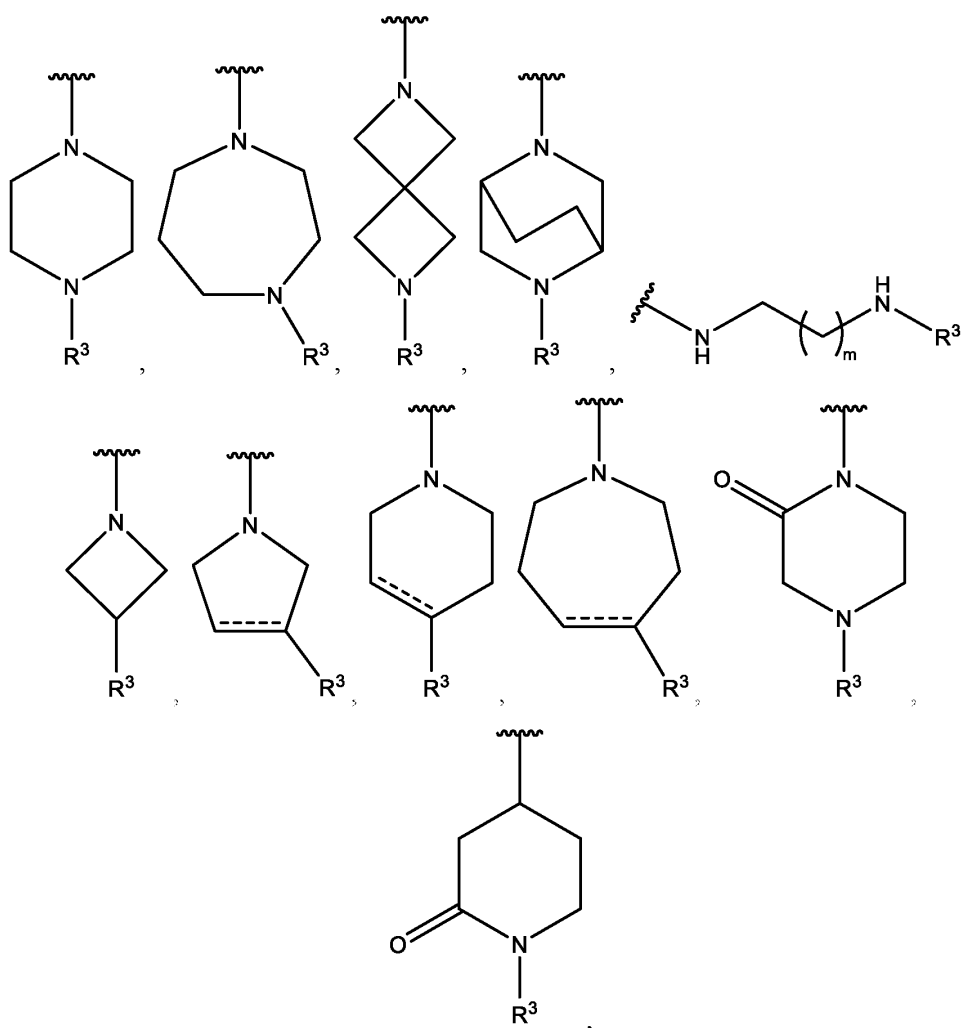


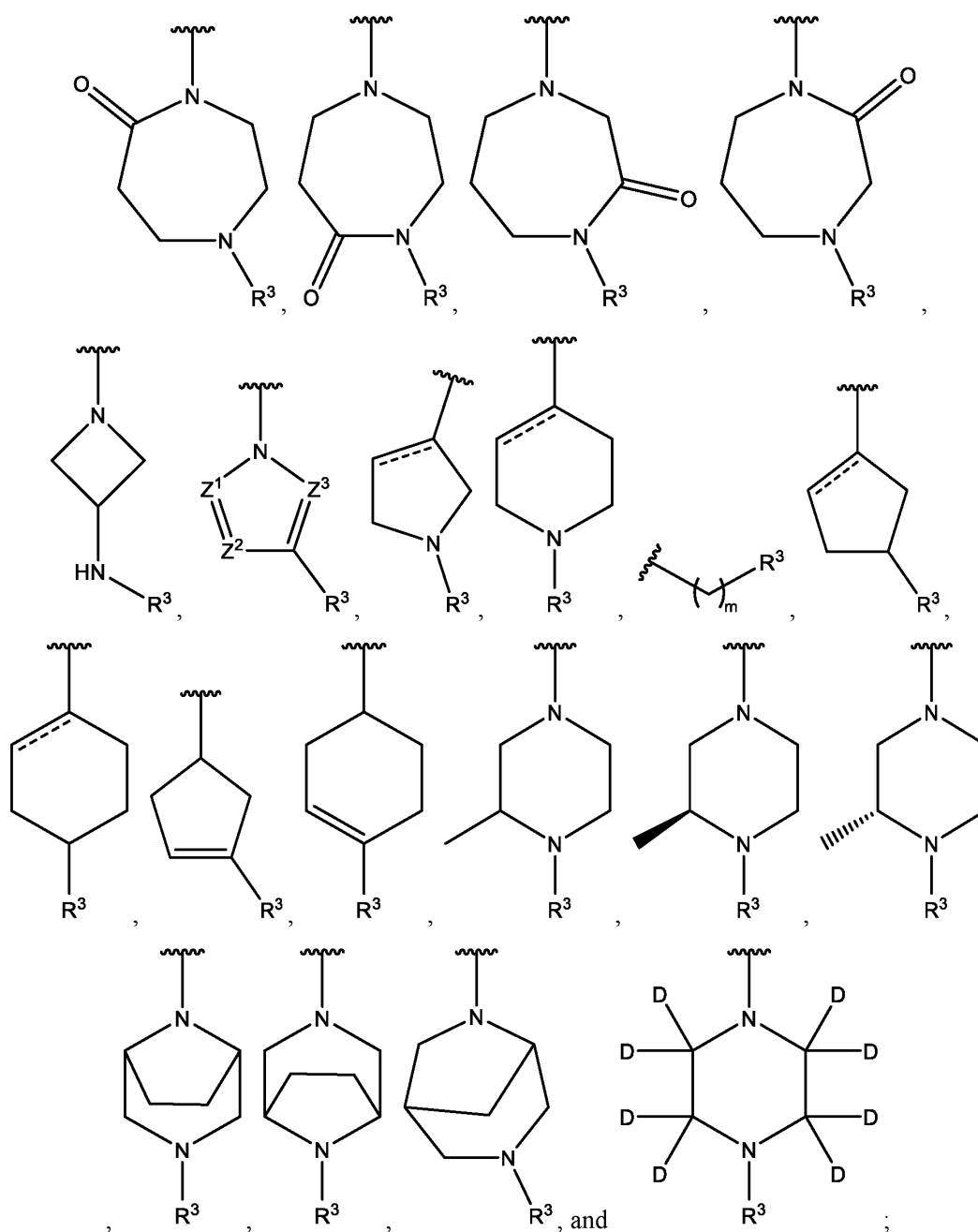
[0330] Clause 13. The compound of clause 11 or 12, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{10} is CH₃.

[0331] Clause 14. The compound of any one of clauses 1 to 13, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is heterocyclyl optionally substituted with C_1 - C_4 alkyl or oxo.

[0332] Clause 15. The compound of any one of clauses 1 to 14, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is substituted with one R^3 .

[0333] Clause 16. The compound of any one of clauses 1 to 15, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is selected from:



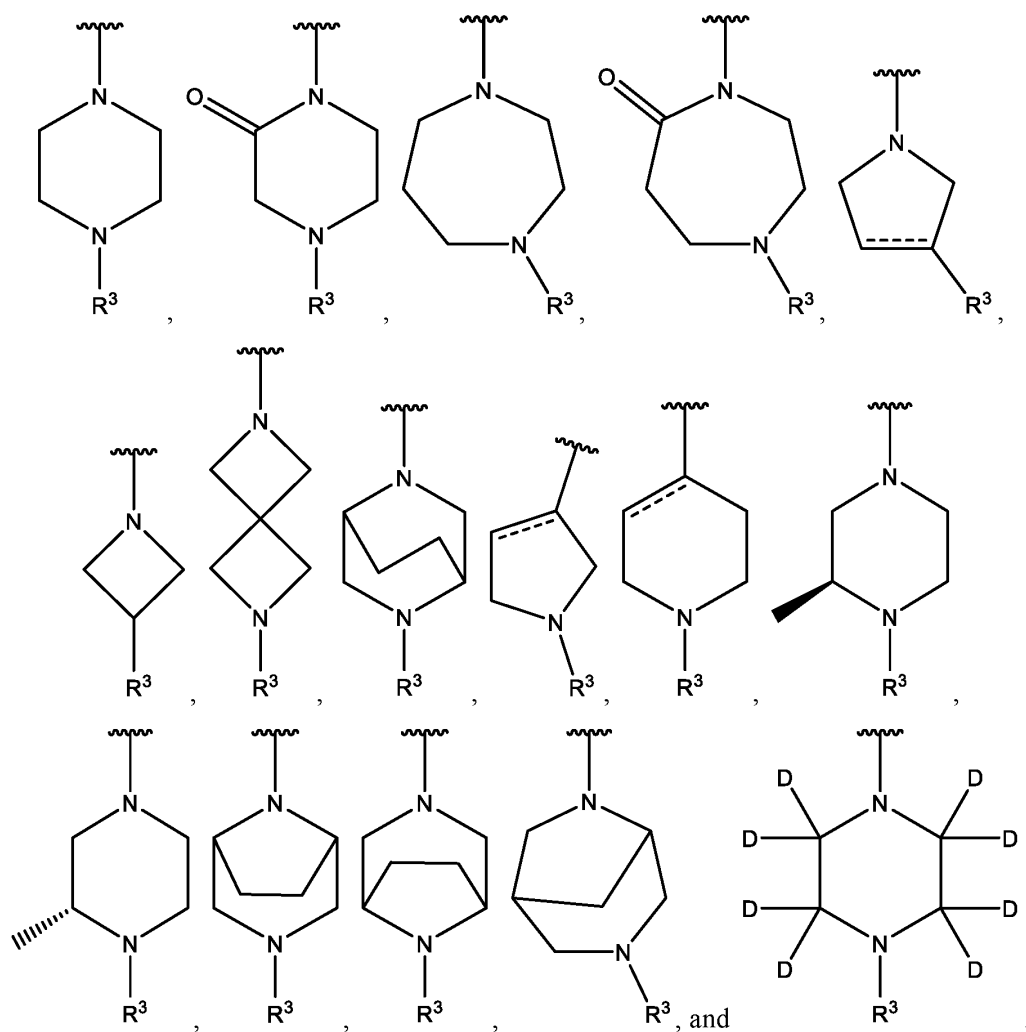


[0334] indicates a single bond or a double bond such that all valences are satisfied;

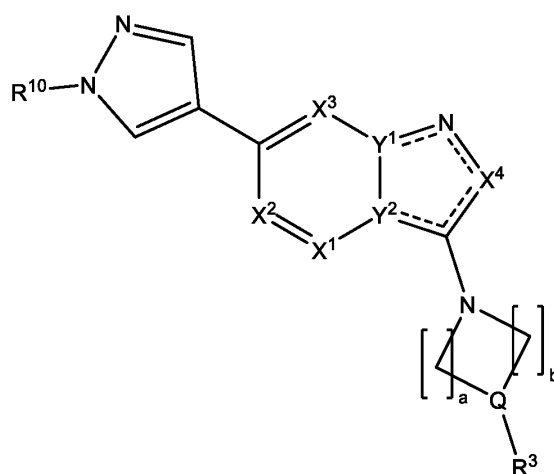
[0335] m is selected from 0, 1, 2, 3, 4, 5, and 6; and

[0336] Z¹, Z², and Z³ are selected from N and CR^a.

[0337] Clause 17. The compound of clause 16, or a pharmaceutically acceptable salt or solvate thereof, wherein R² is selected from:



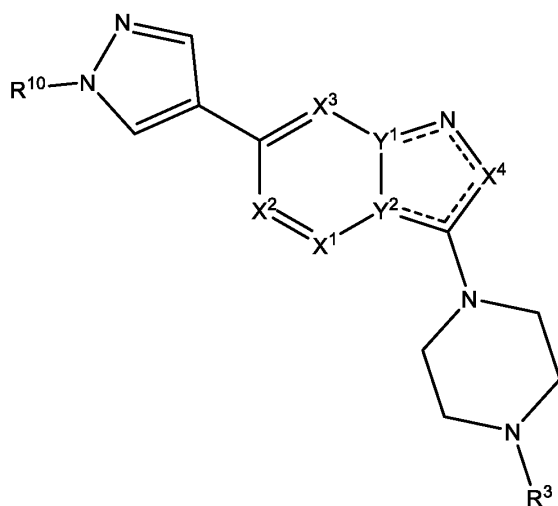
[0338] Clause 18. The compound of any one of clauses 1 to 17, or a pharmaceutically acceptable salt or solvate thereof, having Formula Ia:



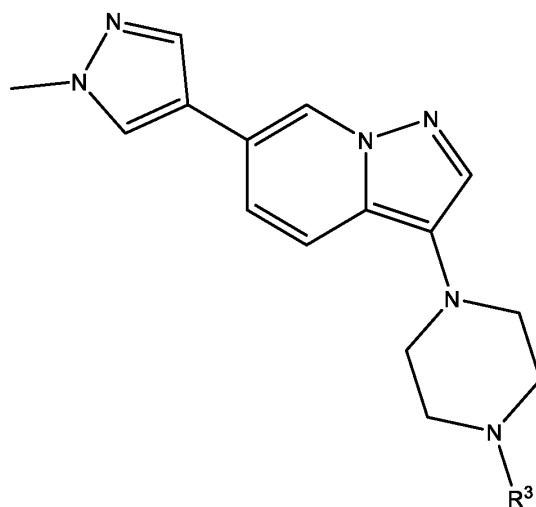
[0339] wherein a and b are each independently selected from 1, 2, and 3; and

[0340] Q is selected from -CH- and -N-, with the proviso that if Q is -N-, a and b are not 1.

[0341] Clause 19. The compound of any one of clauses 1 to 18, or a pharmaceutically acceptable salt or solvate thereof, having Formula II:

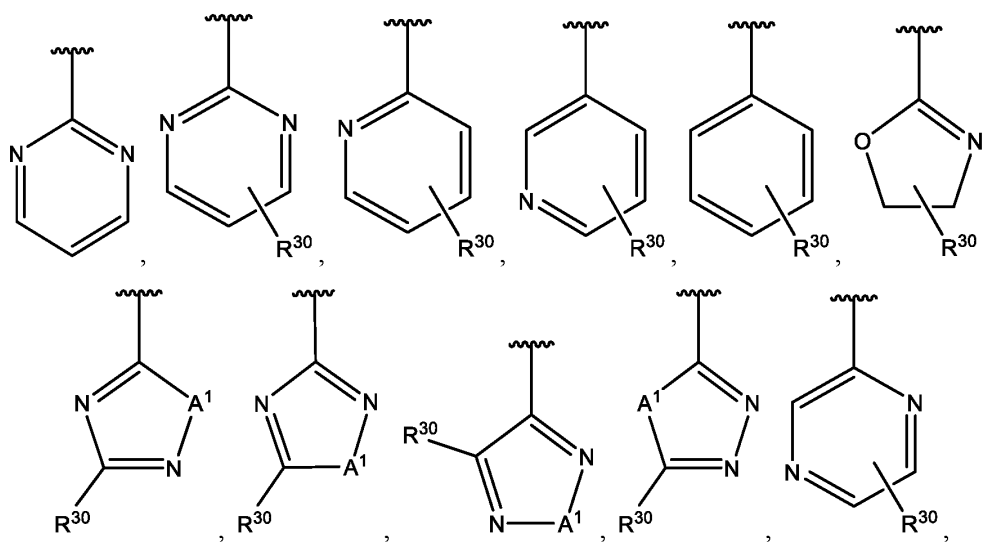


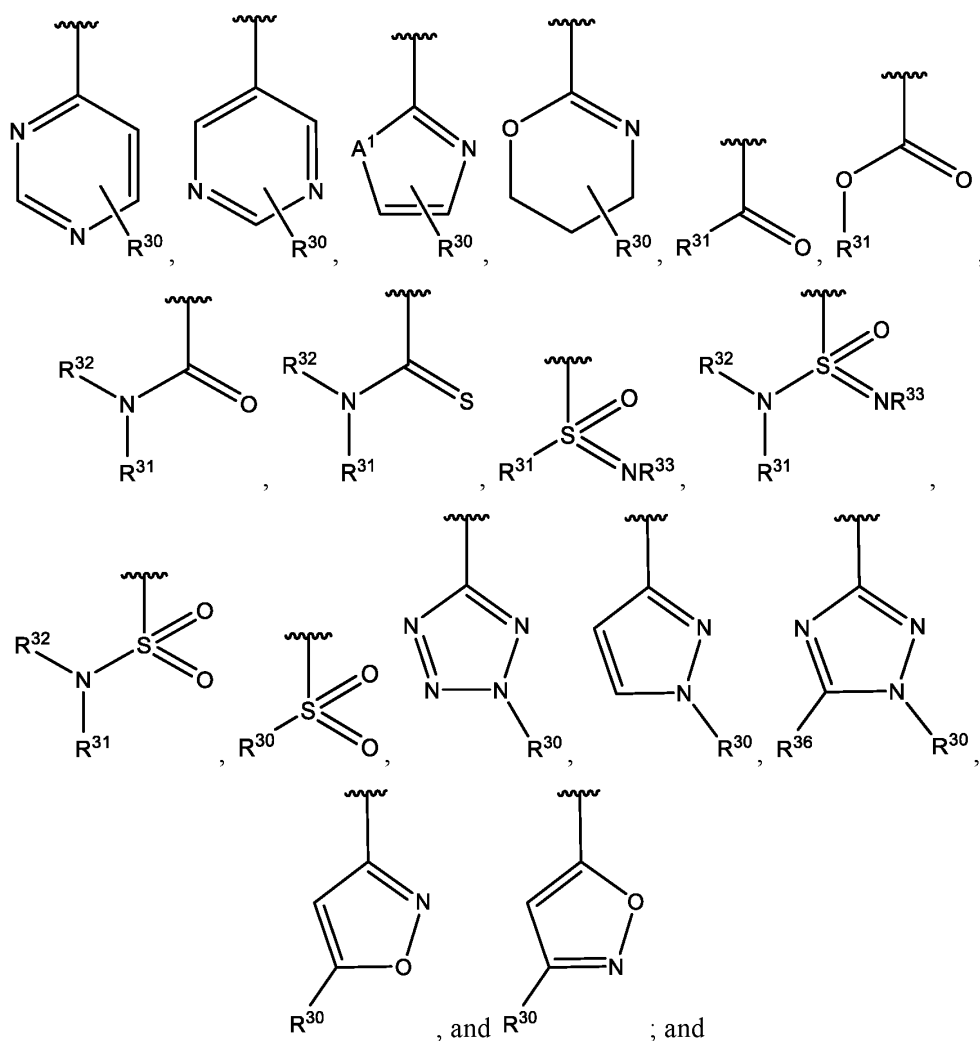
[0342] Clause 20. The compound of any one of clauses 1 to 19, or a pharmaceutically acceptable salt or solvate thereof, having Formula IIa:



[0343] Clause 21. The compound of any one of clauses 1 to 20, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is heteroaryl optionally substituted with one, two, three, four, or five R^{30} .

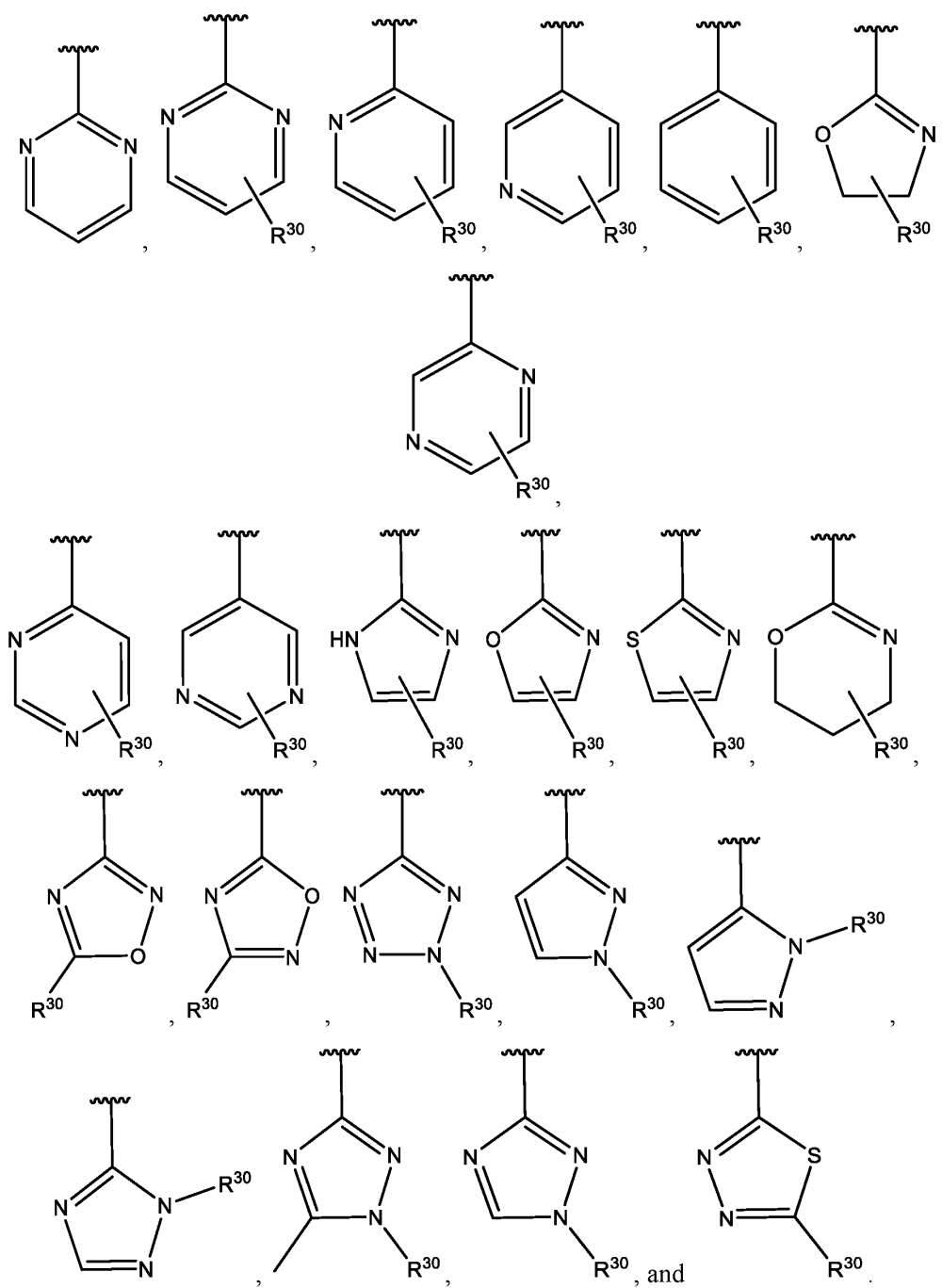
[0344] Clause 22. The compound of any one of clauses 1 to 21, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is selected from:



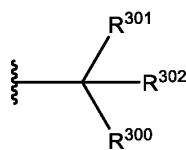


[0345] wherein A¹ is selected from O, S, and N and R³⁶ is selected from hydrogen, optionally substituted C₁-C₆alkyl, and optionally substituted C₁-C₆alkylaryl.

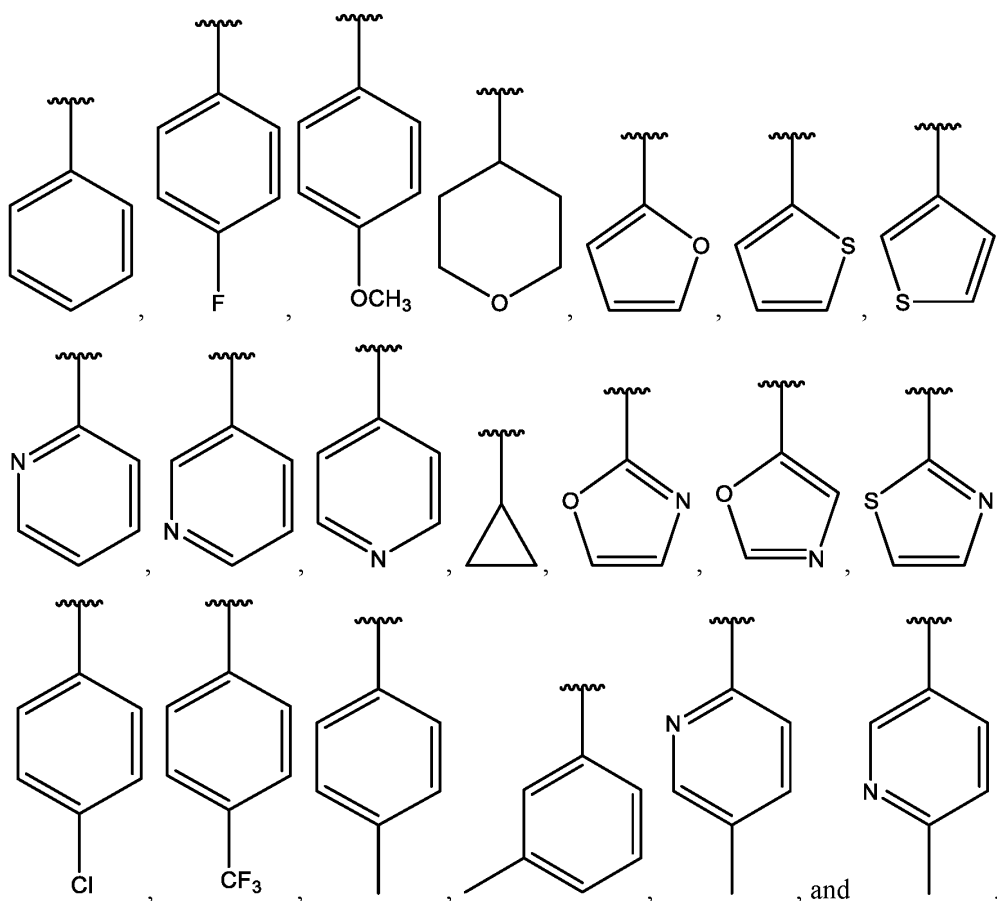
[0346] Clause 23. The compound of any one of clauses 1 to 22, or a pharmaceutically acceptable salt or solvate thereof, wherein R³ is selected from:



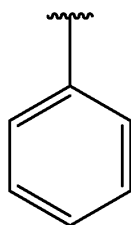
[0347] Clause 24. The compound of any of clauses 1 to 23, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{30} is:



[0348] Clause 25. The compound of clause 24, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{300} is selected from:

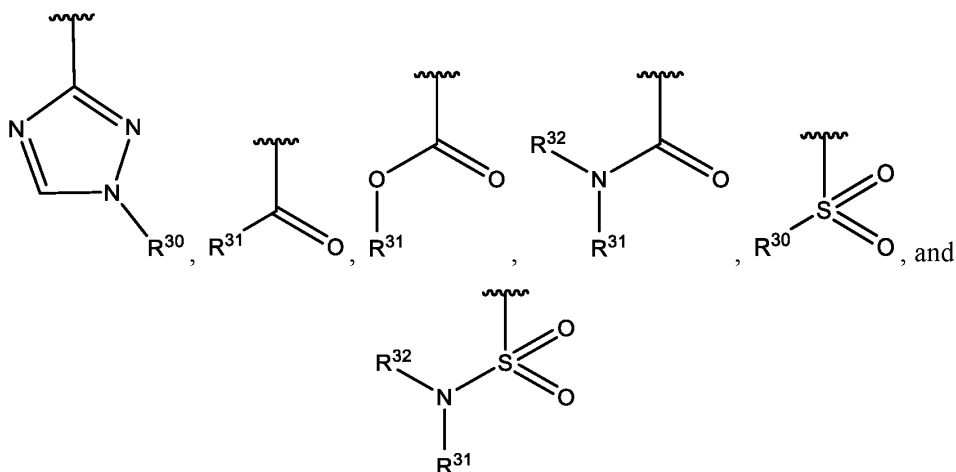


[0349] Clause 26. The compound of clause 25, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{300} is:

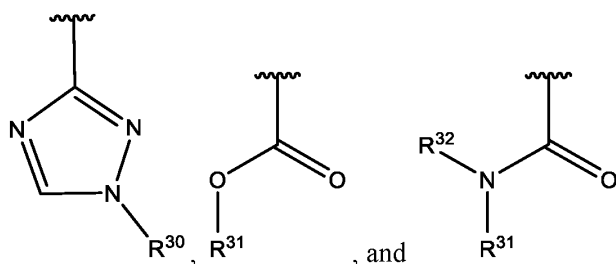


[0350] Clause 27. The compound of any one of clauses 1 to 26, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{301} is H and R^{302} is H or CH_3 .

[0351] Clause 28. The compound of any of clauses 1 to 22, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is selected from:

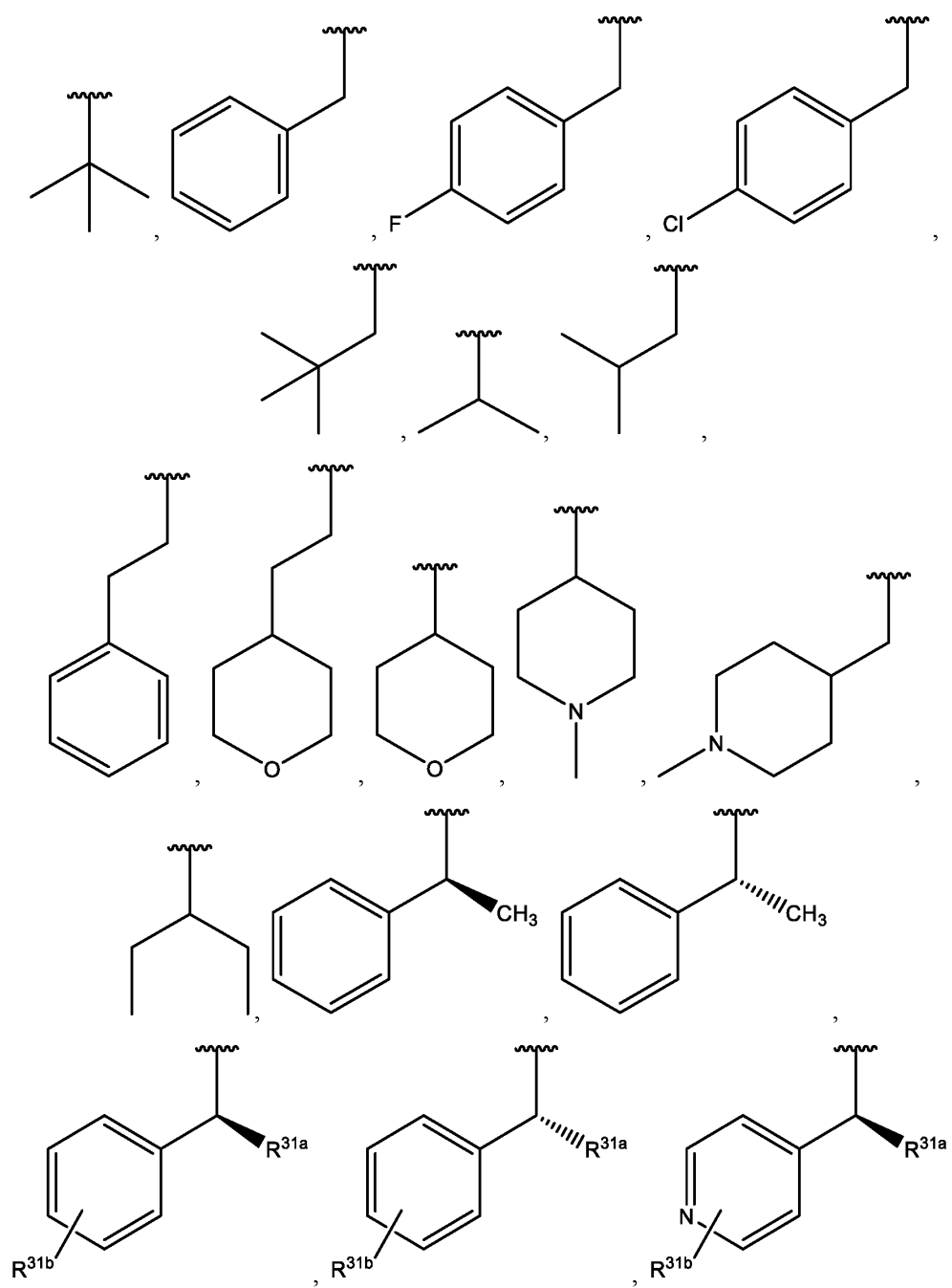


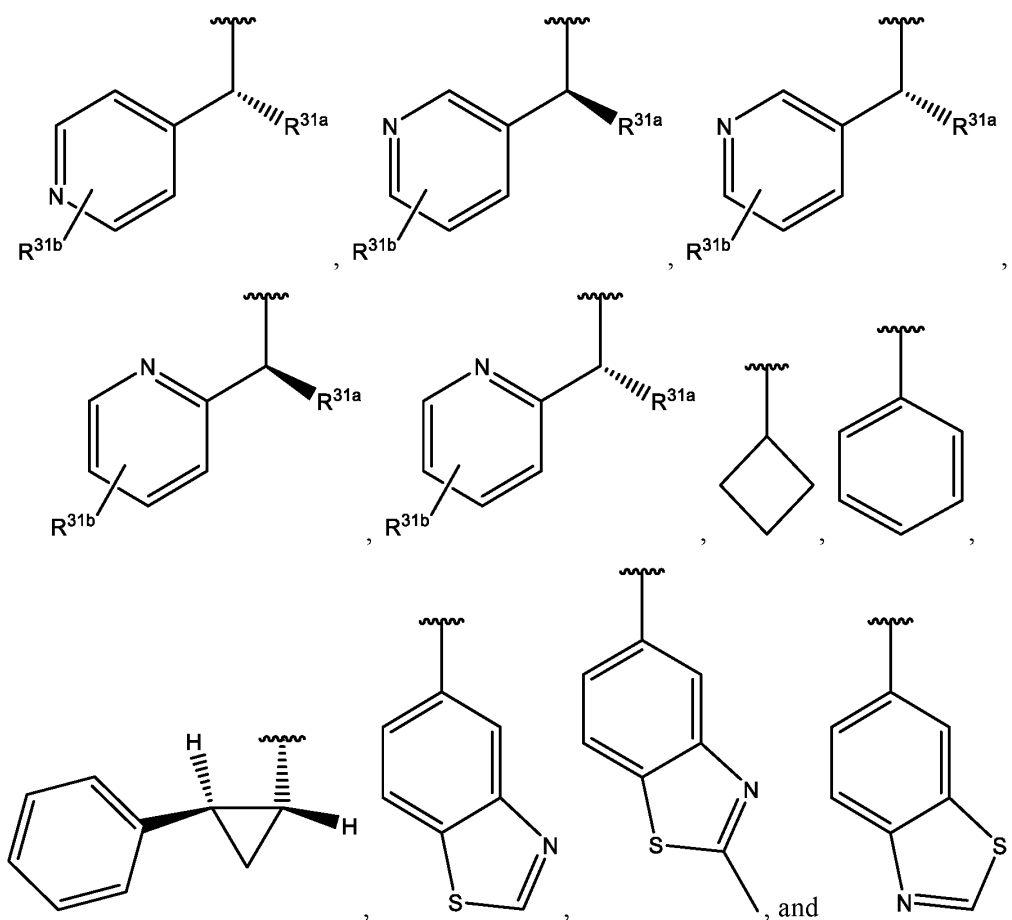
[0352] Clause 29. The compound of clause 28, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is selected from:



[0353] Clause 30. The compound of clause 29, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{32} is H.

[0354] Clause 31. The compound of any one of clauses 28 to 30, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{31} is selected from:





[0355] wherein R^{31a} is selected from H, D, alkylamino, C₁-C₄alkyl, and -CF₃, and

[0356] R^{31b} is selected from H, D, halo, hydroxy, amino, alkylamino, C₁-C₄alkyl, -CF₃, and -OCF₃.

[0357] Clause 32. The compound of clause 1, or a pharmaceutically acceptable salt or solvate thereof, selected from any one of compounds 156, 250, 275 and 326-406 of Table 1.

[0358] Clause 33. The compound of any one of clauses 1 to 32, which can exhibit one or more of the following properties: (i) promote the differentiation of an OPC into an oligodendrocyte, (ii) promote the expression of a protein associated with oligodendrocyte differentiation and/or myelination (*e.g.*, G-protein coupled receptor 17 (GPR17), myelin basic protein (MBP), ASPA, GST-pi, CC1, myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, or a combination thereof), (iii) promote the myelination of an axon, (iv) promote the remyelination of a demyelinated

axon, (v) inhibit PDGFR α kinase activity, (vi) achieve a brain to plasma ratio of greater than 0.1 when systemically administered to a subject, and (vii) any combination thereof.

- [0359] Clause 34. The compound of clause 33, which can inhibit PDGFR α kinase activity.
- [0360] Clause 35. The compound of clause 34, which can inhibit PDGFR α kinase activity with an IC₅₀ of less than 500 nM, less than 400 nM, less than 300 nM, less than 200 nM, less than 100 nM, less than 75 nM, less than less than 50 nM, less than 40 nM, less than 30 nM, less than 20 nM, less than 10 nM, or less than 5 nM.
- [0361] Clause 36. The compound of clause 35, wherein the IC₅₀ of the PDGFR α inhibitor is determined using an enzymatic PDGFR α kinase assay (*e.g.*, Promega kinase assay described in Example 131).
- [0362] Clause 37. The compound of clause 36, wherein the enzymatic PDGFR α kinase assay comprises 20 ng of purified PDGFR α protein, 150 μ M of ATP and 1 μ g of substrate, Poly (Glu4Tyr1) in a volume of 15 μ l.
- [0363] Clause 38. A pharmaceutical composition comprising the compound of any one of clauses 1 to 37, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.
- [0364] Clause 39. A kit comprising the compound of any one of clauses 1 to 37, or a pharmaceutically acceptable salt or solvate thereof, or the composition of clause 38, and instructions for use.
- [0365] Clause 40. A compound of any one of clauses 1 to 37, or the pharmaceutical composition of clause 38, for use in therapy.
- [0366] Clause 41. A method of treating a demyelinating disease in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the compound of any one of clauses 1 to 37 or the pharmaceutical composition of clause 38.
- [0367] Clause 42. A method of improving a subject's performance in a test for assessing one or more symptoms associated with a demyelinating disease, comprising administering to the subject a therapeutically effective amount of the compound of any one of clauses 1 to 37 or the pharmaceutical composition of clause 38, wherein after the administration, the subject's performance in the test is improved as compared to a reference subject (*e.g.*, the subject prior to the administration).

[0368] Clause 43. The method of clause 42, wherein the test is selected from a visual evoked potential (VEP) test, a multifocal visual evoked potential (mfVEP) test, a low contrast visual acuity (LC-VA) test, a magnetic resonance imaging (MRI) (*e.g.*, magnetic transfer resonance, myelin water fraction (MWF), and quantitative susceptibility mapping (QSM)), an electromyography (EMG), a nerve conduction velocity (NCV) test, an Extended Disability Status Scale (EDSS), a timed walk test (*e.g.*, timed 25-foot walk), a Nine-Hole Peg Test (9HPT), an ocular coherence tomograph (OCT), a quality of life measure test (*e.g.*, Multiple Sclerosis Quality of Life-54 and Vision-Related Quality of Life), cognitive assessment (*e.g.*, Montreal Cognitive Assessment), or combinations thereof.

[0369] Clause 44. The method of any one of clauses 41 to 43, wherein the demyelinating disease comprises an acute disseminated encephalomyelitis (ADEM), acute hemorrhagic leukoencephalitis, acute transverse myelitis, adrenoleukodystrophy, adrenomyeloneuropathy, Alexander disease, Alzheimer's disease, aminoacidurias, amyotrophic lateral sclerosis, anti-MAG peripheral neuropathy, anti-MOG associated spectrum, Baló concentric sclerosis, brain injury, CAMFAK syndrome, Canavan disease, carbon monoxide toxicity, central pontine myelinolysis, cerebral hypoxia, cerebral ischemia, Charcot–Marie–Tooth disease, chronic inflammatory demyelinating polyneuropathy, chronic traumatic encephalopathy, clinically isolated syndrome (CIS), congenital cataract, copper deficiency associated condition, delayed post-hypoxic leukoencephalopathy, diffuse cerebral sclerosis of Schilder, diffuse myelinoclastic sclerosis, extrapontine myelinolysis Gaucher disease, Guillain–Barré syndrome, hereditary neuropathy, hereditary neuropathy with liability to pressure palsy, HTLV-1–associated myelopathy, Hurler syndrome, hypomyelination, hypoxic brain injury, Krabbe disease, Leber hereditary optic atrophy and related mitochondrial disorders, leukodystrophic disorders, Marchiafava-Bignami disease, metachromatic leukodystrophy, multiple sclerosis (*e.g.*, primary progressive multiple sclerosis (PPMS), relapsing-remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), progressive relapsing multiple sclerosis, Marburg multiple sclerosis, tumefactive multiple sclerosis, and optic-spinal multiple sclerosis), multiple system atrophy, myelinoclastic disorders, myelopathy, nerve injury, neuromyelitis optica (NMO), Niemann-Pick disease, optic neuropathy, optic neuritis (*e.g.*, acute optic neuritis and chronic relapsing inflammatory optic neuritis

(CRION)), osmotic demyelination syndrome, Parkinson's disease, Pelizaeus-Merzbacher disease, peripheral neuropathy, phenylketonuria, progressive inflammatory neuropathy, progressive multifocal leukoencephalopathy, progressive subcortical ischemic demyelination, reperfusion injury, Schilder disease, solitary sclerosis, spinal cord injury, subacute sclerosing panencephalitis, Tabes dorsalis, Tay-Sachs disease, transverse myelitis, traumatic brain injury, tropical spastic paraparesis, vitamin B12 deficiency, cerebral palsy, or a combination thereof.

[0370] Clause 45. The method of any one of clauses 41 to 44, wherein the demyelinating disease is characterized by demyelination of one or more cells within the CNS of the subject.

[0371] Clause 46. The method of any one of clauses 41 to 45, wherein the demyelinating disease is multiple sclerosis.

[0372] Clause 47. The method of clause 46, wherein the multiple sclerosis comprises a clinically isolated syndrome ("CIS"), relapsing-remitting MS ("RRMS"), secondary progressive MS ("SPMS"), primary progressive MS ("PPMS"), optic neuritis or transverse myelitis.

[0373] Clause 48. The method of any one of clauses 41 to 45, wherein the demyelinating disease is an optic neuritis.

[0374] Clause 49. The method of any one of clauses 41 to 48, wherein treating the demyelinating disease comprises reducing one or more symptoms associated with the demyelinating disease.

[0375] Clause 50. The method of clause 49, wherein the one or more symptoms comprise fatigue, dizziness, malaise, elevated fever and high body temperature, extreme sensitivity to cold in the hands and feet, weakness and stiffness in muscles and joints, weight changes, digestive or gastrointestinal problems, low blood pressure, high blood pressure, irritability, anxiety, depression, impaired vision (*e.g.*, blurred vision, double vision, reduction in low contrast visual acuity (LC-VA)), ataxia, clonus, spasms, dysarthria, weakness, clumsiness, hand paralysis, hemiparesis, genital anesthesia, sexual dysfunction, incoordination, paresthesias, ocular paralysis, impaired muscle coordination, loss of sensation, tingling, numbness, pain, neurological symptoms, impaired cognition, unsteady gait, balance problems, dizziness, spastic paraparesis, incontinence, hearing problems, speech problems, loss of olfaction, agusia, or combinations thereof.

- [0376] Clause 51. A method of promoting the myelination of an axon in a subject in need thereof, the method comprising administering to the subject an effective amount of the compound of any one of clauses 1 to 37 or the pharmaceutical composition of clause 38.
- [0377] Clause 52. The method of clause 51, wherein promoting the myelination of an axon results in an increase in the expression of one or more of the following markers within the subject: myelin basic protein (MBP) Myelin Oligodendrocyte Glycoprotein (MOG), Oligodendrocyte Specific Protein/Claudin-11, CNPase, or any combination thereof.
- [0378] Clause 53. The method of clause 51 or 52, wherein the myelination of an axon can be determined by visualizing and/or quantifying the expression of one or more of the following markers: myelin basic protein (MBP) Myelin Oligodendrocyte Glycoprotein (MOG), Oligodendrocyte Specific Protein/Claudin-11, CNPase, or any combination thereof.
- [0379] Clause 54. A method of promoting the remyelination of a demyelinated axon in a subject in need thereof, the method comprising administering to the subject an effective amount of the compound of any one of clauses 1 to 37 or the pharmaceutical composition of clause 38.
- [0380] Clause 55. The method of clause 54, wherein promoting the remyelination of a demyelinated axon results in an increase in the expression of one or more of the following markers within the subject: myelin basic protein (MBP) Myelin Oligodendrocyte Glycoprotein (MOG), Oligodendrocyte Specific Protein/Claudin-11, CNPase, or any combination thereof.
- [0381] Clause 56. The method of clause 54 or 55, wherein the remyelination of a demyelinated axon can be determined by visualizing and/or quantifying the expression of one or more of the following markers: myelin basic protein (MBP) Myelin Oligodendrocyte Glycoprotein (MOG), Oligodendrocyte Specific Protein/Claudin-11, CNPase, or any combination thereof.
- [0382] Clause 57. A method of reducing the demyelination of a myelinated neuronal axon in a subject in need thereof, the method comprising administering to the subject an effective amount of the compound of any one of clauses 1 to 37 or the pharmaceutical composition of clause 38.

- [0383] Clause 58. The method of clause 57, wherein reducing the demyelination of a myelinated neuronal axon results in an increase in the expression of one or more of the following markers: myelin basic protein (MBP) Myelin Oligodendrocyte Glycoprotein (MOG), Oligodendrocyte Specific Protein/Claudin-11, CNPase, or any combination thereof.
- [0384] Clause 59. The method of clause 57 or 58, wherein the reduction in the demyelination of a myelinated neuronal axon can be determined by visualizing and/or quantifying the expression of one or more of the following markers: myelin basic protein (MBP) Myelin Oligodendrocyte Glycoprotein (MOG), Oligodendrocyte Specific Protein/Claudin-11, CNPase, or any combination thereof.
- [0385] Clause 60. A method of activating an oligodendrocyte progenitor cell (OPC) within the central nervous system (CNS) of a subject in need thereof, the method comprising administering to the subject an effective amount of the compound of any one of clauses 1 to 37 or the pharmaceutical composition of clause 38.
- [0386] Clause 61. A method according to any one of clauses 51 to 60, wherein the subject has, or is at risk of developing a demyelinating disease, for example a disease according to any one of clauses 44 to 50.
- [0387] Clause 62. A method according to any one of clauses 51 to 60, wherein the method is a method of treating or preventing a demyelinating disease, for example a disease according to any one of clauses 44 to 50.
- [0388] Clause 63. The method of any one of clauses 41 to 62, wherein the compound or the pharmaceutical composition is administered to the subject once.
- [0389] Clause 64. The method of any one of clauses 41 to 62, wherein the compound or the pharmaceutical composition is administered to the subject more than once using intermittent dosing.
- [0390] Clause 65. The method of clause 64, wherein the intermittent dosing comprises administering the compound or the pharmaceutical composition to the subject every other day, every three days, every four days, every five days, every six days, once a week, every eight days, every nine days, every 10 days, every 11 days, every 12 days, every 13 days, once every two weeks, once every three weeks, once a month, once every two months, once every three months, once every four months, once every five months, once every six months, or once every twelve months.

- [0391] Clause 66. The method of clause 64 or 65, wherein the intermittent dosing comprises administering to the subject a first dose and a second dose of the compound or the pharmaceutical composition, wherein the second dose is administered at least one day, at least two days, at least three days, at least four days, at least five days, at least six days, at least seven days, at least eight days, at least nine days, at least 10 days, at least 11 days, at least 12 days, at least 13 days, at least two weeks, at least three weeks, at least one month, at least two months, at least three months, at least four months, at least five months, at least six months, or at least 12 months after administering the first dose.
- [0392] Clause 67. The method of clause 66, wherein the second dose is administered to the subject one day, two days, three days, four days, five days, six days, seven days, eight days, nine days, 10 days, 11 days, 12 days, 13 days, two weeks, three weeks, one month, two months, three months, four months, five months, six months, or 12 months after administering the first dose.
- [0393] Clause 68. The method of any one of clauses 41 to 67, wherein after the administration, the compound or the pharmaceutical composition can achieve a brain to plasma ratio of greater than 0.1, greater than 0.2, greater than 0.3, greater than 0.4, greater than 0.5, greater than 0.6, greater than 0.7, greater than 0.8, greater than 0.9, greater than 1.0, greater than 1.1, greater than 1.2, greater than 1.3, greater than 1.4, greater than 1.5, greater than 1.6, greater than 1.7, greater than 1.8, greater than 1.9, or greater than 2.0.
- [0394] Clause 69. The method of any one of clauses 41 to 68, further comprising administering to the subject an additional therapeutic agent.
- [0395] Clause 70. The method of clause 69, wherein the additional therapeutic agent comprises a standard care of treatment.
- [0396] Clause 71. The method of clause 69 or 70, wherein the additional therapeutic agent comprises an immunomodulatory agent.
- [0397] Clause 72. The method of clause 71, wherein the additional therapeutic agent is selected from interferon beta-1b, interferon beta-1a, peginterferon beta-1a, alemtuzumab, natalizumab, ocrelizumab, ofatumumab, glatiramer acetate, teriflunomide, dimethyl fumarate, monomethyl fumarate, diroximel fumarate, fingolimod hydrochloride, siponimod fumaric acid, ozanimod hydrochloride, BTK inhibitor, or a pharmaceutically acceptable salt thereof

- [0398] Clause 73. The method of any one of clauses 69 to 72, wherein the additional therapeutic agent is administered to the subject prior to, concurrently, or after the administration of the compound or the pharmaceutical composition.
- [0399] Clause 74. A method of inducing the differentiation of an oligodendrocyte progenitor cell (OPC) into an oligodendrocyte, the method comprising contacting the OPC with an effective amount of the compound of any one of clauses 1 to 37 or the pharmaceutical composition of clause 38.
- [0400] Clause 75. The method of clause 74, wherein inducing the differentiation of the OPC into an oligodendrocyte results in an increase in the expression of the following markers in the subject: GPR17, MBP, ASPA, GST-pi, CC1, myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, or a combination thereof.
- [0401] Clause 76. The method of clause 74 or 75, wherein the differentiation of the OPC into an oligodendrocyte is measured by determining the expression of GPR17, MBP, ASPA, GST-pi, CC1, myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, or a combination thereof.
- [0402] Clause 77. A method of inhibiting PDGFR α activity in a cell, the method comprising contacting the cell with an effective amount of the compound of any one of clauses 1 to 37 or the pharmaceutical composition of clause 38.
- [0403] Clause 78. The method of clause 77, wherein the inhibition of the PDGFR α activity is measured by one or more of the following: an *in vitro* OPC differentiation assay (*e.g.*, as described in Example 132), a cuprizone model for demyelination (*e.g.*, as described in Example 134), an *in vivo* OPC differentiation assay (*e.g.*, as described in Example 134), an enzymatic PDGFR α kinase assay (*e.g.*, as described in Example 131), or any combination thereof.
- [0404] Clause 79. The method of any one of clauses 74 to 78, wherein the contacting occurs *ex vivo* or *in vivo*.
- [0405] Clause 80. The method of any one of clauses 74 to 79, wherein the method is a method of treating by a therapy.
- [0406] Clause 81. A method of treating a relapsing form of multiple sclerosis in a subject in need thereof, the method comprising administering to the subject an effective

amount of the compound of any one of clauses 1 to 37 or the pharmaceutical composition of clause 38.

- [0407] Clause 82. The method of clause 81, wherein inducing the differentiation of the OPC into an oligodendrocyte results in an increase in the expression of the following marker in the subject: GPR17, MBP, ASPA, GST-pi, CC1, myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, or a combination thereof.
- [0408] Clause 83. The method of clause 81 or 82, wherein the differentiation of the OPC into an oligodendrocyte is measured by determining the expression of GPR17, MBP, ASPA, GST-pi, CC1, myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, or a combination thereof.
- [0409] Clause 84. The method of any one of clauses 81 to 83, wherein the relapsing form of multiple sclerosis comprises a clinically isolated syndrome ("CIS"), relapsing-remitting MS ("RRMS"), secondary progressive MS ("SPMS"), primary progressive MS ("PPMS"), or transverse myelitis.
- [0410] Clause 85. The compound of any one of clauses 1 to 37 or the pharmaceutical composition of clause 38, for use in a method of one or more of the following: (i) promote the differentiation of an OPC into an oligodendrocyte, (ii) promote the expression of a protein associated with oligodendrocyte differentiation and/or myelination (*e.g.*, G-protein coupled receptor 17, myelin basic protein (MBP), ASPA, GST-pi, CC1, myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, or a combination thereof), (iii) promote the myelination of an axon, (iv) promote the remyelination of a demyelinated axon, (v) inhibit PDGFR α kinase activity, (vi) achieve a brain to plasma ratio of greater than 0.1 when systemically administered to a subject, and (vii) any combination thereof.
- [0411] Clause 86. A method of treating a PDGF-associated tumor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound of any one of clauses 1 to 37 or the pharmaceutical composition of clause 38, wherein after the administration, PDGFR α activity is reduced in the subject.
- [0412] Clause 87. The method of clause 86, wherein the PDGF-associated tumor comprises an oligodendroglioma.

[0413] Clause 88. The method of clause 86 or 87, wherein the method is a method of treatment by therapy.

[0414] The specification is most thoroughly understood in light of the teachings of the references cited within the specification. The embodiments within the specification provide an illustration of embodiments and should not be construed to limit the scope. The skilled artisan readily recognizes that many other embodiments are encompassed. All publications and patents cited in this disclosure are incorporated by reference in their entirety. To the extent the material incorporated by reference contradicts or is inconsistent with this specification, the specification will supersede any such material. The citation of any references herein is not an admission that such references are prior art.

[0415] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification, including claims, are to be understood as being modified in all instances by the term "about." Accordingly, unless otherwise indicated to the contrary, the numerical parameters are approximations and can vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding approaches.

[0416] The following examples are offered by way of illustration and not by way of limitation. The contents of all references cited throughout this application are expressly incorporated herein by reference.

EXAMPLES

[0417] As further detailed below, the present disclosure demonstrates that compounds that inhibit PDGFR α kinase activity in OPCs can induce oligodendrocyte differentiation (*e.g.*, *in vitro* and *in vivo*), and that the effect is likely specific to the inhibition of PDGFR α kinase activity. Furthermore, the present disclosure demonstrates that such compounds can induce remyelination in an animal model of demyelination.

[0418] Table 3 below defines the different abbreviations used in the below examples and else wherein the present disclosure.

Table 3. Abbreviations

Term	Abbreviation
1,1'-Bis(diphenylphosphino)ferrocene	dppf
Acetic acid ($\text{CH}_3\text{CO}_2\text{H}$)	AcOH
Acetonitrile (CH_3CN)	MeCN
Aqueous	aq.
<i>Bis</i> (trichloromethyl)carbonate (triphosgene)	BTC
Chloro[2-(di-tert-butylphosphino)- 2',4',6'-triisopropyl-1,1'-biphenyl][2-(2- aminoethyl)phenyl]palladium(II)	tBuXPhos Pd G1
[(2-Di-tert-butylphosphino-2',4',6'- triisopropyl-1,1'-biphenyl)-2-(2'-amino- 1,1'-biphenyl)] palladium(II) methanesulfonate	tBuXPhos Pd G3
Column volume	CV
[Dicyclohexyl[3-(1-methylethoxy)- 2',4',6'-tris(1-methylethyl)[1,1'-biphenyl]- 2-yl]phosphine- κP](methanesulfonato- κO)[2'-(methylamino- κN)[1,1'-biphenyl]- 2-yl- κC]palladium	EPhos Pd G4
Diethylaminosulfur trifluoride	DAST
Diisobutylaluminum hydride	DIBAL-H
Dichloromethane (CH_2Cl_2)	DCM
Diethyl ether ($(\text{CH}_3\text{CH}_2)_2\text{O}$)	Et_2O
3,4-Dihydro-2H-pyran	DHP
Dimethyl sulfoxide ($(\text{CH}_3)_2\text{SO}$)	DMSO
Diphenylphosphoryl azide	DPPA
Electrospray ionization	ESI
Ethanol ($\text{CH}_3\text{CH}_2\text{OH}$)	EtOH
Ethyl acetate	EtOAc
Ethylene dichloride (1,2-Dichloroethane)	EDC

Dicyclohexyl(3-isopropoxy-2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)phosphine	EPhos
Ethanol (CH ₃ CH ₂ OH)	EtOH
Ethyl acetate	EtOAc
N-Chloromethyl-N'-fluorotriethylenediammonium bis(tetrafluoroborate) (Selectfluor)	F-TEDA
Formic acid	FA
1,2-Dichloroethane	DCE
1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (hexafluorophosphate azabenzotriazole tetramethyl uronium)	HATU
N-Hydroxybenzotriazole	HOBt
High performance liquid chromatography	HPLC
Isopropyl alcohol	IPA
Liquid chromatograph-mass spectrometry	LCMS
Lithium bis(trimethylsilyl)amide	LiHMDS
Mass spectrometry	MS
Methanol (CH ₃ OH)	MeOH
Methyl tert-butyl ether	MTBE
N,N-Diisopropylethylamine	DIEA
N,N-dimethylformamide	DMF
N-bromosuccinimide	NBS
N-chlorosuccinimide	NCS
1-Methylimidazole	NMI
N-Methyl-2-pyrrolidone	NMP
Nuclear magnetic resonance	NMR
Palladium on carbon	Pd/C
Parts per million	ppm

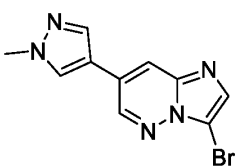
Petroleum ether	PE
Potassium trimethylsilanolate	KOTMS
Sodium trimethylsilanolate	NaOTMS
Room temperature	rt
Saturated	sat'd
Starting material	SM
2-(Trimethylsilyl)ethoxymethyl chloride	SEMCl
Tert-butyl dimethylsilyl chloride	TBSCl
Chloro-N,N,N',N'-tetramethylformamidium hexafluorophosphate	TCFH
Chloro tert-butyl dimethylsilane	TBSCl
Tetrahydrofuran	THF
1-tetrahydro-2H-pyran-2-yl	THP
Thin-layer chromatography	TLC
1,5,7-Triazabicyclo[4.4.0]dec-5-ene	TBD
Trifluoroacetic acid (CF ₃ CO ₂ H)	TFA
Triethylamine ((CH ₃ CH ₂) ₃ N)	Et ₃ N, TEA
Tris(dibenzylideneacetone)dipalladium(0)	Pd ₂ (dba) ₃
4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene	Xantphos
(SP-4-1)-[1,3-Bis[2,6-bis(1-ethylpropyl)phenyl]-4,5-dichloro-1,3-dihydro-2H-imidazol-2-ylidene]dichloro(2-methylpyridine)palladium	Pd-PEPPSI-IPent ^{Cl} -2-methylpyridine
palladium(2+) 1,3-bis[2,6-bis(heptan-4-yl)phenyl]-4,5-dichloro-1,2-didehydro-1λ ⁵ -imidazole 3-chloropyridine dichloride	Pd-PEPPSI-Ihept ^{Cl} -3-chloropyridine

[0419] In general, for compounds having stereoisomers that were separated, e.g., using chiral chromatography, the absolute stereochemistry of each compound was arbitrarily assigned.

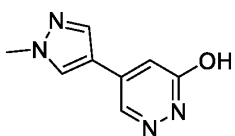
Preparation of Compounds for Synthesis of Exemplary PDGFR α Inhibitors

[0420] To synthesize the exemplary compounds disclosed herein, intermediate compounds were first prepared as described below.

Synthesis of 3-bromo-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (Compound S3)

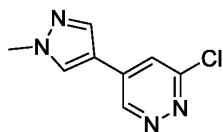


Step 1. Preparation of 5-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-ol



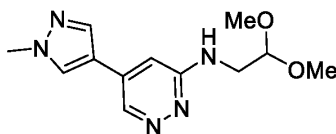
[0421] To a solution of 5-chloropyridazin-3-ol (1.00 g, 7.66 mmol) and 1-methylpyrazole-4-boronic acid pinacol ester (1.59 g, 7.66 mmol) in dioxane (18 mL) was added 2M Na₂CO₃ (15.3 mL, 30.6 mmol). The biphasic mixture was sparged for 10 min with argon then Pd(dppf)Cl₂ (0.28 g, 0.38 mmol) was added. The reaction was sparged with argon for 10 min, then heated to 75°C for 6 h under an argon. The reaction was cooled to rt and stirred overnight. The mixture was concentrated under reduced pressure then water (30 mL) was added. The aqueous mixture was extracted with 10% EtOH in EtOAc (4 x 50 mL) and 50% EtOAc in THF (3 x 50 mL). Brine (30 mL) was added to the aqueous layer, then extracted with 10% EtOH in EtOAc (3 x 50 mL). The organic layers were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 0-10% MeOH in DCM to afford 0.93 g (69%) of 5-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-ol as a pale yellow solid. MS (ESI) *m/z* [M+H]⁺ calcd. for C₈H₉N₄O, 171.1; found, 171.0.

Step 2. Preparation of 3-chloro-5-(1-methyl-1H-pyrazol-4-yl)pyridazine



[0422] 5-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-ol (6.0 g, 30 mmol, as prepared in the previous step) was treated with POCl₃ (75 mL, 0.80 mol). The suspension was warmed at 80°C for 1.5 h. The reaction was cooled to rt and the excess POCl₃ was removed in vacuo. Toluene was added to the residue then the solvent was removed under reduced pressure. This was repeated twice more. The residue was slowly treated with ice water (350 mL) then solid NaHCO₃ was slowly added to adjust the pH to 8. The reaction was stirred for 30 min, then extracted with 10% MeOH in DCM (2 x 200 mL). The aqueous layer was diluted with water (100 mL) and extracted with 10% MeOH in DCM (2 x 200 mL) and 10% trifluoroethanol in DCM (3 x 200 mL). The organic layers were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 0-100% of 5% MeOH in DCM solution/DCM to afford 5.14 g (87%) of 3-chloro-5-(1-methyl-1H-pyrazol-4-yl)pyridazine as a white solid. MS (ESI) *m/z* [M+H]⁺ calcd. for C₈H₈ClN₄, 195.0; found, 195.0.

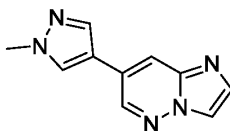
Step 3. Preparation of N-(2,2-dimethoxyethyl)-5-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-amine



[0423] A suspension of 3-chloro-5-(1-methyl-1H-pyrazol-4-yl)pyridazine (5.10 g, 26.2 mmol, as prepared in the previous step) and aminoacetaldehyde dimethyl acetal (29 mL, 0.27 mol) was warmed in an oil bath at 120°C for 20 h, then additional aminoacetaldehyde dimethyl acetal (15 mL, 0.14 mol) was added. The reaction was stirred at 120°C for 27 h, then cooled to rt, and concentrated under reduced pressure. The residue was partitioned between sat. aqueous NaHCO₃ (100 mL) and 10% MeOH in DCM (100 mL). The aqueous layer was washed with 10% MeOH in DCM (4 x 100 mL). The organic layers were combined, dried with anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under

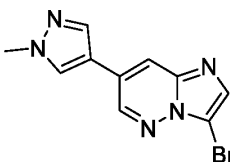
reduced pressure then the residue was purified by silica gel chromatography eluting with 0-100% of 10% MeOH in DCM solution/ DCM to afford 6.56 g (95%) of N-(2,2-dimethoxyethyl)-5-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-amine as a tan solid. MS (ESI) m/z $[M+H]^+$ calcd. for $C_{12}H_{18}N_5O_2$, 264.2; found, 264.0.

Step 4. 7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine



[0424] Conc. H_2SO_4 (52 mL) was cautiously added to N-(2,2-dimethoxyethyl)-5-(1-methyl-1H-pyrazol-4-yl)pyridazin-3-amine (15.7 g, 59.6 mmol, as prepared in the previous step) while stirring. After 15 minutes, the reaction was cooled in an ice bath and 1M NaOH (100 mL) was carefully added to the reaction. 50% NaOH (approx. 210 mL) was slowly added to the cold reaction until basic (pH 12). The pH was adjusted to pH 8 with slow addition of 1M H_2SO_4 . The reaction was partitioned between DCM (400 mL) and water (1200 mL). The aqueous layer was washed with DCM (2 x 300 mL). The aqueous layer containing an emulsion was filtered through a pad of Celite. The filter pad was washed with DCM which was then used to wash the aqueous layer (2 x 300 mL). The filter pad was then washed with 10% MeOH in DCM that was in turn used to wash the aqueous layer (4 x 300 mL). The aqueous layer was washed again with 10% MeOH in DCM (4 x 100 mL) or until no product was evident in the aqueous layer by HPLC. The organic layers were combined, dried with anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure to afford 10.5 g (89%) of 7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine as a tan solid. MS (ESI) m/z $[M+H]^+$ calcd. for $C_{10}H_{10}N_5$, 200.1; found, 200.0.

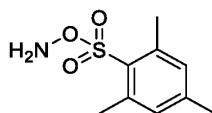
Step 5. Preparation of 3-bromo-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (Compound S3)



[0425] A solution of 7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (2.98 g, 15.0 mmol, as prepared in the previous step) in DMF (85.0 mL) was cooled in an ice bath then

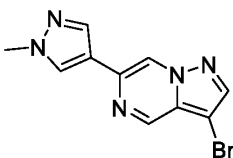
NBS (2.93 g, 16.4 mmol) was added. The reaction was stirred at 0°C for 2.5 h, then was poured into a solution of sat. aqueous Na₂S₂O₃ (28.6 mL, 112 mmol) and sat. aqueous NaHCO₃ (66.1 mL, 68.3 mmol). The reaction was diluted with water (120 mL). The ice bath was removed, and the reaction allowed to warm to rt. After stirring 1 h, the reaction was further diluted with water (270 mL). The solids were filtered off, washed with water (2 x 45 mL) and dried under a nitrogen press to afford 3.80 g (91%) of 3-bromo-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (Compound **S3**) as a yellow solid. (400 MHz, DMSO-*d*₆) δ (ppm) 9.00 (d, *J*=1.96 Hz, 1H) 8.45 (s, 1H) 8.33 (d, *J*=2.08 Hz, 1H) 8.17 (s, 1H) 7.85 (s, 1H) 3.90 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₀H₉BrN₅, 278.0; found, 277.9; HPLC purity: 210 nm: 97.9%; 254 nm: 97.5%.

Synthesis of O-(mesitylsulfonyl)hydroxylamine (Compound **S4**)

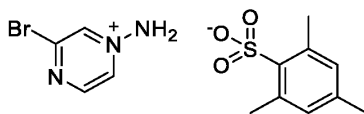


[0426] To a solution of ethyl N-hydroxyacetimidate (40.0 g, 329.2 mmol) and 2,4,6-trimethylbenzenesulfonyl chloride (40.0 g, 182.8 mmol) in DMF (300 mL) was added TEA (27.7 g, 274.3 mmol) dropwise at rt then the mixture was stirred at rt for 2 h. The reaction was poured into ice water (900 mL) then the mixture was filtered, and the filter cake was washed with H₂O (3 x 200 mL) and dried under reduced pressure. The solids were dissolved in dioxane (26 mL), then solution was cooled to 0°C, then HClO₄ (16 mL) was added dropwise at 0°C. After completion of addition, the mixture was stirred at 0°C for 30 min, then poured into ice water (400 mL). The mixture was filtered, then the filter cake was washed with H₂O (3 x 200 mL). The solids were dissolved in DCM (200 mL) to afford a DCM solution of O-(mesitylsulfonyl)hydroxylamine (Compound **S4**).

Synthesis of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine (Compound **S5**)

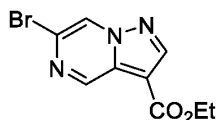


Step 1. Synthesis of 1-amino-3-bromopyrazin-1-ium 2,4,6-trimethylbenzenesulfonate



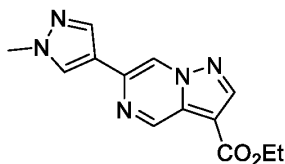
[0427] To a solution of 2-bromopyrazine (22.0 g, 138.3 mmol) in DCM (154 mL) was added a solution of O-(mesitylsulfonyl)hydroxylamine (Compound **S4**) (38.6 g, 179.8 mmol) in DCM (308 mL) dropwise at rt, then the mixture was stirred at rt overnight. The reaction was concentrated under reduced pressure then the residue was triturated with MTBE (100 mL) and dried under reduced pressure to afford 34.0 g (66%) of 1-amino-3-bromopyrazin-1-ium 2,4,6-trimethylbenzenesulfonate as a black solid.

Step 2. Synthesis of ethyl 6-bromopyrazolo[1,5-a]pyrazine-3-carboxylate



[0428] To a solution of K₂CO₃ (12.4 g, 97.4 mmol) and ethyl propiolate (27.0 g, 108.2 mmol) in DMF (270 mL) was added 1-amino-3-bromopyrazin-1-ium 2,4,6-trimethylbenzenesulfonate (27.0 g, 72.1 mmol, as prepared in the previous step) in portions at rt, then the reaction mixture was stirred at rt overnight. The mixture was diluted with H₂O, the mixture was extracted with MTBE (3 x 200 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography to afford 2.0 g (10%) of ethyl 6-bromopyrazolo[1,5-a]pyrazine-3-carboxylate as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 9.41 (s, 1H), 8.66 (d, *J*=0.8 Hz, 1H), 8.46 (s, 1H), 4.45 (q, *J*=7.2 Hz, 2H), 1.45 (t, *J*=7.2 Hz, 3H).

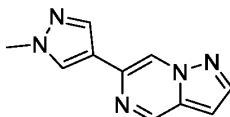
Step 3. Synthesis of ethyl 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine-3-carboxylate



[0429] To a mixture of ethyl 6-bromopyrazolo[1,5-a]pyrazine-3-carboxylate (5.0 g, 18.5 mmol, as prepared in the previous step) in dioxane (80 mL) and water (20 mL) was added

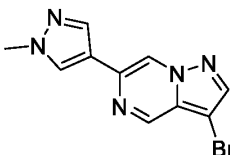
1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (5.7g, 27.7 mmol), Na_2CO_3 (5.7 g, 55.4 mmol), and $\text{Pd}(\text{dppf})\text{Cl}_2$ (1.0 g) under nitrogen. The mixture was heated to reflux and stirred under nitrogen for 2.5 h. The mixture was cooled to rt and filtered. The filtrate was poured into cold water, extracted with DCM/MeOH (10/1) ten times, the organic phase was washed with brine, dried over Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography to afford 3.5 g (70%) of ethyl 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine-3-carboxylate as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ (ppm) 9.56 (d, $J=1.6$ Hz, 1H), 8.59 (d, $J=1.2$ Hz, 1H), 8.45 (s, 1H), 7.96 (d, $J=7.2$ Hz, 2H), 4.45 (q, $J=7.2$ Hz, 2H), 4.01 (s, 3H), 1.46 (t, $J=7.2$ Hz, 3H).

Step 4. Synthesis of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine



[0430] To a mixture of ethyl 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine-3-carboxylate (3.5 g, 12.9 mmol, as prepared in the previous step) in 40% aqueous H_2SO_4 (35 mL) was stirred at 100°C overnight, then the mixture was poured into water, and the pH was adjusted to 8 with aqueous NaOH. The precipitate was isolated by filtration, the filter cake was washed with water, and dried to afford 1.7 g (66%) of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine as yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 9.19 (d, $J=1.6$ Hz, 1H), 9.14 (d, $J=0.8$ Hz, 1H), 8.26 (s, 1H), 8.12 (d, $J=2.4$ Hz, 1H), 8.05 (s, 1H), 6.956 (dd, $J=0.8, 2.4$ Hz, 1H), 3.89 (s, 3H).

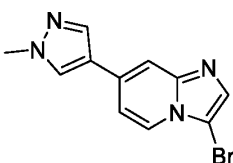
Step 5. Synthesis of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine (Compound S5)



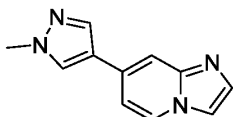
[0431] To a mixture of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine (1.0 g, 5.0 mmol, as prepared in the previous step) in DMF (30 mL) was added NBS (1.76 g, 5.0 mmol) in portions. The mixture was stirred at rt for 1 h, poured into water, and extracted with EtOAc three times. The combined organic phase was washed with water and brine,

dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography eluting with DCM/MeOH from 1:0 to 100:1 to afford 600 mg (43%) of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine (Compound **S5**) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 9.19 (d, $J=1.2$ Hz, 1H), 9.09 (d, $J=1.2$ Hz, 1H), 8.28 (s, 2H), 8.07 (s, 1H), 3.90 (s, 3H).

Synthesis of 3-bromo-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine (Compound **S7**)

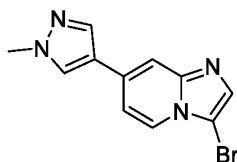


Step 1. Synthesis of 7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine



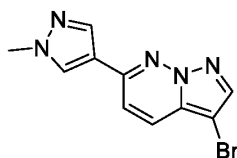
[0432] To a mixture of 7-bromoimidazo[1,2-a]pyridine (4.5 g, 22.8 mmol) in dioxane (100 mL) and H_2O (20 mL) was added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (7.1 g, 34.3 mmol), Na_2CO_3 (5.3 g, 50.3 mmol), and $\text{Pd}(\text{dppf})\text{Cl}_2$ (0.9 g) under nitrogen. The mixture was heated to reflux and stirred under nitrogen for 6 h. The mixture was cooled to rt and filtered. The filtrate was poured into cold water, extracted with DCM/MeOH (10/1) ten times, then the combined organic phase was washed with brine, dried over Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography to afford 3.4 g (75%) of 7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.50 (d, $J=7.2$ Hz, 1H), 8.29 (s, 1H), 8.03 (s, 1H), 7.86 (s, 1H), 7.76 (s, 1H), 7.52 (s, 1H), 7.14 - 7.16 (m, 1H), 3.88 (s, 3H).

Step 2. Synthesis of 3-bromo-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine (Compound **S7**)

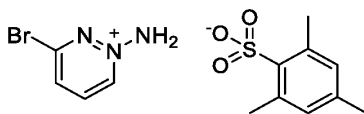


[0433] To a mixture of 7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine (4.1 g, 20.7 mmol, as prepared in the previous step) in ACN (120 mL) was added NBS (3.7 g, 20.7 mmol) in portions. The mixture was stirred at rt for 2 h, poured into water and extracted with DCM/MeOH (10/1) ten times. The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography to afford 2.2 g (39%) of 3-bromo-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine (Compound **S7**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.36 (s, 1H), 8.29 (d, *J*=7.2 Hz, 1H), 8.08 (s, 1H), 7.85 (s, 1H), 7.67 (s, 1H), 7.32 - 7.35 (m, 1H), 3.88 (s, 3H).

Synthesis of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-b]pyridazine (Compound **S8**)

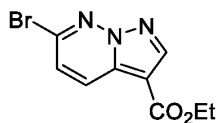


Step 1. Synthesis of 1-amino-3-bromopyridazin-1-ium 2,4,6-trimethylbenzenesulfonate



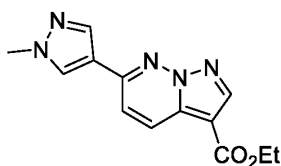
[0434] To a solution of 3-bromopyridazine (20.0 g, 125.7 mmol) in DCM (300 mL) was added the solution of O-(mesitylsulfonyl)hydroxylamine (Compound **S4**) (35.1 g, 125.7 mmol) in DCM (300 mL) dropwise at rt then the reaction mixture was stirred overnight at rt. The mixture was concentrated under reduced pressure then the residue was triturated with MTBE (80 mL) and filtered to afford 24.0 g (51%) of 1-amino-3-bromopyridazin-1-ium 2,4,6-trimethylbenzenesulfonate as black solid.

Step 2. Synthesis of ethyl 6-bromopyrazolo[1,5-b]pyridazine-3-carboxylate



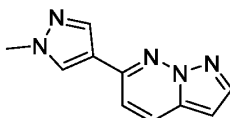
[0435] To a solution of K_2CO_3 (12.4 g, 89.8 mmol) and ethyl propiolate (7.5 g, 77.0 mmol) in DMF (230 mL) was added 1-amino-3-bromopyridazin-1-ium 2,4,6-trimethylbenzenesulfonate (24.0 g, 64.1 mmol, as prepared in the previous step) in portions at rt then the reaction mixture was stirred overnight at rt. The mixture was diluted with H_2O and extracted with MTBE (3x200 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by chromatography to afford 2.2 g (13%) of ethyl 6-bromopyrazolo[1,5-b]pyridazine-3-carboxylate as a yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.40-8.44 (m, 2H), 7.40 (d, $J=9.6$ Hz, 1H), 4.43 (q, $J=7.2$ Hz, 2H), 1.44 (t, $J=7.2$ Hz, 3H).

Step 3. Synthesis of ethyl 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-b]pyridazine-3-carboxylate



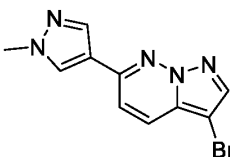
[0436] To a mixture of ethyl 6-bromopyrazolo[1,5-b]pyridazine-3-carboxylate (9.0 g, 33.3 mmol, as prepared in the previous step) in dioxane (144 mL) and water (36 mL) was added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (10.4 g, 49.9 mmol), Na_2CO_3 (10.6g, 99.9 mmol), and $Pd(dppf)Cl_2$ (1.0 g) under nitrogen. The mixture was heated to reflux and stirred under nitrogen for 2 h. The mixture was cooled to rt and filtered. The filtrate was poured into cold water and extracted with DCM/MeOH (10/1) ten times. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography to afford 9 g (99%) of ethyl 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-b]pyridazine-3-carboxylate as a yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.48 (d, $J=9.2$ Hz, 1H), 8.42(s, 1H), 8.06 (d, $J=4.4$ Hz, 1H), 7.45 (d, $J=9.2$ Hz, 1H), 7.86 (s, 1H), 4.43 (q, $J=7.2$ Hz, 2H), 4.03 (s, 3H), 1.45 (t, $J=7.2$ Hz, 3H).

Step 4. Synthesis of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-b]pyridazine



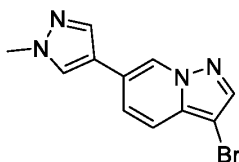
[0437] To a mixture of ethyl 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-b]pyridazine-3-carboxylate (4.5 g, 16.6 mmol, as prepared in the previous step) in 40% aqueous H₂SO₄ (45 mL) was stirred at 100°C overnight, then the mixture was poured into water and extracted with DCM/MeOH (10/1) ten times. The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was washed with MTBE to afford 2.5 g (76%) of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-b]pyridazine as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.04 (d, *J*=7.2 Hz, 2H), 7.98 (d, *J*=2.4 Hz, 1H), 7.93 (d, *J*=9.6 Hz, 1H), 7.21 (d, *J*=9.2 Hz, 1H), 6.61 (d, *J*=2.4 Hz, 1H), 4.00 (s, 3H).

Step 5. Synthesis of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-b]pyridazine (Compound **S8**)

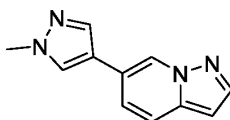


[0438] To a mixture of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-b]pyridazine (2.5 g, 12.5 mmol, as prepared in the previous step) in ACN (50 mL) was added NBS (2.2 g, 12.5 mmol) in portions. The mixture was stirred at rt for 1 h, then poured into water and extracted with DCM/MeOH (10/1) ten times. The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to afford 2.5 g (71%) of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-b]pyridazine (Compound **S8**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.51 (s, 1H), 8.14-8.19 (m, 3H), 7.65 (d, *J*=9.6 Hz, 1H), 3.93 (s, 3H).

Synthesis of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound S9)

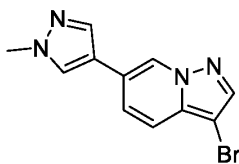


Step 1. Synthesis of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine



[0439] To a mixture of 6-bromopyrazolo[1,5-a]pyridine (4.5 g, 22.8 mmol) in dioxane (90 mL) and water (18 mL) was added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (7.1 g, 34.2 mmol), Na₂CO₃ (7.2 g, 68.8 mmol), and Pd(dppf)Cl₂ (0.45 g) under nitrogen. The mixture was heated to reflux and stirred under nitrogen for 3 h. The mixture was cooled to rt and filtered. The filtrate was poured into cold water and extracted with DCM/MeOH (10/1) ten times. The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography to afford 3.5 g (78%) of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.61 (s, 1H), 7.95(d, *J*=1.6 Hz, 1H), 7.77 (s, 1H), 7.63 (s, 1H), 7.57 (d, *J*=9.2 Hz, 1H), 7.23-7.26 (m, 1H), 6.52 (d, *J*=1.6 Hz, 1H), 3.99 (s, 3H).

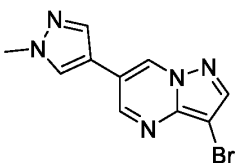
Step 2. Synthesis of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound S9)



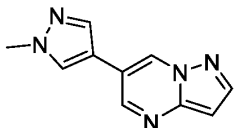
[0440] To a mixture of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (4.0 g, 20.2 mmol, as prepared in the previous step) in ACN (80 mL) was added NBS (4.3 g, 24.2 mmol) in portions. The mixture was stirred at rt for 1 h, then poured into water and extracted with DCM/MeOH (10/1) ten times. The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure

then the residue was purified by silica gel chromatography to afford 2.5 g (45%) of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **S9**) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.55 (s, 1H), 7.92 (s, 1H), 7.77 (s, 1H), 7.65 (s, 1H), 7.53 (d, *J*=8.8 Hz, 1H), 7.53 (dd, *J*=0.8, 9.2 Hz, 1H), 4.00 (s, 3H).

Synthesis of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine (Compound **S10**)

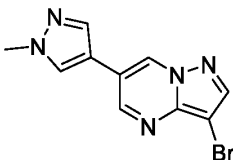


Step 1. Synthesis of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine



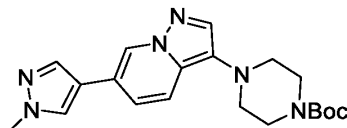
[0441] To a mixture of 6-bromopyrazolo[1,5-a]pyrimidine (4.5 g, 22.7 mmol) in dioxane (90 mL) and water (18 mL) was added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (7.0 g, 34.1 mmol), Na₂CO₃ (7.2g, 68.1 mmol), and Pd(dppf)Cl₂ (0.45 g) under nitrogen. The mixture was heated to reflux and stirred under nitrogen for 3 h. The mixture was cooled to at rt and filtered. The filtrate was poured into cold water and extracted with DCM/MeOH (10/1) ten times. The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography to afford 3.5 g (78%) of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.75-8.76 (m, 1H), 8.64 (d, *J*=2 Hz, 1H), 8.12 (d, *J*=2.4 Hz, 1H), 7.80 (s, 1H), 7.70 (s, 1H), 6.72-6.73 (m, 1H), 4.02 (s, 3H).

Step 2. Synthesis of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine (Compound **S10**)



[0442] To a mixture of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine (7.0 g, 35.1 mmol, as prepared in the previous step) in ACN (140 mL) was added NBS (7.5 g, 42.1 mmol) in portions. The mixture was stirred at rt for 1 h, poured into water and extracted with DCM/MeOH (10/1) ten times. The combined organic phase was washed with brine, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography to afford 5 g (51%) of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine (Compound **S10**) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.72-8.69 (m, 2H), 8.10 (s, 1H), 7.79 (s, 1H), 7.72 (s, 1H), 4.02 (s, 3H).

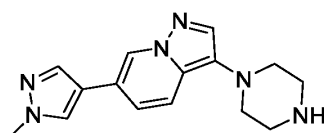
Synthesis of *tert*-butyl 4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxylate (Compound **11**)



[0443] To a round bottom flask containing 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **S9**) (4.00 g, 14.4 mmol) and *tert*-butyl-1-piperazinecarboxylate (3.23 g, 17.3 mmol) was added tBuOH (202 mL) and dioxane (124 mL). The solution was sparged with nitrogen for 20 min at 25°C. To the solution was added tBuXPhos Pd G1 (248 mg, 5.41 mmol) and NaOtBu (520 mg, 0.54 mmol) and the reaction mixture was sparged with nitrogen for an additional 10 min at 25°C. The flask was heated in a 55°C bath for 1.5 h, cooled to rt and diluted with EtOAc. The mixture was washed with H₂O and brine, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 10-90% EtOAc/DCM. The solids obtained were dried under reduced pressure to afford 1.62 g (29%) of *tert*-butyl 4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxylate (Compound **11**) as a yellow solid. ¹H NMR (400 MHz, CDCl₃)

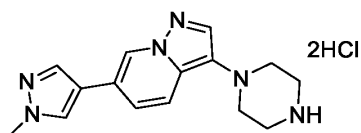
δ (ppm) 8.46 (s, 1H), 7.74 (s, 1H), 7.70 (s, 1H), 7.63 (s, 1H), 7.50 (d, $J = 7.3$ Hz, 1H), 7.14 (d, $J = 1.47$ Hz, 1H), 4.03-4.01 (m, 4H), 3.98 (s, 3H), 3.64 (m, 4H), 3.02 (m, 4H), 1.50 (s, 9H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{20}H_{27}N_6O_2$, 383.2; found, 383.3; HPLC purity: 210 nm: 99.4%; 254 nm: 99.2%.

Synthesis of 6-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylpyrazolo[1,5-a]pyridine (Compound **12**)



[0444] To a round bottom flask containing *tert*-butyl 4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxylate (Compound **11**) (0.340 g, 0.89 mmol) was added DCM (6.80 mL) then the solution was cooled on an ice bath and TFA (1.70 mL, 22.1 mmol) was added slowly. After 1 h the solvent was removed under reduced pressure, then MTBE was added to the residue and concentrated under reduced pressure to remove excess TFA. The residue was dissolved in DCM and swirled with sat. aqueous $NaHCO_3$, diluted with H_2O , and diluted with MTBE. The aqueous layer was washed with MTBE then extracted with DCM. The DCM layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to afford 105 mg (42%) of 6-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylpyrazolo[1,5-a]pyridine (Compound **12**) as a yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.45 (s, 1H), 7.74 (s, 1H), 7.70 (s, 1H), 7.60 (s, 1H), 7.52 (d, $J = 9.17$ Hz, 1H), 7.11 (d, $J = 9.05$ Hz, 1H), 3.97 (s, 3H), 3.08 (bs, 5H), 3.06 (bs, 4H); MS (ESI+, m/z): Calcd. for $C_{15}H_{19}N_6$: 283.2. Found: 283.1; HPLC purity: 210 nm: 100%; 254 nm: 100%.

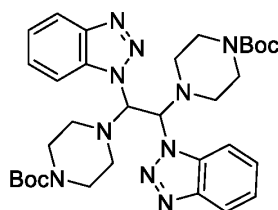
Synthesis of 6-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylpyrazolo[1,5-a]pyridine dihydrochloride salt (Compound **S19**)



[0445] To a round bottom flask containing *tert*-butyl 4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxylate (Compound **11**) (0.250 g, 0.65 mmol) was added MeOH (5.00 mL) and 4M HCl in dioxane (2 mL). The reaction was

stirred at 27°C for 24 h, then stirred another 5 h at 24°C. The mixture was filtered through a frit, and the solid was rinsed with MeOH (5 mL). The solid was dried under reduced pressure to afford 227 mg (98%) of 6-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylpyrazolo[1,5-a]pyridine dihydrochloride salt (Compound **S19**) as a light gray solid. MS (ESI) m/z $[M+H]^+$ calcd. for $C_{15}H_{21}Cl_2N_6$, 283.2; found, 283.2.

Synthesis of di-tert-butyl 4,4'-(1,2-bis(1H-benzo[d][1,2,3]triazol-1-yl)ethane-1,2-diyl)bis(piperazine-1-carboxylate) (Compound **S47**)



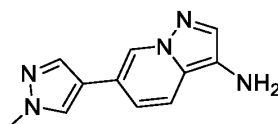
[0446] A solution of 1H-1,2,3-benzotriazole (19.2 g, 161.1 mmol) and tert-butyl piperazine-1-carboxylate (30.0 g, 161.1 mmol) in EtOH (300 mL) was stirred under nitrogen at 25°C for 20 min. Then glyoxal (40 wt.% in H₂O, 4.7 g, 80.5 mmol) was added to the mixture at 25°C. The reaction mixture was stirred at 30°C for 16 h. The reaction mixture was concentrated under reduced pressure then PE was added. The mixture was stirred for 30 min and filtered, the filter cake was dried to afford 42.0 g (32%) of di-tert-butyl 4,4'-(1,2-bis(1H-benzo[d][1,2,3]triazol-1-yl)ethane-1,2-diyl)bis(piperazine-1-carboxylate) (Compound **S47**) as a white solid.

[0447] Using the procedures described for Compound **S47** and reagents, starting materials, and conditions known to those skilled in the art, the following compounds representative of the present disclosure were prepared:

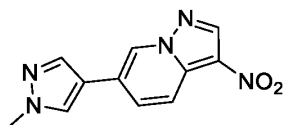
Compound Data

S48	di-tert-butyl 4,4'-(1,2-bis(1H-benzo[d][1,2,3]triazol-1-yl)ethane-1,2-diyl)bis(1,4-diazepane-1-carboxylate)
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Synthesis of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-amine (Compound **S56**)

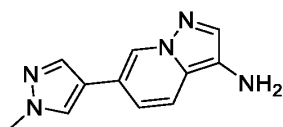


Step 1. Synthesis of 6-(1-methyl-1H-pyrazol-4-yl)-3-nitropyrazolo[1,5-a]pyridine



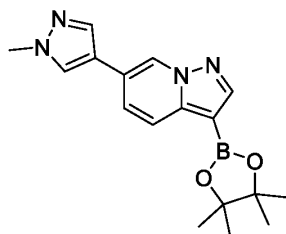
[0448] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (4.0 g, 5.05 mmol, as prepared in Compound **S9**, Step 1) dissolved in conc. H₂SO₄ (10 mL) was added KNO₃ (2.24 g, 5.55 mmol). The reaction mixture was stirred for 1 h at rt under nitrogen. The mixture was cooled to 0°C and diluted with water (300 mL). The mixture was neutralized to pH 8 with sat. aqueous Na₂CO₃. The precipitated solids were collected by filtration and washed with water (3x300 mL). The filter cake was dried under reduced pressure to afford 3.5 g (71%) of 6-(1-methyl-1H-pyrazol-4-yl)-3-nitropyrazolo[1,5-a]pyridine as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.34 (s, 1H), 8.90 (s, 1H), 8.38 (s, 1H), 8.24 (d, *J* = 9.1 Hz, 1H), 8.15 (d, *J* = 9.3 Hz, 1H), 8.11 (s, 1H), 3.90 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₁H₉N₅O₂, 244.1; found, 244.1.

Step 2. Synthesis of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-amine (Compound **S56**)

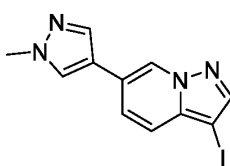


[0449] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-nitropyrazolo[1,5-a]pyridine (3.0 g, 12.33 mmol, as prepared in the previous step) dissolved in aqueous HBr (50 mL) was added SnCl₂·2H₂O (8.42 g, 37.0 mmol). The resulting solution was stirred for 4 h at 90°C under nitrogen. The mixture was cooled to rt, the pH was adjusted to pH 9 with aqueous NaOH, and extracted with EtOAc (3 x 500 mL). The combined organic extracts were washed with brine (3x100 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to afford 2.5 g (90%) of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-amine (Compound **S56**) as a yellow-brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.63 (s, 1H), 8.15 (s, 1H), 7.92 (s, 1H), 7.59 (d, *J* = 9.2 Hz, 1H), 7.44 (s, 1H), 7.11 (d, *J* = 9.2 Hz, 1H), 4.33 (s, 2H), 3.86 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₁H₁₁N₅, 214.1; found, 214.1.

Synthesis of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (Compound **S57**)

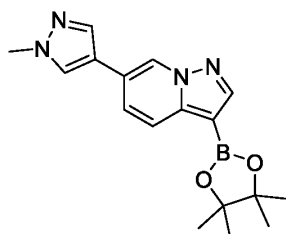


Step 1. Preparation of 3-iodo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine



[0450] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (7.0 g, 35.3 mmol, as prepared in Compound **S9**, Step 1) in DMF (70 mL) was added NIS (9.53 g, 42.4 mmol). The resulting mixture was stirred for 1 h at rt. The reaction was poured into a stirred mixture of 2.8M aqueous Na₂S₂O₃ (64 mL) and 1.14M aqueous NaHCO₃ (144 mL). The mixture was stirred vigorously for 1 h resulting in an off-white precipitate. The solids were collected by filtration, washed with H₂O (2 x 10 mL), and dried under high vacuum to afford 10 g (79%) of 3-iodo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.06 (s, 1H), 8.28 (s, 1H), 8.08 (s, 1H), 8.02 (d, *J* = 0.8 Hz, 1H), 7.60 (d, *J* = 9.2 Hz, 1H), 7.52 (d, *J* = 9.2 Hz, 1H), 3.88 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₁H₉IN₄, 325.0; found, 325.1.

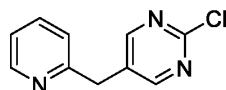
Step 2. Preparation of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (Compound **S57**)



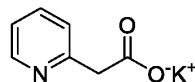
[0451] To a solution of 3-iodo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (9.0 g, 27.8 mmol, as prepared in the previous step) in THF (180 mL) was added 2-isopropoxy-

4,4,5,5-tetramethyl-1,3,2-dioxaborolane (17.1 g, 91.7 mmol) then cooled to 0°C under nitrogen and 1.3M iPrMgCl·LiCl in THF (31.9 mL, 41.7 mmol) was added dropwise. The reaction was stirred for 3 h at 0°C under nitrogen, diluted with DCM (160 mL), and filtered through a pad of silica gel. The pad was washed with EtOAc (100 mL) and the combined filtrates were concentrated under reduced pressure to afford 5.0 g (42%) of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazolo[1,5-a]pyridine (Compound **S57**) as a grey white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.08 (s, 1H), 8.26 (s, 1H), 8.12 (s, 1H), 8.01 (d, *J* = 0.8 Hz, 1H), 7.82 (d, *J* = 9.1 Hz, 1H), 7.65 (d, *J* = 9.1 Hz, 1H), 3.89 (s, 3H), 1.32 (s, 12H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₇H₂₁BN₄O₂, 325.2; found, 325.2.

Synthesis of 2-chloro-5-(pyridin-2-ylmethyl)pyrimidine (Compound **S80**, Steps 1-2)

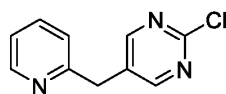


Step 1. Preparation of potassium pyridine-2-ylacetate



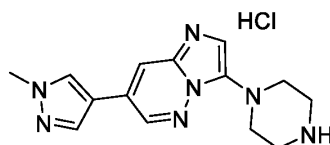
[0452] In dried glassware, a solution of methyl 2-pyridylacetate (0.500 g, 3.31 mmol), absolute ethanol (6.6 mL), and water (0.63 mL, 3.47 mmol) was heated at 60°C. A solution of potassium tert-butoxide (0.390 g, 3.47 mmol) was prepared in absolute ethanol (3.3 mL) in dried glassware, and then added dropwise to the initial solution at 60°C over 30 min. After complete conversion, the solvent was removed under vacuum and the residue was stirred in anhydrous Et₂O (6.6 mL) for 30 min. The solids were filtered through a frit and washed in quick sequence with ethanol/ether (1:1, 0.6 mL x2) and Et₂O (3 mL x3). The white solid was transferred to a dried flask and placed under vacuum in a 30°C bath for 2 h to afford 468 mg (81%) of potassium pyridine-2-ylacetate as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.33 (d, *J* = 4.3 Hz, 1H) 7.57 (td, *J* = 7.6, 1.8, 1H) 7.27 (d, *J* = 7.8 Hz, 1H) 7.06 (dd, *J* = 6.6, 5.4 Hz 1H) 3.32 (s, 2H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ (ppm) 49.5, 119.9, 123.8, 135.1, 147.8, 160.5, 171.5; MS (ESI) *m/z* [M+H]⁺ calcd. for C₇H₈NO₂: 138.1; found, 138.0.

Step 2. 2-Chloro-5-(pyridin-2-ylmethyl)pyrimidine (Compound **S80**)

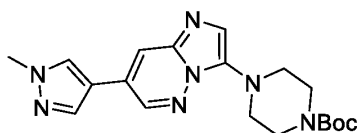


[0453] 5-Bromo-2-chloropyrimidine (110 mg, 0.590 mmol), Xantphos (22 mg, 0.04 mmol), Pd₂(dba)₃ (10 mg, 0.01 mmol), potassium pyridin-2-ylacetate (125 mg, 0.713 mmol, as prepared in the previous step), and mesitylene (1.2 mL) were added to a pressure tube that was pre-flushed with argon. It was sparged with more argon, sealed, and heated at 150°C for 24 h. The mixture was cooled to rt and purified by silica gel flash chromatography (acetone with 0.1% Et₃N/DCM) to afford 72 mg (59%) of 2-chloro-5-(pyridin-2-ylmethyl)pyrimidine (Compound **S80**) as an oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.59 (s, 2H) 8.57 (m, 1H) 7.68 (td, *J*=7.6, 1.8 Hz 1H) 7.21 (m, 2H) 4.13 (s, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₀H₉ClN₃: 206.5; found, 206.0; HPLC purity: 210 nm: 93.3%; 254 nm: 100.0%.

Synthesis of 7-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)imidazo[1,2-b]pyridazine hydrochloride salt (Compound **S83**)



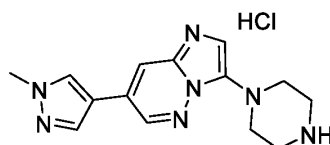
Step 1. Synthesis of tert-butyl 4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl)piperazine-1-carboxylate



[0454] To a 20 mL vial containing 3-bromo-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (Compound **S3**) (300.4 mg, 1.080 mmol) and tert-butyl 1-piperazinecarboxylate (1.00 g, 5.40 mmol) was added tBuOH (3.0 mL) and dioxane (1.5 mL) then the solution was sparged with argon for 10 min. KOtBu (182 mg, 1.62 mmol) was added and the mixture was sparged again for 10 min with argon. tBuXPhos Pd G1 (111 mg, 0.162 mmol) was added, and the mixture was sparged for 10 min with argon. The mixture was stirred at 55°C under an argon for 1 h. The reaction was cooled to rt, diluted

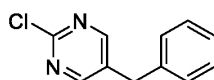
with DCM (40 mL), and washed with 10% citric acid solution (3 x 10 mL), H₂O (3 x 10 mL), and sat. aqueous NaHCO₃ (2 x 10 mL). The organic layer was dried over anhydrous Na₂SO₄ and filtered, then the filtrate was concentrated under reduced pressure. The residue was purified by silica gel flash chromatography eluted with 0-100% (10% MeOH in DCM)/DCM to afford 280.8 mg (68%) of tert-butyl 4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl)piperazine-1-carboxylate as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.51 (d, *J* = 2.0 Hz, 1H), 7.91 (d, *J* = 2.0 Hz, 1H), 7.84 (s, 1H), 7.75 (s, 1H), 7.25 (s, 1H), 4.00 (s, 3H), 3.75 - 3.64 (m, 4H), 3.29 - 3.20 (m, 4H), 1.51 (s, 9H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₉H₂₅N₇O₂: 384.2, Found: 384.2; HPLC purity: 210 nm: 97.8%; 254 nm: 100.0%.

Step 2. Synthesis of 7-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)imidazo[1,2-b]pyridazine hydrochloride salt (Compound **S83**)



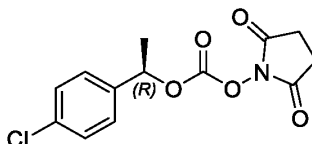
[0455] A solution of tert-butyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]piperazine-1-carboxylate (274.5 mg, 0.7159 mmol, as prepared in the previous step) in DCM (30 mL) was cooled to 0°C then a solution of 4M HCl in dioxane (1.8 mL, 7.3 mmol) was added dropwise. After completion of addition, the mixture was warmed to rt and stirred for 7 h. The reaction was concentrated under reduced pressure, then the residue was triturated with ether and filtered. The solid was dried under reduced pressure to afford 214.6 mg (94%) of 7-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)imidazo[1,2-b]pyridazine hydrochloride salt (Compound **S83**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.69 (br s, 2H), 9.34 (d, *J* = 2.0 Hz, 1H), 8.69 (s, 1H), 8.44 (d, *J* = 2.0 Hz, 1H), 8.34 (s, 1H), 7.98 (s, 1H), 3.94 (s, 3H), 3.54 - 3.49 (m, 4H), 3.37 - 3.25 (m, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₄H₁₇N₇: 284.2, Found: 284.2; HPLC purity: 210 nm: 95.9%; 254 nm: 100.0%.

Synthesis of 5-benzyl-2-chloropyrimidine (Compound **S88**)



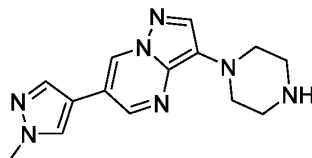
[0456] To a mixture of (2-chloropyrimidin-5-yl)boronic acid (20 g, 0.126 mol) and Na_2CO_3 (40.43 g, 0.381 mol) in dioxane (200 mL) and H_2O (80 mL) stirred under nitrogen at 25°C was added ($\text{Ph}_3\text{P}_2\text{PdCl}_2$) (4.43 g, 0.0063 mol); benzyl bromide (23.76 g, 0.138 mol) was added after 20 min. The reaction mixture was stirred at 100°C for 1 h. The mixture was diluted with water and extracted with EtOAc (3x50 mL). The combined organic layers were concentrated under vacuum to give crude product, which was purified by silica gel column eluting with DCM/MeOH (30:1~15:1) to afford 18.18 g (69%) of 5-benzyl-2-chloropyrimidine (Compound **S88**) as a white solid. ^1H NMR (400 MHz, CDCl_3) δ (ppm) 8.48 (s, 2H), 7.34~7.37 (m, 2H), 7.27~7.31 (m, 1H), 7.19 (d, $J=7.2\text{ Hz}$, 2H), 3.98 (s, 2H).

Synthesis of (R)-1-(4-chlorophenyl)ethyl (2,5-dioxopyrrolidin-1-yl) carbonate (Compound **S95**)

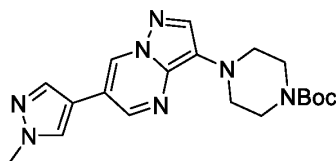


[0457] To a solution of (1R)-1-(4-chlorophenyl)ethanol (20.00 g, 127.7 mmol) in ACN (240 mL) was added di(N-succinimidyl) carbonate (49.07 g, 191.6 mmol) then the mixture was cooled to 0°C . TEA (53 mL, 380 mmol) was added dropwise over 5 min then stirred at 0°C for 30 min. The solution was warmed to rt and stirred overnight, then the mixture was concentrated under reduced pressure. The residue was diluted with EtOAc (250 mL) and washed with sat. aqueous NaHCO_3 . Additional EtOAc (100 mL) was added, then the organic layer was washed with water and brine, then dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure. To the residue was added MTBE (150 mL) and the mixture was heated to 45°C . Hexanes (100 mL) was added hot, then the mixture was allowed to cool with efficient stirring. The solids were isolated by filtration, washed with hexanes (100 mL), and dried under reduced pressure to afford 31.85 g (84%) of (R)-1-(4-chlorophenyl)ethyl (2,5-dioxopyrrolidin-1-yl) carbonate (Compound **S95**) as a light tan solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 7.49 (s, 4H), 5.89 (q, $J=6.8\text{ Hz}$, 1H), 2.80 (s, 4H), 1.62 (d, $J=6.8\text{ Hz}$, 3H).

Synthesis of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyrimidine (Compound **S98**)

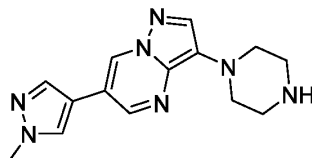


Step 1. Preparation of tert-butyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperazine-1-carboxylate



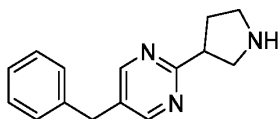
[0458] To a vial was added 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine (Compound **S10**) (0.150 g, 0.539 mmol) and tert-butyl 1-piperazinecarboxylate (0.120 g, 0.647 mmol) followed by tBuOH (1.5 mL) and dioxane (3 mL) then the mixture was sparged with argon for 5 min. NaOtBu (0.0778 g, 0.809 mmol) was added then the mixture was sparged for 5 min with argon. tBuXPhos Pd G1 (37.0 mg, 0.0539 mmol) was added then the mixture was sparged with argon for 5 min. The reaction was heated to 80°C for 2.5 h then additional tBuXPhos Pd G1 (15 mg) was added as a slurry in dioxane (0.5 mL) and the mixture was stirred at 80°C overnight. The reaction was cooled to rt, quenched with sat. aqueous NaHCO₃, and extracted with DCM (3x). The combined organic extracts were washed with water, then dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography to afford 95 mg (46%) of tert-butyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperazine-1-carboxylate as a yellow-orange solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.58 (d, *J* = 2.0 Hz, 1H), 8.45 (d, *J* = 2.4 Hz, 1H), 7.78 (s, 1H), 7.77 (s, 1H), 7.68 (s, 1H), 4.01 (s, 3H), 3.71 – 3.65 (m, 4H), 3.30 – 3.24 (m, 4H), 1.51 (s, 9H). MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₉H₂₅N₇O₂, 384.2; found, 384.3.

Step 2. Preparation of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyrimidine (Compound **S98**)

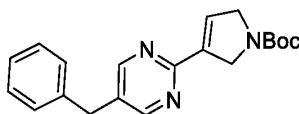


[0459] To a solution of tert-butyl 4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl]piperazine-1-carboxylate (0.09 g, 0.2 mmol, as prepared in the previous step) in DCM (2 mL) was added TFA (0.2 mL) and the reaction was stirred at rt overnight. The mixture was diluted with DCM (20 mL) and washed with sat. aqueous NaHCO₃ (25 mL). The aqueous layer was extracted with DCM (2 x 20 mL) and the combined organic extracts were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure to afford 65 mg (93%) of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyrimidine (Compound **S98**) as an orange solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.58 (d, *J* = 2.0 Hz, 1H), 8.45 (d, *J* = 2.4 Hz, 1H), 7.79 (s, 1H), 7.77 (s, 1H), 7.68 (s, 1H), 4.01 (s, 3H), 3.37 – 3.31 (m, 4H), 3.20 – 3.14 (m, 4H). MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₄H₁₇N₇, 284.2; found, 284.1.

Synthesis of 5-benzyl-2-pyrrolidin-3-ylpyrimidine (Compound **S100**)



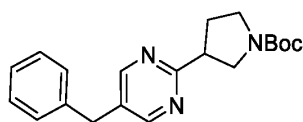
Step 1. Preparation of tert-butyl 3-(5-benzylpyrimidin-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate



[0460] A mixture of tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (500.0 mg, 1.69 mmol), 5-benzyl-2-chloropyrimidine (Compound **S88**) (289 mg, 1.41 mmol) and K₃PO₄ (599 mg, 2.82 mmol) in dioxane (14.3 mL) and H₂O (5.1 mL) was sparged with argon for 20 min. (tBu₃P)₂Pd (108 mg, 0.21 mmol) was added then the mixture was heated to 80°C for 4 h. The reaction was cooled to rt, diluted with H₂O (40 mL), and extracted with EtOAc (2 x 25 mL). The combined organic

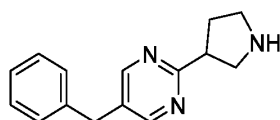
extracts were washed with H₂O (25 mL), dried over anhydrous MgSO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 20-30% EtOAc/hexanes to afford 420 mg (88%) of tert-butyl 3-(5-benzylpyrimidin-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate as a white solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.56 (s, 2H), 7.31 - 7.39 (m, 2H), 7.24 - 7.31 (m, 1H), 7.20 (d, *J*=6.97 Hz, 2H), 6.83 - 6.95 (m, 1H), 4.53 - 4.69 (m, 2H), 4.33 - 4.49 (m, 2H), 3.89 - 4.03 (m, 2 H), 1.53 (s, 9H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₀H₂₄N₃O₂: 338.2; found, 338.3; HPLC purity 210 nm: 98.3%; 254 nm: 100.0%.

Step 2. Preparation of tert-butyl 3-(5-benzylpyrimidin-2-yl)pyrrolidine-1-carboxylate



[0461] To a solution of tert-butyl 3-(5-benzylpyrimidin-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (437 mg, 1.30 mmol, as prepared in the previous step) in EtOAc (20 mL) was added 10% Pd/C (100 mg, 50% H₂O). The reaction flask was evacuated and filled with hydrogen gas three times and allowed to stir under an atmosphere of hydrogen. After 19 h, the reaction mixture was filtered through a pad of celite, and the pad was washed with an additional 40 mL of EtOAc. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 25-40% EtOAc/hexanes to afford 377 mg (86%) of tert-butyl 3-(5-benzylpyrimidin-2-yl)pyrrolidine-1-carboxylate as a colorless, viscous oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.52 (s, 2H), 7.30 - 7.39 (m, 2H), 7.22 - 7.30 (m, 1H), 7.19 (d, *J*=7.09 Hz, 2H), 3.95 (s, 2H), 3.83 (m, 1H), 3.53 - 3.73 (m, 3H), 3.43 (m, 1H), 2.18 - 2.43 (m, 2H), 1.47 (s, 9H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₀H₂₅N₃O₂: 340.2; found, 340.3; HPLC purity: 210 nm: 100.0%; 254 nm 100.0%.

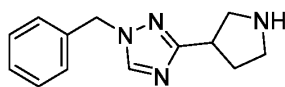
Step 3. Preparation of 5-benzyl-2-pyrrolidin-3-ylpyrimidine (Compound S100)



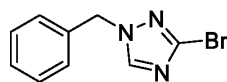
[0462] A solution of tert-butyl 3-(5-benzylpyrimidin-2-yl)pyrrolidine-1-carboxylate (377 mg, 1.11 mmol, as prepared in the previous step) in DCM (9.0 mL) was cooled to 0°C, then TFA (1.0 mL) was added dropwise. The mixture was stirred for 30 min at 0°C then warmed to rt for 3 h. The reaction was concentrated under reduced pressure then the residue was

dissolved in DCM (10 mL) and concentrated again. The residue was dissolved in DCM (20 mL) and washed with 20 mL sat. aqueous NaHCO_3 . The organic phase was dried over anhydrous Na_2SO_4 and filtered, then the filtrate was concentrated under reduced pressure to afford 211 mg (79%) of 5-benzyl-2-pyrrolidin-3-ylpyrimidine (Compound **S100**) as a light pink viscous oil. ^1H NMR (400 MHz, CD_3OD) δ (ppm) 8.58 (s, 2H), 7.27 - 7.36 (m, 2H), 7.19 - 7.27 (m, 3H), 3.99 (s, 2H), 3.56 - 3.69 (m, 1H), 3.32 - 3.38 (m, 1H), 3.23 - 3.30 (m, 1H), 3.13 - 3.23 (m, 1H), 3.08 (dt, $J=11.19, 7.37$ Hz, 1H), 2.24 - 2.38 (m, 1H), 2.07 - 2.24 (m, 1H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{15}\text{H}_{17}\text{N}_3$: 240.2; found, 240.1; HPLC purity: 210 nm: 100.0%; 254 nm: 100.0%.

Synthesis of 1-benzyl-3-(pyrrolidin-3-yl)-1H-1,2,4-triazole (Compound **S101**)

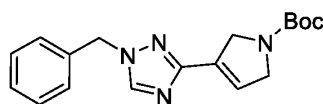


Step 1. Preparation of 1-benzyl-3-bromo-1H-1,2,4-triazole



[0463] A mixture of 3-bromo-1H-1,2,4-triazole (5.0 g, 33.8 mmol), benzyl bromide (5.8 g, 33.8 mmol) and NaOMe (1.8 g, 33.8 mmol) in DMF (50 mL) was stirred under nitrogen at 35°C for 6 h, then diluted with water and extracted with EtOAc (5 x 100 mL). The combined organic extracts were concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 1:50 EtOAc/PE to 1:20 EtOAc/PE to afford 2.5 g (31%) of 1-benzyl-3-bromo-1H-1,2,4-triazole as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.72 (s, 1H), 7.30~7.40 (m, 5H), 5.40 (s, 2H).

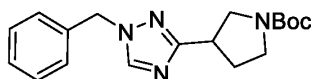
Step 2. Preparation of tert-butyl 3-(1-benzyl-1H-1,2,4-triazol-3-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate



[0464] To a solution of 1-benzyl-3-bromo-1H-1,2,4-triazole (3.0 g, 12.6 mmol, as prepared in the previous step) in a mixture of dioxane (10 mL) and H_2O (30 mL) was added tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (4.5 g, 15.1 mmol), K_3PO_4 (5.4 g, 25.2 mmol), and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.4 g, 0.6

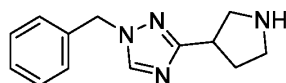
mmol) under nitrogen. The reaction was stirred at 80°C for 4 h under nitrogen, then poured into water (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 1:10 EtOAc/PE to 1:1 EtOAc/PE to afford 3.3 g (80%) of tert-butyl 3-(1-benzyl-1H-1,2,4-triazol-3-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.67 (d, *J*=4.4Hz, 1H), 7.26~7.35 (m, 5H), 6.42 (d, *J*=12.8Hz, 1H), 5.41 (s, 1H), 4.32 (s, 2H), 4.18 (s, 2H), 1.41~1.43 (m, 12H).

Step 3. Preparation of tert-butyl 3-(1-benzyl-1H-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate



[0465] A mixture of tert-butyl 3-(1-benzyl-1H-1,2,4-triazol-3-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (3.0 g, 9.2 mmol, as prepared in the previous step) and 10% Pd/C (50% water, 1.6 g) in EtOAc (30 mL) was stirred at 25°C for 5 h under an atmosphere of hydrogen (20 psi). The mixture was filtered and the filtrate was concentrated to afford 3.0 g (99%) of tert-butyl 3-(1-benzyl-1H-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.94 (s, 1H), 7.37 (d, *J*=7.2Hz, 3H), 7.25-7.29 (m, 2H), 5.28 (d, *J*=7.2Hz, 2H), 3.79 (s, 1H), 3.42~3.52 (m, 3H), 3.26~3.28 (m, 1H), 2.20~2.23 (m, 2H), 1.37~1.45 (m, 9H).

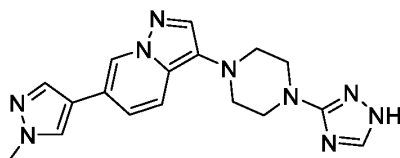
Step 4. Preparation of 1-benzyl-3-(pyrrolidin-3-yl)-1H-1,2,4-triazole (Compound **S101**)



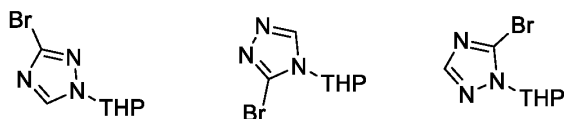
[0466] To a solution of tert-butyl 3-(1-benzyl-1H-1,2,4-triazol-3-yl)pyrrolidine-1-carboxylate (2.9 g, 8.8 mmol, as prepared in the previous step) in DCM (30 mL) was added TFA (10 mL) at 0°C. The reaction mixture was stirred at 25°C for 3 h under nitrogen. The pH of the mixture was adjusted to pH 9 with sat. aqueous NaHCO₃, then extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to afford 1.1 g (55%) of 1-benzyl-3-(pyrrolidin-3-yl)-1H-1,2,4-triazole (Compound **S101**) as

a yellow solid. ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ (ppm) 8.53 (s, 1H), 7.31~7.34 (m, 3H), 7.26~7.30 (m, 2H), 5.33 (s, 2H), 3.21~3.38 (m, 2H), 2.86~2.96 (m, 3H), 1.87 ~2.05 (m, 2H).

Synthesis of 3-(4-(1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **S102**)



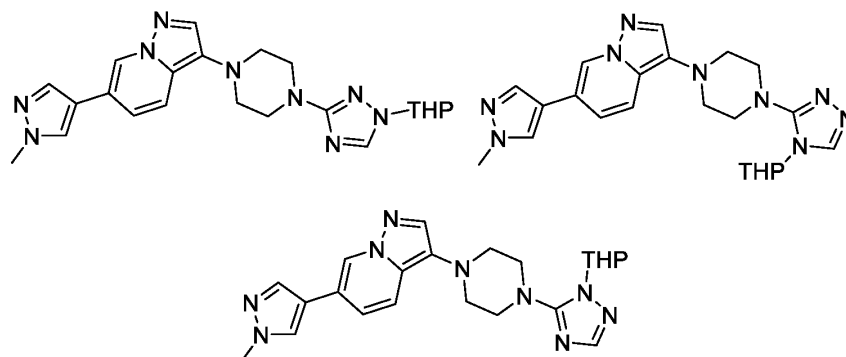
Step 1. Preparation of a mixture of 3-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazole and 3-bromo-4-(tetrahydro-2H-pyran-2-yl)-4H-1,2,4-triazole and 5-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazole



[0467] To a solution of 3-bromo-1H-1,2,4-triazole (500 mg, 3.37 mmol) and 3,4-dihydro-2H-pyran (426.3 mg, 5.06 mmol) in toluene (20 mL) was added $\text{TsOH} \cdot \text{H}_2\text{O}$ (64.2 mg, 0.33 mmol) then the mixture was heated to 105°C and stirred overnight under nitrogen. The reaction was cooled to rt then concentrated under reduced pressure. The residue was dissolved in water (100 mL) and extracted with DCM (3 x 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered, then the filtrate was concentrated under reduced pressure to afford 700 mg (89%) of a mixture of 3-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazole and 3-bromo-4-(tetrahydro-2H-pyran-2-yl)-4H-1,2,4-triazole and 5-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazole as a black oil. MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_7\text{H}_{10}\text{BrN}_3\text{O}$, 232.0; found, 232.0. LCMS purity: 254 nm:85%.

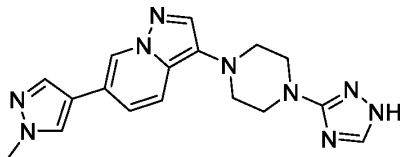
Step 2. Preparation of a mixture of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine, 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(4-(tetrahydro-2H-pyran-2-yl)-4H-1,2,4-triazol-3-yl)piperazin-1-

yl)pyrazolo[1,5-a]pyridine, and 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-5-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine



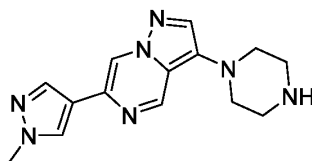
[0468] To a solution of the mixture of 3-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazole and 3-bromo-4-(tetrahydro-2H-pyran-2-yl)-4H-1,2,4-triazole and 5-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazole (600 mg, 2.58 mmol, as prepared in the previous step) and 6-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylpyrazolo[1,5-a]pyridine (Compound **12**) (364.9 mg, 1.29 mmol) in dioxane (20 mL) were added Cs₂CO₃ (1.68 g, 5.17 mmol) and Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (326.1 mg, 0.38 mmol), then the reaction was heated to 100°C and stirred overnight under nitrogen. The mixture was cooled to rt then concentrated under reduced pressure. The residue was dissolved in water (100 mL) and extracted with DCM (3 x 100 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography with a C18 silica gel column eluting with 10% to 50% ACN / water (10mM NH₄HCO₃ to afford 450 mg (40%) of a mixture of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine, 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(4-(tetrahydro-2H-pyran-2-yl)-4H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine, and 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-5-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 – 8.76 (m, 1H), 8.36 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.78 (s, 1H), 7.67 (dd, *J* = 9.3, 0.9 Hz, 1H), 7.32 (dd, *J* = 9.2, 1.5 Hz, 1H), 5.33 (dd, *J* = 9.9, 2.3 Hz, 1H), 3.97 – 3.90 (m, 1H), 3.87 (s, 3H), 3.67 – 3.57 (m, 1H), 3.49-3.47 (m, 4H), 3.07 (t, *J* = 5.0 Hz, 4H), 2.05 – 1.90 (m, 3H), 1.67 – 1.52 (m, 3H). MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₂H₂₇N₉O, 434.2; found, 434.2. LCMS purity: 254 nm: 90%.

Step 3. 3-(4-(1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **S102**)



[0469] To a solution of a mixture of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine, 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(4-(tetrahydro-2H-pyran-2-yl)-4H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine, and 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-5-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (400 mg, 0.92 mmol, as prepared in the previous step) in DCM (20 mL) was added 4M HCl in dioxane (336.4 mg, 9.23 mmol) then the reaction was stirred at rt for 2 h under nitrogen. The mixture was concentrated under reduced pressure then the pH of the residue was adjusted to pH 7 with aqueous NH₃. The residue was purified by reversed-phase flash chromatography with a C18 silica gel column eluting with 10% to 50% ACN / water (10mM NH₄HCO₃) to afford 270 mg (84%) of 3-(4-(1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **S102**) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 13.13-12.70 (m, 1H), 8.82 (s, 1H), 8.57-8.20 (m, 2H), 7.97 (s, 1H), 7.78 (s, 1H), 7.68 (d, *J* = 9.2 Hz, 1H), 7.34-7.30 (m, 1H), 3.87 (s, 3H), 3.50 (t, *J* = 4.8 Hz, 4H), 3.08 (t, *J* = 4.8 Hz, 4H). MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₇H₁₉N₉, 350.2; found, 350.2. LCMS purity: 254 nm: 95%.

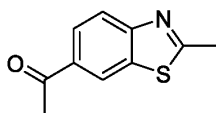
Synthesis of 1-[6-(1-methylpyrazol-4-yl)pyrazolo[1,5-a]pyrazin-3-yl]piperazine (Compound **S103**)



[0470] To a solution of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine (Compound **S5**) (900 mg, 3.25 mmol) in dioxane (20 mL) was added piperazine (1.39 g, 16.18 mmol), Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (272.2 mg, 0.32 mmol), and Cs₂CO₃ (2.11 g, 6.47 mmol) then the mixture was heated to 100°C and stirred for 16 h under

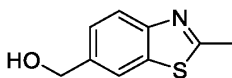
nitrogen. The mixture was cooled to rt, diluted with water (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (3 x 10 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography with a C18 silica gel column eluting with 10% to 100% ACN / water (0.1% FA) to afford 500 mg (42%) of 1-[6-(1-methylpyrazol-4-yl)pyrazolo[1,5-a]pyrazin-3-yl]piperazine as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.17 (s, 1H), 8.89 (s, 1H), 8.28 (d, *J* = 5.6 Hz, 1H), 8.21 (s, 1H), 8.00 (s, 1H), 7.81 (s, 1H), 3.88 (s, 3H), 3.21 – 3.11 (m, 4H), 3.08 – 2.94 (m, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₄H₁₇N₇, 284.1; found, 284.1; LCMS purity: 254 nm: 98.6%.

Synthesis of 1-(2-methylbenzo[d]thiazol-6-yl)ethan-1-one (Compound **S104**)



[0471] To a solution of 6-bromo-2-methylbenzo[d]thiazole (5 g, 21.92 mmol) and tributyl(1-ethoxyvinyl)stannane (11.87 g, 32.88 mmol) in dioxane (500 mL) was added Pd(PPh₃)₄ (2.53 g, 2.19 mmol) then the mixture was heated to 90°C and stirred for 16 h under nitrogen. The reaction was cooled to rt and concentrated under reduced pressure. Water (150 mL) was added to the residue then the mixture was extracted with EtOAc (3x300 mL). The organic extracts were combined, washed with brine (50 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 3.5 g (83%) of 1-(2-methylbenzo[d]thiazol-6-yl)ethan-1-one (Compound **S104**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.72 (d, *J* = 1.8 Hz, 1H), 8.06 – 7.95 (m, 2H), 2.85 (s, 3H), 2.65 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₀H₉NOS, 192.0; found, 192.1.

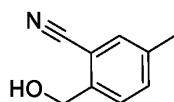
Synthesis of (2-methylbenzo[d]thiazol-6-yl)methanol (Compound **S105**)



[0472] To a stirred solution of 2-methylbenzo[d]thiazole-6-carboxylic acid (1 g, 5.17 mmol) in THF (20 mL) cooled to 0°C was added a 2M solution of LiAlH₄ in THF (5.2 mL) then the mixture was warmed to rt and stirred for 3 h. The reaction was cooled to 0°C and

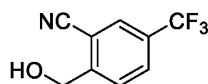
quenched by the addition of saturated aqueous NaHCO_3 solution. The mixture was filtered, and the filter cake was washed with DCM (3x30 mL). The filtrate was extracted with DCM/MeOH (10:1) (3x80 mL), then the organic extracts were combined, dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel column chromatography, eluted with PE/EtOAc (1:1) to afford 400 mg (43%) of (2-methylbenzo[d]thiazol-6-yl)methanol (Compound **S105**) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 7.93 (d, $J = 1.5$ Hz, 1H), 7.84 (d, $J = 8.3$ Hz, 1H), 7.41 (dd, $J = 8.3, 1.5$ Hz, 1H), 5.31 (t, $J = 5.7$ Hz, 1H), 4.61 (d, $J = 5.7$ Hz, 2H), 2.78 (s, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_9\text{H}_9\text{NOS}$, 180.0; found, 180.1.

Synthesis of 2-(hydroxymethyl)-5-methylbenzonitrile (Compound **S106**)

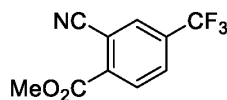


[0473] To a stirred solution of methyl 2-cyano-4-methylbenzoate (500 mg, 2.85 mmol) and NaBH_4 (323.91 mg, 8.56 mmol) in MeOH (10 mL) cooled to 0°C was added LiCl (241.97 mg, 5.70 mmol) in portions then the mixture was warmed to rt and stirred for 1 h. The reaction was diluted with water (30 mL) and extracted with EtOAc (3x50 mL). The organic extracts were combined, washed with brine (2x2 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure to afford 400 mg (38%) of 2-(hydroxymethyl)-5-methylbenzonitrile (Compound **S106**) as a yellow solid. MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_9\text{H}_9\text{NO}$, 148.2; found, 148.0.

Synthesis of 2-(hydroxymethyl)-5-(trifluoromethyl)benzonitrile (Compound **S107**)



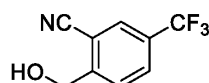
Step 1. Preparation of methyl 2-cyano-4-(trifluoromethyl)benzoate



[0474] To a solution of 2-bromo-5-(trifluoromethyl)benzonitrile (5 g, 19.99 mmol) in MeOH (30 mL) was added $\text{Pd}(\text{dppf})\text{Cl}_2$ (1.46 g, 2 mmol) in a pressure vessel then the mixture was pressurized to 15 atm with carbon monoxide at 80°C overnight. The reaction was cooled to rt and filtered, then the filtrate was concentrated under reduced pressure. The

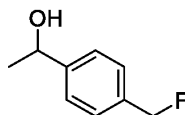
residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 3 g (65%) of methyl 2-cyano-4-(trifluoromethyl)benzoate as a brown solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.55 – 8.50 (m, 1H), 8.30 (d, $J = 8.2$ Hz, 1H), 8.24 (dd, $J = 8.3, 1.9$ Hz, 1H), 3.96 (s, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{10}\text{H}_6\text{F}_3\text{NO}_2$, 229.0; found, 229.2.

Step 2. Preparation of 2-(hydroxymethyl)-5-(trifluoromethyl)benzonitrile (Compound **S107**)

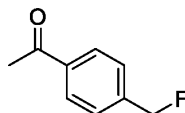


[0475] To a stirred solution of methyl 2-cyano-4-(trifluoromethyl)benzoate (2.9 g, 12.65 mmol, as prepared in the previous step) in MeOH (29 mL) cooled to 0°C was added NaBH_4 (0.96 g, 25.3 mmol) in portions then the mixture was warmed to rt and stirred for 2 h. The reaction was concentrated under reduced pressure then the residue was dissolved in water (300 mL) and extracted with EtOAc (2x200 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure to afford 1.5 g (59%) of 2-(hydroxymethyl)-5-(trifluoromethyl)benzonitrile (Compound **S107**) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.05 – 7.94 (m, 2H), 7.82 (d, $J = 3.8$ Hz, 1H), 5.43 (d, $J = 8.7$ Hz, 2H), 4.55 – 4.53 (m, 1H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_9\text{H}_6\text{F}_3\text{NO}$, 201.0; found, 201.1.

Synthesis of 1-(4-(fluoromethyl)phenyl)ethan-1-ol (Compound **S108**)



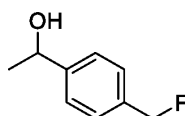
Step 1. Preparation of 1-(4-(fluoromethyl)phenyl)ethan-1-one



[0476] To a stirred solution of 1-(*p*-tolyl)ethan-1-one (3 g, 22.3 mmol) and $\text{K}_2\text{S}_2\text{O}_8$ (18.13 g, 67 mmol) in ACN (30 mL) and H_2O (30 mL) was added F-TEDA (23.7 g, 67 mmol) in portions at rt then the mixture was heated to 80°C and stirred overnight. The reaction was cooled to rt and extracted with EtOAc (3x200 mL). The organic extracts were combined,

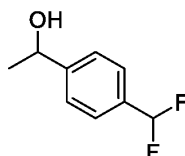
washed with brine (3x100 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 2 g (59%) of 1-(4-(fluoromethyl)phenyl)ethan-1-one as colorless liquid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.00 (dd, $J = 8.3, 1.3$ Hz, 2H), 7.62 – 7.49 (m, 2H), 5.53 (d, $J = 48$ Hz, 2H), 2.60 (d, $J = 0.8$ Hz, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_9\text{H}_9\text{FO}$, 153.0; found, 153.0.

Step 2. Preparation of 1-(4-(fluoromethyl)phenyl)ethan-1-ol (Compound **S108**)



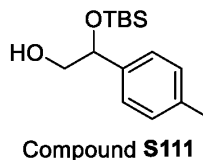
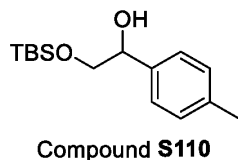
[0477] To a solution of 1-(4-(fluoromethyl)phenyl)ethan-1-one (800 mg, 5.2 mmol, as prepared in the previous step) in MeOH (10 mL) cooled to 0°C was added NaBH_4 (238 mg, 6.3 mmol) then the mixture was stirred for 1 h. The reaction was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 600 mg (74%) of 1-(4-(fluoromethyl)phenyl)ethan-1-ol (Compound **S108**) as colorless liquid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 7.43 – 7.29 (m, 4H), 5.38 (d, $J = 48$ Hz, 2H), 5.20 (d, $J = 4.2$ Hz, 1H), 4.87 – 4.68 (m, 1H), 1.33 (d, $J = 6.4$ Hz, 3H).

Synthesis of 1-(4-(difluoromethyl)phenyl)ethan-1-ol (Compound **S109**)

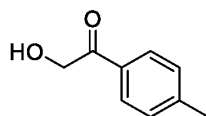


[0478] To a solution of 1-(4-(difluoromethyl)phenyl)ethan-1-one (600 mg, 3.5 mmol) in MeOH (8 mL) cooled to 0°C was added NaBH_4 (267 mg, 7 mmol) then the mixture was stirred for 2 h. The reaction was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 550 mg (91%) of 1-(4-(difluoromethyl)phenyl)ethan-1-ol (Compound **S109**) as a colorless oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 7.76 – 7.41 (m, 4H), 7.01 (t, $J = 56.0$ Hz, 1H), 5.29 (d, $J = 4.3$ Hz, 1H), 4.95 – 4.61 (m, 1H), 1.34 (d, $J = 6.5$ Hz, 3H).

Synthesis of 2-((*tert*-butyldimethylsilyl)oxy)-1-(*p*-tolyl)ethan-1-ol (Compound **S110**) and 2-((*tert*-butyldimethylsilyl)oxy)-2-(*p*-tolyl)ethan-1-ol (Compound **S111**)

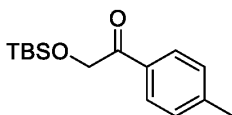


Step 1. Preparation of 2-hydroxy-1-(*p*-tolyl)ethan-1-one



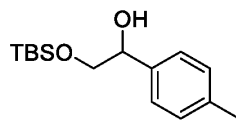
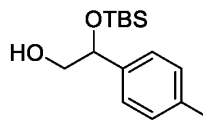
[0479] To a solution of 2-bromo-1-(4-methylphenyl)ethanone (3 g, 14.08 mmol) in MeOH (20 mL) was added NaOAc (9.24 g, 112.64 mmol) then the mixture was heated to 80°C and stirred for 12 h under nitrogen. The reaction was cooled to rt and concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (5:1) to afford 1.47 g (70%) of 2-hydroxy-1-(4-methylphenyl)ethanone as a white solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.82 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.85 (s, 2H), 3.50 (d, *J* = 7.4 Hz, 1H), 2.43 (s, 3H).

Step 2. Preparation of 2-((*tert*-butyldimethylsilyl)oxy)-1-(*p*-tolyl)ethan-1-one



[0480] To a solution of 2-hydroxy-1-(4-methylphenyl)ethanone (1.27 g, 8.45 mmol, as prepared in the previous step) in THF (20 mL) was added TBSCl (1.91 g, 12.68 mmol) and imidazole (0.87 g, 12.68 mmol) then the mixture was stirred at rt for 2 h. The reaction was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (5:1) to afford 2.17 g (97%) of 2-((*tert*-butyldimethylsilyl)oxy)-1-(*p*-tolyl)ethan-1-one as a colorless liquid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 7.83 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.99 (s, 2H), 2.37 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H).

Step 3. Preparation of 2-((*tert*-butyldimethylsilyl)oxy)-1-(*p*-tolyl)ethan-1-ol (Compound **S110**) and 2-((*tert*-butyldimethylsilyl)oxy)-2-(*p*-tolyl)ethan-1-ol (Compound **S111**)

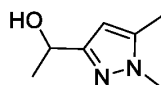
Compound **S110**Compound **S111**

[0481] To a stirred solution of 2-((*tert*-butyldimethylsilyl)oxy)-1-(*p*-tolyl)ethan-1-one (1 g, 3.78 mmol, as prepared in the previous step) in MeOH (10 mL) cooled to 0°C was added NaBH₄ (0.22 g, 5.673 mmol) in portions then the mixture was warmed to rt and stirred at rt for 2 h under nitrogen. The reaction was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a Prep Phenyl column eluting with 35-65% MeOH/water (10mM NH₄HCO₃) to afford 250 mg (25%) of 2-((*tert*-butyldimethylsilyl)oxy)-1-(*p*-tolyl)ethan-1-ol (Compound **S110**) as colorless liquid and 200 mg (20%) of 2-((*tert*-butyldimethylsilyl)oxy)-2-(*p*-tolyl)ethan-1-ol (Compound **S111**) as a colorless oil.

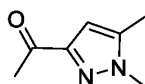
[0482] 2-((*tert*-butyldimethylsilyl)oxy)-1-(*p*-tolyl)ethan-1-ol (Compound **S110**). ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 7.21 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 5.16 (d, *J* = 4.3 Hz, 1H), 4.49 (q, *J* = 5.7 Hz, 1H), 3.65 – 3.58 (m, 1H), 3.55 – 3.48 (m, 1H), 2.27 (s, 3H), 0.81 (s, 9H), -0.04 (s, 3H), -0.07 (s, 3H).

[0483] 2-((*tert*-butyldimethylsilyl)oxy)-2-(*p*-tolyl)ethan-1-ol (Compound **S111**). ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 7.20 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 4.70 (t, *J* = 5.7 Hz, 1H), 4.66 – 4.61 (m, 1H), 3.44 – 3.31 (m, 2H), 2.28 (s, 3H), 0.85 (s, 9H), 0.05 (s, 3H), -0.05 (s, 3H).

Synthesis of 1-(1,5-dimethyl-1*H*-pyrazol-3-yl)ethan-1-ol (Compound **S112**)



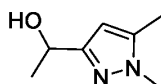
Step 1. Preparation of 1-(5-methyl-1*H*-pyrazol-3-yl)ethan-1-one



[0484] To a solution of 1-(5-methyl-1*H*-pyrazol-3-yl)ethan-1-one (1 g, 8.05 mmol) in DCM (20 mL) was added MeI (1.72 g, 12.08 mmol) then the mixture was stirred at rt for 2

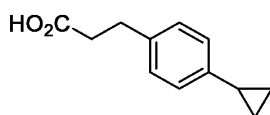
h. The reaction was filtered, and the filter cake was washed with DCM (2x20 mL), then the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 20-30% ACN/water (10mM NH_4HCO_3) to afford 240 mg (22%) of 1-(1,5-dimethyl-1*H*-pyrazol-3-yl)ethan-1-one as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 6.47 (s, 1H), 3.81 (s, 3H), 2.41 (s, 3H), 2.27 (s, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_7\text{H}_{10}\text{N}_2\text{O}$, 139.1; found, 139.2.

Step 2. Preparation of 1-(1,5-dimethyl-1*H*-pyrazol-3-yl)ethan-1-ol (Compound **S112**)



[0485] To a stirred mixture of 1-(1,5-dimethyl-1*H*-pyrazol-3-yl)ethan-1-one (220 mg, 1.59 mmol, as prepared in the previous step) in MeOH (5 mL) cooled to 0°C was added NaBH_4 (90.3 mg, 2.38 mmol) in portions then the mixture was warmed to rt and stirred for 2 h. The reaction was cooled to 0°C, quenched with water, and extracted with EtOAc (3x20 mL). The organic extracts were combined, washed with water (3x20 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 5-10% ACN/water (10mM NH_4HCO_3) to afford 140 mg (63%) of 1-(1,5-dimethyl-1*H*-pyrazol-3-yl)ethan-1-ol (Compound **S112**) as yellow liquid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 5.92 (s, 1H), 4.83 (d, $J = 4.7$ Hz, 1H), 4.63 – 4.52 (m, 1H), 3.63 (s, 3H), 2.19 (s, 3H), 1.29 (d, $J = 6.5$ Hz, 3H).

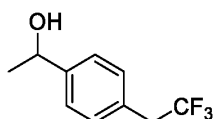
Synthesis of 3-(4-cyclopropylphenyl)propanoic acid (Compound **S113**)



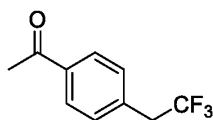
[0486] To a stirred mixture of 3-(4-bromophenyl)propanoic acid (1 g, 4.36 mmol) and cyclopropylboronic acid (449.9 mg, 5.23 mmol) in dioxane (10 mL) were added $\text{Pd}(\text{dppf})\text{Cl}_2$ (319.4 mg, 0.43 mmol) and Cs_2CO_3 (2.8 g, 8.73 mmol) in portions at rt under nitrogen then the mixture was heated to 100°C and stirred for 2 h. The reaction was cooled to rt, diluted with water (200 mL), and extracted with DCM (2x150 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash

chromatography using a C18 silica gel column eluting with 5-100% ACN/water (10mM NH_4HCO_3) to afford 500 mg (60%) of 3-(4-cyclopropylphenyl)propanoic acid (Compound **S113**) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 7.08 (d, $J = 7.9$ Hz, 2H), 6.97 (d, $J = 7.9$ Hz, 2H), 2.75 (t, $J = 7.7$ Hz, 2H), 2.44 (t, $J = 7.7$ Hz, 2H), 1.92 – 1.78 (m, 1H), 0.96 – 0.82 (m, 2H), 0.67 – 0.55 (m, 2H).

Synthesis of 1-(4-(2,2,2-trifluoroethyl)phenyl)ethan-1-ol (Compound **S114**)

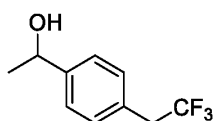


Step 1. Preparation of 1-(4-(2,2,2-trifluoroethyl)phenyl)ethan-1-one



[0487] To a stirred mixture of 4-acetylphenylboronic acid (1 g, 6.1 mmol) and 1,1,1-trifluoro-2-iodoethane (5.1 g, 24.3 mmol) in dioxane (20 mL) were added Cs_2CO_3 (5.96 g, 18.3 mmol), $\text{Pd}_2(\text{dba})_3$ (1.1 g, 1.2 mmol), and XantPhos (705 mg, 1.2 mmol) in portions at rt under nitrogen then the mixture was heated to 100°C and stirred overnight under nitrogen. The reaction was cooled to rt and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with PE/EtOAc (5:1) to afford 800 mg (65%) of 1-(4-(2,2,2-trifluoroethyl)phenyl)ethan-1-one as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.02 – 7.95 (m, 2H), 7.52 (d, $J = 8.0$ Hz, 2H), 3.77 (q, $J = 11.5$ Hz, 2H), 2.59 (s, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{10}\text{H}_9\text{F}_3\text{O}$, 203.1; found, 203.1.

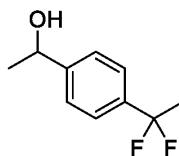
Step 2. Preparation of 1-(4-(2,2,2-trifluoroethyl)phenyl)ethan-1-ol (Compound **S114**)



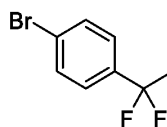
[0488] To a stirred solution of 1-(4-(2,2,2-trifluoroethyl)phenyl)ethan-1-one (400 mg, 2 mmol) in MeOH (10 mL) cooled to 0°C was added NaBH_4 (89.8 mg, 2.4 mmol) in portions then the mixture was warmed to rt and stirred for 1 h. The reaction was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 150 mg (37%) of 1-(4-(2,2,2-trifluoroethyl)phenyl)ethan-1-

ol (Compound **S114**) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 7.38 – 7.32 (m, 2H), 7.32 – 7.23 (m, 2H), 5.16 (d, $J = 4.2$ Hz, 1H), 4.85 – 4.53 (m, 1H), 3.61 (q, $J = 11.6$ Hz, 2H), 1.32 (d, $J = 6.4$ Hz, 3H).

Synthesis of 1-(4-(1,1-difluoroethyl)phenyl)ethan-1-ol (Compound **S115**)

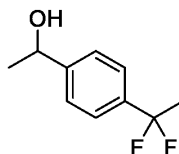


Step 1. Preparation of 1-bromo-4-(1,1-difluoroethyl)benzene



[0489] To a solution of 1-(4-bromophenyl)ethan-1-one (10 g, 50.23 mmol) in DCM (60 mL) was added DAST (64.7 g, 401.9 mmol) dropwise at rt then the mixture was heated to 50°C and stirred overnight. The reaction was cooled to 0°C , quenched with water, and extracted with DCM (2x100 mL). The organic extracts were combined, washed with water (2x100 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with DCM/PE (50:1) to afford 3.4 g (31%) of 1-bromo-4-(1,1-difluoroethyl)benzene as colorless liquid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 7.70 (d, $J = 8.7$ Hz, 2H), 7.53 (d, $J = 8.7$ Hz, 2H), 1.97 (t, $J = 18.9$ Hz, 3H).

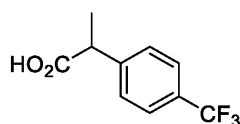
Step 2. Preparation of 1-(4-(1,1-difluoroethyl)phenyl)ethan-1-ol (Compound **S115**)



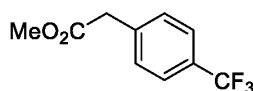
[0490] To a stirred solution of 1-bromo-4-(1,1-difluoroethyl)benzene (500 mg, 2.26 mmol, as prepared in the previous step) in THF (10 mL) cooled to -78°C was added 2.5M nBuLi in hexane (1.4 mL, 3.39 mmol) dropwise under nitrogen then the mixture was stirred at -78°C for 30 minutes under nitrogen. A solution of 5M acetaldehyde in THF (0.6 mL, 2.71 mmol) was added dropwise over 5 minutes at -78°C then the reaction was warmed to rt and stirred for 1 h. The reaction was cooled to 0°C , quenched with saturated aqueous NH_4Cl

solution, and extracted with EtOAc (2x30 mL). The organic extracts were combined, washed with water (2x30 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 30-40% ACN/water (10mM NH₄HCO₃) to afford 180 mg (43%) of 1-(4-(1,1-difluoroethyl)phenyl)ethan-1-ol (Compound **S115**) as yellow liquid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 7.50 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 5.25 (d, *J* = 4.3 Hz, 1H), 4.81 – 4.71 (m, 1H), 1.95 (t, *J* = 18.8 Hz, 3H), 1.32 (d, *J* = 6.5 Hz, 3H).

Synthesis of 2-(4-(trifluoromethyl)phenyl)propanoic acid (Compound **S116**)

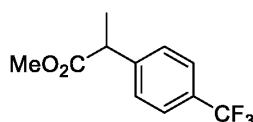


Step 1. Preparation of methyl 2-(4-(trifluoromethyl)phenyl)acetate



[0491] To a stirred solution of 2-(4-(trifluoromethyl)phenyl)acetic acid (1.2 g, 5.878 mmol) in MeOH (20 mL) was added conc. H₂SO₄ (1.15 g, 11.756 mmol) dropwise at rt then the mixture was heated to 80°C and stirred overnight. The reaction was cooled to rt, diluted with water (50 mL), and the pH was adjusted to pH 7 with saturated aqueous NaHCO₃ solution. The resulting mixture was extracted with Et₂O (3x100mL) then the organic extracts were combined, washed with brine (3x10 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 800 mg (62%) of methyl 2-(4-(trifluoromethyl)phenyl)acetate as a yellow oil. The product was used without further purification.

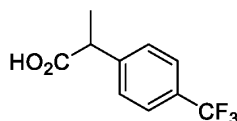
Step 2. Preparation of methyl 2-(4-(trifluoromethyl)phenyl)propanoate



[0492] To a stirred solution of methyl 2-(4-(trifluoromethyl)phenyl)acetate (500 mg, 2.292 mmol, as prepared in the previous step) in THF (20 mL) cooled to -78°C was added NaH

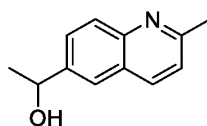
(60% wt., 183.2 mg, 4.584 mmol) in portions under nitrogen then the mixture was stirred at -78°C for 30 minutes under nitrogen. To the stirred reaction at -78°C was added MeI (650.5 mg, 4.584 mmol) in portions then the mixture was warmed to rt and stirred overnight. The reaction was poured into a water /ice mixture, then extracted with EtOAc (3x100 mL). The organic extracts were combined, washed with brine (3x50 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 130 mg (24%) of methyl 2-(4-(trifluoromethyl)phenyl)propanoate as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 7.70 (d, $J = 8.0$ Hz, 2H), 7.55 (d, $J = 8.0$ Hz, 2H), 3.97 (q, $J = 7.2$ Hz, 1H), 3.61 (s, 3H), 1.43 (d, $J = 7.2$ Hz, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{11}\text{H}_{11}\text{F}_3\text{O}$, 231.0; found, 231.2.

Step 3. Preparation of 2-(4-(trifluoromethyl)phenyl)propanoic acid (Compound **S116**)

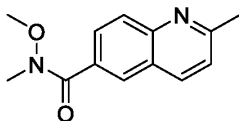


[0493] To a stirred solution of methyl 2-(4-(trifluoromethyl)phenyl)propanoate (110 mg, 0.474 mmol, as prepared in the previous step) in MeOH (10 mL) was added LiOH (22.6 mg, 0.948 mmol) in portions at rt then the mixture was heated to 50°C and stirred overnight. The reaction was cooled to rt, diluted with water (20 mL), and the pH was adjusted to pH 4 with 1M HCl solution. The mixture was extracted with EtOAc (3x50 mL) then the organic extracts were combined, washed with brine (3x10 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 150 mg (145%) of 2-(4-(trifluoromethyl)phenyl)propanoic acid (Compound **S116**) as a yellow green solid. The solid was used without further purification. MS (ESI) m/z $[\text{M}-\text{H}]^-$ calcd. for $\text{C}_{10}\text{H}_9\text{F}_3\text{O}_2$, 217.2; found, 217.0.

Synthesis of 1-(2-methylquinolin-6-yl)ethan-1-ol (Compound **S117**)

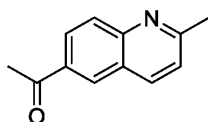


Step 1. Preparation of N-methoxy-N,2-dimethylquinoline-6-carboxamide



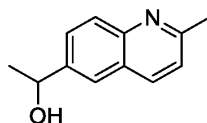
[0494] To a stirred mixture of 2-methylquinoline-6-carboxylic acid (2 g, 10.7 mmol) and N,O-dimethylhydroxylamine hydrochloride (1.5 g, 16.11 mmol) in DCM (30 mL) were added HATU (6.1 g, 16 mmol) and DIEA (5.5 g, 42.71 mmol) then the mixture was stirred at rt for 3 h. The reaction was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 1.6 g (65%) of N-methoxy-N,2-dimethylquinoline-6-carboxamide as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.35 (d, *J* = 8.4 Hz, 1H), 8.22 (d, *J* = 1.8 Hz, 1H), 8.00 – 7.93 (m, 1H), 7.88 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 3.57 (s, 3H), 3.32 (s, 3H), 2.68 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₃H₁₄N₂O₂, 231.1; found, 231.1.

Step 2. 1-(2-methylquinolin-6-yl)ethan-1-one



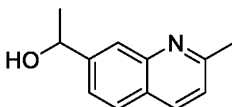
[0495] To a stirred solution of N-methoxy-N,2-dimethylquinoline-6-carboxamide (1.5 g, 6.5 mmol, as prepared in the previous step) in THF (20 mL) cooled to -78°C was added 3M MeMgBr in THF (5 mL, 19.5 mmol) dropwise under nitrogen then the mixture was stirred at -78°C for 1 h under nitrogen. The reaction was warmed to 0°C, quenched with saturated aqueous NH₄Cl solution, and extracted with DCM (3x300 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 800 mg (66%) of 1-(2-methylquinolin-6-yl)ethan-1-one as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.67 (d, *J* = 2.1 Hz, 1H), 8.49 – 8.39 (m, 1H), 8.17 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.99 (d, *J* = 8.8 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 2.71 (s, 3H), 2.70 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₂H₁₁NO, 186.1; found, 186.1.

Step 3. 1-(2-methylquinolin-6-yl)ethan-1-ol (Compound **S117**)

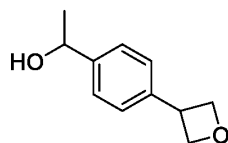


[0496] To a mixture of 1-(2-methylquinolin-6-yl)ethan-1-one (500 mg, 2.7 mmol, as prepared in the previous step) in MeOH (10 mL) cooled to 0°C was added NaBH₄ (204 mg, 5.4 mmol) then the mixture was stirred for 1 h. The reaction was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 320 mg (63%) of 1-(2-methylquinolin-6-yl)ethan-1-ol (Compound **S117**) as colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.21 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.88 (d, *J* = 8.7 Hz, 1H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.71 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 5.37 (d, *J* = 4.2 Hz, 1H), 5.07 – 4.86 (m, 1H), 2.64 (s, 3H), 1.42 (d, *J* = 6.4 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₂H₁₃NO, 188.1; found, 188.1.

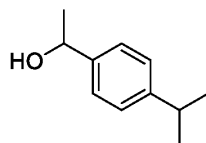
Synthesis of 1-(2-methylquinolin-7-yl)ethan-1-ol (Compound **S118**)



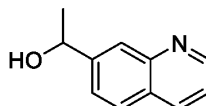
[0497] To a solution of 7-bromo-2-methylquinoline (500 mg, 2.25 mmol) in THF (10 mL) cooled to -78°C was added 2.5M nBuLi in hexane (1.4 mL, 3.37 mmol) dropwise over 5 minutes under nitrogen, followed by the dropwise addition of 5M acetaldehyde in THF solution (0.54 mL, 2.70 mmol) at -78°C then the mixture was warmed to rt and stirred for 1 h. The reaction was cooled to 0°C, quenched with saturated aqueous NH₄Cl solution, and extracted with DCM (3x20 mL). The organic extracts were combined, washed with water (3x20 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 40-50% ACN/water (10mM NH₄HCO₃) to afford 210 mg (50%) of 1-(2-methylquinolin-7-yl)ethanol (Compound **S118**) as a yellow solid. MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₂H₁₃NO, 188.1; found, 188.1.

Synthesis of 1-(4-(oxetan-3-yl)phenyl)ethan-1-ol (Compound **S119**)

[0498] To a stirred solution of 3-(4-bromophenyl)oxetane (500 mg, 2.34 mmol) in THF (6 mL) cooled to -78°C was added 2.5M nBuLi in hexane (1.4 mL, 3.52 mmol) dropwise under nitrogen then the mixture was stirred for 30 minutes. To the stirred reaction was added 5M acetaldehyde in THF solution (0.56 mL, 2.81 mmol) dropwise at -78°C then the mixture was warmed to rt and stirred for 2 h. The reaction was quenched with water (100 mL) and extracted with EtOAc (2x150 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 5-100% ACN/water (10mM NH_4HCO_3) to afford 200 mg (48%) of 1-(4-(oxetan-3-yl)phenyl)ethan-1-ol (Compound **S119**) as a yellow solid. MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{11}\text{H}_{14}\text{O}_2$, 178.1; found, 178.2.

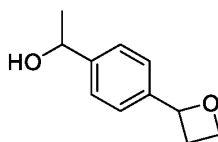
Synthesis of 1-(4-isopropylphenyl)ethan-1-ol (Compound **S120**)

[0499] To a stirred solution of 1-(4-isopropylphenyl)ethan-1-one (500 mg, 3.1 mmol) in MeOH (10 mL) cooled to 0°C was added NaBH_4 (140 mg, 3.7 mmol) in portions then the mixture was warmed to rt and stirred for 2 h. The reaction was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 500 mg (99%) of 1-(4-isopropylphenyl)ethan-1-ol (Compound **S120**) as colorless oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 7.28 – 7.22 (m, 2H), 7.18 – 7.16 (m, 2H), 5.04 (d, $J = 4.2$ Hz, 1H), 4.73 – 4.62 (m, 1H), 2.92 – 2.79 (m, 1H), 1.30 (d, $J = 6.5$ Hz, 3H), 1.19 (d, $J = 6.9$ Hz, 6H).

Synthesis of 1-(quinolin-7-yl)ethan-1-ol (Compound **S121**)

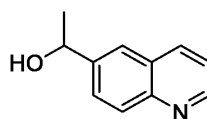
[0500] To a stirred solution of 1-(quinolin-7-yl)ethan-1-one (400 mg, 2.33 mmol) in MeOH (10 mL) cooled to 0°C was added NaBH₄ (132.5 mg, 3.50 mmol) in portions then the mixture was warmed to rt and stirred for 2 h. The reaction was quenched with water (50 mL) and extracted with DCM (2x150 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to afford 350 mg (86%) of 1-(quinolin-7-yl)ethan-1-ol (Compound **S121**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.89 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.33 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.00 – 7.90 (m, 2H), 7.62 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.49 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.45 – 5.38 (m, 1H), 5.01 – 4.91 (m, 1H), 1.44 (d, *J* = 6.4 Hz, 3H).

Synthesis of 1-(4-(oxetan-2-yl)phenyl)ethan-1-ol (Compound **S122**)



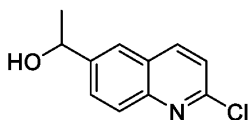
[0501] To a stirred solution of 2-(4-bromophenyl)oxetane (500 mg, 2.34 mmol) in THF (10 mL) cooled to -78°C was added 2.5M nBuLi in hexane (1.4 mL, 3.52 mmol) dropwise under nitrogen followed by the addition of 5M acetaldehyde in THF solution (0.56 mL, 2.81 mmol) dropwise at -78°C then the mixture was warmed to rt and stirred for 1 h. The reaction was cooled to 0°C, quenched with saturated aqueous NH₄Cl solution, and extracted with DCM (3x20 mL). The organic extracts were combined, washed with water (3x20 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 15-20% ACN/water (10mM NH₄HCO₃) to afford 170 mg (41%) of 1-(4-(oxetan-2-yl)phenyl)ethan-1-ol (Compound **S122**) as a yellow liquid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 7.40 – 7.33 (m, 4H), 5.69 (t, *J* = 7.5 Hz, 1H), 5.13 (d, *J* = 4.2 Hz, 1H), 4.77 – 4.62 (m, 2H), 4.56 – 4.48 (m, 1H), 3.00 – 2.90 (m, 1H), 2.60 – 2.52 (m, 1H), 1.31 (d, *J* = 6.4 Hz, 3H).

Synthesis of 1-(quinolin-6-yl)ethan-1-ol (Compound **S123**)

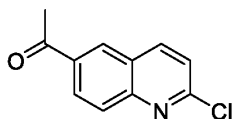


[0502] To a stirred solution of 1-(quinolin-7-yl)ethan-1-one (300 mg, 1.75 mmol) in MeOH (5 mL) cooled to 0°C was added NaBH₄ (132.5 mg, 3.50 mmol) in portions then the mixture was warmed to rt and stirred for 2 h. The reaction was quenched with water (20 mL) and extracted with EtOAc (3x20 mL). The organic extracts were combined, washed with brine (2x3 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to afford 300 mg (99%) of 1-(quinolin-7-yl)ethan-1-ol (Compound **S123**) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.89 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 8.11 (d, *J* = 8.7 Hz, 1H), 7.82 (d, *J* = 1.5 Hz, 1H), 7.74 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.41 (dd, *J* = 8.3, 4.3 Hz, 1H), 5.12 (q, *J* = 6.5 Hz, 1H), 3.49 (s, 1H), 1.60 (d, *J* = 6.5 Hz, 3H).

Synthesis of 1-(2-chloroquinolin-6-yl)ethan-1-ol (Compound **S124**)

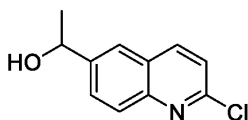


Step 1. Preparation of 1-(2-chloroquinolin-6-yl)ethan-1-one



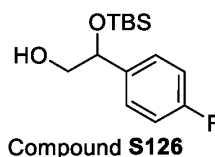
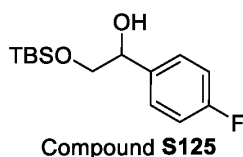
[0503] To a stirred solution of 6-bromo-2-chloroquinoline (1 g, 4.1 mmol) and tributyl(1-ethoxyethenyl)stannane (1.8 g, 4.9 mmol) in dioxane (15 mL) was added Pd(dppf)Cl₂ (0.6 g, 0.8 mmol) in portions under nitrogen then the mixture was heated to 100°C and stirred overnight. The reaction was cooled to rt and 0.1M HCl solution (15 mL, 2 mmol) was added dropwise over 5 minutes. The reaction was stirred at rt for 1 h then extracted with DCM (3x300 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with DCM/MeOH (10:1) to afford 200 mg (24%) of 1-(2-chloroquinolin-6-yl)ethan-1-one as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.80 (d, *J* = 2.0 Hz, 1H), 8.65 (d, *J* = 8.6 Hz, 1H), 8.28 (dd, *J* = 8.8, 2.0 Hz, 1H), 8.05 (d, *J* = 8.9 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 1H), 2.73 (s, 3H).

Step 2. 1-(2-chloroquinolin-6-yl)ethan-1-ol (Compound **S124**)

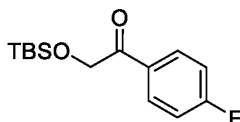


[0504] To a solution of 1-(2-chloroquinolin-6-yl)ethan-1-one (190 mg, 0.9 mmol, as prepared in the previous step) in MeOH (10 mL) cooled to 0°C was added NaBH₄ (41.9 mg, 1.1 mmol) in portions then the mixture was stirred at 0°C for 1 h. The reaction concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 170 mg (89%) of 1-(2-chloroquinolin-6-yl)ethan-1-ol (Compound **S124**) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.45 (dd, *J* = 8.7, 0.8 Hz, 1H), 7.98 (d, *J* = 1.9 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.83 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 5.43 (d, *J* = 4.2 Hz, 1H), 4.98 – 4.88 (m, 1H), 1.42 (d, *J* = 6.5 Hz, 3H).

Synthesis of 2-((tert-butyldimethylsilyl)oxy)-1-(4-fluorophenyl)ethan-1-ol (Compound **S125**) and 2-((tert-butyldimethylsilyl)oxy)-2-(4-fluorophenyl)ethan-1-ol (Compound **S126**)

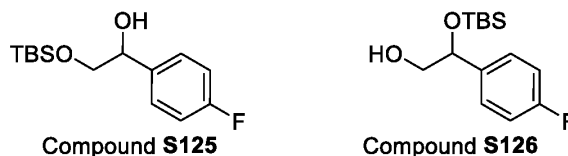


Step 1. Preparation of 2-((tert-butyldimethylsilyl)oxy)-1-(4-fluorophenyl)ethan-1-one



[0505] To a stirred mixture of 1-(4-fluorophenyl)-2-hydroxyethan-1-one (1 g, 6.49 mmol) and imidazole (0.88 g, 12.9 mmol) in THF (20 mL) cooled to 0°C was added TBSCl (1.6 g, 9.73 mmol) in portions then the mixture was warmed to rt and stirred overnight. The reaction was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 600 mg (34%) of 2-((tert-butyldimethylsilyl)oxy)-1-(4-fluorophenyl)ethan-1-one as colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.06 – 7.98 (m, 2H), 7.40 – 7.32 (m, 2H), 5.03 (s, 2H), 0.90 (s, 9H), 0.08 (s, 6H).

Step 2. Preparation of 2-((*tert*-butyldimethylsilyl)oxy)-1-(4-fluorophenyl)ethan-1-ol (Compound **S125**) and 2-((*tert*-butyldimethylsilyl)oxy)-2-(4-fluorophenyl)ethan-1-ol (Compound **S126**)

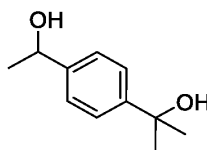


[0506] To a stirred solution of 2-((*tert*-butyldimethylsilyl)oxy)-1-(4-fluorophenyl)ethan-1-ol (1 g, 3.72 mmol, as prepared in the previous step) in MeOH (20 mL) cooled to 0°C was added NaBH₄ (84.5 mg, 2.23 mmol) in portions then the mixture was warmed to rt and stirred overnight. The reaction was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 700 mg (69%) of 2-((*tert*-butyldimethylsilyl)oxy)-1-(4-fluorophenyl)ethan-1-ol (Compound **S125**) as a yellow solid and 350 mg (35%) of 2-((*tert*-butyldimethylsilyl)oxy)-2-(4-fluorophenyl)ethan-1-ol (Compound **S126**) as a yellow solid.

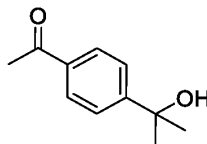
[0507] 2-((*tert*-butyldimethylsilyl)oxy)-1-(4-fluorophenyl)ethan-1-ol (Compound **S125**).
¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 7.42 – 7.32 (m, 2H), 7.18 – 7.08 (m, 2H), 5.33 (d, *J* = 4.4 Hz, 1H), 4.60 – 4.51 (m, 1H), 3.66 (dd, *J* = 10.1, 6.0 Hz, 1H), 3.53 (dd, *J* = 10.1, 5.9 Hz, 1H), 0.81 (s, 9H), -0.05 (s, 3H), -0.08 (s, 3H).

[0508] 2-((*tert*-butyldimethylsilyl)oxy)-2-(4-fluorophenyl)ethan-1-ol (Compound **S126**).
¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 7.40 – 7.30 (m, 2H), 7.18 – 7.09 (m, 2H), 4.77 (t, *J* = 5.7 Hz, 1H), 4.68 (dd, *J* = 6.8, 5.2 Hz, 1H), 3.47 – 3.38 (m, 2H), 0.84 (s, 9H), 0.05 (s, 6H).

Synthesis of 2-(4-(1-hydroxyethyl)phenyl)propan-2-ol (Compound **S127**)

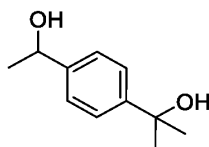


Step 1. Preparation of 1-(4-(2-hydroxypropan-2-yl)phenyl)ethan-1-one



[0509] To a stirred mixture of N,O-dimethylhydroxylamine hydrochloride (5.47 g, 56.12 mmol) in THF (30 mL) cooled to 0°C was added 1.5M DIBAL-H in toluene (38 mL, 56.12 mmol) dropwise under nitrogen then the mixture was warmed to rt and stirred for 2 h. The reaction was cooled to 0°C, methyl 4-acetylbenzoate (5 g, 28.06 mmol) was added, and the mixture was stirred at 0 °C for 1 h. To the stirred mixture at 0°C was added 1M MeMgBr in THF (33.7 mL, 33.672 mmol) dropwise over 30 minutes then the reaction was stirred at 0°C for 2 h. The reaction was cooled to -78°C and 3M MeLi in Et₂O (11.2 mL, 33.672 mmol) was added dropwise over 30 minutes then the mixture was stirred at -78°C for 1 h. The reaction was poured into a water/ice mixture and extracted with EtOAc (3x100 mL). The organic extracts were combined, washed with brine (3x10 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 1 g (20%) of 1-(4-(2-hydroxypropan-2-yl)phenyl)ethan-1-one as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 7.92 – 7.90 (m, 2H), 7.59 – 7.57 (m, 2H), 2.58 (s, 3H), 1.59 (s, 6H).

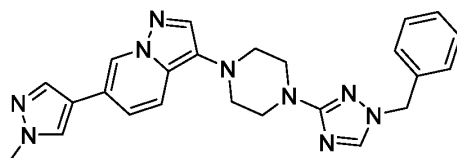
Step 2. Preparation of 2-(4-(1-hydroxyethyl)phenyl)propan-2-ol (Compound **S127**)



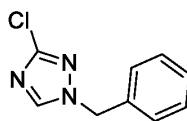
[0510] To a stirred solution of 1-(4-(2-hydroxypropan-2-yl)phenyl)ethan-1-one (1.8 g, 10.09 mmol, as prepared in the previous step) in MeOH (10 mL) cooled to 0°C was added NaBH₄ (460 mg, 12.11 mmol) in portions under nitrogen then the mixture was warmed to rt and stirred overnight. The reaction was concentrated under reduced pressure to afford 300 mg of 2-(4-(1-hydroxyethyl)phenyl)propan-2-ol (Compound **S127**) was used directly without further purification.

Example 1: Synthesis of Exemplary Compound 156

3-(4-(1-benzyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **156**)

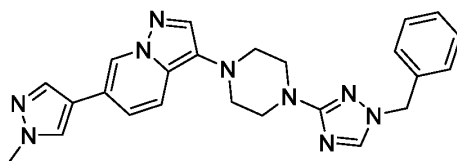


Step 1. Preparation of 1-benzyl-3-chloro-1H-1,2,4-triazole



[0511] To a solution of 3-chloro-1H-1,2,4-triazole (5 g, 48.3 mmol) and benzyl bromide (9.09 g, 53.14 mmol) in DMF (200 mL) was added K_2CO_3 (13.35 g, 96.61 mmol) then the reaction was stirred at 80°C under nitrogen for 16 h. The mixture was cooled to rt, then concentrated under reduced pressure. The residue was filtered, then the filter cake was washed with DCM (3 x 100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with a C18 silica gel column eluting with 10% to 100% ACN / water (10mM NH_4HCO_3) to afford 3.9 g (42%) of 1-benzyl-3-chloro-1H-1,2,4-triazole as a white solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.76 (s, 1H), 7.46 – 7.26 (m, 5H), 5.40 (s, 2H).; MS (ESI) m/z $[M+H]^+$ calcd. for $C_9H_8ClN_3$, 194.1; found, 194.2.

Step 2. 3-(4-(1-benzyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **156**)

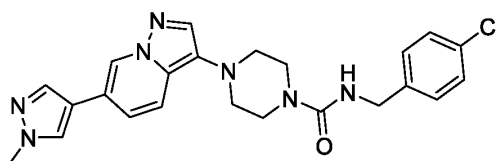


[0512] To a solution of 1-benzyl-3-chloro-1H-1,2,4-triazole (5 g, 25.82 mmol, as prepared in the previous step) and 6-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylpyrazolo[1,5-a]pyridine (Compound **12**) (7.29 g, 25.82 mmol) in dioxane (200 mL) were added Cs_2CO_3 (16.83 g, 51.64 mmol) and $Pd-PEPPSI-IPent^{Cl}$ 2-methylpyridine (2.17 g, 2.58 mmol). The

reaction was stirred at 90°C under nitrogen for 16 h then the resulting mixture was concentrated under reduced pressure. The residue was diluted with water and extracted with DCM (6 x 100 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with MeOH/DCM (1:15) then recrystallized from ACN/THF (5:1) to afford 5.14 g (45%) of 3-(4-(1-benzyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **156**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.32 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.77 (s, 1H), 7.66 (d, *J* = 9.2 Hz, 1H), 7.43 – 7.25 (m, 6H), 5.24 (s, 2H), 3.87 (s, 3H), 3.46 (t, *J* = 4.8 Hz, 4H), 3.06 (t, *J* = 4.8 Hz, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₅N₉, 440.2; found, 440.05; LCMS purity: 254 nm: 99.7%.

Example 2: Synthesis of Exemplary Compound 275

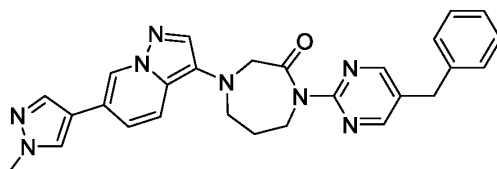
1-(5-benzylpyrimidin-2-yl)-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepan-2-one (Compound **275**).



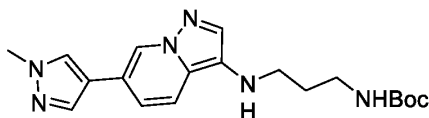
[0513] 6-(1-Methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylpyrazolo[1,5-a]pyridine hydrochloride salt (Compound **S19**) (5.25 g, 16.5 mmol) was added to a solution of 1-chloro-4-(isocyanatomethyl)benzene (2.76 g, 16.5 mmol) in ACN (110 mL) and DIEA (14.0 mL, 80.4 mmol). The reaction was stirred at rt for 1 h, then the mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with acetone (0.1% TEA additive)/EtOAc to afford 5.90 g (80%) of *N*-(4-chlorobenzyl)-4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxamide (Compound **275**) as a solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.81 (s, 1H), 8.22 (s, 1H), 7.96 (s, 1H), 7.77 (s, 1H), 7.66 (d, *J* = 8.7 Hz, 1H), 7.37 (m, 2H), 7.31 (m, 3H), 7.21 (t, *J* = 5.9 Hz, 1H), 4.25 (d, *J* = 5.7 Hz, 2H), 3.87 (s, 3H), 3.52 (m, 4H), 2.95 (m, 4H); MS (ESI) *m/z* [M+Na]⁺ calcd. for C₂₃H₂₄ClN₇NaO: 472.2. Found: 472.2; HPLC purity: 210 nm: 98.7%; 254 nm: 98.3%.

Example 3: Synthesis of Exemplary Compound 326

1-(5-benzylpyrimidin-2-yl)-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepan-2-one (Compound **326**)

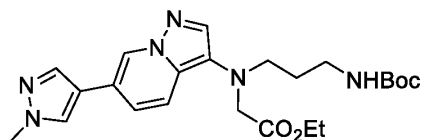


Step 1. Preparation of tert-butyl (3-(((6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)amino)propyl)carbamate



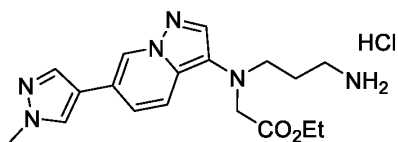
[0514] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-amine (Compound **S56**) (1.0 g, 4.69 mmol) in DMF (30 mL) was added tert-butyl (3-bromopropyl)carbamate (1.34 g, 5.63 mmol) and K_2CO_3 (1.94 g, 14.07 mmol). The reaction was stirred at 90°C under nitrogen for 16 h, cooled to rt, and diluted with water (50 mL). The mixture was extracted with EtOAc (3 x 200 mL), then the combined organic extracts were washed with brine (3x100 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-TLC (MeOH / DCM 1:20) to afford 500 mg (19%) of tert-butyl (3-(((6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)amino)propyl)carbamate as a yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.67 (s, 1H), 8.17 (s, 1H), 7.93 (s, 1H), 7.60 (dd, J = 9.2, 1.2 Hz, 1H), 7.49 (s, 1H), 7.14 (dd, J = 9.2, 1.6 Hz, 1H), 6.88 (t, J = 5.6 Hz, 1H), 4.70 (t, J = 6.4 Hz, 1H), 3.86 (s, 3H), 3.09 – 2.98 (m, 4H), 1.73 – 1.62 (m, 2H), 1.38 (s, 9H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{19}H_{26}N_6O_2$, 371.2; found, 371.2.

Step 2. Preparation of ethyl N-(3-((tert-butoxycarbonyl)amino)propyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)glycinate



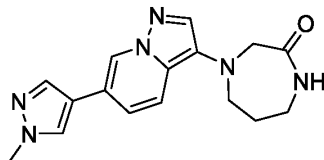
[0515] To a solution of tert-butyl (3-((6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)amino)propyl)carbamate (500 mg, 1.35 mmol, as prepared in the previous step) and ethyl 2-iodoacetate (346.6 mg, 1.62 mmol) in DMF (10 mL) was added K₂CO₃ (373.1 mg, 2.70 mmol) then the reaction was stirred at rt under nitrogen for 16 h. The mixture was concentrated under reduced pressure then the residue was dissolved in water (30 mL). The mixture was extracted with EtOAc (3 x 50 mL), then the combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography with a C18 silica gel column eluting with 10% to 100% ACN / water (0.1% FA) to afford 300 mg (49%) of ethyl N-(3-((tert-butoxycarbonyl)amino)propyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)glycinate as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.77 (s, 1H), 8.20 (s, 1H), 7.95 (s, 1H), 7.76 (s, 1H), 7.57 (d, *J* = 9.3 Hz, 1H), 7.29 (dd, *J* = 9.3, 1.2 Hz, 1H), 6.79 (t, *J* = 5.3 Hz, 1H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.93 - 3.82 (m, 5H), 3.22 - 3.13 (m, 2H), 2.96 (q, *J* = 6.3 Hz, 2H), 1.52 (q, *J* = 6.3 Hz, 2H), 1.35 (s, 9H), 1.14 (t, *J* = 7.1 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₃H₃₂N₆O₄, 457.2; found, 457.3.

Step 3. Preparation of ethyl N-(3-aminopropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)glycinate hydrochloride salt



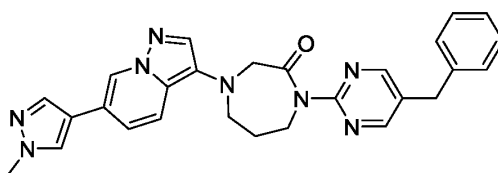
[0516] To a solution of ethyl N-(3-((tert-butoxycarbonyl)amino)propyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)glycinate (300 mg, 0.68 mmol, as prepared in the previous step) in DCM (10 mL) was added 4M HCl in dioxane (3 mL) then the mixture was stirred at rt under nitrogen for 2 h. The reaction was concentrated under reduced pressure to afford 200 mg (77%) of ethyl N-(3-aminopropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)glycinate hydrochloride salt as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.77 (s, 1H), 8.19 (s, 1H), 7.95 (s, 1H), 7.77 (s, 1H), 7.63 - 7.54 (m, 1H), 7.29 (d, *J* = 9.3 Hz, 1H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.94 - 3.88 (m, 2H), 3.86 (s, 3H), 3.26 - 3.18 (m, 2H), 2.98 (q, *J* = 5.8 Hz, 1H), 2.58 (t, *J* = 6.7 Hz, 1H), 1.58 - 1.43 (m, 2H), 1.14 (t, *J* = 7.1 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₉H₂₅N₂O₂, 356.2 found, 356.2.

Step 4. Preparation of 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepan-2-one



[0517] To a solution of ethyl N-(3-aminopropyl)-N-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)glycinate hydrochloride (200 mg, 0.55 mmol, as prepared in the previous step) in MeOH (5 mL) was added 1,5,7-triazabicyclo[4.4.0]dec-5-ene (152.6 mg, 1.10 mmol) then the mixture was stirred at 90°C under nitrogen for 16 h. The reaction was concentrated under reduced pressure then the residue was dissolved in water (30 mL). The mixture was extracted with EtOAc (3 x 50 mL), then the combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-TLC (MeOH / DCM 1:3) to afford 160 mg (84%) of 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepan-2-one as a white solid. ¹H NMR (400 MHz, CD₃OD) δ (ppm) 8.56 (s, 1H), 8.03 (s, 1H), 7.87 (s, 1H), 7.80 (s, 1H), 7.66 (d, *J* = 9.3 Hz, 1H), 7.34 (dd, *J* = 9.3, 1.4 Hz, 1H), 3.95 (d, *J* = 5.5 Hz, 1H), 3.59 - 3.52 (m, 2H), 3.45 - 3.39 (m, 2H), 1.94 - 1.85 (m, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₆H₁₈N₆O, 311.2; found, 311.3.

Step 5. 1-(5-benzylpyrimidin-2-yl)-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepan-2-one (Compound **326**)

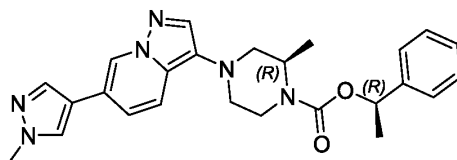


[0518] To a solution of 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepan-2-one (150.0 mg, 0.48 mmol, as prepared in the previous step) and 5-benzyl-2-chloropyrimidine (Compound **S88**) (118.7 mg, 0.58 mmol) in dioxane (10 mL) were added Pd₂(dba)₃ (88.5 mg, 0.01 mmol), XantPhos (55.9 mg, 0.01 mmol), and K₃PO₄ (205.2 mg, 0.97 mmol), then the mixture was stirred at 90°C under nitrogen for 16 h. The reaction was concentrated under reduced pressure then the residue was purified by Prep-TLC (MeOH /

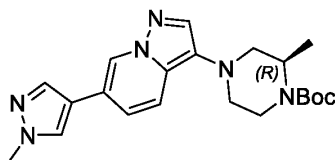
DCM 1:10) and by Prep-HPLC to afford 42.3 mg (18%) of 1-(5-benzylpyrimidin-2-yl)-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepan-2-one (Compound **326**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.87(s, 1H), 8.70 (m, 3H), 8.21 (s, 1H), 7.90 (s, 1H), 7.65 (dd, *J* = 9.2, 1.0 Hz, 1H), 7.35 - 7.27 (m, 5H), 7.26 - 7.18 (m, 1H), 4.15 (d, *J* = 7.2 Hz, 4H), 4.00-3.80 (m, 5H), 3.52 (t, *J* = 5.4 Hz, 2H), 1.94 - 1.81 (m, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₇H₂₆N₈O, 479.2; found, 479.1; LCMS purity: 254 nm: 99.0%

Example 4: Synthesis of Exemplary Compound 327

(R)-1-phenylethyl (R)-2-methyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **327**)



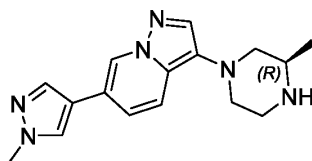
Step 1. Preparation of tert-butyl (R)-2-methyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate



[0519] To a solution of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **S9**) (2.0 g, 7.22 mmol) dissolved in dioxane (30 mL) and tBuOH (30 mL) was added tert-butyl (R)-2-methylpiperazine-1-carboxylate (7.21 g, 36.08 mmol), tBuXPhos Pd G1 (0.99 g, 1.44 mmol), and KOtBu (1.62 g, 14.43 mmol), then the reaction was stirred at 90°C under nitrogen for 16 h. The reaction was cooled rt then diluted with water (200 mL). The mixture was extracted with EtOAc (3 x 200 mL) then the combined organic extracts were washed with brine (3 x 200 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with EtOAc / PE (3:2) to afford 1.2 g (42%) of tert-butyl (R)-2-methyl-4-[6-(1-methylpyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxylate as a light blue solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H),

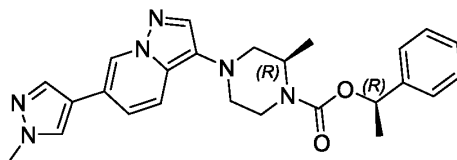
7.96 (s, 1H), 7.75 (s, 1H), 7.57 (d, $J = 9.2$ Hz, 1H), 7.33 (dd, $J = 9.2, 1.6$ Hz, 1H), 4.22 (dd, $J = 7.6, 4.0$ Hz, 1H), 3.87 (s, 3H), 3.84 – 3.76 (m, 1H), 3.22 – 3.19 (m, 1H), 3.14 – 3.07 (m, 1H), 2.77 (dd, $J = 11.6, 3.6$ Hz, 1H), 2.68 – 2.58 (m, 1H), 2.08 – 1.93 (m, 1H), 1.43 (s, 9H), 1.34 (d, $J = 6.8$ Hz, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{21}H_{28}N_6O_2$, 397.2; found, 397.2.

Step 2. Preparation of (R)-6-(1-methyl-1H-pyrazol-4-yl)-3-(3-methylpiperazin-1-yl)pyrazolo[1,5-a]pyridine



[0520] To a solution of tert-butyl (R)-2-methyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (800 mg, 2.02 mmol, as prepared in the previous step) in DCM (10 mL) cooled to 0°C was added 4M HCl in dioxane (3 mL) then the reaction was stirred at 0°C under nitrogen for 1 h. The mixture was neutralized to pH 8 with sat. aqueous Na_2CO_3 then extracted with MeOH / DCM (1:10) (3 x 100 mL). The combined organic extracts were washed with brine (3 x 100 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure to afford 500 mg (83%) of (R)-6-(1-methyl-1H-pyrazol-4-yl)-3-(3-methylpiperazin-1-yl)pyrazolo[1,5-a]pyridine as a light yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.79 (s, 1H), 8.21 (s, 1H), 7.96 (d, $J = 0.8$ Hz, 1H), 7.70 (s, 1H), 7.60 (dd, $J = 9.2, 1.0$ Hz, 1H), 7.27 (dd, $J = 9.2, 1.2$ Hz, 1H), 3.86 (s, 3H), 3.21 – 3.11 (m, 2H), 2.91 (dd, $J = 8.4, 2.8$ Hz, 3H), 2.67 – 2.54 (m, 1H), 2.28 (d, $J = 10.4$ Hz, 1H), 1.23 (s, 1H), 1.00 (d, $J = 6.4$ Hz, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{16}H_{20}N_6$, 297.2; found, 297.2.

Step 3. Preparation of (R)-1-phenylethyl (R)-2-methyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound 327)

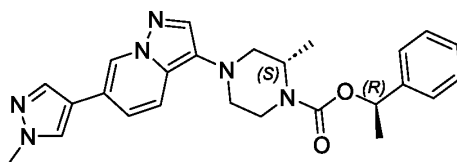


[0521] To a solution of (R)-6-(1-methyl-1H-pyrazol-4-yl)-3-(3-methylpiperazin-1-yl)pyrazolo[1,5-a]pyridine (400 mg, 1.35 mmol, as prepared in the previous step) and (R)-

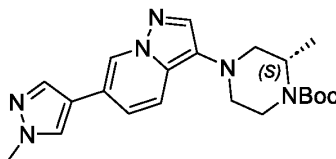
1-phenylethan-1-ol (494.6 mg, 4.05 mmol) in pyridine (15 mL) cooled to 0°C was added triphosgene (400.5 mg, 1.35 mmol) in portions over 1 min. The reaction was warmed to rt and stirred for 1 h, then diluted with water (100 mL) and extracted with EtOAc (6 x 100 mL). The combined organic extracts were washed with brine (6 x 100 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 158 mg (26%) of (R)-1-phenylethyl (R)-2-methyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **327**) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.84 (s, 1H), 8.23 (s, 1H), 7.98 (d, *J* = 0.8 Hz, 1H), 7.76 (s, 1H), 7.59 (dd, *J* = 9.2, 1.0 Hz, 1H), 7.43 – 7.31 (m, 5H), 7.31 – 7.26 (m, 1H), 5.76 (q, *J* = 6.4 Hz, 1H), 4.33 (s, 1H), 3.92 (d, *J* = 13.2 Hz, 1H), 3.88 (s, 3H), 3.38 – 3.28 (m, 1H), 3.26 (d, *J* = 12.4 Hz, 1H), 3.18 – 3.09 (m, 1H), 2.81 (dd, *J* = 11.4, 4.0 Hz, 1H), 2.73 – 2.63 (m, 1H), 1.49 (d, *J* = 6.8 Hz, 3H), 1.38 (d, *J* = 6.0 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₈N₆O₂, 445.2; found, 445.1; LCMS purity: 254 nm: 98.5%; chiral purity: 100%.

Example 5: Synthesis of Exemplary Compound 329

(R)-1-phenylethyl (S)-2-methyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **329**)



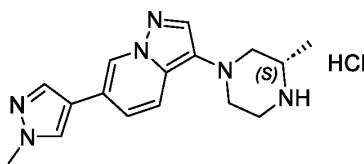
Step 1. Preparation of tert-butyl (S)-2-methyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate



[0522] To a solution of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **S9**) (2 g, 7.21 mmol) and tert-butyl (S)-2-methylpiperazine-1-carboxylate (7.23 g, 36.08 mmol) in dioxane (50 mL) and tBuOH (50 mL) were added KOtBu (1.62 g, 14.43 mmol) and tBuXPhos Pd G1 (0.99 g, 1.44 mmol) then the mixture was stirred at

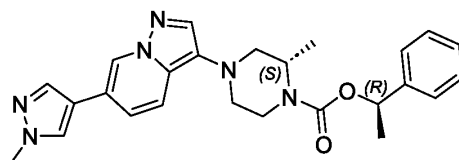
90°C under nitrogen overnight. The reaction was cooled to rt and concentrated under reduced pressure. The mixture was diluted with water (100 mL) and extracted with DCM (3 x 100 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography with a C18 silica gel column eluting with 10% to 50% ACN / water (0.1% FA) to afford 370 mg (13%) of tert-butyl (S)-2-methyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.84 (t, *J* = 1.3 Hz, 1H), 8.23 (s, 1H), 7.97 (d, *J* = 0.8 Hz, 1H), 7.76 (s, 1H), 7.59 – 7.57 (m, 1H), 7.35 – 7.33 (m, 1H), 4.22 (s, 1H), 3.87 (s, 3H), 3.85 – 3.77 (m, 1H), 3.25 – 3.20 (m, 2H), 3.13 – 3.09 (m, 1H), 2.79 – 2.75 (m, 1H), 2.69 – 2.58 (m, 1H), 1.43 (s, 9H), 1.34 (d, *J* = 6.7 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₁H₂₈N₆O₂, 397.2; found, 397.2.

Step 2. Preparation of (S)-6-(1-methyl-1H-pyrazol-4-yl)-3-(3-methylpiperazin-1-yl)pyrazolo[1,5-a]pyridine hydrochloride salt



[0523] To a solution of (S)-2-methyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (360 mg, 0.90 mmol, as prepared in the previous step) in dioxane (10 mL) was added 4M HCl in dioxane (2.3 mL, 9.0 mmol) then the mixture was stirred at rt for 30 minutes. The reaction was concentrated under reduced pressure to afford 300 mg (78%) of (S)-6-(1-methyl-1H-pyrazol-4-yl)-3-(3-methylpiperazin-1-yl)pyrazolo[1,5-a]pyridine hydrochloride salt as a white solid. MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₆H₂₀N₆, 297.1; found, 297.1.

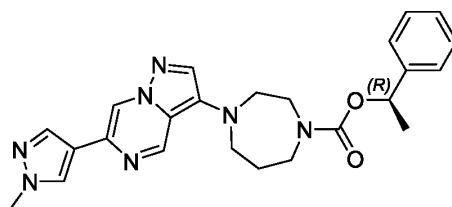
Step 3. (R)-1-phenylethyl (S)-2-methyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound 329)



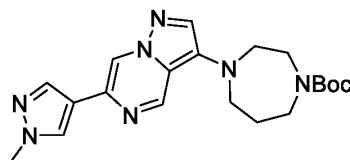
[0524] To a solution of (S)-6-(1-methyl-1H-pyrazol-4-yl)-3-(3-methylpiperazin-1-yl)pyrazolo[1,5-a]pyridine hydrochloride salt (200 mg, 0.67 mmol, as prepared in the previous step) and (R)-1-phenylethan-1-ol (247.3 mg, 2.02 mmol) in pyridine (15 mL) was added triphosgene (200.2 mg, 0.67 mmol), then the mixture was stirred at rt under nitrogen overnight. The reaction was concentrated under reduced pressure then the residue was dissolved in water (50 mL) and the mixture was extracted with DCM (3 x 50 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 57.2 mg (19%) of (R)-1-phenylethyl (S)-2-methyl-4-[6-(1-methylpyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxylate (Compound **329**) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.84 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.76 (s, 1H), 7.59 (d, *J* = 9.2 Hz, 1H), 7.43 – 7.26 (m, 6H), 5.75 (q, *J* = 6.6 Hz, 1H), 4.34 (s, 1H), 3.92 (d, *J* = 12.9 Hz, 1H), 3.87 (s, 3H), 3.28 – 3.11 (m, 3H), 2.80 (d, *J* = 11.3 Hz, 1H), 2.72 – 2.62 (m, 1H), 1.49 (d, *J* = 6.6 Hz, 3H), 1.37 (d, *J* = 6.7 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₈N₆O₂, 445.1; found, 445.1. LCMS purity: 254 nm: 99.9%; chiral purity: 99.6%.

Example 6: Synthesis of Exemplary Compound 330

(R)-1-phenylethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazin-3-yl)-1,4-diazepane-1-carboxylate (Compound **330**)

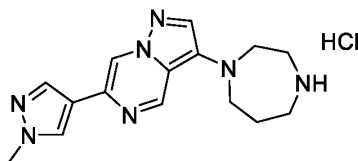


Step 1. Preparation of tert-butyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazin-3-yl)-1,4-diazepane-1-carboxylate



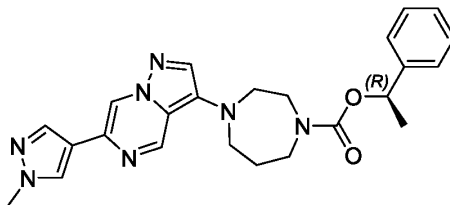
[0525] To a solution of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine (Compound **S5**) (500 mg, 1.80 mmol) and tert-butyl 1,4-diazepane-1-carboxylate (1.80 g, 9.00 mmol) in tBuOH (6 mL) and dioxane (3 mL) was added KOtBu (302 mg, 2.70 mmol) and tBuXPhos Pd G1 (185 mg, 0.27 mmol) under nitrogen then the reaction was stirred at 60°C under nitrogen for 16 h. The mixture was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with EtOAc / PE (2:1) and reversed-phase flash chromatography with a C18 silica gel column eluting with 10% to 70% ACN / water (10mM NH₄HCO₃) to afford 150 mg (19%) of tert-butyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazin-3-yl)-1,4-diazepane-1-carboxylate as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.06 (d, *J* = 4.4 Hz, 1H), 8.74 (d, *J* = 5.6 Hz, 1H), 8.16 (s, 1H), 7.97 (s, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 3.87 (s, 3H), 3.71 – 3.63 (m, 1H), 3.60 – 3.48 (m, 5H), 3.35 – 3.24 (m, 2H), 1.90 – 1.81 (m, 2H), 1.37 – 1.01 (m, 9H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₀H₂₇N₇O₂, 398.2; found, 398.3.

Step 2. Preparation of 3-(1,4-diazepan-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine hydrochloride salt



[0526] To a solution of tert-butyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepane-1-carboxylate (150 mg, 0.38 mmol, as prepared in the previous step) in dioxane (5 mL) was added 4M HCl in dioxane (5 mL) then the reaction was stirred at rt for 1 h. The mixture was concentrated under reduced pressure to afford 170 mg (135%) of 3-(1,4-diazepan-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine hydrochloride salt as a red solid. MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₅H₁₉N₇, 298.2; found, 298.3.

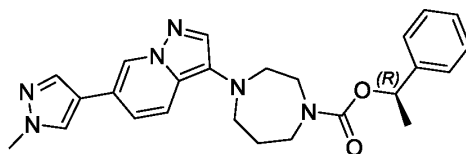
Step 3. Preparation of (R)-1-phenylethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazin-3-yl)-1,4-diazepane-1-carboxylate (Compound **330**).



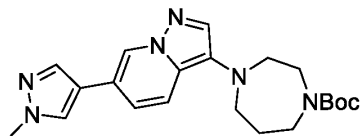
[0527] To a solution of 3-(1,4-diazepan-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine hydrochloride salt (75 mg, 0.25 mmol, as prepared in the previous step), (R)-1-phenylethanol (37.0 mg, 0.30 mmol), and pyridine (79.8 mg, 1.01 mmol) in DCM (2 mL) cooled to 0°C was added triphosgene (22.5 mg, 0.08 mmol) in small portions then the reaction was stirred at 0°C for 1h. MeOH (2 mL) was added then the mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC to afford 16.3 mg (14%) of (R)-1-phenylethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazin-3-yl)-1,4-diazepane-1-carboxylate (Compound **330**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.11 – 9.02 (m, 1H), 8.79 – 8.71 (m, 1H), 8.17 (s, 1H), 7.97 (s, 1H), 7.66 (d, *J* = 3.0 Hz, 1H), 7.34 – 7.15 (m, 4H), 7.15 – 7.06 (m, 1H), 5.66 – 5.47 (m, 1H), 3.88 (s, 3H), 3.83 – 3.69 (m, 1H), 3.69 – 3.34 (m, 7H), 2.03 – 1.70 (m, 2H), 1.41 – 1.15 (m, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₇N₇O₂, 446.2; found, 446.1; LCMS purity: 254 nm: 99.0%.

Example 7: Synthesis of Exemplary Compound **328**

(R)-1-phenylethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepane-1-carboxylate (Compound **328**)

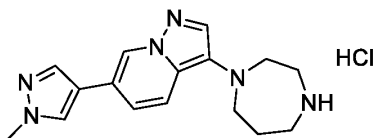


Step 1. Preparation of tert-butyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepane-1-carboxylate



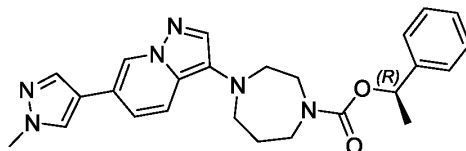
[0528] To a solution of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **S9**) (500 mg, 1.80 mmol) and tert-butyl 1,4-diazepane-1-carboxylate (1.81 g, 9.02 mmol) in tBuOH (6 mL) and dioxane (3 mL) were added KOtBu (304 mg, 2.71 mmol) and tBuXPhos Pd G1 (186 mg, 0.27 mmol) under nitrogen, then the reaction was stirred at 60°C under nitrogen for 16 h. The mixture was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with EtOAc / PE (1:1) and reversed-phase flash chromatography with a C18 silica gel column eluting with 10% to 70% ACN / water (10mM NH₄HCO₃) to afford 255 mg (32%) of tert-butyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepane-1-carboxylate as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.73 (s, 1H), 8.19 (s, 1H), 7.94 (s, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.57 (d, *J* = 9.4 Hz, 1H), 7.24 – 7.14 (m, 1H), 3.86 (s, 3H), 3.55 – 3.49 (m, 2H), 3.46 – 3.39 (m, 1H), 3.39 – 3.32 (m, 4H), 3.30 (s, 1H), 1.91 – 1.79 (m, 2H), 1.46 – 1.13 (m, 9H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₁H₂₈N₆O₂, 397.2; found, 397.3.

Step 2. Preparation of 3-(1,4-diazepan-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine hydrochloride salt



[0529] To a solution of tert-butyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepane-1-carboxylate (245 mg, 0.62 mmol, as prepared in the previous step) in dioxane (6 mL) was added 4M HCl in dioxane (12 mL) then the reaction was stirred at rt for 1 h. The mixture was concentrated under reduced pressure to afford 290 mg (87%) of 3-(1,4-diazepan-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine hydrochloride salt as a light yellow solid. MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₆H₂₀N₆, 297.2; found, 297.3.

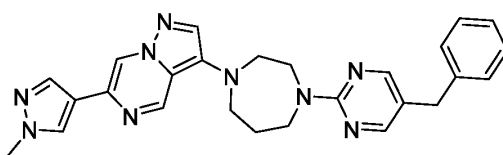
Step 3. Preparation of (R)-1-phenylethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepane-1-carboxylate (Compound **328**)



[0530] To a solution of 3-(1,4-diazepan-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine hydrochloride salt (50 mg, 0.17 mmol, as prepared in the previous step), (R)-1-phenylethanol (25 mg, 0.20 mmol) and pyridine (20 mg, 0.25 mmol) in DCM (2 mL) cooled to 0°C was added triphosgene (15 mg, 0.05 mmol) in small portions then the reaction was stirred at 0°C for 1 h. The mixture was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 54 mg (72%) of (R)-1-phenylethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepane-1-carboxylate (Compound **328**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.76 – 8.71 (m, 1H), 8.20 (s, 1H), 7.95 (s, 1H), 7.66 (d, *J* = 1.2 Hz, 1H), 7.60 – 7.53 (m, 1H), 7.34 (d, *J* = 4.3 Hz, 2H), 7.31 – 7.18 (m, 4H), 5.75 – 5.59 (m, 1H), 3.87 (s, 3H), 3.75 – 3.49 (m, 3H), 3.49 – 3.41 (m, 2H), 3.41 – 3.33 (m, 2H), 3.31 – 3.22 (m, 1H), 2.01 – 1.73 (m, 2H), 1.50 – 1.27 (m, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₈N₆O₂, 445.2; found, 445.1; LCMS purity: 254 nm: 99.4%

Example 8: Synthesis of Exemplary Compound 331

3-(4-(5-benzylpyrimidin-2-yl)-1,4-diazepan-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine (Compound **331**)

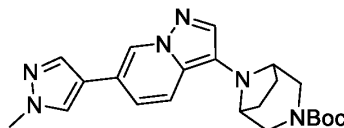


[0531] To a solution of 3-(1,4-diazepan-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine hydrochloride salt (50.0 mg, 0.15 mmol, as prepared in Example 6, Step 2) and DIEA (58.1 mg, 0.45 mmol) in IPA (2 mL) was added 5-benzyl-2-chloropyrimidine (Compound **S88**) (30.7 mg, 0.15 mmol) then the reaction was stirred at 100°C for 16 h. The mixture was cooled to rt and concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 26.1 mg (37%) of 3-(4-(5-benzylpyrimidin-2-yl)-1,4-

diazepan-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine (Compound **331**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.04 (d, *J* = 1.5 Hz, 1H), 8.70 (d, *J* = 1.4 Hz, 1H), 8.19 (s, 2H), 8.16 (s, 1H), 7.96 (d, *J* = 0.8 Hz, 1H), 7.63 (s, 1H), 7.32 – 7.23 (m, 2H), 7.22 – 7.14 (m, 3H), 3.96 (t, *J* = 5.4 Hz, 2H), 3.87 (s, 3H), 3.73 (s, 2H), 3.67 (t, *J* = 6.0 Hz, 2H), 3.65 – 3.60 (m, 2H), 3.51 – 3.46 (m, 2H), 2.01 – 1.91 (m, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₆H₂₇N₉, 466.2; found, 466.1; LCMS purity: 254 nm: 99.1%

Example 9: Synthesis of Exemplary Compound 332

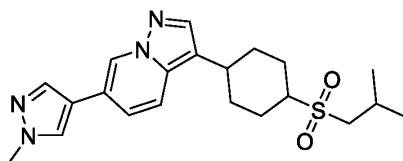
tert-butyl 8-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (Compound **332**)



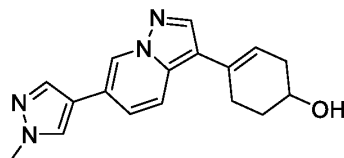
[0532] To a round bottom flask containing 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **S9**) (200 mg, 0.72 mmol) and *tert*-butyl 3,8-diazabicyclo[3.2.1]octane-3-carboxylate (613 mg, 2.89 mmol) was added *t*BuOH (2 mL) and dioxane (1 mL). The solution was sparged with nitrogen for 20 min at rt then *t*BuXPhos Pd G1 (50 mg, 0.07 mmol) and K^{*o*}tBu (121 mg, 1.08 mmol) were added and the reaction mixture was sparged with nitrogen for 5 min at rt. The reaction was heated to 60°C for 4 h, cooled to rt, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 10-60% acetone / DCM to afford 166 mg (56%) of *tert*-butyl 8-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-3,8-diazabicyclo[3.2.1]octane-3-carboxylate (Compound **332**). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.42 (s, 1H), 7.74 (s, 1H) 7.61 (s, 1H) 7.57 (s, 1H) 7.51 (d, *J* = 9.3 Hz, 1H) 7.27 (s, 1H) 7.10 (dd, *J* = 9.2, 1.5 Hz, 1H) 3.98 (s, 3H) 3.75-3.91 (m, 4H) 3.25-3.36 (m, 2H) 2.04 (d, *J* = 4 Hz, 2H) 1.81 (dd, *J* = 13, 7.4 Hz, 2H) 1.49 (s, 9H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₂H₂₉N₆O₂, 409.2; found, 409.2; HPLC purity: 210 nm: 100%; 254 nm: 100%.

Example 10: Synthesis of Exemplary Compound 333

3-(4-(isobutylsulfonyl)cyclohexyl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **333**)

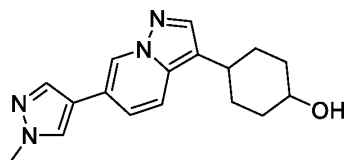


Step 1. Preparation of 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)cyclohex-3-en-1-ol



[0533] To a solution of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **S9**) (1.20 g, 4.33 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohex-3-en-1-ol (0.97 g, 4.33 mmol) in dioxane (10 mL) and H₂O (1 mL) was added XPhos Pd G3 (0.37 g, 0.43 mmol), XPhos (0.21 g, 0.43 mmol), and K₃PO₄ (1.84 g, 8.66 mmol) under nitrogen, then the reaction was stirred at 90°C under nitrogen for 16 h. The mixture was cooled to rt, then concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc / PE (3:1) to afford 1.79 g (98%) of 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)cyclohex-3-en-1-ol as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.93 (s, 1H), 8.25 – 8.23 (m, 1H), 8.04 – 7.97 (m, 2H), 7.85 – 7.77 (m, 1H), 7.46 (dd, *J* = 9.3, 1.7 Hz, 1H), 6.02 – 5.92 (m, 1H), 4.67 (d, *J* = 4.1 Hz, 1H), 3.87 (s, 3H), 3.85 – 3.76 (m, 1H), 2.64 – 2.54 (m, 1H), 2.47 – 2.38 (m, 1H), 2.14 – 1.84 (m, 3H), 1.67 – 1.56 (m, 1H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₇H₁₈N₄O, 295.1; found, 295.2.

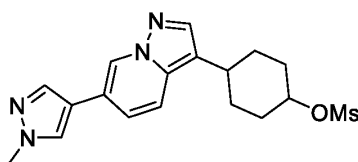
Step 2. Preparation of 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)cyclohexan-1-ol



[0534] To a solution of 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)cyclohex-3-en-1-ol (1.5 g, 5.10 mmol, as prepared in the previous step) in MeOH (20 mL) was added Pd/C (0.54 g, 5.10 mmol) then the reaction was stirred at rt under an

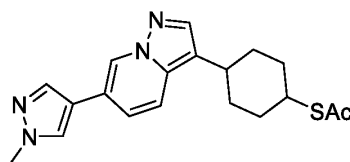
atmosphere of hydrogen for 40 h. The mixture was filtered, and the filter cake was washed with MeOH (2 x 5 mL). The filtrate was concentrated under reduced pressure to afford 760 mg (45%) of 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)cyclohexan-1-ol as a grey solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.92 – 8.83 (m, 1H), 8.22 (s, 1H), 7.97 (d, *J* = 0.8 Hz, 1H), 7.80 (d, *J* = 5.1 Hz, 1H), 7.73 – 7.61 (m, 1H), 7.42 – 7.33 (m, 1H), 4.38 (d, *J* = 3.3 Hz, 1H), 3.89 (s, 1H), 3.87 (d, *J* = 1.0 Hz, 3H), 2.91 – 2.62 (m, 1H), 2.01 – 1.44 (m, 8H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₇H₂₀N₄O, 297.2; found, 297.3.

Step 3. Preparation of 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)cyclohexyl methanesulfonate



[0535] To a solution of 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)cyclohexan-1-ol (615 mg, 2.08 mmol, as prepared in the previous step) and TEA (420 mg, 4.15 mmol) in DCM (10 mL) was added Ms₂O (542 mg, 3.11 mmol) at 0°C then the reaction was stirred at rt for 2 h. The mixture was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with MeOH / DCM (1:20) to afford 580 mg (678%) of 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)cyclohexyl methanesulfonate as a green solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.90 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.87 – 7.79 (m, 1H), 7.78 – 7.66 (m, 1H), 7.45 – 7.36 (m, 1H), 5.00 (s, 1H), 3.87 (s, 3H), 3.21 (s, 3H), 2.99 – 2.79 (m, 1H), 2.17 (s, 1H), 2.10 – 1.94 (m, 1H), 1.90 – 1.60 (m, 6H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₈H₂₂N₄O₃S, 375.1; found, 375.2.

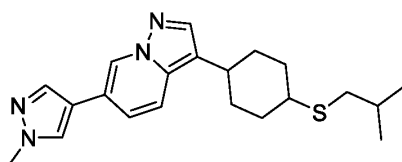
Step 4. Preparation of S-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)cyclohexyl) ethanethioate



[0536] To a solution of 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)cyclohexyl methanesulfonate (500 mg, 1.34 mmol, as prepared in the previous step) in

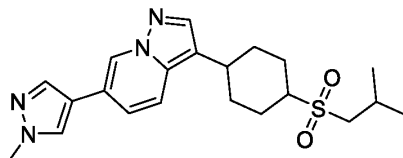
DMF (10 mL) was added potassium thioacetate (610 mg, 5.34 mmol) then the reaction was stirred at 90°C for 16 h. The mixture was cooled to rt, water (100 mL) was added, then the mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-TLC (EtOAc) to afford 200 mg (42%) of S-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)cyclohexyl) ethanethioate as a yellow oil. MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₆H₁₉N₃, 254.2; found, 254.3.

Step 5. Preparation of 3-(4-(isobutylthio)cyclohexyl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine



[0537] To a solution of S-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)cyclohexyl) ethanethioate (200 mg, 0.11 mmol, as prepared in the previous step) in DMSO (3 mL) and H₂O (1 mL) was added KOH (13.3 mg, 0.24 mmol) then the reaction was stirred at rt for 1 h. To the mixture was added 1-bromo-2-methylpropane (15.5 mg, 0.11 mmol) and the reaction was stirred at rt for 1 h. H₂O (20 mL) was added then the mixture was extracted with EtOAc (3 x 40 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and filtered then the filtrate was concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with a C18 silica gel column eluting with 10% to 90% ACN / water (10mM NH₄HCO₃) to afford 20 mg (10%) of 3-(4-(isobutylthio)cyclohexyl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine as a colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.91 – 8.85 (m, 1H), 8.22 (s, 1H), 7.96 (s, 1H), 7.83 – 7.77 (m, 1H), 7.74 – 7.63 (m, 1H), 7.43 – 7.34 (m, 1H), 3.87 (s, 3H), 3.20 – 3.10 (m, 1H), 2.46 – 2.39 (m, 2H), 2.11 – 2.03 (m, 1H), 1.99 – 1.81 (m, 4H), 1.79 – 1.68 (m, 2H), 1.64 – 1.37 (m, 3H), 1.03 – 0.89 (m, 6H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₁H₂₈N₄S, 369.2; found, 369.3.

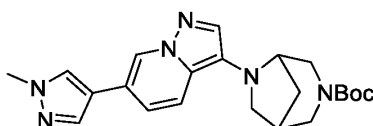
Step 6. Preparation of 3-(4-(isobutylsulfonyl)cyclohexyl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **333**)



[0538] To a solution of 3-(4-(isobutylthio)cyclohexyl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (15 mg, 0.04 mmol, as prepared in the previous step) in DCM (2 mL) cooled to 0°C was added mCPBA (35 mg, 0.21 mmol) then the reaction was stirred at 0°C for 1 h. The mixture was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 3.5 mg (21%) of 3-(4-(isobutylsulfonyl)cyclohexyl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **333**) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.97 – 8.83 (m, 1H), 8.23 (s, 1H), 7.98 (d, *J* = 0.8 Hz, 1H), 7.88 – 7.78 (m, 1H), 7.79 – 7.66 (m, 1H), 7.47 – 7.36 (m, 1H), 3.87 (s, 3H), 3.29 – 3.10 (m, 2H), 3.05 – 2.97 (m, 2H), 2.31 – 2.10 (m, 3H), 2.09 – 1.87 (m, 3H), 1.86 – 1.76 (m, 1H), 1.71 – 1.57 (m, 2H), 1.10 – 1.03 (m, 6H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₁H₂₈N₄O₂S, 401.2; found, 401.2; LCMS purity: 254 nm: 99.9%.

Example 11: Synthesis of Exemplary Compound 334

tert-butyl 6-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-3,6-diazabicyclo[3.2.1]octane-3-carboxylate (Compound **334**)

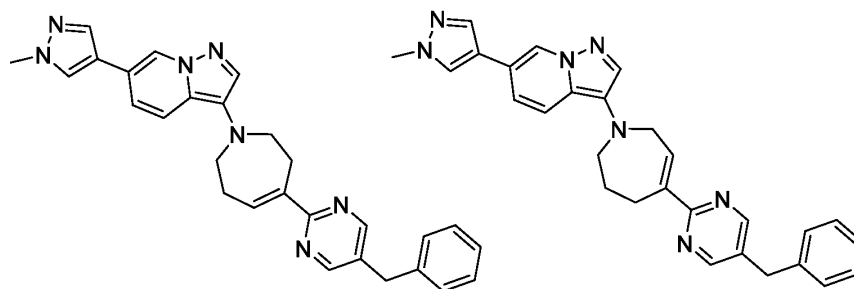


[0539] To a stirred solution of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **S9**) (1.20 g, 4.33 mmol) and tert-butyl 3,6-diazabicyclo[3.2.1]octane-3-carboxylate (1.84 g, 8.66 mmol) in tBuOH (20 mL) and dioxane (10 mL) were added KOtBu (728.8 mg, 6.50 mmol) and tBuXPhos Pd G1 (594.7 mg, 0.87 mmol) at rt then the reaction was stirred at 50°C under nitrogen for 48 h. The mixture was cooled to rt, concentrated under reduced pressure, and the residue was dissolved in water (100 mL). The resulting mixture was extracted with DCM (3 x 80 mL) then the combined organic extracts were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel

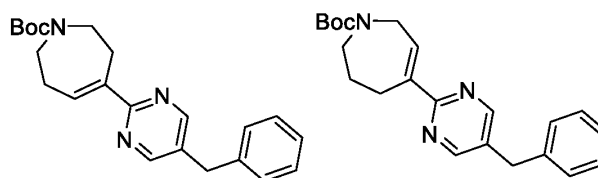
chromatography eluting with EtOAc / PE (10:1) and by Prep-HPLC to afford 20.4 mg (1%) of tert-butyl 6-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-3,6-diazabicyclo[3.2.1]octane-3-carboxylate (Compound **334**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.76 – 8.55 (m, 1H), 8.17 (s, 1H), 7.93 (s, 1H), 7.64 (d, *J* = 9.3 Hz, 1H), 7.51 – 7.43 (m, 1H), 7.10 – 7.01 (m, 1H), 4.23 – 3.70 (m, 6H), 3.64 – 3.48 (m, 1H), 3.23 – 3.00 (m, 1H), 2.91 – 2.63 (m, 2H), 2.49 – 2.43 (m, 1H), 2.13 – 1.92 (m, 1H), 1.87 – 1.73 (m, 1H), 1.30 (s, 3H), 0.92 (s, 6H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₂H₂₈N₆O₂, 409.2; found, 409.15; LCMS purity: 254 nm: 98.9%.

Example 12: Synthesis of Exemplary Compound 335

Mixture of 3-(4-(5-benzylpyrimidin-2-yl)-2,3,6,7-tetrahydro-1H-azepin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine and 3-(5-(5-benzylpyrimidin-2-yl)-2,3,4,7-tetrahydro-1H-azepin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **335**)



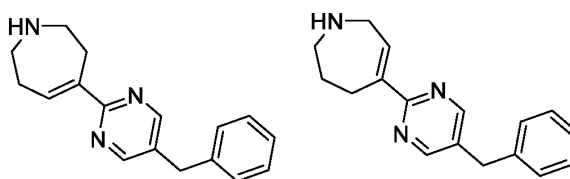
Step 1. Preparation of tert-butyl 4-(5-benzylpyrimidin-2-yl)-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate and tert-butyl 5-(5-benzylpyrimidin-2-yl)-2,3,4,7-tetrahydro-1H-azepine-1-carboxylate



[0540] To a solution of 5-benzyl-2-chloropyrimidine (Compound **S88**) (500 mg, 2.44 mmol) in dioxane (25 mL) and H₂O (5 mL) was added a mixture of tert-butyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3,4,7-tetrahydro-1H-azepine-1-carboxylate and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3,6,7-tetrahydro-1H-azepine-

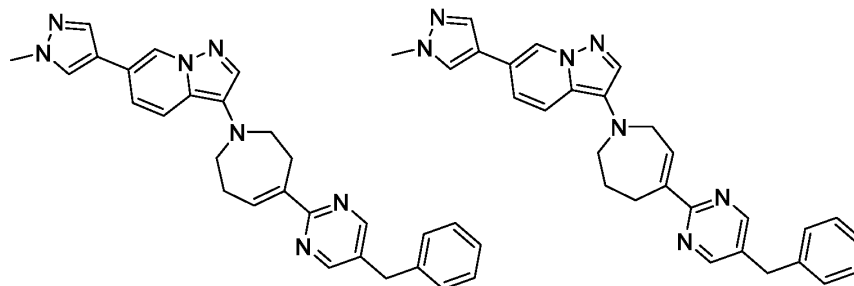
1-carboxylate (789.7 mg, 2.44 mmol), Pd(dppf)Cl₂ (268.1 mg, 0.37 mmol), and Cs₂CO₃ (1.59 g, 4.89 mmol) then the reaction was stirred at 90°C under nitrogen for 16 h. The mixture was cooled to rt and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (3x100 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with EtOAc/ PE (1:2) to afford 700 mg (78%) of a mixture of tert-butyl 4-(5-benzylpyrimidin-2-yl)-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate and tert-butyl 5-(5-benzylpyrimidin-2-yl)-2,3,4,7-tetrahydro-1H-azepine-1-carboxylate as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.67 (s, 2H), 7.35 – 7.24 (m, 4H), 7.24 – 7.16 (m, 2H), 4.12 – 4.04 (m, 2H), 3.96 (s, 2H), 3.56 – 3.48 (m, 2H), 2.89 – 2.81 (m, 2H), 1.79 (s, 2H), 1.38 (s, 5H), 1.36 (s, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₂H₂₇N₃O₂, 366.2; found, 366.2.

Step 2. Preparation of 4-(5-benzylpyrimidin-2-yl)-2,3,6,7-tetrahydro-1H-azepine and 5-(5-benzylpyrimidin-2-yl)-2,3,4,7-tetrahydro-1H-azepine



[0541] To a solution of a mixture of tert-butyl 4-(5-benzylpyrimidin-2-yl)-2,3,6,7-tetrahydro-1H-azepine-1-carboxylate and tert-butyl 5-(5-benzylpyrimidin-2-yl)-2,3,4,7-tetrahydro-1H-azepine-1-carboxylate (700 mg, 1.92 mmol, as prepared in the previous step) in DCM (15 mL) cooled to 0°C was added TFA (5 mL) then the reaction was stirred at 0°C under nitrogen for 1 h. The mixture was neutralized to pH 8 with sat. aqueous Na₂CO₃ then extracted with MeOH / DCM (1:10) (3 x 100 mL). The combined organic extracts were washed with brine (3x100 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to afford 460 mg (90%) of a mixture of 4-(5-benzylpyrimidin-2-yl)-2,3,6,7-tetrahydro-1H-azepine and 5-(5-benzylpyrimidin-2-yl)-2,3,4,7-tetrahydro-1H-azepine as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.69 – 8.62 (m, 2H), 7.37 – 7.18 (m, 6H), 4.12 – 4.06 (m, 1H), 3.96 (s, 2H), 3.59 – 3.52 (m, 1H), 3.46 – 3.41 (m, 1H), 2.99 – 2.86 (m, 3H), 1.81 – 1.76 (m, 1H), 1.72 – 1.61 (m, 1H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₇H₁₉N₃, 266.2; found, 266.2.

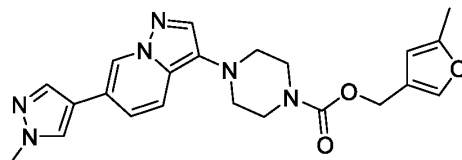
Step 3. Preparation of a mixture of 3-(4-(5-benzylpyrimidin-2-yl)-2,3,6,7-tetrahydro-1H-azepin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine and 3-(5-(5-benzylpyrimidin-2-yl)-2,3,4,7-tetrahydro-1H-azepin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **335**)



[0542] To a solution of a mixture of 4-(5-benzylpyrimidin-2-yl)-2,3,6,7-tetrahydro-1H-azepine and 5-(5-benzylpyrimidin-2-yl)-2,3,4,7-tetrahydro-1H-azepine (200 mg, 0.75 mmol, as prepared in the previous step) in dioxane (8 mL) was added 3-iodo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (293.2 mg, 0.91 mmol, as prepared for Compound **S57**, Step 1), Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (95.1 mg, 0.11 mmol) and Cs₂CO₃ (491.1 mg, 1.51 mmol), then the reaction was stirred at 100°C under nitrogen for 16 h. The mixture was cooled to rt, diluted with water (30 mL), and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (3 x 30 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 13 mg (3.65%) of a mixture of 3-(4-(5-benzylpyrimidin-2-yl)-2,3,6,7-tetrahydro-1H-azepin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine and 3-(5-(5-benzylpyrimidin-2-yl)-2,3,4,7-tetrahydro-1H-azepin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **335**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.86 – 8.82 (m, 1H), 8.62 – 8.57 (m, 2H), 8.22 – 8.18 (m, 1H), 7.97 – 7.93 (m, 1H), 7.80 – 7.76 (s, 1H), 7.76 – 7.62 (m, 1H), 7.57 – 7.50 (m, 1H), 7.43 – 7.33 (m, 1H), 7.33 – 7.14 (m, 5H), 5.16 – 5.09 (m, 1H), 3.93 – 3.80 (m, 5H), 3.44 – 3.34 (m, 1H), 3.12 – 3.05 (m, 1H), 3.03 – 2.94 (m, 1H), 2.63 – 2.53 (m, 2H), 2.49 – 2.38 (m, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₈H₂₇N₇, 462.2; found, 462.1; HPLC purity: 254 nm: 97.7%

Example 13: Synthesis of Exemplary Compound 336

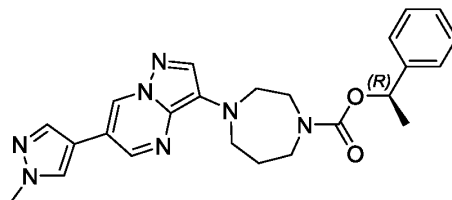
(5-methylfuran-3-yl)methyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **336**)



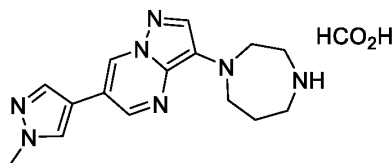
[0543] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (200 mg, 0.71 mmol) and (5-methylfuran-3-yl)methanol (95 mg, 0.85 mmol) in pyridine (5 mL) was added triphosgene (63.1 mg, 0.21 mmol) then the reaction was stirred at rt under nitrogen for 6 h. The mixture was concentrated under reduced pressure then the residue was dissolved in water (30 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 80.8 mg (27%) of (5-methylfuran-3-yl)methyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **336**) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.77 (s, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.56 (s, 1H), 7.33 (dd, *J* = 9.2, 1.5 Hz, 1H), 6.15 (s, 1H), 4.90 (s, 2H), 3.87 (s, 3H), 3.57 (t, *J* = 5.0 Hz, 4H), 2.96 (t, *J* = 4.9 Hz, 4H), 2.25 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₂H₂₄N₆O₃, 421.2; found, 421.1; LCMS purity: 254 nm: 99.7%

Example 14: Synthesis of Exemplary Compound 337

(R)-1-phenylethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,4-diazepane-1-carboxylate (Compound **337**)

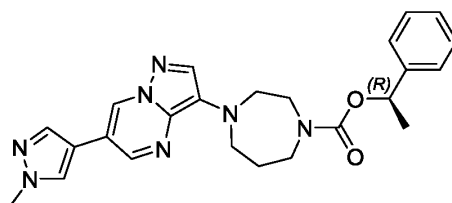


Step 1. Preparation of 3-(1,4-diazepan-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine formic acid salt



[0544] To a solution of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine (Compound **S10**) (2.00 g, 7.19 mmol) and 1,4-diazepane (3.60 g, 35.96 mmol) in DMF (120 mL) were added Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (1.21 g, 1.44 mmol) and Cs₂CO₃ (4.69 g, 14.38 mmol) then the reaction was stirred at 90°C under nitrogen for 16 h. The mixture was cooled to rt then concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with a C18 silica gel column eluting with 10% to 100% ACN / water (0.1% FA) to afford 550 mg (22%) of 3-(1,4-diazepan-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine formic acid salt as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.08 (d, *J* = 2.1 Hz, 1H), 8.52 (d, *J* = 2.1 Hz, 1H), 8.33-8.24 (m, 2H), 8.01 (s, 1H), 7.81 (s, 1H), 3.88 (s, 3H), 3.73 (t, *J* = 5.1 Hz, 2H), 3.60 (t, *J* = 6.0 Hz, 2H), 3.15 - 3.12 (m, 2H), 3.04 - 2.98 (m, 2H), 2.04 - 1.93 (m, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₅H₁₉N, 298.2 found, 298.1.

Step 2. (R)-1-phenylethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,4-diazepane-1-carboxylate (Compound **337**)

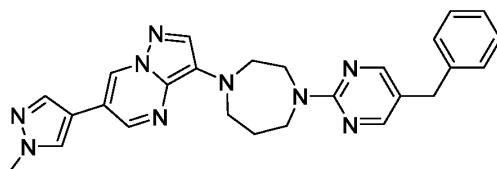


[0545] To a solution of 3-(1,4-diazepan-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine formic acid salt (200 mg, 0.61 mmol, as prepared in the previous step) and (R)-1-phenylethanol (89 mg, 0.73 mmol) in pyridine (5 mL) was added triphosgene (54.1 mg, 0.18 mmol) then the reaction was stirred at rt under nitrogen for 6 h. The mixture was concentrated under reduced pressure then the residue was dissolved in water (30 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 47.7 mg (18%) of

(R)-1-phenylethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,4-diazepane-1-carboxylate (Compound **337**) as a red solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm) 9.06 (dd, $J = 6.1, 2.1$ Hz, 1H), 8.51 (dd, $J = 6.5, 2.2$ Hz, 1H), 8.25 (s, 1H), 8.01 (d, $J = 0.8$ Hz, 1H), 7.79 (d, $J = 1.7$ Hz, 1H), 7.36 – 7.09 (m, 5H), 5.70 – 5.48 (m, 1H), 3.89 (s, 3H), 3.85 – 3.48 (m, 6H), 3.59–3.34 (m, 2H), 2.03 – 1.68 (m, 2H), 1.44 – 1.25 (m, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{24}\text{H}_{27}\text{N}_7\text{O}_2$, 446.2, found, 446.2; LCMS purity: 254 nm: 99.4%

Example 15: Synthesis of Exemplary Compound 338

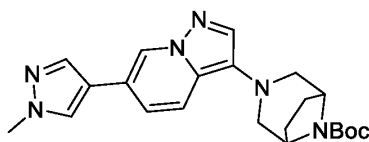
3-(4-(5-benzylpyrimidin-2-yl)-1,4-diazepan-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine (Compound **338**)



[0546] To a solution of 3-(1,4-diazepan-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine formate (200 mg, 0.58 mmol, as prepared in Example 12, Step 1) and 5-benzyl-2-chloropyrimidine (Compound **S88**) (143 mg, 0.70 mmol) in IPA (3 mL) was added DIEA (225.8 mg, 1.72 mmol) then the reaction was stirred at 90°C under nitrogen for 16 h. The mixture was cooled to rt and concentrated under reduced pressure, then the residue was purified by Prep-HPLC to afford 15.6 mg (6%) of 3-(4-(5-benzylpyrimidin-2-yl)-1,4-diazepan-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine (Compound **338**) as a red solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm) 9.01 (s, 1H), 8.50 (s, 1H), 8.27–8.18 (m, 3H), 8.00 (s, 1H), 7.77 (s, 1H), 7.32–7.24 (m, 2H), 7.23–7.14 (m, 3H), 3.96 – 3.86 (m, 5H), 3.78 – 3.62 (m, 6H), 3.53 (t, $J = 5.9$ Hz, 2H), 1.97 (t, $J = 5.9$ Hz, 2H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{26}\text{H}_{27}\text{N}_9$, 466.2; found, 466.2; LCMS purity: 254 nm: 99.2%

Example 16: Synthesis of Exemplary Compound 339

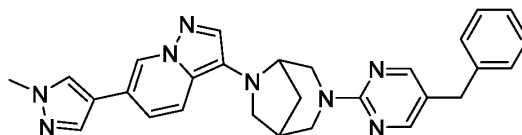
tert-butyl 3-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (Compound **339**)



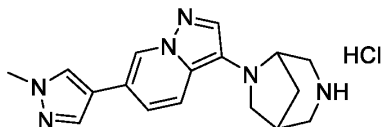
[0547] To a glass vial containing 3-iodo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (220 mg, 0.68 mmol, as prepared for Compound **S57**, Step 1), *tert*-butyl-3,8-diazabicyclo[3.2.1]octane-8 carboxylate (433 mg, 2.04 mmol), CuI (52 mg, 0.27 mmol), and K₃PO₄ (288 mg, 1.36 mmol) under nitrogen was added 1-butanol (4 mL) and 1,2-ethanediol (0.66 mL), then the reaction was heated to 100°C for 44 h. The mixture was cooled to rt, diluted with DCM and washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with acetone / DCM to afford 154 mg (56%) of *tert*-butyl 3-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (Compound **339**). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.45 (br. s., 1H) 7.74 (s, 1H) 7.70 (s, 1H) 7.67 (br. s., 1H) 7.61 (s, 1H) 7.47 (d, *J* = 8.7 Hz, 1H) 7.11 (d, *J* = 8.6 Hz, 1H) 4.34 (br. s., 4H) 3.97 (s, 3H) 3.09 (br. s., 4H) 2.09 (m, 2H) 1.99 (m, 2H) 1.51 (s, 9H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₂H₂₉N₆O₂, 409.2; found, 409.2; HPLC purity: 210 nm: 98.8%; 254 nm: 97.6%.

Example 17: Synthesis of Exemplary Compound 340

3-(3-(5-benzylpyrimidin-2-yl)-3,6-diazabicyclo[3.2.1]octan-6-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **340**)

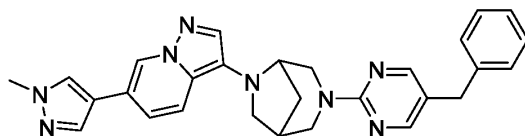


Step 1. Preparation of 3-(3,6-diazabicyclo[3.2.1]octan-6-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine hydrochloride salt



[0548] To a solution of tert-butyl 6-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-3,6-diazabicyclo[3.2.1]octane-3-carboxylate (Compound **334**) (40 mg, 0.10 mmol) in DCM (0.5 mL) cooled to 0°C was added 4M HCl in dioxane (2.6 mL) then the reaction was warmed to rt and stirred for 1 h. The mixture was concentrated under reduced pressure to afford 30 mg (89%) of 3-(3,6-diazabicyclo[3.2.1]octan-6-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine hydrochloride salt as a yellow solid. MS (ESI) m/z $[M+H]^+$ calcd. for $C_9H_8N_2O_2$, 309.2; found, 309.3.

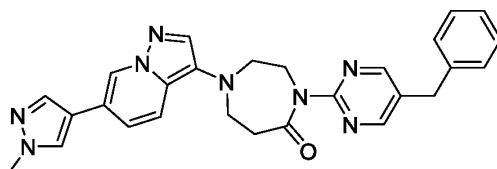
Step 2. Preparation of 3-(3-(5-benzylpyrimidin-2-yl)-3,6-diazabicyclo[3.2.1]octan-6-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **340**)



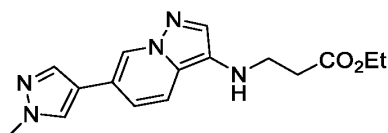
[0549] To a solution of 3-(3,6-diazabicyclo[3.2.1]octan-6-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine hydrochloride salt (28 mg, 0.08 mmol, as prepared in the previous step) and 5-benzyl-2-chloropyrimidine (Compound **S88**) (16.6 mg, 0.08 mmol) in IPA (2 mL) was added DIEA (31.5 mg, 0.24 mmol) then the reaction was stirred at 100°C for 24 h. The resulting mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by Prep-HPLC to afford 16.7 mg (43%) of 3-(3-(5-benzylpyrimidin-2-yl)-3,6-diazabicyclo[3.2.1]octan-6-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **340**) as a yellow solid. 1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.62 (s, 1H), 8.17 (s, 1H), 8.14 (s, 2H), 7.92 (d, $J = 0.4$ Hz, 1H), 7.66 (d, $J = 9.4$ Hz, 1H), 7.46 (s, 1H), 7.30 – 7.20 (m, 2H), 7.19 – 7.12 (m, 3H), 7.06 (dd, $J = 9.3, 1.6$ Hz, 1H), 4.40 (d, $J = 12.6$ Hz, 1H), 4.29 (d, $J = 12.4$ Hz, 1H), 4.19 – 4.11 (m, 1H), 3.87 (s, 3H), 3.70 (s, 2H), 3.63 – 3.56 (m, 1H), 3.17 (d, $J = 8.5$ Hz, 1H), 3.08 (d, $J = 12.0$ Hz, 1H), 2.85 (d, $J = 12.5$ Hz, 1H), 2.72 – 2.60 (m, 1H), 2.13 – 2.02 (m, 1H), 1.88 (d, $J = 10.7$ Hz, 1H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{28}H_{28}N_8$, 477.2; found, 477.50; HPLC purity: 254 nm: 95.5%.

Example 18: Synthesis of Exemplary Compound 341

4-(5-benzylpyrimidin-2-yl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepan-5-one (Compound **341**)

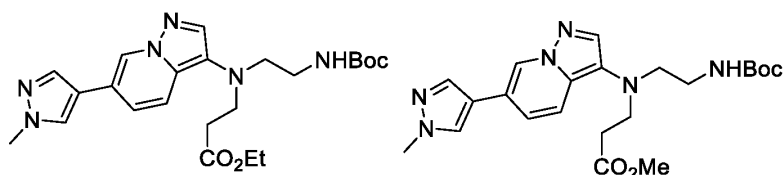


Step 1. Preparation of ethyl 3-((6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)amino)propanoate



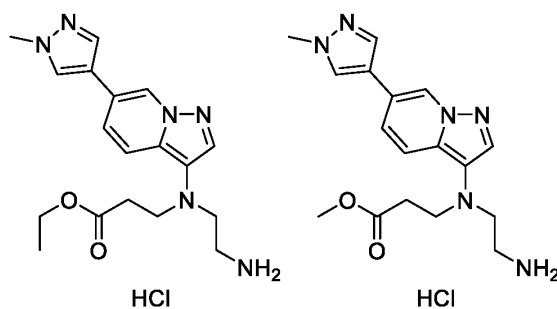
[0550] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-amine (Compound **S56**) (800 mg, 3.75 mmol) and ethyl 3-iodopropanoate (1.28 g, 5.62 mmol) in DMF (50 mL) was added K_2CO_3 (1.04 g, 7.50 mmol) then the reaction was stirred at 90°C under nitrogen overnight. The mixture was cooled to rt then purified by reversed-phase flash chromatography with a C18 silica gel column eluting with 10% to 60% ACN / water (0.1%FA) to afford 370 mg (31%) of ethyl 3-((6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)amino)propanoate as a yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.68 (s, 1H), 8.17 (s, 1H), 7.93 (s, 1H), 7.62 – 7.52 (m, 2H), 7.16 (d, $J = 9.2$ Hz, 1H), 4.75 (t, $J = 6.6$ Hz, 1H), 4.06 (q, $J = 7.1$ Hz, 2H), 3.86 (s, 3H), 3.30 (t, $J = 6.6$ Hz, 2H), 2.56 (t, $J = 6.7$ Hz, 2H), 1.18 (t, $J = 7.1$ Hz, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{16}H_{19}N_5O_2$, 314.1; found, 314.1.

Step 2. Preparation of a mixture of ethyl 3-((2-((tert-butoxycarbonyl)amino)ethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)amino)propanoate and methyl 3-((2-((tert-butoxycarbonyl)amino)ethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)amino)propanoate



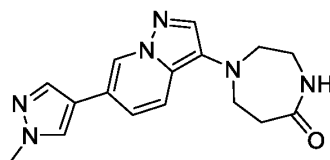
[0551] To a solution of ethyl 3-{[6-(1-methylpyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]amino}propanoate (320 mg, 1.02 mmol, as prepared in the previous step) and tert-butyl N-(2-oxoethyl)carbamate (812.7 mg, 5.10 mmol) in MeOH (10 mL) was added NaHCO_3 (257.3 mg, 3.06 mmol) then the reaction was stirred at 60°C under nitrogen for 72 h. The mixture was cooled to rt and concentrated under reduced pressure. The residue was dissolved in THF (10mL), the solution was cooled to 0°C then borane THF (877.6 mg, 10.21 mmol) was added dropwise over 1 minute. The resulting mixture was warmed to rt and stirred overnight. The reaction was concentrated under reduced pressure, then the residue was dissolved in water (50 mL) and extracted with DCM (3 x 50mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 40 mg (9%) of ethyl 3-((2-((tert-butoxycarbonyl)amino)ethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)amino)propanoate as a white solid and 110 mg (24%) of methyl 3-((2-((tert-butoxycarbonyl)amino)ethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)amino)propanoate as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.81 (t, $J = 1.2$ Hz, 1H), 8.21 (s, 1H), 7.96 (d, $J = 0.8$ Hz, 1H), 7.84 (s, 1H), 7.55 (d, $J = 9.3$ Hz, 1H), 7.34 – 7.31 (m, 1H), 6.71 – 6.70 (m, 1H), 3.87 (s, 3H), 3.54 (s, 3H), 3.17 (d, $J = 5.3$ Hz, 2H), 3.08 – 2.87 (m, 4H), 2.40 (t, $J = 6.8$ Hz, 2H), 1.36 (s, 9H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{23}\text{H}_{32}\text{N}_6\text{O}_4$, 457.2; found, 457.2 and MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{22}\text{H}_{30}\text{N}_6\text{O}_4$, 443.2; found, 443.2

Step 3. Preparation of a mixture of ethyl 3-((2-aminoethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)amino)propanoate hydrochloride salt and methyl 3-((2-aminoethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)amino)propanoate hydrochloride salt



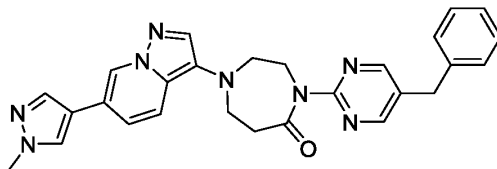
[0552] To a solution of a mixture of ethyl 3-((2-((tert-butoxycarbonyl)amino)ethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)amino)propanoate and methyl 3-((2-((tert-butoxycarbonyl)amino)ethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)amino)propanoate (150 mg, 0.33, as prepared in the previous step) in DCM (5 mL) was added 4M HCl in dioxane (119.7 mg, 3.30 mmol) then the reaction was stirred at rt under nitrogen for 1 h. The mixture was concentrated under reduced pressure to afford 150 mg of a mixture of ethyl 3-((2-aminoethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)amino)propanoate hydrochloride salt and methyl 3-((2-aminoethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)amino)propanoate hydrochloride salt as a white solid. MS (ESI) m/z $[M+H]^+$ calcd. for $C_{18}H_{24}N_6O_2$, 357.2; found, 357.2 and MS (ESI) m/z $[M+H]^+$ calcd. for $C_{17}H_{22}N_6O_2$, 343.2; found, 343.2.

Step 4. Preparation of 1-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepan-5-one



[0553] To a solution of the mixture of ethyl 3-((2-aminoethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)amino)propanoate hydrochloride salt and methyl 3-((2-aminoethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)amino)propanoate hydrochloride salt (150 mg, 0.43 mmol, as prepared in the previous step) in MeOH (5 mL) was added 1,5,7-triazabicyclo[4.4.0]dec-5-ene (121.9 mg, 0.87 mmol) then the reaction was stirred at 80°C under nitrogen overnight. The mixture was cooled to rt, then concentrated under reduced pressure. The residue was dissolved in water (20 mL) then extracted with DCM (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-TLC (MeOH / DCM 1:1) to afford 100 mg (74%) of 1-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepan-5-one as a yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.81 (s, 1H), 8.22 (s, 1H), 7.96 (s, 1H), 7.79 (s, 1H), 7.68 – 7.65 (m, 1H), 7.59 (dd, J = 9.2, 1.0 Hz, 1H), 7.32 (dd, J = 9.3, 1.5 Hz, 1H), 5.76 (s, 1H), 3.86 (s, 3H), 3.18 – 3.09 (m, 4H), 2.64 – 2.57 (m, 2H), 1.23 (s, 1H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{16}H_{18}N_6O$, 311.1; found, 311.1.

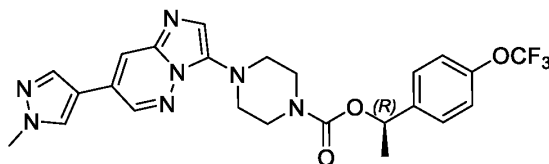
Step 5. 4-(5-benzylpyrimidin-2-yl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepan-5-one (Compound **341**)



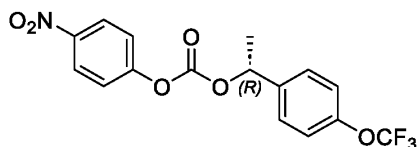
[0554] To a solution of 1-[6-(1-methylpyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]-1,4-diazepan-5-one (100 mg, 0.32 mmol, as prepared in the previous step) and 5-benzyl-2-chloropyrimidine (Compound **S88**) (79.1 mg, 0.38 mmol) in dioxane (10 mL) were added $\text{Pd}_2(\text{dba})_3$ (44.2 mg, 0.05 mmol), XantPhos (27.9 mg, 0.05 mmol), and K_3PO_4 (136.7 mg, 0.64 mmol) then the reaction was stirred at 90°C under nitrogen overnight. The mixture was cooled to rt and concentrated under reduced pressure. The residue was dissolved in water (20 mL) then extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 52.7 mg (34%) of 4-(5-benzylpyrimidin-2-yl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepan-5-one (Compound **341**) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.83 (s, 1H), 8.72 (s, 2H), 8.23 (s, 1H), 7.97 (s, 1H), 7.84 (s, 1H), 7.63 (d, $J = 9.3$ Hz, 1H), 7.42 – 7.28 (m, 5H), 7.25 – 7.21 (m, 1H), 4.18 – 4.16 (m, 2H), 4.00 (s, 2H), 3.87 (s, 3H), 3.29 – 3.25 (m, 4H), 3.00 – 2.92 (m, 2H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{27}\text{H}_{28}\text{N}_8\text{O}$, 479.2; found, 479.2; LCMS purity: 254 nm: 99.7%.

Example 19: Synthesis of Exemplary Compound 342

(R)-1-(4-(trifluoromethoxy)phenyl)ethyl 4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl)piperazine-1-carboxylate (Compound **342**)

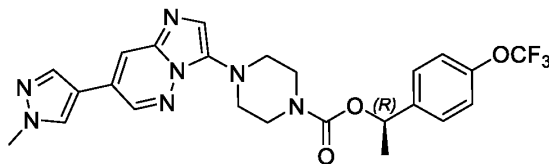


Step 1. Preparation of 4-nitrophenyl (1R)-1-[4-(trifluoromethoxy)phenyl]ethyl carbonate



[0555] To a solution of (R)-1-[4-(trifluoromethoxy)phenyl]ethanol (300 mg, 1.46 mmol) in DCM (15 mL) cooled to 0°C was added pyridine (0.50 mL, 6.2 mmol) then the mixture was stirred for 10 minutes, then 4-nitrophenyl chloroformate (1.21 g, 2.94 mmol) was added in one portion. The reaction was warmed to rt and stirred overnight. The mixture was filtered, then the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 0-80% DCM / hexanes to afford 0.54 g (94%) of 4-nitrophenyl (1R)-1-[4-(trifluoromethoxy)phenyl]ethyl carbonate as a white solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.27 (d, *J*=9.17 Hz, 2H) 7.47 (d, *J*=8.56 Hz, 2H) 7.37 (d, *J*=9.17 Hz, 2H) 7.20 - 7.30 (m, 2H) 5.85 (q, *J*=6.60 Hz, 1H) 1.71 (d, *J*=6.72 Hz, 3H).

Step 2. Preparation of (R)-1-[4-(trifluoromethoxy)phenyl]ethyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]piperazine-1-carboxylate (Compound **342**)

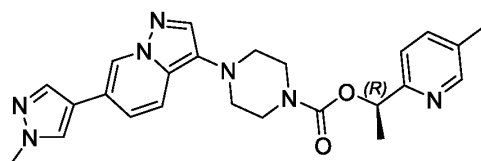


[0556] To a solution of 4-nitrophenyl (R)-1-[4-(trifluoromethoxy)phenyl]ethyl carbonate (144 mg, 0.39 mmol, as prepared in the previous step) in ACN (3.1 mL) was added 7-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylimidazo[1,2-b]pyridazine trihydrochloride salt (84 mg, 0.21 mmol, as prepared in Example **64**, Step 2) followed by DIEA (1.1 mL, 6.4 mmol) then the reaction was stirred at rt under nitrogen for 22 h. The mixture was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 0-100% (10% IPA in DCM)/ DCM, then the combined fractions were concentrated under reduced pressure. The residue was suspended in 25% ether in hexanes then concentrated under reduced pressure. This was repeated four times to afford 78 mg (70%) of (R)-1-[4-(trifluoromethoxy)phenyl]ethyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]piperazine-1-carboxylate (Compound **342**) as a yellow solid. ¹H NMR (400 MHz, CD₃OD) δ (ppm) 8.74 (d, *J*=2.08 Hz, 1H) 8.21 (s, 1H) 8.02 (s, 1H) 7.97 (d, *J*=1.96 Hz, 1H) 7.49 (d, *J*=8.68 Hz, 2H) 7.28 (d, *J*=7.95 Hz, 3H) 5.83

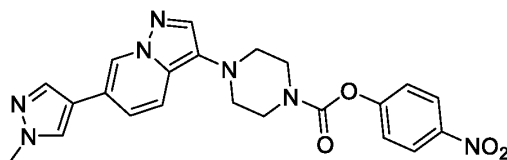
(q, $J=6.56$ Hz, 1H) 3.97 (s, 3H) 3.60 - 3.90 (m, 4H) 3.27 (br. s., 4H) 1.57 (d, $J=6.60$ Hz, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{25}F_3N_7O_3$, 516.2; found, 516.2; HPLC purity: 210 nm: 97.0%; 254 nm: 97.0%.

Example 20: Synthesis of Exemplary Compound 343

(R)-1-(5-methylpyridin-2-yl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound 343)

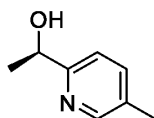


Step 1. Preparation of 4-nitrophenyl 4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxylate



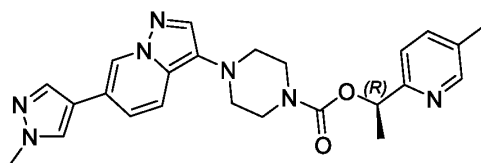
[0557] Pyridine (0.229 mL, 2.83 mmol) was added to a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylpyrazolo[1,5-a]pyridine (Compound 12) (0.400 g, 1.42 mmol) and 4-nitrophenyl chloroformate (0.314 g, 1.56 mmol) in ACN (10 mL) at rt. The solvent was removed under reduced pressure, then MTBE (50 mL) was added to the residue and the mixture was stirred at rt overnight. The solid was collected by filtration and air dried to give 600 mg (100%) of 4-nitrophenyl 4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxylate as a yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.50 (s, 1H), 8.23 - 8.37 (m, 2H), 7.72 - 7.82 (m, 2H), 7.64 (s, 1H), 7.48 - 7.58 (m, 1H), 7.33 - 7.41 (m, 2H), 7.20 (dd, $J=9.17, 1.47$ Hz, 1H), 4.00 (s, 3H) 3.91 (br. s., 2H), 3.82 (br. s., 2H), 3.08 - 3.21 (m, 4H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{22}H_{22}N_7O_4$: 448.4; found: 448.1; HPLC purity: 210 nm: 90.4%; 254 nm: 89.3%

Step 2. Preparation of (R)-1-(5-methylpyridin-2-yl)ethanol



[0558] To a solution of (R,R)-Ts-DENEB (0.0480 g, 0.0740 mmol) in toluene (5 mL) was added 1-(5-methylpyridin-2-yl)ethanone (1.00 g, 7.40 mmol) under nitrogen at rt. TEA (2.58 mL, 18.5 mmol) was added followed by formic acid (0.698 mL, 18.5 mmol) then the reaction was stirred at rt overnight. The mixture was partitioned between sat. aqueous NaHCO₃ (20 mL) and EtOAc (20 mL) then the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with sat. aqueous NaHCO₃ (20 mL), then the combined aqueous layers were extracted with EtOAc (20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 0-80% acetone / DCM to afford 700 mg (69%) of (R)-1-(5-methylpyridin-2-yl)ethanol as a light brown oil. ¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.36 (s, 1H), 7.50 (ddt, J=7.96, 1.40, 0.63, 0.63 Hz, 1H), 7.18 (d, J=7.92 Hz, 1H), 4.86 (q, J=6.52 Hz, 1H), 4.29 (br. s., 1H), 2.34 (s, 3H), 1.49 (d, J=6.61 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₈H₁₂NO: 138.2; found: 138.0.

Step 3. Preparation of (R)-1-(5-methylpyridin-2-yl)ethyl 4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1, 5-a]pyridin-3-yl]piperazine-1-carboxylate (Compound **343**)

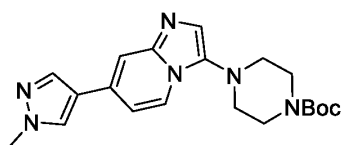


[0559] To a solution of (R)-1-(5-methylpyridin-2-yl)ethanol (0.100 g, 0.729 mmol, as prepared in the previous step) in DMF (6 mL) cooled to 0°C under nitrogen was added NaH (267.3 mg, 0.67 mmol) then the reaction was stirred at 0°C for 20 minutes. 4-Nitrophenyl 4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxylate (0.309 g, 0.607 mmol, as prepared in Step 1) was added then the reaction was stirred at 0°C for 30 minutes, then warmed to rt and stirred overnight. The mixture was diluted with sat. aqueous NaHCO₃ (50 mL) and EtOAc (50 mL). The layers were separated and the EtOAc layer was washed with water (3 x 20 mL) and sat. aqueous NaHCO₃ (20 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 5% MeOH / DCM to afford 40 mg (15%) of (R)-1-(5-methylpyridin-2-yl)ethyl 4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxylate (Compound **343**) as an orange

solid. ^1H NMR (300 MHz, CDCl_3) δ (ppm) 8.37 - 8.56 (m, 2H), 7.71 (s, 1H), 7.75 (s, 1H), 7.61 (s, 1H), 7.50 (d, $J=9.22$ Hz, 2H), 7.20 - 7.34 (m, 1H), 7.15 (dd, $J=9.17, 1.26$ Hz, 1H), 5.87 (q, $J=6.67$ Hz, 1H), 3.98 (s, 3H), 3.74 (br. s., 4H), 2.96 - 3.14 (m, 4H), 2.34 (s, 3H), 1.63 (d, $J=6.61$ Hz, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{24}\text{H}_{28}\text{N}_7\text{O}_2$: 446.5; found: 446.2; HPLC purity: 210 nm: 100.0%; 254 nm: 100.0%.

Example 21: Synthesis of Exemplary Compound 345

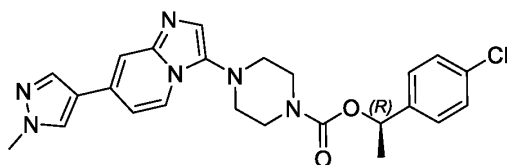
tert-butyl 4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridin-3-yl)piperazine-1-carboxylate (Compound 345)



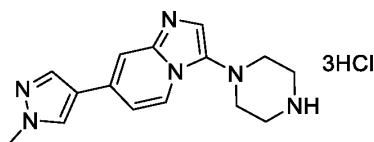
[0560] To a glass vial containing 3-bromo-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine (Compound S7) (0.250 g, 0.90 mmol) and *tert*-butyl-1-piperazinecarboxylate (0.672 g, 3.61 mmol) was added NaOtBu (0.152 g, 1.35 mmol) and tBuXPhos Pd G1 (0.062 g, 0.09 mmol) and the headspace was flushed with nitrogen. To another glass vial was added tBuOH (2 mL) and dioxane (2 mL) and the mixture was sparged with nitrogen for 15 minutes at rt. The solvent mixture was added to the vial containing the solids then the reaction was heated to 50°C for 2 h, cooled to rt, and concentrated under reduced pressure. The residue was treated with ACN then concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 20% MeOH (0.1%TEA) / DCM to afford 312 mg (90%) of tert-butyl 4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridin-3-yl)piperazine-1-carboxylate (Compound 345) as an amber oil. ^1H NMR (400 MHz, CDCl_3) δ (ppm) 7.97 (d, $J=7.1$ Hz, 1H), 7.82 (s, 1H), 7.73 (s, 1H), 7.64 (s, 1H), 7.26 (s, 1H), 3.98 (s, 3H), 3.98 (s, 3H), 3.65 (m, 4H), 3.01 (m, 4H), 1.50 (s, 9H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{27}\text{N}_6\text{O}_2$, 383.2; found, 383.3; HPLC purity: 210 nm: 86.8%; 254 nm: 87.4%.

Example 22: Synthesis of Exemplary Compound 344

(R)-1-(4-chlorophenyl)ethyl 4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **344**)

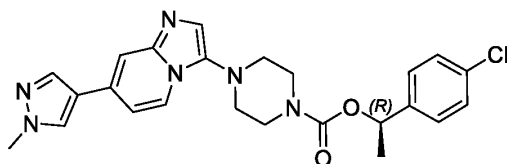


Step 1. Preparation of 7-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylimidazo[1,2-a]pyridine trihydrochloride salt



[0561] To solution of tert-butyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridin-3-yl]piperazine-1-carboxylate (Compound **345**) (0.300 g, 0.78 mmol) in EtOAc (5 mL) was heated to 50°C then conc. HCl (0.32 mL, 3.92 mmol) was slowly added. After 1 h MTBE (9 mL) was added with vigorous stirring at 50°C for 30 minutes, then the mixture was cooled to rt, filtered, and the filter cake was washed with MTBE. The solid was dried in a vacuum oven to afford 296 mg (97%) of 7-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylimidazo[1,2-a]pyridine trihydrochloride salt as a tan solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.73 (s, 1H), 8.64 (s, 1H), 8.25 (s, 1H), 8.03 (s, 1H), 7.96 (s, 1H), 7.73 (dd, *J* = 7.2, 1.5 Hz, 1H), 3.92(s, 3H), 3.31 (bs, 8H); MS (ESI+, *m/z*): Calcd. for C₁₅H₁₉N₆: 283.2. Found: 283.1; HPLC purity: 210 nm: 66%; 254 nm: 74%.

Step 2. Preparation of (R)-1-(4-chlorophenyl)ethyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridin-3-yl]piperazine-1-carboxylate (Compound **344**)

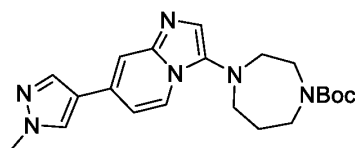


[0562] To a solution of (R)-1-(4-chlorophenyl)ethyl (2,5-dioxopyrrolidin-1-yl) carbonate (Compound **S95**) (297 mg, 1.00 mmol) in ACN (9 mL) was added 7-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylimidazo[1,2-a]pyridine trihydrochloride salt (290 mg, 0.740 mmol,

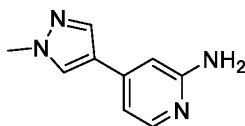
as prepared in the previous step) and DIEA (3 mL, 18.0 mmol), then the reaction was stirred for 90 minutes. The mixture was concentrated under reduced pressure then the residue was partitioned between water (adjusted to pH 9) and EtOAc. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with MeOH (0.1% TEA) / DCM to afford 185 mg (54%) of (R)-1-(4-chlorophenyl)ethyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridin-3-yl]piperazine-1-carboxylate (Compound **344**) as a foam solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.30 (s, 1H) 8.16 (d, *J*=7 Hz, 1H) 8.02 (s, 1H) 7.70 (s, 1H) 7.44 (m, 4H), 7.24 (s, 1H) 7.15 (dd, *J*=7.2, 1.5 Hz, 1H) 5.75 (q, *J*=6.5, 1H) 3.88 (s, 3H) 3.64 (m, 4H) 2.97 (br. s., 4H) 1.49 (d, *J*=6.6, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₆ClN₆O₂: 465.2, Found: 465.2; HPLC purity: 210 nm: 100.0%; 254 nm: 100.0%.

Example 23: Synthesis of Exemplary Compound 346

tert-butyl 4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridin-3-yl)-1,4-diazepane-1-carboxylate (Compound **346**)



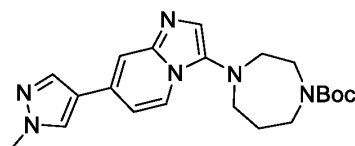
Step 1. Preparation of 4-(1-methyl-1H-pyrazol-4-yl)pyridin-2-amine



[0563] To a solution of 4-bromopyridin-2-amine (10.0 g, 57.8 mmol) in dioxane (175 mL) and H₂O (35 mL) was added 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (15.6 g, 75.1 mmol), Na₂CO₃ (12.2 g, 115.6 mmol), and Pd(dppf)Cl₂ (1.2 g, 1.7 mmol) at rt under nitrogen then the reaction was stirred at 100°C under nitrogen for 4 h. The mixture was cooled to rt, filtered through a Celite pad, and the filtrate was poured into H₂O (300 mL) and extracted with EtOAc (4 x 150 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel

chromatography to afford 9.8 g (95%) of 4-(1-methyl-1H-pyrazol-4-yl)pyridin-2-amine as a yellow solid. ¹HNMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.14 (s, 1H), 7.84 (d, *J*= 5.2Hz, 2H), 7.82 (s, 1H), 6.67 (d, *J*=5.2Hz, 1H), 6.55 (s, 1H), 5.80 (s, 2H), 3.86 (s, 3H).

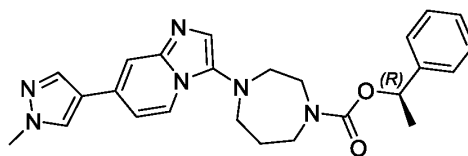
Step 2. Preparation of tert-butyl 4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridin-3-yl)-1,4-diazepane-1-carboxylate (Compound **346**)



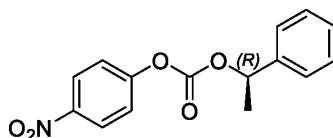
[0564] To a solution of 4-(1-methyl-1H-pyrazol-4-yl)pyridin-2-amine (1.0 g, 5.7 mmol, as prepared in the previous step), di-tert-butyl 4,4'-(1,2-bis(1H-benzo[d][1,2,3]triazol-1-yl)ethane-1,2-diyl)bis(1,4-diazepane-1-carboxylate) (Compound **S48**) (5.6 g, 8.5 mmol) in DCM (10 mL) was added ZnBr₂ (3.8 g, 17.1 mmol) then the reaction was stirred at reflux under nitrogen for 5 h. The reaction mixture was cooled to rt, poured into 1N NaOH (40 mL), and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography and prep-HPLC to afford 120 mg (5%) of tert-butyl 4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridin-3-yl)-1,4-diazepane-1-carboxylate (Compound **346**) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.26 (s, 1H), 8.20~8.22 (m, 1H), 7.86 (s, 1H), 7.82~7.84 (m, 1H), 7.23~7.33 (d, *J*=6.8 Hz, 1H), 7.28 (s, 1H), 3.89 (s, 3H), 3.52~3.54 (m, 4H), 3.14~3.18 (m, 4H), 1.82~1.83 (m, 2H), 1.41 (d, *J*=11.6 Hz, 9H).

Example 24: Synthesis of Exemplary Compound 347

(R)-1-phenylethyl 4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridin-3-yl)-1,4-diazepane-1-carboxylate (Compound **347**)

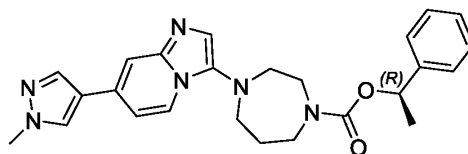


Step 1. Preparation of (R)-4-nitrophenyl (1-phenylethyl) carbonate



[0565] To a solution of 4-nitrophenyl chloroformate (4.0 g, 19.8 mmol) and (R)-1-phenylethanol (1.21 g, 9.9 mmol) in DCM (50 mL) was added pyridine (1.57 g, 19.8 mmol) at rt then the reaction was stirred at rt for 3h. The mixture was concentrated under reduced pressure then the residue was purified by silica gel chromatography to afford 3.7 g (65%) of (R)-4-nitrophenyl (1-phenylethyl) carbonate as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.21-8.28 (m, 2H), 7.25-7.41 (m, 7H), 5.82-5.87 (m, 1H), 1.70 (d, *J*= 6.4 Hz, 3H).

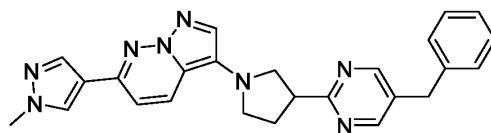
Step 2. Preparation of (R)-1-phenylethyl 4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridin-3-yl)-1,4-diazepane-1-carboxylate (Compound **347**)



[0566] To a solution of 3-(1,4-diazepan-1-yl)-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine hydrochloride salt (1.69 g, 5.1 mmol, as prepared in Example **29**, Step 1) in ACN (15 mL) was added (R)-4-nitrophenyl (1-phenylethyl) carbonate (1.47 g, 5.1 mmol, as prepared in the previous step) and DIEA (1.98 g, 15.3 mmol) then the reaction was stirred at 80°C under nitrogen for 4 h. The mixture was cooled to rt, then poured into water (100 mL) and extracted with EtOAc (4 x 30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by prep-HPLC to afford 169 mg (8%) of (R)-1-phenylethyl 4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridin-3-yl)-1,4-diazepane-1-carboxylate (Compound **347**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.28 (s, 1H), 8.02 (s, 1H), 8.00 (s, 1H), 7.71 (s, 1H), 7.15~7.35 (m, 7H), 5.75~5.78 (m, 1H), 3.88 (s, 3H), 3.66~3.68 (m, 2H), 3.56~3.61 (m, 2H), 3.12~3.24 (m, 4H), 1.86 (s, 2H), 1.45~1.49 (m, 3H).

Example 25: Synthesis of Exemplary Compound 348

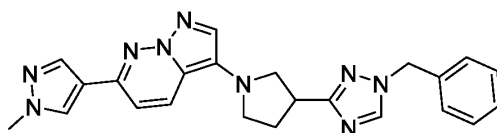
3-(3-(5-benzylpyrimidin-2-yl)pyrrolidin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-b]pyridazine (Compound **348**)



[0567] To a solution of 5-benzyl-2-pyrrolidin-3-ylpyrimidine (Compound **S100**) (344.2 mg, 1.44 mmol) in dioxane (8 mL) was added 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-b]pyridazine (Compound **S8**) (200.0 mg, 0.72 mmol), Cs₂CO₃ (468.6 mg, 1.44 mmol), and tBuXPhos Pd G1 (74.1 mg, 0.11 mmol) at rt under nitrogen then the reaction was stirred at 110°C under nitrogen for 10 h. The mixture was cooled to rt, then concentrated under reduced pressure. The residue purified by prep-HPLC to afford 7.0 mg (2%) of 3-(3-(5-benzylpyrimidin-2-yl)pyrrolidin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-b]pyridazine (Compound **348**) as a yellow solid. ¹HNMR (400 MHz, CDCl₃) δ (ppm) 8.55 (s, 2H), 7.94-7.98 (m, 3H), 7.45 (s, 2H), 7.31-7.35 (m, 1H), 7.27-7.28 (m, 1H), 7.19 (d, *J* = 7.6 Hz, 2H), 6.83 (d, *J* = 9.6 Hz, 1H), 3.97 (s, 3H), 3.82-3.84 (m, 2H), 3.76-3.80 (m, 3H), 3.53-3.59 (m, 2H), 2.48-2.52 (m, 2H).

Example 26: Synthesis of Exemplary Compound 349

3-(3-(1-benzyl-1H-1,2,4-triazol-3-yl)pyrrolidin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-b]pyridazine (Compound **349**)

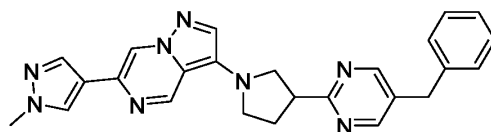


[0568] To a solution of 1-benzyl-3-(pyrrolidin-3-yl)-1H-1,2,4-triazole (Compound **S101**) (492.5 mg, 2.16 mmol) in dioxane (10 mL) was added 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-b]pyridazine (Compound **S8**) (300.0 mg, 1.08 mmol), Cs₂CO₃ (1.05 g, 3.24 mmol), and tBuXPhos Pd G1 (111.1 mg, 0.16 mmol) at rt under nitrogen then the reaction was stirred at 110°C under nitrogen for 16 h. The reaction mixture was cooled to rt, then concentrated under reduced pressure. The residue was purified by prep-HPLC to afford 4.0 mg (1%) of 3-(3-(1-benzyl-1H-1,2,4-triazol-3-yl)pyrrolidin-1-yl)-6-(1-methyl-

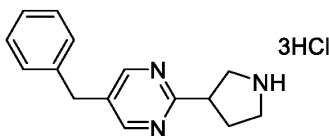
1H-pyrazol-4-yl)pyrazolo[1,5-b]pyridazine (Compound **349**) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 9.24 (d, *J* = 9.2 Hz, 1H), 8.43 (s, 1H), 8.38 (s, 1H), 8.05 (d, *J* = 10.0 Hz, 2H), 7.40-7.45 (m, 2H), 7.33-7.36 (m, 3H), 7.21-7.22 (m, 1H), 5.38 (s, 2H), 4.35-4.42 (m, 3H), 4.10-4.23 (m, 2H), 4.01 (s, 3H), 2.95-3.00 (m, 1H), 2.64-2.70 (m, 1H).

Example 27: Synthesis of Exemplary Compound 350

3-(3-(5-benzylpyrimidin-2-yl)pyrrolidin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine (Compound **350**)

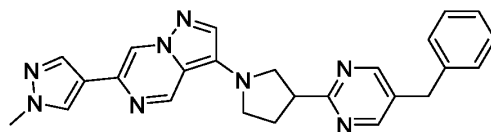


Step 1. Preparation of 5-benzyl-2-(pyrrolidin-3-yl)pyrimidine trihydrochloride salt



[0569] To a solution of tert-butyl 3-(5-benzylpyrimidin-2-yl)pyrrolidine-1-carboxylate (3.00 g, 8.84 mmol, as prepared for Compound **S100**, Step 2) in dioxane (20 mL) was added 4M HCl in dioxane (10 mL) at rt then the reaction was stirred at rt for 2 h. The precipitated solids were collected by filtration, washed with dioxane (2 x 3 mL), and dried to afford 2.4 g (113%) of 5-benzyl-2-(pyrrolidin-3-yl)pyrimidine trihydrochloride salt as a dark green oil: MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₅H₁₇N₃, 240.1; found, 240.1.

Step 2. Preparation of 3-(3-(5-benzylpyrimidin-2-yl)pyrrolidin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine (Compound **350**)

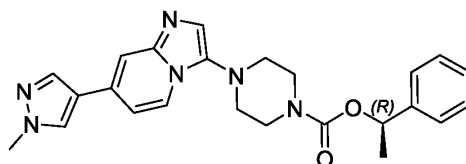


[0570] To a solution of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine (Compound **S5**) (200 mg, 0.719 mmol) and 5-benzyl-2-(pyrrolidin-3-yl)pyrimidine trihydrochloride salt (502 mg, 1.44 mmol, as prepared in the previous step) in tBuOH (12 mL) and dioxane (4 mL) was added KOtBu (807 mg, 7.19 mmol) and tBuXPhos Pd G1 (99 mg, 0.144 mmol) under nitrogen then the reaction was stirred at 90°C under nitrogen for

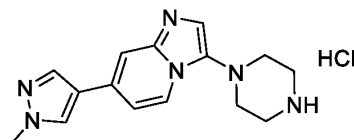
40 h. The mixture was cooled to rt, then concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc / PE (1:1) and Prep-HPLC to afford 3.6 mg (1%) of 3-(3-(5-benzylpyrimidin-2-yl)pyrrolidin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine (Compound **350**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.08 (d, *J* = 1.4 Hz, 1H), 8.73 (d, *J* = 1.4 Hz, 1H), 8.70 (s, 2H), 8.16 (s, 1H), 7.99 – 7.94 (m, 1H), 7.55 (s, 1H), 7.36 – 7.25 (m, 4H), 7.25 – 7.17 (m, 1H), 3.97 (s, 2H), 3.87 (s, 3H), 3.85 – 3.77 (m, 2H), 3.71 – 3.65 (m, 1H), 3.61 – 3.53 (m, 2H), 2.49 – 2.29 (m, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₄N₈, 437.2; found, 437.2; LCMS purity: 254 nm: 99.5%

Example 28: Synthesis of Exemplary Compound 351

(R)-1-phenylethyl 4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **351**)

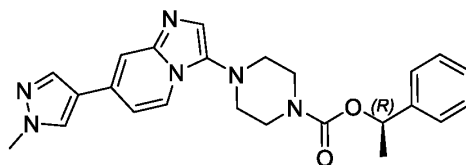


Step 1. Preparation of 7-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)imidazo[1,2-a]pyridine hydrochloride salt



[0571] To a solution of tert-butyl 4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **345**) (8.2 g, 21.4 mmol) in DCM (80 mL) cooled to 0°C was added 4M HCl in dioxane (22 mL) then the reaction was warmed to rt and stirred for 2 h. The mixture was filtered and the filter cake was dried to afford 6.2 g (91%) of 7-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)imidazo[1,2-a]pyridine hydrochloride salt as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.74 (d, *J* = 6.8 Hz, 1H), 8.65 (s, 1H), 8.26 (s, 1H), 7.91 (s, 1H), 7.72~7.74 (m, 1H), 7.43~7.45 (m, 1H), 3.92 (s, 3H), 3.56 (s, 2H), 3.32~3.34 (m, 6H).

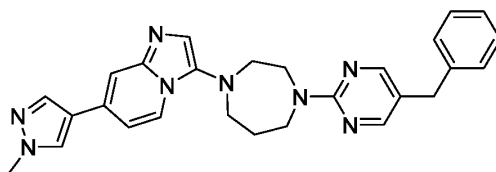
Step 2. Preparation of (R)-1-phenylethyl 4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **351**)



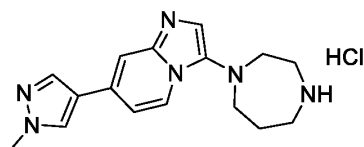
[0572] To a solution of 7-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)imidazo[1,2-a]pyridine hydrochloride salt (3.0 g, 9.4 mmol, as prepared in the previous step) in ACN (30 mL) was added (R)-4-nitrophenyl (1-phenylethyl) carbonate (2.7 g, 9.4 mmol, as prepared in Example **23**, Step 1) and DIEA (3.6 g, 28.2 mmol) then the reaction was stirred at 80°C under nitrogen for 4 h. The reaction mixture was cooled to rt, poured into water (80 mL), and extracted with EtOAc (4 x 30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by prep-HPLC to afford 65 mg (2%) of (R)-1-phenylethyl 4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **351**) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.93~7.95 (m, 1H), 7.80 (s, 1H), 7.68 (s, 1H), 7.59 (s, 1H), 7.36~7.37 (m, 4H), 7.30~7.32 (m, 1H), 7.24~7.25 (m, 1H), 6.93~6.95 (m, 1H), 5.86~5.89 (m, 1H), 3.97 (s, 3H), 3.71 (s, 4H), 3.02 (s, 4H), 1.57~1.59 (d, *J*=6.4Hz, 3H).

Example 29: Synthesis of Exemplary Compound **352**

3-(4-(5-benzylpyrimidin-2-yl)-1,4-diazepan-1-yl)-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine (Compound **352**)

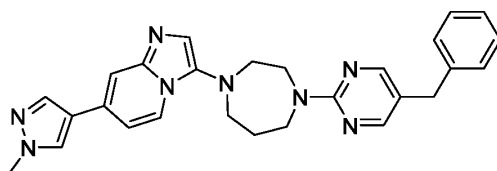


Step 1. Preparation of 3-(1,4-diazepan-1-yl)-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine hydrochloride salt



[0573] To a solution of tert-butyl 4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridin-3-yl)-1,4-diazepane-1-carboxylate (Compound **346**) (5.5 g, 13.9 mmol) in DCM (55 mL) cooled to 0°C was added 4M HCl in dioxane (18 mL) then the reaction was warmed to rt and stirred for 2 h. The mixture was filtered and the filter cake was dried to afford 5.9 g (128%) of 3-(1,4-diazepan-1-yl)-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine hydrochloride salt as a yellow solid. ¹HNMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.74 (d, *J* = 7.2 Hz, 1H), 8.62 (s, 1H), 7.95 (s, 1H), 7.71 (d, *J* = 7.2 Hz, 1H), 7.65~7.68 (m, 1H), 7.43~7.45 (m, 1H), 3.92 (m, 3H), 3.46~3.53 (m, 4H), 3.24~3.32 (m, 3H), 2.13 (s, 3H).

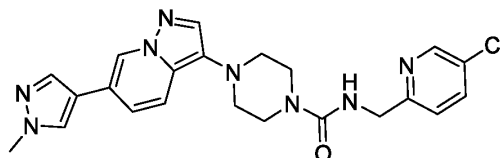
Step 2. Preparation of 3-(4-(5-benzylpyrimidin-2-yl)-1,4-diazepan-1-yl)-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine (Compound **352**)



[0574] To a solution of 3-(1,4-diazepan-1-yl)-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine hydrochloride salt (0.2 g, 0.6 mmol, as prepared in the previous step) in dioxane (10 mL) was added Cs₂CO₃ (0.59 g, 1.8 mmol), 5-benzyl-2-chloropyrimidine (Compound **S88**) (0.12 g, 0.6 mmol), and tBuXPhos Pd G1 (0.12 g, 0.18 mmol) then the reaction was stirred at 90°C under nitrogen for 6 h. The reaction mixture was cooled to rt, poured into water (40 mL), and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by prep-HPLC to afford 30 mg (11%) of 3-(4-(5-benzylpyrimidin-2-yl)-1,4-diazepan-1-yl)-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine (Compound **352**) as a yellow solid. ¹HNMR (400 MHz, CDCl₃) δ (ppm) 8.20 (s, 2H), 7.79~7.82 (m, 1H), 7.71 (s, 1H), 7.65 (s, 1H), 7.34 (s, 1H), 7.28~7.32 (m, 2H), 7.15~7.24 (m, 4H), 6.85~6.87 (m, 1H), 3.99~4.02 (m, 4H), 3.96 (s, 3H), 3.81 (s, 2H), 3.55~3.62 (m, 2H), 3.18~3.20 (m, 2H), 2.04~2.07 (m, 2H).

Example 30: Synthesis of Exemplary Compound 353

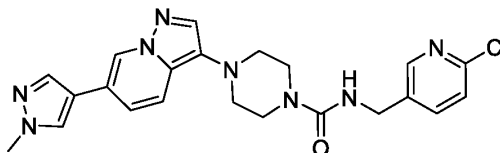
N-((5-chloropyridin-2-yl)methyl)-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxamide (Compound **353**)



[0575] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylpyrazolo[1,5-a]pyridine (Compound **12**) (300 mg, 1.06 mmol), TEA (323 mg, 3.19 mmol) in DCM (15 mL) was added triphosgene (94.6 mg, 0.32 mmol) at 0°C. The resulting mixture was stirred for 0.5 h at 0°C. Then resulting mixture was added 1-(5-chloropyridin-2-yl)methanamine (303 mg, 2.13 mmol) at 0°C. The resulting mixture was stirred for 16h at rt. Desired product could be detected. The resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluted with DCM / MeOH (10:1). The crude product (600 mg) was purified by Prep-HPLC with the following conditions (Column: Xselect CSH Prep Fluoro-Phenyl Column, 19*250 mm, 5µm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 25 mL/min mL/min; Gradient: 33% B to 43% B in 12min; Wave Length: 254nm/220nm nm; RT1(min): 8.65) to afford N-((5-chloropyridin-2-yl)methyl)-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxamide (279.7 mg, 57.97%) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.87 (s, 1H), 8.55 (d, *J* = 2.5 Hz, 1H), 8.25 (s, 1H), 7.99 (s, 1H), 7.94 – 7.85 (m, 2H), 7.77 (d, *J* = 9.2 Hz, 1H), 7.42 – 7.32 (m, 3H), 4.35 (s, 2H), 3.88 (s, 3H), 3.64 – 3.57 (m, 4H), 3.09 (s, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₂H₂₃ClN₈O, 451.2; found, 451.2; LCMS purity: 254 nm: 99.3%

Example 31: Synthesis of Exemplary Compound 354

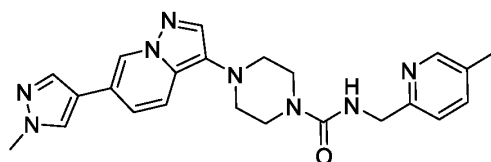
N-((6-chloropyridin-3-yl)methyl)-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxamide (Compound **354**)



[0576] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (400 mg, 1.42 mmol) in DCM (5 mL) cooled to 0°C was added triphosgene (126.1 mg, 0.43 mmol) then the reaction was stirred at 0°C under nitrogen for 16 h. The mixture was added dropwise to a DCM (5 mL) solution of (6-chloropyridin-3-yl)methanamine (148.8 mg, 1.10 mmol) and TEA (176.1 mg, 1.74 mmol) cooled to 0°C, then stirred at 0°C under nitrogen for 2 h. The mixture was concentrated under reduced pressure then the residue was dissolved in water (30 mL) and extracted with DCM (3 x 50 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 131.6 mg (33%) of N-((6-chloropyridin-3-yl)methyl)-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxamide (Compound **354**) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.37 – 8.21 (m, 2H), 7.98 (s, 1H), 7.79 – 7.23 (m, 2H), 7.70 – 7.63 (m, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.36 – 7.24 (m, 2H), 4.27 (d, *J* = 5.6 Hz, 2H), 3.87 (s, 3H), 3.52 (t, *J* = 4.9 Hz, 4H), 2.95 (t, *J* = 4.9 Hz, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₂H₂₃ClN₈O, 451.2; found, 451.1; LCMS purity: 254 nm: 99.7%

Example 32: Synthesis of Exemplary Compound 355

4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-N-((5-methylpyridin-2-yl)methyl)piperazine-1-carboxamide (Compound **355**)

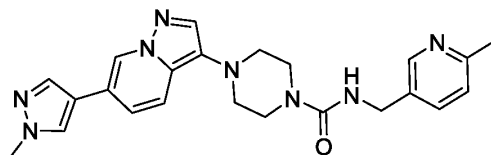


[0577] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (500 mg, 1.77 mmol) in DCM (20 mL) cooled to 0°C was added TEA (537.6 mg, 5.31 mmol) and triphosgene (173.4 mg, 0.58 mmol) at 0°C then the reaction was warmed to rt and stirred under nitrogen for 30 minutes. To the reaction was added (5-methylpyridin-2-yl)methanamine (432.7 mg, 3.54 mmol) dropwise over 1 minute then the reaction was stirred at rt for 16 h. The mixture was diluted with water (100 mL) and extracted with DCM (3 x 50 mL). The combined organic extracts were washed with brine (3x50 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 250.1 mg

(32%) of 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-N-((5-methylpyridin-2-yl)methyl)piperazine-1-carboxamide (Compound **355**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.32 (d, *J* = 2.2 Hz, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.78 (s, 1H), 7.68 (dd, *J* = 9.2, 0.8 Hz, 1H), 7.57 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.33 (dd, *J* = 9.2, 1.5 Hz, 1H), 7.24 (t, *J* = 6.0 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 4.32 (d, *J* = 5.6 Hz, 2H), 3.88 (s, 3H), 3.55 (d, *J* = 9.9 Hz, 4H), 2.97 (t, *J* = 4.8 Hz, 4H), 2.27 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₃H₂₆N₈O, 431.2; found, 431.2; LCMS purity: 254 nm: 99.3%.

Example 33: Synthesis of Exemplary Compound 356

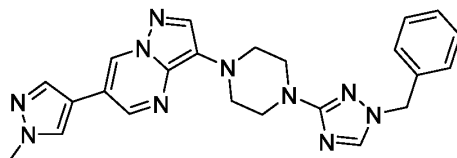
4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-N-((6-methylpyridin-3-yl)methyl)piperazine-1-carboxamide (Compound **356**)



[0578] To a solution of (6-methylpyridin-3-yl)methanamine (400 mg, 3.27 mmol) and TEA (994 mg, 9.82 mmol) in DCM (5 mL) cooled to 0°C was added triphosgene (291.5 mg, 0.98 mmol) then the reaction was stirred at 0°C under nitrogen for 2 h. The mixture was added to a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (686 mg, 2.43 mmol) and TEA (409.8 mg, 4.05 mmol) in DCM (5 mL) cooled to 0°C, then the reaction was stirred at 0°C under nitrogen for 2 h. The mixture was concentrated under reduced pressure, then water (30 mL) was added and the mixture was extracted with EtOAc (3 x 30 mL). Then combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 100 mg (11%) of 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-N-((6-methylpyridin-3-yl)methyl)piperazine-1-carboxamide (Compound **356**) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.35 (d, *J* = 2.3 Hz, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.77 (s, 1H), 7.66 (d, *J* = 9.2 Hz, 1H), 7.56 (dd, *J* = 8.0, 2.3 Hz, 1H), 7.32 (dd, *J* = 9.3, 1.5 Hz, 1H), 7.23-7.16 (m, 2H), 4.23 (d, *J* = 5.6 Hz, 2H), 3.87 (s, 3H), 3.51 (t, *J* = 4.8 Hz, 4H), 2.94 (t, *J* = 4.8 Hz, 4H), 2.43 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₃H₂₆N₈O, 430.2; found, 431.1; LCMS purity: 254 nm: 99.5%

Example 34: Synthesis of Exemplary Compound 357

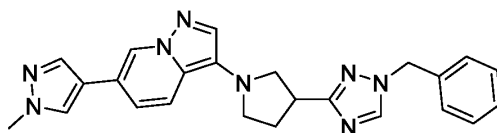
3-(4-(1-benzyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine (Compound **357**)



[0579] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyrimidine (Compound **S98**) (250 mg, 0.88 mmol) and 1-benzyl-3-chloro-1H-1,2,4-triazole (256.2 mg, 1.32 mmol, as prepared in Example 1, Step 1) in dioxane (20 mL) were added Pd-PEPSI-IPent^{Cl} 2-methylpyridine (111.3 mg, 0.13 mmol) and Cs₂CO₃ (574.9 mg, 1.76 mmol) then the reaction was stirred at 100°C under nitrogen overnight. The mixture was cooled to rt and concentrated under reduced pressure. The residue was dissolved in water (50 mL), then the mixture was extracted with DCM (3 x 50 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 74.3 mg (19%) of 3-(4-(1-benzyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine (Compound **357**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.17 (d, *J* = 2.2 Hz, 1H), 8.63 (d, *J* = 2.1 Hz, 1H), 8.31 – 8.29 (m, 2H), 8.03 (s, 1H), 7.90 (s, 1H), 7.44 – 7.20 (m, 5H), 5.23 (s, 2H), 3.89 (s, 3H), 3.46 – 3.43 (m, 4H), 3.32 – 3.29 (m, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₃H₂₄N₁₀, 441.2; found, 441.15. LCMS purity: 254 nm: 99.1%.

Example 35: Synthesis of Exemplary Compound 358

3-(3-(1-benzyl-1H-1,2,4-triazol-3-yl)pyrrolidin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **358**)

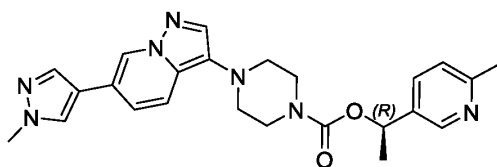


[0580] To a vial pre-sparged with argon 20 minutes containing 3-iodo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (234 mg, 0.72 mmol, as prepared for Compound **S57**, Step 1), 1-benzyl-3-pyrrolidin-3-yl-1H-1,2,4-triazole (Compound **S101**) (110 mg, 0.48

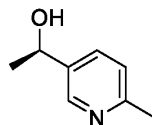
mmol), K_3PO_4 (307 mg, 1.44 mmol), and CuI (37 mg, 0.193 mmol) was added 1-butanol (2.8 mL) and 1, 2-ethanediol (0.6 mL) then the reaction was heated to 100°C for 48 h. The mixture was cooled to rt, diluted with 10% IPA / DCM, and washed with (7:3) sat. aqueous NH_4Cl / conc. NH_4OH (3 times) and brine, then dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 0-6% MeOH / DCM. The pure fractions were concentrated under reduced pressure then the residue was stirred with a mixture of (6:1:2) MTBE/MeOH/heptane. The solvent was removed under reduced pressure then the solid was triturated with MTBE (1 mL) overnight. The solid was collected by filtration and dried under reduced pressure to afford 29 mg (16%) of 3-[3-(1-benzyl-1H-1,2,4-triazol-3-yl)pyrrolidin-1-yl]-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **358**) as a yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.69 (s, 1H), 8.55 (s, 1H), 8.18 (s, 1H), 7.93 (s, 1H), 7.68 (d, $J = 9.3$ Hz, 1H), 7.53 (s, 1H), 7.40-7.25 (m, 5H), 7.11 (m, 1H), 5.36 (s, 2H), 3.86 (s, 3H), 3.70-3.54 (m, 2H), 3.48-3.32 (m, 3H), 2.40-2.17 (m, 2H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{25}N_8$, 425.2; found, 425.2; HPLC purity: 210 nm: 95.8%; 254 nm: 96.2%.

Example 36: Synthesis of Exemplary Compound 359

(R)-1-(6-methylpyridin-3-yl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **359**)



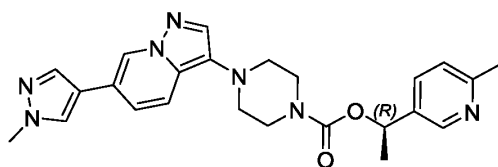
Step 1. Preparation of (1R)-1-(6-methylpyridin-3-yl)ethanol



[0581] To a solution of (R,R)-Ts-DENEB (0.263 g, 0.405 mmol) in toluene (5 mL) under nitrogen was added 3-acetyl-6-methylpyridine (5.48 g, 40.5 mmol) at rt then TEA (14.1 mL, 101 mmol) and formic acid (3.82 mL, 101 mmol) were added. The reaction was stirred at rt overnight then the mixture was partitioned between sat. aqueous $NaHCO_3$ (100 mL)

and EtOAc (100 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with sat. aqueous NaHCO₃ (50 mL). The combined aqueous layers were extracted with EtOAc (100 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 30-100% acetone / DCM to afford 4 g (72%) of (R)-1-(6-methylpyridin-3-yl)ethanol as a dark solid. ¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.30 - 8.46 (m, 1H), 7.62 (dd, J=7.96, 2.10 Hz, 1H), 7.12 (d, J=8.01 Hz, 1H), 4.90 (q, J=6.33 Hz, 1H), 3.12 (s, 1H), 2.51 (s, 3H), 1.49 (d, J=6.43 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₈H₁₂NO: 138.2; found: 137.9.

Step 2. Preparation of (R)-1-(6-methylpyridin-3-yl)ethyl 4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1, 5-a]pyridin-3-yl]piperazine-1-carboxylate (Compound **359**)

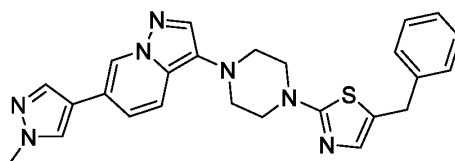


[0582] To a solution of (R)-1-(6-methylpyridin-3-yl)ethanol (1.30 g, 9.44 mmol, as prepared in the previous step) in NMP (20 mL) cooled to 0°C was added 1M LiHMDS in THF (8.64 mL, 8.64 mmol) under nitrogen over 10 minutes, then the reaction was stirred at 0°C for 20 minutes. 4-nitrophenyl 4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxylate (4.00 g, 7.87 mmol, as prepared in Example **18**, Step 1) was added portion wise as a solid, then the mixture was stirred at 0°C for 15 minutes. The reaction was warmed to rt and stirred overnight. The reaction mixture was diluted with EtOAc (100 mL) then washed with sat. aqueous NaHCO₃ (3 x 100 mL) and water (4 x 100 mL). The combined aqueous washes were extracted with EtOAc (50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 5% MeOH / DCM followed by silica gel chromatography eluting with 20-80% acetone / DCM to afford 2.3g (54%) of (R)-1-(6-methylpyridin-3-yl)ethyl 4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxylate (Compound **359**) as a yellow foam. ¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.54 (d, J=2.05 Hz, 1H), 8.46 (s, 1H), 7.74 (s, 1H), 7.70 (s, 1H), 7.53 -

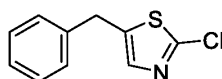
7.65 (m, 2H), 7.49 (d, $J=9.22$ Hz, 1H), 7.07 - 7.21 (m, 2H), 5.86 (q, $J=6.61$ Hz, 1H), 3.89 - 4.09 (m, 3H), 3.70 (br. s., 4H), 2.93 - 3.13 (m, 4H), 2.56 (s, 3H), 1.60 (d, $J=6.61$ Hz, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{28}N_7O_2$: 446.5; found: 446.0; HPLC purity: 210 nm: 100.0%; 254 nm: 100.0%

Example 37: Synthesis of Exemplary Compound 360

5-benzyl-2-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)thiazole (Compound 360)

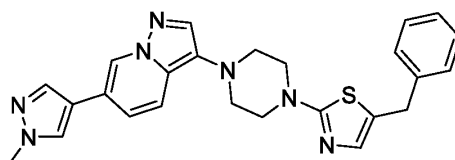


Step 1. Preparation of 5-benzyl-2-chlorothiazole



[0583] To a solution of $CuCl_2$ (848 mg, 6.31 mmol) in ACN (20 mL) was added tert-butyl nitrite (867.2 mg, 8.41 mmol) at rt. The reaction was stirred for 30 minutes then 5-benzyl-1,3-thiazol-2-amine (1 g, 5.26 mmol) was added. The mixture was stirred at rt for 1 h then 1M HCl was added and the reaction was stirred at rt for 1 h, then concentrated under reduced pressure. Then residue was purified by silica gel chromatography eluting with EtOAc / PE (1:5) to afford 800 mg (73%) of 5-benzyl-2-chlorothiazole as a light yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 2H), 7.32 – 7.29 (m, 2H), 7.24 (dd, $J = 6.8, 1.6$ Hz, 2H), 4.11 (s, 2H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{10}H_8ClNS$, 210.0; found, 210.1.

Step 2. Preparation of 5-benzyl-2-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)thiazole (Compound 360)

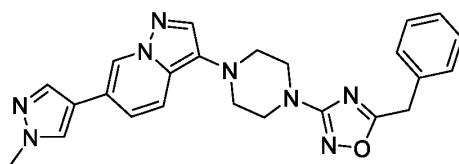


[0584] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound 12) (200 mg, 0.71 mmol) and 5-benzyl-2-chlorothiazole (222.8 mg,

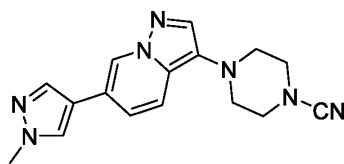
1.06 mmol, as prepared in the previous step) in ACN (15 mL) was added Cs₂CO₃ (577 mg, 1.77 mmol) then the reaction was stirred at 90°C for 48 h. The mixture was cooled to rt, then concentrated under reduced pressure. The residue was diluted with water (100 mL) and extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with brine (2x100 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 175.3 mg (54%) of 5-benzyl-2-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)thiazole (Compound **360**) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.79 (s, 1H), 7.67 (dd, *J* = 9.2, 1.0 Hz, 1H), 7.38 – 7.18 (m, 6H), 7.00 (s, 1H), 4.00 (s, 2H), 3.87 (s, 3H), 3.52 (t, *J* = 4.4 Hz, 4H), 3.13 – 3.03 (m, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₅N₇S, 456.1; found, 456.1; LCMS purity: 254 nm: 99.1%

Example 38: Synthesis of Exemplary Compound 361

5-benzyl-3-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-1,2,4-oxadiazole (Compound **361**)



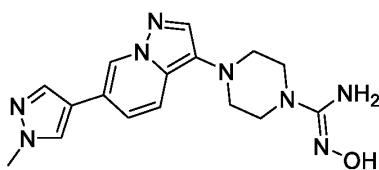
Step 1. Preparation of 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carbonitrile



[0585] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (500 mg, 1.77 mmol) and TEA (268.8 mg, 2.66 mmol) in DCM (6 mL) cooled to 0°C was added BrCN (187.6 mg, 1.77 mmol) then the reaction was stirred at 0°C for 3 h. The mixture was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with MeOH / DCM (1:30) to afford 410 mg (75%) of 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-

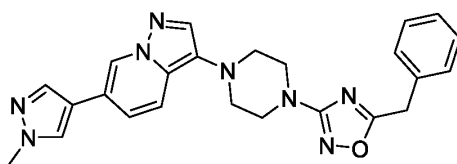
carbonitrile as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.84 (s, 1H), 8.24 (s, 1H), 7.98 (d, $J = 0.6$ Hz, 1H), 7.81 (s, 1H), 7.66 (dd, $J = 9.2, 0.7$ Hz, 1H), 7.35 (dd, $J = 9.2, 1.5$ Hz, 1H), 3.87 (s, 3H), 3.41 (t, $J = 4.9$ Hz, 4H), 3.06 (t, $J = 4.9$ Hz, 4H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{17}\text{N}_7$, 308.1; found, 308.2.

Step 2. Preparation of N'-hydroxy-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboximidamide



[0586] To a solution of 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carbonitrile (400 mg, 1.30 mmol, as prepared in the previous step) and TEA (263.4 mg, 2.60 mmol) in EtOH (6 mL) cooled to 0°C was added $\text{NH}_2\text{OH}\cdot\text{HCl}$ (90.4 mg, 1.30 mmol) then the reaction was warmed to rt and stirred for 5 h. The mixture was filtered, the filter cake was washed with EtOH (3 x 20 mL), and dried under reduced pressure to afford 400 mg (90%) of N'-hydroxy-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboximidamide as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 10.73 (s, 1H), 10.02 (s, 1H), 8.85 (s, 1H), 8.25 (s, 1H), 8.10 (s, 2H), 7.99 (s, 1H), 7.80 (s, 1H), 7.71 (d, $J = 9.2$ Hz, 1H), 7.36 (dd, $J = 9.3, 1.4$ Hz, 1H), 3.88 (s, 3H), 3.59 (t, $J = 4.6$ Hz, 4H), 3.06 (t, $J = 4.6$ Hz, 4H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{16}\text{H}_{20}\text{N}_8\text{O}$, 341.1; found, 341.2.

Step 3. Preparation of 5-benzyl-3-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-1,2,4-oxadiazole (Compound 361)

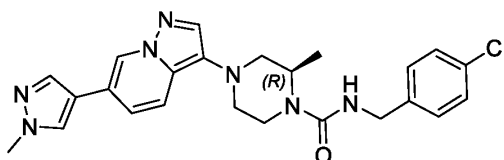


[0587] To a solution of 2-phenylacetic acid (160 mg, 1.17 mmol) in THF (6 mL) was added CDI (191 mg, 1.17 mmol) then the reaction was stirred for 1 h at 55°C . The mixture was cooled to rt and N'-hydroxy-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboximidamide (400 mg, 1.17 mmol, as prepared in the previous step) was added. The reaction was heated to 55°C and stirred for 1 h then the mixture was heated

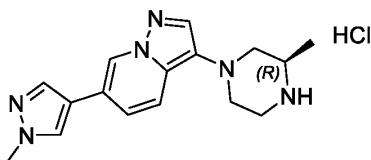
to 150°C for 20 minutes. The reaction was cooled to rt and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with MeOH / DCM (1:15) then the pure fractions were concentrated under reduced pressure. The residue was triturated with MeOH to afford 100.5 mg (19%) of 5-benzyl-3-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-1,2,4-oxadiazole (Compound **361**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.78 (s, 1H), 7.67 (d, *J* = 9.3 Hz, 1H), 7.44 – 7.18 (m, 6H), 4.23 (s, 2H), 3.87 (s, 3H), 3.52 (t, *J* = 4.9 Hz, 4H), 3.07 (t, *J* = 4.9 Hz, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₄N₈O, 441.1; found, 441.20; LCMS purity: 254 nm: 99.5%.

Example 39: Synthesis of Exemplary Compound 362

(R)-N-(4-chlorobenzyl)-2-methyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxamide (Compound **362**)

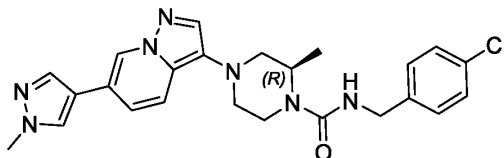


Step 1. Preparation of (R)-6-(1-methyl-1H-pyrazol-4-yl)-3-(3-methylpiperazin-1-yl)pyrazolo[1,5-a]pyridine hydrochloride salt



[0588] To a solution of tert-butyl (R)-2-methyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (600 mg, 1.51 mmol, as prepared in Example 4, Step 1) in DCM (20 mL) cooled to 0°C was added 4M HCl in dioxane (10 mL) dropwise then the reaction was warmed to rt and stirred for 5 h. The mixture was concentrated under reduced pressure to afford 690 mg (137%) (R)-6-(1-methyl-1H-pyrazol-4-yl)-3-(3-methylpiperazin-1-yl)pyrazolo[1,5-a]pyridine hydrochloride salt as a brown solid: MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₆H₂₀N₆, 297.2; found, 297.3.

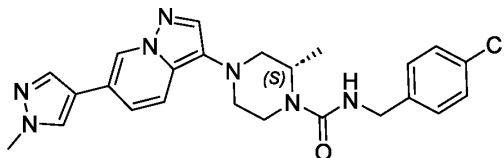
Step 2. Preparation of (R)-N-(4-chlorobenzyl)-2-methyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxamide (Compound **362**)



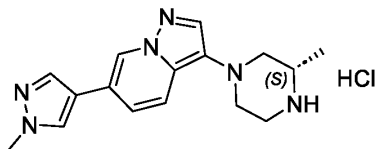
[0589] To a solution of (R)-6-(1-methyl-1H-pyrazol-4-yl)-3-(3-methylpiperazin-1-yl)pyrazolo[1,5-a]pyridine hydrochloride salt (300 mg, 0.68 mmol, as prepared in the previous step) and TEA (410 mg, 4.05 mmol) in DCM (5 mL) cooled to 0°C was added triphosgene (60.1 mg, 0.20 mmol) then the reaction was stirred for 30 minutes. To the mixture at 0°C was added 1-(4-chlorophenyl)methanamine (191 mg, 1.35 mmol), then the reaction was warmed to rt and stirred for 2 h. The mixture was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with EtOAc / PE (5:1) followed by Prep-HPLC to afford 150.5 mg (48%) of (R)-N-(4-chlorobenzyl)-2-methyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxamide (Compound **362**) as a light green solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.76 (s, 1H), 7.59 (d, *J* = 9.2 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.35 – 7.25 (m, 3H), 7.16 (t, *J* = 5.9 Hz, 1H), 4.33 – 4.17 (m, 3H), 3.93 – 3.78 (m, 4H), 3.25 – 3.09 (m, 3H), 2.82 – 2.74 (m, 1H), 2.70 – 2.59 (m, 1H), 1.33 (d, *J* = 6.6 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₆ClN₇O, 464.2; found, 464.2; LCMS purity: 254 nm: 99.4%.

Example 40: Synthesis of Exemplary Compound 363

(S)-N-(4-chlorobenzyl)-2-methyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxamide (Compound **363**)

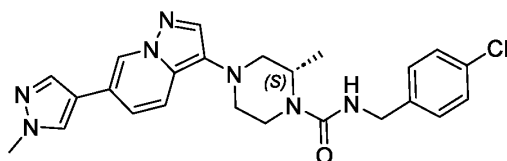


Step 1. Preparation of (S)-6-(1-methyl-1H-pyrazol-4-yl)-3-(3-methylpiperazin-1-yl)pyrazolo[1,5-a]pyridine hydrochloride salt



[0590] To a solution of (S)-2-methyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (600 mg, 1.51 mmol, as prepared in Example 5, Step 1) in DCM (20 mL) was added 4M HCl in dioxane (551.7 mg, 15.13 mmol) then the reaction was stirred at rt under nitrogen overnight. The mixture was concentrated under reduced pressure to afford 500 mg (89%) of (S)-6-(1-methyl-1H-pyrazol-4-yl)-3-(3-methylpiperazin-1-yl)pyrazolo[1,5-a]pyridine hydrochloride salt as a grey solid. MS (ESI) m/z $[M+H]^+$ calcd. for $C_{16}H_{20}N_6$, 297.1; found, 297.1.

Step 2. (S)-N-(4-chlorobenzyl)-2-methyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxamide (Compound **363**)

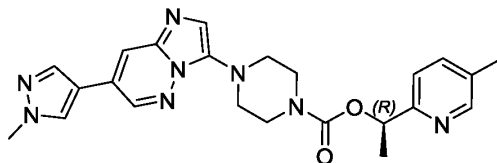


[0591] To a solution of 1-(4-chlorophenyl)methanamine (500 mg, 3.53 mmol) in DCM (20 mL) was added triphosgene (1 mg, 3.53 mmol) then the reaction was stirred at rt under nitrogen for 4 h. The solution was added dropwise to a mixture of (S)-6-(1-methyl-1H-pyrazol-4-yl)-3-(3-methylpiperazin-1-yl)pyrazolo[1,5-a]pyridine hydrochloride salt (265.2 mg, 0.89 mmol, as prepared in the previous step) and TEA (1.63 g, 16.11 mmol) in DCM (20 mL), then the reaction was stirred under nitrogen overnight. The mixture was concentrated under reduced pressure then the residue was dissolved in water (50 mL). The mixture was extracted with DCM (3 x 50 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure, then the residue was purified by Prep-HPLC to afford 80.9 mg (10%) of (S)-N-[(4-chlorophenyl)methyl]-2-methyl-4-[6-(1-methylpyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxamide (Compound **363**) as a yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.76 (s, 1H), 7.59 (d, $J = 9.2$ Hz, 1H), 7.40 – 7.29 (m, 4H), 7.16 (t, $J = 5.9$ Hz, 1H), 4.29-4.23 (m, 3H), 3.87-3.83 (m, 4H), 3.28 – 3.11 (m, 3H), 2.80 – 2.76 (m, 1H), 2.64

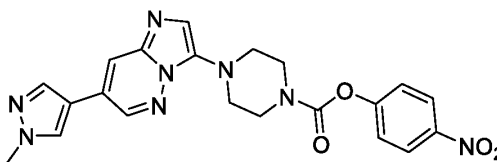
– 2.54 (m, 1H), 1.33 (d, $J = 6.6$ Hz, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{26}ClN_7O$, 464.2; found, 464.2. LCMS purity: 254 nm: 99.5%; HPLC purity: 98.2%.

Example 41: Synthesis of Exemplary Compound 364

(R)-1-(5-methylpyridin-2-yl)ethyl 4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl)piperazine-1-carboxylate (Compound 364)

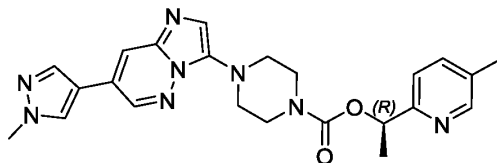


Step 1. Preparation of 4-nitrophenyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]piperazine-1-carboxylate



[0592] To a suspension of 7-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylimidazo[1,2-b]pyridazine hydrochloride salt (Compound S84) (0.201 g, 0.564 mmol) in ACN (4 mL) was added TEA (0.314 mL, 2.26 mmol) then the mixture was stirred for 5 minutes at rt. 4-Nitrophenyl chloroformate (0.125 g, 0.620 mmol) was added and the mixture was stirred at rt overnight. The reaction was concentrated under reduced pressure then the residue was partitioned between 1N NaOH (10 mL) and DCM (10 mL). The layers were separated, and the DCM layer was extracted with 1N NaOH (2 x 10 mL). The combined aqueous layers were extracted with DCM (10 mL) then the combined DCM layers were dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to afford 190 mg (75%) of 4-nitrophenyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]piperazine-1-carboxylate as a yellow solid. 1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.52 (d, $J=2.08$ Hz, 1H), 8.23 - 8.36 (m, 2H), 7.82 - 7.92 (m, 2H), 7.75 (s, 1H), 7.34 - 7.41 (m, 2H), 7.32 (s, 1H), 4.02 (s, 3H), 3.98 (br. s., 2H), 3.89 (br. s., 2H), 3.35 - 3.46 (m, 4H); MS (ESI) m/z $[M+H]^+$ calcd. For $C_{21}H_{21}N_8O_4$: 449.4; found: 449.1; HPLC purity: 210 nm: 100.0%; 254 nm: 100.0%

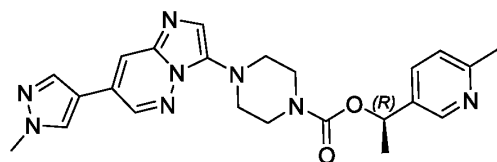
Step 2. Preparation of (1R)-1-(5-methylpyridin-2-yl)ethyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]piperazine-1-carboxylate (Compound **364**)



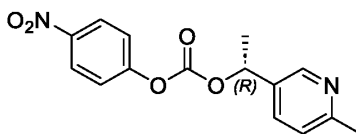
[0593] To a solution of (R)-1-(5-methylpyridin-2-yl)ethanol (0.0697 g, 0.508 mmol, as prepared in Example **20**, Step 2) in DMF (4 mL) cooled to 0°C was added 60% NaH in mineral oil (0.0203 g, 0.508 mmol) under nitrogen, then the mixture was stirred at 0°C for 20 minutes. 4-Nitrophenyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]piperazine-1-carboxylate (0.190 g, 0.424 mmol, as prepared in the previous step) was added as a solid and the reaction was stirred at 0°C for 30 minutes, then warmed to rt and stirred overnight. The mixture was diluted with sat. aqueous NaHCO₃ (20 mL) and EtOAc (20 mL). The layers were separated and the EtOAc layer was extracted with water (3 x 20 mL) and sat. aqueous NaHCO₃ (20 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 5% MeOH / DCM to afford 74 mg (39%) of (R)-1-(5-methylpyridin-2-yl)ethyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]piperazine-1-carboxylate (Compound **364**) as a yellow foam. ¹H NMR (300 MHz, DMSO-*d*₆) δ (ppm) 8.75 - 8.90 (m, 1H), 8.32 - 8.43 (m, 2H), 8.13 - 8.20 (m, 1H), 8.10 (s, 1H), 7.62 (d, J=6.98 Hz, 1H), 7.31 (d, J=6.78 Hz, 1H), 7.29 (s, 1H), 5.71 (q, J=6.61 Hz, 1H), 3.89 (s, 3H), 3.64 (br. s., 4H), 3.19 (br. s., 4H), 2.29 (s, 3H), 1.50 (d, J=6.61 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₃H₂₇N₈O₂: 447.5; found: 447.2; HPLC purity: 210 nm: 100.0%; 254 nm: 100.0%

Example 42: Synthesis of Exemplary Compound **365**

(R)-1-(6-methylpyridin-3-yl)ethyl 4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl)piperazine-1-carboxylate (Compound **365**)

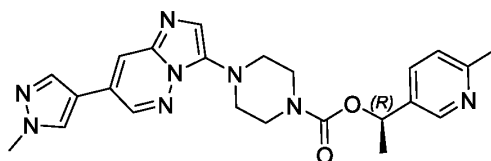


Step 1. Preparation of (R)-1-(6-methylpyridin-3-yl)ethyl 4-nitrophenyl carbonate



[0594] To a solution of (R)-1-(6-methylpyridin-3-yl)ethanol (600 mg, 4.37 mol, as prepared in Example 36, Step 1) in ACN (6 mL) was added pyridine (0.708 mL, 0.00875 mol) then p-nitrophenyl chloroformate (0.970 g, 0.00481 mol) was added and the reaction was stirred at rt overnight. The mixture was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 0-50% EtOAc / DCM to afford 900 mg (68%) of (R)-1-(6-methylpyridin-3-yl)ethyl 4-nitrophenyl carbonate as a clear oil. ¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.59 (d, J=1.86 Hz, 1H), 8.21 - 8.34 (m, 2H), 7.67 (dd, J=7.96, 2.37 Hz, 1H), 7.31 - 7.44 (m, 2H), 7.21 (d, J=8.01 Hz, 1H), 5.86 (q, J=6.61 Hz, 1H), 2.50 - 2.68 (m, 3H), 1.73 (d, J=6.71 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. For C₁₅H₁₅N₂O₅: 303.3; found: 303.3; HPLC purity: 210 nm: 94.3%; 254 nm: 96.1%

Step 2. Preparation of (1R)-1-(6-methylpyridin-3-yl)ethyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]piperazine-1-carboxylate (Compound 365)

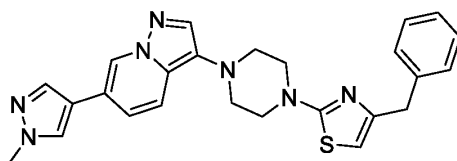


[0595] To a mixture of 7-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylimidazo[1,2-b]pyridazine hydrochloride salt (Compound S84) (0.150 g, 0.421 mmol) in ACN (2 mL) was added TEA (0.196 mL, 1.40 mmol). The mixture was stirred at rt for 5 minutes then (1R)-1-(6-methylpyridin-3-yl)ethyl 4-nitrophenyl carbonate (0.106 g, 0.351 mmol, as prepared in the previous step) was added and the reaction was stirred at rt for 2 h. The mixture was concentrated under reduced pressure then the residue was dissolved in DCM (20 mL). The mixture was washed with 1N NaOH (2 x 10 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 5% MeOH / DCM and further purified by silica gel chromatography eluting with acetone to afford 70 mg (45%) of (R)-1-(6-methylpyridin-3-yl)ethyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]piperazine-1-carboxylate (Compound 365) as a yellow glass. ¹H NMR (400 MHz,

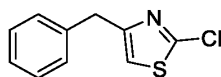
CDCl₃) δ (ppm) 8.55 (d, $J=2.08$ Hz, 1H), 8.49 (d, $J=1.96$ Hz, 1H), 7.80 - 7.90 (m, 2H), 7.73 (s, 1H), 7.59 (dd, $J=7.95, 2.32$ Hz, 1H), 7.23 - 7.30 (m, 1H), 7.17 (d, $J=8.07$ Hz, 1H), 5.88 (q, $J=6.60$ Hz, 1H), 4.01 (s, 3H), 3.78 (br. s., 4H), 3.27 (br. s., 4H), 2.58 (s, 3H), 1.62 (d, $J=6.72$ Hz, 3 H); MS (ESI) m/z $[M+H]^+$ calcd. For C₂₃H₂₇N₈O₂: 447.5; found: 447.2; HPLC purity: 210 nm: 100.0%; 254 nm: 100.0%.

Example 43: Synthesis of Exemplary Compound 366

4-benzyl-2-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)thiazole (Compound 366)

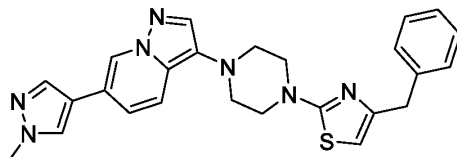


Step 1. Preparation of 4-benzyl-2-chlorothiazole



[0596] To a solution of 4-benzyl-1,3-thiazol-2-amine (1 g, 5.25 mmol) and tert-butyl nitrite (1.08 g, 10.51 mmol) in ACN (20 mL) was added CuCl₂ (1.06 g, 7.88 mmol) then the reaction was stirred at rt under nitrogen for 4 h. The mixture was concentrated under reduced pressure then the residue was dissolved in water (100 mL). The mixture was extracted with DCM (3 x 100 mL), then the combined organic extracts were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with EtOAc / PE (1:10) to afford 250 mg (23%) of 4-benzyl-2-chlorothiazole as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 7.36 – 7.18 (m, 6H), 4.01 (s, 2H); MS (ESI) m/z $[M+H]^+$ calcd. for C₁₀H₈ClNS, 210.0; found, 210.0.

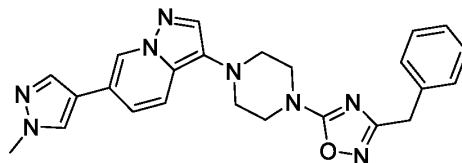
Step 2. 4-benzyl-2-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)thiazole (Compound 366)



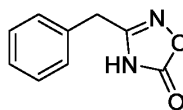
[0597] To a solution of 4-benzyl-2-chloro-1,3-thiazole (222.8 mg, 1.06 mmol, as prepared in the previous step) and 6-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylpyrazolo[1,5-a]pyridine (Compound 12) (200 mg, 0.70 mmol) in dioxane (20 mL) were added Cs₂CO₃ (461.5 mg, 1.41 mmol) and Pd-PEPSI-IPent^{Cl} 2-methylpyridine (59.5 mg, 0.07 mmol) under nitrogen then the reaction was heated to 100°C and stirred overnight. The mixture was cooled to rt then concentrated under reduced pressure. The residue was dissolved in water (50 mL) then the mixture was extracted with DCM (3 x 50 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 126.7 mg (39%) of 4-benzyl-2-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)thiazole as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.84 (s, 1H), 8.24 (s, 1H), 7.98 (s, 1H), 7.80 (s, 1H), 7.69 – 7.67 (m, 1H), 7.38 – 7.32 (m, 1H), 7.32 – 7.31 (m, 1H), 7.30 – 7.26 (m, 3H), 7.24 – 7.18 (m, 1H), 6.41 (s, 1H), 3.88 – 3.84 (m, 5H), 3.56 (t, *J* = 5.1 Hz, 4H), 3.10 (t, *J* = 5.1 Hz, 4H). MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₅N₇S, 456.2; found, 455.95. LCMS purity: 254 nm: 99.7%.

Example 44: Synthesis of Exemplary Compound 367

3-benzyl-5-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-1,2,4-oxadiazole (Compound 367)



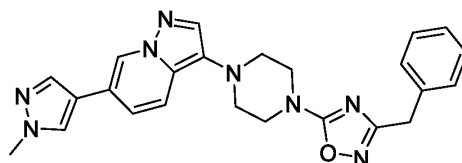
Step 1. Preparation of 3-benzyl-1,2,4-oxadiazol-5(4H)-one



[0598] To a solution of N¹-hydroxy-2-phenylethananimidamide (5.00 g, 33.3 mmol) in dioxane (50 mL) was added CDI (8.10 g, 49.9 mmol) and DBU (5.48 mL, 36.6 mmol). The solution was warmed to 105°C and stirred for 3 h. The reaction was cooled to rt then partitioned between EtOAc and water. The pH of the aqueous layer was adjusted to pH 2 with 1M HCl, then the aqueous layer was extracted with EtOAc (3 times). The combined

organic extracts were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 0-100% (10% MeOH in DCM) / DCM to afford 4.18 g (71%) of 3-benzyl-1,2,4-oxadiazol-5(4H)-one as a white solid. MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_9\text{H}_9\text{N}_2\text{O}_2$, 177.1; found, 176.9.

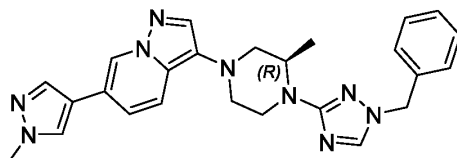
Step 2. Preparation of 3-[4-(3-benzyl-1,2,4-oxadiazol-5-yl)piperazin-1-yl]-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **367**)



[0599] To a solution of 3-benzyl-1,2,4-oxadiazol-5(4H)-one (0.15 g, 0.85 mmol, as prepared in the previous step) and PyBroP (0.40 g, 0.85 mmol) in dioxane (5 mL) was added DIEA (0.43 mL, 2.4 mmol). The reaction was heated to 50°C for 2 h, cooled rt, then 6-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylpyrazolo[1,5-a]pyridine (Compound **12**) (0.12 g, 0.43 mmol) was added. The reaction was stirred at rt overnight then concentrated under reduced pressure. The residue was partitioned between DCM (20 mL) and water (10 mL). The DCM layer was washed with brine, dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 0-100% (10% MeOH in DCM) / DCM. The pure fractions were concentrated under reduced pressure then the residue was dissolved in DCM and extracted with water (x3) and aqueous LiCl (x3), then dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue was stirred with hexane and concentrated to dryness (x3) to afford 52 mg (28%) of 3-[4-(3-benzyl-1,2,4-oxadiazol-5-yl)piperazin-1-yl]-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **367**) as a grey solid. ^1H NMR (400 MHz, CD_3OD) δ (ppm) 8.60 (s, 1H) 8.03 (s, 1H) 7.87 (s, 1H) 7.80 (s, 1H) 7.66 (d, $J=9.29$ Hz, 1H) 7.37 (dd, $J=9.23$, 1.41 Hz, 1H) 7.31 (d, $J=4.28$ Hz, 4H) 7.21 - 7.27 (m, 1H) 3.94 (s, 3H) 3.87 (s, 2H) 3.77 - 3.83 (m, 4H) 3.12 - 3.19 (m, 4H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{24}\text{H}_{25}\text{N}_8\text{O}$, 441.2; found, 441.2; HPLC purity: 210 nm: 100.0%; 254 nm: 100.0%.

Example 45: Synthesis of Exemplary Compound 368

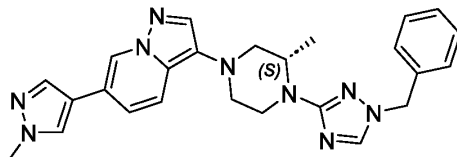
(R)-3-(4-(1-benzyl-1H-1,2,4-triazol-3-yl)-3-methylpiperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **368**)



[0600] To a solution of (R)-6-(1-methyl-1H-pyrazol-4-yl)-3-(3-methylpiperazin-1-yl)pyrazolo[1,5-a]pyridine hydrochloride salt (300 mg, 0.90 mmol, as prepared in Example **39**, Step 1) and 1-benzyl-3-chloro-1H-1,2,4-triazole (174 mg, 0.90 mmol, as prepared in Example **1**, Step 1) in dioxane (10 mL) were added Cs₂CO₃ (1.17 g, 3.61 mmol) and Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (76 mg, 0.09 mmol) then the reaction was heated to 90°C and stirred for 16 h under nitrogen. The mixture was cooled to rt and filtered, then the filter cake was washed with EtOAc (2 x 5 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc and further purified by Prep-HPLC to afford 194.3 mg (47%) of (R)-3-(4-(1-benzyl-1H-1,2,4-triazol-3-yl)-3-methylpiperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **368**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.84 – 8.80 (m, 1H), 8.30 – 8.20 (m, 2H), 7.96 (s, 1H), 7.75 (s, 1H), 7.58 (d, *J* = 9.2 Hz, 1H), 7.41 – 7.23 (m, 6H), 5.23 (s, 2H), 4.26 – 4.12 (m, 1H), 3.87 (s, 3H), 3.74 – 3.64 (m, 1H), 3.31 – 3.22 (m, 2H), 3.18 – 3.10 (m, 1H), 2.92 (dd, *J* = 11.3, 3.6 Hz, 1H), 2.85 – 2.75 (m, 1H), 1.29 (d, *J* = 6.5 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₇N₉, 454.2; found, 454.2; LCMS purity: 254 nm: 99.8%

Example 46: Synthesis of Exemplary Compound 369

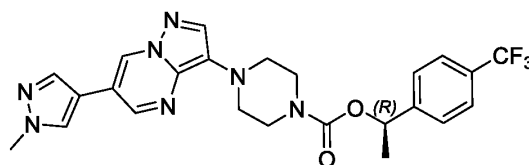
(S)-3-(4-(1-benzyl-1H-1,2,4-triazol-3-yl)-3-methylpiperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **369**)



[0601] To a solution of (S)-6-(1-methyl-1H-pyrazol-4-yl)-3-(3-methylpiperazin-1-yl)pyrazolo[1,5-a]pyridine hydrochloride salt (300 mg, 1.01 mmol, as prepared in Example 40, Step 1) and 1-benzyl-3-chloro-1H-1,2,4-triazole (215.6 mg, 1.11 mmol, as prepared in Example 1, Step 1) in dioxane (20 mL) were added Cs₂CO₃ (1.32 g, 4.04 mmol) and Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (85.1 mg, 0.10 mmol) then the reaction was heated to 90°C and stirred overnight under nitrogen. The mixture was cooled to rt then concentrated under reduced pressure. The residue was dissolved in water (50 mL). The resulting mixture was extracted with DCM (3 x 50 mL) then the combined organic extracts were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 145.9 mg (32%) of (S)-3-(4-(1-benzyl-1H-1,2,4-triazol-3-yl)-3-methylpiperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **369**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.29 (s, 1H), 8.22 (s, 1H), 7.96 (s, 1H), 7.75 (s, 1H), 7.60 – 7.57 (m, 1H), 7.45 – 7.18 (m, 6H), 5.23 (s, 2H), 4.27 – 4.13 (m, 1H), 3.87 (s, 3H), 3.74 – 3.62 (m, 1H), 3.31 – 3.21 (m, 2H), 3.16 – 3.13 (m, 1H), 2.93 – 2.91 (m, 1H), 2.80 – 2.79 (m, 1H), 1.29 (d, *J* = 6.5 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₇N₉, 454.2; found, 453.90. LCMS purity: 254 nm: 99.9%; ANAL_SFC purity: 97.9%.

Example 47: Synthesis of Exemplary Compound 370

(R)-1-(4-(trifluoromethyl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperazine-1-carboxylate (Compound **370**)

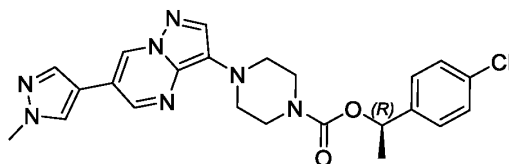


[0602] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyrimidine (Compound **S98**) (150 mg, 0.53 mmol) and ((R)-1-(4-(trifluoromethyl)phenyl)ethan-1-ol (120.8 mg, 0.63 mmol) in pyridine (5 mL) was added triphosgene (63.5 mg, 0.21 mmol) then the reaction was stirred at rt under nitrogen for 16 h. The mixture was concentrated under reduced pressure. The residue was treated with water (30 mL), then the mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified

by Prep-HPLC to afford 54.0 mg (20%) of (R)-1-(4-(trifluoromethyl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperazine-1-carboxylate (Compound **370**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.19 (d, *J* = 2.1 Hz, 1H), 8.65 (d, *J* = 2.1 Hz, 1H), 8.30 (s, 1H), 8.04 (s, 1H), 7.91 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 2H), 5.82 (q, *J* = 6.5 Hz, 1H), 3.89 (s, 3H), 3.80 - 3.45 (m, 4H), 3.33 (s, 4H), 1.51 (d, *J* = 6.6 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₄F₃N₇O₂, 500.2; found, 500.0; LCMS purity: 254 nm: 99.7%

Example 48: Synthesis of Exemplary Compound 371

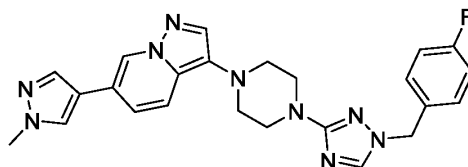
(R)-1-(4-chlorophenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperazine-1-carboxylate (Compound **371**)



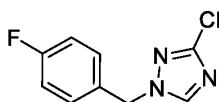
[0603] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyrimidine (Compound **S98**) (250 mg, 0.88 mmol) and (R)-1-(4-chlorophenyl)ethanol (207.3 mg, 1.32 mmol) in pyridine (5 mL) cooled to 0°C was added triphosgene (105.8 mg, 0.35 mmol) then the reaction was stirred at 0°C under nitrogen for 16 h. The mixture was concentrated under reduced pressure then the residue was treated with water (30 mL). The mixture was extracted with EtOAc (3 x 50 mL) then the combined organic extracts were washed with brine (10 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 101.1 mg (24%) of (R)-1-(4-chlorophenyl)ethyl 4-(6-(1-methyl-4,5-dihydro-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperazine-1-carboxylate (Compound **371**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.19 (d, *J* = 2.1 Hz, 1H), 8.64 (d, *J* = 2.1 Hz, 1H), 8.30 (s, 1H), 8.03 (d, *J* = 0.9 Hz, 1H), 7.90 (s, 1H), 7.47 – 7.37 (m, 4H), 5.73 (q, *J* = 6.5 Hz, 1H), 3.89 (s, 3H), 3.75 – 3.45 (m, 4H), 3.22 (s, 3H), 1.47 (d, *J* = 6.6 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₃H₂₄ClN₇O₂, 466.2; found, 466.2; LCMS purity: 254 nm: 99.3%

Example 49: Synthesis of Exemplary Compound 372

3-(4-(1-(4-fluorobenzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **372**)

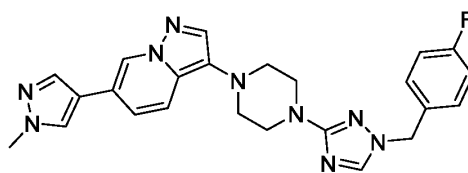


Step 1. Preparation of 3-chloro-1-(4-fluorobenzyl)-1H-1,2,4-triazole



[0604] To a solution of 3-chloro-1H-1,2,4-triazole (3.00 g, 28.9 mmol) dissolved in DMF (60 mL) was added 1-(bromomethyl)-4-fluorobenzene (6.57 g, 34.8 mmol) and K_2CO_3 (8.01 g, 58.0 mmol) then the reaction was heated to 80°C and stirred for 16 h. The mixture was cooled to rt and filtered, then the filter cake was washed with DMF (2 x 1 mL). The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 4.5 g (58.7%) of 3-chloro-1-(4-fluorobenzyl)-1H-1,2,4-triazole as a white solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.73 (s, 1H) 7.42 – 7.37 (m, 2H) 7.25 – 7.19 (m, 2H) 5.38 (s, 2H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_9H_7ClFN_3$, 212.0; found, 212.0.

Step 2. 3-(4-(1-(4-fluorobenzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **372**)

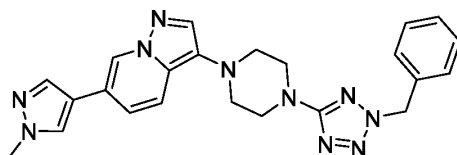


[0605] To a solution of 3-chloro-1-(4-fluorobenzyl)-1H-1,2,4-triazole (300 mg, 1.42 mmol, as prepared in the previous step) dissolved in dioxane (8 mL) was added 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (400 mg, 1.42 mmol), Cs_2CO_3 (924 mg, 2.84 mmol), and Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (119 mg, 0.142 mmol), then the reaction under nitrogen was heated to 100°C and stirred for 16 h at 100°C. The mixture was cooled to rt and concentrated under reduced pressure.

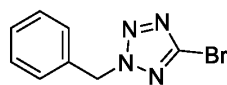
The residue was purified by Prep-Achiral-SFC to afford 161.6 mg (25%) of 3-(4-(1-(4-fluorobenzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **372**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (t, *J* = 1.3 Hz, 1H) 8.31 (s, 1H) 8.23 (s, 1H) 7.97 (s, 1H) 7.77 (s, 1H) 7.66 (d, *J* = 9.3 Hz, 1H) 7.39 – 7.28 (m, 3H) 7.25 – 7.16 (m, 2H) 5.23 (s, 2H) 3.87 (s, 3H) 3.45 (t, *J* = 4.9 Hz, 4H) 3.06 (t, *J* = 5.0 Hz, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₄FN₉, 458.2; found, 458.5; LCMS purity: 254 nm: 99.7%

Example 50: Synthesis of Exemplary Compound 373

3-(4-(2-benzyl-2H-tetrazol-5-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **373**)

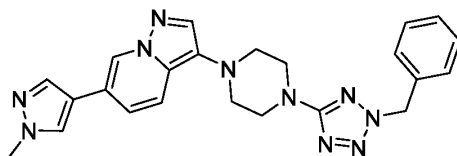


Step 1. Preparation of 2-benzyl-5-bromo-2H-tetrazole



[0606] To a solution of 5-bromo-2H-1,2,3,4-tetrazole (100 mg, 0.67 mmol) and K₂CO₃ (92.8 mg, 0.67 mmol) in ACN (10 mL) was added benzyl bromide (114.8 mg, 0.67 mmol) at rt then the reaction was heated to 80°C and stirred for 3 h. The mixture was cooled to rt, filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by Prep-TLC (EtOAc / PE 1:5) to afford 45 mg (28%) of 2-benzyl-5-bromo-2H-tetrazole as a colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 7.48 – 7.32 (m, 5H), 5.98 (s, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₈H₇BrN₄, 239.0; found, 239.1.

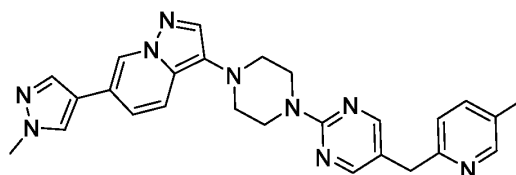
Step 2. Preparation of 3-(4-(2-benzyl-2H-tetrazol-5-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **373**)



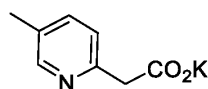
[0607] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylpyrazolo[1,5-a]pyridine (Compound **12**) (413.3 mg, 1.46 mmol), Cs₂CO₃ (954 mg, 2.93 mmol), and 2-benzyl-5-bromo-2H-tetrazole (350 mg, 1.46 mmol, as prepared in the previous step) in dioxane (15 mL) was added Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (123.1 mg, 0.15 mmol) under nitrogen, then the reaction was heated to 90°C and stirred for 16 h. The mixture was cooled to rt, concentrated under reduced pressure, and the residue was purified by Prep-TLC (MeOH / DCM 1:10), then the crude product was re-crystallized from THF/ACN (1:5) (5 mL) to afford 164.5 mg (26%) of 3-(4-(2-benzyl-2H-tetrazol-5-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **373**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (t, *J* = 1.3 Hz, 1H), 8.23 (s, 1H), 7.98 (d, *J* = 0.8 Hz, 1H), 7.79 (s, 1H), 7.67 (dd, *J* = 9.2, 0.9 Hz, 1H), 7.46 – 7.30 (m, 6H), 5.75 (s, 2H), 3.87 (s, 3H), 3.56 (t, *J* = 5.0 Hz, 4H), 3.14 – 3.18 (m, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₃H₂₄N₁₀, 441.2; found, 441.3; LCMS purity: 254 nm: 98.6%.

Example 51: Synthesis of Exemplary Compound 374

6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(5-((5-methylpyridin-2-yl)methyl)pyrimidin-2-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **374**)



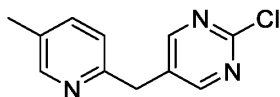
Step 1. Preparation of potassium 2-(5-methylpyridin-2-yl)acetate



[0608] To a solution of methyl 2-(5-methylpyridin-2-yl)acetate (2.00 g, 12.11 mmol) dissolved in EtOH (20 mL) was added H₂O (0.23 g, 12.71 mmol). The resulting mixture was stirred for 10 minutes at 60°C under nitrogen. A solution of KOtBu (1.43 g, 12.71 mmol) was prepared in absolute EtOH (10 mL) in dried glassware, and then added dropwise over 10 minutes to the initial solution at 60°C. After complete conversion as monitored by HPLC, the mixture was concentrated under reduced pressure and the residue was stirred in anhydrous MTBE (10 mL) for 30 minutes. The solids were isolated by filtration and washed with EtOH/MTBE (1:1) (2 x 10 mL) and MTBE (3 x 10 mL). The solids were dried under

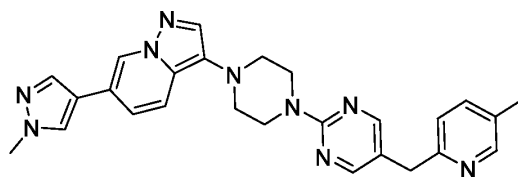
reduced pressure to afford 1.85 g (77%) of potassium 2-(5-methylpyridin-2-yl)acetate as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.17 (s, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 3.29 (s, 2H), 2.21 (s, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_8\text{H}_8\text{KNO}_2$, 190.0; found, 152.1.

Step 2. Preparation of 2-chloro-5-((5-methylpyridin-2-yl)methyl)pyrimidine



[0609] To a solution of potassium 2-(5-methylpyridin-2-yl)acetate (1.3 g, 6.87 mmol, as prepared in the previous step) dissolved in mesitylene (50 mL) was added 5-bromo-2-chloropyrimidine (1.06 g, 5.50 mmol), $\text{Pd}_2(\text{dba})_3$ (0.09 g, 0.10 mmol), and Xantphos (0.24 g, 0.41 mmol) under nitrogen, then the reaction was heated to 135°C and stirred for 24 h. The mixture was cooled to rt, diluted with water (50 mL), and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with brine (3 x 30 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with EtOAc / PE (1:3) to afford 1.0 g (53%) of 2-chloro-5-((5-methylpyridin-2-yl)methyl)pyrimidine as an orange solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.70 (s, 2H), 8.30 (d, J = 2.4 Hz, 1H), 7.54 (dt, J = 7.9, 1.5 Hz, 1H), 7.27 (d, J = 7.9 Hz, 1H), 4.10 (s, 2H), 2.23 (s, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{11}\text{H}_{10}\text{ClN}_3$, 220.1; found, 220.1.

Step 3. Preparation of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(5-((5-methylpyridin-2-yl)methyl)pyrimidin-2-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound 374)

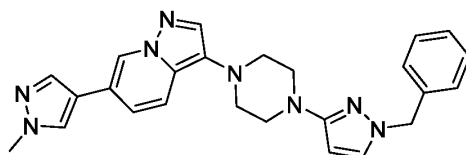


[0610] To a solution of 2-chloro-5-((5-methylpyridin-2-yl)methyl)pyrimidine (400 mg, 1.82 mmol, as prepared in the previous step) dissolved in NMP (10 mL) was added 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound 12) (411.3 mg, 1.46 mmol) and K_2CO_3 (755 mg, 5.46 mmol) under nitrogen, then the reaction was heated to 110°C and stirred for 16 h. The mixture was cooled to rt, diluted with water (50 mL), and extracted with DCM (3 x 50 mL). The combined organic extracts were

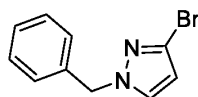
washed with brine (3 x 50 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 120.6 mg (14%) of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(5-((5-methylpyridin-2-yl)methyl)pyrimidin-2-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **374**) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.82 (s, 1H), 8.34 – 8.29 (m, 3H), 8.23 (s, 1H), 7.97 (d, $J = 0.9$ Hz, 1H), 7.77 (s, 1H), 7.68 (dd, $J = 9.3, 1.0$ Hz, 1H), 7.53 (dd, $J = 8.1, 2.4$ Hz, 1H), 7.32 (dd, $J = 9.2, 1.6$ Hz, 1H), 7.20 (d, $J = 8.0$ Hz, 1H), 3.92 – 3.84 (m, 9H), 3.03 (t, $J = 5.0$ Hz, 4H), 2.25 (s, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{26}\text{H}_{27}\text{N}_9$, 466.2; found, 466.2; LCMS purity: 254 nm: 99.0%.

Example 52: Synthesis of Exemplary Compound 375

3-(4-(1-benzyl-1H-pyrazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **375**)

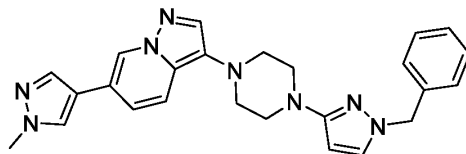


Step 1. Preparation of 1-benzyl-3-bromo-1H-pyrazole



[0611] To a solution of 3-bromo-1H-pyrazole (3 g, 20.41 mmol) and K_2CO_3 (4.23 g, 30.62 mmol) in ACN (50 mL) cooled to 0°C was added benzyl bromide (4.19 g, 24.49 mmol), then the reaction was heated to 80°C and stirred for 5 h. The mixture was cooled to rt, the precipitated solids were collected by filtration and washed with DCM (3 x 60 mL). The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with EtOAc / PE (1:5) to afford 3.2 g (66%) of 1-benzyl-3-bromo-1H-pyrazole as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 7.88 (d, $J = 2.3$ Hz, 1H), 7.41 – 7.19 (m, 5H), 6.40 (d, $J = 2.3$ Hz, 1H), 5.30 (s, 2H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{10}\text{H}_9\text{BrN}_2$, 237.0; found, 237.1.

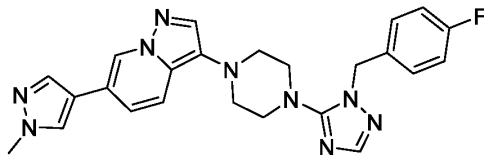
Step 2. Preparation of 3-(4-(1-benzyl-1H-pyrazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **375**)



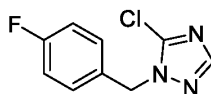
[0612] To a solution of 1-benzyl-3-bromo-1H-pyrazole (1 g, 4.22 mmol, as prepared in the previous step) and 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (1.19 g, 4.22 mmol) in dioxane (30 mL) under nitrogen were added Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (354.77 mg, 0.42 mmol) and K₃PO₄ (1.79 g, 8.44 mmol) then the reaction was heated to 100°C and stirred for 16 h. The mixture was cooled to rt, concentrated under reduced pressure, and the residue was dissolved in water. The aqueous mixture was extracted with DCM (5 x 80 mL), then the combined organic extracts were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with MeOH / DCM (1:15) and Prep-HPLC to afford 158.2 mg (8%) of 3-(4-(1-benzyl-1H-pyrazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **375**) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.77 (s, 1H), 7.67 – 7.57 (m, 2H), 7.38 – 7.16 (m, 6H), 5.80 (d, *J* = 2.3 Hz, 1H), 5.15 (s, 2H), 3.87 (s, 3H), 3.26 (t, *J* = 4.8 Hz, 4H), 3.08 (t, *J* = 4.8 Hz, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₆N₈, 439.2; found, 439.15; LCMS purity: 254 nm: 99.3%.

Example 53: Synthesis of Exemplary Compound 376

3-(4-(1-(4-fluorobenzyl)-1H-1,2,4-triazol-5-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **376**)

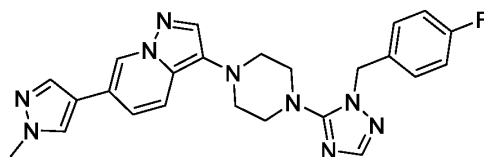


Step 1. Preparation of 5-chloro-1-(4-fluorobenzyl)-1H-1,2,4-triazole



[0613] To a solution of 3-chloro-1H-1,2,4-triazole (3 g, 28.9 mmol) dissolved in DMF (60 mL) was added 1-(bromomethyl)-4-fluorobenzene (6.57 g, 34.8 mmol) and K_2CO_3 (8.01 g, 58.0 mmol) then the reaction was heated to 80°C and stirred for 16 h. The mixture was cooled to rt, filtered, and the filter cake was washed with DMF (2 x 5 mL). The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 180 mg (0.3%) of 5-chloro-1-(4-fluorobenzyl)-1H-1,2,4-triazole as a white solid. MS (ESI) m/z $[M+H]^+$ calcd. for $C_9H_7ClFN_3$, 212.0; found, 212.0; LCMS purity: 254 nm: 70%.

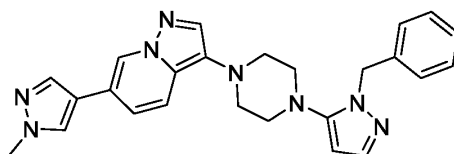
Step 2. Preparation of 3-(4-(1-(4-fluorobenzyl)-1H-1,2,4-triazol-5-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **376**)



[0614] To a solution of 5-chloro-1-(4-fluorobenzyl)-1H-1,2,4-triazole (20 mg, 0.095 mmol, as prepared in the previous step) in dioxane (2 mL) under nitrogen was added 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (26.7 mg, 0.095 mmol), Cs_2CO_3 (61.6 mg, 0.19 mmol), and Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (7.95 mg, 0.01 mmol), then the reaction was heated to 100°C and stirred for 16 h under nitrogen. The mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by Prep-Achiral-SFC to afford 7.2 mg (17%) of 3-(4-(1-(4-fluorobenzyl)-1H-1,2,4-triazol-5-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **376**) as a yellow solid. 1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.83 (t, J = 1.2 Hz, 1H) 8.23 (s, 1H) 7.98 (d, J = 0.9 Hz, 1H) 7.77 (d, J = 7.3 Hz, 2H) 7.68 (dd, J = 9.3, 1.0 Hz, 1H) 7.36 – 7.25 (m, 3H) 7.24 – 7.17 (m, 2H) 5.27 (s, 2H) 3.87 (s, 3H) 3.27 – 3.22 (m, 4H) 3.15 – 3.09 (m, 4H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{24}FN_9$, 458.2; found, 458.2; LCMS purity: 254 nm: 99.5%.

Example 54: Synthesis of Exemplary Compound 377

3-(4-(1-benzyl-1H-pyrazol-5-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **377**)

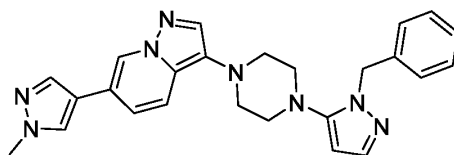


Step 1. Preparation of 1-benzyl-5-bromo-1H-pyrazole



[0615] To a stirred solution of 3-bromo-1H-pyrazole (3 g, 20.41 mmol) and K_2CO_3 (4.23 g, 30.62 mmol) in ACN (60 mL) cooled to $0^\circ C$ was added benzyl bromide (4.19 g, 24.49 mmol) then the reaction was heated to $80^\circ C$ and stirred for 16 h. The mixture was cooled to rt then the precipitated solids were collected by filtration and washed with DCM (3 x 60 mL). The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with EtOAc / PE (1:5) to afford 800 mg (17%) of 1-benzyl-5-bromo-1H-pyrazole as a white solid. MS: (ESI) m/z $[M+H]^+$ calcd. for $C_{10}H_9BrN_2$, 237.0; found, 237.1.

Step 2. Preparation of 3-(4-(1-benzyl-1H-pyrazol-5-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **377**)

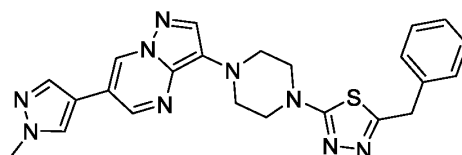


[0616] To a solution of 1-benzyl-5-bromo-1H-pyrazole (300 mg, 1.26 mmol, as prepared in the previous step) and 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (357.3 mg, 1.26 mmol) in dioxane (5 mL) under nitrogen were added Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (106.4 mg, 0.13 mmol) and K_3PO_4 (537.2 mg, 2.53 mmol), then the reaction was heated to $100^\circ C$ and stirred for 16 h under nitrogen. The mixture was cooled to rt, concentrated under reduced pressure, and the residue was dissolved in water. The aqueous mixture was extracted with DCM (3 x 80 mL) then the

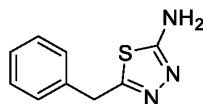
combined organic extracts were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure, then the residue was purified by Prep-TLC (MeOH / DCM 1:15) and Prep-HPLC to afford 27.1 mg (5%) of 3-(4-(1-benzyl-1H-pyrazol-5-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **377**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.98 (d, *J* = 0.6 Hz, 1H), 7.79 (s, 1H), 7.65 (dd, *J* = 0.6 Hz, 9.2 Hz 1H), 7.42 (d, *J* = 1.9 Hz, 1H), 7.38 – 7.15 (m, 6H), 6.07 (d, *J* = 1.9 Hz, 1H), 5.25 (s, 2H), 3.87 (s, 3H), 3.12 (t, *J* = 4.6 Hz, 4H), 2.98 (t, *J* = 4.6 Hz, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₆N₈, 439.2; found, 439.15; LCMS purity: 254 nm: 99.6%.

Example 55: Synthesis of Exemplary Compound 378

2-benzyl-5-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperazin-1-yl)-1,3,4-thiadiazole (Compound **378**)

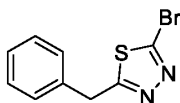


Step 1. Preparation of 5-benzyl-1,3,4-thiadiazol-2-amine



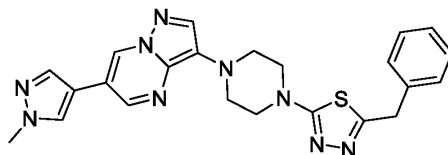
[0617] To a solution of 2-phenylacetic acid (1.3 g, 9.55 mmol) in POCl₃ (5.86 g, 38.19 mmol) was added hydrazinecarbothioamide (1.31 g, 14.32 mmol) then the reaction was heated to 80°C and stirred for 4 h under nitrogen. The mixture was cooled in an ice bath, neutralized to pH 8 with 50% NaOH solution, and filtered. The filter cake was washed with EtOH (3 x 20 mL) then the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with EtOAc / PE (2:1) to afford 1.1 g (60%) of 5-benzyl-1,3,4-thiadiazol-2-amine as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 7.37 – 7.20 (m, 5H), 7.03 (s, 2H), 4.14 (s, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₉H₉N₃S, 192.1; found, 192.1.

Step 2. Preparation of 2-benzyl-5-bromo-1,3,4-thiadiazole



[0618] To a solution of 5-benzyl-1,3,4-thiadiazol-2-amine (500 mg, 2.61 mmol, as prepared in the previous step) in ACN (20 mL) was added CuBr_2 (700.7 mg, 3.137 mmol) and tert-butyl nitrite (404.4 mg, 3.92 mmol) then the reaction was stirred at rt for 16 h under nitrogen. The reaction was cooled to 0°C then quenched by the addition of sat. aqueous NH_4Cl (30 mL). The resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (3 x 10 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with EtOAc / PE (1:2) to afford 400 mg (59%) of 2-benzyl-5-bromo-1,3,4-thiadiazole as a light-yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 7.40 – 7.24 (m, 5H), 4.49 (s, 2H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_9\text{H}_7\text{BrN}_2\text{S}$, 255.0; found, 255.0.

Step 3. Preparation of 2-benzyl-5-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperazin-1-yl)-1,3,4-thiadiazole (Compound **378**)

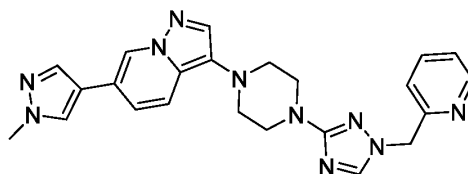


[0619] To a solution of 2-benzyl-5-bromo-1,3,4-thiadiazole (200 mg, 0.78 mmol, as prepared in the previous step) in DMSO (5 mL) was added 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyrimidine (Compound **S98**) (222.1 mg, 0.78 mmol) and DIEA (202.6 mg, 1.57 mmol), then the reaction was heated to 110°C and stirred for 16 h under nitrogen. The mixture was cooled to rt, diluted with water (30 mL), and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine (3x30 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 27.5 mg (7%) of 2-benzyl-5-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)piperazin-1-yl)-1,3,4-thiadiazole (Compound **378**) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 9.20 (d, J = 2.1 Hz, 1H), 8.65 (d, J = 2.1 Hz, 1H), 8.30 (s, 1H), 8.04 (d, J = 0.8 Hz, 1H), 7.93 (s, 1H), 7.40 – 7.23 (m, 5H), 4.25 (s, 2H), 3.89 (s, 3H), 3.59 (dd, J = 6.6, 3.8 Hz,

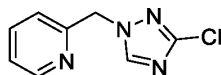
4H), 3.39 – 3.34 (m, 4H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{23}H_{23}N_9S$, 458.1; found, 458.1; LCMS purity: 254 nm: 98.9%.

Example 56: Synthesis of Exemplary Compound 379

6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(pyridin-2-ylmethyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound 379)

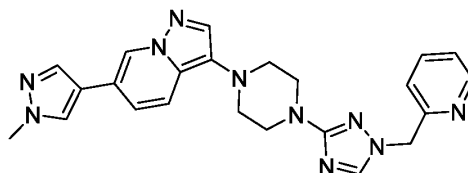


Step 1. Preparation of 2-((3-chloro-1H-1,2,4-triazol-1-yl)methyl)pyridine



[0620] To a solution of 2-(bromomethyl)pyridine hydrobromide (8.8 g, 34.8 mmol) in DMF (30 mL) was added 3-chloro-1H-1,2,4-triazole (3.00 g, 29.0 mmol) and K_2CO_3 (8.01 g, 58.0 mmol) then the reaction was heated to 80°C and stirred for 16 h under nitrogen. The mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with a C18 silica gel column eluting with 10-50% ACN / water (10mM NH_4HCO_3) to afford 5.4 g (48%) of 2-((3-chloro-1H-1,2,4-triazol-1-yl)methyl)pyridine as a brown liquid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.76 (s, 1H), 8.56 – 8.45 (m, 1H), 7.86 – 7.78 (m, 1H), 7.38 – 7.27 (m, 2H), 5.55 – 5.50 (m, 2H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_8H_7ClN_4$, 195.0; found, 195.0.

Step 2. Preparation of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(pyridin-2-ylmethyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound 379)

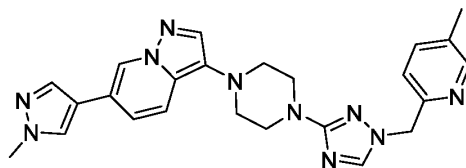


[0621] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylpyrazolo[1,5-a]pyridine (Compound 12) (300 mg, 1.06 mmol) and 2-((3-chloro-1H-1,2,4-triazol-1-yl)methyl)pyridine (248 mg, 1.28 mmol, as prepared in the previous step) in dioxane (10

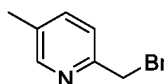
mL) under nitrogen was added Cs₂CO₃ (692 mg, 2.13 mmol) and Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (90 mg, 0.11 mmol) then the reaction was heated to 90°C and stirred for 16 h under nitrogen. The mixture was cooled to rt, filtered, and the filter cake was washed with EtOAc (2 x 5 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with MeOH / DCM (1:25) and Prep-Achiral-SFC to afford 120.9 mg (26%) of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(pyridin-2-ylmethyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **379**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.81 (s, 1H), 8.57 – 8.51 (m, 1H), 8.33 (s, 1H), 8.22 (s, 1H), 7.96 (s, 1H), 7.84 – 7.77 (m, 1H), 7.76 (s, 1H), 7.68 – 7.61 (m, 1H), 7.37 – 7.27 (m, 2H), 7.25 – 7.18 (m, 1H), 5.33 (s, 2H), 3.86 (s, 3H), 3.48 – 3.41 (m, 4H), 3.09 – 3.02 (m, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₃H₂₄N₁₀, 441.2; found, 441.1; LCMS purity: 254 nm: 99.0%

Example 57: Synthesis of Exemplary Compound 380

6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-((5-methylpyridin-2-yl)methyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **380**)

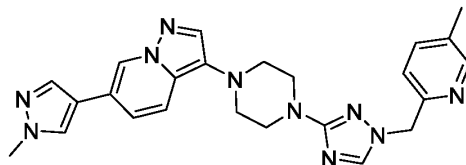


Step 1. Preparation of 2-(bromomethyl)-5-methylpyridine



[0622] To a solution of (5-methylpyridin-2-yl)methanol (300 mg, 2.43 mmol) in DCM (6 mL) was added POBr₃ (698.3 mg, 2.43 mmol) then the reaction was stirred at rt for 30 minutes under nitrogen.

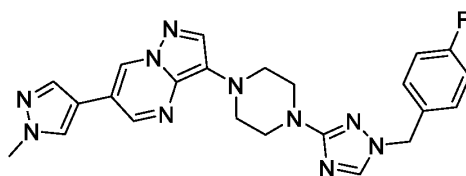
Step 2. 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-((5-methylpyridin-2-yl)methyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **380**).



[0623] To a solution of 3-(4-(1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **S102**) (120 mg, 0.34 mmol) in DMF (10 mL) were added K_2CO_3 (189.8 mg, 1.37 mmol) and 2-(bromomethyl)-5-methylpyridine (127.8 mg, 0.68 mmol, as prepared in the previous step) then the reaction was heated to 90°C and stirred overnight under nitrogen. The mixture was cooled to rt and concentrated under reduced pressure. The residue was dissolved in water (50 mL) and the aqueous mixture was extracted with DCM (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 15.1 mg (10%) of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-((5-methylpyridin-2-yl)methyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **380**) as a yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.81 (s, 1H), 8.37 (s, 1H), 8.31 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.76 (s, 1H), 7.66-7.60 (m, 2H), 7.32-7.30 (m, 1H), 7.15-7.13 (m, 1H), 5.27 (s, 2H), 3.86 (s, 3H), 3.44 (t, $J = 5.0$ Hz, 4H), 3.05 (t, $J = 5.0$ Hz, 4H), 2.28 (s, 3H). MS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{26}N_{10}$, 455.2; found, 455.15. LCMS purity: 254 nm: 99.2%.

Example 58: Synthesis of Exemplary Compound 381

3-(4-(1-(4-fluorobenzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine (Compound **381**)

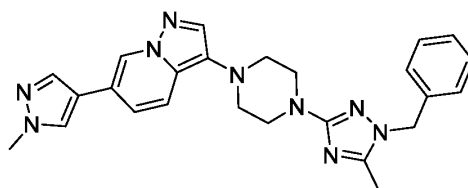


[0624] To a solution of 3-chloro-1-(4-fluorobenzyl)-1H-1,2,4-triazole (194.1 mg, 0.91 mmol, as prepared in Example 49, Step 1) and 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyrimidine (Compound **S98**) (200 mg, 0.706 mmol) in dioxane (20 mL) under nitrogen were added Cs_2CO_3 (460.5 mg, 1.41 mmol) and Pd-PEPPSI-IPent^{Cl} 2-

methylpyridine (59.3 mg, 0.07 mmol) then the reaction was heated to 100°C and stirred overnight under nitrogen. The mixture was cooled to rt and concentrated under reduced pressure. The residue was dissolved in water (50 mL) then the aqueous mixture was extracted with DCM (3 x 50 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 12.9 mg (4%) of 3-(4-(1-(4-fluorobenzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine (Compound **381**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.18 (d, *J* = 2.1 Hz, 1H), 8.63 (d, *J* = 2.1 Hz, 1H), 8.31-8.28 (m, 2H), 8.03 (s, 1H), 7.90 (s, 1H), 7.44 – 7.26 (m, 2H), 7.26 – 7.12 (m, 2H), 5.22 (s, 2H), 3.89 (s, 3H), 3.47-3.42 (m, 4H), 3.32-3.29 (m, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₃H₂₃FN₁₀, 459.2; found, 459.20. LCMS purity: 254 nm: 99.6%.

Example 59: Synthesis of Exemplary Compound 382

3-(4-(1-benzyl-5-methyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **382**)

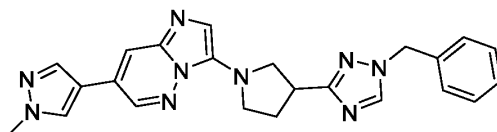


[0625] To a stirred solution of 1-benzyl-3-chloro-5-methyl-1H-1,2,4-triazole (150 mg, 0.72 mmol) and 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (204 mg, 0.72 mmol) in dioxane (5 mL) under nitrogen were added Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (60.8 mg, 0.072 mmol) and Cs₂CO₃ (470.7 mg, 1.44 mmol) then the reaction was heated to 90°C and stirred for 16 h under nitrogen. The mixture was cooled to rt, diluted with water, and extracted with DCM (3x60 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with MeOH / DCM (1:15) and Prep-HPLC to afford 166.7 mg (51%) of 3-(4-(1-benzyl-5-methyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **382**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (d, *J* = 0.5 Hz, 1H), 7.76 (s, 1H),

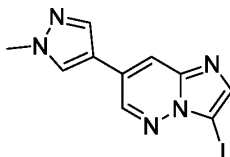
7.65 (dd, $J = 0.5$ Hz, 9.2 Hz, 1H), 7.45 – 7.15 (m, 6H), 5.19 (s, 2H), 3.87 (s, 3H), 3.43 (t, $J = 4.8$ Hz, 4H), 3.05 (t, $J = 4.8$ Hz, 4H), 2.32 (s, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{25}H_{27}N_9$, 454.2; found, 454.10; LCMS purity: 254 nm: 99.7%.

Example 60: Synthesis of Exemplary Compound 383

3-(3-(1-benzyl-1H-1,2,4-triazol-3-yl)pyrrolidin-1-yl)-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (Compound 383)

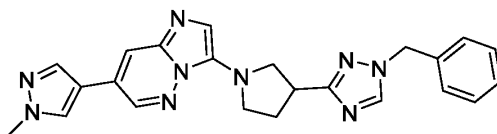


Step 1. Preparation of 3-iodo-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine



[0626] To a round bottom flask containing 7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (1.00 g, 5.02 mmol, as prepared for Compound S3, Step 4) was added DMF (10 mL) then the solution was cooled to 0°C and NIS (1.36 g, 6.02 mmol) was added at a rate to keep the temperature <10°C. The reaction was warmed to rt and stirred for 75 minutes then the mixture was added to a stirred solution of $Na_2S_2O_3$ (1.98 g, 12.5 mmol) and $NaHCO_3$ (1.05 g, 12.5 mmol) in water (10 mL). The reaction flask was rinsed with THF (2 x 1.5 mL) and the slurry was stirred vigorously for 1 h. The mixture was filtered and the solids were washed with water (3 x 5.5 mL) and dried to afford 1.54 g (94%) of 3-iodo-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine as a white solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.97 (d, $J = 2.1$ Hz, 1H), 8.43 (s, 1H), 8.27 (d, $J = 2.1$ Hz, 1H), 8.16 (s, 1H), 7.83 (s, 1H), 3.90 (s, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{10}H_9IN_5$, 326.1; found, 325.8; HPLC purity: 210 nm: 100.0%; 254 nm: 100.0%.

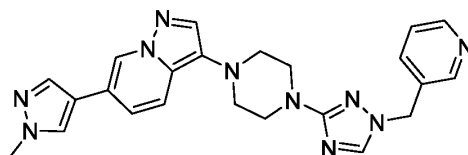
Step 2. Preparation of 3-(3-(1-benzyl-1H-1,2,4-triazol-3-yl)pyrrolidin-1-yl)-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (Compound 383)



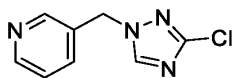
[0627] To a round bottom flask containing 3-iodo-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (1.45 g, 4.46 mmol, as prepared in the previous step), 1-benzyl-3-pyrrolidin-3-yl-1H-1,2,4-triazole (Compound **S101**) (750 mg, 3.30 mmol), K_3PO_4 (2.09 g, 9.86 mmol), and CuI (256 mg, 1.35 mmol) (pre-sparged with argon for 20 minutes) was added 1-butanol (19 mL) and 1,2-ethanediol (3.8 mL) under nitrogen, then the reaction was heated to 100°C and stirred for 60 h under nitrogen. The mixture was cooled to rt and diluted with MeOH (100 mL). After stirring rapidly for 20 minutes, the mixture was filtered through a bed of Celite, and the filtrate was concentrated under reduced pressure. The residue was dissolved in 10% IPA/DCM, washed with an equal volume of (7:3) sat. aqueous NH_4Cl /conc. NH_4OH (3 times), brine, dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with of 0-10% MeOH / DCM. The pure fractions were concentrated under reduced pressure then the residue was dissolved in a warm mixture of acetone / MTBE. After cooling to rt, the solid was collected by filtration and dried under reduced pressure to afford 463 mg (33%) of 3-[3-(1-benzyl-1H-1,2,4-triazol-3-yl)pyrrolidin-1-yl]-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (Compound **383**) as a yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.72 (m, 1H), 8.56 (s, 1H), 8.33 (s, 1H), 8.07 (s, 2H), 7.40-7.25 (m, 5H), 7.13 (s, 1H), 5.36 (s, 2H), 3.88 (s, 3H), 3.80 (m, 1H), 3.66-3.51 (m, 3H), 3.50-3.43 (m, 1H), 2.42-2.31 (m, 1H); 2.30-2.19 (m, 1H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{24}N_8$, 426.2; found, 426.1; HPLC purity: 210 nm: 98.5%; 254 nm: 98.0%.

Example 61: Synthesis of Exemplary Compound 384

6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(pyridin-3-ylmethyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **384**)

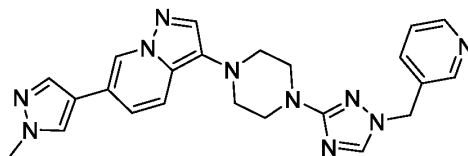


Step 1. Preparation of 3-((3-chloro-1H-1,2,4-triazol-1-yl)methyl)pyridine



[0628] To a solution of 3-chloro-1H-1,2,4-triazole (3 g, 28.98 mmol) and 3-(bromomethyl)pyridine hydrobromide (8.8 g, 34.78 mmol) in DMF (40 mL) was added K_2CO_3 (8.01 g, 57.97 mmol) under nitrogen then the reaction was heated to 80°C and stirred overnight. The mixture was cooled to rt, diluted with water (110 mL), and extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine (2 x 80 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 1.70 g (30%) of 3-((3-chloro-1H-1,2,4-triazol-1-yl)methyl)pyridine as a white solid. 1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.76 (s, 1H), 8.59 (d, J = 2.0 Hz, 1H), 8.55 (dd, J = 4.8, 1.6 Hz, 1H), 7.74 (dt, J = 8.0, 2.0 Hz, 1H), 7.42 (dd, J = 7.8, 4.8 Hz, 1H), 5.45 (s, 2H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_8H_7ClN_4$, 195.0; found, 195.1.

Step 2. Preparation of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(pyridin-3-ylmethyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **384**)

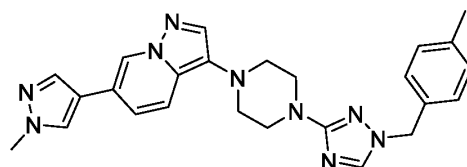


[0629] To a solution of 3-((3-chloro-1H-1,2,4-triazol-1-yl)methyl)pyridine (200 mg, 1.03 mmol, as prepared in the previous step), 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (290.2 mg, 0.77 mmol), and Cs_2CO_3 (837.1 mg, 2.57 mmol) in dioxane (10 mL) under nitrogen was added Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (86.4 mg, 0.10 mmol) then the reaction was heated to 100°C and stirred overnight under nitrogen. The mixture was cooled to rt and concentrated under reduced pressure. The residue was diluted with water (60 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine (2 x 40 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography with a C18 silica gel column eluting with 10-50% ACN / water (10mM NH_4HCO_3) to afford 155.1 mg (34%) of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(pyridin-3-ylmethyl)-1H-1,2,4-triazol-3-yl)

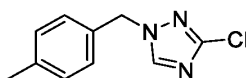
piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **384**) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.81 (s, 1H), 8.58 – 8.50 (m, 2H), 8.35 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.76 (s, 1H), 7.71 – 7.69 (m, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.40 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.31 (dd, *J* = 9.2, 1.5 Hz, 1H), 5.29 (s, 2H), 3.86 (s, 3H), 3.50 – 3.40 (m, 4H), 3.06 – 3.04 (m, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₃H₂₄N₁₀, 441.2; found, 441.2; LCMS purity: 254 nm: 98.9%

Example 62: Synthesis of Exemplary Compound **385**

6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(4-methylbenzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **385**)

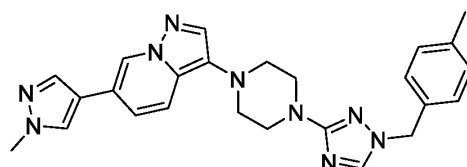


Step 1. Preparation of 3-chloro-1-(4-methylbenzyl)-1H-1,2,4-triazole



[0630] To a solution of 3-chloro-1H-1,2,4-triazole (1 g, 9.66 mmol) and 1-(bromomethyl)-4-methylbenzene (2.15 g, 11.59 mmol) in DMF (20 mL) were added K₂CO₃ (2.67 g, 19.32 mmol) then the reaction was heated to 80°C and stirred for 16 h under nitrogen. The mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with a C18 silica gel column eluting with 10-100% ACN / water (10mM NH₄HCO₃) to afford 1.5 g (75%) of 3-chloro-1-[(4-methylphenyl)methyl]-1,2,4-triazole as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.72 (s, 1H), 7.29-7.14 (m, 4H), 5.34 (s, 2H), 2.29 (s, 3H). MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₀H₁₀ClN₃, 208.0; found, 208.

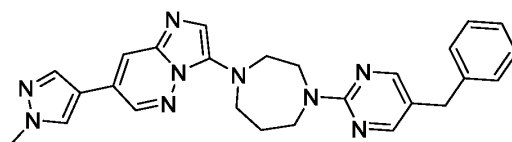
Step 2. Preparation of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(4-methylbenzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **385**)



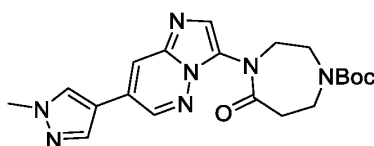
[0631] To a solution of 3-chloro-1-[(4-methylphenyl)methyl]-1,2,4-triazole (264.7 mg, 1.27 mmol, as prepared in the previous step) and 6-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylpyrazolo[1,5-a]pyridine (Compound **12**) (300 mg, 1.06 mmol) in dioxane (20 mL) under nitrogen were added Cs₂CO₃ (692.3 mg, 2.12 mmol) and Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (89.3 mg, 0.10 mmol) then the reaction was heated to 100°C and stirred for 16 h under nitrogen. The mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by Prep-TLC (MeOH / DCM 1:10) and Prep-HPLC to afford 122.7 mg (25%) of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(4-methylbenzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **385**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.81 (d, *J* = 1.6 Hz, 1H), 8.28 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.76 (s, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.31 (d, *J* = 9.2, 1H), 7.17 (s, 4H), 5.17 (s, 2H), 3.87 (s, 3H), 3.44 (t, *J* = 4.9 Hz, 4H), 3.05 (t, *J* = 4.9 Hz, 4H), 2.28 (s, 3H). MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₇N₉, 454.1; found, 454.10. LCMS purity: 254 nm: 99.9%.

Example 63: Synthesis of Exemplary Compound 386

3-(4-(5-benzylpyrimidin-2-yl)-1,4-diazepan-1-yl)-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (Compound **386**)



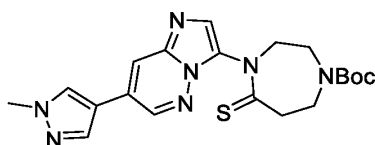
Step 1. Preparation of tert-butyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]-5-oxo-1,4-diazepane-1-carboxylate



[0632] A suspension of 3-bromo-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (Compound **S3**) (3.91 g, 13.3 mmol) and tert-butyl 5-oxo-1,4-diazepane-1-carboxylate (3.13 g, 14.6 mmol) in dioxane (72 mL) under nitrogen was treated with *N,N'*-dimethyl-1,2-ethanediamine (0.57 mL, 5.3 mmol), CuI (0.507 g, 2.66 mL), and K₃PO₄ (8.47 g, 39.9 mmol) then the reaction was heated to 100°C and stirred overnight under nitrogen. The mixture was cooled to rt and filtered through a pad of Celite. The filter pad was washed

with DCM and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with 0-100% of (10% MeOH in DCM) / DCM to afford 2.18 g (40%) of tert-butyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]-5-oxo-1,4-diazepane-1-carboxylate as a tan solid. MS (ESI) m/z $[M+H]^+$ calcd. for $C_{20}H_{26}N_7O_3$, 412.2; found, 411.7

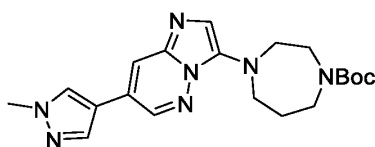
Step 2. Preparation of tert-butyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]-5-thioxo-1,4-diazepane-1-carboxylate



[0633] A suspension of tert-butyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]-5-oxo-1,4-diazepane-1-carboxylate (1.95 g, 4.74 mmol, as prepared in the previous step) in THF (75 mL) was warmed to 55°C then 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane (1.3 g, 3.3 mmol) was added. The reaction warmed to 60°C and stirred for 2 h, then additional 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane (1.34 g, 3.32 mmol) was added and the reaction was stirred at 60°C for 4.5 h. Additional 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane (1.50 g, 3.71 mmol) was added and the reaction was stirred at 60°C for 1.5 h at 60°C. The mixture was cooled to rt and stirred overnight then rewarmed to 60°C, 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane (1.4 g, 3.5 mmol) was added, and the mixture was stirred for 2.5 h. The reaction was cooled to rt, concentrated under reduced pressure, and the residue was dissolved in DCM (100 mL). The mixture was washed with a mixture of sat. aqueous NaHCO_3 (50 mL) and water (100 mL). DCM (100 mL) was added to the aqueous layer resulting in an emulsion. The mixture was filtered through a pad of Celite, and the layers separated. The filter pad was washed with DCM and this filtrate was used to extract the aqueous layer. The filter pad was washed with DCM and the filtrate was used to extract the aqueous layer an additional three times until the aqueous layer showed no desired product by HPLC. The filter pad was washed with DCM until HPLC showed no additional product eluted from the Celite pad. All the DCM extracts were combined, dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel

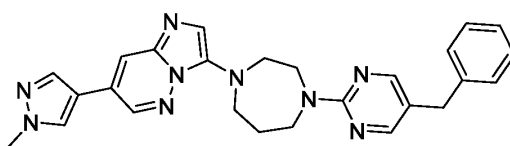
chromatography eluting with 20% DCM in acetone to afford 1.83 g (90%) of tert-butyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]-5-thioxo-1,4-diazepane-1-carboxylate as a yellow solid. MS (ESI) m/z $[M+H]^+$ calcd. for $C_{20}H_{26}N_7O_2S$, 428.2; found, 428.1

Step 3. Preparation of tert-butyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]-1,4-diazepane-1-carboxylate



[0634] To a mixture of tert-butyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]-5-thioxo-1,4-diazepane-1-carboxylate (107 mg, 0.25 mmol, as prepared in the previous step) in MeOH (6 mL) was added Raney nickel (1.5 g, 26 mmol) as a suspension in MeOH (5 mL) then the reaction was stirred vigorously at rt overnight. The mixture was filtered through a pad of Celite then the filter pad was washed well with THF. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 20% DCM in acetone to afford 65 mg (66%) of tert-butyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]-1,4-diazepane-1-carboxylate as an orange foam. MS (ESI) m/z $[M+H]^+$ calcd. for $C_{20}H_{28}N_7O_2$, 398.2; found, 398.0

Step 4. Preparation of 3-[4-(5-benzylpyrimidin-2-yl)-1,4-diazepan-1-yl]-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (Compound **386**)

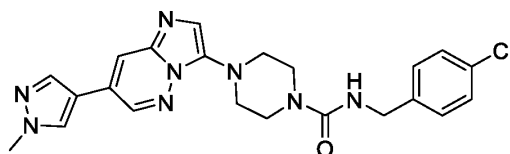


[0635] To a solution of tert-butyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]-1,4-diazepane-1-carboxylate (124 mg, 0.31 mmol, as prepared in the previous step) in DCM (6.3 mL) cooled to 0°C was added TFA (1.3 mL, 17 mmol) dropwise then the reaction was stirred for 30 minutes. The mixture was concentrated under reduced pressure then the residue was stirred with toluene and concentrated under reduced pressure. This was repeated two more times. The residue was then stirred with DCM and concentrated under reduced pressure. This was repeated two more times and the residue

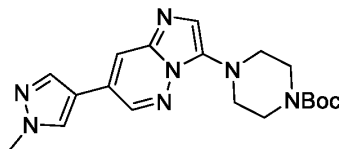
placed under high vacuum. The residue was dissolved in NMP (2.3 mL) then 5-benzyl-2-chloropyrimidine (67 mg, 0.33 mmol) and K_2CO_3 (216 mg, 1.57 mmol) were added. The mixture was heated to 110°C for 3.5 h, cooled to rt, and stirred overnight. The reaction was rewarmed to 110°C and stirred for another 4.5 h. The reaction was cooled to rt, diluted with EtOAc (30 mL), and washed with water (2 x 10 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 0-100% of (10% MeOH in DCM) / DCM. The pure fractions were combined and concentrated under reduced pressure then the residue was stirred with hexane and concentrated (x3), then dried under reduced pressure overnight. The solid residue was triturated with 25% ether in hexane, filtered, washed with hexane and dried at 50°C overnight under reduced pressure to afford 77 mg (53%) of 3-[4-(5-benzylpyrimidin-2-yl)-1,4-diazepan-1-yl]-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (Compound **386**) as a yellow solid. 1H NMR (400 MHz, CD_3OD) δ (ppm) 8.66 (d, $J=2.08$ Hz, 1H) 8.12 - 8.19 (m, 3H) 7.98 (s, 1H) 7.87 (d, $J=2.20$ Hz, 1H) 7.24 - 7.32 (m, 2H) 7.15 - 7.22 (m, 3H) 7.11 (s, 1H) 3.98 - 4.04 (m, 2H) 3.96 (s, 3H) 3.91 (t, $J=6.05$ Hz, 2H) 3.79 (s, 2H) 3.62 - 3.69 (m, 2H) 3.44 - 3.53 (m, 2H) 2.06 (quin, $J=5.87$ Hz, 2H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{26}H_{28}N_9$, 466.3; found, 466.1; HPLC purity: 210 nm: 99.6%; 254 nm: 99.6%.

Example 64: Synthesis of Exemplary Compound 387

N-(4-chlorobenzyl)-4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl)piperazine-1-carboxamide (Compound **387**)

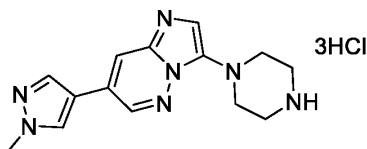


Step 1. Preparation of tert-butyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]piperazine-1-carboxylate



[0636] A suspension of 3-bromo-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (Compound **S3**) (6.56 g, 23.6 mmol), tert-butyl 1-piperazinecarboxylate (22.0 g, 118 mmol) and KOtBu (3.97 g, 35.4 mmol) in tBuOH (66 mL) and dioxane (33 mL) was sparged with argon for 10 minutes. The reaction was treated with tBuXPhos Pd G1 (2.43 g, 3.54 mmol) and the mixture sparged again for another 10 minutes. The reaction was sparged an additional 2 minutes while being agitated in an ultrasound bath. The reaction was then warmed at 55°C under argon for 3 h. The reaction was concentrated under reduced pressure and the residue was diluted with DCM (300 mL). The mixture was washed with 10% citric acid (4 x 100 mL). The combined citric acid washes were extracted with DCM (100 mL). The combined DCM extracts were washed with water (3 x 100 mL). The combined water washes were extracted with DCM (100 mL). The combined DCM extracts were washed with sat. aqueous NaHCO₃ (100 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 0-100% of (10% MeOH in DCM) / DCM to afford 6.62 g (73%) of tert-butyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]piperazine-1-carboxylate as a yellow green solid. MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₉H₂₆N₇O₂, 384.2; found, 394.0.

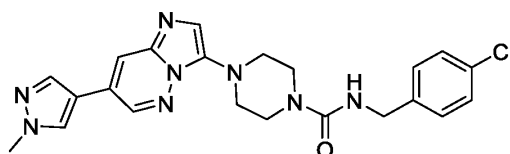
Step 2. Preparation of 7-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylimidazo[1,2-b]pyridazine trihydrochloride salt



[0637] To a suspension of tert-butyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]piperazine-1-carboxylate (4.6 g, 12 mmol, as prepared in the previous step) in EtOAc (69 mL) heated to 40°C was added conc. HCl (5.1 mL, 60 mmol) slowly over 10 minutes while under nitrogen. The slurry was stirred at 45°C for 3 h, cooled to rt,

and diluted with MTBE (180 mL). After stirring 10 minutes, the mixture was filtered, and the filter pad washed with MTBE (4 x 40 mL). The solids were air dried to afford 4.50 g (96%) of 7-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylimidazo[1,2-b]pyridazine trihydrochloride salt as a yellow-green solid. MS (ESI) m/z $[M+H]^+$ calcd. for $C_{14}H_{18}N_7$, 284.2; found, 284.1.

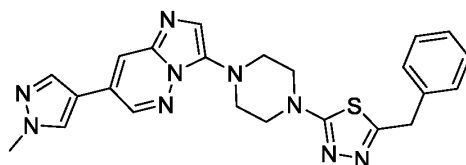
Step 3. Preparation of N-(4-chlorobenzyl)-4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxamide (Compound **387**)



[0638] A mixture of 7-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylimidazo[1,2-b]pyridazine trihydrochloride salt (100 mg, 25 mmol, as prepared in the previous step) in ACN (3 mL) was cooled to 0°C then DIEA (0.22 mL, 1.3 mmol) and 1-chloro-4-(isocyanatomethyl)benzene (34 μ L, 0.26 mmol) were added. The reaction was warmed to rt and stirred for 30 minutes, then additional ACN (3 mL) was added. After stirring 1 h, the reaction was concentrated under reduced pressure. The residue was partitioned between water (10 mL), DCM (10 mL), and 10% MeOH in DCM (5 mL). The water layer was washed with 10% MeOH in DCM (3 x 5 mL). The combined organic extracts were washed with sat. aqueous $NaHCO_3$ (5 mL), and brine (5 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 0-100% (10% MeOH in DCM) / DCM to afford 73 mg (64%) of N-(4-chlorobenzyl)-4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxamide (Compound **387**) as a yellow solid; 1H NMR (400 MHz, CD_3OD) δ (ppm) 8.74 (d, $J=1.96$ Hz, 1H) 8.20 (s, 1H) 8.02 (s, 1H) 7.96 (d, $J=2.08$ Hz, 1H) 7.23 - 7.35 (m, 5H) 4.36 (s, 2H) 3.96 (s, 3H) 3.62 - 3.71 (m, 4H) 3.23 - 3.30 (m, 4H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{22}H_{24}ClN_8O$, 451.2; found, 451.0; HPLC purity: 210 nm: 99.5%; 254 nm: 99.4%.

Example 65: Synthesis of Exemplary Compound 388

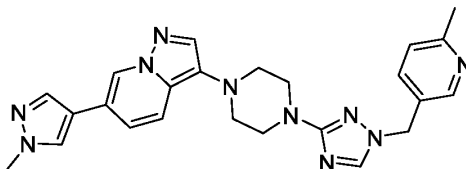
2-benzyl-5-(4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl)piperazin-1-yl)-1,3,4-thiadiazole (Compound **388**)



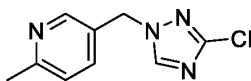
[0639] To a mixture of 2-benzyl-5-bromo-1,3,4-thiadiazole (243 mg, 0.95 mmol, as prepared in Example **55**, Step 2) and 7-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylimadazo[1,2-b]pyridazine trihydrochloride salt (404 mg, 1.03 mmol, as prepared in Example **64**, Step 2) in DMAc (6.8 mL) was added DIEA (1.60 mL, 9.18 mmol) under a nitrogen then the reaction was heated to 100°C and stirred for 25 h. The mixture was cooled to rt, diluted with EtOAc, was washed with water (3 times) and brine, then dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 0-15% MeOH/DCM to afford 114 mg (26%) of 3-[4-(5-benzyl-1,3,4-thiadiazol-2-yl)piperazin-1-yl]-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (Compound **388**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (d, *J* = 2.1 Hz, 1H), 8.36 (s, 1H), 8.17 (d, *J* = 2.1 Hz, 1H), 8.10 (s, 1H), 7.40-7.21 (m, 6H), 4.25 (s, 2H), 3.89 (s, 3H), 3.62 (m, 4H), 3.31 (m, 5H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₃H₂₄N₉S, 458.2; found, 458.1; HPLC purity: 210 nm: 97.2%; 254 nm: 98.1%.

Example 66: Synthesis of Exemplary Compound 389

6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-((6-methylpyridin-3-yl)methyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **389**)

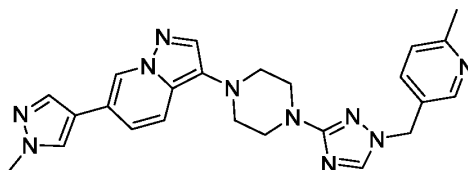


Step 1. Preparation of 5-((3-chloro-1H-1,2,4-triazol-1-yl)methyl)-2-methylpyridine



[0640] To a solution of 3-chloro-1H-1,2,4-triazole (1.00 g, 9.66 mmol) and 5-(bromomethyl)-2-methylpyridine hydrobromide (3.09 g, 11.59 mmol) in DMF (100 mL) was added K_2CO_3 (2.67 g, 19.32 mmol) then the reaction was heated to 90°C and stirred for 16 h under nitrogen. The mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with a C18 silica gel column eluting with 10-100% ACN / water (10 mM NH_4HCO_3) to afford 240 mg (12%) of 5-((3-chloro-1H-1,2,4-triazol-1-yl)methyl)-2-methylpyridine as a yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.74 (s, 1H), 8.46 (s, 1H), 7.65-7.62 (m, 1H), 7.28-7.25 (m, 1H), 5.40 (s, 2H), 2.46 (s, 3H). MS (ESI) m/z $[M+H]^+$ calcd. for $C_9H_9ClN_4$, 209.0; found, 209.0.

Step 2. 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-((6-methylpyridin-3-yl)methyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **389**)

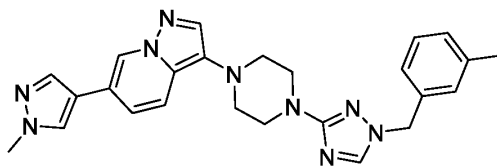


[0641] To a solution of 5-((3-chloro-1H-1,2,4-triazol-1-yl)methyl)-2-methylpyridine (221.6 mg, 1.06 mmol, as prepared in the previous step) and 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (300 mg, 1.06 mmol) in dioxane (20 mL) under nitrogen were added Cs_2CO_3 (692.3 mg, 2.12 mmol) and Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (89.3 mg, 0.10 mmol) then the reaction was heated to 100°C and stirred overnight under nitrogen. The mixture was cooled to rt and concentrated under reduced pressure. The residue was dissolved in water (100 mL) then the aqueous mixture was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 122.7 mg (25%) of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-((6-methylpyridin-3-yl)methyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **389**) as a yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.81 (s, 1H), 8.42 (d, J = 2.3 Hz, 1H), 8.32 (s, 1H), 8.22 (s, 1H), 7.97

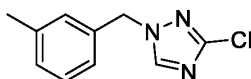
(s, 1H), 7.76 (s, 1H), 7.66-7.63 (m, 1H), 7.60-7.58 (m, 1H), 7.32-7.30 (m, 1H), 7.26-7.24 (m, 1H), 5.23 (s, 2H), 3.86 (s, 3H), 3.44 (t, $J = 5.0$ Hz, 4H), 3.05 (t, $J = 5.0$ Hz, 4H), 2.45 (s, 3H). MS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{26}N_{10}$, 455.2; found, 455.25. LCMS purity: 254 nm: 99.8%.

Example 67: Synthesis of Exemplary Compound 390

6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(3-methylbenzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound 390)

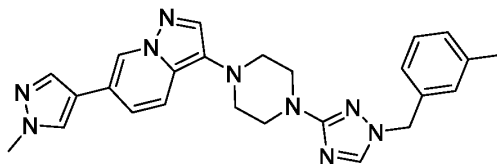


Step 1. Preparation of 3-chloro-1-(3-methylbenzyl)-1H-1,2,4-triazole



[0642] To a solution of 3-chloro-1H-1,2,4-triazole (2 g, 19.32 mmol) and 1-(bromomethyl)-3-methylbenzene (4.29 g, 23.19 mmol) in DMF (20 mL) was added K_2CO_3 (5.34 g, 38.64 mmol) in portions at rt then the reaction was heated to 80°C and stirred overnight. The mixture was cooled to rt and purified by Prep-AChiral-HPLC to afford 2.75 g (69%) of 3-chloro-1-(3-methylbenzyl)-1H-1,2,4-triazole as a colorless oil: 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.73 (s, 1H), 7.23 – 7.24 (m, 1H), 7.15 – 7.09 (m, 3H), 5.34 (s, 2H), 2.29 (s, 3H). MS (ESI) m/z $[M+H]^+$ calcd. for $C_{10}H_{10}ClN_3$, 208.0; found, 208.1.

Step 2. Preparation of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(3-methylbenzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound 390)

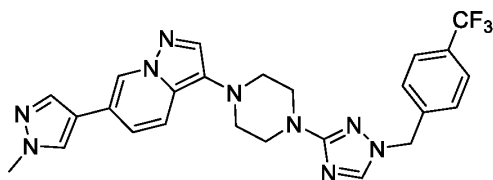


[0643] To a solution of 3-chloro-1-(3-methylbenzyl)-1H-1,2,4-triazole (200 mg, 0.96 mmol, as prepared in the previous step), 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound 12) (271.9 mg, 0.96 mmol) and Cs_2CO_3 (784.5 mg,

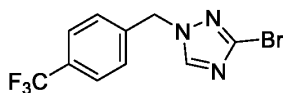
2.41 mmol) in dioxane (10 mL) under nitrogen was added Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (81 mg, 0.10 mmol) then the reaction was heated to 100°C and stirred overnight under nitrogen. The mixture was cooled to rt and concentrated under reduced pressure. The residue was diluted with water (60 mL) then the aqueous mixture was extracted with EtOAc (2 x 50 mL). The combined organic extracts were washed with brine (2 x 40 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 158.3 mg (36%) of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(3-methylbenzyl)-1H-1,2,4-triazol-3-yl) piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **390**) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.30 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.77 (s, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.31 (dd, *J* = 9.3, 1.4 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.10 (dd, *J* = 14.2, 8.0 Hz, 3H), 5.19 (s, 2H), 3.87 (s, 3H), 3.51 – 3.39 (m, 4H), 3.12 – 2.99 (m, 4H), 2.30 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₇N₉, 454.3; found, 454.3; LCMS purity: 254 nm: 99.9%

Example 68: Synthesis of Exemplary Compound 391

6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(4-(trifluoromethyl)benzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **391**)



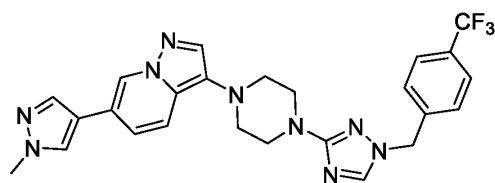
Step 1. Preparation of 3-bromo-1-(4-(trifluoromethyl)benzyl)-1H-1,2,4-triazole



[0644] To a solution of 3-bromo-1H-1,2,4-triazole (3 g, 20.27 mmol) in DMF (30 mL) were added 1-(bromomethyl)-4-(trifluoromethyl)benzene (5.82 g, 24.33 mmol) and K₂CO₃ (5.60 g, 40.55 mmol) then the reaction was warmed to 80°C and stirred for 16 h. The mixture was cooled to rt, and filtered, then the filter cake was washed with DMF (2 x 1 mL). The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography with a C18 silica gel column eluting with 10-80%

ACN / water to afford 4 g (58%) of 3-bromo-1-(4-(trifluoromethyl)benzyl)-1H-1,2,4-triazole as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.75 (s, 1H), 7.76 (d, $J = 8.1$ Hz, 2H), 7.51 (d, $J = 8.0$ Hz, 2H), 5.53 (s, 2H). MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{10}\text{H}_7\text{BrF}_3\text{N}_3$, 306.0; found, 306.0.

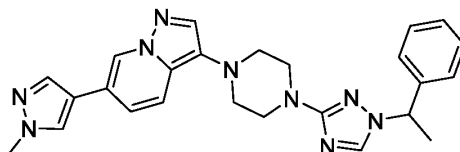
Step 2. Preparation of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(4-(trifluoromethyl)benzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **391**)



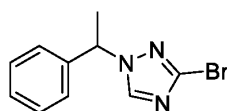
[0645] To a solution of 3-bromo-1-(4-(trifluoromethyl)benzyl)-1H-1,2,4-triazole (277.9 mg, 1.06 mmol, as prepared in the previous step) and 6-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylpyrazolo[1,5-a]pyridine (Compound **12**) (200 mg, 0.71 mmol) in dioxane (10 mL) under nitrogen were added Cs_2CO_3 (461.5 mg, 1.41 mmol) and Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (59.5 mg, 0.07 mmol) then the reaction was warmed to 100°C and stirred overnight under nitrogen. The mixture was cooled to rt and concentrated under reduced pressure. The residue was dissolved in water (50 mL) then the aqueous mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 105.3 mg (29%) of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(4-(trifluoromethyl)benzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **391**) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.82 (s, 1H), 8.37 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.78 – 7.71 (m, 3H), 7.65 (d, $J = 9.2$ Hz, 1H), 7.47 (d, $J = 8.0$ Hz, 2H), 7.33–7.29 (m, 1H), 5.36 (s, 2H), 3.86 (s, 3H), 3.45 (t, $J = 4.8$ Hz, 4H), 3.06 (t, $J = 4.9$ Hz, 4H). MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{25}\text{H}_{24}\text{F}_3\text{N}_9$, 508.2; found, 508.25. LCMS purity: 254 nm: 99.9%.

Example 69: Synthesis of Exemplary Compound 392

6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(1-phenylethyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **392**)

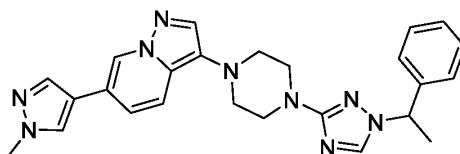


Step 1. Preparation of 3-bromo-1-(1-phenylethyl)-1H-1,2,4-triazole



[0646] To a solution of 3-bromo-1H-1,2,4-triazole (3 g, 20.3 mmol) in DMF (30 mL) was added (1-bromoethyl)benzene (4.5 g, 24.3 mmol) and K_2CO_3 (5.6 g, 40.5 mmol) then the reaction was warmed to 80°C and stirred for 16 h. The mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography with a C18 silica gel column eluting with 10-50% ACN / water (10mM NH_4HCO_3) and Prep-HPLC to afford 2.9 g (51%) of 3-bromo-1-(1-phenylethyl)-1,2,4-triazole as a light yellow oil. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.75 (s, 1H), 7.41 – 7.27 (m, 5H), 5.79 – 5.69 (m, 1H), 1.81 (d, $J = 7.1$ Hz, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{10}H_{10}BrN_3$, 252.0; found, 252.1.

Step 2. Preparation of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(1-phenylethyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **392**)

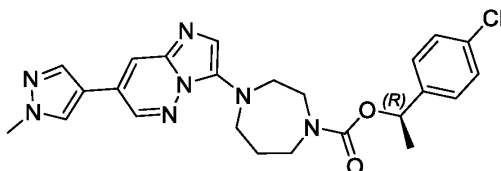


[0647] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylpyrazolo[1,5-a]pyridine (Compound **12**) (200 mg, 0.71 mmol) and 3-bromo-1-(1-phenylethyl)-1H-1,2,4-triazole (214 mg, 0.85 mmol, as prepared in the previous step) in dioxane (5 mL) under nitrogen was added Cs_2CO_3 (462 mg, 1.42 mmol) and Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (60 mg, 0.07 mmol) then the reaction was warmed to 90°C and stirred for 16 h under nitrogen. The mixture was cooled to rt and filtered, then the filter cake was washed with

EtOAc (2x5 mL). The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with MeOH / DCM (1:25) and Prep-HPLC to afford 111.5 mg (35%) of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(1-phenylethyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **392**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.81 (s, 1H), 8.34 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.76 (s, 1H), 7.65 (d, *J* = 6.2 Hz, 1H), 7.41 – 7.24 (m, 6H), 5.51 (q, *J* = 7.0 Hz, 1H), 3.87 (s, 3H), 3.48 – 3.41 (m, 4H), 3.09 – 3.02 (m, 4H), 1.77 (d, *J* = 7.1 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₇N₉, 454.2; found, 454.2; LCMS purity: 254 nm: 99.7%

Example 70: Synthesis of Exemplary Compound 393

(R)-1-(4-chlorophenyl)ethyl 4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl)-1,4-diazepane-1-carboxylate (Compound **393**)

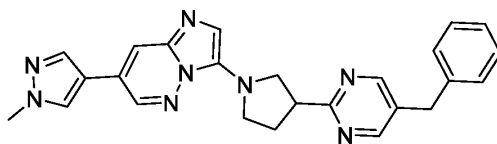


[0648] To a solution of tert-butyl 4-[7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl]-1,4-diazepane-1-carboxylate (182 mg, 0.31 mmol, as prepared in Example **63**, Step 3) in DCM (9.1 mL) cooled to 0°C was added TFA (2 mL, 25 mmol) dropwise, then the reaction was stirred for 30 minutes. The mixture was concentrated under reduced pressure then the residue was stirred with toluene and concentrated under reduced pressure. This was repeated three more times, then the residue was suspended in EtOAc (3 mL) and cooled to 0°C. TEA (0.277 mL, 1.99 mmol) was added and the mixture was stirred at 0°C for 5 minutes, then (R)-1-(4-chlorophenyl)ethyl (2,5-dioxopyrrolidin-1-yl) carbonate (Compound **S95**) (118 mg, 0.40 mmol) was added and the reaction was stirred at 0°C for 2 h. The mixture was filtered through a pad of Celite and the filter pad was washed with EtOAc (6 x 5mL). The combined filtrates were washed with sat. aqueous NaHCO₃ (2 x 8 mL) and water (8 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 0-100% (10% MeOH in DCM) / DCM. The pure fractions were combined and concentrated under reduced pressure then the residue was stirred with hexane and concentrated several times then dried under vacuum at 40°C to afford 158 mg

(91%) of (1R)-1-(4-chlorophenyl)ethyl 4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxylate (Compound **393**) as a yellow solid. ¹H NMR (400 MHz, METHANOL-*d*₄) δ ppm 8.66 (dd, *J*=10.64, 1.96 Hz, 1H) 8.17 (s, 1H) 8.00 (s, 1H) 7.88 (dd, *J*=9.41, 2.08 Hz, 1H) 7.28 - 7.38 (m, 2H) 7.13 - 7.23 (m, 3H) 5.61 - 5.78 (m, 1H) 3.96 (d, *J*=1.47 Hz, 3H) 3.43 - 3.85 (m, 8H) 1.89 - 2.12 (m, 2H) 1.40 - 1.57 (m, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₇ClN₇O₂, 480.2; found, 480.1; HPLC purity: 210 nm: 100.0%; 254 nm: 100.0%.

Example 71: Synthesis of Exemplary Compound 394

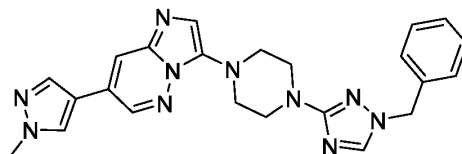
3-(3-(5-benzylpyrimidin-2-yl)pyrrolidin-1-yl)-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (Compound **394**)



[0649] A mixture of 3-bromo-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (Compound **S3**) (0.186 g) and 5-benzyl-2-pyrrolidin-3-ylpyrimidine (Compound **S100**) (0.400 g, 1.67 mmol) in tBuOH (1.85 mL) and dioxane (0.939 mL) was sparged with argon for 15 minutes then tBuXPhos Pd G1 (0.0459 g, 0.0668 mmol) and KOtBu (0.112 g, 1.00 mmol) were added and the mixture was sparged again for 10 minutes with argon. The reaction was warmed to 30°C and stirred for 12 h. The mixture was concentrated under reduced pressure and the residue was taken up in EtOAc (50 mL). The mixture was washed with water (3 x 50 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 5% MeOH / DCM to afford 39 mg (13%) of 3-[3-(5-benzylpyrimidin-2-yl)pyrrolidin-1-yl]-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (Compound **394**) as an orange solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.57 (s, 2H), 8.42 (d, *J*=2.20 Hz, 1H), 7.82 (s, 1H), 7.79 (d, *J*=2.20 Hz, 1H), 7.71 (s, 1H), 7.32 - 7.39 (m, 2H), 7.26 - 7.30 (m, 1H), 7.17 - 7.24 (m, 3H), 4.02 - 4.07 (m, 1H), 4.00 (s, 3H), 3.91 - 3.99 (m, 3H), 3.72 - 3.84 (m, 2H), 3.61 (td, *J*=8.68, 5.50 Hz, 1H), 2.53 - 2.64 (m, 1H), 2.44 - 2.53 (m, 1H); MS (ESI) *m/z* [M+H]⁺ calcd. For C₂₅H₂₅N₈: 437.5; found: 437.1; HPLC purity: 210 nm: 100.0%; 254 nm: 100.0%

Example 72: Synthesis of Exemplary Compound 395

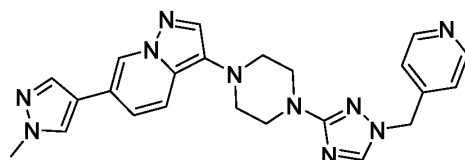
3-(4-(1-benzyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (Compound **395**)



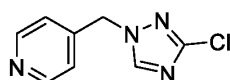
[0650] A mixture of tBuOH (0.73 mL), dioxane (0.12 mL), and water (5 μ L) sparged with a slow stream of argon for 20 minutes was added to a mixture of 1-benzyl-3-bromo-1H-1,2,4-triazole (85 mg, 0.36 mmol, as prepared for Compound **S101**, Step 1), 7-(1-methyl-1H-pyrazol-4-yl)-3-pyridazine trihydrochloride (155 mg, 0.39 mmol, as prepared in Example **64**, Step 2), KOtBu (181 mg, 1.61 mmol), and tBuXPhos Pd G1 (12 mg, 0.02 mmol) under argon, then the reaction was evacuated and back filled with argon three times. The reaction was warmed to 60°C and stirred for 1 h. The reaction was cooled to rt and concentrated under reduced pressure. The residue was partitioned between EtOAc (40 mL) and water (10 mL). The aqueous layer was washed with EtOAc (3 x 40 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 0-100% (10% MeOH in DCM) / DCM. The pure fractions were combined and concentrated under reduced pressure then the residue was dissolved in hexane and concentrated under reduced pressure. This was repeated until a yellow solid formed. The residue was dried under reduced pressure at 50°C to afford 107 mg (68%) of 3-[4-(1-benzyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl]-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (Compound **395**) as a yellow solid; ¹H NMR (400 MHz, CD₃OD) δ (ppm) 8.73 (d, J =2.08 Hz, 1H) 8.20 (d, J =1.59 Hz, 2H) 8.02 (s, 1H) 7.96 (d, J =2.08 Hz, 1H) 7.24 - 7.41 (m, 6H) 5.25 (s, 2H) 3.96 (s, 3H) 3.56 - 3.64 (m, 4H) 3.33 - 3.41 (m, 4H); MS (ESI) m/z [M+H]⁺ calcd. for C₂₃H₂₅N₁₀, 441.2; found, 441.2; HPLC purity: 210 nm: 100.0%; 254 nm: 100.0%.

Example 73: Synthesis of Exemplary Compound 396

6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(pyridin-4-ylmethyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **396**)

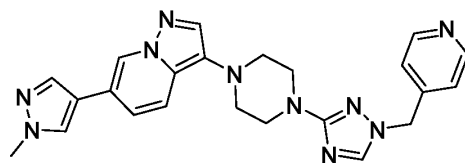


Step 1. 4-((3-chloro-1H-1,2,4-triazol-1-yl)methyl)pyridine



[0651] To a solution of 3-chloro-1H-1,2,4-triazole (2.00 g, 19.32 mmol) and 4-(bromomethyl)pyridine (3.99 g, 23.19 mmol) in DMF (40 mL) was added K₂CO₃ (5.34 g, 38.64 mmol) then the reaction was warmed to 80°C and stirred overnight. The mixture was cooled to rt and purified by reversed-phase flash chromatography with a C18 silica gel column eluting with 10-50% ACN / water (10mM NH₄HCO₃) to afford 600 mg (16%) of 4-((3-chloro-1H-1,2,4-triazol-1-yl)methyl)pyridine as a black oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.78 (s, 1H), 8.57 (d, *J* = 4.9 Hz, 2H), 7.24 (d, *J* = 4.7 Hz, 2H), 5.48 (s, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₈H₇ClN₄, 195; found, 195.

Step 2. 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(pyridin-4-ylmethyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **396**)

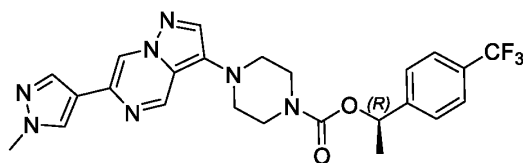


[0652] To a solution of 4-((3-chloro-1H-1,2,4-triazol-1-yl)methyl)pyridine (520 mg, 2.67 mmol, as prepared in the previous step) and 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (0.75 g, 2.67 mmol) in dioxane (20 mL) under nitrogen were added Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (0.22 g, 0.27 mmol) and Cs₂CO₃ (1.74 g, 5.34 mmol) then the reaction was warmed to 100°C and stirred overnight under nitrogen. The mixture was cooled to rt and purified by Prep-HPLC to afford 116.7 mg, 10%) of 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(pyridin-4-ylmethyl)-1H-1,2,4-triazol-3-

yl)piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **396**) as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.82 (t, $J = 1.2$ Hz, 1H), 8.57 – 8.53 (m, 2H), 8.36 (s, 1H), 8.22 (s, 1H), 7.97 (d, $J = 0.8$ Hz, 1H), 7.76 (s, 1H), 7.65 (dd, $J = 9.3, 1.0$ Hz, 1H), 7.31 (dd, $J = 9.3, 1.6$ Hz, 1H), 7.25 – 7.16 (m, 2H), 5.31 (s, 2H), 3.86 (s, 3H), 3.46 (t, $J = 5.0$ Hz, 4H), 3.06 (t, $J = 5.0$ Hz, 4H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{23}\text{H}_{24}\text{N}_{10}$, 441.2; found, 441.2; LCMS purity: 254 nm: 99.7%

Example 74: Synthesis of Exemplary Compound 397

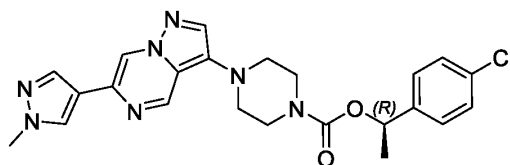
(R)-1-(4-(trifluoromethyl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazin-3-yl)piperazine-1-carboxylate (Compound **397**)



[0653] To a solution of 1-[6-(1-methylpyrazol-4-yl)pyrazolo[1,5-a]pyrazin-3-yl]piperazine (Compound **S103**) (120 mg, 0.42 mmol) and (1R)-1-[4-(trifluoromethyl)phenyl]ethanol (242 mg, 1.27 mmol) in pyridine (2 mL) cooled to 0°C was added triphosgene (377 mg, 1.27 mmol) then the reaction was stirred at 0°C for 2 h. The mixture was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with MeOH / DCM (1:20) and Prep-HPLC to afford 73.6 mg (35%) of (R)-1-(4-(trifluoromethyl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazin-3-yl)piperazine-1-carboxylate (Compound **397**) as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm) 9.19 (d, $J = 1.4$ Hz, 1H), 8.91 (d, $J = 1.4$ Hz, 1H), 8.22 (s, 1H), 8.01 (s, 1H), 7.83 (s, 1H), 7.74 (d, $J = 8.2$ Hz, 2H), 7.61 (d, $J = 8.1$ Hz, 2H), 5.82 (q, $J = 6.5$ Hz, 1H), 3.88 (s, 3H), 3.80 – 3.48 (m, 4H), 3.14 (s, 4H), 1.51 (d, $J = 6.5$ Hz, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{24}\text{H}_{24}\text{F}_3\text{N}_7\text{O}_2$, 500.2; found, 500.2; LCMS purity: 254 nm: 99.8%

Example 75: Synthesis of Exemplary Compound 398

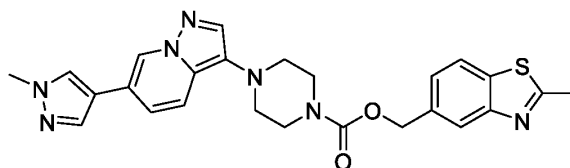
(R)-1-(4-chlorophenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazin-3-yl)piperazine-1-carboxylate (Compound **398**)



[0654] To a solution of 1-[6-(1-methylpyrazol-4-yl)pyrazolo[1,5-a]pyrazin-3-yl]piperazine (Compound **S103**) (120 mg, 0.42 mmol) and (R)-1-(4-chlorophenyl)ethanol (199 mg, 1.27 mmol) in pyridine (2 mL) cooled to 0°C was added triphosgene (377 mg, 1.27 mmol) then the reaction was stirred at 0°C for 2 h. The mixture was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with MeOH / DCM (1:20) and Prep-HPLC to afford 65.6 mg (32%) of (R)-1-(4-chlorophenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazin-3-yl)piperazine-1-carboxylate (Compound **398**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.19 (s, 1H), 8.91 (s, 1H), 8.22 (s, 1H), 8.01 (s, 1H), 7.83 (s, 1H), 7.47 – 7.37 (m, 4H), 5.74 (q, *J* = 6.5 Hz, 1H), 3.88 (s, 3H), 3.74 – 3.50 (m, 4H), 3.12 (s, 4H), 1.48 (d, *J* = 6.6 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₃H₂₄ClN₇O₂, 466.2; found, 466.1; LCMS purity: 254 nm: 97.7%

Example 76: Synthesis of Exemplary Compound 399

(2-methylbenzo[d]thiazol-5-yl)methyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **399**)

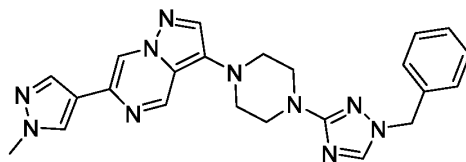


[0655] To a stirred solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-*a*]pyridine (Compound **12**) (200 mg, 0.71 mmol) and (2-methylbenzo[d]thiazol-5-yl)methanol (190.4 mg, 1.06 mmol) in pyridine (10 mL) was added triphosgene (84.1 mg, 0.28 mmol) then the reaction was stirred at rt for 16 h. The mixture was concentrated under reduced pressure then the residue was purified by silica

gel chromatography eluting with MeOH / DCM (1:40) and Prep-HPLC to afford 132.7 mg (38%) of (2-methylbenzo[*d*]thiazol-5-yl)methyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **399**) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (t, *J* = 1.2 Hz, 1H), 8.23 (s, 1H), 8.04 (d, *J* = 8.2 Hz, 1H), 7.98 – 7.95 (m, 1H), 7.93 – 7.90 (m, 1H), 7.76 (s, 1H), 7.67 – 7.61 (m, 1H), 7.42 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.32 (dd, *J* = 9.2, 1.5 Hz, 1H), 5.26 (s, 2H), 3.87 (s, 3H), 3.62 (s, 4H), 3.03 – 2.91 (m, 4H), 2.81 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₅N₇O₂S, 488.2; found, 488.2; purity: 254 nm: 99.9%

Example 77: Synthesis of Exemplary Compound 400

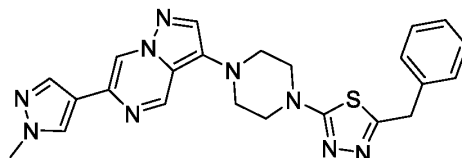
3-(4-(1-benzyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrazine (Compound **400**)



[0656] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-*a*]pyrazine (Compound **S103**) (120 mg, 0.42 mmol) in dioxane (5 mL) under nitrogen was added 1-benzyl-3-bromo-1H-1,2,4-triazole (121 mg, 0.51 mmol, as prepared for Compound **S101**, Step 1), Pd-PEPSI-IPent^{Cl} 2-methylpyridine (35.6 mg, 0.04 mmol), and Cs₂CO₃ (414 mg, 1.27 mmol) then the reaction was heated to 100°C and stirred for 16 h under nitrogen. The mixture was cooled to rt, diluted with water (20 mL), and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (3 x 10 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 101 mg (52%) of 3-(4-(1-benzyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-*a*]pyrazine (Compound **400**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.20 (d, *J* = 1.2 Hz, 1H), 8.90 (d, *J* = 1.2 Hz, 1H), 8.33 (s, 1H), 8.22 (s, 1H), 8.01 (s, 1H), 7.83 (s, 1H), 7.42 – 7.25 (m, 5H), 5.24 (s, 2H), 3.89 (s, 3H), 3.51-3.44 (m, 3.8 Hz, 4H), 3.24-3.18 (m, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₃H₂₄N₁₀, 441.2; found, 441.2; LCMS purity: 254 nm: 97.7%.

Example 78: Synthesis of Exemplary Compound 401

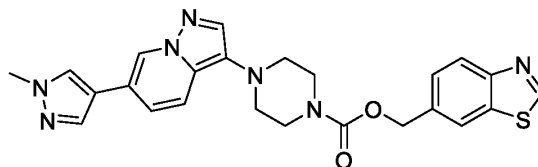
2-benzyl-5-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazin-3-yl)piperazin-1-yl)-1,3,4-thiadiazole (Compound **401**)



[0657] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyrazine (Compound **S103**) (60 mg, 0.21 mmol) in DMSO (2 mL) under nitrogen was added 2-benzyl-5-bromo-1,3,4-thiadiazole (64.8 mg, 0.25 mmol, as prepared in Example **55**, Step 2) and DIEA (82.1 mg, 0.64 mmol) then the reaction was heated to 110°C and stirred 16 h under nitrogen. The mixture was cooled to rt, diluted with water (20 mL), and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (3 x 10 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 35.4 mg (36%) of 2-benzyl-5-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazin-3-yl)piperazin-1-yl)-1,3,4-thiadiazole (Compound **401**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.21 (d, *J* = 1.2 Hz, 1H), 8.92 (d, *J* = 1.2 Hz, 1H), 8.23 (s, 1H), 8.02 (s, 1H), 7.86 (s, 1H), 7.40 – 7.23 (m, 5H), 4.26 (s, 2H), 3.89 (s, 3H), 3.65 – 3.57 (m, 4H), 3.28 – 3.22 (m, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₃H₂₃N₉S, 458.2; found, 458.2; LCMS purity: 254 nm: 98.4%.

Example 79: Synthesis of Exemplary Compound 402

benzo[d]thiazol-6-ylmethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **402**)

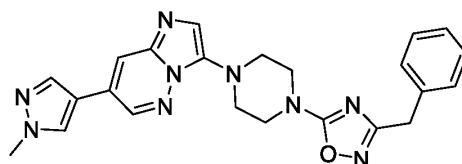


[0658] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylpyrazolo[1,5-a]pyridine (Compound **12**) (150 mg, 0.53 mmol) and 1,3-benzothiazol-6-ylmethanol (263 mg, 1.59 mmol) in pyridine (2 mL) cooled to 0°C was added triphosgene (473 mg, 1.59

mmol) then the reaction was stirred at 0°C for 1 h. The mixture was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with MeOH / DCM (1:20) and Prep-HPLC to afford 114.1 mg (45%) of benzo[d]thiazol-6-ylmethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **402**) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.41 (s, 1H), 8.82 (s, 1H), 8.24 – 8.18 (m, 2H), 8.10 (d, *J* = 8.3 Hz, 1H), 7.97 (s, 1H), 7.76 (s, 1H), 7.64 (d, *J* = 9.2 Hz, 1H), 7.57 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.32 (dd, *J* = 9.2, 1.5 Hz, 1H), 5.27 (s, 2H), 3.86 (s, 3H), 3.61 (s, 4H), 2.98 (t, *J* = 5.0 Hz, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₃N₇O₂S, 474.2; found, 474.2; LCMS purity: 254 nm: 99.6%

Example 80: Synthesis of Exemplary Compound 403

3-benzyl-5-(4-(7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazin-3-yl)piperazin-1-yl)-1,2,4-oxadiazole (Compound **403**)

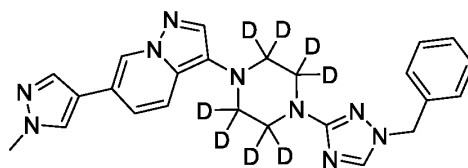


[0659] To a solution of 3-benzyl-1,2,4-oxadiazol-5-(4*H*)-one (0.18 g, 1.02 mmol, as prepared in Example **44**, Step 1) and PyBroP (0.48 g, 1.02 mmol) in dioxane (6 mL) was added DIEA (0.53 mL, 3.06 mmol) then the reaction was warmed to 50°C and stirred for 2 h. 7-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylimidazo[1,2-b]pyridazine trihydrochloride salt (0.20 g, 0.51 mmol, as prepared in Example **64**, Step 2) was added and the reaction was stirred at 50°C overnight. The reaction was cooled to rt and concentrated under reduced pressure. The residue was partitioned between DCM (20 mL) and water (10 mL). The aqueous layer was extracted with DCM (2 x 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with 0-100% (10% MeOH in DCM) / DCM. The pure fractions were combined and concentrated under reduced pressure. The residue was triturated with hexane. The resulting solid was further purified by silica gel chromatography eluting with 5% MeOH in EtOAc to afford 29 mg (13%) of 3-[4-(3-benzyl-1,2,4-oxadiazol-5-yl)piperazin-1-yl]-7-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-b]pyridazine (Compound

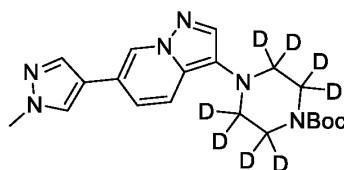
403) as a yellow solid. ^1H NMR (400 MHz, CD_3OD) δ (ppm) 8.75 (d, $J=2.08$ Hz, 1H) 8.21 (s, 1H) 8.03 (s, 1H) 7.97 (d, $J=2.20$ Hz, 1H) 7.20 - 7.35 (m, 6H) 3.97 (s, 3H) 3.80 - 3.90 (m, 6H) 3.35 - 3.41 (m, 4H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{23}\text{H}_{24}\text{N}_9\text{O}$, 442.2; found, 442.1; HPLC purity: 210 nm: 95.9%; 254 nm: 95.6%.

Example 81: Synthesis of Exemplary Compound 404

3-(4-(1-benzyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl-2,2,3,3,5,5,6,6-d₈)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **404**)



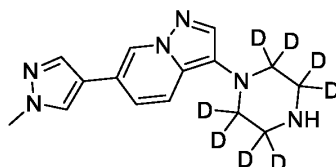
Step 1. Preparation of tert-butyl 4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxylate-(d₉, d₁₀)



[0660] To a mixture of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **S9**) (1.290 g, 4.66 mmol) and tert-butyl piperazine-1-carboxylate-d₈ (0.950 g, 4.9 mmol) in $t\text{BuOH-d}_{10}$ (13.1 mL) and dioxane (6.6 mL) was sparged with argon for 10 minutes was added KOtBu (784 mg, 6.98 mmol) and the mixture was sparged with argon for 5 minutes. $t\text{BuXPhos Pd G1}$ (0.480 g, 0.70 mmol) was added and the mixture was sparged for 5 minutes with argon, then the reaction was heated to 55°C and stirred for 2 h under argon. The mixture was cooled to rt, diluted with EtOAc , washed with water and brine, dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with a gradient of MeOH in DCM to afford 1.058 g (58%) of tert-butyl 4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxylate-(d₉ and d₁₀ mixture). ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.82 (s, 0.15H), 8.21 (br. s., 0.16H), 7.97 (s, 1H), 7.77 (s, 0.89H), 7.65 (d, $J=9.29$ Hz, 1H), 7.32 (d, $J=9.29$ Hz, 1H), 3.87 (s, 3H), 1.43 (s, 9H). MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{20}\text{H}_{18}\text{D}_9\text{N}_6\text{O}_2$, 392.27; found, 392.1 (42% of base

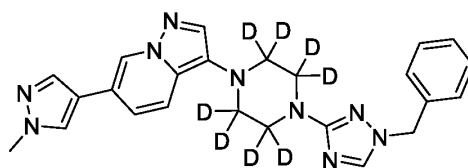
peak); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{20}H_{17}D_{10}N_6O_2$, 393.27; found, 393.1 (base peak); HPLC purity: 210 nm: 100.0%; 254 nm: 100.0%.

Step 2. Preparation of 6-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylpyrazolo[1,5-a]pyridine-(d₉, d₁₀)



[0661] To a mixture of tert-butyl 4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxylate-(d₉,d₁₀) (0.950 g, 2.43 mmol, as prepared in the previous step) in EtOAc (20 mL) warmed to 35°C was slowly added conc. HCl (1.01 mL, 12.2 mmol) then the mixture was stirred at 35°C for 1 h. The mixture was cooled to rt, diluted with EtOAc (40 mL) and stirred for 10 minutes. The solids were collected by filtration and washed with MTBE (2 X 20 mL). The solids were partially dissolved in a solution of 2N NaOH (6 mL) and water (10 mL) and extracted several times with DCM. The combined organic extracts were washed with water, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to afford 660 mg (93%) of 4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxylate-(d₉, d₁₀) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.47 (s, 0.14H), 7.75 (s, 1H), 7.72 (s, 0.83H), 7.62 (s, 0.16H), 7.53 (d, J = 9.17 Hz, 1H), 7.28 (s, 1H), 7.13 (d, J = 9.17 Hz, 1H), 3.99 (s, 3H); HPLC purity: 210 nm: 100.0%; 254 nm: 100.0%.

Step 3. Preparation of 3-[4-(1-benzyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl]-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine-d₈ (Compound **404**)

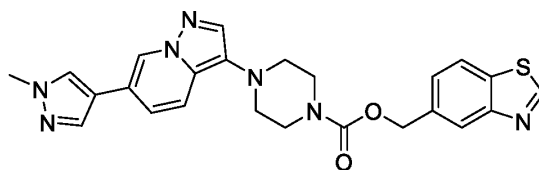


[0662] A mixture of 6-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-ylpyrazolo[1,5-a]pyridine-(d₉,d₁₀) (0.650 g, 2.24 mmol, as prepared in the previous step) and 1-benzyl-3-bromo-1H-1,2,4-triazole (0.640 g, 2.69 mmol, as prepared for Compound **S101**, Step 1) in tBuOH (9.8 mL), dioxane (1.5 mL), THF (3.0 mL), and water (0.032 mL, 1.79 mmol) was sparged with argon for 5 minutes then KOtBu (0.377 g, 3.36 mmol) and tBuXPhos Pd G1

(0.154 g, 0.22 mmol) were added. The mixture was sparged with argon for 5 minutes then the reaction was heated to 50°C under argon and stirred for 2 h. Additional K_{OT}Bu (0.126 g, 1.12 mmol), tBuXPhos Pd G1 (0.154 g, 0.22 mmol) and water (0.032 mL, 1.79 mmol) were added, and the reaction was stirred under argon at 55°C overnight. The mixture was cooled to rt, diluted with EtOAc, and washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was suspended in a mixture of tBuOH (9.8 mL), dioxane (1.5 mL), THF (3.0 mL), and water (0.032 mL, 1.79 mmol) and sparged with argon for 10 minutes. To the mixture was added K_{OT}Bu (0.377 g, 3.36 mmol) and tBuXPhos Pd G1 (0.154 g, 0.22 mmol) then the mixture was sparged with argon for 5 minutes, heated to 55°C, and stirred overnight. The mixture was cooled to rt, diluted with EtOAc, washed with water and brine, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel chromatography eluting with a gradient of MeOH in DCM to afford 680 mg (66%) of 3-[4-(1-benzyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl]-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine-d₈ (Compound **404**) as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.48 (s, 1H), 7.76 (s, 1H), 7.74 (d, *J* = 4.28 Hz, 2H), 7.63 (s, 1H), 7.55 (d, *J* = 9.29 Hz, 1H), 7.35 - 7.44 (m, 3H), 7.29 - 7.33 (m, 2H), 7.15 (dd, *J* = 1.35, 9.17 Hz, 1H), 5.21 (s, 2H), 3.99 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₁₈D₈N₉, 448.3; found, 448.2; HPLC purity: 210 nm: 100.0%; 254 nm: 100.0%.

Example 82: Synthesis of Exemplary Compound 405

benzo[d]thiazol-5-ylmethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **405**)

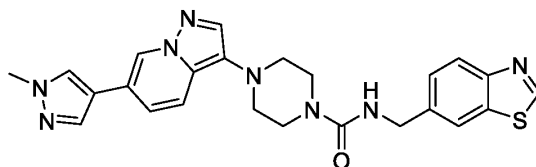


[0663] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (250 mg, 0.89 mmol) and benzo[d]thiazol-5-ylmethanol (175.5 mg, 1.01 mmol) in pyridine (10 mL) were added triphosgene (106.2 mg, 0.36 mmol) then the reaction was stirred at rt for 16 h under nitrogen. The mixture was concentrated under

reduced pressure then the residue was purified by Prep-TLC (MeOH / DCM 1:10) and Prep-HPLC to afford 161.5 mg (38%) of benzo[d]thiazol-5-ylmethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **405**) as a green solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.43 (s, 1H), 8.81 (t, *J* = 1.3 Hz, 1H), 8.23 – 8.16 (m, 2H), 8.11 (d, *J* = 1.5 Hz, 1H), 7.97 (s, 1H), 7.77 (s, 1H), 7.65 (dd, *J* = 9.2, 1.0 Hz, 1H), 7.54 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.33 (dd, *J* = 9.2, 1.6 Hz, 1H), 5.30 (s, 2H), 3.87 (s, 3H), 3.62 (s, 4H), 2.98 (t, *J* = 5.0 Hz, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₃N₇O₂S, 474.2; found, 474.1; LCMS purity: 254 nm: 99.7%

Example 83: Synthesis of Exemplary Compound 406

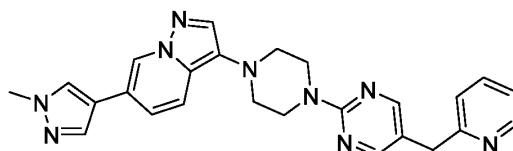
N-(benzo[d]thiazol-6-ylmethyl)-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxamide (Compound **406**)



[0664] To a solution of 2-(benzo[d]thiazol-6-yl)acetic acid (200 mg, 1.04 mmol) and DPPA (341.8 mg, 1.24 mmol) in THF (10 mL) was added TEA (314.2 mg, 3.11 mmol) dropwise at rt. The resulting mixture was stirred at rt for 5 h then concentrated under reduced pressure. The residue was dissolved in toluene (20 mL) then 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-*a*]pyridine (Compound **12**) (155.3 mg, 0.55 mmol) was added followed by dropwise addition of TEA (166.9 mg, 1.65 mmol) at rt. The reaction was warmed to 110°C and stirred overnight. The mixture was cooled to rt and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with MeOH / DCM (1:40) and Prep-HPLC to afford 142.7 mg (55%) of N-(benzo[d]thiazol-6-ylmethyl)-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxamide (Compound **406**) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.34 (s, 1H), 8.82 (s, 1H), 8.23 (s, 1H), 8.06 – 8.01 (m, 2H), 7.97 (s, 1H), 7.77 (s, 1H), 7.67 (d, *J* = 9.2 Hz, 1H), 7.48 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.35 – 7.28 (m, 2H), 4.42 (d, *J* = 5.6 Hz, 2H), 3.87 (s, 3H), 3.58 – 3.51 (m, 4H), 3.00 – 2.93 (m, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₄N₈OS, 473.2; found, 473.2; LCMS purity: 254 nm: 99.9%

Example 84: Synthesis of Exemplary Compound 250

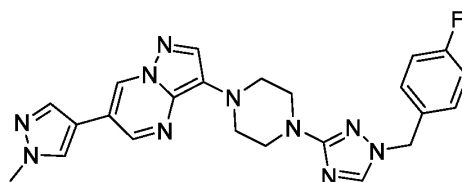
6-(1-methyl-1H-pyrazol-4-yl)-3-{4-[5-(pyridine-2-ylmethyl)pyrimidin-2-yl]piperazin-1-yl}pyrazolo[1,5-a]pyridine (Compound **250**)



[0665] A mixture of 6-(1-methyl-1H-pyrazol-4-yl)-3-piperazin-1-pyrazolo[1,5-a]pyridine hydrochloride (Compound **S19**) (92 mg, 0.29 mmol), 2-chloro-5-(pyridine-2-ylmethyl)pyrimidine (Compound **S80**) (70 mg, 0.34 mmol), K₂CO₃ (123 mg, 0.892 mmol), and NMP (3.7 mL) was sparged for 1 min with argon. The reaction was heated at 110°C for 2 h then cooled to rt and partitioned between water and DCM. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and filtered. The Filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (IPA/DCM) then further purified by C18 reverse-phase silica gel flash chromatography (ACN/water) to yield 30 mg (23%) of 6-(1-methyl-1H-pyrazol-4-yl)-3-{4-[5-(pyridine-2-ylmethyl)pyrimidin-2-yl]piperazin-1-yl}pyrazolo[1,5-a]pyridine (Compound **250**) as a solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.81 (s, 1H), 8.48 (m, 1H), 8.34 (s, 2H), 8.22 (s, 1H), 7.97 (s, 1H), 7.77 (s, 1H), 7.71 (m, 2H), 7.32 (m, 2H), 7.22 (dd, *J*=6.9, 5.3 Hz, 1H), 3.94 (s, 2H), 3.89 (m, 4H), 3.87 (s, 3H), 3.04 (m, 4H). MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₆N₉: 452.2; found, 452.3; HPLC purity: 210 nm: 100.0%; 254 nm: 100.0%.

Example 85: Synthesis of Exemplary Compound 407

3-(4-(1-(4-fluorobenzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine (Compound **407**)



[0666] To a solution of 3-chloro-1-[(4-fluorophenyl)methyl]-1,2,4-triazole (194.1 mg, 0.91 mmol, as prepared in Example 49, Step 1) and 1-[6-(1-methylpyrazol-4-yl)pyrazolo[1,5-

a]pyrimidin-3-yl]piperazine (Compound **S98**) (200 mg, 0.706 mmol) in dioxane (20 mL) were added Cs₂CO₃ (460.5 mg, 1.41 mmol) and Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (59.3 mg, 0.07 mmol) then the mixture was stirred overnight at 100°C under nitrogen. The reaction was cooled to rt and concentrated under reduced pressure. The residue was dissolved in water (50 mL) then extracted with DCM (3 x 50 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and filtered, then the filtrate was concentrated under reduced pressure. The residue was purified by Prep-HPLC to afford 12.9 mg (4%) of 3-(4-(1-(4-fluorobenzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine (Compound **407**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.18 (d, *J* = 2.1 Hz, 1H), 8.63 (d, *J* = 2.1 Hz, 1H), 8.31-8.28 (m, 2H), 8.03 (s, 1H), 7.90 (s, 1H), 7.44 – 7.26 (m, 2H), 7.26 – 7.12 (m, 2H), 5.22 (s, 2H), 3.89 (s, 3H), 3.47-3.42 (m, 4H), 3.32-3.29 (m, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₃H₂₃FN₁₀, 459.2; found, 459.20; HPLC purity: 254 nm:99.6%.

[0667] Using the procedures described in Example 85 and reagents, starting materials, and conditions known to those skilled in the art, the following compounds representative of the present disclosure were prepared:

Compound	Data
416	3-(4-(1-(4-fluorobenzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ (ppm) 9.20 (d, <i>J</i> = 1.5 Hz, 1H), 8.89 (d, <i>J</i> = 1.4 Hz, 1H), 8.31 (s, 1H), 8.21 (s, 1H), 8.00 (s, 1H), 7.83 (s, 1H), 7.39 – 7.30 (m, 2H), 7.25 – 7.15 (m, 2H), 5.22 (s, 2H), 3.88 (s, 3H), 3.50-3.42 (m, 4H), 3.24 – 3.17 (m, 4H); MS (ESI) <i>m/z</i> [M+H] ⁺ calcd. for C ₂₃ H ₂₃ FN ₁₀ , 459.2; found, 459.2; HPLC purity:254 nm: 98.4%.
417	6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(4-methylbenzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyrimidine ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ (ppm) 9.17 (d, <i>J</i> = 2.1 Hz, 1H), 8.63 (d, <i>J</i> = 2.1 Hz, 1H), 8.28 (d, <i>J</i> = 3.5 Hz, 2H), 8.03 (s, 1H), 7.89 (s, 1H), 7.17 (s, 4H), 5.17 (s, 2H), 3.89 (s, 3H), 3.47 – 3.40 (m, 4H), 3.33 – 3.29 (m, 4H), 2.29 (d, <i>J</i> = 5.1 Hz, 3H); MS (ESI)

m/z $[M+H]^+$ calcd. for $C_{24}H_{26}N_{10}$, 455.2; found, 455.2; HPLC

purity: 254 nm: 99.8%.

418 6-(1-methyl-1H-pyrazol-4-yl)-3-(4-(1-(4-methylbenzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)pyrazolo[1,5-a]pyrazine

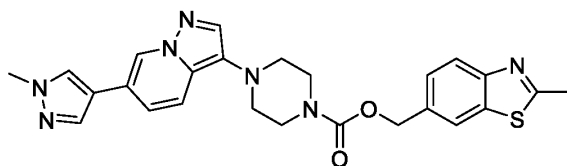
1H NMR (400 MHz, DMSO- d_6) δ (ppm) 9.20 (d, J = 1.4 Hz, 1H), 8.90 (d, J = 1.4 Hz, 1H), 8.29 (s, 1H), 8.22 (s, 1H), 8.01 (s, 1H), 7.83 (s, 1H), 7.20–7.15 (m, 4H), 5.18 (s, 2H), 3.89 (s, 3H), 3.47 (dd, J = 6.4, 3.6 Hz, 4H), 3.21 (t, J = 5.0 Hz, 4H), 2.29 (s, 3H);

MS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{26}N_{10}$, 455.2; found, 455.2;

HPLC purity: 254 nm: 99.7%.

Example 86: Synthesis of Exemplary Compound 408

(2-methylbenzo[d]thiazol-6-yl)methyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound 408)



[0668] To a stirred solution of (2-methylbenzo[d]thiazol-6-yl)methanol (Compound **S105**) (229 mg, 1.28 mmol) and 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (180.4 mg, 0.64 mmol) in pyridine (5 mL) cooled to 0°C was added BTC (379.1 mg, 1.28 mmol) then the mixture was warmed to rt and stirred for 16 h. The reaction was concentrated under reduced pressure then the residue was purified by Prep-TLC (PE/EtOAc 1:100) and then further purified by Prep-HPLC to afford 123.9 mg (20%) of (2-methylbenzo[d]thiazol-6-yl)methyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **408**) as an off-white solid. 1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 8.06 (d, J = 1 Hz, 1H), 7.97 (s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.76 (s, 1H), 7.64 (d, J = 9.2 Hz, 1H), 7.49 (dd, J = 8.4, 1.6 Hz, 1H), 7.32 (dd, J = 9.3, 1.4 Hz, 1H), 5.23 (s, 2H), 3.86 (s, 3H), 3.70–3.51 (m, 4H), 2.97 (t, J = 4.7 Hz, 4H), 2.80 (s, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{25}H_{25}N_7O_2S$, 488.1; found, 488.2; HPLC purity: 254 nm: 99.3%.

[0669] Using the procedures described in Example 86 and reagents, starting materials, and conditions known to those skilled in the art, the following compounds representative of the present disclosure were prepared:

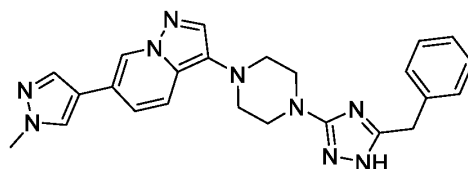
Compound	Data
430	4-(trifluoromethyl)benzyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm) 8.83 (t, <i>J</i> = 1.3 Hz, 1H), 8.23 (d, <i>J</i> = 0.8 Hz, 1H), 7.97 (d, <i>J</i> = 0.8 Hz, 1H), 7.80 – 7.73 (m, 3H), 7.69 – 7.58 (m, 3H), 7.33 (dd, <i>J</i> = 9.3, 1.6 Hz, 1H), 5.22 (s, 2H), 3.87 (s, 3H), 3.62 (s, 4H), 3.02 – 2.96 (m, 4H); MS (ESI) <i>m/z</i> [M+H]⁺ calcd. for C₂₄H₂₃F₃N₆O₂, 485.2; found, 485.0; HPLC purity: 254 nm: 99.8%
444	4-methylbenzyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm) 8.82 (t, <i>J</i> = 1.3 Hz, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.76 (s, 1H), 7.64 (dd, <i>J</i> = 9.3, 0.9 Hz, 1H), 7.32 (dd, <i>J</i> = 9.3, 1.5 Hz, 1H), 7.27 (d, <i>J</i> = 7.9 Hz, 2H), 7.19 (d, <i>J</i> = 7.9 Hz, 2H), 5.06 (s, 2H), 3.86 (s, 3H), 3.58 (t, <i>J</i> = 5.0 Hz, 4H), 2.96 (t, <i>J</i> = 5.0 Hz, 4H), 2.30 (s, 3H); MS (ESI) <i>m/z</i> [M+H]⁺ calcd. for C₂₄H₂₆N₆O₂, 431.2; found, 431.0; HPLC purity: 254 nm: 99.1%
453	4-chloro-2-cyanobenzyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm) 8.83 – 8.82 (m, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.85 (d, <i>J</i> = 2.0 Hz, 1H), 7.79 (d, <i>J</i> = 8.9 Hz, 2H), 7.71 – 7.63 (m, 2H), 7.33 (dd, <i>J</i> = 9.3 Hz, 1.5 Hz, 1H), 5.54 (s, 2H), 3.87 (s, 3H), 3.70 (t, <i>J</i> = 4.0 Hz, 2H), 3.58 (t, <i>J</i> = 4.0 Hz, 2H), 3.01 (t, <i>J</i> = 4.0 Hz, 2H), 2.94 (t, <i>J</i> = 4.0 Hz, 2H); MS (ESI) <i>m/z</i> [M+H]⁺ calcd. for C₂₄H₂₂ClN₇O₂, 475.9; found, 476.10; HPLC purity: 254 nm: 95.3%.

-
- 454** 2-cyano-4-methylbenzyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (t, *J* = 1.2 Hz, 1H), 8.22 (s, 1H), 7.97 (d, *J* = 1.2 Hz, 1H), 7.78 (s, 1H), 7.65 – 7.63 (m, 2H), 7.55 – 7.51 (m, 2H), 7.32 (dd, *J* = 9.3 Hz, 1.5 Hz, 1H), 5.48 (s, 2H), 3.86 (s, 3H), 3.70 (t, *J* = 5.0 Hz, 2H), 3.56 (t, *J* = 4.9 Hz, 2H), 3.01 (t, *J* = 5.1 Hz, 2H), 2.93 (t, *J* = 4.9 Hz, 2H), 2.42 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₅N₇O₂, 456.2; found, 456.1; HPLC purity: 254 nm: 95.7%.
-
- 467** 2-cyano-4-(trifluoromethyl)benzyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.84 (t, *J* = 1.2 Hz, 1H), 8.23 (s, 1H), 8.15 – 8.07 (m, 2H), 7.98 (d, *J* = 0.8 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.78 (s, 1H), 7.66 (dd, *J* = 9.3, 1.0 Hz, 1H), 7.34 (dd, *J* = 9.2, 1.5 Hz, 1H), 5.66 (s, 2H), 3.87 (s, 3H), 3.72 (t, *J* = 5.0 Hz, 2H), 3.61 (t, *J* = 4.9 Hz, 2H), 3.03 (t, *J* = 5.0 Hz, 2H), 2.95 (t, *J* = 5.0 Hz, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₂F₃N₇O₂, 510.2; found, 510.2; HPLC purity: 254 nm: 98.9%.
-
- 473** 1-(4-cyclopropylphenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (d, *J* = 0.6 Hz, 1H), 7.76 (s, 1H), 7.67 – 7.62 (m, 1H), 7.32 (dd, *J* = 9.3, 1.5 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 5.69 (q, *J* = 6.5 Hz, 1H), 3.87 (s, 3H), 3.58 (s, 4H), 2.96 (s, 4H), 1.95 – 1.84 (m, 1H), 1.46 (d, *J* = 6.6 Hz, 3H), 1.00 – 0.89 (m, 2H), 0.71 – 0.60 (m, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₇H₃₀N₆O₂, 471.2; found, 471.2; HPLC purity: 254 nm: 98.5%.
-

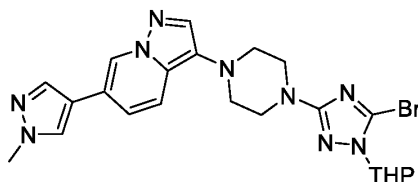
-
- 474** 1-(4-cyanophenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.78 (s, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.33 (dd, *J* = 9.3, 1.4 Hz, 1H), 5.80 (q, *J* = 6.5 Hz, 1H), 3.87 (s, 3H), 3.62 (d, *J* = 57.5 Hz, 4H), 2.98 (s, 4H), 1.49 (d, *J* = 6.6 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₅N₇O₂, 456.2; found, 456.2; HPLC purity: 254 nm: 97.8%.
-
- 481** 1-(4-(methoxymethyl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.84 (t, *J* = 1.2 Hz, 1H), 8.24 (s, 1H), 7.98 (d, *J* = 0.8 Hz, 1H), 7.78 (s, 1H), 7.66 (dd, *J* = 9.3, 1.0 Hz, 1H), 7.39 – 7.28 (m, 5H), 5.79 – 5.69 (m, 1H), 4.41 (s, 2H), 3.88 (s, 3H), 3.70 (s, 4H), 3.30 (s, 3H), 2.98 (s, 4H), 1.50 (d, *J* = 6.6 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₆H₃₀N₆O₃, 475.2; found, 475.1; HPLC purity: 254 nm: 99.4%.
-
- 505** 1-(4-(2,2,2-trifluoroethyl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.24 (s, 1H), 7.98 (s, 1H), 7.78 (d, *J* = 1.3 Hz, 1H), 7.66 (dd, *J* = 9.2, 1.1 Hz, 1H), 7.45 – 7.25 (m, 5H), 5.75 (q, *J* = 6.5 Hz, 1H), 3.87 (s, 3H), 3.65 – 3.55 (m, 6H), 2.98 (s, 4H), 1.50 (d, *J* = 6.4 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₆H₂₇F₃N₆O₂, 513.2; found, 513.1; HPLC purity: 254 nm: 99.6%.
-

Example 87: Synthesis of Exemplary Compound 409

3-(4-(5-benzyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound 409)

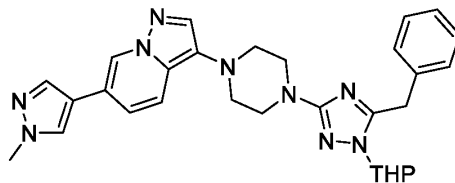


Step 1. Preparation of 3-(4-(5-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine



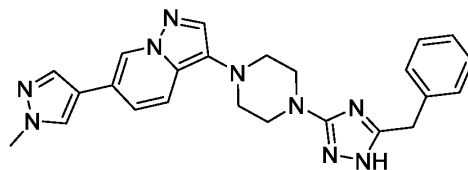
[0670] To a stirred solution of 3,5-dibromo-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazole (700 mg, 2.25 mmol) and 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound 12) (572 mg, 2.03 mmol) in IPA (5 mL) was added DIEA (581.9 mg, 4.50 mmol) at rt then the mixture was heated to 100°C and stirred for 16 h. The reaction was cooled to rt and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:100) to afford 600 mg (52%) of 3-(4-(5-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.80 (s, 1H), 7.69 (d, *J* = 9.2 Hz, 1H), 7.33 (dd, *J* = 9.2, 1.3 Hz, 1H), 5.28 (dd, *J* = 9.7, 2.3 Hz, 1H), 4.00 – 3.93 (m, 1H), 3.87 (s, 3H), 3.71 – 3.57 (m, 1H), 3.53 – 3.45 (m, 2H), 3.39 – 3.33 (m, 2H), 3.25 – 3.17 (m, 2H), 3.16 – 3.06 (m, 2H), 2.24 – 2.06 (m, 1H), 1.98 – 1.89 (m, 1H), 1.87 – 1.77 (m, 1H), 1.75 – 1.61 (m, 1H), 1.58 – 1.48 (m, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₂H₂₆BrN₉O, 512.0; found, 512.1.

Step 2. Preparation of 3-(4-(5-benzyl-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine



[0671] To a stirred solution of 3-(4-(5-bromo-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (300 mg, 0.58 mmol, as prepared in the previous step) and potassium benzyltrifluoroborate (231.9 mg, 1.17 mmol) in toluene (5 mL) and H₂O (1 mL) were added Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (49.25 mg, 0.06 mmol) and K₃PO₄ (497.1 mg, 2.34 mmol) at rt then the mixture was heated to 80°C and stirred for 16 h under nitrogen. The reaction was cooled to rt and concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM/MeOH 20:1) to afford 200 mg (32%) of 3-(4-(5-benzyl-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.78 (s, 1H), 7.67 (d, *J* = 9.2 Hz, 1H), 7.39 – 7.12 (m, 6H), 5.21 (dd, *J* = 9.9, 2.0 Hz, 1H), 4.01 – 3.92 (m, 1H), 3.90 – 3.82 (m, 5H), 3.67 – 3.55 (m, 1H), 3.50 – 3.39 (m, 2H), 3.30 – 3.06 (m, 6H), 2.30 – 2.13 (m, 1H), 2.03 – 1.88 (m, 1H), 1.83 – 1.74 (m, 1H), 1.72 – 1.60 (m, 1H), 1.59 – 1.46 (m, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₉H₃₃N₉O, 524.0; found, 524.1.

Step 3. Preparation of 3-(4-(5-benzyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound 409)

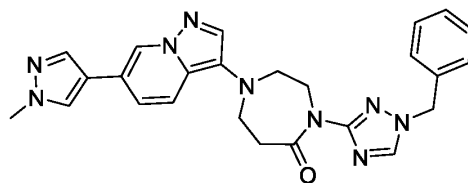


[0672] To a solution of 4M HCl in dioxane (5 mL) was added 3-(4-(5-benzyl-1-(tetrahydro-2H-pyran-2-yl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (190 mg, 0.36 mmol, as prepared in the previous step) at rt then the mixture was stirred for 3 h at rt. The reaction was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 53.4 mg (33%) of 3-(4-(5-

benzyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **409**) as a light yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ 13.01 – 12.20 (m, 1H), 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.77 (s, 1H), 7.66 (d, J = 9.2 Hz, 1H), 7.40 – 7.12 (m, 6H), 4.01 – 3.74 (m, 5H), 3.55 – 3.39 (m, 4H), 3.06 (t, J = 4.7 Hz, 4H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{24}\text{H}_{25}\text{N}_9$, 440.0; found, 440.2; HPLC purity: 254 nm: 99.7%.

Example 88: Synthesis of Exemplary Compound 410

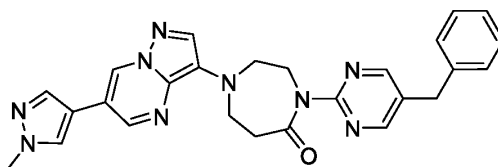
4-(1-benzyl-1H-1,2,4-triazol-3-yl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepan-5-one (Compound **410**)



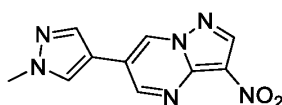
[0673] To a solution of 1-[6-(1-methylpyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]-1,4-diazepan-5-one (300 mg, 0.967 mmol, as prepared in Example 18, Step 4) and 1-benzyl-3-bromo-1H-1,2,4-triazole (276.1 mg, 1.160 mmol, as prepared in Compound **S101**, Step 1) in dioxane (20 mL) were added Cs_2CO_3 (787.3 mg, 2.417 mmol), EPhos Pd G4 (133.1 mg, 0.145 mmol), and EPhos (77.5 mg, 0.145 mmol) then the mixture was heated to 100°C and stirred overnight under nitrogen. The reaction was cooled to rt and concentrated under reduced pressure. The crude product was purified by Prep-HPLC to afford 48.1 mg (11%) of 4-(1-benzyl-1H-1,2,4-triazol-3-yl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-1,4-diazepan-5-one (Compound **410**) as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.83 (s, 1H), 8.60 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.84 (s, 1H), 7.62 (d, J = 9.2 Hz, 1H), 7.42 – 7.28 (m, 6H), 5.37 (s, 2H), 4.01 – 3.95 (m, 2H), 3.86 (s, 3H), 3.31 – 3.27 (m, 2H), 3.27 – 3.23 (m, 2H), 2.94 – 2.88 (m, 2H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{25}\text{H}_{25}\text{N}_9\text{O}$, 468.2; found, 468.2; HPLC purity: 254 nm: 99.6%.

Example 89: Synthesis of Exemplary Compound 411

4-(5-benzylpyrimidin-2-yl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,4-diazepan-5-one (Compound **411**)

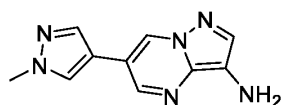


Step 1. Preparation of 6-(1-methyl-1H-pyrazol-4-yl)-3-nitropyrazolo[1,5-a]pyrimidine



[0674] To a stirred solution of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine (10 g, 50.2 mmol, as prepared in Compound **S10**, Step 1) in H₂SO₄ (60 mL) cooled to 0°C was added KNO₃ (5.58 g, 55.22 mmol) then the mixture was warmed to rt and stirred for 16 h. The reaction was diluted with water then the solids were isolated by filtration and the filter cake was washed with water (3x60 mL). The filter cake was triturated with saturated aqueous NaHCO₃ solution then the solids were isolated by filtration and the filter cake was washed with water (3x60 mL). The solids were triturated with water (200 mL), filtered, and dried to afford 8.8 g (72%) of 6-(1-methyl-1H-pyrazol-4-yl)-3-nitropyrazolo[1,5-a]pyrimidine as a red solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.70 (d, *J* = 2.2 Hz, 1H), 9.34 (d, *J* = 2.2 Hz, 1H), 9.04 (s, 1H), 8.45 (s, 1H), 8.16 (d, *J* = 0.5 Hz, 1H), 3.92 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₀H₈N₆O₂, 245.1; found, 245.2.

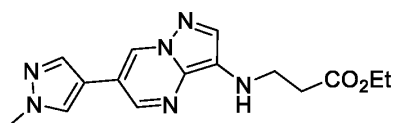
Step 2. Preparation of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-amine



[0675] To a stirred solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-nitropyrazolo[1,5-a]pyrimidine (8.8 g, 36.03 mmol, as prepared in the previous step) in conc. HBr (100 mL) cooled to 0°C was added SnCl₂·2H₂O (24.61 g, 108.1 mmol) then the mixture was heated to 90°C and stirred for 16 h. The reaction was cooled to rt and diluted with water (200 mL), then the pH of the solution was adjusted to pH 8 with 6N NaOH. The mixture was extracted with DCM (3x80 mL) then the organic extracts were combined, dried over anhydrous

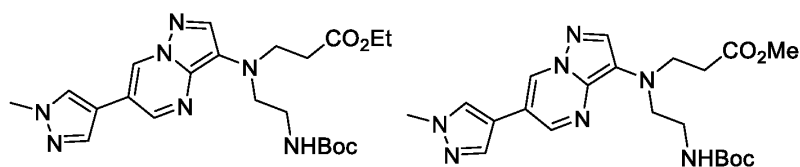
Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to afford 5.6 g (72%) of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-amine as a red solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.03 (d, *J* = 2.1 Hz, 1H), 8.50 (d, *J* = 2.1 Hz, 1H), 8.27 (s, 1H), 8.00 (d, *J* = 0.7 Hz, 1H), 7.66 (s, 1H), 4.30 (s, 2H), 3.88 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₀H₁₀N₆, 215.1; found, 215.2.

Step 3. Preparation of ethyl 3-((6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)amino)propanoate



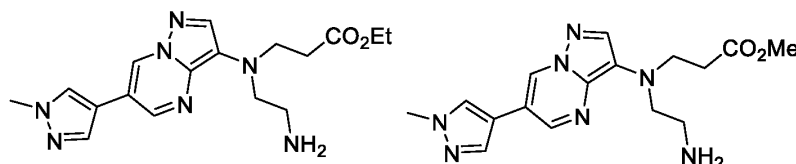
[0676] To a stirred solution of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-amine (8 g, 37.34 mmol, as prepared in the previous step) and ethyl 3-iodopropanoate (12.77 g, 56.01 mmol) in DMF (150 mL) was added Al₂O₃ (7.61 g, 74.69 mmol) at rt then the mixture was heated to 55°C and stirred for 1 h. The reaction was cooled to rt, diluted with water, and the pH was adjusted to pH 8 with saturated aqueous NaHCO₃ solution. The resulting mixture was extracted with DCM (5x80 mL) then the organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by prep HPLC to afford 3.3 g (28%) of ethyl 3-((6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)amino)propanoate as a red solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.07 (d, *J* = 2.1 Hz, 1H), 8.53 (d, *J* = 2.1 Hz, 1H), 8.27 (s, 1H), 8.01 (s, 1H), 7.75 (s, 1H), 4.74 (t, *J* = 6.7 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 3.41 (q, *J* = 6.8 Hz, 2H), 2.59 (t, *J* = 6.8 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₅H₁₈N₆O₂, 315.1; found, 315.2.

Step 4. Preparation of a mixture of ethyl 3-((2-((tert-butoxycarbonyl)amino)ethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)amino)propanoate and methyl 3-((2-((tert-butoxycarbonyl)amino)ethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)amino)propanoate



[0677] To a stirred solution of ethyl 3-((6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)amino)propanoate (500 mg, 1.59 mmol, as prepared in the previous step) and tert-butyl (2-oxoethyl)carbamate (3.29 g, 20.68 mmol) in MeOH (15 mL) was added NaHCO₃ (267.24 mg, 3.18 mmol) at rt then the mixture was heated to 60°C and stirred for 16 h. The reaction was cooled to 0°C, then NaBH₃CN (149.93 mg, 2.39 mmol) was added in portions to the stirred mixture. The reaction was stirred for 10 min at 0°C then AcOH (9.55 mg, 0.16 mmol) was added. The resulting mixture was warmed to rt, stirred for 16 h, then concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:100) to afford 428 mg (59%) of a mixture of ethyl 3-((2-((tert-butoxycarbonyl)amino)ethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)amino)propanoate and methyl 3-((2-((tert-butoxycarbonyl)amino)ethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)amino)propanoate as a red solid. MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₂H₃₁N₇O₄, 458.2; found, 458.5; C₂₁H₂₉N₇O₄, 444.2; found, 444.5.

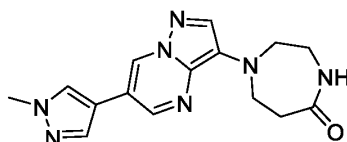
Step 5. Preparation of a mixture of ethyl 3-((2-aminoethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)amino)propanoate hydrochloride and methyl 3-((2-aminoethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)amino)propanoate hydrochloride



[0678] To a stirred solution of a mixture of ethyl 3-((2-((tert-butoxycarbonyl)amino)ethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)amino)propanoate and methyl 3-((2-((tert-butoxycarbonyl)amino)ethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)amino)propanoate (1.5 g, 3.278 mmol, as prepared in the previous step) in MeOH (10 mL) cooled to 0°C was added a 4M HCl solution in dioxane (15 mL) at 0°C then the mixture was warmed to rt and stirred for 1 h, then concentrated under reduced pressure to afford 1.2 g of a crude mixture of ethyl 3-((2-aminoethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)amino)propanoate hydrochloride and methyl 3-((2-aminoethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)amino)propanoate hydrochloride as a white

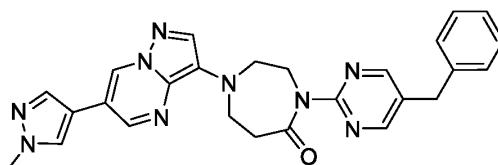
solid. The crude product was used in the next step directly without further purification. MS (ESI) m/z $[M+H]^+$ calcd. for $C_{17}H_{23}N_7O_2$, 358.2; found, 358.4; $C_{16}H_{21}N_7O_2$, 344.2; found, 344.4.

Step 6. Preparation of 1-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,4-diazepan-5-one



[0679] To a stirred solution of a mixture of ethyl 3-((2-aminoethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)amino)propanoate hydrochloride and methyl 3-((2-aminoethyl)(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)amino)propanoate hydrochloride (1.2 g, 3.36 mmol, as prepared in the previous step) in MeOH (15 mL) was added TBD (934.72 mg, 6.71 mmol) at rt then the mixture was heated to 80°C and stirred for 16 h. The reaction was cooled to rt, concentrated under reduced pressure, and the residue was dissolved in water. The resulting mixture was extracted with DCM (3x60 mL) then the organic extracts were combined, dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-TLC (DCM/MeOH 15:1) to afford 400 mg (38%) of 1-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,4-diazepan-5-one as a yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 9.16 (d, $J = 2.1$ Hz, 1H), 8.61 (d, $J = 2.1$ Hz, 1H), 8.28 (s, 1H), 8.02 (s, 1H), 7.89 (s, 1H), 7.69 – 7.58 (m, 1H), 3.89 (s, 3H), 3.55 – 3.49 (m, 2H), 3.49 – 3.44 (m, 2H), 3.29 – 3.23 (m, 2H), 2.61 – 2.55 (m, 2H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{15}H_{17}N_7O$, 312.1; found, 312.3.

Step 7. Preparation of 4-(5-benzylpyrimidin-2-yl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,4-diazepan-5-one (Compound 411)

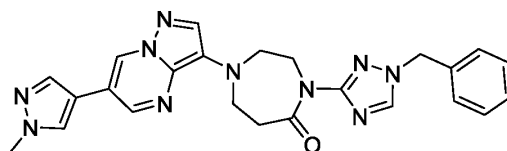


[0680] To a stirred solution of 1-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,4-diazepan-5-one (160 mg, 0.51 mmol, as prepared in the previous step) and 5-

benzyl-2-chloropyrimidine (Compound **S88**) (115.69 mg, 0.56 mmol) in dioxane (5 mL) were added Pd₂(dba)₃ (70.59 mg, 0.08 mmol), XantPhos (44.60 mg, 0.08 mmol) and K₃PO₄ (218.16 mg, 1.03 mmol) at rt then the mixture was heated to 100°C and stirred for 16 h under nitrogen. The reaction was cooled to rt and concentrated under reduced pressure. The residue was dissolved in water (20 mL) and extracted with DCM (3x50 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-TLC (DCM/MeOH 15:1) and Prep-HPLC to afford 112 mg (45%) of 4-(5-benzylpyrimidin-2-yl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,4-diazepan-5-one (Compound **411**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.18 (d, *J* = 2.1 Hz, 1H), 8.70 (s, 2H), 8.64 (d, *J* = 2.1 Hz, 1H), 8.29 (s, 1H), 8.03 (s, 1H), 7.94 (s, 1H), 7.37 – 7.19 (m, 5H), 4.20 – 4.09 (m, 2H), 3.99 (s, 2H), 3.89 (s, 3H), 3.68 – 3.58 (m, 4H), 2.98 – 2.86 (m, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₆H₂₅N₉O, 480.2; found, 480.2; HPLC purity: 254 nm: 99.9%.

Example 90: Synthesis of Exemplary Compound 412

4-(1-benzyl-1H-1,2,4-triazol-3-yl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,4-diazepan-5-one (Compound **412**)

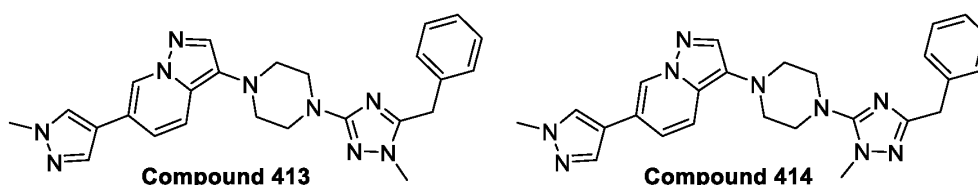


[0681] To a stirred solution of 1-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,4-diazepan-5-one (200 mg, 0.64 mmol, as prepared in Example 89, Step 6) and 1-benzyl-3-bromo-1H-1,2,4-triazole (305.88 mg, 1.28 mmol, as prepared in Compound **S101**, Step 1) in dioxane (6 mL) were added EPhos Pd G4 (100.31 mg, 0.11 mmol), EPhos (58.4 mg, 0.11 mmol) and Cs₂CO₃ (523.24 mg, 1.60 mmol) at rt then the mixture was heated to 100°C and stirred for 16 h under nitrogen. The reaction was cooled to rt, then filtered, and the filter cake was washed with DCM (3x30 mL). The filtrate was concentrated under reduced pressure then the residue was purified by Prep-TLC (DCM/MeOH 15:1) and Prep-HPLC to afford 28.9 mg (10%) of 4-(1-benzyl-1H-1,2,4-triazol-3-yl)-1-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-1,4-diazepan-5-one (Compound **412**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.18 (d, *J* = 2.1 Hz, 1H), 8.64 (d, *J*

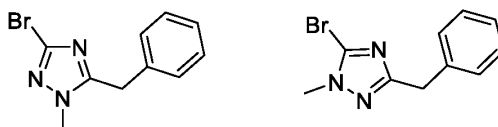
= 2.1 Hz, 1H), 8.59 (s, 1H), 8.29 (s, 1H), 8.03 (s, 1H), 7.93 (s, 1H), 7.44 – 7.25 (m, 5H), 5.37 (s, 2H), 4.00 – 3.92 (m, 2H), 3.89 (s, 3H), 3.64 – 3.55 (m, 4H), 2.92 – 2.82 (m, 2H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{24}N_{10}O$, 469.2; found, 469.2; HPLC purity: 254 nm: 99.5%.

Example 91: Synthesis of Exemplary Compound 413 and Compound 414

3-(4-(5-benzyl-1-methyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **413**) and 3-(4-(3-benzyl-1-methyl-1H-1,2,4-triazol-5-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **414**)



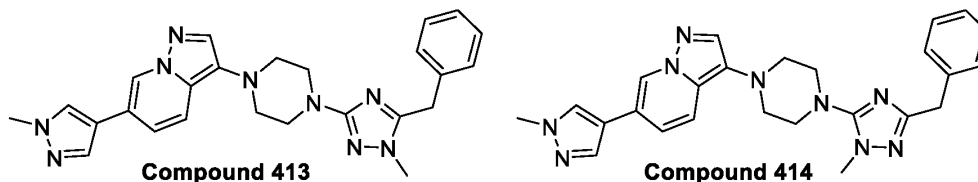
Step 1. Preparation of a mixture of 5-benzyl-3-bromo-1-methyl-1H-1,2,4-triazole and 3-benzyl-5-bromo-1-methyl-1H-1,2,4-triazole



[0682] To a solution of 3,5-dibromo-1-methyl-1H-1,2,4-triazole (2 g, 8.30 mmol) and potassium benzyltrifluoroborate (1.32 g, 6.64 mmol) in a mixture of toluene (15 mL) and H_2O (3 mL) was added K_3PO_4 (3.52 g, 16.61 mmol) and Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (0.35 g, 0.42 mmol) then the mixture was heated to 80°C and stirred for 16 h under nitrogen. The reaction was cooled to rt, the organic layer was separated, dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 240 mg (6%) of a mixture of 5-benzyl-3-bromo-1-methyl-1H-1,2,4-triazole and 3-benzyl-5-bromo-1-methyl-1H-1,2,4-triazole as a colorless oil. MS (ESI) m/z $[M+H]^+$ calcd. for $C_{10}H_{10}BrN_3$, 252.0; found, 252.1.

Step 2. Preparation of 3-(4-(5-benzyl-1-methyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **413**) and 3-(4-(3-benzyl-

1-methyl-1H-1,2,4-triazol-5-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **413**)



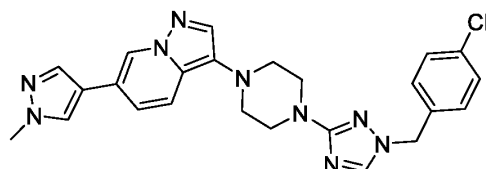
[0683] To a solution of a mixture of 5-benzyl-3-bromo-1-methyl-1H-1,2,4-triazole and 3-benzyl-5-bromo-1-methyl-1H-1,2,4-triazole (240 mg, 0.95 mmol, as prepared in the previous step) and 1-[6-(1-methylpyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine (Compound **12**) (269 mg, 0.95 mmol) in dioxane (5 mL) were added Cs₂CO₃ (620 mg, 1.90 mmol) and Pd-PEPPSI-IPent^{Cl} methylpyridine (80 mg, 0.01 mmol) then the mixture was heated to 90°C and stirred for 6 h under nitrogen. The reaction was cooled to rt, then concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with DCM/MeOH (15:1) then by Prep-HPLC to afford 90.8 mg (21%) of 3-(4-(5-benzyl-1-methyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **413**) as a green solid and 63 mg (15%) of 3-(4-(3-benzyl-1-methyl-1H-1,2,4-triazol-5-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **414**) as a light green solid.

[0684] 3-(4-(5-benzyl-1-methyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **413**). ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.81 (s, 1H), 8.22 (s, 1H), 7.96 (s, 1H), 7.77 (s, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.37 – 7.27 (m, 3H), 7.31 – 7.19 (m, 3H), 4.07 (s, 2H), 3.87 (s, 3H), 3.62 (s, 3H), 3.47 – 3.40 (m, 4H), 3.06 (t, *J* = 5.0 Hz, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₇N₉, 454.2; found, 454.2; HPLC purity: 254 nm: 99.3%.

[0685] 3-(4-(3-benzyl-1-methyl-1H-1,2,4-triazol-5-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **414**). ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.79 (s, 1H), 7.66 (d, *J* = 9.3 Hz, 1H), 7.32 (dd, *J* = 9.3, 1.5 Hz, 1H), 7.30 – 7.25 (m, 4H), 7.25 – 7.15 (m, 1H), 3.87 (s, 3H), 3.83 (s, 2H), 3.63 (s, 3H), 3.31 – 3.24 (m, 4H), 3.17 – 3.10 (m, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₇N₉, 454.2; found, 454.2; HPLC purity: 254 nm: 99.9%.

Example 92: Synthesis of Exemplary Compound 415

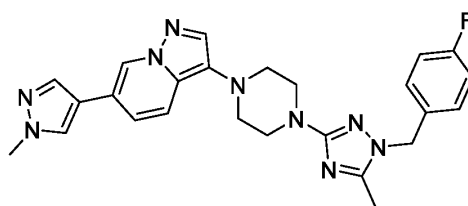
3-(4-(1-(4-chlorobenzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **415**)



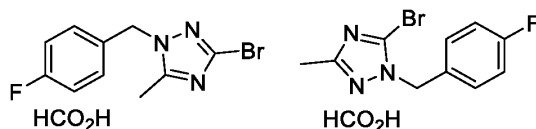
[0686] To a solution of 3-(4-(1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **S102**) (100 mg, 0.28 mmol) and 1-(bromomethyl)-4-chlorobenzene (88.2 mg, 0.42 mmol) in DMF (10 mL) was added K_2CO_3 (158.2 mg, 1.14 mmol) then the mixture was stirred overnight at rt under nitrogen. The reaction was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 52.9 mg (39%) of 3-(4-(1-(4-chlorobenzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **415**) as a yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.82 (s, 1H), 8.32 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.76 (s, 1H), 7.65 (d, $J = 8.4$ Hz, 1H), 7.50 – 7.38 (m, 2H), 7.36 – 7.26 (m, 3H), 5.23 (s, 2H), 3.86 (s, 3H), 3.52 – 3.40 (m, 4H), 3.06 (t, $J = 4.9$ Hz, 4H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{24}ClN_9$, 474.2; found, 474.2; HPLC purity: 254 nm: 99.4%.

Example 93: Synthesis of Exemplary Compound 419

3-(4-(1-(4-fluorobenzyl)-5-methyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **419**)

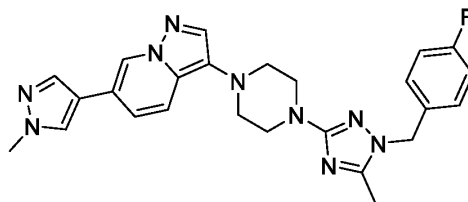


Step 1. Preparation of a mixture of 5-bromo-1-(4-fluorobenzyl)-3-methyl-1H-1,2,4-triazole formic acid salt and 3-bromo-1-(4-fluorobenzyl)-5-methyl-1H-1,2,4-triazole formic acid salt



[0687] To a solution of 3-bromo-5-methyl-1H-1,2,4-triazole (2 g, 12.34 mmol) and 1-(bromomethyl)-4-fluorobenzene (2.8 g, 14.81 mmol) in DMF (20 mL) was added K_2CO_3 (3.41 g, 24.69 mmol) then the mixture was stirred at for 16 h under nitrogen. The reaction was concentrated under reduced pressure then the residue was purified by reversed-phase column chromatography using a C18 silica gel column eluting with a 10-100% gradient of ACN/water (0.1% FA) to afford 2.1 g (51%) of a mixture of 5-bromo-1-(4-fluorobenzyl)-3-methyl-1H-1,2,4-triazole formic acid salt and 3-bromo-1-(4-fluorobenzyl)-5-methyl-1H-1,2,4-triazole formic acid salt as a white solid. MS (ESI) m/z $[M+H]^+$ calcd. for $C_{10}H_{10}BrFN_3$, 270.0; found, 270.1.

Step 2. 3-(4-(1-(4-fluorobenzyl)-5-methyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound 419)



[0688] To a solution of the mixture of 5-bromo-1-(4-fluorobenzyl)-3-methyl-1H-1,2,4-triazole formic acid salt and 3-bromo-1-(4-fluorobenzyl)-5-methyl-1H-1,2,4-triazole formic acid salt (351.1 mg, 1.11 mmol, as prepared in the previous step) and 1-[6-(1-methylpyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine (Compound 12) (531.6 mg, 1.88 mmol) in dioxane (30.00 mL) were added Cs_2CO_3 (1.02 g, 3.13 mmol) and Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (132 mg, 0.16 mmol) then the mixture was heated to 90°C and stirred for 16 h under nitrogen. The reaction was cooled to rt and concentrated under reduced pressure. The residue was purified by Prep-TLC (DCM/MeOH 10:1) and by Prep-HPLC to afford 125 mg (17%) of 3-(4-(1-(4-fluorobenzyl)-5-methyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine

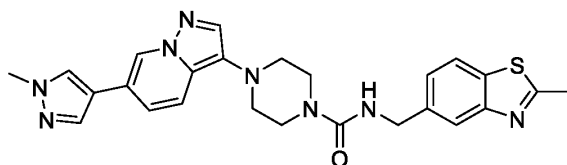
(Compound **419**) as a yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.82 (t, J = 1.3 Hz, 1H), 8.22 (s, 1H), 7.97 (d, J = 0.9 Hz, 1H), 7.77 (s, 1H), 7.68 – 7.61 (m, 1H), 7.35 – 7.24 (m, 3H), 7.24 – 7.14 (m, 2H), 5.18 (s, 2H), 3.87 (s, 3H), 3.43 (t, J = 5.0 Hz, 4H), 3.05 (t, J = 5.0 Hz, 4H), 2.33 (s, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{25}\text{H}_{26}\text{FN}_9$, 472.2; found, 472.1; HPLC purity: 254 nm: 99.8%.

[0689] Using the procedures described in Example 93 and reagents, starting materials, and conditions known to those skilled in the art, the following compounds representative of the present disclosure were prepared:

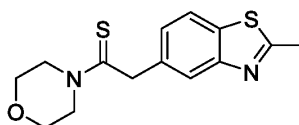
Compound	Data
420	3-(4-(5-methyl-1-(4-methylbenzyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.82 (t, J = 1.2 Hz, 1H), 8.22 (s, 1H), 7.97 (d, J = 0.8 Hz, 1H), 7.76 (s, 1H), 7.65 (dd, J = 9.3, 0.9 Hz, 1H), 7.31 (dd, J = 9.3, 1.5 Hz, 1H), 7.20 – 7.07 (m, 4H), 5.13 (s, 2H), 3.87 (s, 3H), 3.43 (t, J = 5.0 Hz, 4H), 3.05 (t, J = 5.0 Hz, 4H), 2.33 – 2.56 (m, 6H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{25}\text{H}_{29}\text{N}_9$, 468.3; found, 468.1; HPLC purity: 254 nm: 99.4%.
421	3-(4-(1-benzyl-5-(trifluoromethyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.78 (s, 1H), 7.66 (d, J = 9.2 Hz, 1H), 7.45 – 7.20 (m, 6H), 5.42 (s, 2H), 3.87 (s, 3H), 3.52 (t, J = 4.9 Hz, 4H), 3.08 (t, J = 4.9 Hz, 4H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{25}\text{H}_{24}\text{F}_3\text{N}_9$, 508.1; found, 508.2; HPLC purity: 254 nm: 96.9%.

Example 94: Synthesis of Exemplary Compound 422

4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-N-((2-methylbenzo[d]thiazol-5-yl)methyl)piperazine-1-carboxamide (Compound **422**)

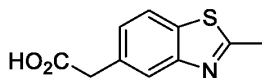


Step 1. Preparation of 2-(2-methylbenzo[d]thiazol-5-yl)-1-morpholinoethane-1-thione



[0690] To a solution of 1-(2-methylbenzo[d]thiazol-5-yl)ethan-1-one (1.0 g, 5.23 mmol) in ACN (20 mL) was added sulfur (251.5 mg, 7.84 mmol), morpholine (683.3 mg, 7.84 mmol) and $\text{Ti}(\text{OiPr})_4$ (2.97 g, 10.46 mmol) then the mixture was heated to 90°C and stirred for 16 h under nitrogen. The reaction was cooled to rt and filtered, then the filter cake was washed with ACN (3x50 mL). The filtrate was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (2:1) to afford 600 mg (37%) of 2-(2-methylbenzo[d]thiazol-5-yl)-1-morpholinoethane-1-thione as a light yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.97 (d, $J = 8.2$ Hz, 1H), 7.86 (d, $J = 1.7$ Hz, 1H), 7.39 (dd, $J = 8.3, 1.7$ Hz, 1H), 4.43 (s, 2H), 4.27 – 4.18 (m, 2H), 3.78 – 3.71 (m, 2H), 3.64 (t, $J = 4.8$ Hz, 2H), 3.42 (t, $J = 4.8$ Hz, 2H), 2.79 (s, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{OS}_2$, 293.1; found, 293.1.

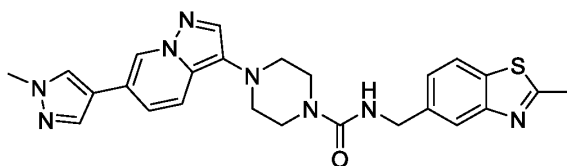
Step 2. Preparation of 2-(2-methylbenzo[d]thiazol-5-yl)acetic acid



[0691] To a solution of 2-(2-methylbenzo[d]thiazol-5-yl)-1-morpholinoethane-1-thione (500 mg, 1.71 mmol, as prepared in the previous step) in EtOH (12 mL) and H_2O (9 mL) was added KOH (575.6 mg, 10.26 mmol) then the mixture was stirred at rt for 8 h under nitrogen. The pH of the reaction was adjusted to pH 5 with conc. HCl then the mixture was extracted with EtOAc (3x30 mL). The organic extracts were combined, washed with brine (3x10 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under

reduced pressure then the residue was purified by silica gel column chromatography eluting with DCM/MeOH (20:1) to afford 400 mg (90%) of 2-(2-methylbenzo[d]thiazol-5-yl)acetic acid as a light yellow solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm) 12.22 (s, 1H), 7.93 (d, J = 8.2 Hz, 1H), 7.79 (d, J = 1.6 Hz, 1H), 7.29 (dd, J = 8.2, 1.7 Hz, 1H), 3.70 (s, 2H), 2.78 (s, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{10}\text{H}_9\text{NO}_2\text{S}$, 208.0 found, 208.0.

Step 3. Preparation of 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-N-((2-methylbenzo[d]thiazol-5-yl)methyl)piperazine-1-carboxamide (Compound **422**)



[0692] To a solution of 2-(2-methylbenzo[d]thiazol-5-yl)acetic acid (200 mg, 0.97 mmol, as prepared in the previous step) in ACN (10 mL) cooled to 0°C was added DPPA (398.4 mg, 1.45 mmol) and TEA (293 mg, 2.90 mmol) then the mixture was warmed to rt and stirred for 2 h under nitrogen. The reaction was concentrated under reduced pressure to afford crude 2-(2-methylbenzo[d]thiazol-5-yl)acetyl azide, which was used directly without purification. MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{10}\text{H}_8\text{N}_4\text{OS}$, 233.0 found, 233.0.

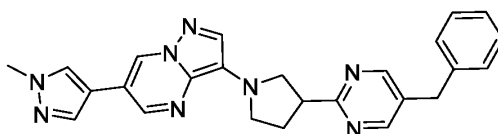
[0693] To a solution of the crude 2-(2-methylbenzo[d]thiazol-5-yl)acetyl azide (200 mg, 0.86 mmol) in toluene (5 mL, 46.99 mmol) were added 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (243.1 mg, 0.86 mmol) and TEA (261.4 mg, 2.58 mmol) then the mixture was heated to 110°C and stirred for 16 h under nitrogen. The reaction was cooled to rt, water (30 mL) was added and the mixture was extracted with EtOAc (3x30 mL). The organic extracts were combined, washed with brine (3x10 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 20.3 mg (5%) of 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-N-((2-methylbenzo[d]thiazol-5-yl)methyl)piperazine-1-carboxamide (Compound **422**) as a white solid. ^1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.82 (s, 1H), 8.23 (s, 1H), 8.00 – 7.92 (m, 2H), 7.82 – 7.76 (m, 2H), 7.67 (d, J = 9.2 Hz, 1H), 7.37 – 7.26 (m, 3H), 4.39 (d, J = 6.0 Hz, 2H), 3.88 (s, 3H), 3.54 (t, J = 4.9 Hz, 4H), 2.96 (t, J = 4.9 Hz, 4H), 2.79 (s, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{25}\text{H}_{26}\text{N}_8\text{OS}$, 487.2; found, 487.2; HPLC purity: 254 nm: 99.2%.

[0694] Using the procedures described in Example 94 and reagents, starting materials, and conditions known to those skilled in the art, the following compounds representative of the present disclosure were prepared:

Compound	Data
429	4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)-N-((2-methylbenzo[d]thiazol-6-yl)methyl)piperazine-1-carboxamide ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ (ppm) 8.82 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.90 – 7.81 (m, 2H), 7.77 (s, 1H), 7.66 (dd, <i>J</i> = 9.2 Hz, 1H), 7.39 (d, <i>J</i> = 8.3, 1.7 Hz, 1H), 7.35 – 7.23 (m, 2H), 4.38 (d, <i>J</i> = 5.7 Hz, 2H), 3.87 (s, 3H), 3.54 (t, <i>J</i> = 4.9 Hz, 4H), 2.96 (t, <i>J</i> = 4.9 Hz, 4H), 2.78 (s, 3H).; MS (ESI) <i>m/z</i> [M+H] ⁺ calcd. for C ₂₅ H ₂₆ N ₈ OS, 487.2; found, 487.1; HPLC purity: 254 nm: 98.9%.

Example 95: Synthesis of Exemplary Compound 423

3-(3-(5-benzylpyrimidin-2-yl)pyrrolidin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine (Compound **423**)

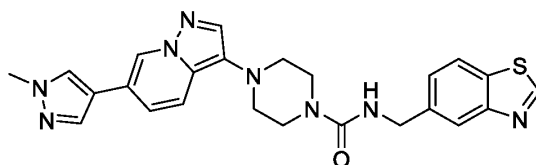


[0695] To a solution of 5-benzyl-2-(pyrrolidin-3-yl)pyrimidine (Compound **S100**) (800 mg, 3.34 mmol) and 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine (Compound **S10**) (743.7 mg, 2.67 mmol) in dioxane (20 mL) were added KOTMS (857.6 mg, 6.68 mmol), tBuXPhos Pd G3 (797.6 mg, 1.00 mmol), and tBuXPhos (425.8 mg, 1.00 mmol) then the mixture was heated to 90°C and stirred overnight under nitrogen. The reaction was cooled to rt and concentrated under reduced pressure. Water (100 mL) was added to the residue then the mixture was extracted with DCM (3x100 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) and Prep-HPLC to afford 107.1 mg (7%) of 3-(3-(5-benzylpyrimidin-2-yl)pyrrolidin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrimidine (Compound **423**) as an orange solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm)

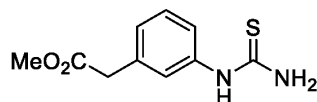
9.06 (d, $J = 2.1$ Hz, 1H), 8.68 (s, 2H), 8.49 (d, $J = 2.1$ Hz, 1H), 8.26 (s, 1H), 8.00 (s, 1H), 7.71 (s, 1H), 7.35 – 7.26 (m, 4H), 7.26 – 7.17 (m, 1H), 3.97 (s, 2H), 3.93-3.85 (m, 4H), 3.82-3.72 (m, 1H), 3.66-3.60 (m, 1H), 3.58-3.48 (m, 2H), 2.40-2.30 (m, 2H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{25}H_{24}N_8$, 437.2; found, 437.1; HPLC purity: 254 nm: 96.3%.

Example 96: Synthesis of Exemplary Compound 424

N-(benzo[d]thiazol-5-ylmethyl)-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxamide (Compound 424)

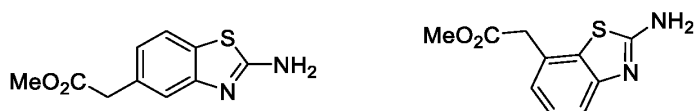


Step 1. Preparation of methyl 2-(3-thioureidophenyl)acetate



[0696] To a solution of methyl 2-(3-aminophenyl)acetate (10 g, 60.5 mmol) in chloroform (150 mL) was added NaSCN (7.36 g, 90.8 mmol) and TFA (17.3 g, 151 mmol) then the mixture was heated to 80°C and stirred for 2 h. The reaction was cooled to rt and water (200 mL) was added then the mixture was extracted with EtOAc (3x200 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 3 g (19%) of methyl 2-(3-thioureidophenyl)acetate as a light yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 9.72 (s, 1H), 7.35 (d, $J = 8.0$ Hz, 1H), 7.30 – 7.18 (m, 2H), 7.01 (d, $J = 7.6$ Hz, 1H), 6.95 – 6.86 (m, 1H), 3.68 – 3.59 (m, 5H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{10}H_{12}N_2O_2S$, 225.1; found, 225.1.

Step 2. Preparation of a mixture of methyl 2-(2-aminobenzo[d]thiazol-5-yl) acetate and methyl 2-(2-aminobenzo[d]thiazol-7-yl) acetate



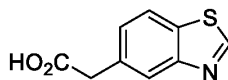
[0697] To a solution of methyl 2-(3-thioureidophenyl)acetate (1.0 g, 4.46 mmol, as prepared in the previous step) in AcOH (10 mL) was added Br₂ (0.86 g, 5.40 mmol) then the mixture was heated to 80°C and stirred for 2 h. The reaction was cooled to rt and concentrated under reduced pressure. To the residue was added an aqueous solution of Na₂S₂O₃ and an aqueous solution of Na₂CO₃, then the mixture was extracted with EtOAc (3x200 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (3:7) to afford 850 mg (34%) of a mixture of methyl 2-(2-aminobenzo[d]thiazol-5-yl) acetate and methyl 2-(2-aminobenzo[d]thiazol-7-yl) acetate as a brown oil. MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₀H₁₀N₂O₂S, 223.0; found, 223.0.

Step 3. Preparation of a mixture of methyl 2-(benzo[d]thiazol-5-yl) acetate and methyl 2-(benzo[d]thiazol-7-yl) acetate



[0698] To a solution of a mixture of methyl 2-(2-aminobenzo[d]thiazol-5-yl) acetate and methyl 2-(2-aminobenzo[d]thiazol-7-yl) acetate (800 mg, 3.60 mmol, as prepared in the previous step) in THF (10 mL) was added isoamyl nitrite (843 mg, 7.20 mmol) then the mixture was heated to 70°C and stirred for 2 h. The reaction was cooled to rt and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with PE/EtOAc (5:1) to afford 490 mg (16%) of a mixture of methyl 2-(benzo[d]thiazol-5-yl) acetate and methyl 2-(benzo[d]thiazol-7-yl) acetate as a yellow oil. MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₀H₉NO₂S, 208.0; found, 208.0.

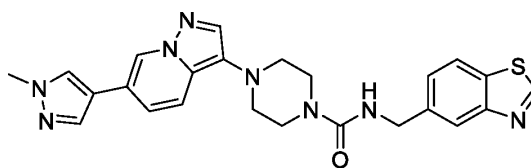
Step 4. Preparation of 2-(benzo[d]thiazol-5-yl) acetic acid



[0699] To a solution of a mixture of methyl 2-(benzo[d]thiazol-5-yl) acetate and methyl 2-(benzo[d]thiazol-7-yl) acetate (450 mg, 2.17 mmol, as prepared in the previous step) in MeOH (6 mL) and H₂O (2 mL) was added NaOH (174 mg, 4.34 mmol) then the mixture was stirred at rt for 2 h. The reaction was concentrated under reduced pressure then water (50mL) was added, and the mixture was extracted with DCM (3x80 mL). The organic

extracts were combined, dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-ACHIRAL-SFC to afford 120 mg (26%) of 2-(benzo[d]thiazol-5-yl) acetic acid as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 9.35 (s, 1H), 8.04 (d, $J = 8.2$ Hz, 1H), 7.95 (s, 1H), 7.37 (dd, $J = 8.3, 1.6$ Hz, 1H), 3.63 (s, 2H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_9\text{H}_7\text{NO}_2\text{S}$, 194.0; found, 194.0.

Step 5. Preparation of N-(benzo[d]thiazol-5-ylmethyl)-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxamide (Compound **424**)

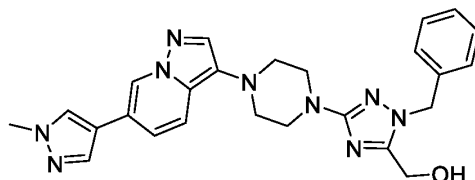


[0700] To a solution of 2-(benzo[d]thiazol-5-yl) acetic acid (90 mg, 0.47 mmol, as prepared in the previous step) and TEA (141 mg, 1.40 mmol) in THF (4 mL) cooled to 0°C was added DPPA (256 mg, 0.93 mmol) then the mixture was warmed to rt and stirred for 2 h. The reaction was concentrated under reduced pressure to afford crude 2-(benzo[d]thiazol-5-yl)acetyl azide, which was used directly without purification.

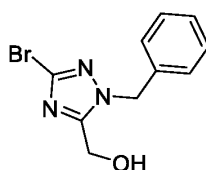
[0701] To a solution of crude 2-(benzo[d]thiazol-5-yl) acetyl azide (100 mg, 0.46 mmol) and TEA (93 mg, 0.92 mmol) in toluene (4 mL) was added 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (129 mg, 0.46 mmol) then the mixture was heated to 100°C and stirred for 2 h. The reaction was cooled to rt and concentrated under reduced pressure. The residue was purified by silica gel column chromatography eluting with DCM/MeOH (20:1) and Prep-HPLC to afford 25.9 mg (12%) of N-(benzo[d]thiazol-5-ylmethyl)-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxamide (Compound **424**) as a white solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 9.38 (s, 1H), 8.82 (s, 1H), 8.22 (s, 1H), 8.10 (d, $J = 8.3$ Hz, 1H), 7.97 (s, 2H), 7.77 (s, 1H), 7.67 (d, $J = 9.3$ Hz, 1H), 7.43 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.35 – 7.28 (m, 2H), 4.43 (d, $J = 5.7$ Hz, 2H), 3.87 (s, 3H), 3.55 (t, $J = 4.9$ Hz, 4H), 2.97 (t, $J = 4.9$ Hz, 4H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{24}\text{H}_{24}\text{N}_8\text{OS}$, 473.2; found, 473.1; HPLC purity: 254 nm: 99.7%.

Example 97: Synthesis of Exemplary Compound 425

(1-benzyl-3-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-1H-1,2,4-triazol-5-yl)methanol (Compound **425**)



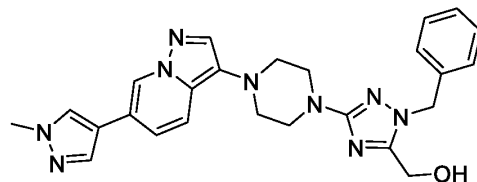
Step 1. Preparation of (1-benzyl-3-bromo-1H-1,2,4-triazol-5-yl)methanol



[0702] To a stirred solution of 3-bromo-1H-1,2,4-triazole-5-carboxylic acid (10 g, 52.09 mmol) in THF (150 mL) cooled to 0°C was added $\text{BH}_3 \cdot \text{THF}$ (208.4 mL, 208.36 mmol) then the mixture was warmed to rt and stirred for 30 minutes. The reaction was heated to 60°C and stirred overnight. The reaction was cooled to 0°C and quenched with MeOH. The resulting mixture was concentrated under reduced pressure then the residue was passed through a silica gel column eluting with DCM/MeOH (40:1) to afford 5.0 g (54%) of crude (3-bromo-1H-1,2,4-triazol-5-yl)methanol as a light yellow oil.

[0703] To a stirred solution of 3-bromo-1H-1,2,4-triazol-5-yl)methanol (5.0 g, 28.1 mmol) and benzyl bromide (9.23 g, 53.94 mmol) in DMF (150 mL) was added K_2CO_3 (12.42 g, 89.89 mmol) then the mixture was heated to 80°C and stirred for 2 h. The reaction was cooled to rt and filtered, then the filter cake was washed with EtOAc (2x100 mL). The filtrate was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with DCM/MeOH (40/1) and reversed-phase flash chromatography using a fluoro-phenyl column eluting with 16-28% ACN/water (0.05% TFA), to afford 195 mg (3%) of (1-benzyl-3-bromo-1H-1,2,4-triazol-5-yl)methanol as a light yellow oil. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 7.44 – 7.25 (m, 5H), 5.86 (t, J = 5.9 Hz, 1H), 5.41 (s, 2H), 4.64 (d, J = 5.8 Hz, 2H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{10}\text{H}_{10}\text{BrN}_3\text{O}$, 268.0; found, 268.1.

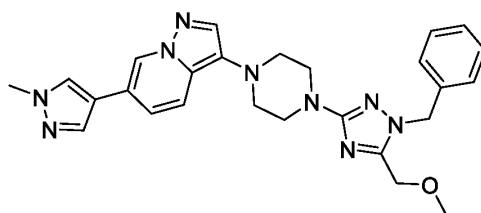
Step 2. (1-benzyl-3-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-1H-1,2,4-triazol-5-yl)methanol (Compound **425**)



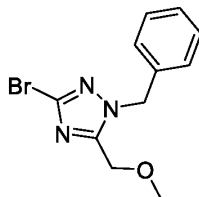
[0704] To a solution of (1-benzyl-3-bromo-1H-1,2,4-triazol-5-yl)methanol (160 mg, 0.60 mmol, as prepared in the previous step) and 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (202.2 mg, 0.72 mmol) in dioxane (20 mL) were added Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (100.4 mg, 0.12 mmol) and Cs₂CO₃ (388.9 mg, 1.20 mmol) then the mixture was heated to 90°C and stirred for 16 h under nitrogen. The reaction was cooled to rt and concentrated under reduced pressure. The residue was purified by Prep-HPLC to afford 44.4 mg (16%) of (1-benzyl-3-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-1H-1,2,4-triazol-5-yl)methanol (Compound **425**) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.76 (s, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.42 – 7.23 (m, 6H), 5.66 (s, 1H), 5.27 (s, 2H), 4.54 (s, 2H), 3.87 (s, 3H), 3.44 (t, *J* = 5.0 Hz, 4H), 3.05 (t, *J* = 5.0 Hz, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₇N₉O, 470.2; found, 470.1; HPLC purity: 254 nm: 99.0%.

Example 98: Synthesis of Exemplary Compound 426

3-(4-(1-benzyl-5-(methoxymethyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **426**)

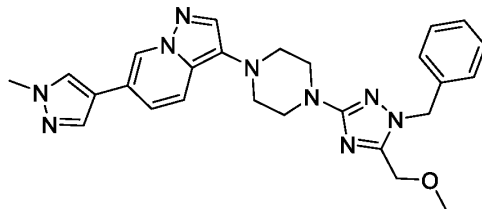


Step 1. Preparation of 1-benzyl-3-bromo-5-(methoxymethyl)-1H-1,2,4-triazole



[0705] To a stirred mixture of 3-bromo-5-(methoxymethyl)-1H-1,2,4-triazole (2 g, 10.41 mmol) and benzyl bromide (2.14 g, 12.49 mmol) in DMF (10 mL) was added K₂CO₃ (2.88 g, 20.83 mmol) in portions at rt then the mixture was heated to 100°C and stirred for 3 h under nitrogen. The reaction was cooled to rt and filtered, then the filter cake was washed with EtOAc (2x10 mL). The filtrate was concentrated under reduced pressure and the residue was purified by Prep-HPLC to afford 580 mg (20%) of 1-benzyl-3-bromo-5-(methoxymethyl)-1H-1,2,4-triazole as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 7.43 – 7.29 (m, 3H), 7.33 – 7.25 (m, 2H), 5.41 (s, 2H), 4.64 (s, 2H), 3.30 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₆H₂₉N₃O, 282.1; found, 281.9.

Step 2. Preparation of 3-(4-(1-benzyl-5-(methoxymethyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **426**)

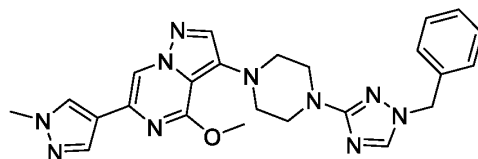


[0706] To a solution of 1-benzyl-3-bromo-5-(methoxymethyl)-1,2,4-triazole (200 mg, 0.70 mmol, as prepared in the previous step) and 1-[6-(1-methylpyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine (Compound **12**) (200.1 mg, 0.70 mmol) in dioxane (3 mL) were added Pd-PEPSI-IPent^{Cl} 2-methylpyridine (59.6 mg, 0.07 mmol) and Cs₂CO₃ (461.9 mg, 1.41 mmol) then the mixture was heated to 100°C and stirred for 2 h under nitrogen. The reaction was cooled to rt, water (100 mL) was added, and the mixture was extracted with EtOAc (2x50 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 131.7 mg (38%) of 3-(4-(1-benzyl-5-(methoxymethyl)-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **426**) as a yellow green solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (t,

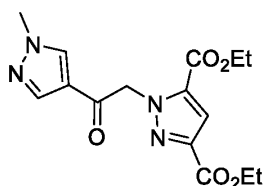
$J = 1.2$ Hz, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.77 (s, 1H), 7.66 (d, $J = 9.3$ Hz, 1H), 7.41 – 7.24 (m, 6H), 5.25 (s, 2H), 4.52 (s, 2H), 3.88 (s, 3H), 3.46 (t, $J = 4.9$ Hz, 4H), 3.29 (s, 3H), 3.06 (t, $J = 5.0$ Hz, 4H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{26}H_{29}N_9O$, 484.3; found, 484.2; HPLC purity: 254 nm: 99.8%.

Example 99: Synthesis of Exemplary Compound 427

3-(4-(1-benzyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-4-methoxy-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine (Compound 427)

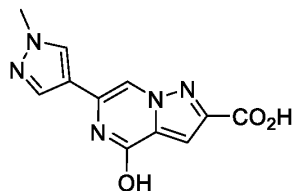


Step 1. Preparation of diethyl 1-(2-(1-methyl-1H-pyrazol-4-yl)-2-oxoethyl)-1H-pyrazole-3,5-dicarboxylate



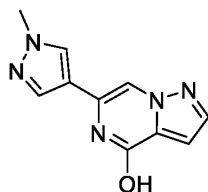
[0707] To a stirred solution of diethyl 1H-pyrazole-3,5-dicarboxylate (18.9 g, 89.06 mmol) and 2-bromo-1-(1-methyl-1H-pyrazol-4-yl)ethan-1-one (18.08 g, 89.06 mmol) in ACN (250 mL) was added CS_2CO_3 (58.04 g, 178.13 mmol) at rt then the mixture was stirred for 4 h. The reaction was filtered, and the filter cake was washed with ACN (100 mL). The filtrate was concentrated under reduced pressure then the residue was dissolved in EtOAc (80 mL), then heptane (200 mL) was added. The mixture was stirred at rt for 2 h, then the suspension was filtered, and the filter cake was washed with heptane. The solid was dried under reduced pressure to afford 25 g (84%) of diethyl 1-(2-(1-methyl-1H-pyrazol-4-yl)-2-oxoethyl)-1H-pyrazole-3,5-dicarboxylate as a yellow solid. 1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.55 (s, 1H), 8.06 (s, 1H), 7.33 (s, 1H), 5.93 (s, 2H), 4.31 (q, $J = 7.1$ Hz, 2H), 4.22 (q, $J = 7.1$ Hz, 2H), 3.93 (s, 3H), 1.30 (t, $J = 7.1$ Hz, 3H), 1.21 (t, $J = 7.1$ Hz, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{15}H_{18}N_4O_5$, 335.1; found, 335.2.

Step 2. Preparation of 4-hydroxy-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine-2-carboxylic acid



[0708] To a stirred solution of diethyl 1-(2-(1-methyl-1H-pyrazol-4-yl)-2-oxoethyl)-1H-pyrazole-3,5-dicarboxylate (50 g, 149.55 mmol, as prepared in the previous step) in HOAc (1 L) was added NH₄OAc (345.84 g, 4.48 mol) then the mixture was heated to 120°C and stirred for 48 h. The reaction was cooled to rt, water (6 L) was added, and the mixture was stirred for 2 h. The suspension was filtered, and the filter cake was washed with water. The solid was added to 6M HCl (350 mL) then heated to 100°C and stirred for 16 h. The reaction was cooled to rt and water (350 mL) was added. The mixture was stirred for 1 h, then filtered and the filter cake was washed with water and dried under reduced pressure to afford (24 g (76%) of 4-hydroxy-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine-2-carboxylic acid as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 13.17 (s, 1H), 11.64 (s, 1H), 8.30 (s, 1H), 8.14 (s, 1H), 8.05 (s, 1H), 7.32 (d, *J* = 0.5 Hz, 1H), 3.88 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₁H₉N₅O₃, 260.1; found, 260.2.

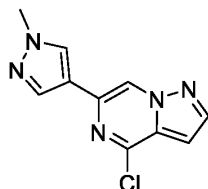
Step 3. Preparation of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazin-4-ol



[0709] To a stirred solution of 4-hydroxy-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine-2-carboxylic acid (2 g, 7.71 mmol, as prepared in the previous step) in NMP (20 mL) were added 1,10-phenanthroline (695.2 mg, 3.86 mmol) and Cu(OAc)₂ (700.7 mg, 3.86 mmol) then the mixture was heated to 165°C and stirred for 48 h. The reaction was cooled to rt, 3M HCl (40 mL) was added, and the mixture was stirred for 3 h. The suspension was filtered, the filter cake was washed with water, and dried under reduced pressure to afford 1.53 g (92%) of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazin-4-ol as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 11.44 (s, 1H), 8.28 (s,

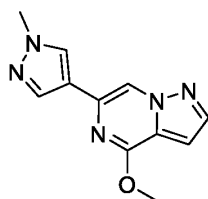
1H), 8.09 (s, 1H), 8.03 (s, 1H), 7.88 (d, $J = 2.2$ Hz, 1H), 6.99 (dd, $J = 2.2, 0.8$ Hz, 1H), 3.87 (s, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{10}H_9N_5O$, 216.1; found, 216.2.

Step 4. Preparation of 4-chloro-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine dihydrochloride



[0710] A solution of 6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazin-4-ol (5.5 g, 25.56 mmol, as prepared in the previous step) in $POCl_3$ (62.69 g, 408.90 mmol) was heated to $80^\circ C$ and stirred for 7 h. The reaction was cooled to $50^\circ C$ then ACN (45 mL) was added. The mixture was then cooled to rt and filtered. The filter cake was washed with ACN (25 mL) then dried under reduced pressure. To the filtrate was added MTBE (90 mL) and the mixture was stirred at rt for 16 h. The suspension was filtered, the filter cake was washed with ACN (25 mL) and dried under reduced pressure. The solids were combined to afford 5 g (64%) of 4-chloro-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine dihydrochloride as an off-white solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 10.08 – 9.39 (m, 2H), 9.21 (s, 1H), 8.27 (s, 1H), 8.20 (d, $J = 2.4$ Hz, 1H), 8.03 (s, 1H), 7.01 (dd, $J = 2.5, 0.9$ Hz, 1H), 3.88 (s, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{10}H_8ClN_5$, 234.1; found, 234.1.

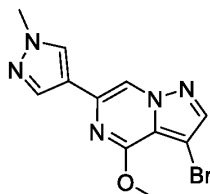
Step 5. Preparation of 4-methoxy-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine



[0711] To a stirred solution of 4-chloro-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine (900 mg, 3.85 mmol, as prepared in the previous step) in MeOH (10 mL) was added NaOMe (416.2 mg, 7.70 mmol) at rt then the mixture was stirred for 1 h. The reaction was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 560 mg (63%) of 4-methoxy-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine as a white solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.75 (s, 1H), 8.21 (s, 1H), 8.11 – 7.94

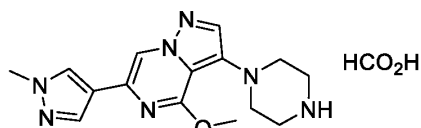
(m, 2H), 6.84 (d, $J = 2.1$ Hz, 1H), 4.11 (s, 3H), 3.89 (s, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{11}H_{11}N_5O$, 230.1; found, 230.2.

Step 6. Preparation of 3-bromo-4-methoxy-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine



[0712] To a stirred solution of 4-methoxy-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine (240 mg, 1.05 mmol, as prepared in the previous step) in ACN (9 mL) cooled to 0°C was added NBS (149.5 mg, 0.84 mmol) then the mixture was stirred for 1 h. The reaction was diluted with water and extracted with DCM (3x30 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-TLC (DCM/MeOH 60:1) to afford 260 mg (81%) of 3-bromo-4-methoxy-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine as a white solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.77 (s, 1H), 8.22 (s, 1H), 8.13 (s, 1H), 8.02 (s, 1H), 4.12 (s, 3H), 3.88 (s, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{11}H_{10}BrN_5O$, 308.1; found, 308.2.

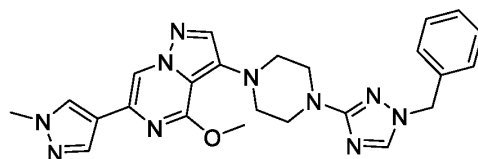
Step 7. Preparation of 4-methoxy-6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyrazine formic acid salt



[0713] To a stirred solution of 3-bromo-4-methoxy-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine (260 mg, 0.84 mmol, as prepared in the previous step) and piperazine (363.4 mg, 4.22 mmol) in DMF (5 mL) were added Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (71 mg, 0.08 mmol) and Cs_2CO_3 (549.8 mg, 1.69 mmol) then the mixture was heated to 90°C and stirred for 16 h under nitrogen. The reaction was cooled to rt and filtered, then the filter cake was washed with MeOH (3x20 mL). The filtrate was concentrated under reduced pressure and the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 5-30% ACN/water (0.1% FA)

to afford 110 mg (36%) of 4-methoxy-6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyrazine formic acid salt as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.54 (s, 1H), 8.30 (s, 1H), 8.18 (s, 1H), 7.98 (s, 1H), 7.74 (s, 1H), 4.08 (s, 3H), 3.87 (s, 3H), 3.07 (d, *J* = 18.5 Hz, 8H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₆H₂₁N₇O₃, 314.1; found, 314.2.

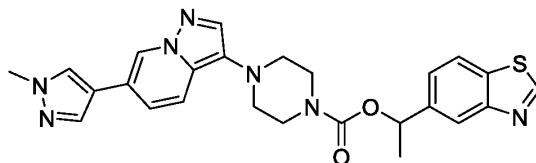
Step 8. Preparation of 3-(4-(1-benzyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-4-methoxy-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine (Compound **427**)



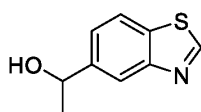
[0714] To a stirred solution of 4-methoxy-6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyrazine formic acid salt (100 mg, 0.28 mmol, as prepared in the previous step) and 1-benzyl-3-bromo-1H-1,2,4-triazole (66.3 mg, 0.28 mmol, as prepared in Compound **S101**, Step 1) in dioxane (4 mL) were added Pd-PEPPSI-IPent^{Cl} 2-methylpyridine (23.4 mg, 0.03 mmol) and Cs₂CO₃ (181.3 mg, 0.56 mmol) then the mixture was heated to 90°C and stirred for 16 h under nitrogen. The reaction was cooled to rt and filtered, then the filter cake was washed with DCM (3x30 mL). The filtrate was concentrated under reduced pressure then the residue was purified by Prep-TLC (DCM/MeOH 15:1) and Prep-HPLC to afford 47 mg (36%) of 3-(4-(1-benzyl-1H-1,2,4-triazol-3-yl)piperazin-1-yl)-4-methoxy-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyrazine (Compound **427**) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.53 (s, 1H), 8.32 (s, 1H), 8.18 (s, 1H), 7.98 (s, 1H), 7.73 (s, 1H), 7.42 – 7.23 (m, 5H), 5.23 (s, 2H), 4.08 (s, 3H), 3.87 (s, 3H), 3.43 (t, *J* = 4.7 Hz, 4H), 3.11 (t, *J* = 4.7 Hz, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₆N₁₀O, 471.2; found, 471.3; HPLC purity: 254 nm: 99.4%.

Example 100: Synthesis of Exemplary Compound 428

1-(benzo[d]thiazol-5-yl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **428**)

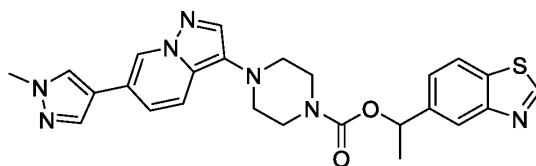


Step 1. 1-(benzo[d]thiazol-5-yl)ethan-1-ol



[0715] To a solution of 1-(1,3-benzothiazol-5-yl)ethanone (500 mg, 2.82 mmol) in MeOH (10 mL) was added NaBH₄ (213.4 mg, 5.64 mmol) at rt then the mixture was stirred for 1 h under nitrogen. The reaction was concentrated under reduced pressure, then the residue was dissolved in water (50 mL) and extracted with DCM (3x50 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to afford 400 mg (79%) of 1-(benzo[d]thiazol-5-yl)ethan-1-ol as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.37 (s, 1H), 8.16 – 7.97 (m, 2H), 7.48 (dd, *J* = 8.3, 1.6 Hz, 1H), 5.31 (d, *J* = 4.3 Hz, 1H), 4.97 – 4.82 (m, 1H), 1.39 (d, *J* = 6.4 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₉H₉NOS, 180.0; found, 180.0; HPLC purity: 254 nm:95%.

Step 2. Preparation of 1-(benzo[d]thiazol-5-yl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **428**)



[0716] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (300 mg, 1.06 mmol) in pyridine (15 mL) were added BTC (1.58 g, 5.31 mmol) and 1-(1,3-benzothiazol-5-yl)ethanol (209.4 mg, 1.16 mmol, as prepared in the previous step) at rt then the mixture was stirred overnight under nitrogen. The reaction

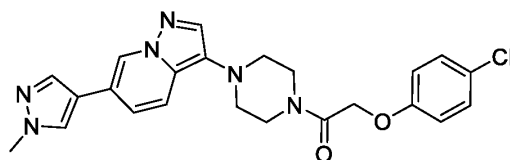
was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with DCM/MeOH (10:1) and Prep-HPLC to afford 130.7 mg (25%) of 1-(benzo[d]thiazol-5-yl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **428**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.42 (s, 1H), 8.82 (s, 1H), 8.22 (s, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 8.08 (d, *J* = 1.6 Hz, 1H), 7.97 (s, 1H), 7.76 (s, 1H), 7.68-7.63 (m, 1H), 7.55-7.50 (m, 1H), 7.35-7.30 (m, 1H), 5.91 (q, *J* = 6.5 Hz, 1H), 3.86 (s, 3H), 3.75-3.50 (m, 4H), 2.97 (br s, 4H), 1.57 (d, *J* = 6.5 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₅N₇O₂S, 488.2; found, 488.1; HPLC purity: 254 nm: 98.4%.

[0717] Using the procedures described in Example 100 and reagents, starting materials, and conditions known to those skilled in the art, the following compounds representative of the present disclosure were prepared:

Compound	Data
434	1-(2-methylbenzo[d]thiazol-5-yl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 8.02 (d, <i>J</i> = 8.3 Hz, 1H), 7.97 (s, 1H), 7.89 (s, 1H), 7.76 (s, 1H), 7.65 (d, <i>J</i> = 9.3 Hz, 1H), 7.42 (dd, <i>J</i> = 8.3, 1.7 Hz, 1H), 7.33 (dd, <i>J</i> = 9.2, 1.5 Hz, 1H), 5.88 (q, <i>J</i> = 6.5 Hz, 1H), 3.86 (s, 3H), 3.74 – 3.47 (m, 4H), 2.97 (s, 4H), 2.80 (s, 3H), 1.55 (d, <i>J</i> = 6.6 Hz, 3H); MS (ESI) <i>m/z</i> [M+H] ⁺ calcd. for C ₂₆ H ₂₇ N ₇ O ₂ S, 502.2; found, 502.1; HPLC purity: 254 nm: 99.2%.

Example 101: Synthesis of Exemplary Compound 431

2-(4-chlorophenoxy)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)ethan-1-one (Compound **431**)

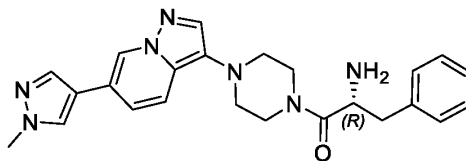


[0718] To a solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (150 mg, 0.53 mmol) and 2-(4-chlorophenoxy)acetyl chloride

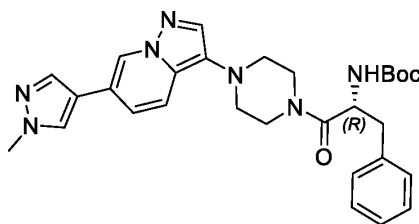
(130.7 mg, 0.64 mmol) in DCM (10 mL) cooled to 0°C was added TEA (107.5 mg, 1.06 mmol) then the mixture was stirred for 2 h under nitrogen. The reaction was warmed to rt and concentrated under reduced pressure then the residue was purified by Prep-TLC (DCM/MeOH 10:1) and Prep-HPLC to afford 151.1 mg (63%) of 2-(4-chlorophenoxy)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)ethan-1-one (Compound 431) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (t, *J* = 1.3 Hz, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.77 (s, 1H), 7.68 (dd, *J* = 9.2, 0.8 Hz, 1H), 7.38 – 7.28 (m, 3H), 7.02 – 6.93 (m, 2H), 4.91 (s, 2H), 3.87 (s, 3H), 3.68 – 3.61 (m, 4H), 3.08 – 2.92 (m, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₃H₂₃ClN₆O₂, 451.2; found, 451.0; HPLC purity: 254 nm: 99.6%.

Example 102: Synthesis of Exemplary Compound 432

(R)-2-amino-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-phenylpropan-1-one (Compound 432)



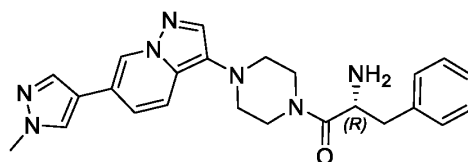
Step 1. Preparation of tert-butyl (R)-(1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-1-oxo-3-phenylpropan-2-yl)carbamate



[0719] To a solution of (tert-butoxycarbonyl)-D-phenylalanine (281.9 mg, 1.06 mmol) in DCM (10 mL) cooled to 0°C was added HATU (606 mg, 1.60 mmol) and DIEA (274.7 mg, 2.13 mmol) then the mixture was stirred for 10 minutes under nitrogen. To the reaction was added 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound 12) (300 mg, 1.06 mmol) at 0°C then the mixture was stirred for 2 h. The reaction was diluted with water (20 mL) and extracted with DCM (3x20 mL). The organic extracts were combined, washed with brine (3x10 mL), dried over anhydrous Na₂SO₄, and

filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with DCM/MeOH (20:1) to afford 550 mg (78%) of tert-butyl (R)-(1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-1-oxo-3-phenylpropan-2-yl)carbamate as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.78 (s, 1H), 8.19 (s, 1H), 7.95 (s, 1H), 7.67 (s, 1H), 7.62 (d, *J* = 9.2 Hz, 1H), 7.34 – 7.23 (m, 5H), 7.22 – 7.09 (m, 2H), 4.71 – 4.58 (m, 1H), 3.86 (s, 3H), 3.79 – 3.58 (m, 4H), 2.93 – 2.57 (m, 6H), 1.31 (s, 9H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₉H₃₅N₇O₃, 530.3; found, 530.3.

Step 2. Preparation of (R)-2-amino-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-phenylpropan-1-one (Compound **432**)



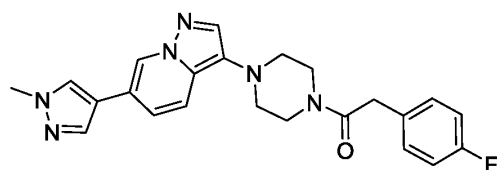
[0720] To a solution of tert-butyl (R)-(1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-1-oxo-3-phenylpropan-2-yl)carbamate (500 mg, 0.94 mmol, as prepared in the previous step) in DCM (5 mL) cooled to 0°C was added 4M HCl in dioxane (2.36 mL, 9.44 mmol) then the mixture was stirred for 2 h under nitrogen. The reaction was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 123.9 mg (30%) of (R)-2-amino-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-phenylpropan-1-one (Compound **432**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.67 (s, 1H), 7.61 (d, *J* = 9.3 Hz, 1H), 7.36 – 7.15 (m, 6H), 3.97 (t, *J* = 7.0 Hz, 1H), 3.87 (s, 3H), 3.74 – 3.64 (m, 1H), 3.61 – 3.48 (m, 2H), 3.47 – 3.38 (m, 1H), 2.98 – 2.82 (m, 2H), 2.80 – 2.73 (m, 2H), 2.72 – 2.65 (m, 1H), 2.49 – 3.39 (m, 1H), 1.84 (s, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₇N₇O, 430.2; found, 430.1; HPLC purity: 254 nm: 99.2%.

[0721] Using the procedures described in Example 102 and reagents, starting materials, and conditions known to those skilled in the art, the following compounds representative of the present disclosure were prepared:

Compound	Data
436	(S)-2-amino-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-phenylpropan-1-one ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ (ppm) 8.82 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.67 (s, 1H), 7.61 (d, <i>J</i> = 9.2 Hz, 1H), 7.38 – 7.15 (m, 6H), 3.97 (t, <i>J</i> = 7.0 Hz, 1H), 3.87 (s, 3H), 3.75 – 3.64 (m, 1H), 3.63 – 3.50 (m, 2H), 3.48 – 3.36 (m, 1H), 3.04 – 2.62 (m, 5H), 2.49 – 2.41 (m, 1H), 1.77 (s, 2H).; MS (ESI) <i>m/z</i> [M+H] ⁺ calcd. for C ₂₄ H ₂₇ N ₇ O, 430.2; found, 430.2; HPLC purity: 254 nm: 96.5%.

Example 103: Synthesis of Exemplary Compound 433

2-(4-fluorophenyl)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)ethan-1-one (Compound **433**)



[0722] To a stirred solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (200 mg, 0.71 mmol), DIEA (183.1 mg, 1.42 mmol) and 2-(4-fluorophenyl)acetic acid (131 mg, 0.85 mmol) in DCM (4 mL) cooled to 0°C was added HATU (404 mg, 1.06 mmol) then the mixture was warmed to rt and stirred for 1 h. The reaction was diluted with DCM (30 mL), washed with water (3x30 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-TLC (DCM/MeOH 40:1) and Prep-HPLC to afford 201 mg (65%) of 2-(4-fluorophenyl)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)ethan-1-one (Compound **433**) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.75 (s, 1H), 7.66 (d, *J* = 9.3 Hz, 1H), 7.36 – 7.26 (m, 3H), 7.19 – 7.10 (m, 2H), 3.87 (s, 3H), 3.78 (s, 2H), 3.74 – 3.61 (m, 4H), 3.02 – 2.86 (m, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₃H₂₃FN₆O, 419.2; found, 419.2; HPLC purity: 254 nm: 95.8%.

[0723] Using the procedures described in Example 103 and reagents, starting materials, and conditions known to those skilled in the art, the following compounds representative of the present disclosure were prepared:

Compound	Data
435	1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-(p-tolyl)propan-1-one ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.75 (s, 1H), 7.66 (d, <i>J</i> = 9.3 Hz, 1H), 7.37 – 7.29 (m, 1H), 7.22 – 7.00 (m, 4H), 3.87 (s, 3H), 3.74 – 3.49 (m, 4H), 3.01 – 2.84 (m, 4H), 2.80 (t, <i>J</i> = 7.6 Hz, 2H), 2.65 (t, <i>J</i> = 7.7 Hz, 2H), 2.55 (s, 3H); MS (ESI) <i>m/z</i> [M+H]⁺ calcd. for C₂₅H₂₈N₆O, 429.2; found, 429.2; HPLC purity: 254 nm: 99.9%.
437	1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-(p-tolyl)ethan-1-one ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm) 8.82 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.73 (s, 1H), 7.65 (d, <i>J</i> = 9.2 Hz, 1H), 7.38-7.23 (d, <i>J</i> = 9.3 Hz, 1H), 7.14 (t, <i>J</i> = 8.8 Hz, 4H), 3.87 (s, 3H), 3.72 (s, 2H), 3.66 (s, 4H), 3.02 – 2.83 (m, 4H), 2.28 (s, 3H).; MS (ESI) <i>m/z</i> [M+H]⁺ calcd. for C₂₄H₂₆N₆O, 415.2; found, 415.2; HPLC purity: 254 nm: 98.0%.
438	2-(4-chlorophenyl)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)ethan-1-one ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.75 (s, 1H), 7.66 (d, <i>J</i> = 9.3 Hz, 1H), 7.39 (d, <i>J</i> = 8.4 Hz, 2H), 7.37 – 7.30 (m, 1H), 7.28 (d, <i>J</i> = 8.4 Hz, 2H), 3.87 (s, 3H), 3.79 (s, 2H), 7.68 (m, 4H), 2.95 (m, 4H); MS (ESI) <i>m/z</i> [M+H]⁺ calcd. for C₂₃H₂₃ClN₆O, 436.2; found, 436.0; HPLC purity: 254 nm: 99.9%.

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- 439** 2-(4-methoxyphenyl)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)ethan-1-one
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.73 (s, 1H), 7.65 (d, *J* = 9.3 Hz, 1H), 7.32 (d, *J* = 9.2 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 3.87 (s, 3H), 3.70 (s, 3H), 3.68-3.60 (m, 6H), 3.02-2.84 (m, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₆N₆O₂, 431.2; found, 431.2; HPLC purity: 220 nm: 97.3%.
-
- 440** 3-(4-methoxyphenyl)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (t, *J* = 1.3 Hz, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.73 (s, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.33 (dd, *J* = 9.3, 1.5 Hz, 1H), 7.22 – 7.14 (m, 2H), 6.89 – 6.81 (m, 2H), 3.87 (s, 3H), 3.71 (s, 3H), 3.64 – 3.59 (m, 4H), 2.91 – 2.87 (m, 4H), 2.79 (t, *J* = 7.6 Hz, 2H), 2.64 (dd, *J* = 8.5, 6.7 Hz, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₈N₆O₂, 445.2; found, 445.2; HPLC purity: 254 nm: 99.6%.
-
- 441** 3-(4-chlorophenyl)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (t, *J* = 1.2 Hz, 1H), 8.23 (s, 1H), 7.98 (d, *J* = 0.8 Hz, 1H), 7.74 (s, 1H), 7.66 (dd, *J* = 9.3, 1.0 Hz, 1H), 7.38 – 7.27 (m, 5H), 3.87 (s, 3H), 3.65 – 3.59 (m, 4H), 2.92 (q, *J* = 4.4 Hz, 4H), 2.85 (t, *J* = 7.5 Hz, 2H), 2.69 (dd, *J* = 8.4, 6.8 Hz, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₅ClN₆O, 449.0; found, 449.2; HPLC purity: 254 nm: 99.3%.
-
- 442** (R)-3-amino-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-phenylpropan-1-one
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (d, *J* = 1.3 Hz, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.72 (s, 1H), 7.64 (dd, *J* = 9.2, 1.0 Hz,
-

-
- 1H), 7.44 – 7.37 (m, 2H), 7.36 – 7.27 (m, 3H), 7.26 – 7.17 (m, 1H), 4.26 (t, $J = 6.6$ Hz, 1H), 3.87 (s, 3H), 3.72 – 3.47 (m, 4H), 2.98 – 2.80 (m, 4H), 2.79 – 2.71 (m, 1H), 2.63 (d, $J = 6.6$ Hz, 2H), 2.14 (s, 2H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{27}N_7O$, 430.2; found, 430.1; HPLC purity: 254 nm: 95.0%
-
- 443** (R)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-phenylbutan-1-one
- 1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.82 (t, $J = 1.2$ Hz, 1H), 8.22 (s, 1H), 7.97 (d, $J = 0.9$ Hz, 1H), 7.71 (s, 1H), 7.63 (dd, $J = 9.3, 1.0$ Hz, 1H), 7.36 – 7.25 (m, 5H), 7.23 – 7.12 (m, 1H), 3.87 (s, 3H), 3.70 – 3.49 (m, 4H), 3.26 – 3.15 (m, 1H), 2.96 – 2.87 (m, 2H), 2.85 – 2.77 (m, 1H), 2.78 – 2.64 (m, 2H), 2.64 – 2.55 (m, 1H), 1.24 (d, $J = 6.9$ Hz, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{25}H_{28}N_6O$, 429.2; found, 429.1; HPLC purity: 254 nm: 99.1%
-
- 445** 3-(4-fluorophenyl)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one
- 1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.82 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.74 (s, 1H), 7.65 (d, $J = 9.2$ Hz, 1H), 7.36 – 7.25 (m, 3H), 7.15 – 7.05 (m, 2H), 3.87 (s, 3H), 3.68 – 3.58 (m, 4H), 7.36 – 7.25 (m, 3H), 2.95 – 2.84 (m, 4H), 2.84 (t, $J = 7.6$ Hz, 2H), 2.67 (t, $J = 7.6$ Hz, 2H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{25}FN_6O$, 433.2; found, 432.9; HPLC purity: 254 nm: 98.1%
-
- 446** 1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-(4-(trifluoromethyl)phenyl)propan-1-one
- 1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.74 (s, 1H), 7.66 – 7.63 (m, 3H), 7.51 (d, $J = 8.0$ Hz, 2H), 7.33 (dd, $J = 9.3, 1.5$ Hz, 1H), 3.87 (s, 3H), 3.69 – 3.61 (m, 4H), 2.99 – 2.89 (m, 6H), 2.75 (t, $J = 7.6$ Hz, 2H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{25}H_{25}F_3N_6O$, 483.2; found, 483.2; HPLC purity: 254 nm: 99.8%.
-

447 (R)-2-hydroxy-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-phenylpropan-1-one

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (t, *J* = 1.2 Hz, 1H), 8.23 (s, 1H), 7.97 (d, *J* = 0.8 Hz, 1H), 7.72 (s, 1H), 7.64 (dd, *J* = 9.3, 1.0 Hz, 1H), 7.36 – 7.22 (m, 5H), 7.22 – 7.15 (m, 1H), 5.14 (d, *J* = 7.9 Hz, 1H), 4.63 – 4.53 (m, 4H), 3.87 (s, 3H), 3.73 – 3.54 (m, 4H), 2.99 – 2.87 (m, 4H), 2.84 – 2.72 (m, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₆N₆O₂, 431.2; found, 431.1; HPLC purity: 254 nm: 99.9%

448 (S)-2-hydroxy-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-phenylpropan-1-one

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.72 (s, 1H), 7.64 (d, *J* = 9.2 Hz, 1H), 7.38 – 7.24 (m, 5H), 7.22 – 7.17 (m, 1H), 5.14 (d, *J* = 7.9 Hz, 1H), 4.75 – 4.43 (m, 1H), 3.87 (s, 3H), 3.71 – 3.47 (m, 4H), 3.09 – 2.83 (m, 4H), 2.84 – 2.72 (m, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₆N₆O₂, 431.2; found, 431.1; HPLC purity: 254 nm: 99.4%.

449 (R)-3-hydroxy-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-phenylpropan-1-one

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (t, *J* = 1.2 Hz, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.73 (s, 1H), 7.65 (d, *J* = 9.3 Hz, 1H), 7.40 (d, *J* = 7.0 Hz, 2H), 7.37 – 7.30 (m, 3H), 7.29 – 7.21 (m, 1H), 5.38 (d, *J* = 4.3 Hz, 1H), 5.01 – 4.97 (m, 1H), 3.88 (s, 3H), 3.66 (s, 4H), 2.93 (s, 3H), 2.80 (dd, *J* = 14.7, 8.4 Hz, 2H), 2.62 (dd, *J* = 14.8, 4.9 Hz, 1H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₆N₆O₂, 431.2; found, 431.2; HPLC purity: 254 nm: 99.5%.

450 (R)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-phenylpropan-1-one

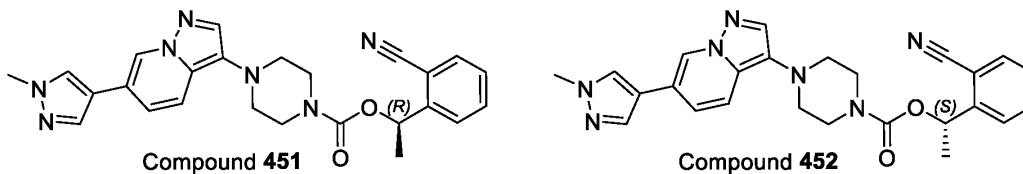
-
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.80 (t, *J* = 1.1 Hz, 1H), 8.21 (s, 1H), 7.96 (s, 1H), 7.65 (s, 1H), 7.60 (d, *J* = 9.3 Hz, 1H), 7.38 – 7.25 (m, 5H), 7.25 – 7.20 (m, 1H), 4.21 – 4.12 (m, 1H), 3.86 (s, 3H), 3.74 – 3.63 (m, 3H), 3.49 – 3.38 (m, 1H), 2.99 – 2.90 (m, 1H), 2.89 – 2.78 (m, 2H), 2.48 – 2.44 (m, 1H), 1.31 (d, *J* = 6.7 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₆N₆O, 415.2; found, 415.0; HPLC purity: 254 nm: 99.6%
-
- 492** 1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-phenylethane-1,2-dione
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 8.02 – 7.89 (m, 3H), 7.87 – 7.76 (m, 2H), 7.71 – 7.60 (m, 3H), 7.35 (dd, *J* = 9.3, 1.5 Hz, 1H), 3.87 – 3.85 (m, 5H), 3.48 (t, *J* = 4.8 Hz, 2H), 3.14 (t, *J* = 5.1 Hz, 2H), 2.97 (t, *J* = 5.0 Hz, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₃H₂₂N₆O₂, 415.2; found, 415.1; HPLC purity: 254 nm: 98.0%.
-
- 493** (R)-3-hydroxy-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-phenylpropan-1-one
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.80 (s, 1H), 8.20 (s, 1H), 7.96 (s, 1H), 7.66 (s, 1H), 7.61 (d, *J* = 9.3 Hz, 1H), 7.39 – 7.29 (m, 5H), 7.30 – 7.21 (m, 1H), 4.72 (t, *J* = 5.4 Hz, 1H), 4.15 (dd, *J* = 8.2, 5.4 Hz, 1H), 4.07 – 3.93 (m, 1H), 3.89 (s, 3H), 3.80 – 3.63 (m, 3H), 3.62 – 3.44 (m, 2H), 3.06 – 2.74 (m, 3H), 2.53 (s, 1H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₆N₆O₂, 431.2; found, 431.1; HPLC purity: 254 nm: 99.9%.
-
- 495** (S)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-(p-tolyl)propan-1-one
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.79 (s, 1H), 8.23 (s, 1H), 7.97 (d, *J* = 0.8 Hz, 1H), 7.68 (s, 1H), 7.61 (d, *J* = 9.3 Hz, 1H), 7.31 (dd, *J* = 9.3, 1.5 Hz, 1H), 7.23 – 7.06 (m, 4H), 4.12 (q, *J* = 6.7 Hz, 1H), 3.87 (s, 3H), 3.67 – 3.65 (m, 3H), 3.50 – 3.39 (m,
-

	1H), 3.00 – 2.86 (m, 3H), 2.55 (s, 1H), 2.28 (s, 3H), 1.30 (d, J = 6.7 Hz, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{25}H_{28}N_6O$, 429.2; found, 429.1; HPLC purity: 254 nm: 99.7%.
498	(S)-3-hydroxy-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-phenylpropan-1-one 1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.80 (s, 1H), 8.23 (s, 1H), 7.96 (s, 1H), 7.66 (s, 1H), 7.60 (d, J = 9.6 Hz, 1H), 7.37 – 7.33 (m, 2H), 7.33 – 7.32 (m, 2H), 7.32 – 7.29 (m, 1H), 7.29 – 7.23 (m, 1H), 4.73 (t, J = 5.4 Hz, 1H), 4.16 (dd, J = 8.2, 5.4 Hz, 1H), 4.06 – 3.96 (m, 1H), 3.88 (s, 3H), 3.77 – 3.62 (m, 3H), 3.57 – 3.47 (m, 2H), 3.02 – 2.79 (m, 3H), 2.51 – 2.48 (m, 1H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{26}N_6O_2$, 431.2; found, 431.2; HPLC purity: 254 nm: 99.5%.
524	1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-(6-methylpyridin-3-yl)propan-1-one 1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.82 (s, 1H), 8.35 (d, J = 2.3 Hz, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.74 (s, 1H), 7.66 (d, J = 9.3 Hz, 1H), 7.57 (dd, J = 8.0, 2.3 Hz, 1H), 7.33 (dd, J = 9.3, 1.5 Hz, 1H), 7.16 (d, J = 7.9 Hz, 1H), 3.88 (s, 3H), 3.71 – 3.49 (m, 4H), 2.91 – 2.88 (m, 4H), 2.82 (t, J = 7.4 Hz, 2H), 2.69 (t, J = 7.7 Hz, 2H), 2.42 (s, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{27}N_7O$, 430.2; found, 430.3; HPLC purity: 254 nm: 99.3%.

Example 104: Synthesis of Exemplary Compound 451

(R)-1-(2-cyanophenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **451**) and (S)-1-(2-cyanophenyl)ethyl 4-(6-(1-

methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound 452)



[0724] To a stirred mixture of 6-(1-methyl-1*H*-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-*a*]pyridine (Compound 12) (500 mg, 1.7 mmol) and 2-(1-hydroxyethyl)benzonitrile (286 mg, 1.9 mmol) in pyridine (10 mL) cooled to 0°C was added BTC (1.05 g, 3.5 mmol) in portions then the mixture was warmed to rt and stirred for 2 h. The reaction was cooled to 0°C, quenched with water, and extracted with DCM (3x200 mL). The organic extracts were combined, then concentrated under reduced pressure. The residue was purified by Prep-HPLC to afford racemic 1-(2-cyanophenyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate as a yellow solid.

[0725] Racemic 1-(2-cyanophenyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate was separated by Chiral-Prep-HPLC to afford 100.7 mg (25%) of (*R*)-1-(2-cyanophenyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound 451, first eluting peak) as a yellow solid and 102.9 mg (25%) of (*S*)-1-(2-cyanophenyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound 452, second eluting peak) as a yellow solid.

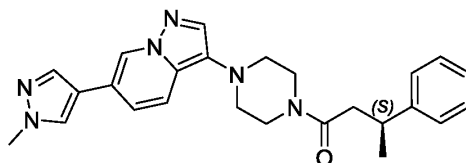
[0726] (*R*)-1-(2-cyanophenyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound 451, first eluting peak). ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.78 (s, 1H), 7.74 (t, *J* = 7.4 Hz, 1H), 7.69 – 7.63 (m, 2H), 7.62 – 7.54 (m, 1H), 7.33 (dd, *J* = 9.2, 1.5 Hz, 1H), 5.84 (q, *J* = 6.6 Hz, 1H), 3.87 (s, 3H), 3.76 – 3.66 (m, 2H), 3.56 (t, *J* = 5.0 Hz, 2H), 3.10 – 2.83 (m, 4H), 1.58 (d, *J* = 6.6 Hz, 3H); MS (ESI) *m/z* [*M*+H]⁺ calcd. for C₂₅H₂₅N₇O₂, 456.2; found, 456.2; HPLC purity: 254 nm: 99.0%.

[0727] (*S*)-1-(2-cyanophenyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound 452, second eluting peak). ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.78 (s, 1H), 7.74 (t, *J* = 7.4 Hz, 1H), 7.69 – 7.63 (m, 2H), 7.62 – 7.54 (m, 1H), 7.33

(dd, $J = 9.2, 1.5$ Hz, 1H), 5.84 (q, $J = 6.6$ Hz, 1H), 3.87 (s, 3H), 3.76 – 3.66 (m, 2H), 3.56 (t, $J = 5.0$ Hz, 2H), 3.10 – 2.83 (m, 4H), 1.58 (d, $J = 6.6$ Hz, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{25}H_{25}N_7O_2$, 456.2; found, 456.2; HPLC purity: 254 nm: 98.3%.

Example 105: Synthesis of Exemplary Compound 455

(S)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-phenylbutan-1-one (Compound 455)



[0728] To a stirred mixture of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound 12) (300 mg, 1.06 mmol) and (S)-3-phenylbutanoic acid (209.36 mg, 1.27 mmol) in DMF (10 mL) cooled to 0°C were added HATU (606 mg, 1.59 mmol) and DIEA (205.99 mg, 1.59 mmol) in portions then the mixture was warmed to rt and stirred for 2 h. The reaction was concentrated under reduced pressure then the residue was dissolved in water (200 mL) and extracted with EtOAc (2x120 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 253.9 mg (56%) of (S)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-phenylbutan-1-one (Compound 455) as a yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.83 (t, $J = 1.2$ Hz, 1H), 8.23 (s, 1H), 7.98 (d, $J = 0.8$ Hz, 1H), 7.72 (s, 1H), 7.64 (dd, $J = 9.3$ Hz, 1.0 Hz, 1H), 7.34 (dd, $J = 9.2$ Hz, 1.6 Hz, 1H), 7.30 (d, $J = 4.3$ Hz, 4H), 7.22 – 7.16 (m, 1H), 3.88 (s, 3H), 3.70 – 3.51 (m, 4H), 3.27 – 3.16 (m, 1H), 2.97 – 2.88 (m, 2H), 2.87 – 2.78 (m, 1H), 2.79 – 2.70 (m, 1H), 2.68 (d, $J = 6.6$ Hz, 1H), 2.61 (dd, $J = 15.1$ Hz, 7.7 Hz, 1H), 1.25 (d, $J = 6.9$ Hz, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{25}H_{28}N_6O$, 429.2; found, 429.2; HPLC purity: 254 nm: 99.6%.

[0729] Using the procedures described in Example 105 and reagents, starting materials, and conditions known to those skilled in the art, the following compounds representative of the present disclosure were prepared:

Compound	Data
456	(S)-3-hydroxy-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-phenylpropan-1-one ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm) 8.83 (s, 1H), 8.24 (s, 1H), 7.98 (s, 1H), 7.73 (s, 1H), 7.65 (d, <i>J</i> = 9.3, 1H), 7.43 – 7.38 (m, 2H), 7.36 – 7.32 (m, 3H), 7.27 – 7.22 (m, 1H), 5.38 (d, <i>J</i> = 4.3 Hz, 1H), 5.03 – 4.99 (m, 1H), 3.88 (s, 3H), 3.70 – 3.58 (m, 4H), 2.96 – 2.85 (m, 3H), 2.81 – 2.76 (m, 2H), 2.63 (dd, <i>J</i> = 14.8, 4.9 Hz, 1H); MS (ESI) <i>m/z</i> [M+H]⁺ calcd. for C₂₄H₂₆N₆O₂, 431.2; found, 431.1; HPLC purity: 254 nm: 99.9%.
461	(R)-2-hydroxy-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-phenylethan-1-one ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm) 8.81 (t, <i>J</i> = 1.2 Hz, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.68 (s, 1H), 7.61 (d, <i>J</i> = 9.3 Hz, 1H), 7.44 – 7.35 (m, 4H), 7.34 – 7.27 (m, 2H), 5.71 (d, <i>J</i> = 6.3 Hz, 1H), 5.48 (d, <i>J</i> = 6.4 Hz, 1H), 3.87 (s, 3H), 3.79 – 3.59 (m, 3H), 3.57 – 3.47 (m, 1H), 3.00 – 2.85 (m, 2H), 2.78 (t, <i>J</i> = 8.4 Hz, 1H), 2.71 – 2.58 (m, 1H); MS (ESI) <i>m/z</i> [M+H]⁺ calcd. for C₂₃H₂₄N₆O₂, 417.2; found, 417.2; HPLC purity: 254 nm: 99.9%.
462	(S)-2-hydroxy-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-phenylethan-1-one ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm) 8.81 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.68 (s, 1H), 7.61 (d, <i>J</i> = 9.3 Hz, 1H), 7.48 – 7.35 (m, 4H), 7.36 – 7.24 (m, 2H), 5.71 (d, <i>J</i> = 6.3 Hz, 1H), 5.47 (d, <i>J</i> = 6.3 Hz, 1H), 3.86 (s, 3H), 3.58 (m, 3H), 3.54 – 3.50 (m, 1H), 2.98 – 2.88 (m, 2H), 2.81 – 2.75 (m, 1H), 2.68 – 2.61 (m, 1H); MS (ESI) <i>m/z</i> [M+H]⁺ calcd. for C₂₃H₂₄N₆O₂, 417.2; found, 417.1; HPLC purity: 254 nm: 99.5%

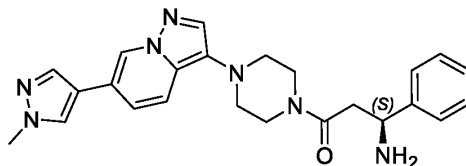
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- 463** (R)-2-methoxy-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-phenylethan-1-one
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.81 (s, 1H), 8.23 (s, 1H), 7.97 (d, *J* = 0.8 Hz, 1H), 7.69 (s, 1H), 7.6 (d, *J* = 9.1 Hz, 1H), 7.45 – 7.38 (m, 4H), 7.37 – 7.25 (m, 2H), 5.26 (s, 1H), 3.87 (s, 3H), 3.72 – 3.55 (m, 4H), 3.35 (s, 3H), 3.70 – 3.62 (m, 2H), 2.81 (s, 1H), 2.75 – 2.61 (m, 1H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₆N₆O₂, 431.2; found, 431.1; HPLC purity: 254 nm: 99.0%.
-
- 464** (S)-2-methoxy-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-phenylethan-1-one
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 – 8.79 (m, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.69 (s, 1H), 7.62 (dd, *J* = 9.2, 0.9 Hz, 1H), 7.44 – 7.37 (m, 4H), 7.36 – 7.33 (m, 1H), 7.32 – 7.29 (m, 1H), 5.25 (s, 1H), 3.86 (s, 3H), 3.72–3.54 (m, 4H), 3.35 (s, 3H), 2.98 – 2.86 (m, 2H), 2.84 – 2.75 (m, 1H), 2.50 – 2.49 (m, 1H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₆N₆O₂, 431.2; found, 431.1; HPLC purity: 254 nm: 99.9%.
-
- 490** 1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-(*m*-tolyl)ethan-1-one
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.23 (s, 1H), 7.97 (d, *J* = 4.4 Hz, 1H), 7.73 (s, 1H), 7.65 (d, *J* = 9.3 Hz, 1H), 7.33 (dd, *J* = 9.3, 1.5 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.10 – 7.01 (m, 3H), 3.87 (s, 3H), 3.73 (s, 2H), 3.70 – 3.62 (m, 4H), 2.95 (t, *J* = 5.1 Hz, 2H), 2.90 (t, *J* = 4.9 Hz, 2H), 2.29 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₆N₆O, 414.2; found, 415.2; HPLC purity: 254 nm: 99.9%.
-
- 491** 1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-(*o*-tolyl)ethan-1-one
-

	¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.77 (s, 1H), 7.67 (d, <i>J</i> = 9.6, 1H), 7.33 (dd, <i>J</i> = 9.2, 1.2 Hz, 1H), 7.18 – 7.09 (m, 4H), 3.87 (s, 3H), 3.81 (s, 2H), 3.75 – 3.69 (m, 4H), 2.98 (t, <i>J</i> = 4.8 Hz, 4H), 2.22 (s, 3H); MS (ESI) <i>m/z</i> [M+H]⁺ calcd. for C₂₄H₂₆N₆O, 415.2; found, 415.1; HPLC purity: 254 nm: 99.4%.
502	3-(4-cyclopropylphenyl)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm) 8.82 (s, 1H), 8.23 (s, 1H), 7.98 (d, <i>J</i> = 0.8 Hz, 1H), 7.74 (s, 1H), 7.64 (d, <i>J</i> = 9.2 Hz, 1H), 7.33 (dd, <i>J</i> = 9.2, 1.6 Hz, 1H), 7.16 – 7.10 (m, 2H), 7.00 – 6.96 (m, 2H), 3.88 (s, 3H), 3.69 – 3.55 (m, 4H), 2.94 – 2.84 (m, 4H), 2.80 (t, <i>J</i> = 8.0 Hz, 2H), 2.64 (t, <i>J</i> = 6.8 Hz, 2H), 1.90 – 1.81 (m, 1H), 0.93 – 0.85 (m, 2H), 0.63 – 0.56 (m, 2H); MS (ESI) <i>m/z</i> [M+H]⁺ calcd. for C₂₇H₃₀N₆O, 455.3; found, 455.3; HPLC purity: 254 nm: 97.4%.
523	4-(3-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-oxopropyl)benzonitrile ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.77 – 7.74 (m, 3H), 7.65 (d, <i>J</i> = 9.2, 1H), 7.49 (d, <i>J</i> = 8.1 Hz, 2H), 7.33 (dd, <i>J</i> = 9.3, 1.6 Hz, 1H), 3.87 (s, 3H), 3.65 – 3.62 (m, 4H), 2.96 – 2.92 (m, 6H), 2.74 (t, <i>J</i> = 7.5 Hz, 2H); MS (ESI) <i>m/z</i> [M+H]⁺ calcd. for C₂₅H₂₅N₇O, 440.2; found, 440.20; HPLC purity: 254 nm: 99.5%.
525	4-(2-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-oxoethyl)benzonitrile ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.79 (d, <i>J</i> = 8.4 Hz, 2H), 7.75 (s, 1H), 7.67 (d, <i>J</i> = 9.3 Hz, 1H), 7.54 – 7.39 (m, 2H), 7.34 (dd, <i>J</i> = 9.2, 1.6 Hz, 1H), 3.91 (s, 2H), 3.87 (s, 3H), 3.71 – 3.66 (m, 4H), 3.09 – 2.88 (m,

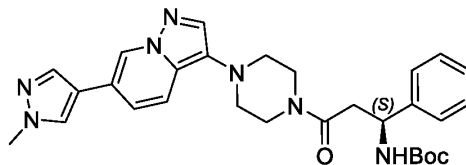
	4H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{23}N_7O$, 426.2; found, 426.2; HPLC purity: 254 nm: 98.4%
526	1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-(6-methylpyridin-3-yl)ethan-1-one 1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.83 (s, 1H), 8.32 (d, J = 2.3 Hz, 1H), 8.24 (s, 1H), 7.98 (d, J = 0.8 Hz, 1H), 7.76 (s, 1H), 7.67 (dd, J = 9.3, 0.9 Hz, 1H), 7.53 (dd, J = 8.0, 2.3 Hz, 1H), 7.34 (dd, J = 9.3, 1.5 Hz, 1H), 7.20 (d, J = 7.9 Hz, 1H), 3.88 (s, 3H), 3.77 (s, 2H), 3.72 (t, J = 5.0 Hz, 2H), 3.67 (t, J = 5.0 Hz, 2H), 3.01 – 2.93 (m, 4H), 2.45 (s, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{23}H_{25}N_7O$, 416.2; found, 416.2; HPLC purity: 254 nm: 96.2%.
532	1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-(5-methylpyridin-2-yl)propan-1-one 1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.83 (s, 1H), 8.32 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.75 (s, 1H), 7.66 (d, J = 9.2 Hz, 1H), 7.51 (dd, J = 7.9, 2.3 Hz, 1H), 7.33 (dd, J = 9.3, 1.6 Hz, 1H), 7.20 (d, J = 7.9 Hz, 1H), 3.87 (s, 3H), 3.64 (t, J = 4.9 Hz, 4H), 2.99 – 2.89 (m, 6H), 2.78 (t, J = 7.4 Hz, 2H), 2.25 (s, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{27}N_7O$, 430.2; found, 430.2; HPLC purity: 254 nm: 98.8%.

Example 106: Synthesis of Exemplary Compound 457

(S)-3-amino-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-phenylpropan-1-one (Compound 457)

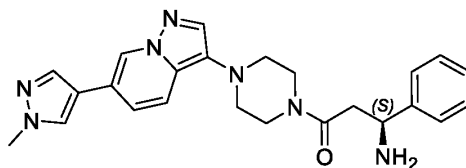


Step 1. Preparation of tert-butyl (S)-(3-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-oxo-1-phenylpropyl)carbamate



[0730] To a stirred solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (300 mg, 1.06 mmol) and (S)-3-((tert-butoxycarbonyl)amino)-3-phenylpropanoic acid (563.8 mg, 2.12 mmol) in DMF (10 mL) cooled to 0°C were added HATU (606 mg, 1.59 mmol) and DIEA (206 mg, 1.59 mmol) in portions then the mixture was warmed to rt and stirred for 1 h. The reaction was diluted with water and extracted with EtOAc. The organic extracts were combined, washed with brine, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 10-50% ACN/water (10mM NH₄HCO₃) to afford 500 mg (89%) of tert-butyl (S)-(3-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-oxo-1-phenylpropyl)carbamate as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.70 (s, 1H), 7.65 (d, *J* = 9.3 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 7.35 – 7.32 (m, 5H), 7.27 – 7.20 (m, 1H), 4.98 (d, *J* = 7.5 Hz, 1H), 3.88 (s, 3H), 3.64 – 3.49 (m, 4H), 2.91 – 2.82 (m, 4H), 2.78 – 2.62 (m, 2H), 1.36 (s, 9H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₉H₃₅N₇O₃, 530.3; found, 530.0.

Step 2. Preparation of (S)-3-amino-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-phenylpropan-1-one (Compound **457**)



[0731] To a stirred solution of tert-butyl (S)-(3-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-oxo-1-phenylpropyl)carbamate (400 mg, 0.75 mmol, as prepared in the previous step) in DCM (9 mL) cooled to 0°C was added TFA (3 mL) dropwise then the mixture was warmed to rt and stirred for 2 h. The reaction was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford

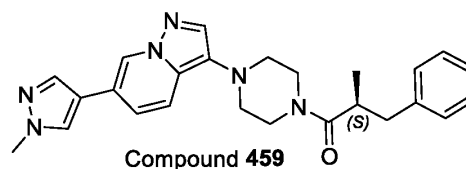
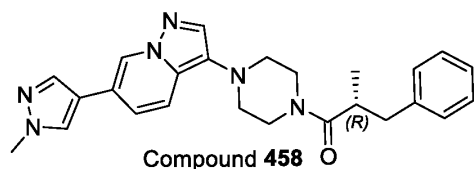
146.7 mg (44%) of (S)-3-amino-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-3-phenylpropan-1-one (Compound **457**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (t, *J* = 1.2 Hz, 1H), 8.22 (s, 1H), 7.97 (d, *J* = 0.8 Hz, 1H), 7.72 (s, 1H), 7.64 (dd, *J* = 9.3, 1.0 Hz, 1H), 7.43 – 7.38 (m, 2H), 7.37 – 7.31 (m, 3H), 7.26 – 7.22 (m, 1H), 4.31 (t, *J* = 6.6 Hz, 1H), 3.87 (s, 3H), 3.71 – 3.51 (m, 4H), 2.96 – 2.84 (m, 3H), 2.81 – 2.78 (m, 1H), 2.69 (d, *J* = 6.7 Hz, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₇N₇O, 430.2; found, 430.2; HPLC purity: 254 nm: 98.2%.

[0732] Using the procedures described in Example 106 and reagents, starting materials, and conditions known to those skilled in the art, the following compounds representative of the present disclosure were prepared:

Compound	Data
465	(R)-2-amino-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-phenylethan-1-one ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ (ppm) 8.81 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.67 (s, 1H), 7.61 (d, <i>J</i> = 9.9 Hz, 1H), 7.38 – 7.33 (m, 4H), 7.31 (dd, <i>J</i> = 9.2, 1.5 Hz, 1H), 7.28 – 7.23 (m, 1H), 4.90 (s, 1H), 3.87 (s, 3H), 3.78 – 3.58 (m, 3H), 3.51 – 3.43 (m, 1H), 2.98 – 2.86 (m, 3H), 2.57 (d, <i>J</i> = 8.5 Hz, 1H), 2.13 (s, 2H); MS (ESI) <i>m/z</i> [M+H] ⁺ calcd. for C ₂₃ H ₂₅ N ₇ O, 416.2; found, 416.2; HPLC purity: 254 nm: 98.8%.
466	(S)-2-amino-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-phenylethan-1-one ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ (ppm) 8.81 (t, <i>J</i> = 1.2 Hz, 1H), 8.22 (s, 1H), 7.97 (d, <i>J</i> = 0.8 Hz, 1H), 7.67 (s, 1H), 7.61 (dd, <i>J</i> = 9.3, 1.0 Hz, 1H), 7.38 – 7.29 (m, 5H), 7.29 – 7.24 (m, 1H), 4.90 (s, 1H), 3.87 (s, 3H), 3.72 (d, <i>J</i> = 16.7 Hz, 3H), 3.54 – 3.39 (m, 1H), 2.94 (d, <i>J</i> = 7.6 Hz, 1H), 2.91 – 2.85 (m, 2H), 2.57 (d, <i>J</i> = 7.9 Hz, 1H), 2.24 (s, 2H); MS (ESI) <i>m/z</i> [M+H] ⁺ calcd. for C ₂₃ H ₂₅ N ₇ O, 416.2; found, 415.9; HPLC purity: 254 nm: 99.9%.

Example 107: Synthesis of Exemplary Compound 458 and Compound 459

(*R*)-2-methyl-1-(4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazin-1-yl)-3-phenylpropan-1-one (Compound **458**) and (*S*)-2-methyl-1-(4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazin-1-yl)-3-phenylpropan-1-one (Compound **459**)



[0733] To a stirred mixture of 6-(1-methyl-1*H*-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-*a*]pyridine (Compound **12**) (600 mg, 2.1 mmol) and 2-methyl-3-phenylpropanoic acid (418 mg, 2.5) in DMF (10 mL) were added HATU (1.21 g, 3.1 mmol) and DIEA (549 mg, 4.2 mmol) then the mixture was stirred at rt for 3 h. The reaction was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford racemic 2-methyl-1-(4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazin-1-yl)-3-phenylpropan-1-one as a yellow solid.

[0734] The racemic 2-methyl-1-(4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazin-1-yl)-3-phenylpropan-1-one (400 mg, 0.933 mmol) was separated by Chiral-Prep-HPLC to afford 114.3 mg (28%) of (*R*)-2-methyl-1-(4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazin-1-yl)-3-phenylpropan-1-one (Compound **458**, first eluting peak) as a yellow solid and 134.7 mg (34%) of (*S*)-2-methyl-1-(4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazin-1-yl)-3-phenylpropan-1-one (Compound **459**, second eluting peak) as a yellow solid.

[0735] (*R*)-2-methyl-1-(4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazin-1-yl)-3-phenylpropan-1-one (Compound **458**, first eluting peak). ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.67 (s, 1H), 7.60 (d, *J* = 9.2 Hz, 1H), 7.33 – 7.28 (m, 3H), 7.22 – 7.16 (m, 3H), 3.87 (s, 3H), 3.72 – 3.69 (m, 1H), 3.59 – 3.48 (m, 3H), 3.20 – 3.15 (m, 1H), 2.93 – 2.82 (m, 3H), 2.74 – 2.70 (m, 1H), 2.69 – 2.67 (m, 1H), 2.48 – 2.45 (1H), 1.04 (d, *J* = 6.4 Hz, 3H); MS (ESI) *m/z* [*M*+*H*]⁺ calcd. for C₂₅H₂₈N₆O, 429.2; found, 429.2; HPLC purity: 254 nm: 99.5%

[0736] (*S*)-2-methyl-1-(4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazin-1-yl)-3-phenylpropan-1-one (Compound **459**, second eluting peak). ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.67 (s, 1H), 7.60

(d, $J = 9.2$ Hz, 1H), 7.33 – 7.28 (m, 3H), 7.22 – 7.16 (m, 3H), 3.87 (s, 3H), 3.72 – 3.69 (m, 1H), 3.59 – 3.48 (m, 3H), 3.20 – 3.15 (m, 1H), 2.93 – 2.82 (m, 3H), 2.74 – 2.70 (m, 1H), 2.69 – 2.67 (m, 1H), 2.48 – 2.45 (1H), 1.04 (d, $J = 6.4$ Hz, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{25}H_{28}N_6O$, 429.2; found, 429.2; HPLC purity: 254 nm: 99.0%.

[0737] Using the procedures described in Example 107 and reagents, starting materials, and conditions known to those skilled in the art, the following compounds representative of the present disclosure were prepared:

Compound	Data
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503	(R)-3-(4-chlorophenyl)-3-hydroxy-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one (first eluting peak)
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1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.72 (s, 1H), 7.64 (d, $J = 9.2$ Hz, 1H), 7.44 – 7.36 (m, 4H), 7.32 (dd, $J = 9.2, 1.2$ Hz, 1H), 5.46 (d, $J = 4.4$ Hz, 1H), 5.02 – 4.97 (m, 1H), 3.87 (s, 3H), 3.69 – 3.54 (m, 4H), 2.95 – 2.93 (m, 2H), 2.90 – 2.83 (m, 1H), 2.82 – 2.75 (m, 2H), 2.65 – 2.60 (m, 1H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{25}ClN_6O_2$, 465.2; found, 465.0; HPLC purity: 254 nm: 98.5%.

504	(S)-3-(4-chlorophenyl)-3-hydroxy-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one (second eluting peak)
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1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.72 (s, 1H), 7.64 (d, $J = 9.2$ Hz, 1H), 7.43 – 7.36 (m, 4H), 7.32 (dd, $J = 9.2, 1.4$ Hz, 1H), 5.46 (d, $J = 4.4$ Hz, 1H), 5.03 – 4.96 (m, 1H), 3.87 (s, 3H), 3.69 – 3.56 (m, 4H), 2.95 – 2.90 (m, 2H), 2.90 – 2.83 (m, 1H), 2.82 – 2.75 (m, 2H), 2.65 – 2.62 (m, 1H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{25}ClN_6O_2$, 465.2; found, 465.0; HPLC purity: 254 nm: 99.4%.

509 (R)-3-(4-chlorophenyl)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)butan-1-one (first eluting peak)

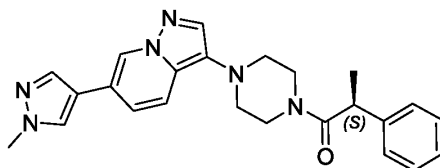
¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (d, *J* = 0.8 Hz, 1H), 7.72 (s, 1H), 7.64 (d, *J* = 9.3 Hz, 1H), 7.38 – 7.28 (m, 5H), 3.87 (s, 3H), 3.68 – 3.51 (m, 4H), 3.21 (q, *J* = 7.0 Hz, 1H), 2.98 – 2.88 (m, 2H), 2.85 – 2.73 (m, 2H), 2.73 – 2.56 (m, 2H), 1.23 (d, *J* = 6.9 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₇ClN₆O, 463.2; found, 463.2; HPLC purity: 254 nm: 99.6%.

510 (S)-3-(4-chlorophenyl)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)butan-1-one (second eluting peak)

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.73 (s, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.36 – 7.32 (m, 5H), 3.88 (s, 3H), 3.67 – 3.55 (m, 4H), 3.23 (q, *J* = 7.1 Hz, 1H), 2.97 – 2.90 (m, 2H), 2.87 – 2.74 (m, 2H), 2.74 – 2.58 (m, 2H), 1.24 (d, *J* = 6.9 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₇ClN₆O, 463.2; found, 463.2; HPLC purity: 254 nm: 97.7%.

Example 108: Synthesis of Exemplary Compound 460

(S)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-phenylpropan-1-one (Compound **460**)

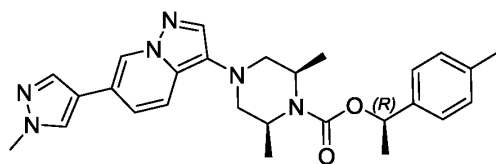


[0738] To a stirred solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (200 mg, 0.70 mmol) and (S)-2-phenylpropanoic acid (212.8 mg, 1.41 mmol) in DMF (10 mL) were added TCFH (298.1 mg, 1.06 mmol) and NMI (87.2 mg, 1.06 mmol) in portions at rt then the mixture was

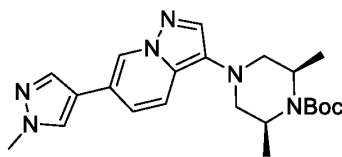
stirred for 1 h. The reaction was diluted with water (50 mL) and extracted with EtOAc (3 x50 mL). The organic extracts were combined, washed with brine (2x3 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 10-50% ACN/water (10mM NH₄HCO₃) to afford 155.6 mg (52%) of (S)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-phenylpropan-1-one (Compound **460**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.80 (t, *J* = 1.2 Hz, 1H), 8.21 (s, 1H), 7.96 (d, *J* = 0.8 Hz, 1H), 7.65 (s, 1H), 7.59 (dd, *J* = 9.3, 1.0 Hz, 1H), 7.36 – 7.28 (m, 5H), 7.25 – 7.23 (m, 1H), 4.16 (q, *J* = 6.8 Hz, 1H), 3.86 (s, 3H), 3.68 – 3.67 (m, 3H), 3.47 – 3.44 (m, 1H), 2.96 – 2.88 (m, 1H), 2.83 (dd, *J* = 12.3, 7.8 Hz, 2H), 2.50 – 2.45 (m, 1H), 1.31 (d, *J* = 6.8 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₆N₆O, 415.2; found, 415.2; HPLC purity: 254 nm: 97.4%.

Example 109: Synthesis of Exemplary Compound 468

(R)-1-(p-tolyl)ethyl (2S,6R)-2,6-dimethyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **468**)



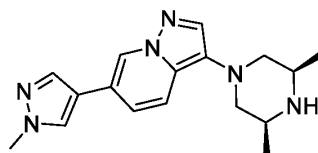
Step 1. Preparation of tert-butyl (2R,6S)-2,6-dimethyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate



[0739] To a stirred mixture of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **S9**) (1 g, 3.60 mmol) and tert-butyl (2S,6R)-2,6-dimethylpiperazine-1-carboxylate (3.87 g, 18.04 mmol) in dioxane (5 mL) and tBuOH (10mL) were added KOtBu (0.61 g, 5.41 mmol) and tBuXPhos Pd G1 (247 mg, 0.36 mmol) then the mixture was heated to 90°C and stirred overnight under nitrogen. The reaction was cooled to rt and concentrated under reduced pressure then water (300 mL) was added to the

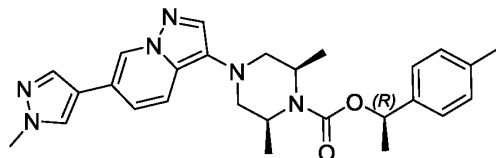
residue and the mixture was extracted with EtOAc (2x200 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 5-100% ACN/water (10mM NH₄HCO₃) to afford 400mg400mg400 mg (27%) of tert-butyl (2*R*,6*S*)-2,6-dimethyl-4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate as a brown solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.86 (t, *J* = 1.2 Hz, 1H), 8.23 (d, *J* = 0.8 Hz, 1H), 7.98 (d, *J* = 0.8 Hz, 1H), 7.77 (s, 1H), 7.54 (dd, *J* = 9.2, 1.0 Hz, 1H), 7.37 (dd, *J* = 9.2, 1.5 Hz, 1H), 4.16 – 4.05 (m, 2H), 3.88 (s, 3H), 3.15 – 3.07 (m, 2H), 2.81 (dd, *J* = 11.8, 4.3 Hz, 2H), 1.45 (s, 9H), 1.39 (d, *J* = 6.8 Hz, 6H).

Step 2. Preparation of 3-((3*R*,5*S*)-3,5-dimethylpiperazin-1-yl)-6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridine



[0740] A solution of tert-butyl (2*R*,6*S*)-2,6-dimethyl-4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (300 mg, 0.73 mmol, as prepared in the previous step) in TFA (1 mL) was stirred at rt for 1 h. The reaction was concentrated under reduced pressure then water (300 mL) was added to the residue and the mixture was extracted with DCM (2x200 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to afford 200 mg (88%) of 3-((3*R*,5*S*)-3,5-dimethylpiperazin-1-yl)-6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridine as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 9.12 (d, *J* = 10.7 Hz, 1H), 8.85 (s, 1H), 8.25 (s, 1H), 7.99 (s, 1H), 7.84 (s, 1H), 7.74 (d, *J* = 9.3 Hz, 1H), 7.38 (d, *J* = 9.2 Hz, 1H), 3.88 (s, 3H), 3.54 (d, *J* = 9.7 Hz, 2H), 3.46 (d, *J* = 12.7 Hz, 2H), 2.70 (t, *J* = 11.6 Hz, 2H), 1.28 (d, *J* = 6.4 Hz, 6H).

Step 3. (*R*)-1-(*p*-tolyl)ethyl (2*R*,6*S*)-2,6-dimethyl-4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **468**)



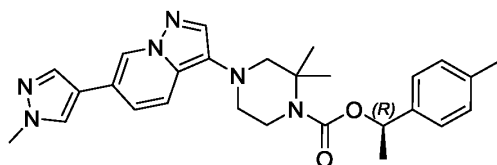
[0741] To a stirred solution of 3-((3*R*,5*S*)-3,5-dimethylpiperazin-1-yl)-6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridine (170 mg, 0.54 mmol, as prepared in the previous step) in THF (10 mL) cooled to 0°C were added DIEA (141.5 mg, 1.09 mmol) and 2,2,2-trichloroethyl chloroformate (232.0 mg, 1.09 mmol) in portions then the mixture was stirred for 1 h. The reaction was concentrated under reduced pressure then water (200 mL) was added to the residue and the resulting mixture was extracted with EtOAc (2x120 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was dissolved in DCE (2 mL) and (*R*)-1-(*p*-tolyl)ethan-1-ol (111.88 mg, 0.82 mmol) was added. To the stirred solution was added NaH (60% wt., 131.2 mg, 3.28 mmol) in portions at rt then the reaction was heated to 90°C and stirred overnight. The reaction was cooled to rt and concentrated under reduced pressure. Water (200 mL) was added to the residue and the resulting mixture was extracted with DCM (2x120 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-TLC (PE/EtOAc 1:1) and Prep-HPLC to afford 51.3 mg (20%) of (*R*)-1-(*p*-tolyl)ethyl (2*R*,6*S*)-2,6-dimethyl-4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **468**) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.85 (t, *J* = 1.3 Hz, 1H), 8.22 (s, 1H), 7.98 (d, *J* = 0.8 Hz, 1H), 7.78 (s, 1H), 7.54 (dd, *J* = 9.2, 1.0 Hz, 1H), 7.37 (dd, *J* = 9.2, 1.5 Hz, 1H), 7.31 – 7.24 (m, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 5.79 – 5.70 (m, 1H), 4.26 – 4.17 (m, 2H), 3.88 (s, 3H), 3.12 (d, *J* = 11.5 Hz, 2H), 2.84 (dd, *J* = 11.9, 4.4 Hz, 2H), 2.30 (s, 3H), 1.48 (d, *J* = 6.6 Hz, 3H), 1.41 (t, *J* = 6.2 Hz, 6H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₇H₃₂N₆O₂, 472.3; found, 473.3; HPLC purity: 254 nm: 99.6%.

[0742] Using the procedures described in Example 109 and reagents, starting materials, and conditions known to those skilled in the art, the following compounds representative of the present disclosure were prepared:

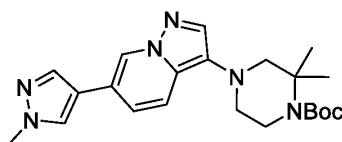
Compound	Data
469	(R)-1-(p-tolyl)ethyl (2S,6S)-2,6-dimethyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm) 8.77 (s, 1H), 8.21 (s, 1H), 7.96 (s, 1H), 7.69 (s, 1H), 7.61 (d, <i>J</i> = 9.3 Hz, 1H), 7.33 – 7.22 (m, 3H), 7.18 (d, <i>J</i> = 7.9 Hz, 2H), 5.71 (q, <i>J</i> = 6.5 Hz, 1H), 4.09 – 4.03 (m, 2H), 3.87 (s, 3H), 3.44 (dd, <i>J</i> = 11.8, 3.7 Hz, 2H), 3.04 (dd, <i>J</i> = 11.8, 4.4 Hz, 2H), 2.30 (s, 3H), 1.48 (d, <i>J</i> = 6.6 Hz, 3H), 1.30 (d, <i>J</i> = 6.5 Hz, 6H); MS (ESI) <i>m/z</i> [M+H]⁺ calcd. for C₂₇H₃₂N₆O₂, 473.2; found, 473.2; HPLC purity: 254 nm: 99.5%.
471	(R)-1-(p-tolyl)ethyl (R)-2-ethyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm) 8.77 (s, 1H), 8.21 (s, 1H), 7.96 (s, 1H), 7.69 (s, 1H), 7.61 (d, <i>J</i> = 9.3 Hz, 1H), 7.33 – 7.22 (m, 3H), 7.18 (d, <i>J</i> = 7.9 Hz, 2H), 5.71 (q, <i>J</i> = 6.5 Hz, 1H), 4.10 – 3.95 (m, 2H), 3.89 (s, 3H), 3.23 – 3.17 (m, 3H), 2.78 – 2.66 (m, 2H), 2.29 (s, 3H), 1.99 – 1.76 (m, 2H), 1.46 (d, <i>J</i> = 6.8 Hz, 3H), 0.88 (s, 3H); MS (ESI) <i>m/z</i> [M+H]⁺ calcd. for C₂₇H₃₂N₆O₂, 473.2; found, 473.2; HPLC purity: 254 nm: 99.8%.
472	(R)-1-(p-tolyl)ethyl (S)-2-ethyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm) 8.83 (t, <i>J</i> = 1.2 Hz, 1H), 8.22 (s, 1H), 7.97 (d, <i>J</i> = 0.8 Hz, 1H), 7.77 (s, 1H), 7.56 (dd, <i>J</i> = 9.3, 1.0 Hz, 1H), 7.35 (dd, <i>J</i> = 9.2, 1.5 Hz, 1H), 7.29 – 7.25 (m, 2H), 7.18 (d, <i>J</i> = 7.9 Hz, 2H), 5.74 – 5.65 (m, 1H), 4.10 (s, 1H), 5.74 – 5.65 (m, 1H), 3.87 (s, 3H), 3.20 (dd, <i>J</i> = 16.8, 11.4 Hz, 3H), 2.76 (s, 1H), 2.70 – 2.60 (m, 1H), 2.30 (s, 3H), 2.02 – 1.75 (m, 2H), 1.47 (d, <i>J</i> = 6.6 Hz, 3H), 0.85 (s, 3H); MS (ESI) <i>m/z</i> [M+H]⁺ calcd. for C₂₇H₃₂N₆O₂, 473.3; found, 473.3; HPLC purity: 254 nm: 99.9%.

Example 110: Synthesis of Exemplary Compound 470

(R)-1-(p-tolyl)ethyl 2,2-dimethyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound 470)

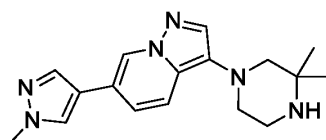


Step 1. Preparation of tert-butyl 2,2-dimethyl-4-[6-(1-methylpyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxylate



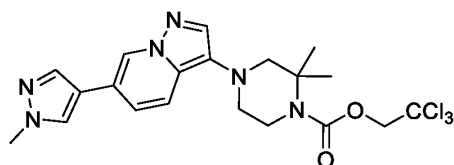
[0743] A mixture of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound S9) (1 g, 3.608 mmol) and tert-butyl 2,2-dimethylpiperazine-1-carboxylate (928 mg, 4.330 mmol), Pd-PEPPSI-IHept^{Cl} 3-chloropyridine (303.5 mg, 0.361 mmol), and NaOTMS (1214.3 mg, 10.824 mmol) in dioxane (20 mL) was heated to 100°C and stirred for 2 h under nitrogen. The reaction was cooled to rt and filtered, then the filter cake was washed with EtOAc (2x10 mL). The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 50-60% ACN/water (10mM NH₄HCO₃) to afford 677 mg (42%) of tert-butyl 2,2-dimethyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.74 (s, 1H), 7.59 (d, *J* = 9.2 Hz, 1H), 7.31 (dd, *J* = 9.2, 1.4 Hz, 1H), 3.87 (s, 3H), 3.56 – 3.51 (m, 2H), 3.07 – 3.01 (m, 2H), 2.81 (s, 2H), 1.44 (s, 6H), 1.43 (s, 9H).

Step 2. Preparation of 3-(3,3-dimethylpiperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine



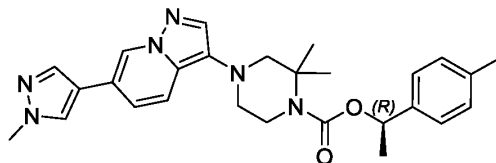
[0744] To a mixture of tert-butyl 2,2-dimethyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (677 mg, 1.649 mmol, as prepared in the previous step) in DCM (6 mL) was added TFA (2 mL) then the mixture was stirred at rt for 2 h. To the reaction was added saturated aqueous Na₂CO₃ solution to adjust the pH to 8, then the mixture was extracted with DCM (3x20mL). The organic extracts were combined, washed with water (3x20 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to afford 490 mg (92%) of 3-(3,3-dimethylpiperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.81 (s, 1H), 8.21 (s, 1H), 7.96 (s, 1H), 7.73 (s, 1H), 7.55 (d, *J* = 9.2 Hz, 1H), 7.31 (dd, *J* = 9.2, 1.3 Hz, 1H), 3.87 (s, 3H), 3.03 – 2.98 (m, 2H), 2.93 – 2.87 (m, 2H), 2.72 (s, 2H), 1.23 (s, 6H).

Step 3. Preparation of 2,2,2-trichloroethyl 2,2-dimethyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate



[0745] To a stirred solution of 3-(3,3-dimethylpiperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (320 mg, 1.031 mmol, as prepared in the previous step) and DIEA (399.7 mg, 3.093 mmol) in THF (10 mL) was added 2,2,2-trichloroethyl chloroformate (305.7 mg, 1.443 mmol) then the mixture was stirred at rt for 2 h. The reaction was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 426 mg (88%) of 2,2,2-trichloroethyl 2,2-dimethyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.77 (s, 1H), 7.62 (d, *J* = 9.2 Hz, 1H), 7.33 (d, *J* = 9.2 Hz, 1H), 4.88 (s, 2H), 3.87 (s, 3H), 3.76 – 3.68 (m, 2H), 3.12 (q, *J* = 4.9, 4.1 Hz, 2H), 2.90 (s, 2H), 1.30 – 1.25 (m, 6H).

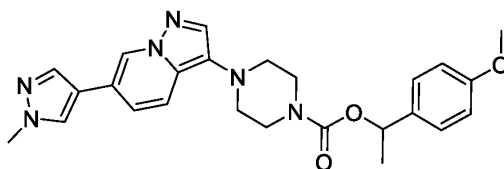
Step 4. Preparation of (*R*)-1-(*p*-tolyl)ethyl 2,2-dimethyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **470**)



[0746] To a solution of (*R*)-1-(*p*-tolyl)ethan-1-ol (196.2 mg, 1.440 mmol) in DCM (6 mL) cooled to 0°C was added NaH (60%wt., 144 mg, 3.6 mmol) in portions then the mixture was stirred for 10 minutes under nitrogen. To the stirred reaction was added 2,2,2-trichloroethyl 2,2-dimethyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (350 mg, 0.720 mmol, as prepared in the previous step) at 0°C, then the reaction was warmed to 90°C and stirred for 1 h. The reaction was cooled to rt, quenched by the addition of MeOH (10 mL), and concentrated under reduced pressure. The residue was purified by reversed-phase flash chromatography using a Prep Phenyl column eluting with 35-65% MeOH/water (10mM NH₄HCO₃) to afford 181.6 mg (53%) of (*R*)-1-(*p*-tolyl)ethyl 2,2-dimethyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **470**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.75 (s, 1H), 7.60 (d, *J* = 9.1 Hz, 1H), 7.32 (dd, *J* = 9.2, 1.4 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 5.69 (q, *J* = 6.7 Hz, 1H), 3.87 (s, 3H), 3.70 – 3.55 (m, 2H), 3.09 – 3.01 (m, 2H), 2.83 (s, 2H), 2.30 (s, 3H), 1.47 – 1.44 (m, 9H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₇H₃₂N₆O₂, 473.3; found, 473.3; HPLC purity: 254 nm: 98.9%.

Example 111: Synthesis of Exemplary Compound 475

1-(4-methoxyphenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **475**)



[0747] To a stirred solution of 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (300 mg, 1.06 mmol) and 2,2,2-trichloroethyl chloroformate (450.2 mg, 2.12 mmol) in THF (10 mL) was added DIEA (274.6 mg, 2.12

mmol) in portions at rt then the mixture was stirred for 2 h. The reaction was concentrated under reduced pressure then water (200 mL) was added to the residue and the mixture was extracted with EtOAc (2x150 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was dissolved in DCE (4 mL). To the stirred solution was added NaH (60%wt., 212.4 mg, 5.31 mmol) and 1-(4-methoxyphenyl)ethan-1-ol (194 mg, 1.27 mmol) in portions at rt then the mixture was heated to 90°C and stirred for 2 h. The reaction was cooled to rt and concentrated under reduced pressure. Water (200 mL) was added to the residue then the resulting mixture was extracted with DCM (2x150 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 224.5 mg (46%) of 1-(4-methoxyphenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **475**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (t, *J* = 1.2 Hz, 1H), 8.23 (s, 1H), 7.98 (d, *J* = 0.8 Hz, 1H), 7.77 (s, 1H), 7.65 (dd, *J* = 9.3, 0.9 Hz, 1H), 7.35 – 7.27 (m, 3H), 6.97 – 6.90 (m, 2H), 5.75 – 5.65 (m, 1H), 3.88 (s, 3H), 3.76 (s, 3H), 3.67 – 3.45 (m, 4H), 2.96 (s, 4H), 1.48 (d, *J* = 6.6 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₈N₆O₃, 461.2; found, 461.2; HPLC purity: 254 nm: 99.3%.

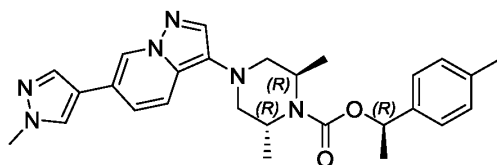
[0748] Using the procedures described in Example 111 and reagents, starting materials, and conditions known to those skilled in the art, the following compounds representative of the present disclosure were prepared:

Compound	Data
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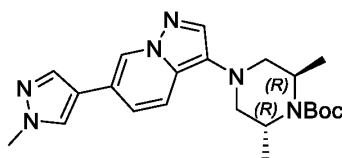
476	1-(1-methyl-1H-pyrazol-4-yl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate ¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ (ppm) 8.83 (t, <i>J</i> = 1.2 Hz, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.77 (s, 1H), 7.72 (s, 1H), 7.65 (dd, <i>J</i> = 9.3, 0.9 Hz, 1H), 7.44 (s, 1H), 7.33 (dd, <i>J</i> = 9.2, 1.5 Hz, 1H), 5.77-5.68 (m, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.55 (t, <i>J</i> = 5.0 Hz, 4H), 2.95 (t, <i>J</i> = 4.9 Hz, 4H), 1.51 (d, <i>J</i> = 6.6 Hz, 3H); MS (ESI) <i>m/z</i> [M+H] ⁺ calcd. for C ₂₂ H ₂₆ N ₈ O ₂ , 434.2; found, 435.2; HPLC purity: 254 nm: 97.6%.
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Example 112: Synthesis of Exemplary Compound 477

(R)-1-(p-tolyl)ethyl (2R,6R)-2,6-dimethyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound 477)

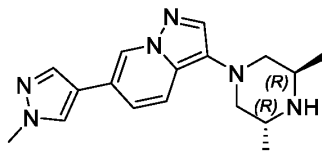


Step 1. Preparation of tert-butyl (2R,6R)-2,6-dimethyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate



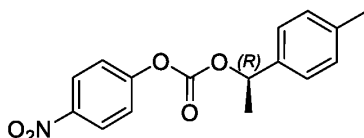
[0749] To a stirred solution of 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **S9**) (1 g, 3.608 mmol) and tert-butyl (2R,6R)-2,6-dimethylpiperazine-1-carboxylate (2.32 g, 10.82 mmol) in dioxane (10 mL) and tBuOH (20 mL) were added tBuXPhos Pd G1 (371.69 mg, 0.54 mmol) and KOtBu (809.84 mg, 7.21 mmol) in portions at rt then the mixture was heated to 55°C and stirred overnight under nitrogen. The reaction was cooled to rt and diluted with water (100 mL), then extracted with EtOAc (3x100 mL). The organic extracts were combined, washed with brine (2x2 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 30-60% ACN/water (10mM NH₄HCO₃) to afford 250 mg (17%) of tert-butyl (2R,6R)-2,6-dimethyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.77 (s, 1H), 8.20 (s, 1H), 7.96 (s, 1H), 7.68 (s, 1H), 7.61 (d, *J* = 9.2 Hz, 1H), 7.24 (dd, *J* = 9.3, 1.6 Hz, 1H), 4.04 – 3.93 (m, 2H), 3.87 (s, 3H), 3.42 (dd, *J* = 11.7, 3.8 Hz, 2H), 3.02 (dd, *J* = 11.7, 4.3 Hz, 2H), 1.43 (s, 9H), 1.31 (d, *J* = 6.5 Hz, 6H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₂H₃₀N₆O₂, 411.2; found, 411.2.

Step 2. Preparation of 3-((3*R*,5*R*)-3,5-dimethylpiperazin-1-yl)-6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridine



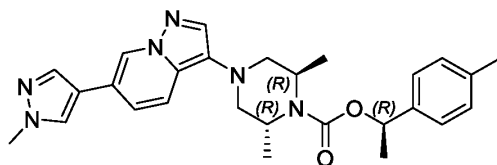
[0750] To a stirred solution of tert-butyl (2*R*,6*R*)-2,6-dimethyl-4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (250 mg, 0.61 mmol, as prepared in the previous step) in DCM (3 mL) cooled to 0°C was added TFA (1 mL) dropwise then the mixture was warmed to rt and stirred for 1 h. The reaction was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 10-50% ACN/water (10mM NH₄HCO₃) to afford 200 mg (90%) of 3-((3*R*,5*R*)-3,5-dimethylpiperazin-1-yl)-6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridine as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.85 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.83 (s, 1H), 7.63 (d, *J* = 9.2 Hz, 1H), 7.38 (dd, *J* = 9.2, 1.5 Hz, 1H), 3.87 (s, 3H), 3.78 – 3.70 (m, 2H), 3.21 (dd, *J* = 12.5, 3.3 Hz, 2H), 2.93 (dd, *J* = 12.5, 6.3 Hz, 2H), 1.40 (d, *J* = 6.6 Hz, 6H), 1.17 (t, *J* = 7.3 Hz, 1H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₇H₂₂N₆, 311.2; found, 311.3.

Step 3. Preparation of (*R*)-4-nitrophenyl (1-(*p*-tolyl)ethyl) carbonate



[0751] To a stirred solution of 4-nitrophenyl chloroformate (1 g, 4.96 mmol) and (*R*)-1-(*p*-tolyl)ethan-1-ol (675.70 mg, 4.96 mmol) in DCM (20 mL) was added pyridine (784.88 mg, 9.92 mmol) dropwise at rt then the mixture was stirred for 2 h. The reaction was concentrated under reduced pressure then the residue was purified by Prep-TLC (PE/EtOAc 1:1) to afford 500 mg (80%) (*R*)-4-nitrophenyl (1-(*p*-tolyl)ethyl) carbonate as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.25 (d, *J* = 8.0 Hz, 2H), 7.37 – 7.32 (m, 4H), 7.21 (d, *J* = 7.9 Hz, 2H), 5.82 (q, *J* = 6.6 Hz, 1H), 2.37 (s, 3H), 1.70 (d, *J* = 6.6 Hz, 3H).

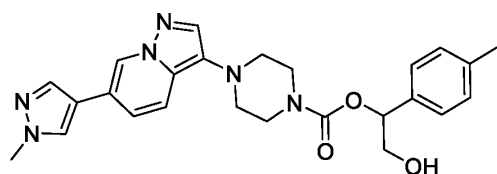
Step 4. Preparation of (*R*)-1-(*p*-tolyl)ethyl (2*R*,6*R*)-2,6-dimethyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **477**)



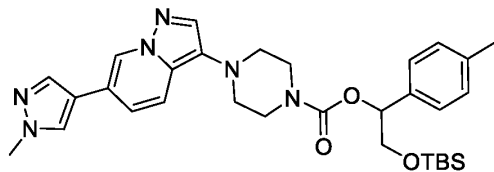
[0752] To a stirred solution of (*R*)-4-nitrophenyl (1-(*p*-tolyl)ethyl) carbonate (200 mg, 0.66 mmol, as prepared in the previous step) and 3-((3*R*,5*R*)-3,5-dimethylpiperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridine (206 mg, 0.66 mmol, as prepared in step 2) in ACN (10 mL) was added DIEA (857.9 mg, 6.64 mmol) dropwise at room temperature. The resulting mixture was stirred at rt overnight. The reaction was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 20.1 mg (6%) of (*R*)-1-(*p*-tolyl)ethyl (2*R*,6*R*)-2,6-dimethyl-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **477**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.77 (s, 1H), 8.21 (s, 1H), 7.96 (s, 1H), 7.69 (s, 1H), 7.62 (d, *J* = 9.3 Hz, 1H), 7.29 – 7.22 (m, 3H), 7.18 (d, *J* = 7.8 Hz, 2H), 5.73 (q, *J* = 6.5 Hz, 1H), 4.14 – 4.02 (m, 2H), 3.87 (s, 3H), 3.45 (dd, *J* = 11.8, 3.7 Hz, 2H), 3.05 (dd, *J* = 11.8, 4.3 Hz, 2H), 2.30 (s, 3H), 1.47 (d, *J* = 6.5 Hz, 3H), 1.34 (d, *J* = 6.5 Hz, 6H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₇H₃₂N₆O₂, 473.3; found, 473.20; HPLC purity: 254 nm: 99.4%.

Example 113: Synthesis of Exemplary Compound **478**

2-hydroxy-1-(*p*-tolyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **478**)

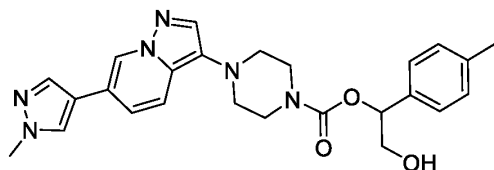


Step 1. Preparation of 2-((*tert*-butyldimethylsilyl)oxy)-1-(*p*-tolyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate



[0753] To a stirred solution of 2-((*tert*-butyldimethylsilyl)oxy)-1-(*p*-tolyl)ethan-1-ol (Compound **S110**) (250 mg, 0.93 mmol) and 6-(1-methyl-1*H*-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-*a*]pyridine (Compound **12**) (198.7 mg, 0.70 mmol) in pyridine (5 mL) cooled to 0°C was added BTC (278.4 mg, 0.94 mmol) in portions then the mixture was warmed to rt and stirred for 1 h. The reaction was cooled to 0°C and quenched with water, then the mixture was extracted with EtOAc (3x20 mL). The organic extracts were combined, washed with water (3x20 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 45-55% ACN/water (10mM NH₄HCO₃) to afford 320 mg (59%) of 2-((*tert*-butyldimethylsilyl)oxy)-1-(*p*-tolyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.75 (s, 1H), 7.66 (d, *J* = 9.7 Hz, 1H), 7.33 (dd, *J* = 9.2, 1.4 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 5.69 – 5.61 (m, 1H), 3.87 (s, 3H), 3.83 – 3.75 (m, 2H), 3.69 (s, 2H), 3.51 (s, 2H), 2.97 (s, 4H), 2.29 (s, 3H), 0.84 (s, 9H), 0.01 (s, 6H); MS (ESI) *m/z* [M+H]⁺ calcd. For C₃₁H₄₂N₆O₃Si, 575.3; found, 575.3.

Step 2. Preparation of 2-hydroxy-1-(*p*-tolyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **478**)

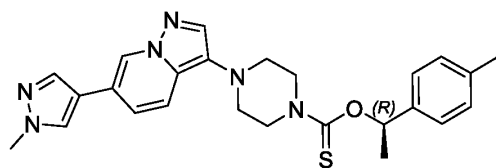


[0754] A solution of 2-((*tert*-butyldimethylsilyl)oxy)-1-(*p*-tolyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (300 mg, 0.52 mmol, as prepared in the previous step) in THF (8 mL) was added Et₃N·3HF (3 mL) then the mixture was stirred at rt for 2 h. To the reaction was added saturated aqueous Na₂CO₃ solution to

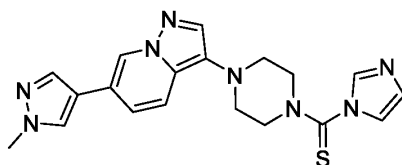
adjust the pH to 8 then the mixture was extracted with EtOAc (3x20 mL). The organic extracts were combined, washed with water (3x20 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a Prep Phenyl column eluting with 35-65% MeOH/water (10mM NH₄HCO₃) to afford 151.8 mg (63%) of 2-hydroxy-1-(*p*-tolyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **478**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.77 (s, 1H), 7.65 (d, *J* = 9.3 Hz, 1H), 7.33 (dd, *J* = 9.2, 1.6 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 5.59 – 5.54 (m, 1H), 5.01 (t, *J* = 6.0 Hz, 1H), 3.87 (s, 3H), 3.74 – 3.48 (m, 6H), 2.96 (s, 4H), 2.28 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. For C₂₅H₂₈N₆O₃, 461.2; found, 461.2; HPLC purity: 254 nm: 99.9%.

Example 114: Synthesis of Exemplary Compound 479

(*R*)-O-(1-(*p*-tolyl)ethyl) 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carbothioate (Compound **479**)



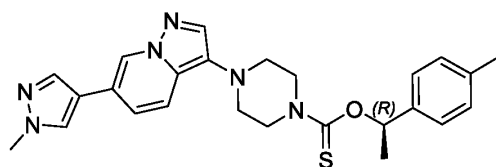
Step 1. Preparation of (1*H*-imidazol-1-yl)(4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazin-1-yl)methanethione



[0755] To a stirred solution of 6-(1-methyl-1*H*-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-*a*]pyridine (Compound **12**) (200 mg, 0.7 mmol) and di(1*H*-imidazol-1-yl)methanethione (189.3 mg, 1.06 mmol) in DMF (10 mL) was added TEA (143.3 mg, 1.41 mmol) in portions at rt then the mixture was stirred for 2 h. The reaction was concentrated under reduced pressure then the water (200 mL) was added to the residue and the resulting mixture was extracted with EtOAc (2x150 mL). The organic extracts were combined, dried

over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-TLC (PE/EtOAc 1:1) to afford 250 mg (90%) of (1H-imidazol-1-yl)(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)methanethione as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.84 (t, $J = 1.2$ Hz, 1H), 8.24 (s, 1H), 8.09 (d, $J = 1.1$ Hz, 1H), 7.98 (s, 1H), 7.81 (s, 1H), 7.71 (dd, $J = 9.3, 1.0$ Hz, 1H), 7.57 (t, $J = 1.4$ Hz, 1H), 7.36 (dd, $J = 9.3, 1.5$ Hz, 1H), 7.07 (t, $J = 1.2$ Hz, 1H), 4.11 (br s, 4H), 3.87 (s, 3H), 3.18 (br s, 4H).

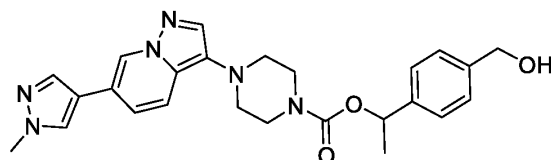
Step 2. (*R*)-*O*-(1-(*p*-tolyl)ethyl) 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carbothioate (Compound **479**)



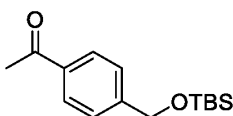
[0756] To a stirred mixture of (1H-imidazol-1-yl)(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)methanethione (250 mg, 0.63 mmol, as prepared in the previous step) and (*R*)-1-(*p*-tolyl)ethan-1-ol (104.1 mg, 0.76 mmol) in DMF (10 mL) was added Cs_2CO_3 (415 mg, 1.27 mmol) in portions at rt then the mixture was stirred overnight. The reaction was concentrated under reduced pressure then water (300 mL) was added to the residue and the resulting mixture was extracted with DCM (2x200 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 107.3 mg (37%) of (*R*)-*O*-(1-(*p*-tolyl)ethyl) 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carbothioate (Compound **479**) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.84 (t, $J = 1.2$ Hz, 1H), 8.24 (s, 1H), 7.98 (d, $J = 0.8$ Hz, 1H), 7.79 (s, 1H), 7.68 (dd, $J = 9.2, 0.9$ Hz, 1H), 7.35 (dd, $J = 9.3, 1.5$ Hz, 1H), 7.32 – 7.26 (m, 2H), 7.19 (d, $J = 7.9$ Hz, 2H), 6.49 – 6.40 (m, 1H), 4.20 – 4.11 (m, 2H), 4.04 – 3.91 (m, 2H), 3.87 (s, 3H), 3.05 – 2.95 (m, 4H), 2.30 (s, 3H), 1.56 (d, $J = 6.6$ Hz, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{25}\text{H}_{28}\text{N}_6\text{OS}$, 461.2; found, 461.2; HPLC purity: 254 nm: 99.7%.

Example 115: Synthesis of Exemplary Compound 480

1-(4-(hydroxymethyl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **480**)

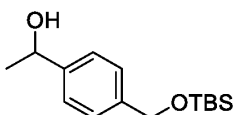


Step 1. Preparation of 1-(4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)ethan-1-one



[0757] To a stirred solution of 1-(4-(hydroxymethyl)phenyl)ethan-1-one (600 mg, 4.0 mmol) and imidazole (544 mg, 8.0 mmol) in THF (10 mL) cooled to 0°C was added TBSCl (1.2 g, 8.0 mmol) in portions then the mixture was warmed to rt and stirred for 2 h. The reaction was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (5:1) to afford 700 mg (66%) of 1-(4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)ethan-1-one as a colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 7.94 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 4.79 (s, 2H), 2.56 (s, 3H), 0.91 (s, 9H), 0.09 (s, 6H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₁₅H₂₄O₂Si, 265.1; found, 265.1.

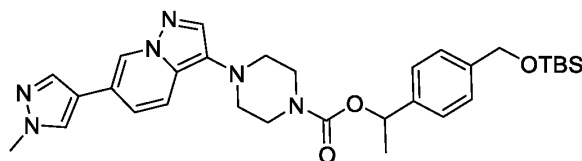
Step 2. 1-(4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)ethan-1-ol



[0758] To a solution of 1-(4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)ethan-1-one (700 mg, 2.6 mmol, as prepared in the previous step) in MeOH (10 mL) cooled to 0°C was added NaBH₄ (120 mg, 3.1 mmol) then the mixture was stirred for 2 h. The reaction was concentrated under reduced pressure then the residue was purified by Prep-TLC (PE/EtOAc 3:1) to afford 550 mg (78%) of 1-(4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)ethan-1-ol as colorless oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 7.31 (d, *J* = 8.1 Hz, 2H), 7.24

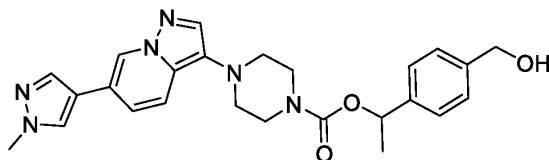
(d, $J = 8.2$ Hz, 2H), 5.10 (d, $J = 4.2$ Hz, 1H), 4.71 – 4.58 (m, 3H), 1.31 (d, $J = 6.4$ Hz, 3H), 0.91 (s, 9H), 0.08 (s, 6H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{15}H_{26}O_2Si$, 267.2; found, 267.2.

Step 3. 1-(4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate



[0759] To a stirred solution of 1-(4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)ethanol (530 mg, 2.0 mmol, as prepared in the previous step) and 4-nitrophenyl 4-[6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl]piperazine-1-carboxylate (0.89 g, 2.0 mmol, as prepared in Example 20, Step 1) in DMF (10 mL) was added Cs_2CO_3 (1.3 g, 4.0 mmol) then the mixture was stirred at rt overnight. The reaction was quenched with water (200 mL) and extracted with EtOAc (3x100 mL). The organic extracts were combined, washed with brine (3x50 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 430 mg (37%) of 1-(4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate as a yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.81 (s, 1H), 8.21 (s, 1H), 7.96 (s, 1H), 7.76 (s, 1H), 7.65 (dd, $J = 9.3, 0.9$ Hz, 1H), 7.39 – 7.21 (m, 5H), 5.73 (q, $J = 6.5$ Hz, 1H), 4.69 (s, 2H), 3.87 (s, 3H), 2.96 (s, 4H), 2.07 (s, 10H), 1.48 (d, $J = 6.5$ Hz, 3H), 0.90 (s, 9H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{31}H_{42}N_6O_3Si$, 575.3; found, 575.3.

Step 4. 1-(4-(hydroxymethyl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound 480)

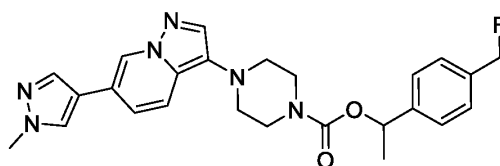


[0760] To a solution of 1-(4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (300 mg, 0.522 mmol, as prepared in the previous step) was added $Et_3N \cdot 3HF$ (2 mL) then the mixture

was stirred at rt for 2 h. A saturated aqueous NaHCO₃ solution was added to the reaction to adjust the pH to 8 then the mixture was extracted with DCM (3x100 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 140.7 mg (59%) of 1-(4-(hydroxymethyl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **480**) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.77 (s, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.39 – 7.21 (m, 5H), 5.73 (q, *J* = 6.5 Hz, 1H), 5.16 (t, *J* = 5.7 Hz, 1H), 4.49 (d, *J* = 5.7 Hz, 2H), 3.87 (s, 3H), 3.69 (s, 4H), 2.97 (s, 4H), 1.49 (d, *J* = 6.6 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₈N₆O₃, 461.2; found, 461.2; HPLC purity: 254 nm: 99.6%.

Example 116: Synthesis of Exemplary Compound 482

1-(4-(fluoromethyl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **482**)



[0761] To a stirred solution of 1-(4-(fluoromethyl)phenyl)ethan-1-ol (Compound **S108**) (103.3 mg, 0.67 mmol) and 4-nitrophenyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (300 mg, 0.67 mmol, as prepared in Example 20, Step 1) in DCE (5 mL) cooled to 0°C was added NaH (60%wt., 134 mg, 3.35 mmol) then the mixture was warmed to rt and stirred for 2 h. The reaction was poured into water (200 mL) and extracted with DCM (3x50 mL). The organic extracts were combined and concentrated under reduced pressure. The residue was purified by Prep-HPLC to afford 135 mg (44%) of 1-(4-(fluoromethyl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **482**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.84 (t, *J* = 1.2 Hz, 1H), 8.24 (s, 1H), 7.98 (d, *J* = 0.8 Hz, 1H), 7.78 (s, 1H), 7.66 (d, *J* = 9.3 Hz, 1H), 7.44 (s, 4H), 7.34 (dd, *J* = 9.3, 1.5 Hz, 1H), 5.84 – 5.69 (m, 1H), 5.41 (d, *J* = 48 Hz, 2H), 3.88 (s, 3H), 3.78 – 3.47 (m, 4H), 2.98 (s, 4H), 1.50 (d, *J* = 6.6 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₇FN₆O₂, 463.2; found, 463.2; HPLC purity: 254 nm: 99.6%.

[0762] Using the procedures described in Example 116 and reagents, starting materials, and conditions known to those skilled in the art, the following compounds representative of the present disclosure were prepared:

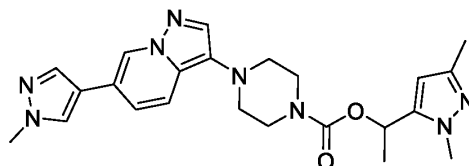
Compound Data

483 1-(4-(difluoromethyl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate

¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (t, *J* = 1.2 Hz, 1H), 8.23 (s, 1H), 7.98 (d, *J* = 0.8 Hz, 1H), 7.78 (s, 1H), 7.65 (d, *J* = 9.3 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.34 (dd, *J* = 9.2, 1.5 Hz, 1H), 7.04 (t, *J* = 55.9 Hz, 1H), 5.79 (q, *J* = 6.5 Hz, 1H), 3.87 (s, 3H), 3.75 – 3.50 (m, 4H), 2.98 (br s, 4H), 1.51 (d, *J* = 6.6 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₆F₂N₆O₂, 481.2; found, 481.1, HPLC purity: 254 nm: 99.8%.

Example 117: Synthesis of Exemplary Compound 484

1-(1,3-dimethyl-1H-pyrazol-5-yl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **484**)



[0763] To a stirred solution of 4-nitrophenyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (250 mg, 0.56 mmol, as prepared in Example 20, Step 1) and 1-(1,3-dimethyl-1H-pyrazol-5-yl)ethan-1-ol (391.6 mg, 2.80 mmol) in DMF (10 mL) was added Cs₂CO₃ (364 mg, 1.12 mmol) in portions then the mixture was stirred at rt overnight. The reaction was diluted with water (100 mL) and extracted with EtOAc (3x150 mL). The organic extracts were combined, washed with brine (3x5 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 30-60% ACN/water (10mM NH₄HCO₃) to afford 151.2 mg (59%) of 1-(1,3-dimethyl-1H-pyrazol-5-yl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **484**) as a

yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.82 (t, $J = 1.2$ Hz, 1H), 8.22 (s, 1H), 7.97 (d, $J = 0.8$ Hz, 1H), 7.76 (s, 1H), 7.64 (dd, $J = 9.3, 1.0$ Hz, 1H), 7.32 (dd, $J = 9.3, 1.6$ Hz, 1H), 6.10 (s, 1H), 5.84 (q, $J = 6.5$ Hz, 1H), 3.86 (s, 3H), 3.71 (s, 3H), 3.55 (t, $J = 5.1$ Hz, 4H), 2.95 (s, 4H), 2.10 (s, 3H), 1.52 (d, $J = 6.6$ Hz, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{23}\text{H}_{28}\text{N}_8\text{O}_2$, 449.2; found, 449.3; HPLC purity: 254 nm: 98.1%.

[0764] Using the procedures described in Example 117 and reagents, starting materials, and conditions known to those skilled in the art, the following compounds representative of the present disclosure were prepared:

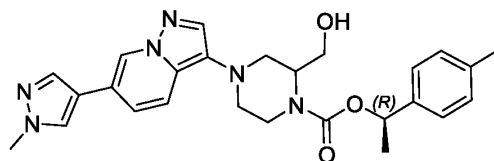
Compound Data

522 1-(2-chloroquinolin-6-yl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate

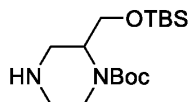
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.83 (s, 1H), 8.49 (d, $J = 8.8$ Hz, 1H), 8.23 (s, 1H), 8.04 (d, $J = 2.1$ Hz, 1H), 8.02 – 7.95 (m, 2H), 7.88 (dd, $J = 8.8, 2.0$ Hz, 1H), 7.78 (s, 1H), 7.69 – 7.59 (m, 2H), 7.34 (dd, $J = 9.2, 1.5$ Hz, 1H), 5.95 (q, $J = 6.5$ Hz, 1H), 3.87 (s, 3H), 3.72 – 3.56 (m, 4H), 2.99 (s, 4H), 1.60 (d, $J = 6.5$ Hz, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{27}\text{H}_{26}\text{ClN}_7\text{O}_2$, 516.2; found, 516.2; HPLC purity: 254 nm: 99.7%.

Example 118: Synthesis of Exemplary Compound 486

(R)-1-(p-tolyl)ethyl 2-(hydroxymethyl)-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **486**)

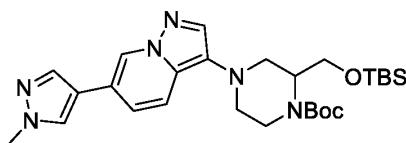


Step 1. Preparation of *tert*-butyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)piperazine-1-carboxylate



[0765] To a stirred solution of *tert*-butyl 2-(hydroxymethyl)piperazine-1-carboxylate (6 g, 27.74 mmol) and imidazole (3.78 g, 55.48 mmol) in THF (100 mL) cooled to 0°C was added TBSCl (6.27 g, 41.61 mmol) in portions then the mixture was warmed to rt and stirred for 2 h. The reaction was diluted with water (500 mL) and extracted with EtOAc (3x500 mL). The organic extracts were combined, washed with brine (3x10 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 8 g (87%) of *tert*-butyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)piperazine-1-carboxylate as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 3.93 – 3.74 (m, 2H), 3.63 (d, *J* = 12.8 Hz, 1H), 3.58 – 3.49 (m, 1H), 2.95 (d, *J* = 12.0 Hz, 1H), 2.79 (d, *J* = 11.2 Hz, 2H), 2.53 – 2.50 (m, 1H), 2.41 (td, *J* = 12.0, 3.2 Hz, 1H), 1.39 (s, 9H), 0.87 (s, 9H), 0.05 (s, 6H).

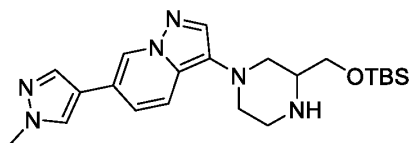
Step 2. Preparation of *tert*-butyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate



[0766] To a stirred solution of *tert*-butyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)piperazine-1-carboxylate (6 g, 18.15 mmol, as prepared in the previous step) and 3-bromo-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (Compound **S9**) (5.03 g, 18.15 mmol) in tBuOH (80 mL) and dioxane (40 mL) were added tBuXPhos Pd G1 (1.53 g, 1.81 mmol) and KOtBu (4.07 g, 36.30 mmol) in portions under nitrogen then the mixture was heated to 90°C and stirred for 2 h under nitrogen. The reaction was cooled to rt, diluted with water (300 mL), and extracted with EtOAc (3x300 mL). The organic extracts were combined, washed with brine (2x10 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with PE/EtOAc (1:1) to afford 3 g (31%) of *tert*-butyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.24 (s, 1H), 7.97 (s, 1H), 7.75 (s, 1H), 7.59 (d, *J* = 9.2 Hz, 1H), 7.29 (dd, *J* = 9.2, 1.2 Hz, 1H), 4.17 – 3.97 (m, 2H), 3.87 (s,

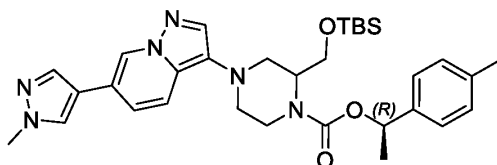
4H), 3.68 – 3.62 (m, 1H), 3.48 – 3.45 (m, 1H), 3.27 – 3.08 (m, 2H), 2.73 – 2.62 (m, 2H), 1.43 (s, 9H), 0.90 (s, 9H), 0.10 (s, 6H).

Step 3. Preparation of 3-(3-(((*tert*-butyldimethylsilyl)oxy)methyl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine



[0767] To a stirred solution of *tert*-butyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (2 g, 3.79 mmol, as prepared in the previous step) in ACN (40 mL) cooled to 0°C was added TMSI (1.60 g, 11.39 mmol) in portions then the mixture was warmed to rt and stirred at rt overnight. The reaction was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 10-80% ACN/water (10mM NH_4HCO_3) to afford 320 mg (20%) of 3-(3-(((*tert*-butyldimethylsilyl)oxy)methyl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine as a brown solid. MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{22}\text{H}_{34}\text{N}_6\text{OSi}$, 427.3; found, 427.3.

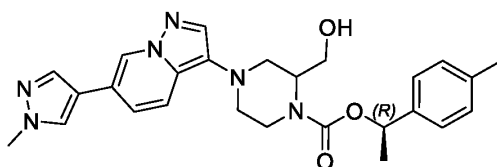
Step 4. Preparation of (*R*)-1-(*p*-tolyl)ethyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate



[0768] To a stirred solution of 3-(3-(((*tert*-butyldimethylsilyl)oxy)methyl)piperazin-1-yl)-6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridine (160 mg, 0.37 mmol, as prepared in the previous step) and (*R*)-4-nitrophenyl (1-(*p*-tolyl)ethyl) carbonate (113.0 mg, 0.37 mmol, as prepared in Example 112, Step 3) in ACN (3 mL) was added DIEA (96.9 mg, 0.75 mmol) dropwise then the mixture was heated to 60°C and stirred for 48 h. The reaction was cooled to 0°C, quenched by the addition of water (20 mL), and extracted with EtOAc (3x30 mL). The organic extracts were combined, washed with brine (3x10 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then

the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 50-100% ACN/water (10mM NH_4HCO_3) to afford 170 mg (77%) of (*R*)-1-(*p*-tolyl)ethyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate as a brown solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.84 (s, 1H), 8.25 (s, 1H), 7.99 (s, 1H), 7.77 (s, 1H), 7.60 (dd, $J = 9.4, 3.4$ Hz, 1H), 7.35 – 7.24 (m, 3H), 7.18 (d, $J = 7.9$ Hz, 2H), 5.76 – 5.68 (m, 1H), 4.19 – 4.06 (m, 2H), 3.88 (s, 3H), 3.48 (d, $J = 11.7$ Hz, 1H), 3.27 – 3.16 (m, 2H), 2.77 – 2.66 (m, 2H), 2.30 (s, 3H), 1.48 (d, $J = 6.5$ Hz, 3H), 1.25 (s, 2H), 0.88 (s, 9H), 0.01 (s, 6H).

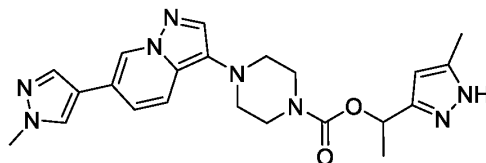
Step 5. Preparation of (*R*)-1-(*p*-tolyl)ethyl 2-(hydroxymethyl)-4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **486**)



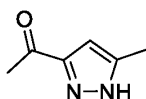
[0769] To a stirred solution of TBAF (124.3 mg, 0.47 mmol) in THF (2 mL) was added (*R*)-1-(*p*-tolyl)ethyl 2-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (140 mg, 0.23 mmol, as prepared in the previous step) in portions then the mixture was stirred at rt for 1 h. The reaction was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 68.5 mg (61%) of (*R*)-1-(*p*-tolyl)ethyl 2-(hydroxymethyl)-4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **486**) as a yellow solid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.75 (s, 1H), 7.64 (d, $J = 9.2$ Hz, 1H), 7.34 (dd, $J = 9.2, 1.2$ Hz, 1H), 7.30 – 7.23 (m, 2H), 7.17 (d, $J = 7.6$ Hz, 2H), 5.76 – 5.65 (m, 1H), 5.01 (s, 1H), 4.21 – 4.04 (m, 1H), 3.98 – 3.89 (m, 2H), 3.87 (s, 3H), 3.50 (d, $J = 11.6$ Hz, 2H), 3.27 – 3.09 (m, 2H), 2.78 – 2.57 (m, 2H), 2.29 (s, 3H), 1.46 (d, $J = 6.6$ Hz, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{26}\text{H}_{30}\text{N}_6\text{O}_3$, 475.2; found, 475.3; HPLC purity: 254 nm: 98.9%.

Example 119: Synthesis of Exemplary Compound 487

1-(5-methyl-1H-pyrazol-3-yl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **487**)

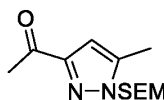


Step 1. Preparation of 1-(5-methyl-1H-pyrazol-3-yl)ethan-1-one



[0770] To a solution of TEA (9.85 g, 97.29 mmol) and CH_3MgI in Et_2O (3M, 32 mL, 97.29 mmol) in THF (130 mL) was added a solution of ethyl 5-methyl-1H-pyrazole-3-carboxylate (5 g, 32.43 mmol) in THF (10 mL) cooled to -10°C dropwise then the mixture was warmed to rt and stirred for 2 h. The reaction was acidified to pH=4 with aqueous HCl solution then the mixture was extracted with EtOAc (3x200 mL). The organic extracts were combined, washed with water (3x200 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 5-10% ACN/water (10mM NH_4HCO_3) to afford 1.6 g (38%) of 1-(5-methyl-1H-pyrazol-3-yl)ethan-1-one as yellow liquid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 13.13 (s, 1H), 6.42 (s, 1H), 2.43 (s, 3H), 2.26 (s, 3H).

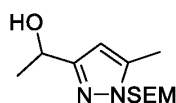
Step 2. Preparation of 1-(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-pyrazol-3-yl)ethan-1-one



[0771] To a mixture of 1-(5-methyl-1H-pyrazol-3-yl)ethan-1-one (1.6 g, 12.88 mmol, as prepared in the previous step), SEM-Cl (1.07 g, 64.44 mmol) in DCM (20 mL) was added Cs_2CO_3 (8.40 mg, 25.77 mmol) then the reaction was stirred at rt for 2 h. Water was added and the mixture was extracted with DCM (3x20 mL). The organic extracts were combined, washed with water (3x20 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was

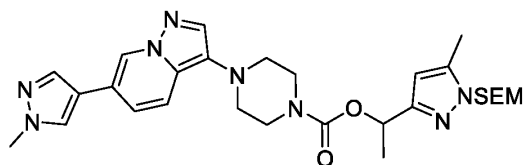
concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 60-70% ACN/water (10mM NH_4HCO_3) to afford 470 mg (14%) of 1-(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)ethan-1-one as yellow liquid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 6.54 (s, 1H), 5.48 (s, 2H), 3.56 (t, $J=8.0$ Hz, 2H), 2.45 (s, 3H), 2.34 (s, 3H), 0.86 – 0.84 (m, 2H), -0.05 (s, 9H).

Step 3. Preparation of 1-(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)ethan-1-ol



[0772] To a solution of 1-(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)ethan-1-one (420 mg, 1.65 mmol, as prepared in the previous step) in MeOH (10 mL) cooled to 0°C was added NaBH_4 (93.6 mg, 2.47 mmol) in portions then the mixture was warmed to rt and stirred for 2 h. The reaction was cooled to 0°C , quenched with water, and extracted with EtOAc (3x30 mL). The organic extracts were combined, washed with water (3x30 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure to afford 400 mg (94%) of 1-(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)ethan-1-ol as yellow liquid. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 6.02 (s, 1H), 5.28 (d, $J=2.4$ Hz, 2H), 4.93 (d, $J=4.9$ Hz, 1H), 4.65 – 4.57 (m, 1H), 3.49 (t, $J=8.0$ Hz, 2H), 2.25 (s, 3H), 1.30 (d, $J=6.5$ Hz, 3H), 0.85 – 0.75 (m, 2H), -0.06 (s, 9H).

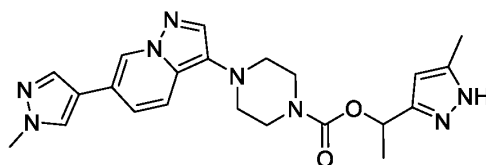
Step 4. Preparation of 1-(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate



[0773] A solution of 1-(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)ethan-1-ol (200 mg, 0.78 mmol, as prepared in the previous step) in DMF (5 mL) cooled to 0°C was added NaH (60% wt., 93.6 mg, 2.34 mmol) in portions then the mixture was

stirred for 10 minutes under nitrogen. The reaction was warmed to rt and 4-nitrophenyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (349.0 mg, 0.78 mmol, as prepared in Example 20, Step 1) in portions then the mixture was stirred at rt for 3 h. The reaction was cooled to 0°C, quenched with water, and extracted with EtOAc (3x30 mL). The organic extracts were combined, washed with water (3x30 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 55-65% ACN/water (10mM NH₄HCO₃) to afford 380 mg (85%) of 1-(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate as yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.96 (s, 1H), 7.76 (s, 1H), 7.64 (d, *J* = 9.3 Hz, 1H), 7.32 (dd, *J* = 9.3, 1.3 Hz, 1H), 6.11 (s, 1H), 5.70 (q, *J* = 6.5 Hz, 1H), 5.32 (s, 2H), 3.86 (s, 3H), 3.55 (s, 4H), 3.52 – 3.47 (m, 2H), 2.95 (s, 4H), 2.27 (s, 3H), 1.48 (d, *J* = 6.6 Hz, 3H), 0.82 – 0.76 (m, 2H), -0.07 (s, 9H).

Step 5. Preparation of 1-(5-methyl-1*H*-pyrazol-3-yl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **487**)

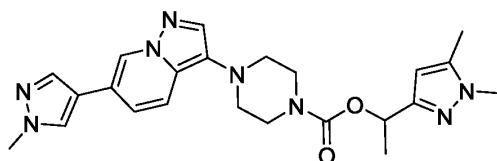


[0774] To a solution of 1-(5-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-3-yl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (340 mg, 0.60 mmol, as prepared in the previous step) in DCM (6 mL) was added TFA (2 mL) then the mixture was stirred at rt for 2 h. The pH of the reaction was adjusted to pH 8 with saturated aqueous Na₂CO₃ solution then the mixture was extracted with DCM (3x20 mL). The organic extracts were combined, washed with water (3x20 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reverse phase flash chromatography using a Prep OBD RP18 column eluting with 17-37% ACN/water (10mM NH₄HCO₃) to afford 146.2 mg (56%) of 1-(5-methyl-1*H*-pyrazol-3-yl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **487**) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 12.35 (s, 1H), 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s,

1H), 7.76 (s, 1H), 7.64 (d, $J = 9.3$ Hz, 1H), 7.32 (dd, $J = 9.2, 1.3$ Hz, 1H), 5.99 (s, 1H), 5.76-5.71 (m, 1H), 3.86 (s, 3H), 3.55 (s, 4H), 2.95 (s, 4H), 2.19 (s, 3H), 1.48 (d, $J = 6.8$ Hz, 3H); MS (ESI) m/z $[M+H]^+$ calcd. For $C_{22}H_{26}N_8O_2$, 435.2; found, 435.1; HPLC purity: 254 nm: 96.8%.

Example 120: Synthesis of Exemplary Compound 488

1-(1,5-dimethyl-1H-pyrazol-3-yl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound 488)



[0775] To a solution of 1-(1,5-dimethyl-1H-pyrazol-3-yl)ethan-1-ol (Compound S112) (130 mg, 0.92 mmol) in DMF (8 mL) cooled to 0°C was added NaH (60% wt., 111.2 mg, 2.78 mmol) then the mixture was stirred for 10 minutes under nitrogen. The reaction was warmed to rt then 4-nitrophenyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (497.9 mg, 1.11 mmol, as prepared in Example 20, Step 1) was added then the mixture was stirred at rt for 1 h. The reaction was cooled to 0°C, quenched with water, and extracted with EtOAc (3x20 mL). The organic extracts were combined, washed with water (3x20 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reverse phase flash chromatography using a Prep OBD C18 column eluting with 21-41% ACN/water (10mM NH_4HCO_3) to afford 144.5 mg (35%) of 1-(1,5-dimethyl-1H-pyrazol-3-yl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound 488) as a yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.76 (s, 1H), 7.64 (d, $J = 9.3$ Hz, 1H), 7.32 (dd, $J = 9.2, 1.4$ Hz, 1H), 6.02 (s, 1H), 5.68 (q, $J = 6.6$ Hz, 1H), 3.87 (s, 3H), 3.67 (s, 3H), 3.54 (s, 4H), 2.95 (s, 4H), 2.22 (s, 3H), 1.47 (d, $J = 6.6$ Hz, 3H); MS (ESI) m/z $[M+H]^+$ calcd. For $C_{23}H_{28}N_8O_2$, 449.2; found, 449.1; HPLC purity: 254 nm: 99.8%.

[0776] Using the procedures described in Example 120 and reagents, starting materials, and conditions known to those skilled in the art, the following compounds representative of the present disclosure were prepared:

Compound	Data
489	1-(1,5-dimethyl-1H-pyrazol-4-yl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.76 (s, 1H), 7.63 (d, <i>J</i> = 9.6 Hz, 1H), 7.39 (s, 1H), 7.32 (dd, <i>J</i> = 9.2, 1.2 Hz, 1H), 5.69 (q, <i>J</i> = 6.8 Hz, 1H), 3.86 (s, 3H), 3.70 (s, 3H), 3.53 (s, 4H), 2.93 (s, 4H), 2.24 (s, 3H), 1.48 (d, <i>J</i> = 6.8 Hz, 3H); MS (ESI) <i>m/z</i> [M+H]⁺ calcd. for C₂₃H₂₈N₈O₂, 449.2; found, 449.3; HPLC purity: 254 nm: 98.2%
506	1-(4-(1,1-difluoroethyl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.78 (s, 1H), 7.66 (d, <i>J</i> = 9.2 Hz, 1H), 7.57 (d, <i>J</i> = 8.4 Hz, 2H), 7.49 (d, <i>J</i> = 8.4 Hz, 2H), 7.33 (dd, <i>J</i> = 9.2, 1.2 Hz, 1H), 5.78 (q, <i>J</i> = 6.4 Hz, 1H), 3.87 (s, 3H), 3.67 (s, 2H), 3.56 (s, 2H), 2.98 (s, 4H), 1.97 (t, <i>J</i> = 18.8 Hz, 3H), 1.50 (d, <i>J</i> = 6.4 Hz, 3H); MS (ESI) <i>m/z</i> [M+H]⁺ calcd. for C₂₆H₂₈F₂N₆O₂, 495.2; found, 495.1; HPLC purity: 254 nm: 99.9%.
511	1-(2-methylquinolin-6-yl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate ¹H NMR (400 MHz, DMSO-<i>d</i>₆) δ (ppm) 8.83 (s, 1H), 8.27 (d, <i>J</i> = 8.5 Hz, 1H), 8.23 (s, 1H), 7.97 (d, <i>J</i> = 0.8 Hz, 1H), 7.93 (d, <i>J</i> = 8.7 Hz, 1H), 7.90 (d, <i>J</i> = 2.0 Hz, 1H), 7.77 (s, 1H), 7.75 (dd, <i>J</i> = 8.7, 2.0 Hz, 1H), 7.65 (d, <i>J</i> = 9.3 Hz, 1H), 7.44 (d, <i>J</i> = 8.4 Hz, 1H), 7.33 (dd, <i>J</i> = 9.2, 1.5 Hz, 1H), 5.93 (q, <i>J</i> = 6.5 Hz, 1H), 3.87 (s, 3H), 3.69 – 3.56 (m, 4H), 2.98 (s, 4H), 2.66 (s, 3H), 1.59 (d, <i>J</i> = 6.6 Hz, 3H); MS (ESI) <i>m/z</i> [M+H]⁺ calcd. for C₂₈H₂₉N₇O₂, 496.2; found, 496.3; HPLC purity: 254 nm: 99.4%.

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- 512** (R)-1-(4-cyanophenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.99 – 7.98 (m, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.80 (s, 1H), 7.66 (d, *J* = 9.6 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.34 (dd, *J* = 9.6, 1.6 Hz, 1H), 5.80 (q, *J* = 6.4 Hz, 1H), 3.87 (s, 3H), 3.84 – 3.70 (m, 2H), 3.62 – 3.47 (m, 2H), 3.05 – 2.88 (m, 4H), 1.50 (d, *J* = 6.8 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₅N₇O₂, 456.2; found, 456.0; HPLC purity: 254 nm: 99.7%.
-
- 515** 1-(2-methylquinolin-7-yl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.24 (d, *J* = 7.6 Hz, 2H), 7.97 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.87 (s, 1H), 7.78 (s, 1H), 7.66 (d, *J* = 9.2 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 9.2 Hz, 1H), 5.93 (q, *J* = 6.4 Hz, 1H), 3.87 (s, 3H), 3.83 – 3.71 (m, 2H), 3.56 – 3.26 (m, 2H), 3.13 – 3.10 (m, 4H), 2.74 (s, 3H), 1.59 (d, *J* = 6.8 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₈H₂₉N₇O₂, 496.2; found, 496.2; HPLC purity: 254 nm: 99.6%.
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- 516** 1-(4-(oxetan-3-yl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.77 (s, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.43 – 7.36 (m, 4H), 7.33 (dd, *J* = 9.2, 1.2 Hz, 1H), 5.74 (q, *J* = 6.5 Hz, 1H), 4.93 (dd, *J* = 8.4, 5.8 Hz, 2H), 4.65 – 4.57 (m, 2H), 4.30 – 4.17 (m, 1H), 3.87 (s, 3H), 3.74 – 3.42 (m, 4H), 2.96 (s, 4H), 1.48 (d, *J* = 6.6 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₇H₃₀N₆O₃, 487.2; found, 487.3; HPLC purity: 254 nm: 99.9%.
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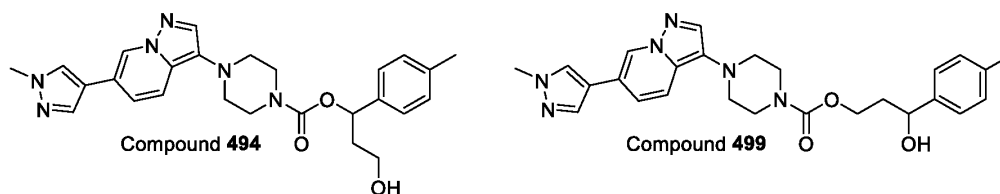
-
- 517** 1-(4-isopropylphenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.84 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.78 (s, 1H), 7.66 (d, *J* = 9.2 Hz, 1H), 7.41 – 7.11 (m, 5H), 5.72 (q, *J* = 6.5 Hz, 1H), 3.88 (s, 3H), 3.61 – 3.57 (m, 4H), 2.97 (s, 4H), 2.91 – 2.84 (m, 1H), 1.48 (d, *J* = 6.6 Hz, 3H), 1.20 (d, *J* = 6.9 Hz, 6H).; MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₇H₃₂N₆O₂, 473.2; found, 473.3, HPLC purity: 254 nm: 99.9%.
-
- 520** 1-(4-(oxetan-2-yl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.77 (s, 1H), 7.65 (d, *J* = 9.3 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.33 (dd, *J* = 9.2, 1.2 Hz, 1H), 5.78 – 5.68 (m, 2H), 4.70 – 4.64 (m, 1H), 4.56 – 4.50 (m, 1H), 3.86 (s, 3H), 3.69 – 3.49 (m, 4H), 3.01 – 2.92 (m, 5H), 2.60 – 2.53 (m, 1H), 1.49 (d, *J* = 6.4 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. For C₂₇H₃₀N₆O₃, 487.2; found, 487.1; HPLC purity: 254 nm: 97.7%.
-
- 521** 1-(quinolin-6-yl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate
- ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.90 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.83 (s, 1H), 8.39 (d, *J* = 8.2 Hz, 1H), 8.23 (s, 1H), 8.04 (d, *J* = 8.7 Hz, 1H), 8.00 – 7.94 (m, 2H), 7.81 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.77 (s, 1H), 7.65 (d, *J* = 9.3 Hz, 1H), 7.55 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.33 (d, *J* = 9.3 Hz, 1H), 5.95 (q, *J* = 6.5 Hz, 1H), 3.87 (s, 3H), 3.71 – 3.55 (m, 4H), 2.98 (s, 4H), 1.60 (d, *J* = 6.6 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₇H₂₇N₇O₂, 482.2; found, 482.2; HPLC purity: 254 nm: 99.6%.
-

531 1-(4-(2-hydroxypropan-2-yl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate

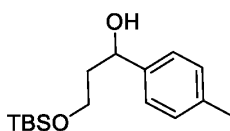
^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 8.83 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.77 (s, 1H), 7.65 (dd, $J = 9.2, 0.9$ Hz, 1H), 7.46 – 7.44 (m, 2H), 7.34 – 7.28 (m, 3H), 5.72 (q, $J = 6.4$ Hz, 1H), 4.98 (s, 1H), 3.87 (s, 3H), 3.63 – 3.55 (m, 4H), 2.97 (s, 4H), 1.48 (d, $J = 6.4$ Hz, 3H), 1.41 (s, 6H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{27}\text{H}_{32}\text{N}_6\text{O}_3$, 489.3; found, 489.3; HPLC purity: 254 nm: 99.1%.

Example 121: Synthesis of Exemplary Compound 494 and Compound 499

3-hydroxy-1-(*p*-tolyl)propyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **494**) and 3-hydroxy-3-(*p*-tolyl)propyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **499**)

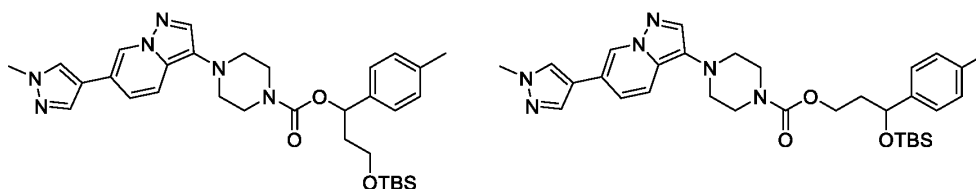


Step 1. Preparation of 3-((*tert*-butyldimethylsilyl)oxy)-1-(*p*-tolyl)propan-1-ol



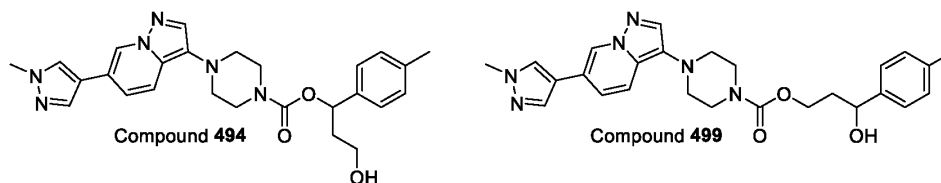
[0777] To a stirred mixture of 1-(*p*-tolyl)propane-1,3-diol (500 mg, 3 mmol) and imidazole (409.5 mg, 6.01 mmol) in THF (10 mL) was added TBSCl (453.3 mg, 3 mmol) in portions at rt then the mixture was stirred for 2 h. The reaction was concentrated under reduced pressure then water 200 mL) was added to the residue and the mixture was extracted with EtOAc (2x150 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure to afford 500 mg (59%) of 3-((*tert*-butyldimethylsilyl)oxy)-1-(*p*-tolyl)propan-1-ol as a yellow solid. The crude product was used for the next step directly without further purification.

Step 2. Preparation of the mixture of 3-((*tert*-butyldimethylsilyl)oxy)-1-(*p*-tolyl)propyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate and 3-((*tert*-butyldimethylsilyl)oxy)-3-(*p*-tolyl)propyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate



[0778] To a stirred mixture of 3-((*tert*-butyldimethylsilyl)oxy)-1-(*p*-tolyl)propan-1-ol (250 mg, 0.89 mmol, as prepared in the previous step) and 4-nitrophenyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (478.5 mg, 1.06 mmol, as prepared in Example 20, Step 1) in DMF (10 mL) was added NaH (60% wt., 71.2 mg, 1.78 mmol) in portions at rt then the mixture was stirred for 2 h. The reaction was quenched with water (200 mL) and extracted with DCM (2x150 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-TLC (DCM/MeOH 10:1) to afford 500 mg (95%) of a mixture of 3-((*tert*-butyldimethylsilyl)oxy)-1-(*p*-tolyl)propyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate and 3-((*tert*-butyldimethylsilyl)oxy)-3-(*p*-tolyl)propyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate as a yellow solid. MS (ESI) *m/z* [M+H]⁺ calcd. for C₃₂H₄₄N₆O₃Si, 589.3; found, 588.8.

Step 3. 3-hydroxy-1-(*p*-tolyl)propyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **494**) and 3-hydroxy-3-(*p*-tolyl)propyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **499**)



[0779] To a stirred solution of the mixture of 3-((*tert*-butyldimethylsilyl)oxy)-1-(*p*-tolyl)propyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate and 3-((*tert*-butyldimethylsilyl)oxy)-3-(*p*-tolyl)propyl 4-(6-(1-methyl-1*H*-

pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (250 mg, 0.42 mmol, as prepared in the previous step) in THF (2 mL) cooled to 0°C was added TEA·HF (1 mL) dropwise, then the mixture was warmed to rt and stirred for 2 h. The reaction was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 98.1 mg (49%) of 3-hydroxy-1-(*p*-tolyl)propyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **494**) as a yellow solid and 82.3 mg (41%) of 3-hydroxy-3-(*p*-tolyl)propyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **499**) as a yellow solid.

[0780] 3-hydroxy-1-(*p*-tolyl)propyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **494**). ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.78 (s, 1H), 7.63 (d, *J* = 9.2 Hz, 1H), 7.34 (dd, *J* = 9.6, 1.6 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 5.71 (dd, *J* = 8.3, 5.6 Hz, 1H), 4.57 (t, *J* = 5.0 Hz, 1H), 3.88 (s, 3H), 3.69 – 3.47 (m, 3H), 3.50 – 3.42 (m, 2H), 3.42 – 3.35 (m, 1H), 2.95 (s, 4H), 2.29 (s, 3H), 2.08 – 1.98 (m, 1H), 1.89 – 1.78 (m, 1H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₆H₃₀N₆O₃, 475.2; found, 475.2; HPLC purity: 254 nm: 99.7%.

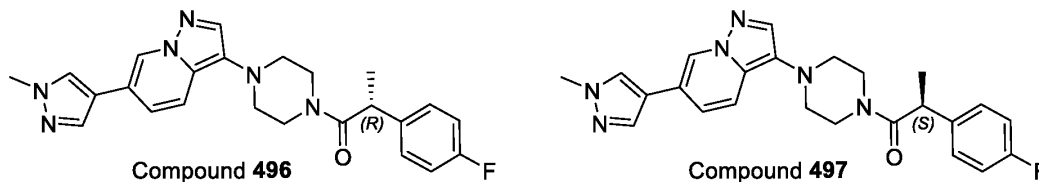
[0781] 3-hydroxy-3-(*p*-tolyl)propyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **499**). ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.24 (s, 1H), 7.97 (s, 1H), 7.78 (s, 1H), 7.66 (d, *J* = 9.2 Hz, 1H), 7.34 (dd, *J* = 9.3, 1.5 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 5.26 (d, *J* = 4.5 Hz, 1H), 4.68 – 4.59 (m, 1H), 4.17 – 4.07 (m, 1H), 4.07 – 3.98 (m, 1H), 3.87 (s, 3H), 3.53 (t, *J* = 4.9 Hz, 4H), 2.96 (t, *J* = 5.0 Hz, 4H), 2.29 (s, 3H), 2.01 – 1.83 (m, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₆H₃₀N₆O₃, 475.2; found, 475.3; HPLC purity: 254 nm: 99.5%.

Example 122: Synthesis of Exemplary Compound 496 and Compound 497

(*R*)-2-(4-fluorophenyl)-1-(4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one (Compound **496**) and (*S*)-2-(4-fluorophenyl)-1-(4-(6-(1-

methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one

(Compound **497**)



[0782] A solution of 2-(4-fluorophenyl)propanoic acid (200 mg, 1.18 mmol), HATU (678.3 mg, 1.78 mmol) and DIEA (307.4 mg, 2.37 mmol) in DMF (10 mL) was stirred at rt for 10 minutes, then 6-(1-methyl-1*H*-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (402.9 mg, 1.42 mmol) was added and the mixture was stirred at rt for 4 h. The reaction was quenched with saturated aqueous NH₄Cl solution then the mixture was extracted with EtOAc (3x20 mL). The organic extracts were combined, washed with water (3x20 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 50-60% ACN/water (10mM NH₄HCO₃) to afford racemic 2-(4-fluorophenyl)-1-(4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one as a yellow solid.

[0783] Racemic 2-(4-fluorophenyl)-1-(4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one was separated by Prep-Chiral-HPLC to afford 165.5 mg (32%) of (*R*)-2-(4-fluorophenyl)-1-(4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one (Compound **496**, first eluting peak) as a yellow solid and 178.2 mg (35%) of (*S*)-2-(4-fluorophenyl)-1-(4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one (Compound **497**, second eluting peak) as a yellow solid.

[0784] (*R*)-2-(4-fluorophenyl)-1-(4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one (Compound **496**, first eluting peak). ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.80 (s, 1H), 8.21 (s, 1H), 7.96 (s, 1H), 7.67 (s, 1H), 7.61 (d, *J* = 9.6 Hz, 1H), 7.36 – 7.28 (m, 3H), 7.19 – 7.12 (m, 2H), 4.21 (q, *J* = 6.4 Hz, 1H), 3.86 (s, 3H), 3.73 – 3.62 (m, 3H), 3.51 – 3.42 (m, 1H), 3.00 – 2.78 (m, 3H), 2.58 – 2.52 (m, 1H), 1.30 (d, *J* = 6.8 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₅FN₆O, 433.2; found, 433.2; HPLC purity: 254 nm: 99.6%.

[0785] (S)-2-(4-fluorophenyl)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one (Compound **497**, second eluting peak). ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.80 (s, 1H), 8.21 (s, 1H), 7.96 (s, 1H), 7.67 (s, 1H), 7.61 (d, *J* = 9.6 Hz, 1H), 7.36 – 7.28 (m, 3H), 7.19 – 7.12 (m, 2H), 4.21 (q, *J* = 6.9 Hz, 1H), 3.86 (s, 3H), 3.73 – 3.62 (m, 3H), 3.51 – 3.42 (m, 1H), 3.00 – 2.78 (m, 3H), 2.58 – 2.52 (m, 1H), 1.30 (d, *J* = 6.4 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₅FN₆O, 433.2; found, 433.2; HPLC purity: 254 nm: 99.6%.

[0786] Using the procedures described in Example 122 and reagents, starting materials, and conditions known to those skilled in the art, the following compounds representative of the present disclosure were prepared:

Compound	Data
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500	(R)-2-(4-chlorophenyl)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one (first eluting peak)
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¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.81 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.68 (s, 1H), 7.61 (d, *J* = 9.2 Hz, 1H), 7.42 – 7.37 (m, 2H), 7.34 – 7.28 (m, 3H), 4.22 (q, *J* = 6.8 Hz, 1H), 3.87 (s, 3H), 3.72 – 3.66 (m, 3H), 3.49 – 3.41 (m, 1H), 2.99 – 2.82 (m, 3H), 2.60 – 2.52 (m, 1H), 1.30 (d, *J* = 6.8 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₅ClN₆O, 449.2; found, 449.1; HPLC purity: 254 nm: 97.9%.

501	(S)-2-(4-chlorophenyl)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one (second eluting peak)
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¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.80 (s, 1H), 8.22 (s, 1H), 7.96 (s, 1H), 7.68 (s, 1H), 7.61 (d, *J* = 9.6 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.34 – 7.28 (m, 3H), 4.22 (q, *J* = 6.8 Hz, 1H), 3.87 (s, 3H), 3.73 – 3.66 (m, 3H), 3.49 – 3.46 (m, 1H), 3.00 – 2.83 (m, 3H), 2.59 – 2.50 (m, 1H), 1.30 (d, *J* = 6.8 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₅ClN₆O, 449.2; found, 449.1; HPLC purity: 254 nm: 97.0%.

507 (R)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-(4-(trifluoromethyl)phenyl)propan-1-one (first eluting peak)

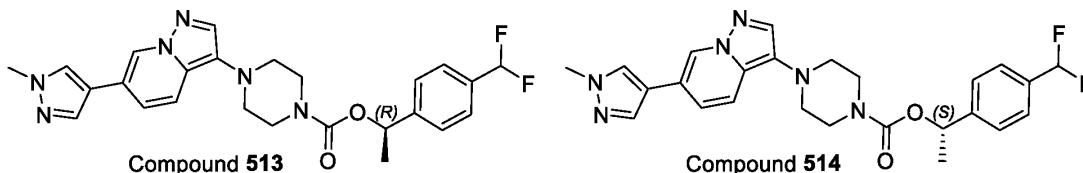
^1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.81 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.68 (s, 1H), 7.62 (d, J = 9.2 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.31 (dd, J = 1.2, 9.2 Hz, 1H), 4.36 (q, J = 6.8 Hz, 1H), 3.87 (s, 3H), 3.71 – 3.65 (m, 3H), 3.49 – 3.44 (m, 1H), 2.95 – 2.88 (m, 3H), 2.62 – 2.58 (m, 1H), 1.35 (d, J = 6.8 Hz, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{25}\text{H}_{25}\text{F}_3\text{N}_6\text{O}$, 483.2; found, 483.2; HPLC purity: 254 nm: 99.2%.

508 (S)-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-(4-(trifluoromethyl)phenyl)propan-1-one (second eluting peak)

^1H NMR (400 MHz, DMSO- d_6) δ (ppm) 8.81 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.72 (d, J = 8.0 Hz, 2H), 7.68 (s, 1H), 7.62 (d, J = 9.2 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.31 (dd, J = 1.2, 9.2 Hz, 1H), 4.36 (q, J = 6.8 Hz, 1H), 3.87 (s, 3H), 3.71 – 3.65 (m, 3H), 3.49 – 3.44 (m, 1H), 2.95 – 2.88 (m, 3H), 2.62 – 2.58 (m, 1H), 1.35 (d, J = 6.8 Hz, 3H); MS (ESI) m/z $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{25}\text{H}_{25}\text{F}_3\text{N}_6\text{O}$, 483.2; found, 483.2; HPLC purity: 254 nm: 99.2%.

Example 123: Synthesis of Exemplary Compound 513 and Compound 514

(R)-1-(4-(difluoromethyl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **513**) and (S)-1-(4-(difluoromethyl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **514**)



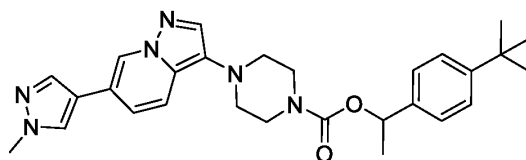
[0787] Racemic 1-(4-(difluoromethyl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **483**) (300 mg, 0.62 mmol) was separated by Prep-Chiral-HPLC to afford 134.8 mg (45%) of (*R*)-1-(4-(difluoromethyl)phenyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **513**, first eluting peak) as a yellow solid and 145.7 mg (49%) of (*S*)-1-(4-(difluoromethyl)phenyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **514**, second eluting peak) as a yellow solid.

[0788] (*R*)-1-(4-(difluoromethyl)phenyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **513**, first eluting peak). ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.78 (s, 1H), 7.65 (d, *J* = 9.3 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.34 (dd, *J* = 9.2, 1.5 Hz, 1H), 7.04 (t, *J* = 55.9 Hz, 1H), 5.79 (q, *J* = 6.5 Hz, 1H), 3.87 (s, 3H), 3.70 – 3.55 (m, 4H), 2.98 (s, 4H), 1.51 (d, *J* = 6.6 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₆F₂N₆O₂, 481.2; found, 481.1, HPLC purity: 254 nm: 99.7%.

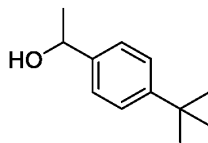
[0789] (*S*)-1-(4-(difluoromethyl)phenyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **514**, second eluting peak). ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.78 (s, 1H), 7.65 (d, *J* = 9.3 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.1 Hz, 2H), 7.34 (dd, *J* = 9.2, 1.5 Hz, 1H), 7.04 (t, *J* = 55.9 Hz, 1H), 5.79 (q, *J* = 6.5 Hz, 1H), 3.87 (s, 3H), 3.70 – 3.55 (m, 4H), 2.98 (s, 4H), 1.51 (d, *J* = 6.6 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₆F₂N₆O₂, 481.2; found, 481.1, HPLC purity: 254 nm: 99.7%.

Example 124: Synthesis of Exemplary Compound 518

1-(4-(tert-butyl)phenyl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate (Compound **518**)

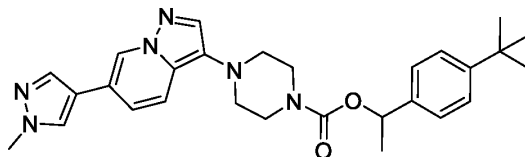


Step 1. Preparation of 1-(4-(*tert*-butyl)phenyl)ethan-1-ol



[0790] To a stirred solution of 1-(4-(*tert*-butyl)phenyl)ethan-1-one (400 mg, 2.26 mmol) in MeOH (5 mL) cooled to 0°C was added NaBH₄ (128.7 mg, 3.40 mmol) in portions then the mixture was warmed to rt and stirred for 2 h. The reaction was quenched with water (50 mL) and extracted with DCM (2x150 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure to afford 330 mg (82%) of 1-(4-(*tert*-butyl)phenyl)ethan-1-ol as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 7.35 – 7.31 (m, 2H), 7.28 – 7.24 (m, 2H), 5.04 (dd, *J* = 4.1, 1.7 Hz, 1H), 4.71 – 4.64 (m, 1H), 1.31 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.28 (s, 9H).

Step 2. 1-(4-(*tert*-butyl)phenyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **518**)



[0791] To a stirred mixture of 1-(4-(*tert*-butyl)phenyl)ethan-1-ol (300 mg, 1.68 mmol, as prepared in the previous step) and 4-nitrophenyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (828.2 mg, 1.85 mmol, as prepared in Example 20, Step 1) in DMF (4 mL) was added Cs₂CO₃ (256.2 mg, 3.36 mmol) in portions then the mixture was heated to 100°C and stirred for 2 h. The reaction was cooled to rt and concentrated under reduced pressure. The residue was purified by Prep-HPLC to afford 95.7 mg (12%) of 1-(4-(*tert*-butyl)phenyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **518**) as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.78 (s, 1H), 7.66 (d, *J* = 9.2 Hz, 1H), 7.43 – 7.37 (m, 2H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.33 – 7.27 (m, 2H), 5.72 (q, *J* = 6.5 Hz, 1H), 3.88 (s, 3H), 3.62 – 3.55 (m, 4H), 2.97 (s, 4H), 1.48 (d, *J* = 6.6 Hz, 3H), 1.28 (s, 9H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₈H₃₄N₆O₂, 487.3; found, 487.3; HPLC purity: 254 nm: 99.5%.

[0792] Using the procedures described in Example 124 and reagents, starting materials, and conditions known to those skilled in the art, the following compounds representative of the present disclosure were prepared:

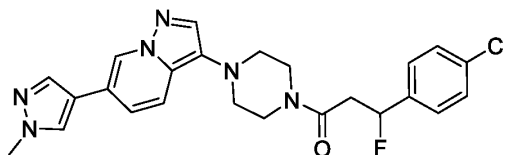
Compound Data

519 1-(quinolin-7-yl)ethyl 4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazine-1-carboxylate

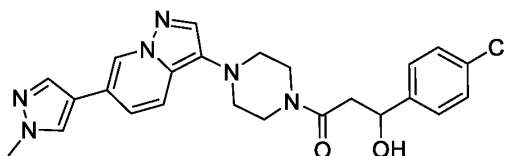
¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.92 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.84 (s, 1H), 8.41 – 8.34 (m, 1H), 8.24 (s, 1H), 8.05 – 7.95 (m, 3H), 7.78 (s, 1H), 7.70 – 7.62 (m, 2H), 7.54 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.34 (dd, *J* = 9.2, 1.6 Hz, 1H), 5.97 (q, *J* = 6.5 Hz, 1H), 3.88 (s, 3H), 3.74 (s, 2H), 3.56 (s, 2H), 3.05 – 2.97 (m, 4H), 1.61 (d, *J* = 6.6 Hz, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₇H₂₇N₇O₂, 482.2; found, 482.2; HPLC purity: 254 nm: 99.5%.

Example 125: Synthesis of Exemplary Compound 527

3-(4-chlorophenyl)-3-fluoro-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one (Compound **527**)



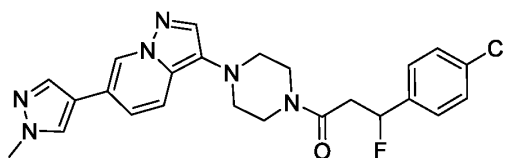
Step 1. Preparation of 3-(4-chlorophenyl)-3-hydroxy-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one



[0793] A mixture of 3-(4-chlorophenyl)-3-hydroxypropanoic acid (1 g, 4.98 mmol), HATU (2.84 g, 7.48 mmol), and DIEA (1.29 g, 9.97 mmol) in DMF (15 mL) was stirred at rt for 10 minutes then 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (1.41 g, 4.98 mmol) was added then the mixture was stirred for 4 h. The reaction was quenched with saturated aqueous NH₄Cl solution and extracted with

EtOAc (3x200 mL). The organic extracts were combined, washed with brine (3x20 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by silica gel column chromatography eluting with DCM/MeOH (10:1) to afford 1 g (43%) of 3-(4-chlorophenyl)-3-hydroxy-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.72 (s, 1H), 7.64 (d, *J* = 9.2 Hz, 1H), 7.44 – 7.36 (m, 4H), 7.32 (dd, *J* = 9.2, 1.2 Hz, 1H), 5.46 (d, *J* = 4.4 Hz, 1H), 5.02 – 4.97 (m, 1H), 3.87 (s, 3H), 3.69 – 3.54 (m, 4H), 2.95 – 2.93 (m, 2H), 2.90 – 2.83 (m, 1H), 2.82 – 2.75 (m, 2H), 2.65 – 2.60 (m, 1H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₅ClN₆O₂, 465.2; found, 465.0.

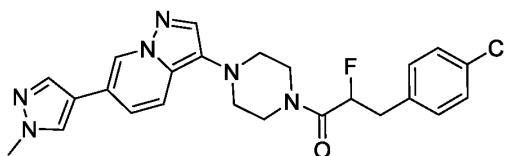
Step 2. Preparation of 3-(4-chlorophenyl)-3-fluoro-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one (Compound **527**)



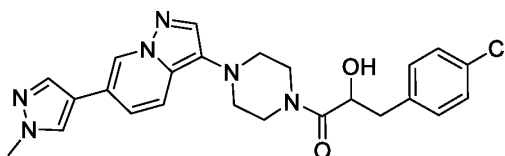
[0794] To a solution of 3-(4-chlorophenyl)-3-hydroxy-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one (1 g, 2.15 mmol, as prepared in the previous step) in DCM (30 mL) cooled to -78°C was added a solution of DAST (571 mg, 2.58 mmol) in DCM (3 mL) dropwise under nitrogen then the mixture was stirred for 10 minutes. The reaction was quenched by the addition of a water/ice mixture (20 mL) at -78°C then the mixture was warmed to rt and extracted with DCM (3x100 mL). The organic extracts were combined, washed with brine (3x10 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 40 mg (4%) of 3-(4-chlorophenyl)-3-fluoro-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one (Compound **527**) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.84 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.76 (s, 1H), 7.67 (d, *J* = 9.3 Hz, 1H), 7.51 (q, *J* = 8.5 Hz, 4H), 7.34 (d, *J* = 9.3 Hz, 1H), 6.19 – 5.82 (m, 1H), 3.88 (s, 3H), 3.74 – 3.54 (m, 4H), 3.26 (dd, *J* = 15.8, 8.4 Hz, 1H), 3.06 – 2.78 (m, 5H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₄ClFN₆O, 467.2; found, 467.1; HPLC purity: 254 nm: 99.6%.

Example 126: Synthesis of Exemplary Compound 528

3-(4-chlorophenyl)-2-fluoro-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one (Compound **528**)

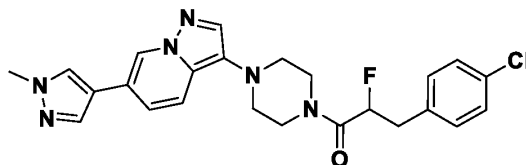


Step 1. Preparation of 3-(4-chlorophenyl)-2-hydroxy-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one



[0795] A solution of 3-(4-chlorophenyl)-2-hydroxypropanoic acid (500 mg, 2.49 mmol), EDC (573.3 mg, 2.99 mmol), HOBT (404.1 mg, 2.99 mmol) and 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (844.4 mg, 2.99 mmol) in DCM (10 mL) was stirred for 16 h at rt. The reaction was quenched with saturated aqueous NH₄Cl solution and extracted with DCM (3x20 mL). The organic extracts were combined, washed with water (3x20 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 40-50% ACN/water (10mM NH₄HCO₃) to afford 390 mg (34%) of 3-(4-chlorophenyl)-2-hydroxy-1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)propan-1-one as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.73 (s, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.37 – 7.26 (m, 5H), 5.18 (d, *J* = 7.9 Hz, 1H), 4.61 – 4.52 (m, 1H), 3.87 (s, 3H), 3.73 – 3.62 (m, 4H), 2.99 – 2.88 (m, 4H), 2.86 – 2.72 (m, 2H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₅ClN₆O₂, 465.2; found, 465.1; HPLC purity: 254 nm: 90%.

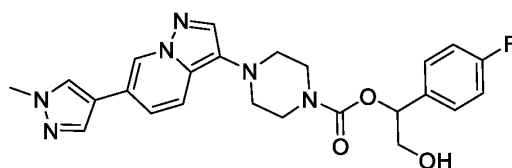
Step 2. Preparation of 3-(4-chlorophenyl)-2-fluoro-1-(4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazin-1-yl)propan-1-one (Compound **528**)



[0796] To a solution of 3-(4-chlorophenyl)-2-hydroxy-1-(4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazin-1-yl)propan-1-one (200 mg, 0.43 mmol, as prepared in the previous step) in DCM (5 mL) cooled to 0°C was added DAST (83.2 mg, 0.51 mmol) then the mixture was stirred for 1 h. The reaction was quenched with water then extracted with DCM (2x20 mL). The organic extracts were combined, washed with water (2x20 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 33.3 mg (17%) of 3-(4-chlorophenyl)-2-fluoro-1-(4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazin-1-yl)propan-1-one (Compound **528**) as a light yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.74 (s, 1H), 7.66 (d, *J* = 9.2 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.37 – 7.31 (m, 3H), 5.78 – 5.60 (m, 1H), 3.87 (s, 3H), 3.84 – 3.58 (m, 4H), 3.19 – 3.06 (m, 2H), 3.04 – 2.88 (m, 3H), 2.87 – 2.78 (m, 1H); MS (ESI) *m/z* [M+H]⁺ calcd. For C₂₄H₂₄ClFN₆O, 467.2; found, 467.1; HPLC purity: 254 nm: 99.8%.

Example 127: Synthesis of Exemplary Compound 529

1-(4-fluorophenyl)-2-hydroxyethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **529**)

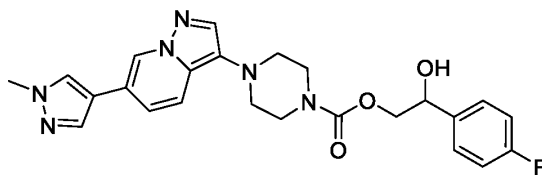


[0797] To a stirred mixture of 2-((tert-butyldimethylsilyl)oxy)-1-(4-fluorophenyl)ethan-1-ol (Compound **S125**) (300 mg, 1.11 mmol) and 4-nitrophenyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (496.4 mg, 1.11 mmol, as prepared in Example 20, Step 1) in DMF (5 mL) cooled to 0°C was added NaH (60%wt., 88.7 mg, 2.2 mmol) in portions then the mixture was warmed to rt and stirred for 2 h. The

reaction was cooled to 0°C, quenched with water, and extracted with EtOAc (3x50 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 29.8 mg (6%) of 1-(4-fluorophenyl)-2-hydroxyethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **529**) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.84 (s, 1H), 8.23 (s, 1H), 7.98 (s, 1H), 7.78 (s, 1H), 7.66 (d, *J* = 9.3 Hz, 1H), 7.43 – 7.37 (m, 2H), 7.34 (dd, *J* = 9.3, 1.5 Hz, 1H), 7.23 – 7.15 (m, 2H), 5.61 (dd, *J* = 7.0, 4.4 Hz, 1H), 5.05 (t, *J* = 5.9 Hz, 1H), 3.88 (s, 3H), 3.77 – 3.41 (m, 6H), 2.98 (s, 4H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₄H₂₅FN₆O₃, 465.2; found, 465.2; HPLC purity: 254 nm: 99.8%.

Example 128: Synthesis of Exemplary Compound 530

2-(4-fluorophenyl)-2-hydroxyethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **530**)

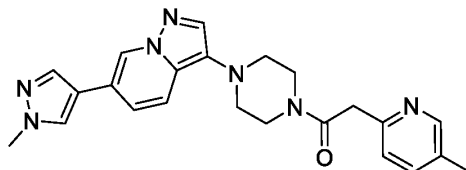


[0798] To a stirred mixture of 2-((tert-butyldimethylsilyl)oxy)-2-(4-fluorophenyl)ethan-1-ol (Compound **S126**) (300 mg, 1.11 mmol) and 4-nitrophenyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (990 mg, 2.22 mmol, as prepared in Example 20, Step 1) in DMF (5 mL) cooled to 0°C was added NaH (60%wt., 88.7 mg, 2.2 mmol) in portions then the mixture was warmed to rt and stirred for 2 h. The reaction was cooled to 0°C, quenched with water, and extracted with EtOAc (3x50 mL). The organic extracts were combined, dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 91.9 mg (18%) of 2-(4-fluorophenyl)-2-hydroxyethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **530**) as an off-white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.83 (s, 1H), 8.24 (s, 1H), 7.98 (s, 1H), 7.77 (s, 1H), 7.66 (d, *J* = 9.2 Hz, 1H), 7.43 (dd, *J* = 8.6, 5.7 Hz, 2H), 7.34 (dd, *J* = 9.2, 1.6 Hz, 1H), 7.18 (t, *J* = 8.9 Hz, 2H), 5.66 (d, *J* = 4.6 Hz, 1H), 4.82 (q, *J* = 5.4 Hz, 1H),

4.11 – 4.03 (m, 2H), 3.88 (s, 3H), 3.54 (s, 4H), 2.94 (s, 4H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{24}H_{25}FN_6O_3$, 465.2; found, 465.3; HPLC purity: 254 nm: 99.7%.

Example 129: Synthesis of Exemplary Compound 533

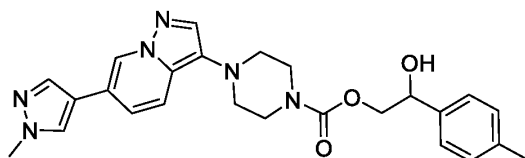
1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-(5-methylpyridin-2-yl)ethan-1-one (Compound **533**)



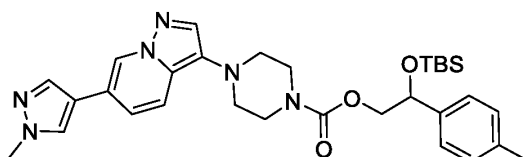
[0799] To a solution of (5-methylpyridin-2-yl)acetic acid (200 mg, 1.32 mmol), HATU (628.84 mg, 1.65 mmol), and DIEA (342 mg, 2.64 mmol) in DMF (5 mL) was added 6-(1-methyl-1H-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-a]pyridine (Compound **12**) (448.2 mg, 1.58 mmol) then the mixture was heated to 60°C and stirred for 3 h. The reaction was cooled to 0°C, quenched with saturated aqueous NH_4Cl solution, and extracted with EtOAc (3x20 mL). The organic extracts were combined, washed with water (3x20 mL), dried over anhydrous Na_2SO_4 , and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by Prep-HPLC to afford 138.5 mg (25%) of 1-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrazolo[1,5-a]pyridin-3-yl)piperazin-1-yl)-2-(5-methylpyridin-2-yl)ethan-1-one (Compound **533**) as a yellow solid. 1H NMR (400 MHz, $DMSO-d_6$) δ (ppm) 8.82 (s, 1H), 8.34 – 8.30 (m, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.74 (s, 1H), 7.65 (d, $J = 9.2$ Hz, 1H), 7.56 (dd, $J = 8.0, 2.1$ Hz, 1H), 7.32 (dd, $J = 9.2, 1.4$ Hz, 1H), 7.20 (d, $J = 7.9$ Hz, 1H), 3.88 (s, 2H), 3.86 (s, 3H), 3.72 – 3.69 (m, 2H), 3.68 – 3.64 (m, 2H), 2.95 – 2.91 (m, 4H), 2.27 (s, 3H); MS (ESI) m/z $[M+H]^+$ calcd. for $C_{23}H_{25}N_7O$, 416.2; found, 416.3; HPLC purity: 254 nm: 99.4%.

Example 130: Synthesis of Exemplary Compound 485

2-hydroxy-2-(*p*-tolyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **485**)

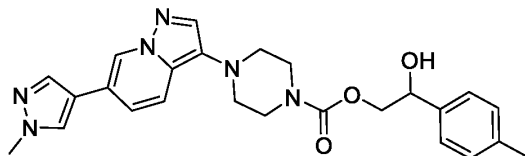


Step 1. Preparation of 2-((*tert*-butyldimethylsilyl)oxy)-2-(*p*-tolyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate



[0800] To a stirred solution of 2-((*tert*-butyldimethylsilyl)oxy)-2-(*p*-tolyl)ethan-1-ol (Compound **S111**) (200 mg, 0.75 mmol) and 6-(1-methyl-1*H*-pyrazol-4-yl)-3-(piperazin-1-yl)pyrazolo[1,5-*a*]pyridine (Compound **12**) (159.0 mg, 0.56 mmol) in pyridine (5 mL) cooled to 0°C was added BTC (222.5 mg, 0.75 mmol) in portions then the mixture was warmed to rt and stirred for 1 h. The reaction was cooled to 0°C, quenched with water, and extracted with EtOAc (3x20 mL). The organic extracts were combined, washed with water (3x20 mL), dried over anhydrous Na₂SO₄, and filtered. The filtrate was concentrated under reduced pressure then the residue was purified by reversed-phase flash chromatography using a C18 silica gel column eluting with 45-55% ACN/water (10mM NH₄HCO₃) to afford 210 mg (49%) of 2-((*tert*-butyldimethylsilyl)oxy)-2-(*p*-tolyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.23 (s, 1H), 7.97 (s, 1H), 7.76 (s, 1H), 7.67 (d, *J* = 9.2 Hz, 1H), 7.33 (dd, *J* = 9.3, 1.4 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 4.96 – 4.91 (m, 1H), 4.06 – 3.99 (m, 2H), 3.87 (s, 3H), 3.56 (s, 4H), 2.95 (s, 4H), 2.29 (s, 3H), 0.85 (s, 9H), 0.04 (s, 3H), -0.09 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. For C₃₁H₄₂N₆O₃Si, 575.3; found, 575.3.

Step 2. Preparation of 2-hydroxy-2-(*p*-tolyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **485**)



[0801] A mixture of 2-((*tert*-butyldimethylsilyl)oxy)-2-(*p*-tolyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (210 mg, 0.36 mmol, as prepared in the previous step) in 4M HCl in EtOAc (5 mL) was stirred at rt for 1 h. The reaction was quenched with saturated aqueous Na₂CO₃ solution adjusting the pH to 8 then the mixture was concentrated under reduced pressure. The residue was purified by Prep-HPLC to afford 52.6 mg (31%) of 2-hydroxy-2-(*p*-tolyl)ethyl 4-(6-(1-methyl-1*H*-pyrazol-4-yl)pyrazolo[1,5-*a*]pyridin-3-yl)piperazine-1-carboxylate (Compound **485**) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 8.82 (s, 1H), 8.22 (s, 1H), 7.97 (s, 1H), 7.75 (s, 1H), 7.66 (d, *J* = 9.2 Hz, 1H), 7.34 (dd, *J* = 9.2, 1.6 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 5.54 (d, *J* = 4.4 Hz, 1H), 4.76 (q, *J* = 5.6 Hz, 1H), 4.05 (d, *J* = 5.6 Hz, 2H), 3.88 (s, 3H), 3.55 (s, 4H), 2.94 (s, 4H), 2.29 (s, 3H); MS (ESI) *m/z* [M+H]⁺ calcd. for C₂₅H₂₈N₆O₃, 461.2; found, 461.2; HPLC purity: 254 nm: 99.2%.

Example 131: Functional Analysis of the Exemplary PDGFRα Inhibitors

[0802] To assess the inhibitory capability of the PDGFRα inhibitors synthesized in Examples 1-130, an enzymatic PDGFRα kinase assay was used as described below.

Methods:

[0803] The PDGFRα enzyme assays were conducted per the manufacturer's directions (Promega PDGFRα Kinase Enzyme System and ADP Glo Assay Cat# V8011). Briefly, exemplary PDGFRα inhibitor compounds described herein were assayed in an 11-point dose response curve with a maximum concentration of 10,000 nM and 3-fold dilutions to a minimum concentration of 0.169 nM. 20 ng of purified PDGFRα protein was added to the test article. Subsequently, 150 μM of ATP and 1 ug of substrate, Poly (Glu4Tyr1) was added to each reaction, and the PDGFRα kinase mediated conversion of ATP (adenosine triphosphate) to ADP (adenosine diphosphate) was allowed to continue for two hours.

ADP-Glo was added to halt the kinase reaction and deplete the remaining ATP. Kinase detection reagent, containing luciferase and luciferin, was used to convert the ADP signal into luminescence. Luminescence was measured using a Molecular Devices Spectramax ID5 and compared to a standard curve to determine kinase activity. IC₅₀s were calculated using Prism 9, Graphpad software.

Results:

[0804] As shown in Table 4 (below), the compounds exhibited varying potency with respect to inhibition of PDGFR α kinase activity. Of those tested, several compounds inhibited PDGFR α kinase activity with an IC₅₀ of less than 1,000 nM. The results confirm the inhibitory activity of the novel PDGFR α inhibitors described herein.

Table 4. IC₅₀ Values for PDGFR α Kinase Inhibition of Exemplary Compounds

Compound	PDGFR α IC ₅₀ (nM)
156	260.3125
275	67.02
326	>10,000
327	6.15
328	6185.5
329	11.3355
330	>10,000
331	1897.5
332	>10,000
333	>10,000
334	>10,000
335	>10,000
336	154.235
337	>10,000
338	4040.5
339	402.15
340	>10,000
341	2.945
342	0.66
343	10.61
344	BLQ
345	128.7
346	957.15

347	4533.5
348	1065.5
349	4711
350	215.05
351	25.06
352	247.235
353	118.65
354	387.2
355	287.25
356	1070.1
357	1694
358	423.25
359	10.621
360	1821
361	257.9
362	15.43
363	43.12
364	17.785
365	11.37
366	762.10
367	98.99
368	646.15
369	29.36
370	BLQ
371	BLQ
372	92.64
373	305.70
374	335.95
375	388.25
376	>10,000
377	>10,000
378	93.835
379	637.05
380	217.1
381	2367
382	343.3
383	486.3
384	1499
385	7.2185
386	1016.1
387	302.1

388	41.79
389	502.25
390	64.77
391	151.6265
392	706.75
393	4704.5
394	1712.5
395	1998
396	2362.5
397	BLQ
398	7.09
399	0.725
400	896.85
401	419.05
402	358.45
403	1528
404	400.45
405	30.335
406	31.095
250	80.44
407	2367
408	107.1
409	177.2
410	36.1
411	3.9
412	65.2
413	212.6
414	>10,000
415	68.5
416	1522
417	>10,000
418	6916
419	38.8
420	115.6
421	1572
422	190.1
423	100.3
424	4.0
425	117.4
426	210.9
427	645

428	BLQ
429	2.4
430	99.3
431	537.5
432	>10,000
433	1981.4
434	BLQ
435	386.8
436	>10,000
437	620.4
438	496.4
439	216.6
440	620.6
441	43.6
442	>10,000
443	2377
444	183.5
445	998.2
446	2.273
447	>10,000
448	3790
449	3117
450	6122
451	1093
452	>10,000
453	281.7
454	662.9
455	541.8
456	802.7
457	4473
458	>10,000
459	8803
460	202.5
461	5420
462	905.1
463	247.8
464	149.3
465	>10,000
466	>10,000
467	65.5
468	1307

469	443.5
470	869.6
471	22.5
472	182.5
473	36.8
474	BLQ
475	2.1
476	>10,000
477	96.7
478	0.6
479	71.3
480	1.5
481	0.7
482	BLQ
483	BLQ
484	323.9
485	367.5
486	BLQ
487	18.2
488	73.9
489	>10,000
490	1446
491	635.2
492	3744
493	2618
494	BLQ
495	174.5
496	3752
497	984.2
498	>10,000
499	133.5
500	2163
501	2.8
502	6.9
503	206.7
504	487.2
505	4.228
506	2.3
507	>10,000
508	BLQ
509	BLQ

510	866
511	11.1
512	BLQ
513	BLQ
514	2723
515	BLQ
516	BLQ
517	155.4
518	68.08
519	BLQ
520	BLQ
521	BLQ
522	0.6131
523	561.9
524	745.5
525	302.9
526	1621
527	49.7
528	19.8
529	0.3
530	56.4
531	BLQ
532	1370
533	1193

BLQ = below limit of quantitation, <0.17 nM

Example 132: Analysis of the Effect of PDGFR α Inhibition on GPR17 Expression *in vitro*

[0805] To assess the effects of the PDGFR α inhibitors on OPC differentiation, primary OPCs were cultured and exposed to compounds disclosed herein. The number of newly generated oligodendrocytes was assessed by monitoring GPR17 expression. GPR17 is preferentially expressed in actively differentiating oligodendrocytes, allowing them to be distinguished from precursors and more differentiated oligodendrocytes.

Methods:*OPC isolation and seeding:*

[0806] Cortices from postnatal day (P) 1-3 rats were dissected and collected into ice cold Hank's Balanced Salt Solution (HBSS). A homogenous cell suspension of the cortices was prepared using the Neural Tissue Dissociation Kit (P) (Miltenyi #130-092-628) as per manufacturer's protocol. Oligodendrocyte progenitor cells (OPCs) were isolated from the mixed cortical cell suspension by positive selection using Anti-A2B5 MicroBeads (Miltenyi #130-093-388), as per manufacturer's protocol. Briefly, the cortical cell suspension was centrifuged and washed with buffer (0.5% BSA in PBS) and labeled with Anti-A2B5 MicroBeads (10 μ L beads per 1×10^7 cells) for 15 minutes at 4°C. Following the incubation, cells were washed once with BSA buffer to remove unlabeled beads. A2B5 positive cells were eluted on the column using the AutoMACS® (Miltenyi, as per manufacturer's protocol using "Possel-s" program). Eluted cells were further washed twice with OPC growth media. Cell counts were performed using Countess III cell counter (ThermoFisher; AMQAX2000) and cells were plated.

[0807] Following cell count, OPCs were seeded at a density of approximately 10,000 cells per well in poly-D-lysine coated 96 well plates (PE Cell Carrier #6005550) or approximately 2500 cells per well in poly-D-lysine coated 384 well plate (PE Cell Carrier # 6057500) in 90 μ L of OPC growth medium (DMEM/F12 + B27 without vitamin A + pen/strep) supplemented with 10 ng/mL of PDGF-AA (Peprotech 100-13A) and 10 ng/mL of FGF (fibroblast growth factor; R&D Systems #233 FB 010). The plates were allowed to sit at room temperature for 15 minutes to ensure proper dispersion of cells in a well. The plates were then transferred to the incubator (37°C; 5% CO₂).

Compound Treatment

[0808] Following 3-4 hours of incubation (to allow cells to adhere), cells (seeded in 90 μ L OPC growth media) were treated with 10 μ L of 10X concentration of vehicle (DMSO; 0.03%) control (Santa Cruz Biotechnology; sc-358801), or PDGFR α inhibitors disclosed herein (3 μ M), resulting in a final 1X concentration of 0.003% for the vehicle or 0.3 μ M for the PDGFR α inhibitors. Cells were then incubated for 72 hours at 37°C, 5% CO₂ before immunostaining for GPR17 marker expression.

Immunocytochemistry:

[0809] Following 72 hours in culture, cells were fixed with 4% paraformaldehyde for 15 minutes and then washed three times in Dulbecco's phosphate buffered saline (DPBS). Prior to immunostaining, cells were treated with a blocking solution (10% normal goat serum containing 1% BSA and 0.1% Triton® X-100 in DPBS) for 15 minutes at room temperature. Primary antibody (anti-GPR17 at 1:2000; Origene TA811615) was applied to cells overnight at 4°C in incubation solution containing 1% normal goat serum, 1% BSA, and 0.1% Triton X-100 in DPBS. Following overnight primary incubation, cells were washed three times in DPBS, and then, secondary antibody (Goat anti-mouse Alexa Fluor 594 at 1:1000, Jackson ImmunoResearch 112-545-003) was applied to the cells. The secondary antibody was applied in incubation solution for 2 hours at room temperature, protected from light. Following incubation with the secondary antibodies, cells were washed three times with DPBS and nuclei stained with Hoechst (BioRad #1351304) before imaging.

Image analysis and quantification:

[0810] Cells were imaged using ImageXpress® confocal system (Molecular Devices; 5150105) and analyzed using a custom protocol developed using MetaXpress Custom Module software. The number of differentiated GPR17+ cells was normalized to the total nuclei count and percent differentiated GPR17+ cells were reported. Statistical analysis was done using one-way ANOVA with multiple comparisons and post-hoc Tukey test in GraphPad Prism (GraphPad Software).

Results:

[0811] Treatment of the OPCs with PDGFR α inhibitors led to an increase in differentiated GPR17+ cells, a marker of oligodendrocyte differentiation. The increase is represented by fold change over vehicle for the PDGFR α inhibitors (Table 5). These results demonstrate that PDGFR α inhibition induces OPC differentiation, indicating that compounds that inhibit PDGFR α activity could be useful for inducing remyelination.

Table 5. *In vitro* GPR17 Expression Induced by Exemplary PDGFR α Inhibitors

Compound	GPR17 Fold Induction (Over vehicle)
156	3.92
275	6.7
326	1.05

Compound	GPR17 Fold Induction (Over vehicle)
327	4.70
328	2.45
329	6.52
330	1.08
331	8.16
332	4.46
333	1.80
334	1.22
335	0.89
336	5.55
337	1.05
338	4.02
339	3.29
340	2.18
341	6.40
342	6.03
343	7.69
344	6.07
345	6.23
346	2.77
347	3.03
348	4.00
349	0.99
350	6.90
351	6.84
352	5.82
353	4.68
354	3.28
355	2.81
356	7.96
357	6.15
358	7.35
359	9.86
360	4.19
361	5.74
362	5.19
363	4.57
364	4.41
365	9.98

Compound	GPR17 Fold Induction (Over vehicle)
366	8.27
367	14.35
368	11.27
369	10.51
370	11.09
371	10.89
372	10.92
373	7.49
374	10.40
375	8.45
376	5.57
377	3.68
378	3.80
379	4.52
380	5.36
381	9.78
382	4.70
383	4.24
384	3.26
385	3.27
386	4.05
387	5.26
388	5.38
389	3.29
390	3.71
391	2.22
392	5.97
393	3.46
394	4.09
395	5.71
396	3.86
397	6.72
398	5.49
399	4.32
400	5.01
401	9.01
402	8.37
403	8.28
404	11.76

Compound	GPR17 Fold Induction (Over vehicle)
405	12.26
406	10.24
250	9.74
407	1.54
408	2.29
409	2.41
410	2.57
411	1.74
412	3.22
413	2.08
414	2.74
415	4.18
416	4.73

Example 133: Analysis of the Effect of PDGFR α Inhibition on MBP Expression *in vitro*

[0812] While expression of GPR17 indicates differentiated or pre-myelinating oligodendrocytes, terminal differentiation of the OPCs to oligodendrocytes and formation of myelin is characterized by expression of myelin basic protein (MBP), which is an important element of myelin.

[0813] To further confirm the results shown in Example 132 that PDGFR α inhibitors can lead to terminal oligodendrocyte differentiation, select PDGFR α inhibitors were tested in the *in vitro* OPC differentiation assay by measuring the number of MBP+ oligodendrocytes.

Methods:

OPC isolation and seeding:

[0814] Cortices from postnatal day (P) 1-3 rats were dissected and collected into ice cold Hank's Balanced Salt Solution (HBSS). A homogenous cell suspension of the cortices was prepared using the Neural Tissue Dissociation Kit (P) (Miltenyi #130-092-628) as per manufacturer's protocol. Oligodendrocyte progenitor cells (OPCs) were isolated from the mixed cortical cell suspension by positive selection using Anti-A2B5 MicroBeads (Miltenyi #130-093-388), as per manufacturer's protocol. Briefly, the cortical cell suspension was centrifuged and washed with buffer (0.5% BSA in PBS) and labeled with Anti-A2B5 MicroBeads (10 μ L beads per 1×10^7 cells) for 15 minutes at 4°C. Following

the incubation, cells were washed once with BSA buffer to remove unlabeled beads. A2B5 positive cells were eluted on the column using the AutoMACS® (Miltenyi, as per manufacturer's protocol using "possel-s" program). Eluted cells were further washed twice with OPC growth media. Cell count was performed using Countess III cell counter (ThermoFisher; AMQAX2000) and cells were plated.

- [0815] A2B5+ OPCs were plated in poly-d-lysine (PDL) coated T75 flask at a density of ~3 million cells per flask. Cells were allowed to expand for 3 days at 37°C, 5% CO₂ in OPC growth media containing 10 ng/mL of PDGF (Peprotech 100-13A) and 10 ng/mL FGF (R&D Systems #233-FB-010). Following three days of expansion (~60-70% confluency), cells were lifted using TrypLE (Thermo 12604013) for 3-5 minutes at 37°C, 5% CO₂. TrypLE was normalized by adding 10mL growth media and cells were centrifuged at 1400 rpm for 10 minutes. Cell count was performed, and cells were plated into PDL coated 96 well plates (PE Cell Carrier #6005550) at approximately 5000 cells per well in 90 µL of OPC growth medium (DMEM/F12 + B27 without vitamin A + pen/strep) supplemented with 10 ng/mL of PDGF-AA (Peprotech 100-13A) and 10 ng/mL of FGF (fibroblast growth factor; R&D Systems #233 FB 010). The plates were allowed to sit at room temperature for 15 minutes to ensure proper dispersion of cells in a well. The plates were then transferred to the incubator (37°C; 5% CO₂).

Compound Treatment

- [0816] Following 3-4 hours of incubation (to allow cells to adhere), cells (seeded in 90µl OPC growth media) were treated with 10µl of 10X concentration of vehicle (DMSO; 0.03%) control (Santa Cruz Biotechnology; sc-358801), or PDGFR α inhibitors disclosed herein (3µM), resulting in a final 1X concentration of 0.3% for the vehicle or 0.3 µM for the PDGFR α inhibitors. Cells were then incubated for 72 hours at 37°C, 5% CO₂ before immunostaining for MBP marker expression.

Immunocytochemistry:

- [0817] Following 72 hours of treatment, cells were fixed with 4% paraformaldehyde for 15 minutes then washed three times in DPBS. Prior to staining, cells were blocked for 15 minutes in 10% normal goat serum containing 1% BSA and 0.1% Triton X-100 in DPBS. Primary antibody (MBP @ 1:2000; Abcam AB7349) was applied to cells overnight at 4°C in incubation solution containing 1% normal goat serum, 1% BSA, and 0.1% Triton X-100 in DPBS. After primary incubation, cells were washed three times in DPBS and

secondary antibodies (Goat anti-Rat Alexa Fluor 488, Jackson ImmunoResearch 112-545-003, 1:1000) were applied in incubation solution for two hours at room temperature, protected from light. Following secondary antibodies, cells were washed three times with DPBS and nuclei stained with Hoechst (BioRad #1351304).

Image analysis and quantification:

[0818] Cells were imaged using ImageXpress® confocal system (Molecular Devices; 5150105) and analyzed using a custom protocol from MetaXpress Custom Module software. The number of differentiated MBP+ cells was normalized to the total nuclei count and percent differentiated MBP+ cells were reported. Statistical analysis was done using one-way ANOVA with multiple comparisons and post-hoc Tukey test in GraphPad Prism (GraphPad Software).

Results:

[0819] Treatment of OPCs with PDGFRα inhibitors led to increases in differentiated MBP+ cells. The increase is represented by fold change over vehicle for the PDGFRα inhibitors (Table 6). In agreement with results from Example 132, these data demonstrate that PDGFRα inhibition can drive OPC differentiation and expression of myelin specific proteins. These findings further support the therapeutic potential of PDGFRα inhibitors in remyelination.

[0820] In parallel with the PDGFRα kinase inhibition data, the novel chemical compounds described herein were also able to induce OPC differentiation and myelin protein formation *in vitro*, as evidenced by the increased GPR17 and MBP expression. Collectively, the above results demonstrate that the novel PDGFRα inhibitors described herein could be useful in inducing remyelination as a therapeutic for the treatment of demyelinating diseases.

Table 6. *In vitro* MBP Expression Induced by Exemplary PDGFRα Inhibitors

Compound	MBP Fold Induction (Over vehicle)
156	17.9
275	2.71
327	6.52
329	6.65
331	1.83
336	3.18

Compound	MBP Fold Induction (Over vehicle)
338	2.05
341	1.49
342	6.47
343	3.70
344	3.61
345	2.41
349	1.83
350	1.99
351	2.11
352	2.02
353	2.29
354	2.48
355	5.46
357	4.15
358	2.52
359	2.99
360	1.77
361	14.96
362	21.34
363	18.62
364	17.49
365	23.59
366	19.10
367	16.84
368	48.82
369	48.50
370	74.04
371	31.45
372	35.21
373	28.20
374	42.14
375	47.40
378	44.38
382	3.10
383	2.51
385	4.08
386	14.21
387	8.03
388	7.82

Compound	MBP Fold Induction (Over vehicle)
389	2.25
390	4.20
391	2.71
392	3.88
393	3.34
394	2.81
395	7.89
397	14.64
398	8.96
399	4.82
405	2.19
406	1.26
250	4.03

Example 134: PDGFR α inhibitors induce OPC differentiation *in vivo*

[0821] The ability of compounds disclosed herein to drive OPC differentiation and myelination *in vivo* was tested. The ability of these compounds to drive OPC differentiation *in vivo* was tested using GPR17 as an indicator of newly differentiated oligodendrocytes.

Materials

Mice:

[0822] Age matched (> 6 months old) adult female C57BL/6 mice (Strain Code 000664) were purchased from The Jackson Laboratory.

Methods:

Compound treatment:

[0823] All experiments were conducted in accordance with animal welfare and IACUC guidelines. Compounds were delivered PO or IP either QD or BID. Mice were dosed once, transiently, or continuously through the treatment period, which ranged from 1-3 days. Table 7 (below) describes the different treatment groups.

Table 7. Treatment Groups with Exemplary PDGFR α Inhibitors

Compound	Dose (mg/kg)	No. of days dosed	Route	Frequency
156	1	1	PO	QD
275	3	1	PO	QD
341	20	1	PO	QD
342	3	1	PO	QD
343	3	1	PO	QD
350	3	1	PO	QD
357	6	1	PO	QD
358	6	1	PO	QD
359	6	1	PO	QD
361	3	1	PO	QD
362	3	1	PO	QD
363	3	1	PO	QD
369	3	1	PO	QD
370	3	1	PO	QD
371	3	1	PO	QD
372	3	1	PO	QD
385	3	1	PO	QD
250	3	1	PO	QD
422	3	1	PO	QD
424	3	1	PO	QD
428	3	1	PO	QD
429	3	1	PO	QD
430	3	1	PO	QD
431	3	1	PO	QD
434	3	1	PO	QD
441	3	1	PO	QD
444	3	1	PO	QD
446	3	1	PO	QD
455	3	1	PO	QD
460	3	1	PO	QD
464	3	1	PO	QD
473	3	1	PO	QD
474	3	1	PO	QD
475	3	1	PO	QD
478	3	1	PO	QD
480	3	1	PO	QD
481	3	1	PO	QD
482	3	1	PO	QD
483	3	1	PO	QD
486	3	1	PO	QD
487	3	1	PO	QD
494	3	1	PO	QD

Histology:

- [0824] Mice were euthanized by isoflurane exposure and transcardially perfused with 14 mL of PBS (Sigma Cat # P4417-50TAB) followed by 22 mL of 3.2% paraformaldehyde in PBS. The brains were removed and postfixed for a minimum of 24 hours in 20 mL of 3.2% paraformaldehyde. 3.2% paraformaldehyde was prepared from 32% paraformaldehyde (Electron microscopy Sciences Cat # 15714-S) diluted in phosphate buffered saline.
- [0825] 50-micron floating sections were cut using a Leica VT1200S vibratome. Every 24th section, extending through the antero-posterior extent of the brain, was stained. The selected brain sections were washed three times in PBS for 3 minutes each. The floating sections were incubated in the primary antibodies (see Table 10, below) diluted in blocking solution overnight at room temperature on a shaker. Blocking solution included: 0.3% Triton X-100 (Sigma, Cat # 234729), 0.02% sodium azide (Sigma, Cat # S2002), 8% fetal bovine serum (Sigma, Cat #F2442), 1X PBS. The next day, the sections were again washed three times in PBS for 3 minutes each and then incubated in the secondary antibodies diluted in blocking solution for 2 hours at room temperature on a shaker. After incubation, the sections were washed three times in PBS for 3 minutes each and mounted on a slide to be imaged using the Olympus Slide Scanner VS200.

Table 10. Primary Antibodies

Antigen	Vendor	Catalog No.	Species	Concentration
GPR17	OriGene	OTI17C1	Mouse	1:2000
Olig2	Millipore Sigma	AB9610	Rabbit	1:2000

Image Analysis and quantification:

- [0826] The images were analyzed using a custom protocol developed using Visiopharm software to count GPR17+ cells. Cells were considered GPR17+ if they contained an Olig2 positive nucleus, and intense GPR17 staining that filled their processes. Statistical analysis was done using one-way ANOVA with multiple comparison in GraphPad Prism software.

Results

- [0827] Treatment of the animals with PDGFR α inhibitors disclosed herein led to an increase in the number of cells with process filling GPR17+ cells, a marker for newly

differentiated oligodendrocytes, throughout the entire brain. The increase is represented by fold change over vehicle treated animals for the PDGFR α inhibitors (Table 11). In agreement with the results from Example 132, many of the PDGFR α inhibitors disclosed herein that are capable of inducing OPC differentiation *in vitro* can also induce OPCs to differentiate *in vivo*.

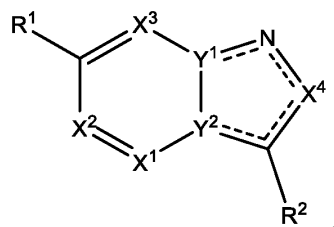
Table 11. *In vivo* GPR17+ cells Induced by Exemplary PDGFR α Inhibitors

Compound	GPR17 Fold Induction (Over Vehicle)
156	11.3
275	5.31
341	0.96
342	9.60
343	6.72
350	13.53
357	9.75
358	3.49
359	12.64
361	1.79
362	1.49
363	1.01
369	1.94
370	1.80
371	2.13
372	3.67
385	3.09
250	5.99
422	0.96
424	0.9
428	2.14
429	1.196
430	10.43
431	1.12
434	1.797
441	0.95
444	1.595
446	1.641
455	0.96
460	0.9
464	0.98
473	1.423
474	9.219

475	1.104
478	2.33
480	0.97
481	1.05
482	0.91
483	3.41
486	0.95
487	1.08
494	0.88

WHAT IS CLAIMED IS:

1. A compound of Formula I:



or a pharmaceutically acceptable salt or solvate thereof, wherein:

----- indicates a single bond or a double bond such that all valences are satisfied;

X^1 , X^2 , X^3 , and X^4 are selected from N and CR^a , with the proviso that not more than two of X^1 , X^2 , X^3 , and X^4 are N;

one of Y^1 and Y^2 is N and the other of Y^1 and Y^2 is C;

each R^a is independently selected from H, halo, C_1 - C_4 alkyl, and C_1 - C_4 alkoxy;

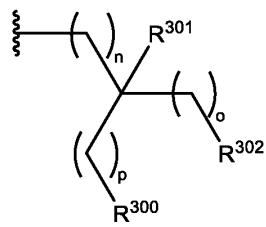
R^1 is selected from C_1 - C_4 alkyl, C_3 - C_8 cycloalkyl, 3-8 membered heterocyclyl, heteroaryl, aryl, and C_1 - C_8 alkoxy, all of which can be optionally substituted with one, two, three, four, five, or six substituents selected from halo, hydroxy, oxo, C_1 - C_4 alkyl, amino C_1 - C_4 alkyl, hydroxy C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 alkoxy C_1 - C_4 alkyl, 3-8 membered heterocyclyl, and 3-8 membered heterocyclyl C_1 - C_4 alkyl, with the proviso that the number of substituents does not exceed the number of substitutable positions;

R^2 is selected from cycloalkyl, cycloalkenyl, alkyl, oxoalkylamino, aminoalkylamino, amino, heterocyclyl, heteroaryl, aminoheterocyclyl, heterocyclylamino, and aminoalkylamino, all of which can be optionally substituted with one or more substituents selected from D, halo, hydroxy, oxo, and C_1 - C_4 alkyl;

R^2 is substituted with one, two, or three R^3 ;

R^3 is selected from aryl, heteroaryl, $-C(O)R^{31}$, $-C(O)OR^{31}$, $-C(O)NR^{31}R^{32}$, $-S(O)_2NR^{31}R^{32}$, $-S(O)(NR^{33})R^{31}$, $-S(O)_2R^{31}$, $-S(O)(NR^{33})NR^{31}R^{32}$, $-C(S)NR^{31}R^{32}$, C_3 - C_8 cycloalkyl, 3-8 membered heterocyclyl, and C_1 - C_4 alkyl, all of which can be optionally substituted with one, two, three, four, or five R^{30} ;

each R^{30} is independently selected from D, halo, aryl, $-OR^{300}$, $-NR^{300}R^{303}$, $-S(O)_rR^{300}$, $-C(O)R^{300}$, $-C(=CR^{34}R^{35})R^{300}$, and



r is selected from 0, 1, and 2;

each R^{300} is independently selected from C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, aryl, heteroaryl, 3-8 membered heterocyclyl, and 3-8 membered heterocyclylaryl, all of which can be optionally substituted with one, two, three, four, or five substituents selected from D, halo, hydroxy, amino, alkylamino, cyano, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, and C_1 - C_4 alkoxy;

each R^{301} is independently selected from H, halo, and C_1 - C_4 alkyl;

each R^{302} is independently selected from H, F, hydroxyl, amino, alkylamino, oxo, and C_1 - C_4 alkoxy;

each R^{303} is independently selected from H and C_1 - C_4 alkyl;

n , o , and p are each independently selected from 0, 1, 2, 3, and 4;

each R^{31} is independently selected from C_1 - C_8 alkyl, aryl C_1 - C_4 alkyl, heteroaryl C_1 - C_4 alkyl, heterocyclyl, heterocyclyl C_1 - C_4 alkyl, cycloalkyl, and cycloalkyl C_1 - C_4 alkyl, all of which can be optionally substituted with one, two, three, four, or five substituents selected from D, halo, cyano, hydroxy, amino, $-OCF_3$, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, hydroxyl C_1 - C_4 alkyl, $-S(O)_2NR^{304}R^{305}$, $-C(O)OR^{304}R^{305}$, $-C(O)NR^{304}R^{305}$, and $-NR^{304}C(O)R^{305}$;

each R^{304} and R^{305} is independently selected from H and C_1 - C_4 alkyl;

each R^{32} is independently selected from H and C_1 - C_4 alkyl; or

R^{31} and R^{32} together with the atom to which they are connected to form a 5-8 membered heterocycyl, optionally substituted with one, two, three, four, or five substituents selected from D, halo, cyano, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, and $-C(O)NR^{34}R^{35}$; and

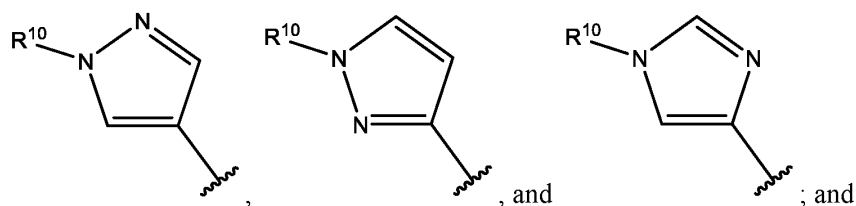
each R^{34} and R^{35} is independently selected from H, C_1 - C_4 alkyl, and C_1 - C_4 haloalkyl; and

each R^{33} is independently selected from H, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, and $-C(O)R^{34}$; or

R^{31} and R^{33} together with the atoms to which they are connected form a 4-8 membered heterocycl.

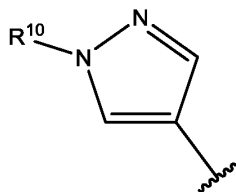
2. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein Y^1 is N and Y^2 is C.
3. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein Y^1 is C and Y^2 is N.
4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is N, X^2 is CR^a , X^3 is CR^a , and X^4 is CR^a .
5. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is CR^a , X^2 is N, X^3 is CR^a , and X^4 is CR^a .
6. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is CR^a , X^2 is CR^a , X^3 is N, and X^4 is CR^a .
7. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is CR^a , X^2 is CR^a , X^3 is CR^a , and X^4 is N.
8. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt or solvate thereof, wherein X^1 is CR^a , X^2 is CR^a , X^3 is CR^a , and X^4 is CR^a .
9. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is 5- or 6-membered heteroaryl.
10. The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is an optionally substituted pyrazolyl.
11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is selected from:

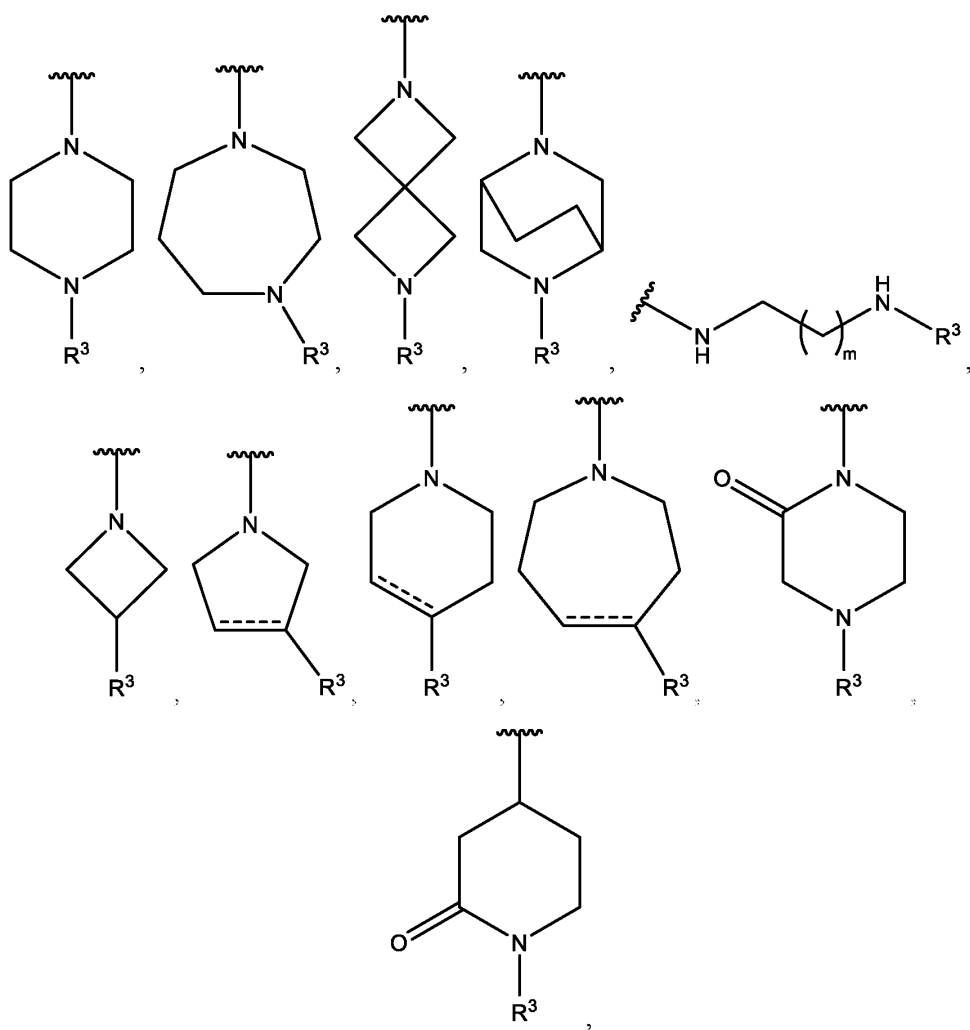


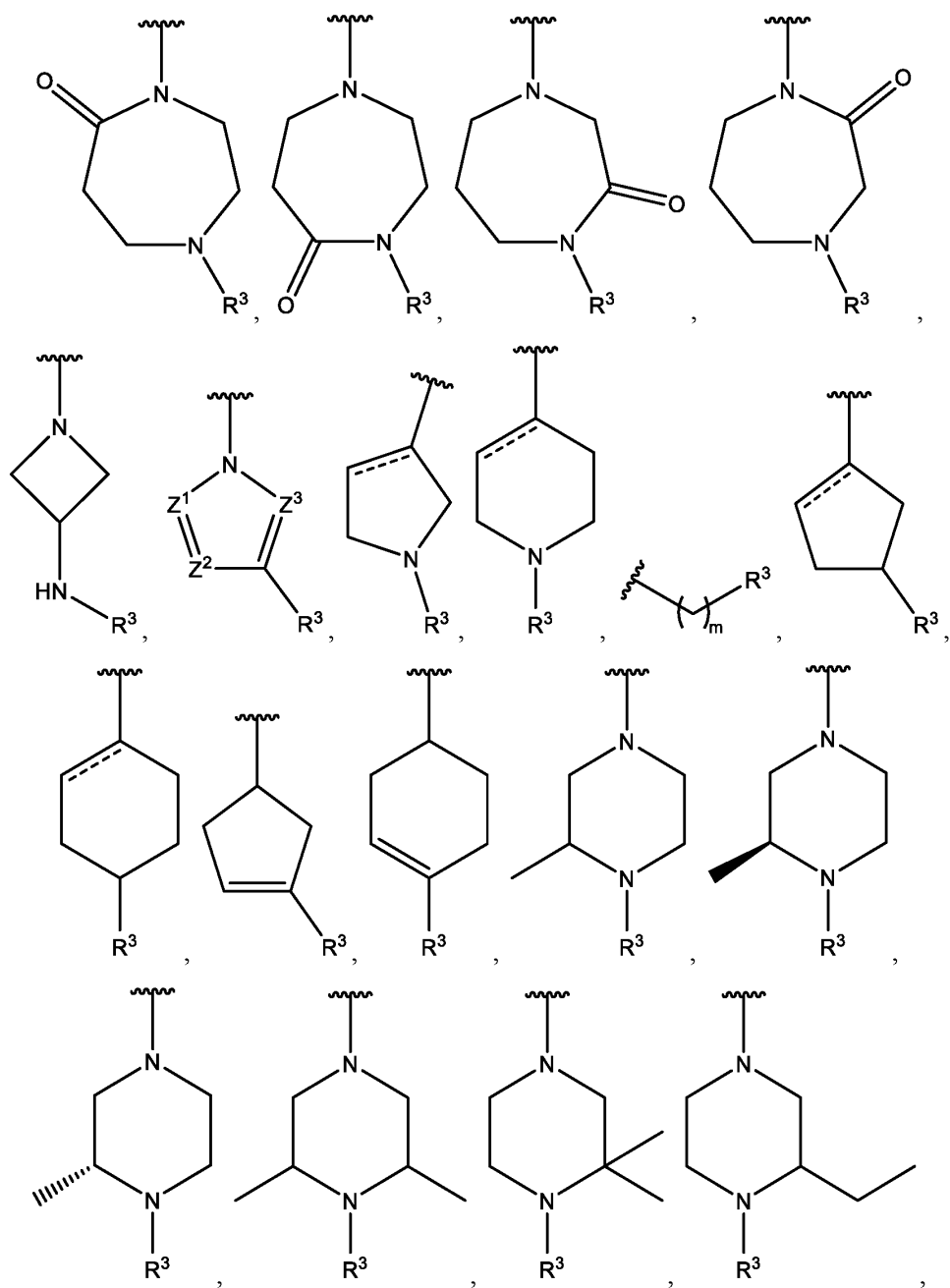
R^{10} is selected from H, C₁-C₄alkyl, C₁-C₄alkoxy, aminoC₁-C₄alkyl, hydroxyC₁-C₄alkyl, and C₁-C₄alkylsulfonyl, wherein the C₁-C₄alkyl, C₁-C₄alkoxy, aminoC₁-C₄alkyl, hydroxyC₁-C₄alkyl, and C₁-C₄alkylsulfonyl can be optionally substituted by one or more substituents selected from hydroxyl, C₁-C₄alkoxy, $NR^{10a}R^{10b}$, halo, and deuterium, wherein R^{10a} and R^{10b} are selected from hydrogen and C₁-C₄alkyl, or wherein R^{10a} and R^{10b} taken together with the nitrogen atom to which they are attached form a 4- to 8-membered ring.

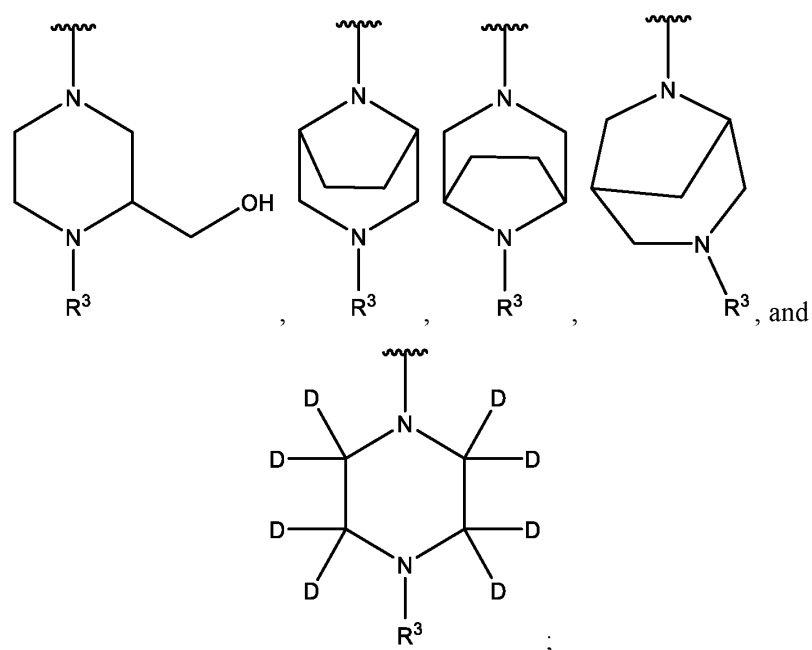
12. The compound of claim 11, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is



13. The compound of claim 11 or 12, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{10} is CH₃.
14. The compound of any one of claims 1 to 13, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is heterocyclyl optionally substituted with C₁-C₄alkyl or oxo.
15. The compound of any one of claims 1 to 14, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is substituted with one R^3 .
16. The compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is selected from:





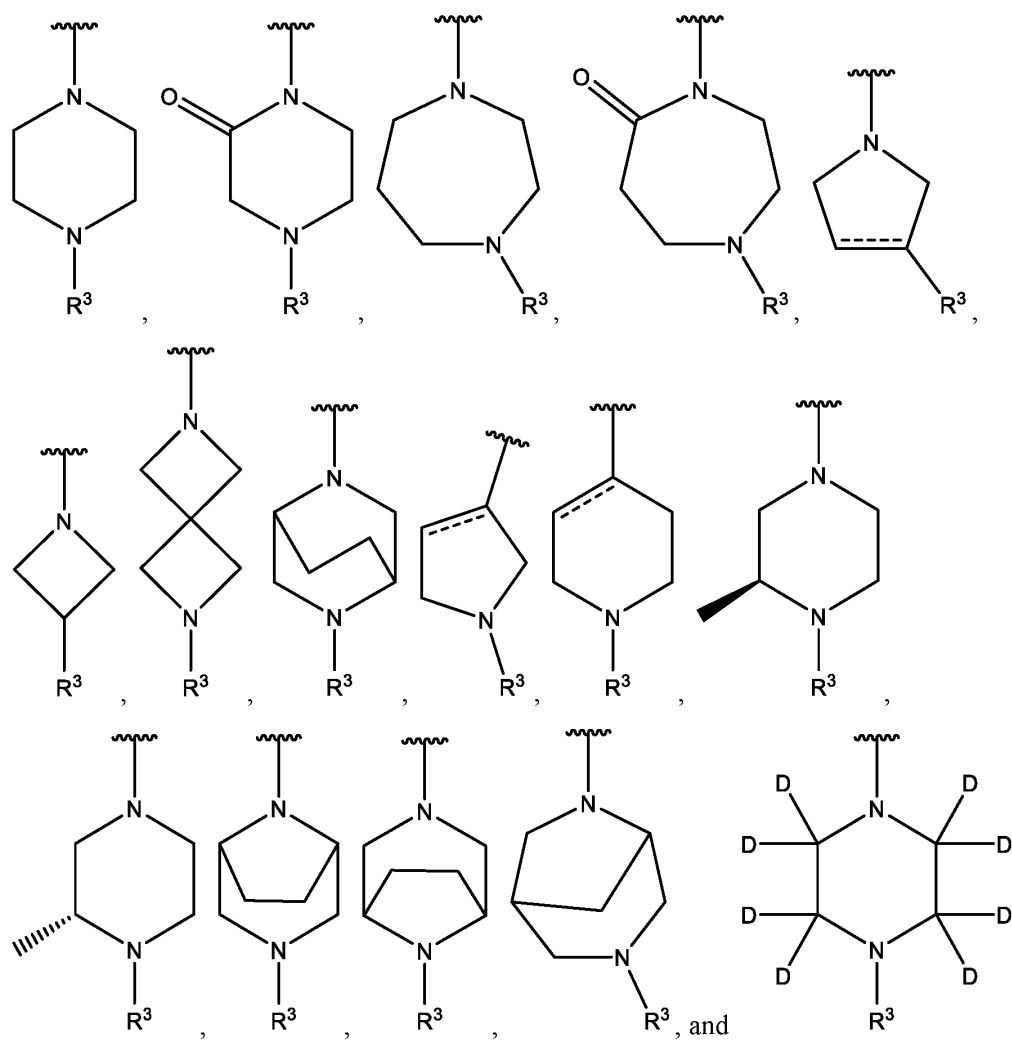


----- indicates a single bond or a double bond such that all valences are satisfied;

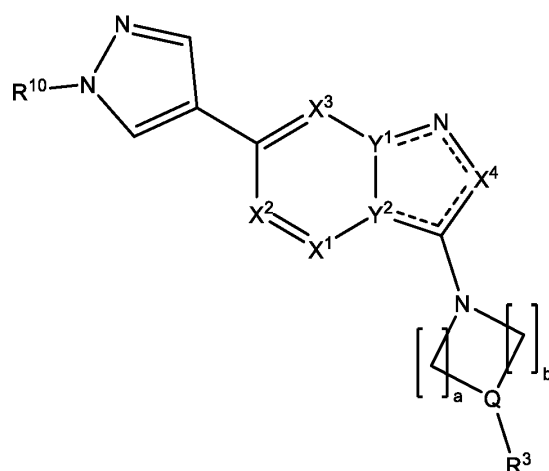
m is selected from 0, 1, 2, 3, 4, 5, and 6; and

Z^1 , Z^2 , and Z^3 are selected from N and CR^a .

17. The compound of claim 16, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is selected from:



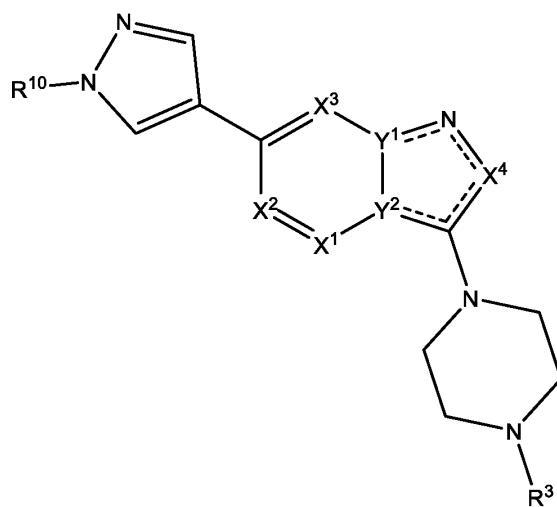
18. The compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt or solvate thereof, having Formula Ia:



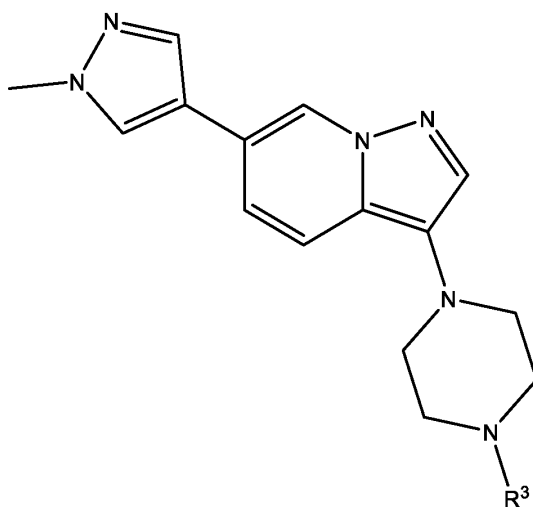
wherein a and b are each independently selected from 1, 2, and 3; and

Q is selected from -CH- and -N-, with the proviso that if Q is -N-, a and b are not 1.

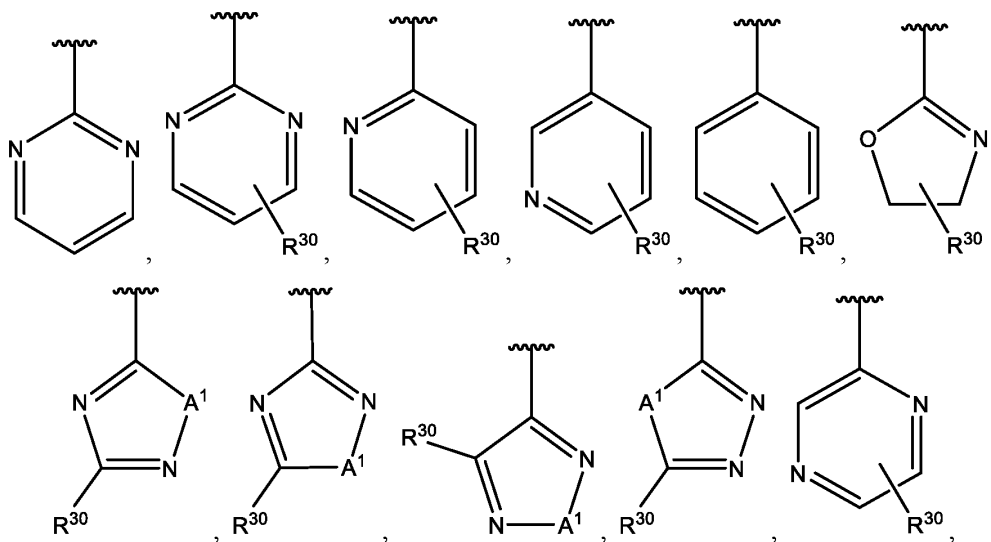
19. The compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt or solvate thereof, having Formula II:

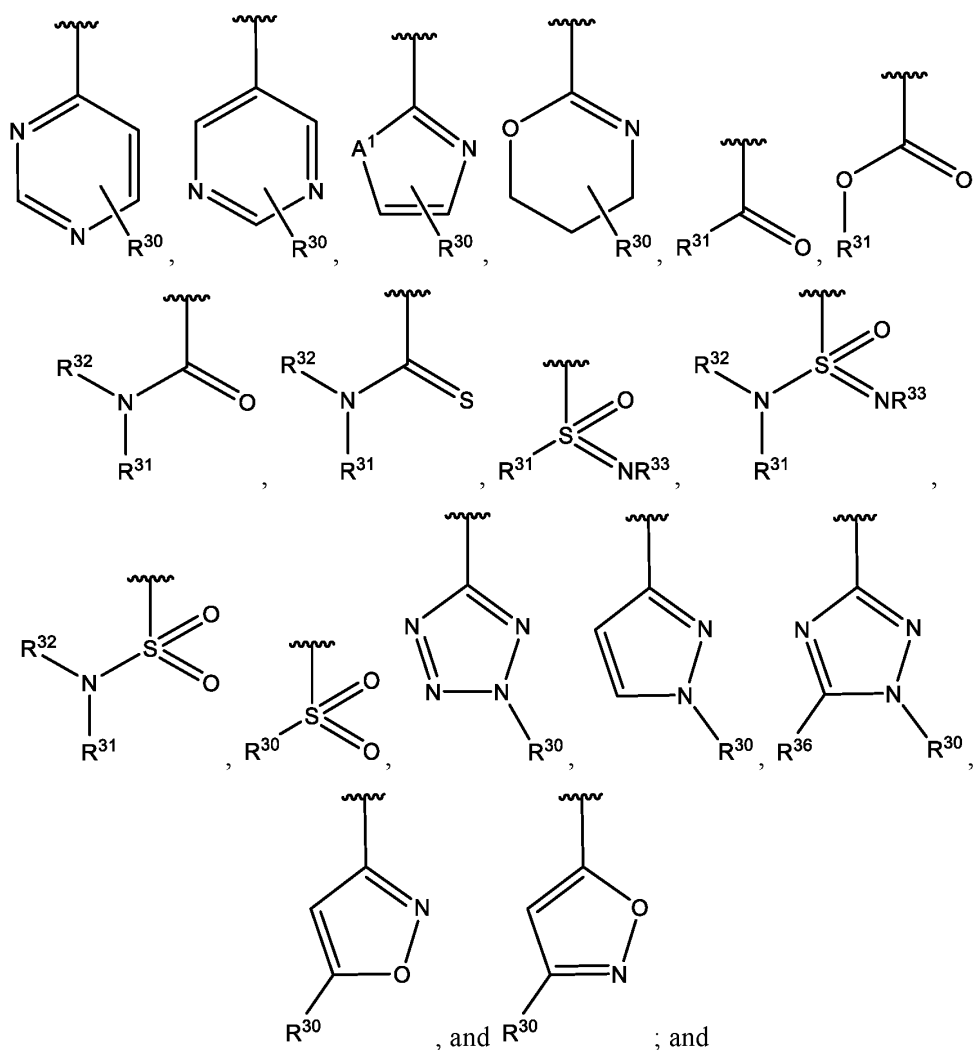


20. The compound of any one of claims 1 to 19, or a pharmaceutically acceptable salt or solvate thereof, having Formula IIa:



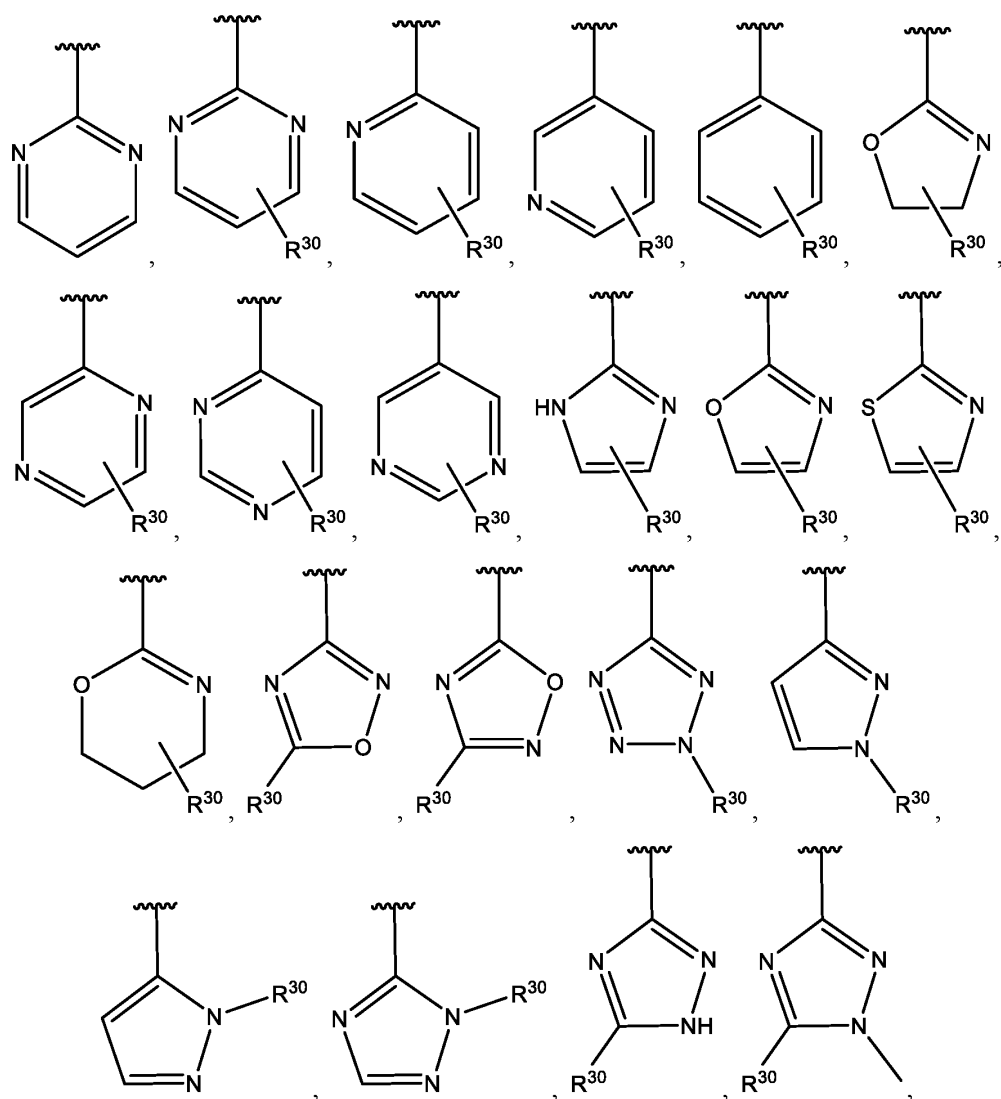
21. The compound of any one of claims 1 to 20, or a pharmaceutically acceptable salt or solvate thereof, wherein R³ is heteroaryl optionally substituted with one, two, three, four, or five R³⁰.
22. The compound of any one of claims 1 to 21, or a pharmaceutically acceptable salt or solvate thereof, wherein R³ is selected from:

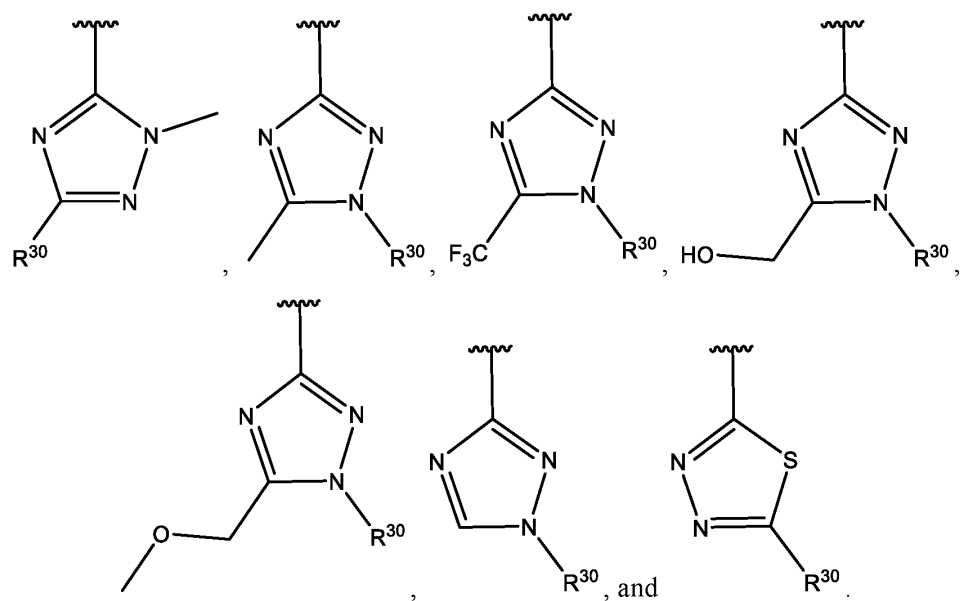




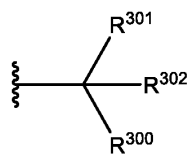
wherein A^1 is selected from O, S, and NR^{37} , R^{36} is selected from hydrogen, optionally substituted C_1 - C_6 alkyl, and optionally substituted C_1 - C_6 alkylaryl, and R^{37} is selected from hydrogen and C_1 - C_6 alkyl.

23. The compound of any one of claims 1 to 22, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is selected from:

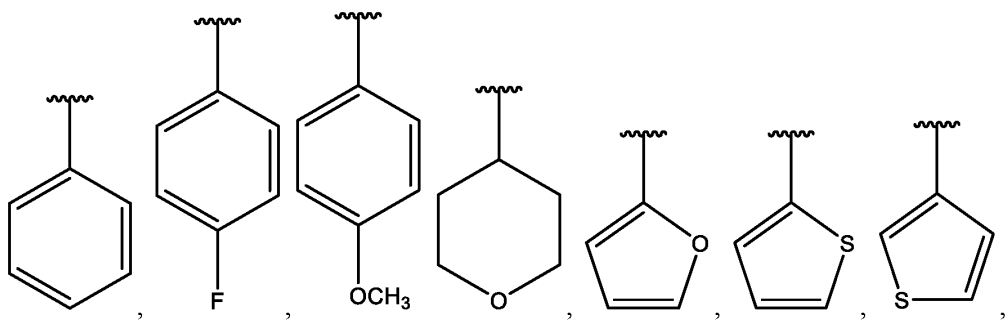


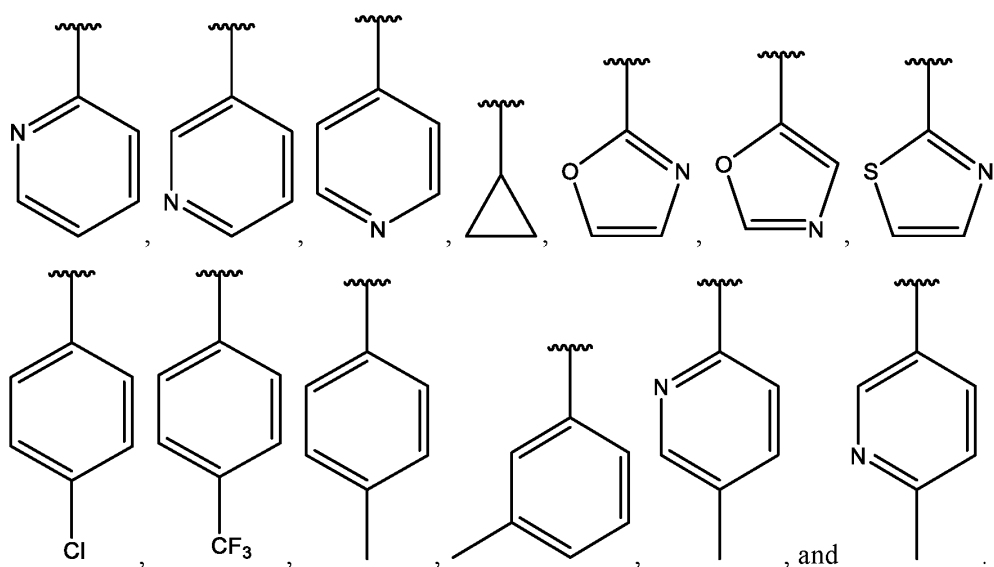


24. The compound of any of claims 1 to 23, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{30} is:

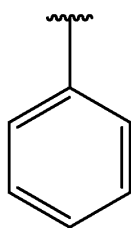


25. The compound of claim 24, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{300} is selected from:

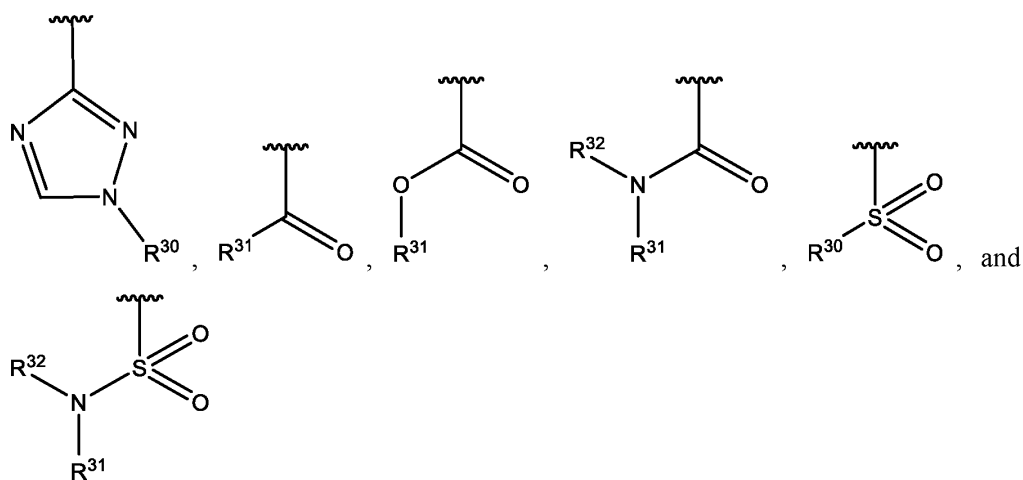




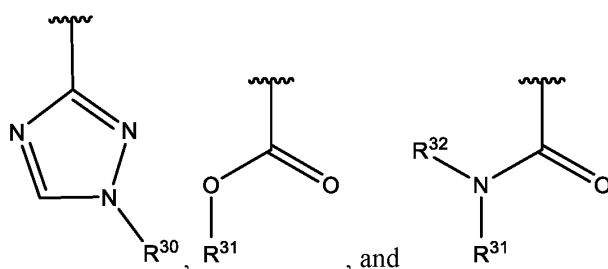
26. The compound of claim 25, or a pharmaceutically acceptable salt or solvate thereof, wherein R³⁰⁰ is:



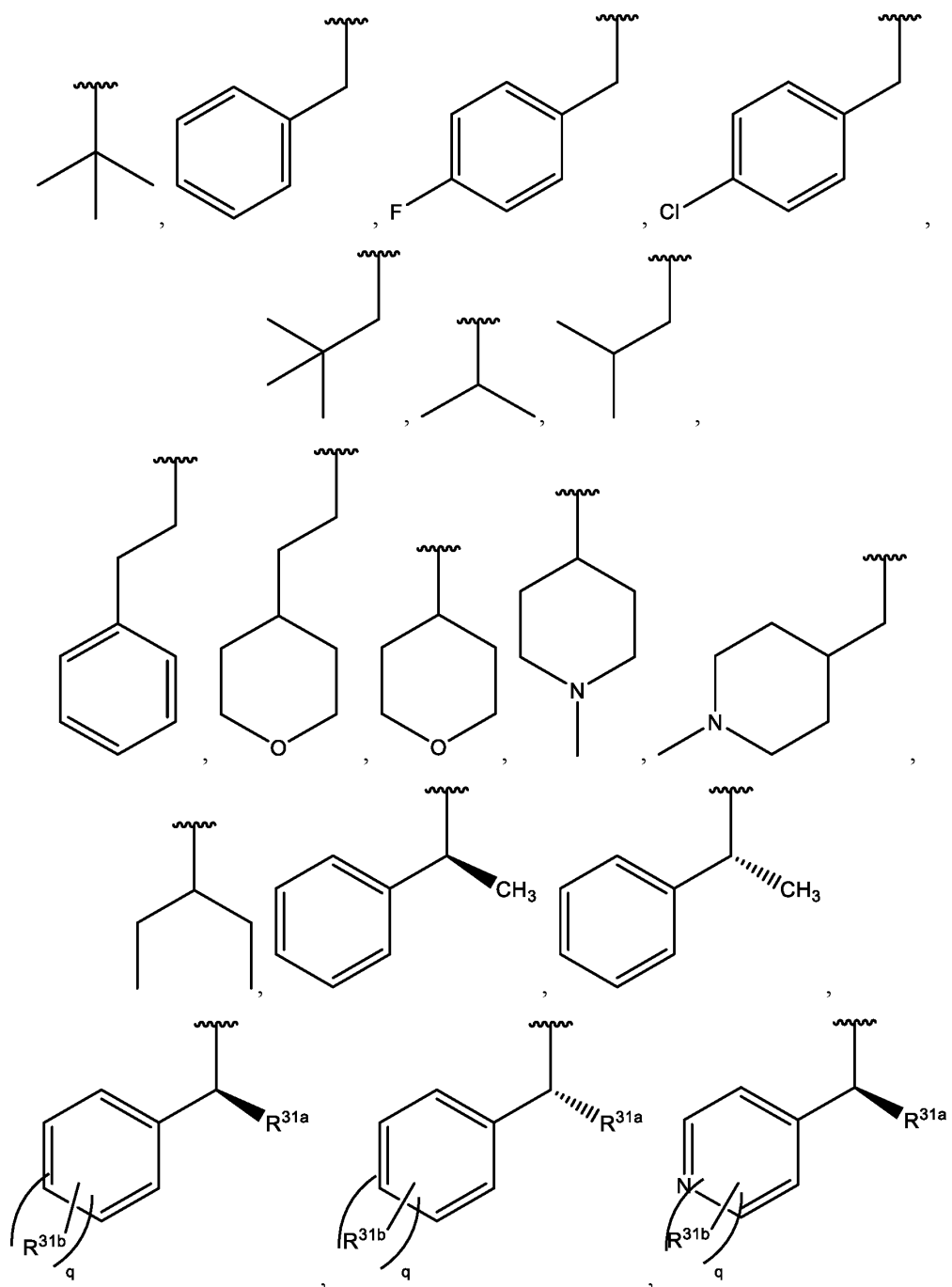
27. The compound of any one of claims 1 to 26, or a pharmaceutically acceptable salt or solvate thereof, wherein R³⁰¹ is H and R³⁰² is H or CH₃.
28. The compound of any of claims 1 to 22, or a pharmaceutically acceptable salt or solvate thereof, wherein R³ is selected from:

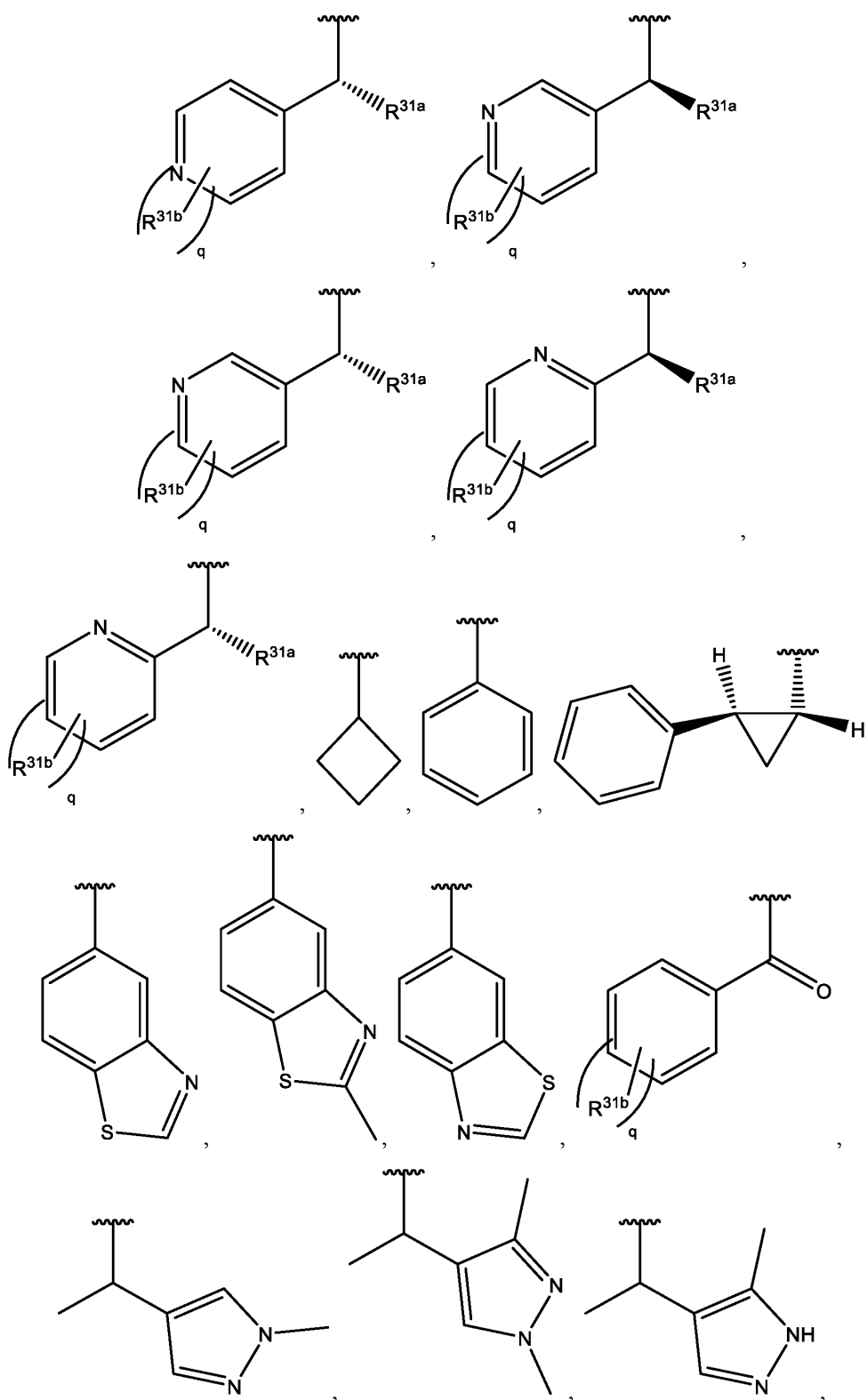


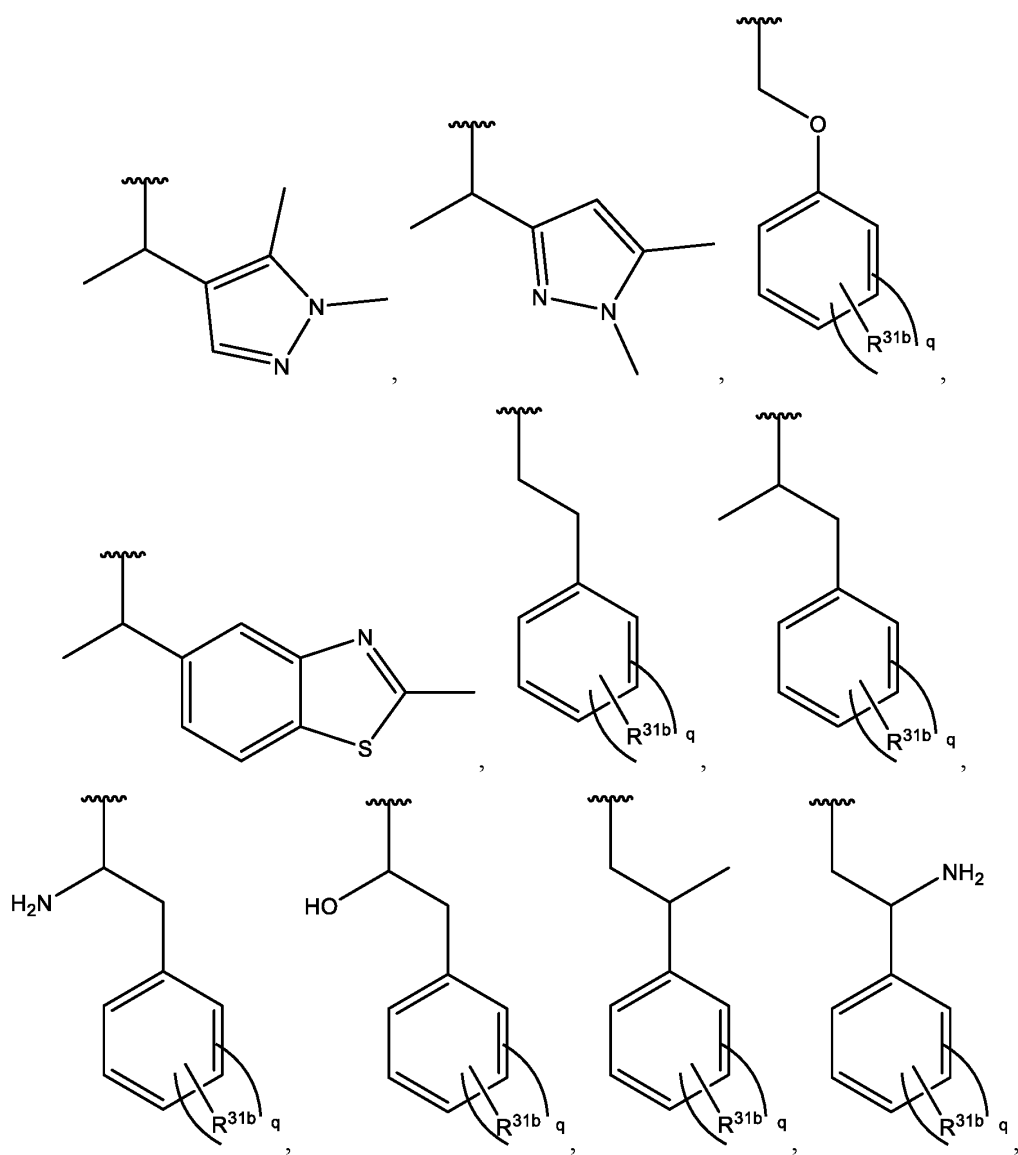
29. The compound of claim 28, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is selected from:

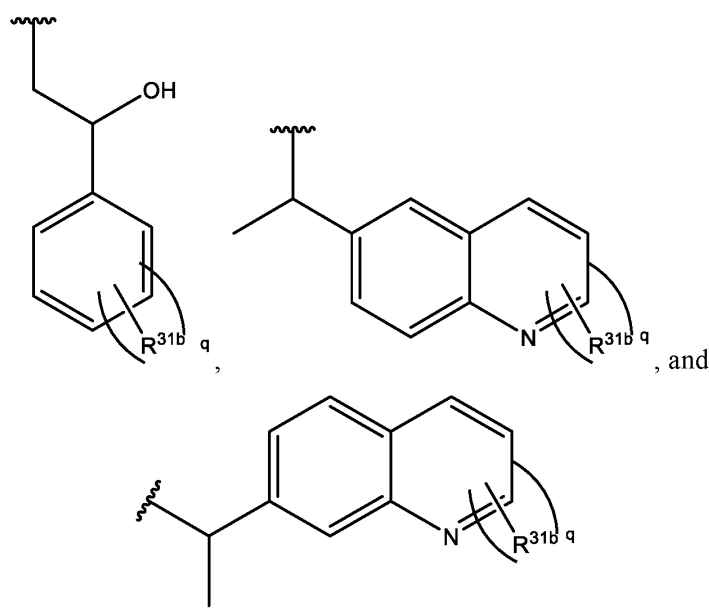


30. The compound of claim 29, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{32} is H.
31. The compound of any one of claims 28 to 30, or a pharmaceutically acceptable salt or solvate thereof, wherein R^{31} is selected from:









wherein R^{31a} is selected from H, D, alkylamino, optionally substituted C₁-C₄alkyl, C₁-C₄alkoxy, amino, and C₁-C₄haloalkyl,

each R^{31b} is independently selected from H, D, halo, hydroxy, amino, cyano, alkylamino, optionally substituted C₁-C₄alkyl, C₁-C₄haloalkyl, optionally substituted C₁-C₄alkoxy, and C₃-C₆cycloalkyl, , and q is 1, 2, or 3.

32. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, selected from any one of the compounds of Table 1.
33. The compound of any one of claims 1 to 32, or a pharmaceutically acceptable salt or solvate thereof, which can exhibit one or more of the following properties: (i) promote the differentiation of an OPC into an oligodendrocyte, (ii) promote the expression of a protein associated with oligodendrocyte differentiation and/or myelination (*e.g.*, G-protein coupled receptor 17 (GPR17), myelin basic protein (MBP), ASPA, GST-pi, CC1, myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, proteolipid protein 1 (PLP1), or a combination thereof), (iii) promote the myelination of an axon, (iv) promote the remyelination of a demyelinated axon, (v) inhibit PDGFR α kinase activity, (vi) achieve a brain to plasma ratio of greater than 0.1 when systemically administered to a subject, and (vii) any combination thereof.

34. The compound of claim 33, or a pharmaceutically acceptable salt or solvate thereof, which can inhibit PDGFR α kinase activity.
35. The compound of claim 34, or a pharmaceutically acceptable salt or solvate thereof, which can inhibit PDGFR α kinase activity with an IC₅₀ of less than 500 nM, less than 400 nM, less than 300 nM, less than 200 nM, less than 100 nM, less than 75 nM, less than less than 50 nM, less than 40 nM, less than 30 nM, less than 20 nM, less than 10 nM, less than 5 nM, less than 2.5 nM, less than 1 nM, less than 0.5 nM, or less than 0.2 nM.
36. The compound of claim 35, or a pharmaceutically acceptable salt or solvate thereof, wherein the IC₅₀ of the PDGFR α inhibitor is determined using an enzymatic PDGFR α kinase assay (*e.g.*, Promega kinase assay described in Example 131).
37. The compound of claim 36, or a pharmaceutically acceptable salt or solvate thereof, wherein the enzymatic PDGFR α kinase assay comprises 20 ng of purified PDGFR α protein, 150 μ M of ATP and 1 μ g of substrate, Poly (Glu4Tyr1) in a volume of 15 μ l.
38. A pharmaceutical composition comprising the compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.
39. A kit comprising the compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt or solvate thereof, or the composition of claim 38, and instructions for use.
40. A compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of claim 38, for use in therapy.
41. A method of treating a demyelinating disease in a subject in need thereof comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of claim 38.
42. A method of improving a subject's performance in a test for assessing one or more symptoms associated with a demyelinating disease, comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of

claim 38, wherein after the administration, the subject's performance in the test is improved as compared to a reference subject (*e.g.*, the subject prior to the administration).

43. The method of claim 42, wherein the test is one or more of a visual evoked potential (VEP) test, a multifocal visual evoked potential (mfVEP) test, a low contrast visual acuity (LCVA) test, a magnetic resonance imaging (MRI) (*e.g.*, magnetization transfer ratio (MTR), myelin water fraction (MWF), quantitative susceptibility mapping (QSM), and T2 imaging), an electromyography (EMG), a nerve conduction velocity (NCV) test, an Extended Disability Status Scale (EDSS), a timed walk test (*e.g.*, timed 25-foot walk), a Nine-Hole Peg Test (9HPT), an ocular coherence tomograph (OCT), a quality of life measure test (*e.g.*, Multiple Sclerosis Quality of Life-54 and Vision-Related Quality of Life), cognitive assessment (*e.g.*, Symbol Digit Modalities Test or Montreal Cognitive Assessment), or combinations thereof.
44. The method of any one of claims 41 to 43, wherein the demyelinating disease comprises one or more of an acute disseminated encephalomyelitis (ADEM), acute hemorrhagic leukoencephalitis, acute transverse myelitis, adrenoleukodystrophy, adrenomyeloneuropathy, Alexander disease, Alzheimer's disease, aminoacidurias, amyotrophic lateral sclerosis, anti-MAG peripheral neuropathy, anti-MOG associated spectrum, Balo concentric sclerosis, brain injury, CAMFAK syndrome, Canavan disease, carbon monoxide toxicity, central pontine myelinolysis, cerebral hypoxia, cerebral ischemia, Charcot–Marie–Tooth disease, chronic inflammatory demyelinating polyneuropathy, chronic traumatic encephalopathy, clinically isolated syndrome (CIS), congenital cataract, copper deficiency associated condition, delayed post-hypoxic leukoencephalopathy, diffuse cerebral sclerosis of Schilder, diffuse myelinoclastic sclerosis, extrapontine myelinolysis Gaucher disease, Guillain–Barré syndrome, hereditary neuropathy, hereditary neuropathy with liability to pressure palsy, HTLV-1–associated myelopathy, Hurler syndrome, hypomyelination, hypoxic brain injury, Krabbe disease, Leber hereditary optic atrophy and related mitochondrial disorders, leukodystrophic disorders, Marchiafava-Bignami disease, metachromatic leukodystrophy, multiple sclerosis (*e.g.*, primary progressive multiple sclerosis (PPMS), relapsing-remitting multiple sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS), progressive relapsing multiple sclerosis, Marburg multiple sclerosis, tumefactive multiple sclerosis, and optic-

spinal multiple sclerosis), multiple system atrophy, myelinoclastic disorders, myelopathy, nerve injury, neuromyelitis optica (NMO), Niemann-Pick disease, optic neuropathy, optic neuritis (*e.g.*, acute optic neuritis and chronic relapsing inflammatory optic neuritis (CRION)), osmotic demyelination syndrome, Parkinson's disease, Pelizaeus-Merzbacher disease, peripheral neuropathy, phenylketonuria, progressive inflammatory neuropathy, progressive multifocal leukoencephalopathy, progressive subcortical ischemic demyelination, reperfusion injury, Schilder disease, solitary sclerosis, spinal cord injury, subacute sclerosing panencephalitis, Tabes dorsalis, Tay-Sachs disease, transverse myelitis, traumatic brain injury, tropical spastic paraparesis, vitamin B12 deficiency, and cerebral palsy.

45. The method of any one of claims 41 to 44, wherein the demyelinating disease is characterized by demyelination of one or more cells within the CNS of the subject.
46. The method of any one of claims 41 to 45, wherein the demyelinating disease is multiple sclerosis.
47. The method of claim 46, wherein the multiple sclerosis comprises a clinically isolated syndrome ("CIS"), relapsing-remitting MS ("RRMS"), secondary progressive MS ("SPMS"), primary progressive MS ("PPMS"), optic neuritis or transverse myelitis.
48. The method of any one of claims 41 to 45, wherein the demyelinating disease is an optic neuritis.
49. The method of any one of claims 41 to 48, wherein treating the demyelinating disease comprises reducing one or more symptoms associated with the demyelinating disease.
50. The method of claim 49, wherein the one or more symptoms comprise one or more of fatigue, dizziness, malaise, elevated fever and high body temperature, extreme sensitivity to cold in the hands and feet, weakness and stiffness in muscles and joints, weight changes, digestive or gastrointestinal problems, low blood pressure, high blood pressure, irritability, anxiety, depression, impaired vision (*e.g.*, blurred vision, double vision, reduction in low contrast visual acuity (LCVA)), ataxia, clonus, spasms, dysarthria, weakness, clumsiness, hand paralysis, hemiparesis, genital anesthesia, sexual dysfunction, incoordination, paresthesias, ocular paralysis, impaired muscle coordination, loss of sensation, tingling,

numbness, pain, neurological symptoms, impaired cognition, unsteady gait, balance problems, dizziness, spastic paraparesis, incontinence, hearing problems, speech problems, loss of olfaction, and agusia.

51. A method of promoting the myelination of an axon in a subject in need thereof, the method comprising administering to the subject an effective amount of the compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of claim 38.
52. The method of claim 51, wherein promoting the myelination of an axon results in an increase in the expression of one or more of the following markers within the subject: myelin basic protein (MBP) Myelin Oligodendrocyte Glycoprotein (MOG), Oligodendrocyte Specific Protein/Claudin-11, CNPase, proteolipid protein 1 (PLP1), or any combination thereof.
53. The method of claim 51 or 52, wherein the myelination of an axon can be determined by visualizing and/or quantifying the expression of one or more of the following markers: myelin basic protein (MBP) Myelin Oligodendrocyte Glycoprotein (MOG), Oligodendrocyte Specific Protein/Claudin-11, CNPase, proteolipid protein 1 (PLP1), or any combination thereof.
54. A method of promoting the remyelination of a demyelinated axon in a subject in need thereof, the method comprising administering to the subject an effective amount of the compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of claim 38.
55. The method of claim 54, wherein promoting the remyelination of a demyelinated axon results in an increase in the expression of one or more of the following markers within the subject: myelin basic protein (MBP) Myelin Oligodendrocyte Glycoprotein (MOG), Oligodendrocyte Specific Protein/Claudin-11, CNPase, proteolipid protein 1 (PLP1), or any combination thereof.
56. The method of claim 54 or 55, wherein the remyelination of a demyelinated axon can be determined by visualizing and/or quantifying the expression of one or more of the following markers: myelin basic protein (MBP) Myelin Oligodendrocyte Glycoprotein (MOG),

Oligodendrocyte Specific Protein/Claudin-11, CNPase, proteolipid protein 1 (PLP1), or any combination thereof.

57. A method of reducing the demyelination of a myelinated neuronal axon in a subject in need thereof, the method comprising administering to the subject an effective amount of the compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of claim 38.
58. The method of claim 57, wherein reducing the demyelination of a myelinated neuronal axon results in an increase in the expression of one or more of the following markers: myelin basic protein (MBP) Myelin Oligodendrocyte Glycoprotein (MOG), Oligodendrocyte Specific Protein/Claudin-11, CNPase, proteolipid protein 1 (PLP1), or any combination thereof.
59. The method of claim 57 or 58, wherein the reduction in the demyelination of a myelinated neuronal axon can be determined by visualizing and/or quantifying the expression of one or more of the following markers: myelin basic protein (MBP) Myelin Oligodendrocyte Glycoprotein (MOG), Oligodendrocyte Specific Protein/Claudin-11, CNPase, proteolipid protein 1 (PLP1), or any combination thereof.
60. A method of activating an oligodendrocyte progenitor cell (OPC) within the central nervous system (CNS) of a subject in need thereof, the method comprising administering to the subject an effective amount of the compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of claim 38.
61. A method according to any one of claims 51 to 60, wherein the subject has, or is at risk of developing a demyelinating disease, for example a disease according to any one of claims 44 to 50.
62. A method according to any one of claims 51 to 60, wherein the method is a method of treating or preventing a demyelinating disease, for example a disease according to any one of claims 44 to 50.

63. The method of any one of claims 41 to 62, wherein the compound or the pharmaceutical composition is administered to the subject once.
64. The method of any one of claims 41 to 62, wherein the compound or the pharmaceutical composition is administered to the subject more than once using intermittent dosing.
65. The method of claim 64, wherein the intermittent dosing comprises administering the compound or the pharmaceutical composition to the subject every other day, every three days, every four days, every five days, every six days, once a week, every eight days, every nine days, every 10 days, every 11 days, every 12 days, every 13 days, once every two weeks, once every three weeks, once a month, once every two months, once every three months, once every four months, once every five months, once every six months, or once every twelve months.
66. The method of claim 64 or 65, wherein the intermittent dosing comprises administering to the subject a first dose and a second dose of the compound or the pharmaceutical composition, wherein the second dose is administered at least one day, at least two days, at least three days, at least four days, at least five days, at least six days, at least seven days, at least eight days, at least nine days, at least 10 days, at least 11 days, at least 12 days, at least 13 days, at least two weeks, at least three weeks, at least one month, at least two months, at least three months, at least four months, at least five months, at least six months, or at least 12 months after administering the first dose.
67. The method of claim 66, wherein the second dose is administered to the subject one day, two days, three days, four days, five days, six days, seven days, eight days, nine days, 10 days, 11 days, 12 days, 13 days, two weeks, three weeks, one month, two months, three months, four months, five months, six months, or 12 months after administering the first dose.
68. The method of any one of claims 41 to 67, wherein after the administration, the compound or the pharmaceutical composition can achieve a brain to plasma ratio of greater than 0.1, greater than 0.2, greater than 0.3, greater than 0.4, greater than 0.5, greater than 0.6, greater than 0.7, greater than 0.8, greater than 0.9, greater than 1.0, greater than 1.1, greater than 1.2, greater than 1.3, greater than 1.4, greater than 1.5, greater than 1.6, greater than 1.7, greater than 1.8, greater than 1.9, or greater than 2.0.

69. The method of any one of claims 41 to 68, further comprising administering to the subject an additional therapeutic agent.
70. The method of claim 69, wherein the additional therapeutic agent comprises a standard care of treatment.
71. The method of claim 69 or 70, wherein the additional therapeutic agent comprises an immunomodulatory agent.
72. The method of claim 71, wherein the additional therapeutic agent is selected from interferon beta-1b, interferon beta-1a, peginterferon beta-1a, alemtuzumab, natalizumab, ocrelizumab, ofatumumab, ublituximab-xiiy, glatiramer acetate, teriflunomide, dimethyl fumarate, monomethyl fumarate, diroximel fumarate, fingolimod hydrochloride, siponimod fumaric acid, ozanimod hydrochloride, ponesimod, cladribine, mitoxantrone, a BTK inhibitor, a statin, or a pharmaceutically acceptable salt thereof.
73. The method of any one of claims 69 to 72, wherein the additional therapeutic agent is administered to the subject prior to, concurrently, or after the administration of the compound or the pharmaceutical composition.
74. A method of inducing the differentiation of an oligodendrocyte progenitor cell (OPC) into an oligodendrocyte, the method comprising contacting the OPC with an effective amount of the compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of claim 38.
75. The method of claim 74, wherein inducing the differentiation of the OPC into an oligodendrocyte results in an increase in the expression of the following markers in the subject: GPR17, MBP, ASPA, GST-pi, CC1, myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, proteolipid protein 1 (PLP1), or a combination thereof.
76. The method of claim 74 or 75, wherein the differentiation of the OPC into an oligodendrocyte is measured by determining the expression of GPR17, MBP, ASPA, GST-pi, CC1, myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, proteolipid protein 1 (PLP1), or a combination thereof.

77. A method of inhibiting PDGFR α activity in a cell, the method comprising contacting the cell with an effective amount of the compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of claim 38.
78. The method of claim 77, wherein the inhibition of the PDGFR α activity is measured by one or more of the following: an *in vitro* OPC differentiation assay (e.g., as described in Example 132), a cuprizone model for demyelination, an *in vivo* OPC differentiation assay (e.g., as described in Example 134), an enzymatic PDGFR α kinase assay (e.g., as described in Example 131), or any combination thereof.
79. The method of any one of claims 74 to 78, wherein the contacting occurs *ex vivo* or *in vivo*.
80. The method of any one of claims 74 to 79, wherein the method is a method of treating by a therapy.
81. A method of treating a relapsing form of multiple sclerosis in a subject in need thereof, the method comprising administering to the subject an effective amount of the compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of claim 38.
82. The method of claim 81, wherein inducing the differentiation of the OPC into an oligodendrocyte results in an increase in the expression of the following marker in the subject: GPR17, MBP, ASPA, GST-pi, CC1, myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, proteolipid protein 1 (PLP1), or a combination thereof.
83. The method of claim 81 or 82, wherein the differentiation of the OPC into an oligodendrocyte is measured by determining the expression of GPR17, MBP, ASPA, GST-pi, CC1, myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, proteolipid protein 1 (PLP1), or a combination thereof.
84. The method of any one of claims 81 to 83, wherein the relapsing form of multiple sclerosis comprises a clinically isolated syndrome ("CIS"), relapsing-remitting MS ("RRMS"),

secondary progressive MS ("SPMS"), primary progressive MS ("PPMS"), or transverse myelitis.

85. The compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of claim 38, for use in a method of one or more of the following: (i) promote the differentiation of an OPC into an oligodendrocyte, (ii) promote the expression of a protein associated with oligodendrocyte differentiation and/or myelination (*e.g.*, G-protein coupled receptor 17, myelin basic protein (MBP), ASPA, GST-pi, CC1, myelin oligodendrocyte glycoprotein (MOG), oligodendrocyte-specific protein/claudin-11, CNPase, proteolipid protein 1 (PLP1), or a combination thereof), (iii) promote the myelination of an axon, (iv) promote the remyelination of a demyelinated axon, (v) inhibit PDGFR α kinase activity, (vi) achieve a brain to plasma ratio of greater than 0.1 when systemically administered to a subject, and (vii) any combination thereof.
86. A method of treating a PDGF-associated tumor in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1 to 37, or a pharmaceutically acceptable salt or solvate thereof, or the pharmaceutical composition of claim 38, wherein after the administration, PDGFR α activity is reduced in the subject.
87. The method of claim 86, wherein the PDGF-associated tumor comprises an oligodendroglioma.
88. The method of claim 86 or 87, wherein the method is a method of treatment by therapy.