TRIAZOLOPYRIDINYL COMPOUNDS AS KINASE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 63/585,635 filed September 27, 2023, the disclosure of which are incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to novel compounds that inhibit receptor interacting protein kinases and methods of making and using the same. Specifically, the present invention relates to triazolopyridinyl compounds as receptor interacting protein kinase 1 (RIPK1) inhibitors.

BACKGROUND OF THE INVENTION

Apoptosis and necrosis represent two different mechanisms of cell death. Apoptosis is a highly regulated process involving the caspase family of cysteine proteases, and characterized by cellular shrinkage, chromatin condensation, and DNA degradation. In contrast, necrosis is associated with cellular and organelle swelling and plasma membrane rupture with ensuing release of intracellular contents and secondary inflammation (Kroemer et al., (2009) Cell Death Differ 16:3-11). Necrosis has been considered a passive, unregulated form of cell death; however, recent evidence indicates that some necrosis can be induced by regulated signal transduction pathways such as those mediated by receptor interacting protein kinases (RIPKs) especially in conditions where caspases are inhibited or cannot be activated efficiently (Golstein P & Kroemer G (2007) Trends Biochem. Sci. 32:37-43; Festjens et al. (2006) Biochim. Biophys. Acta 1757:1371-1387). Stimulation of the Fas and TNFR family of death domain receptors (DRs) is known to mediate apoptosis in most cell types through the activation of the extrinsic caspase pathway. In addition, in certain cells deficient for caspase-8 or treated with pan-caspase inhibitor Z-VAD, stimulation of death domain receptors (DR) causes a receptor interacting protein kinase 1 (RIPK1) dependent programmed necrotic cell death instead of apoptosis (Holler et al. (2000) Nat. Immunol. 1:489-495; Degterev et al. (2008) Nat. Chem. Biol. 4:313-321). This novel mechanism of cell death is termed

"programmed necrosis" or "necroptosis" (Degterev et al., (2005) Nat Chem Biol 1:112-119).

Necroptosis can be triggered by a number of mechanisms including of TNF receptor activation, Toll-like receptor engagement, genotoxic stress and viral infection. Downstream of the various stimuli, the signaling pathway that results in necroptosis is dependent on RIPK1 and RIPK3 kinase activity. (He et al., (2009) Cell 137:1100-1111; Cho et. al., (2009) Cell 137:1112-1123; Zhang et al., (2009) Science 325:332-336).

Dysregulation of the necroptosis signaling pathway has been linked to neuroinflammation and neurodegeneration such as multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Parkinson's and Alzheimer's disease, spinal cord injury, and traumatic brain injury (TBI), detachment of the retina, ischemia, Gaucher's disease, and AAV (ANCA-associated vasculitis) and other inflammatory diseases such as macrophage necrosis in atherosclerosis development, virus induced inflammation, systemic inflammatory response syndrome and ethanol induced liver injury - (Yan et al., (2019) Nature Rev. Neuro. 20, 19-33; Trichonas et al., (2010) Proc. Natl. Acad. Sci. 107, 21695-21700; Lin et al., (2013) Cell Rep. 3, 200-210; Cho et al., (2009) Cell, 137, 1112-1123; Duprez et al., (2011) Immunity 35, 908-918; Roychowdhury et al., Hepatology 57, 1773-1783; Vandenabeele et al., (2010) Nature 10, 700-714; Vandenabeele et al., (2010) Sci. Signaling 3, 1-8; Zhang et al., (2010) Cellular & Mol. Immunology 7, 243-249; Moriwaki et al., (2013) Genes Dev. 27, 1640-1649; Ito et al., (2016) Science 353, 603-608; Vitner et al., (2014) Nature Med. 20, 204-208) (Schreiber et al., (2017) Proc. Natl. Acad. Sci. 114, E9618-E9625). To be useful in the treatment of neurodegenerative diseases, compounds should preferably be brain penetrant. Brain penetrance can be predicted by a brain transporter assay and measured through direct determination of brain concentration.

A potent, selective, small molecule inhibitor of RIPK1 activity would block RIPK1-dependent pro-inflammatory signaling and thereby provide a therapeutic benefit in inflammatory diseases characterized by increased and/or dysregulated RIPK1 kinase activity.

SUMMARY OF THE INVENTION

The present invention provides novel triazolopyridinyl compounds including stereoisomers, tautomers, isotopes, prodrugs, pharmaceutically acceptable salts, salts, or solvates thereof, which are useful as inhibitors of RIPK1.

The present invention also provides processes and intermediates for making the compounds of the present invention.

The present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention or stereoisomers, tautomers, isotopes, prodrugs, pharmaceutically acceptable salts, salts, or solvates thereof.

The compounds of the invention may be used in the treatment and/or prophylaxis of conditions associated with aberrant RIPK1 activity.

The compounds of the present invention may be used in therapy.

The compounds of the present invention may be used for the manufacture of a medicament for the treatment and/or prophylaxis of a condition associated with aberrant RIPK1 activity.

In another aspect, the present invention is directed to a method of treating diseases mediated at least partially by RIPK1 including inflammatory diseases and neurological inflammatory diseases, which method comprises administering to a patient in need of such treatment a compound of the present invention as described above.

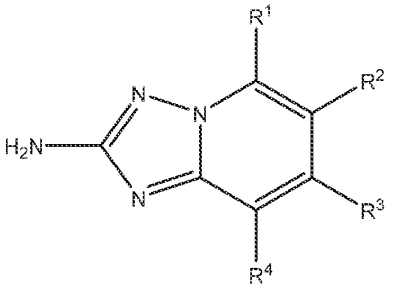
In another aspect, the present invention is directed to a method of treating diseases mediated at least partially by RIPK1 including inflammatory diseases and neurological inflammatory diseases, such as multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Parkinson's and Alzheimer's disease, spinal cord injury, and traumatic brain injury (TBI), detachment of the retina, ischemia, Gaucher's disease, and AAV (ANCA-associated vasculitis) and other inflammatory diseases such as macrophage necrosis in atherosclerosis development, virus induced inflammation, systemic inflammatory response syndrome and ethanol induced liver injury, which method comprises administering to a patient in need of such treatment a compound of the present invention as described above.

The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more, or with one to two other agent(s).

These and other features of the invention will be set forth in expanded form as the disclosure continues.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

In one aspect, the present invention provides, *inter alia*, compounds of Formula (I) or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

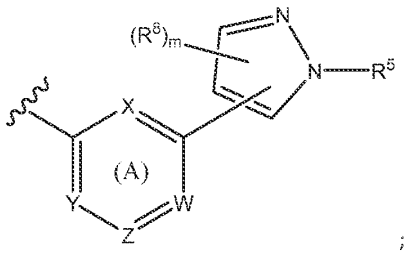


(I)

wherein, independently for each occurrence:

R^1 is –H, -T, -F, -OH, C_{1-3} alkyl, or C_{1-3} alkoxy;

one of R^2 or R^3 is -H, -T, -F, $-OCH_3$, or C_{1-3} alkyl; and the other is



;

W and Y are –N= or –C(R^{10})=;

Z is –N= or –C(R^{11})=;

X is –N= or –C(R^9)=;

wherein ring A contains 0-2 nitrogen atoms;

R^4 is −H, −F, -OH, C_{1-3} alkyl, or C_{1-3} alkoxy;

R^5 is, $-(CR^aR^b)-(CR^cH)_n-R^{5a}$, or $-(CR^aR^b)-(CO)-R^{5a}$;

n, at each occurrence, is independently 0 or 1;

R^a is -H, -D, F, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl substituted with 0-2 -F or C_{1-3} alkyl, C_{1-3} deuteroalkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{2-4} alkoxyalkyl, or oxetanyl;

R^b is -H, -D, or C_{1-3} alkyl;

alternatively, R^a and R^b, along with the carbon to which they are attached, join to form a C_{3-6} cycloalkyl substituted with 0-2 -F;

R^c is -H, C_{1-3} alkyl, or -OH;

R^{5a} is C_{6-10} carbocycle or a 5-6 membered heterocycle, the carbocycle or heterocycle being substituted with 0-3 R^6;

R^6 is H, -T, -F, $-^{18}F$, -Cl, −I, −CN, C_{1-3} alkyl, C_{1-3} alkoxy, nitro, C_{1-3} haloalkyl, or C_{1-3} haloalkoxy;

R^8 is −H, -T, -halo, -CN, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} haloalkyl;

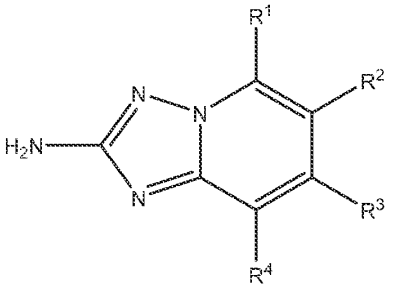
R^9 is −H, -halo, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} haloalkyl;

R^{10} is −H, -T, -halo, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} haloalkyl;

R^{11} is −H, -CN, $-C(O)NH_2$, - C(O)OH, -halo, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} haloalkyl; and

m is 0 or 1.

In another aspect, the present invention provides compounds of Formula (I) or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

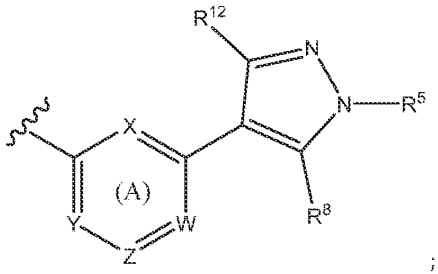


(I)

wherein, independently for each occurrence:

R^1 is –H, C_{1-3} alkyl, or C_{1-3} alkoxy;

one of R^2 or R^3 is -H and the other is



;

W and Y are –N= or –C(R^{10})=;

Z is –N= or –C(R^{11})=;

X is –N= or –C(R^9)=;

wherein ring A contains 0-2 nitrogen atoms;

R^4 is –H, –F, C_{1-3} alkyl, or C_{1-3} alkoxy;

R^5 is, -(CR^a R^b)$_n$-(CR^cH)$_n$-R^{5a}, or -(CR^a R^b)$_n$-(CO)-R^{5a};

n, at each occurrence, is independently 0 or 1;

R^a is -H, -D, -F, C_{1-3} alkyl, C_{3-6} cycloalkyl, cyclopropyl, C_{1-3} deuteroalkyl, C_{1-3} haloalkyl, or C_{1-3} hydroxyalkyl;

R^b is -H, -D, or C_{1-3} alkyl;

R^c is -H, C_{1-3} alkyl, or -OH;

R^{5a} is C_{6-10} carbocycle or a 5-6 membered heterocycle, the carbocycle or heterocycle being substituted with 0-3 R^6;

R^6 is H, -F, -Cl, –I, –CN, C_{1-3} alkyl, C_{1-3} alkoxy, nitro, C_{1-3} haloalkyl, or C_{1-3} haloalkoxy;

R^8 is –H, -halo, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} haloalkyl;

R^9 is –H, -halo, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} haloalkyl;

R^{10} is –H, -halo, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} haloalkyl;

R^{11} is –H, -halo, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} haloalkyl; and

R^{12} is –H, -halo, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} haloalkyl.

Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

X and Z are N;

Y is $C(R^{10})$; and

W is $C(R^{10})$.

Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

X is N;

Y is $C(R^{10})$;

Z is $C(R^{11})$; and

W is $C(R^{10})$;

Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

X is $C(R^9)$;

Y is $C(R^{10})$;

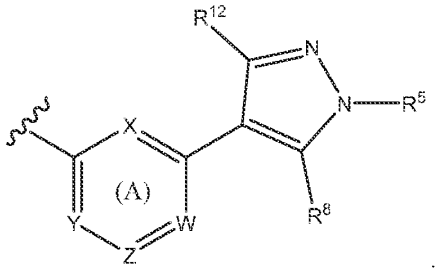
Z is $C(R^{11})$; and

W is $C(R^{10})$;

Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R^2 is H; and

R^3 is



Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R^{5a} is phenyl, pyridyl, oxanyl, tetrahydronaphthalene, or dihydroindene, any of which are substituted with 0-2 R^6; and

R^6 is H, -F, -Cl, −CN, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} haloalkyl.

Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R^5 is $-(CR^a R^b)_n-(CR^cH)_n-R^{5a}$; and

R^a is -H, -D, C_{1-3} alkyl, C_{1-3} alkoxy, or $-CF_3$.

Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R^5 is $-(CR^a R^b)-(CR^cH)-R^{5a}$, $-(CR^aR^b)-R^{5a}$, or $-(CH_2)-(CH_2)-R^{5a}$.

Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R^8 is H;

R^9 is H or F;

R^{10} is H, F, Cl, CH_3, or OCH_3;

R^{11} is H, F, Cl, or CF_3; and

R^{12} is H.

Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R^4 is H;

R^8 is H;

R^9 is H or F;

R^{10} is H or F;

R^{11} is H; and

R^{12} is H.

Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

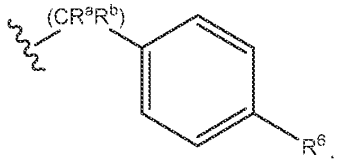
R^5 is $-(CR^aR^b)-R^{5a}$;

R^{5a} is phenyl or pyridyl, any of which are substituted with 0-2 R^6;

R^6 is H, -F, -Cl, CH_3, or OCH_3.

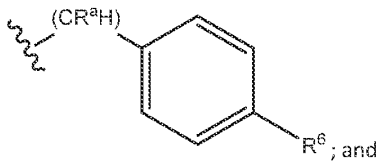
Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R^5 is



Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

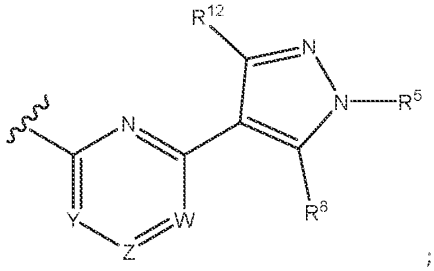
R^5 is



R^a is H, CH_3, CH_2CH_3, or $(CF_2)CH_3$.

Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R^3 is



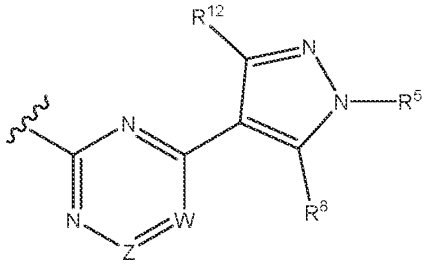
;

W and Y are $-C(R^{10})=$;

Z is $-C(R^{11})=$.

Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R^3 is

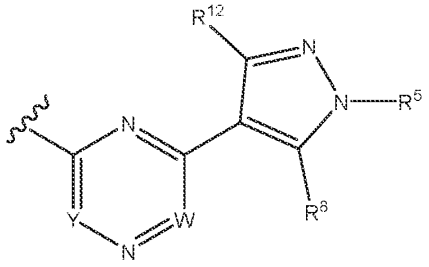


W is $-C(R^{10})=$;

Z is $-N=$ or $-C(R^{11})=$.

Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

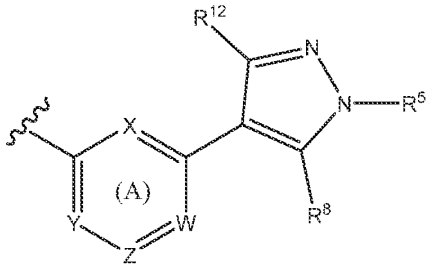
R^3 is



W and Y are $-C(R^{10})=$.

Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R^3 is



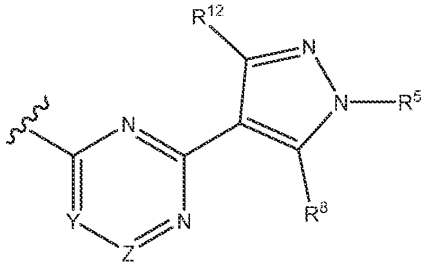
W and Y are $-N=$ or $-C(R^{10})=$;

Z is $-N=$ or $-C(R^{11})=$;

X is $-N=$ or $-C(R^{9})=$;

Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R^3 is



Y is $-C(R^{10})=$; and

Z is $-C(R^{11})=$.

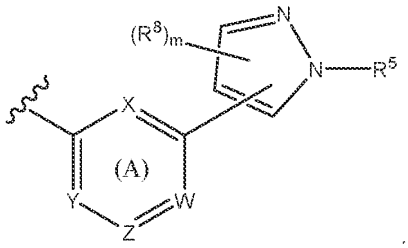
Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R^1 is $-H$ or C_{1-3} alkyl; and

R^4 is $-H$, $-F$, C_{1-3} alkyl, or C_{1-3} alkoxy.

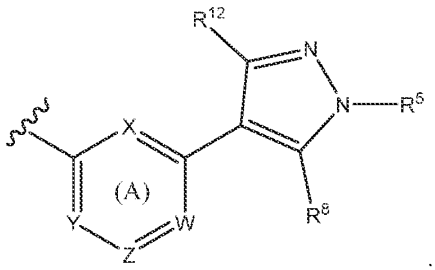
Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

one of R^2 or R^3 is -H, -F, $-OCH_3$, or $-CH_3$; and the other is



Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

one of R^2 or R^3 is -H, -F, $-OCH_3$, or $-CH_3$; and the other is



Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

W and Y are –N= or –C(R^{10})=;

Z is –N= or –C(R^{11})=; and

X is –N= or –C(F)=.

Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R^{10} is –H, -F, or CH_3;

R^{11} is –H, -F, or CH_3; and

X is –N= or –C(F)=.

Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R^8 is –H, -F, or -CN;

or alternatively, R^8 and R^{12} are independently –H, -F, or -CN.

Another embodiment provides a compound of Formula (I), or any other aspect or embodiment, or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein

R^5 is -(CR^aR^b)-R^{5a};

R^a is -H, C_{1-3} alkyl, or C_{1-3} fluoroalkyl;

R^b is -H;

R^{5a} is phenyl or pyridyl, any of which are substituted with 0-2 R^6; and

R^6 is H, -F, CH_3, OCH_3, or CF_3.

Another embodiment provides a compound of Formula (I), or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, wherein the compound is selected from the examples.

The present invention is also directed to pharmaceutical compositions useful in treating diseases associated with kinase modulation, including the modulation of receptor interacting protein kinases such as RIPK1, comprising compounds of formula (I), or pharmaceutically acceptable salts thereof, and pharmaceutically acceptable carriers or diluents.

The invention further relates to methods of treating diseases associated with kinase modulation, including the modulation of receptor interacting protein kinases such as RIPK1, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound according to formula (I), or pharmaceutically acceptable salt thereof.

The present invention also provides processes and intermediates for making the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

The present invention also provides a method for treating proliferative diseases, allergic diseases, autoimmune diseases and inflammatory diseases and fibrotic diseases, comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

The present invention also provides a method for treating a disease, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula (I), or pharmaceutically acceptable salt thereof, wherein the disease is inflammatory bowel disease, Crohn's disease or ulcerative colitis, psoriasis, systemic lupus erythematosus (SLE), rheumatoid arthritis, multiple sclerosis (MS),

Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), transplant rejection, nonalcoholic steatohepatitis (NASH), or ischemia reperfusion.

The present invention also provides a method of treating a condition comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula (I), or pharmaceutically acceptable salt thereof, wherein the condition is selected from systemic lupus erythematosus (SLE), multiple sclerosis (MS), Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), transplant rejection, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, solid tumors, ocular neovascularization, and infantile haemangiomas, B cell lymphoma, systemic lupus erythematosus (SLE), psoriatic arthritis, multiple vasculitides, idiopathic thrombocytopenic purpura (ITP), myasthenia gravis, allergic rhinitis, multiple sclerosis (MS), transplant rejection, Type I diabetes, membranous nephritis, autoimmune hemolytic anemia, autoimmune thyroiditis, cold and warm agglutinin diseases, Evan's syndrome, hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP), sarcoidosis, Sjogren's syndrome, peripheral neuropathies, pemphigus vulgaris and asthma, nonalcoholic steatohepatitis (NASH), or ischemia reperfusion.

The present invention also provides a method of treating a condition comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula (I), or pharmaceutically acceptable salt thereof, wherein the condition is selected from macrophage necrosis in atherosclerosis development, virus induced inflammation, systemic inflammatory response syndrome and ethanol induced liver injury, neurodegeneration such as detachment of the retina, retinal degeneration, wet and dry age-related macular degeneration (AMD), ischemia, amyotrophic lateral sclerosis (ALS), and Gaucher's disease.

The present invention also provides a method for treating a disease, comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula (I), or pharmaceutically acceptable salt thereof, wherein the disease is multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Parkinson's and Alzheimer's disease, spinal cord injury, and traumatic brain injury (TBI), detachment of the retina, ischemia, Gaucher's disease, and AAV (ANCA-associated vasculitis) and other inflammatory diseases such as macrophage necrosis in atherosclerosis development,

virus induced inflammation, systemic inflammatory response syndrome and ethanol induced liver injury.

The present invention also provides a method of treating a condition comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula (I), or pharmaceutically acceptable salt thereof, wherein the condition is selected from multiple sclerosis (MS), Alzheimer's disease (AD), and amyotrophic lateral sclerosis (ALS), Parkinson's and Alzheimer's disease.

The present invention also provides a method of treating a condition comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula (I), or pharmaceutically acceptable salt thereof, wherein the condition is selected from inflammatory bowel disease, Crohn's disease, ulcerative colitis, and psoriasis. In another embodiment, the condition is selected from inflammatory bowel disease, Crohn's disease, and ulcerative colitis.

The present invention also provides a method of treating a condition comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula (I), or pharmaceutically acceptable salt thereof, wherein the condition is selected from nonalcoholic steatohepatitis (NASH), and ischemia reperfusion.

The present invention also provides a method for treating multiple sclerosis (MS), comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula (I) or pharmaceutically acceptable salt thereof.

The present invention also provides a method for treating Alzheimer's disease (AD), comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula (I) or pharmaceutically acceptable salt thereof.

The present invention also provides a method for treating amyotrophic lateral sclerosis (ALS), comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of formula (I) or pharmaceutically acceptable salt thereof.

The present invention also provides a method of treating diseases, comprising administering to a patient in need of such treatment a therapeutically effective amount of

a compound of formula (I), or pharmaceutically acceptable salt thereof, in combination with other therapeutic agents.

The present invention also provides the compounds of the present invention or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, for use in therapy.

In another embodiment, compounds of formula (I), or pharmaceutically acceptable salt thereof, are selected from exemplified examples or combinations of exemplified examples or other embodiments herein.

The present invention also provides the use of the compounds of the present invention or stereoisomers, tautomers, isotopes, salts, pharmaceutically acceptable salts, solvates, or prodrugs thereof, for the manufacture of a medicament for the treatment of cancers, an allergic disease, an autoimmune disease or an inflammatory disease.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of preferred aspects and/or embodiments of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional embodiments. It is also to be understood that each individual element of the embodiments is its own independent embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

The following are definitions of terms used in this specification and appended claims. The initial definition provided for a group or term herein applies to that group or term throughout the specification and claims, individually or as part of another group, unless otherwise indicated.

Unless specifically stated otherwise herein, references made in the singular may also include the plural. For example, "a" and "an" may refer to either one, or one or more.

When any variable (e.g., R^3) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^3, then said group may optionally be substituted with up to two R^3 groups and R^3 at

each occurrence is selected independently from the definition of R^3. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Unless otherwise indicated, any carbon or heteroatom with unsatisfied valences is assumed to have hydrogen atoms sufficient to satisfy the valences.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

In cases wherein there are nitrogen atoms (e.g., amines) on compounds of the present invention, these can be converted to N-oxides by treatment with an oxidizing agent (e.g., MCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, all shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

In accordance with a convention used in the art,



is used in structural formulas herein to depict the bond that is the point of attachment of the moiety or substituent to the core or backbone structure.

A dash "-" that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, $-CONH_2$ is attached through the carbon atom.

The term "optionally substituted" in reference to a particular moiety of the compound of Formula (I), (*e.g.*, an optionally substituted heteroaryl group) refers to a moiety having 0, 1, 2, or more substituents. For example, "optionally substituted alkyl" encompasses both "alkyl" and "substituted alkyl" as defined below. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical, synthetically non-feasible and/or inherently unstable.

As used herein, the term "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, "C_{1-10} alkyl" (or alkylene), is intended to include

C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, and C_{10} alkyl groups. Additionally, for example, "C_1-C_6 alkyl" denotes alkyl having 1 to 6 carbon atoms. Alkyl groups can be unsubstituted or substituted so that one or more of its hydrogens are replaced by another chemical group. Example alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (*e.g.*, n-propyl and isopropyl), butyl (*e.g.*, n-butyl, isobutyl, t-butyl), pentyl (*e.g.*, n-pentyl, isopentyl, neopentyl), and the like.

When the term "alkyl" is used together with another group, such as in "arylalkyl", this conjunction defines with more specificity at least one of the substituents that the substituted alkyl will contain. For example, "arylalkyl" refers to a substituted alkyl group as defined above where at least one of the substituents is an aryl, such as benzyl. Thus, the term aryl(C_{0-4})alkyl includes a substituted lower alkyl having at least one aryl substituent and also includes an aryl directly bonded to another group, *i.e.*, aryl(C_0)alkyl. The term "heteroarylalkyl" refers to a substituted alkyl group as defined above where at least one of the substituents is a heteroaryl.

"Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either straight or branched configuration and having one or more double carbon-carbon bonds that may occur in any stable point along the chain. For example, "C_{2-6} alkenyl" (or alkenylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. Examples of alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3, pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, 4-methyl-3-pentenyl, and the like.

"Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either straight or branched configuration and having one or more triple carbon-carbon bonds that may occur in any stable point along the chain. For example, "C_{2-6} alkynyl" (or alkynylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups; such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like.

When reference is made to a substituted alkenyl, alkynyl, alkylene, alkenylene, or alkynylene group, these groups are substituted with one to three substituents as defined above for substituted alkyl groups.

The term "alkoxy" refers to an oxygen atom substituted by alkyl or substituted alkyl, as defined herein. For example, the term "alkoxy" includes the group -O-C_{1-6}alkyl such as methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy,

pentoxy, 2-pentyloxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, 3-methylpentoxy, and the like. "Lower alkoxy" refers to alkoxy groups having one to four carbons.

It should be understood that the selections for all groups, including for example, alkoxy, thioalkyl, and aminoalkyl, will be made by one skilled in the field to provide stable compounds.

The term "substituted", as used herein, means that any one or more hydrogens on the designated atom or group is replaced with a selection from the indicated group, provided that the designated atom's normal valence is not exceeded. When a substituent is oxo, or keto, (*i.e.*, =O) then 2 hydrogens on the atom are replaced. Unless otherwise specified, substituents are named into the core structure. For example, it is to be understood that when (cycloalkyl)alkyl is listed as a possible substituent, the point of attachment of this substituent to the core structure is in the alkyl portion. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (e.g., C=C, C=N, or N=N).

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds or useful synthetic intermediates. A stable compound or stable structure is meant to imply a compound that is sufficiently robust to survive isolation from a reaction mixture to a useful degree of purity, and subsequent formulation into an efficacious therapeutic agent. It is preferred that the presently recited compounds do not contain a N-halo, $S(O)_2H$, or S(O)H group.

The term "carbocyclyl" or "carbocyclic" refers to a saturated or unsaturated, or partially unsaturated, monocyclic or bicyclic ring in which all atoms of all rings are carbon. Thus, the term includes cycloalkyl and aryl rings, or bicyclic rings containing both saturated or unsaturated rings, or rings being partially unsaturated. Monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, e.g., arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl,

naphthyl, indanyl, adamantyl, anthracenyl, and tetrahydronaphthyl (tetralin). As shown above, bridged rings are also included in the definition of carbocycle (*e.g.*, [2.2.2]bicyclooctane). Carbocycles can include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and phenyl. When the term "carbocycle" is used, it is intended to include "aryl". A bridged ring occurs when one or more carbon atoms link two nonadjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a bicyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

The term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having 6 to 12 carbon atoms in the ring portion, such as phenyl, and naphthyl groups, each of which may be substituted. A preferred aryl group is optionally substituted phenyl.

The term "cycloalkyl" refers to cyclized alkyl groups, including monocyclic, bicyclic or polycyclic ring systems. C_{3-7} cycloalkyl is intended to include C_3, C_4, C_5, C_6, and C_7 cycloalkyl groups. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like, which optionally may be substituted at any available atoms of the ring(s).

The terms "heterocycloalkyl", "heterocyclo", "heterocycle", "heterocyclic", or "heterocyclyl" may be used interchangeably and refer to substituted and unsubstituted aromatic or nonaromatic, or partially unsaturated, 3-to 7-membered monocyclic groups, 7-to 11-membered bicyclic groups, and 10-to 15-membered tricyclic groups, in which at least one of the rings has at least one heteroatom (O, S or N), said heteroatom containing ring preferably having 1, 2, or 3 heteroatoms selected from O, S, and N. Each ring of such a group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less, and further provided that the ring contains at least one carbon atom. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The heterocyclo group may be attached at any available nitrogen or carbon atom. The term "heterocycle" includes "heteroaryl" groups. As valence allows, if said

further ring is cycloalkyl or heterocyclo it is additionally optionally substituted with =O (oxo).

Exemplary monocyclic heterocyclyl groups include azetidinyl, pyrrolidinyl, oxetanyl, imidazolinyl, oxazolidinyl, isoxazolinyl, thiazolidinyl, isothiazolidinyl, tetrahydrofuranyl, piperidyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 1-pyridonyl, 4-piperidonyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl and the like, including the exemplary groups listed under "heteroaryl". Exemplary bicyclic heterocyclo groups include quinuclidinyl.

The term "heteroaryl" refers to substituted and unsubstituted aromatic 5- or 6-membered monocyclic groups, 9- or 10-membered bicyclic groups, and 11- to 14-membered tricyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings, said heteroatom-containing ring preferably having 1, 2, or 3 heteroatoms selected from O, S, and N. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic and tricyclic groups may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings may be aromatic or nonaromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring. As valence allows, if said further ring is cycloalkyl or heterocyclo it is additionally optionally substituted with =O (oxo).

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thienyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like.

Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxazolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl,

coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridyl, dihydroisoindolyl, tetrahydroquinolinyl, and the like.

Exemplary tricyclic heteroaryl groups include carbazolyl, benzindolyl, phenanthrollinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

Unless otherwise indicated, when reference is made to a specifically named aryl (*e.g.*, phenyl), cycloalkyl (*e.g.*, cyclohexyl), heterocyclo (*e.g.*, pyrrolidinyl, piperidinyl, and morpholinyl) or heteroaryl (*e.g.*, tetrazolyl, imidazolyl, pyrazolyl, triazolyl, thiazolyl, and furyl) the reference is intended to include rings having 0 to 3, preferably 0-2, substituents, as appropriate.

The term "halo" or "halogen" refers to chloro, bromo, fluoro and iodo.

The term "haloalkyl" means a substituted alkyl having one or more halo substituents. For example, "haloalkyl" includes mono, bi, and trifluoromethyl.

The term "haloalkoxy" means an alkoxy group having one or more halo substituents. For example, "haloalkoxy" includes OCF_3.

The term "deuteroalkyl" means a substituted alkyl having one or more deuterium atom. For example, the term "deuteroalkyl" includes mono, bi, and trideuteromethyl.

The term "heteroatoms" shall include oxygen, sulfur and nitrogen.

When the term "unsaturated" is used herein to refer to a ring or group, the ring or group may be fully unsaturated or partially unsaturated.

One skilled in the field will understand that, when the designation "CO_2" is used herein, this is intended to refer to the group $-\overset{O}{\overset{\|}{C}}-O-$.

Throughout the specification, groups and substituents thereof may be chosen by one skilled in the field to provide stable moieties and compounds and compounds useful as pharmaceutically acceptable compounds and/or intermediate compounds useful in making pharmaceutically acceptable compounds.

The compounds of formula (I) may exist in a free form (with no ionization) or can form salts which are also within the scope of this invention. Unless otherwise indicated, reference to an inventive compound is understood to include reference to the free form and to salts thereof. The term "salt(s)" denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, the term "salt(s) may include zwitterions (inner salts), *e.g.*, when a compound of formula (I), contains both a basic moiety, such as an amine or a pyridine or imidazole ring, and an acidic moiety, such as a

carboxylic acid. Pharmaceutically acceptable (*i.e.*, non-toxic, physiologically acceptable) salts are preferred, such as, for example, acceptable metal and amine salts in which the cation does not contribute significantly to the toxicity or biological activity of the salt. However, other salts may be useful, *e.g.*, in isolation or purification steps which may be employed during preparation, and thus, are contemplated within the scope of the invention. Salts of the compounds of the formula (I) may be formed, for example, by reacting a compound of the formula (I) with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides (formed with hydrochloric acid), hydrobromides (formed with hydrogen bromide), hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates (formed with maleic acid), methanesulfonates (formed with methanesulfonic acid), 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts; alkaline earth metal salts such as calcium and magnesium salts; barium, zinc, and aluminum salts; salts with organic bases (for example, organic amines) such as trialkylamines such as triethylamine, procaine, dibenzylamine, N-benzyl-β-phenethylamine, 1-ephenamine, N,N'-dibenzylethylene-diamine, dehydroabietylamine, N-ethylpiperidine, benzylamine, dicyclohexylamine or similar pharmaceutically acceptable amines and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (*e.g.*, methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (*e.g.*, dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain

halides (*e.g.*, decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (*e.g.*, benzyl and phenethyl bromides), and others. In one embodiment, salts include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate or nitrate salts.

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

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 18th ed., Mack Publishing Company, Easton, PA, **1990**, the disclosure of which is hereby incorporated by reference.

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. As an example, an alkyl substituent is intended to cover alkyl groups have either hydrogen, deuterium, and/or some combination thereof. Isotopes of carbon include ^{13}C and ^{14}C. Isotopically labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically labeled reagent in place of the non-labeled reagent otherwise employed.

Prodrugs and solvates of the inventive compounds are also contemplated. The term "prodrug" denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula (I), and/or a salt and/or solvate thereof. Any compound that will be converted *in vivo* to provide the bioactive agent (*i.e.*, the compound for formula (I)) is a prodrug within the scope and spirit of the invention. For example, compounds containing a carboxy group can form physiologically hydrolyzable esters which serve as prodrugs by being hydrolyzed in the body to yield formula (I) compounds *per se*. Such prodrugs are preferably administered orally since hydrolysis in many instances occurs principally under the influence of the digestive enzymes. Parenteral administration may be used where the ester *per se* is active, or in those instances where hydrolysis occurs in the blood. Examples of physiologically hydrolyzable esters of compounds of formula (I) include C_{1-6}alkylbenzyl, 4-methoxybenzyl, indanyl, phthalyl, methoxymethyl, C_{1-6}alkanoyloxy-C_{1-6}alkyl, *e.g.* acetoxymethyl, pivaloyloxymethyl or propionyloxymethyl, C_{1-6}alkoxycarbonyloxy-C_{1-6}alkyl, *e.g.* methoxycarbonyl-oxymethyl or ethoxycarbonyloxymethyl, glycyloxymethyl, phenylglycyloxymethyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)-methyl and other well-known physiologically hydrolyzable esters used, for example, in the penicillin and cephalosporin arts. Such esters may be prepared by conventional techniques known in the art.

Various forms of prodrugs are well known in the art. For examples of such prodrug derivatives, see:

a) *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985) and *Methods in Enzymology*, Vol. 112, pp. 309-396, edited by K. Widder, et al. (Academic Press, 1985);

b) *A Textbook of Drug Design and Development*, edited by Krosgaard-Larsen and H. Bundgaard, Chapter 5, "Design and Application of Prodrugs," by H. Bundgaard, pp. 113-191 (1991); and

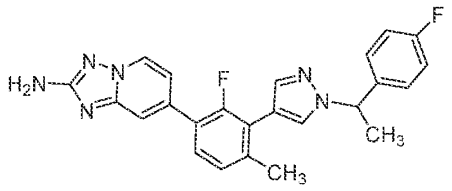
c) H. Bundgaard, *Advanced Drug Delivery Reviews*, Vol. 8, pp. 1-38 (1992), each of which is incorporated herein by reference.

Compounds of the formula (I) and salts thereof may exist in their tautomeric form, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that all tautomeric forms, insofar as they may exist, are included within the invention.

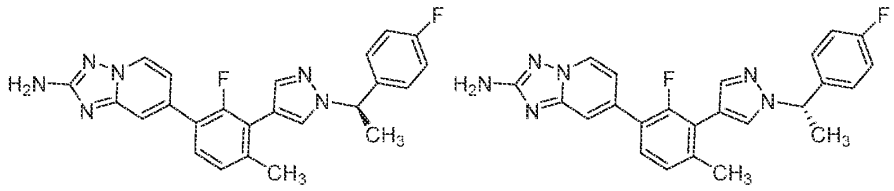
Compounds of this invention may have one or more asymmetric centers. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms of compounds of the present invention are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. The present compounds can be isolated in optically active or racemic forms. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation, or crystallization of diastereomeric derivatives or separation by chiral column chromatography. All chiral, (enantiomeric and diastereomeric) and racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated. All geometric isomers, tautomers, atropisomers, hydrates, solvates, polymorphs, and isotopically labeled forms of the compounds referred to herein, and mixtures thereof, are considered within the scope of the present invention. Methods of solvation are generally known in the art.

For some examples of the present invention, the absolute stereochemistry of the enantiomers and/or diastereomers has not been specifically identified. However, the racemic mixtures and all enantiomers and diastereomers are included in the present invention. Even

where the specific enantiomers and/or diastereomers are isolated, but the absolute stereochemistry was not specifically determined and drawn, one of skill in the art can easily identify and draw the structures of the individual stereoisomers or diastereomers. For example, Examples 4 and 5 are represented by the structure:



The enantiomers are:



, which one of skill in the art is able to identify, even if the structure of each of the examples is not specifically described.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. The present invention is intended to embody stable compounds.

UTILITY

The compounds of the invention modulate kinase activity, including the modulation of RIPK1. Accordingly, compounds of formula (I) have utility in treating conditions associated with the modulation of kinase activity, and particularly the selective inhibition of RIPK1 activity. In another embodiment, compounds of formula (I) have advantageous selectivity for RIPK1 activity preferably from at least 10-fold, or alternatively, 20-fold, to over 1,000-fold more selective over other kinases.

As used herein, the terms "treating" or "treatment" encompass the treatment of a disease state in a mammal, particularly in a human, and include: (a) preventing or

delaying the occurrence of the disease state in a mammal, in particular, when such mammal is predisposed to the disease state but has not yet been diagnosed as having it; (b) inhibiting the disease state, i.e., arresting its development; and/or (c) achieving a full or partial reduction of the symptoms or disease state, and/or alleviating, ameliorating, lessening, or curing the disease or disorder and/or its symptoms.

In view of their activity as inhibitors of RIPK1, compounds of Formula (I) are useful in treating RIPK1-associated conditions including, but not limited to, inflammatory diseases such as Crohn's disease and ulcerative colitis, inflammatory bowel disease, asthma, graft versus host disease, chronic obstructive pulmonary disease; autoimmune diseases such as Graves' disease, rheumatoid arthritis, systemic lupus erythematosis, psoriasis; destructive bone disorders such as bone resorption disease, osteoarthritis, osteoporosis, multiple myeloma related bone disorder; proliferative disorders such as acute myelogenous leukemia, chronic myelogenous leukemia; angiogenic disorders such as angiogenic disorders including solid tumors, ocular neovascularization, and infantile haemangiomas; infectious diseases such as sepsis, septic shock, and Shigellosis; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, cerebral ischemias or neurodegenerative disease caused by traumatic injury, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), spinal cord injury, and traumatic brain injury (TBI), detachment of the retina, ischemia, Gaucher's disease, and AAV (ANCA-associated vasculitis) and other inflammatory diseases such as macrophage necrosis in atherosclerosis development, virus induced inflammation, systemic inflammatory response syndrome and ethanol induced liver injury, oncologic and viral diseases such as metastatic melanoma, Kaposi's sarcoma, multiple myeloma, and HIV infection and CMV retinitis, AIDS; fibrotic conditions such as, nonalcoholic steatohepatitis (NASH); and cardiac conditions such as, ischemia reperfusion; respectively.

More particularly, the specific conditions or diseases that may be treated with the inventive compounds include, without limitation, pancreatitis (acute or chronic), asthma, allergies, adult respiratory distress syndrome, chronic obstructive pulmonary disease, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosis, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, ALS, multiple sclerosis, inflammatory bowel disease,

ulcerative colitis, Crohn's disease, psoriasis, graft vs. host disease, inflammatory reaction induced by endotoxin, tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, gout, traumatic arthritis, rubella arthritis, acute synovitis, pancreatic β-cell disease; diseases characterized by massive neutrophil infiltration; rheumatoid spondylitis, gouty arthritis and other arthritic conditions, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption disease, allograft rejections, fever and myalgias due to infection, cachexia secondary to infection, myeloid formation, scar tissue formation, ulcerative colitis, pyresis, influenza, osteoporosis, osteoarthritis, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, sepsis, septic shock, and Shigellosis; Alzheimer's disease, Parkinson's disease, cerebral ischemias or neurodegenerative disease caused by traumatic injury; angiogenic disorders including solid tumors, ocular neovascularization, and infantile haemangiomas; viral diseases including acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), HIV infection and CMV retinitis, AIDS, ARC or malignancy, and herpes; stroke, myocardial ischemia, ischemia in stroke heart attacks, organ hypoxia, vascular hyperplasia, cardiac and renal reperfusion injury, thrombosis, cardiac hypertrophy, thrombin induced platelet aggregation, endotoxemia and/or toxic shock syndrome, conditions associated with prostaglandin endoperoxidase syndase-2, and pemphigus vulgaris. In another aspect, methods of treatment are those wherein the condition is selected from inflammatory bowel disease, Crohn's disease and ulcerative colitis, allograft rejection, rheumatoid arthritis, psoriasis, ankylosing spondylitis, psoriatic arthritis, and pemphigus vulgaris, and nonalcoholic steatohepatitis (NASH), and ischemia reperfusion. In a further aspect, methods of treatment are those wherein the condition is selected from multiple sclerosis, amyotrophic lateral sclerosis, and Alzheimer's.

Alternatively preferred methods of treatment are those wherein the condition is selected from ischemia reperfusion injury, including cerebral ischemia reperfusions injury arising from stroke and cardiac ischemia reperfusion injury arising from myocardial infarction.

When the terms "RIPK1-associated condition" or "RIPK1 -associated disease or disorder" are used herein, each is intended to encompass all of the conditions identified

above as if repeated at length, as well as any other condition that is affected by RIPK1 kinase activity.

The present invention thus provides methods for treating such conditions, comprising administering to a subject in need thereof a therapeutically effective amount of at least one compound of Formula (I) or a salt thereof. "Therapeutically effective amount" is intended to include an amount of a compound of the present invention that is effective when administered alone or in combination to inhibit RIPK1.

The methods of treating RIPK1 kinase associated conditions may comprise administering compounds of Formula (I) alone or in combination with each other and/or other suitable therapeutic agents useful in treating such conditions. Accordingly, "therapeutically effective amount" is also intended to include an amount of the combination of compounds claimed that is effective to inhibit RIPK1 and/or treat diseases associated with RIPK1.

Exemplary of such other therapeutic agents include corticosteroids, rolipram, calphostin, cytokine suppressive anti-inflammatory drugs (CSAIDs), Interleukin-10, glucocorticoids, salicylates, nitric oxide, and other immunosuppressants; nuclear translocation inhibitors, such as deoxyspergualin (DSG); nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, celecoxib and rofecoxib; steroids such as prednisone or dexamethasone; anti-inflammatory antibodies such as vedolizumab and ustekinumab, anti-inflammatory kinase inhibitors such as TYK2 inhibitors, antiviral agents such as abacavir; antiproliferative agents such as methotrexate, leflunomide, FK506 (tacrolimus, Prograf); cytotoxic drugs such as azathiprine and cyclophosphamide; TNF-α inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor, rapamycin (sirolimus or Rapamune) or derivatives thereof, and agonists of FGF21.

Combination strategies include therapies intended to target the accumulation and/or downstream effects of amyloid beta and/or tau, including but not limited to antibodies that bind to these toxic species, ligand-directed degradation or other degraders such as CELMoD agents. In addition to small molecule and/or antibody-based therapeutic combinations, other options include siRNA and/or ASO approaches as well as the use of delivery technologies designed to augment central exposure to peripherally administered therapeutic agents in addition to ICV or intrathecal administration.

The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with, or following the administration of the inventive compounds. The present invention also provides pharmaceutical compositions capable of treating RIPK1 kinase associated conditions, including IL-1, IL-6, IL-8, IFNγ and TNF-α-mediated conditions, as described above.

The inventive compositions may contain other therapeutic agents as described above and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (*e.g.*, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

Accordingly, the present invention further includes compositions comprising one or more compounds of Formula (I) and a pharmaceutically acceptable carrier.

A "pharmaceutically acceptable carrier" refers to media generally accepted in the art for the delivery of biologically active agents to animals, in particular, mammals. Pharmaceutically acceptable carriers are formulated according to a number of factors well within the purview of those of ordinary skill in the art. These include without limitation the type and nature of the active agent being formulated; the subject to which the agent containing composition is to be administered; the intended route of administration of the composition; and, the therapeutic indication being targeted. Pharmaceutically acceptable carriers include both aqueous and nonaqueous liquid media, as well as a variety of solid and semisolid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, *e.g.*, stabilization of the active agent, binders, etc., well known to those of ordinary skill in the art. Descriptions of suitable pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources such as, for example, *Remington's Pharmaceutical Sciences*, 17th ed., 1985, which is incorporated herein by reference in its entirety.

The compounds of Formula (I) may be administered by any means suitable for the condition to be treated, which may depend on the need for site-specific treatment or quantity of drug to be delivered. Topical administration is generally preferred for skin related diseases, and systematic treatment preferred for cancerous or precancerous conditions, although other modes of delivery are contemplated. For example, the compounds may be delivered orally, such as in the form of tablets, capsules, granules, powders, or liquid formulations including syrups; topically, such as in the form of solutions, suspensions, gels or ointments; sublingually; bucally; parenterally, such as by subcutaneous, intravenous, intramuscular or intrasternal injection or infusion techniques (*e.g.*, as sterile injectable aqueous or nonaqueous solutions or suspensions); nasally such as by inhalation spray; topically, such as in the form of a cream or ointment; rectally such as in the form of suppositories; or liposomally. Dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents may be administered. The compounds may be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved with suitable pharmaceutical compositions or, particularly in the case of extended release, with devices such as subcutaneous implants or osmotic pumps.

Exemplary compositions for topical administration include a topical carrier such as PLASTIBASE® (mineral oil gelled with polyethylene).

Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The inventive compounds may also be orally delivered by sublingual and/or buccal administration, *e.g.*, with molded, compressed, or freeze-dried tablets. Exemplary compositions may include fast dissolving diluents such as mannitol, lactose, sucrose, and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (AVICEL®) or polyethylene glycols (PEG); an excipient to aid mucosal adhesion such as hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), sodium carboxymethyl

cellulose (SCMC), and/or maleic anhydride copolymer (*e.g.*, GANTREZ®); and agents to control release such as polyacrylic copolymer (*e.g.*, CARBOPOL 934®). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include solutions which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance absorption and/or bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

Exemplary compositions for rectal administration include suppositories which may contain, for example, suitable non-irritating excipients, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures but liquefy and/or dissolve in the rectal cavity to release the drug.

The therapeutically effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for a mammal of from about 0.05 to 1000 mg/kg; 1-1000 mg/kg; 1-50 mg/kg; 5-250 mg/kg; 250-1000 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors, including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats, horses, and the like. Thus, when the term "patient" is used

herein, this term is intended to include all subjects, most preferably mammalian species, that are affected by mediation of RIPK1 enzyme levels.

Biological Assays

Necroptosis is a regulated pathway of cell death that is induced by both inflammatory factors (TNFalpha) as well as viral triggers such as TLR agonists. The process of necroptosis induction occurs following activation and phosphorylation of RIPK1 to form a complex with RIPK3 (referred to as necrosome). Mixed Lineage Kinase domain-like protein (MLKL) is recruited to RIPK3 and is a downstream target of RIPK3 kinase, leading to MLKL phosphorylation at Thr357 and Ser358. Phosphorylated MLKL (pMLKL) leads to MLKL oligomerization, translocation to the plasma membrane, and subsequent pore formation leading to membrane integrity defects (Moriwaki, K., and F. K. Chan. 2013. RIP3: a molecular switch for necrosis and inflammation. Genes Dev. 27: 1640–1649). Thus, understanding the potency of RIPK1 compounds based on RIPK1 direct binding as well as a functional readout of necroptosis activity (pMLKL) is important for evaluating RIPK1 inhibitor activity and potency.

MLKL Phosphorylation High-Content Assay

HT29-L23 human colorectal adenocarcinoma cells were maintained in RPMI 1640 medium containing 10% heat-inactivated FBS, 1% Penicillin-Streptomycin and 10 mM HEPES. Cells were seeded at 2,000 cells/well in 384 well tissue culture-treated microplates (Greiner # 781090-3B) and incubated at 37 °C (5% CO_2/95% O_2) for 2 d. On the day of the assay, the cells were treated with test compounds at final concentrations of 6.25 to 0.106 μM for 30 min at 37 °C (5% CO_2/95% O_2). Necroptosis was induced using a mixture of human TNFα (35 ng/mL) (Peprotech #300-01A), SMAC mimetic (from US 2015/0322111 A1) (700 nM) and Z-VAD (140 nM) (BD pharmingen #51-6936). Following 6 h incubation at 37 °C (5% CO_2/95% O_2), the cells were fixed with 4% formaldehyde (ACROS 11969-0010) for 15 min at rt, then permeabilized with phosphate buffered saline (PBS) containing 0.2% Triton-X-100 for 10 min. MLKL phosphorylation was detected using anti-MLKL (phospho S358) antibody (Abcam #ab187091) (1:1000 dilution in Blocking Buffer [PBS supplemented with 0.1% BSA]) with ON incubation at 4 °C. After washing three times in PBS, goat anti-rabbit Alexa-488 (1:1000 dilution)

(Life Technologies, A11008) and Hoechst 33342 (Life Technologies, H3570) (1:2000 dilution) in Blocking Buffer were added for 1 h at rt. Following another three cycles of washes in PBS, the microplates were sealed, and cellular images were acquired in the Cellomics ArrayScan VTI high-content imager equipped with an X1 camera. Fluorescent images were taken using a 10x objective and the 386-23 BGRFRN_BGRFRN and 485-20 BGRFRN_BGRFRN filter sets, for nuclei and MLKL phosphorylation, respectively. The image sets were analyzed using the Compartmental Analysis Bioapplication software (Cellomics). The level of MLKL phosphorylation was quantified as MEAN_CircRingAvgIntenRatio. The maximal inhibitory response was defined by the activity induced by Nec1s (CAS #: 852391-15-2, 6.25 μM). The IC50 value was defined as the concentration of compound that produces 50% of the maximal inhibition. The data were fitted using the 4-parameter logistic equation to calculate the IC_{50} and Y_{max} values.

Compounds were tested in the above identified assays with the following results:

Example Number	LE pMLKL HC IC50 (nM)
1	176.3
2	46.0
3	176.4
4	152.3
5	1.6
6	61.2
7	0.9
8	0.9
9	5.2
10	22.6
11	231.1
12	3.7
13	248.7

Example Number	LE pMLKL HC IC50 (nM)
14	0.1
15	29.7
16	0.3
17	1.6
18	79.2
19	24.5
20	0.3
21	9.2
22	6.0
23	3.8
24	3.6
25	2.8
26	5.5

Example Number	LE pMLKL HC IC50 (nM)
27	0.5
28	3.1
29	27.5
30	0.1
31	19.9
32	0.2
33	39.0
34	246.0
35	0.9
36	59.6
37	10.9
38	4.7
39	211.0
40	0.2
41	86.4
42	5.5
43	5.7
44	2.8
45	0.3
46	140.3
47	0.0
48	4.5
49	0.6
50	1.6
51	75.4
52	3.3
53	0.7

Example Number	LE pMLKL HC IC50 (nM)
54	0.4
55	2.3
56	3.8
57	0.9
58	2.1
59	271.2
60	0.7
61	89.8
62	6.5
63	1.8
64	35.8
65	0.7
66	0.2
67	0.4
68	1.0
69	45.5
70	1.0
71	0.5
72	270.5
73	0.9
74	0.7
75	244.0
76	0.2
77	0.4
78	0.7
79	14.0
80	74.0

Example Number	LE pMLKL HC IC50 (nM)
81	103.0
82	486.0
83	7.1
84	444.8
85	25.5
86	26.6
87	8.6
88	227.8
89	33.2
90	149.5
91	27.5
92	1.6
93	34.7
94	2.7
95	120.9
96	151.1
97	258.9
98	2.0
99	89.2
100	25.9
101	0.3
102	0.2
103	17.2
104	50.8
105	9.7
106	238.8
107	0.1

Example Number	LE pMLKL HC IC50 (nM)
108	121.8
109	0.7
110	5.1
111	15.4
112	2.0
113	18.5
114	3.4
115	31.2
116	4.6
117	83.0
118	0.8
119	1.8
120	1.5
121	52.0
122	88.0
123	10.2
124	369.2
125	0.6
126	380.5
127	0.7
128	77.4
129	0.7
130	0.8
131	70.2
132	0.5
133	10.5
134	0.4

Example Number	LE pMLKL HC IC50 (nM)
135	0.4
136	2.0
137	4.0
138	6.8
139	1.0
140	0.8
141	0.3
142	11.1
143	0.6
144	0.3
145	42.6
146	0.5
147	0.7
148	115.8
149	1.3
150	3.6
151	315.7
152	77.2
153	32.7
154	43.5
155	103.2
156	5.9
157	28.0
158	11.5
159	1.0
160	79.8
161	8.6

Example Number	LE pMLKL HC IC50 (nM)
162	289.2
163	18.3
164	9.0
165	180.4
166	0.4
167	373.0
168	0.4
169	0.2
170	13.9
171	2.5
172	1.4
173	0.2
174	33.5
175	3.4
176	5.7
177	20.3
178	62.2
179	0.8
180	1.5
181	1.0
182	2.1
183	6.2
184	1.2
185	74.3
186	132.8
187	0.9
188	44.5

Example Number	LE pMLKL HC IC50 (nM)
189	0.5
190	0.3
191	73.1
192	0.2
193	41.3
194	0.2
195	0.3
196	64.2
197	0.2
198	3.1
199	286.5
200	22.3
201	1.0
202	1.4
203	0.2
204	0.2
205	2.6
206	1.3
207	37.6
208	24.6
209	4.8
210	0.9
211	50.3
212	49.4
213	0.8
214	4.0
215	159.2

Example Number	LE pMLKL HC IC50 (nM)
216	1.5
217	32.6
218	1.0
219	32.1
220	183.9
221	1.4
222	0.5
223	97.8
224	0.5
225	3.9
226	0.5
227	0.7
228	1.1
229	5.1
230	1.7
231	0.4
232	1.1
233	1.5
234	11.4
235	2.0
236	0.8
237	0.4
238	402.6
239	266.4
240	94.8
241	66.6

Example	LE pMLKL HC IC50 (nM)
242	3.6
243	34.7
244	0.4
245	8.0
246	1.0
247	8.8
248	3.6
249	96.2
250	12.0
251	51.5
252	51.2
253	355
254	1.4
255	9.5
256	2.4
257	2.7
258	1.2
259	1.3
260	2206
261	14.6
262	0.7
263	11.1
264	5.3
265	29.2
266	1.0
267	5.7
268	1.3
269	2.5
270	71.4
271	95.2
272	82.8
273	26.7
274	3.4
275	3.6
276	16.6
277	27.4
278	77.7
279	0.4
280	0.3

Example	LE pMLKL HC IC50 (nM)
281	0.5
282	3.3
283	31.9
284	3.11
285	57.67
286	1.33
287	18.88
288	1.61
289	13.95
290	0.39
291	33.35
292	39.1
293	132.4
294	1.53
295	37.23
296	13.82
297	4.48
298	147.50
299	1.11
300	281.08
301	4.22
302	28.49
303	12.13
304	2392.51
305	0.55
306	1.3
307	0.3
308	0.5
309	1.3
310	4.0
311	0.5
312	2.8
313	0.6
314	1.1
315	100.6
316	92.6
317	2.3
318	0.5
319	1.1

Example	LE pMLKL HC IC50 (nM)
320	1.0
321	0.4
322	0.7
323	0.6
324	1.3
325	17.3
326	0.4
327	0.7
328	17.4
329	583
330	0.5
331	240
332	0.3
333	1.9
334	0.3
335	0.2
336	1.0
337	2.3
338	181
339	1.5
340-	5.8
341	12.1
342	1.0
343	16.5
344	0.5
345	11.8
346	0.3
347	3.5
348	1.4
349	1.7
350	3.5
351	87.5
352	4.4
353	10.7
354	1.1
355	0.4
356	5.7
357	2.2
358	0.7
359	3.4
360	0.3
361	0.9

Example	LE pMLKL HC IC50 (nM)
362	25
363	287
364	2.7
365	0.3
366	6.1
367	3.6
368	0.5
369	122
370	4.8
371	0.9
372	8.3
373	0.9
374	12.6
375	1.8
376	4.4
377	0.9
378	34
379	2.1
380	66
381	0.4
382	403
383	102
384	1200
385	8.4
386	6.5
387	7.2
388	4.4
389	0.3
390	8.8
391	1.2
392	12

Transporter Assays

Compounds may be assessed as substrates of MDR1 P-glycoprotein (P-gp) and mouse Breast Cancer Resistance Protein (mBcrp) at 0.1uM, for 2 hours, in bi-directional transport assays using recombinant MDCK cell lines as described previously (Feng et al. *Drug Metabolism and Disposition* 2008, Vol. 36:268-275). MDCK-MDR1 and MDCK-mBcrp cells were acquired from the National Institutes of Health (Bethesda, MD) and the Netherlands Cancer Institute respectively, and used under license agreement. Data are expressed as efflux ratios, where transport across the cell monolayer in the basolateral to apical direction is divided by transport in the apical to basolateral direction. Efflux ratios >2 indicate the test compound is a substrate of the transporter tested.

Determining actual brain concentrations

Aliquots of brain homogenate can be frozen at -80°C in polypropylene tubes. The total concentration of Compound A in brain tissue can be measured using liquid chromatography tandem mass spectrometry (LC/MS) analysis. The samples for the LC/MS analysis can be prepared using a protein precipitation procedure described below.

Acetonitrile (100 µL), containing an internal standard [1 mM], along with the sample (30 µL), can be added to a 96-well Filter Plate (Multiscreen Solvinert 0.45 mm Low Binding Hydrophilic PTFE, Millipore) fitted on top of the final autosampler plate (96-well 1 ml Collection Plate, Waters) including an insert (Ultra Amp 96-well 0.2 ml Ultraplate, Sorenson Bioscience). The assembly can be vortex mixed for 5 min at room temperature, centrifuged at 3,700 rpm at 4°C for 10 min, then capped. The supernatant (3 µL) can be injected to an Ultra Performance LC System (Waters Acquity iClass) interfaced with a Quadrapole MS/MS (Thermo Scientific TSQ Quantiva) tandem mass spectrometer. The analyte can be separated on a C18 column (Waters Acquity HSS T3, 2.1 x 50 mm, 1.8 µm) at 40°C, with a gradient flow rate of 0.7 ml/min, consisting of two buffer solutions (A: water, 5 mM Ammonium Formate, 0.1% formic acid; B: acetonitrile, 0.1% formic acid). The detection is possible by using multiple reaction monitoring (MRM) in the positive electrospray ionization mode, representing the precursor (M+H)+ species.

The assays described above (transporter and brain assay) may be used to illustrate that the compounds of the present invention are brain penetrant, and therefore are useful for the treatment of neurodegenerative diseases as described above.

METHODS OF PREPARATION

Compounds of Formula (I), and intermediates used in the preparation of compounds of Formula (I), can be prepared using procedures shown in the following examples and related procedures. The methods and conditions used in these examples, and the actual compounds prepared in these examples, are not meant to be limiting, but are meant to demonstrate how the compounds of Formula (I) can be prepared. Starting materials and reagents used in these examples, when not prepared by a procedure described herein, are generally either commercially available, or are reported in the chemical literature, or may be prepared by using procedures described in the chemical literature.

Abbreviations as used herein, are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "L" for liter or liters, "mL" for milliliter or milliliters, "µL" for microliter or microliters, "N" for normal, "M" for molar, "mmol" for millimole or millimoles, "µmol" for micromole or micromoles, "min" for minute or minutes, "h" for hour or hours, "RT" for room temperature, "ON" for overnight, "atm" for atmosphere, "psi" for pounds per square inch, "conc." for concentrate, "approx." for approximate or approximately, "sat" or "saturated" for saturated, "CV" or "CVs" for column volume or column volumes, "MW" for molecular weight, "mp" for melting point, "ee" for enantiomeric excess, "MS" or "Mass Spec" for mass spectrometry, "m/z" for mass per unit charge, "ESI" for electrospray ionization mass spectroscopy, "HR" for high resolution, "HRMS" for high resolution mass spectrometry, "APCI" for atmospheric pressure chemical ionization, "LCMS" or "LC/MS" for liquid chromatography mass spectrometry, "HPLC" for high pressure liquid chromatography, "RP HPLC" for reverse phase HPLC, "prep" for preparative, "SFC" for supercritical fluid chromatography, "TLC" or "tlc" for thin layer chromatography, "Rf" for retention factor, "UV" for ultraviolet, "NMR" for nuclear magnetic resonance spectroscopy, "nOe" for nuclear Overhauser effect spectroscopy, "^{1}H" for proton, "δ" for delta, "s" for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "m"

for multiplet, "br" for broad, "MHz" for megahertz, and "α", "β", "R", "S", "E", and "Z" are stereochemical designations familiar to one skilled in the art.

Me	methyl
Et	ethyl
Pr	propyl
i-Pr	isopropyl
Bu	butyl
n-BuLi	n-butyllithium
i-Bu	isobutyl
t-Bu	*tert*-butyl
Ph	phenyl
Bn	benzyl
BISPIN	bis(pinacolato)diboron
Boc	*tert*-butyloxycarbonyl
AcOH or HOAc	acetic acid
BOP	benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate
CBz	carbobenzyloxy
DAST	Diethylaminosulfur trifluoride
DCE	1,2-dichloroethane
DCM	dichloromethane
DEA	diethylamine
DIAD	Diisopropyl azodicarboxylate
DIEA/DIPEA/Hünig's Base	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
EDC/EDCI	*N*-(3-dimthylaminopropyl)-*N'*-ethylcarbodiimide
Et_3N or TEA	triethylamine
EtOAc	ethyl acetate

Et_2O	diethyl ether
EtOH	ethanol
HCl	hydrochloric acid
HATU	O-(7-azabenzotriazol-1-yl)-*N*,*N*,N′,N′-tetramethyluronium hexafluorophosphate
Hex	hexane
HOBt or HOBT	1-hydroxybenzotriazole
i-PrOH or IPA	isopropanol
KOAc	potassium acetate
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LG	leaving group
MeCN or ACN	acetonitrile
MeOH	methanol
MeI	iodomethane
$MgSO_4$	magnesium sulfate
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NH_4OAc	ammonium acetate
NIS	*N*-iodosuccinimide
NH_4OH	ammonium hydroxide
OTf	triflate or trifluoromethanesulfonate
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
$Pd(OAc)_2$	palladium(II) acetate
Pd/C	palladium on carbon
$PdCl_2(dtbpf)$	[1,1'-Bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II)
$Pd(dppf)Cl_2$	[1,1′-bis(diphenylphosphino)-ferrocene]dichloropalladium(II)
PG	protecting group
PTFE	polytetrafluoroethylene or Teflon

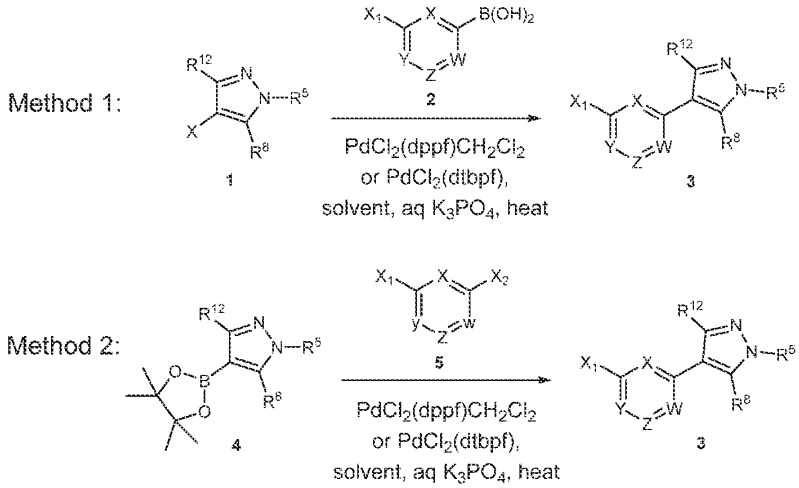
SiO_2	silica oxide or silica gel
S-Phos or SPhos	dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphine
TBAF	tetra-*N*-butylammonium fluoride
TBAI	tetra-*N*-butylammonium iodide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
X-Phos or XPhos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl
XPhos Pd G2	2nd generation XPhos precatalyst, chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)

The compounds of the present invention may be synthesized by many methods available to those skilled in the art of organic chemistry (Maffrand, J. P. et al., Heterocycles, 16(1):35-7 (1981)). General synthetic schemes for preparing compounds of the present invention are described below. These schemes are illustrative and are not meant to limit the possible techniques one skilled in the art may use to prepare the compounds disclosed herein. The numbering of R groups within the scheme are for illustrative purposes and are not intended to limit the claims. Different methods to prepare the compounds of the present invention will be evident to those skilled in the art. Additionally, the various steps in the synthesis may be performed in an alternate sequence in order to give the desired compound or compounds.

Examples of compounds of the present invention prepared by methods described in the general schemes are given in the intermediates and examples section set out hereinafter. Example compounds are typically prepared as racemic mixtures. Preparation of homochiral examples may be carried out by techniques known to one skilled in the art. For example, homochiral compounds may be prepared by separation of racemic products by chiral phase preparative HPLC or SFC. Alternatively, the example compounds may be prepared by methods known to give enantiomerically enriched products. These include, but are not limited to, the incorporation of chiral auxiliary functionalities into racemic intermediates which serve to control the diastereoselectivity of transformations, providing enantio-enriched products upon cleavage of the chiral auxiliary.

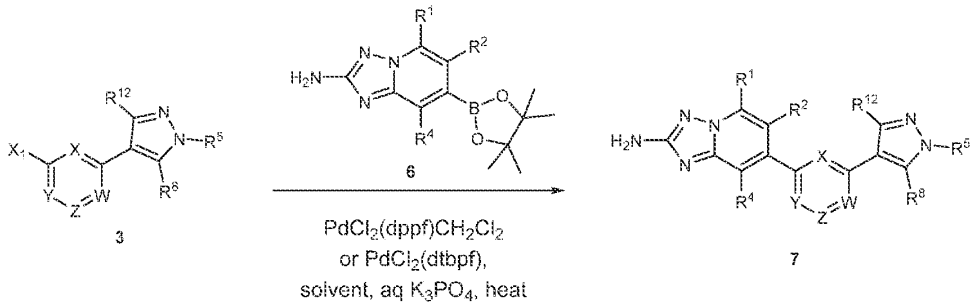
Scheme 1 illustrates two possible approaches to the synthesis of intermediates exemplified by **3**. In Method 1, a Suzuki coupling reaction between 1-alkyl-4-halopyrazoles **1** and haloarylboronic acids **2** (Miyaura, N. and Suzuki, A. Chemical Reviews, 95:2457-2483, 1995) can be performed to provide intermediates **3**. Alternatively, Method 2 can provide intermediates **3** via Suzuki coupling reaction between 1-alkylpyrazole-4-boronates **4** and dihaloaryl compounds **5**.

Scheme 1



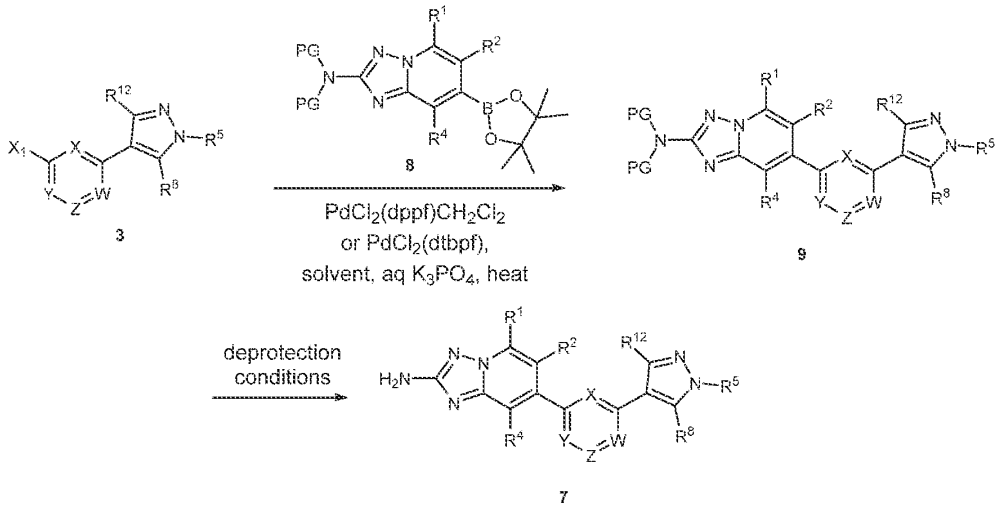
Scheme 2 summarizes one approach to compounds **7**. Suzuki coupling of intermediates **3** with boronate esters **6** can provide products **7** in a single step.

Scheme 2



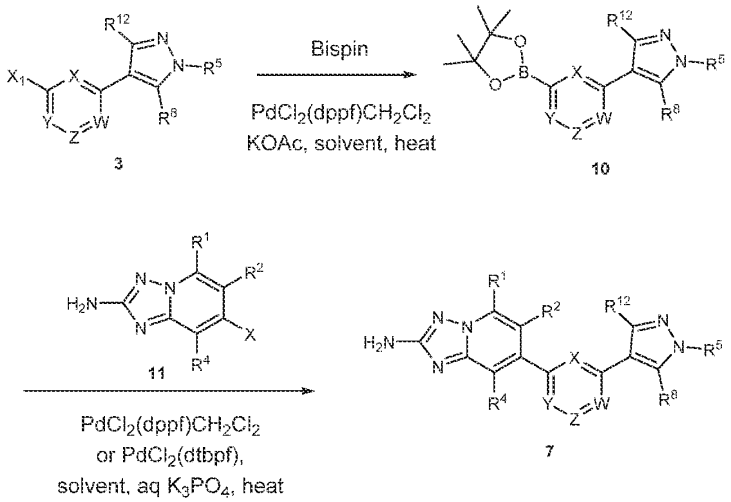
Scheme 3 illustrates an alternative approach to compounds **7**. Suzuki coupling of intermediates **3** with *N*-protected boronate esters **8**, where *N*-protection of **8** can be achieved either via incorporation of two *tert*-butoxycarbonyl groups on the nitrogen atom, or via incorporation of the nitrogen atom into a 2,5-dimethylpyrrole ring to serve as protection, or via some other *N*-protecting group or groups known to those skilled in the art, can provide products such as **9**. Compounds such as **9** can be converted to products **7** in a subsequent step through use of various *N*-deprotection conditions known to those skilled in the art.

Scheme 3



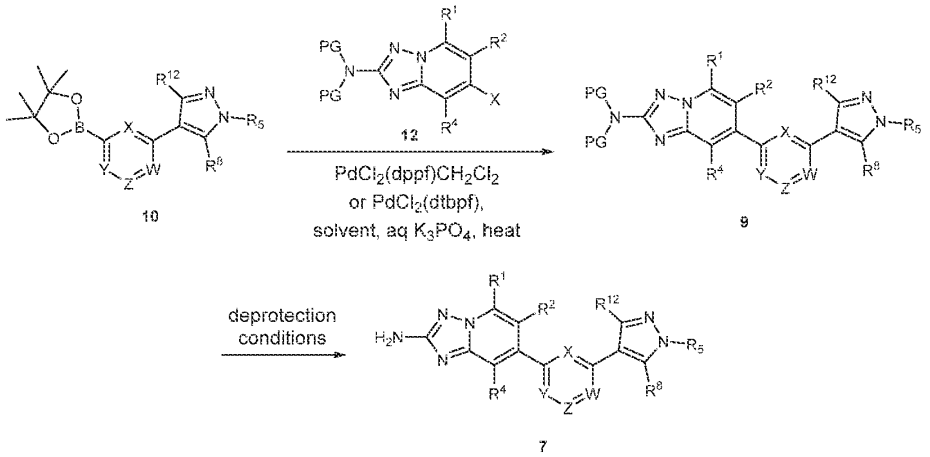
Scheme 4 exemplifies yet another approach to compounds **7**. Intermediates **3** can be converted to boronate esters **10** via standard conditions. Compounds such as **10** can then act as reactants in a Suzuki coupling step with halides **11** to provide products **7**.

Scheme 4



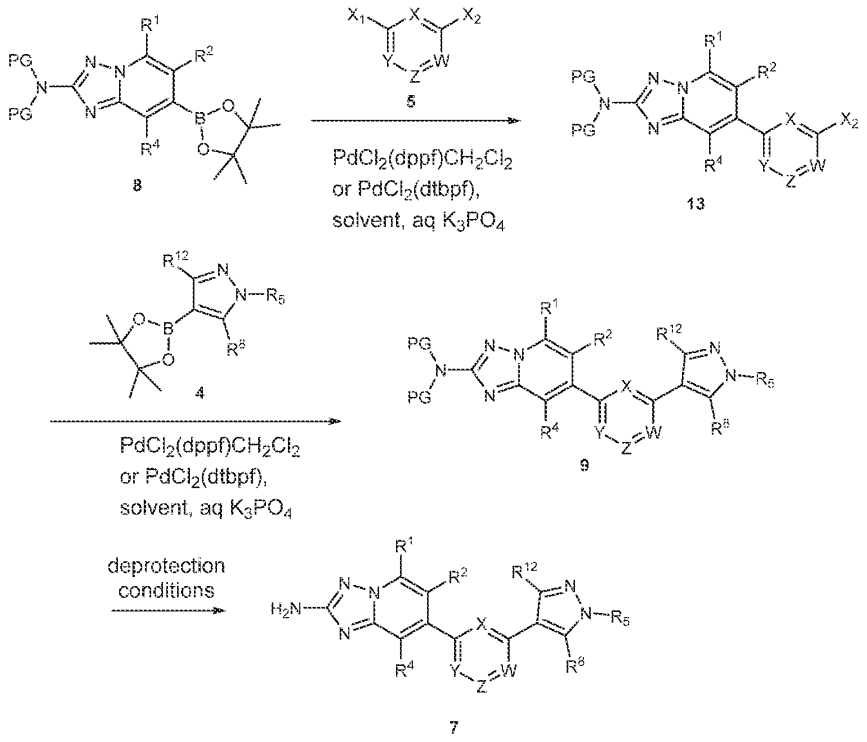
Scheme 5 illustrates yet another approach to compounds **7**. Compounds **10** are made to react with *N*-protected halides **12** via a Suzuki reaction to give materials such as **9**. *N*-protection of **12** can be achieved either via incorporation of two *tert*-butoxycarbonyl groups on the nitrogen atom, or via incorporation of the nitrogen atom into a 2,5-dimethylpyrrole ring to serve as protection, or via some other *N*-protecting group or groups known to those skilled in the art. Subsequent *N*-deprotection of **9** to give products **7** can be achieved through use of various *N*-deprotection conditions known to those skilled in the art.

Scheme 5



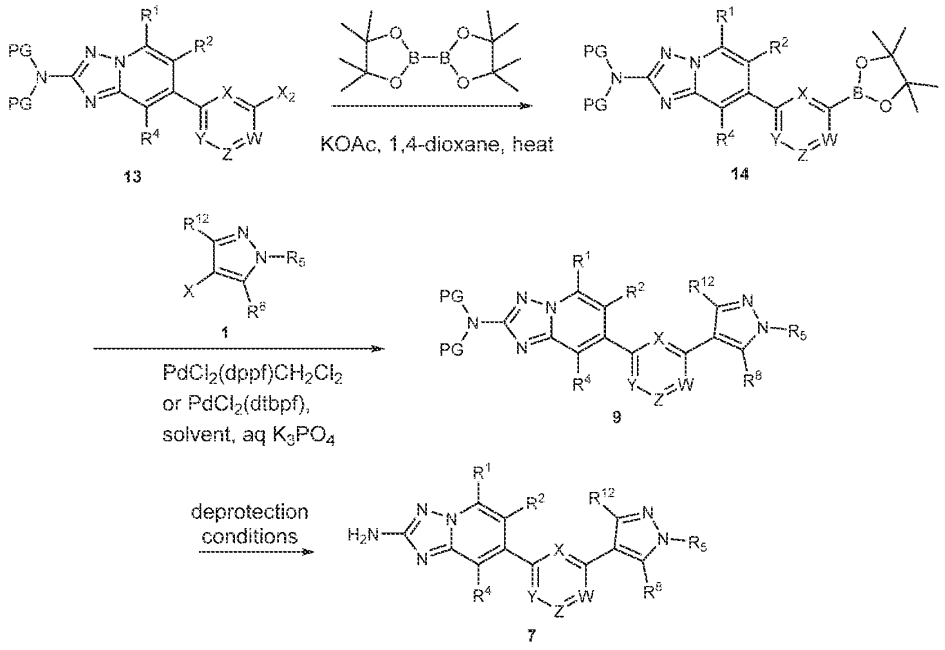
Scheme 6 provides yet another approach to compounds **7**. Here, a Suzuki coupling between *N*-protected boronate **8** and dihaloaryl **5** provides intermediates such as **13**. Careful selection of the two halogen substituents of starting materials **5** by one skilled in the art can provide for regiochemical control of products **13** in terms of various substitutions on the six-membered ring of **13**. Further modification of halides **13** by another Suzuki coupling with boronate esters such as **4** gives rise to compounds **9**, which, upon removal of *N*-protection, provide products **7**.

Scheme 6



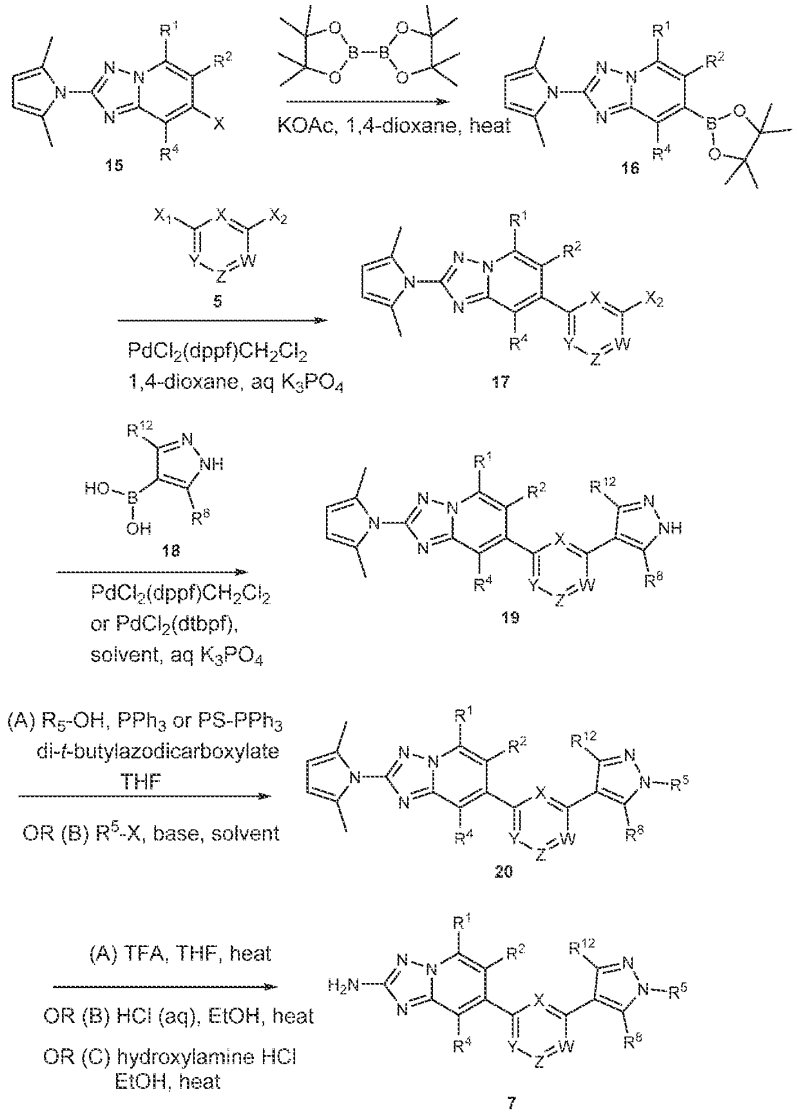
Scheme 7 represents yet another method for the procurement of compounds such as **7**. These preparations involve the transformation of intermediates **13** into boronate esters **14**. Esters such as **14** can then participate in a Suzuki coupling with substituted halopyrazoles **1** to furnish compounds such as **9**. Finally, an *N*-deprotection step provides products **7**.

Scheme 7



Scheme 8 summarizes an alternate method for the preparation of compounds **7**. The dimethylpyrrole protected ATP halide **15** is first converted to pinacol boronate ester **16** via typical conditions. Ester **16** then serves as a Suzuki coupling partner with various dihaloaryl species **5** to provide compounds such as **17**, which further becomes a coupling partner with 1-H-pyrazole-4-boronic acid **18** in a second Suzuki coupling reaction to provide products **19**. Functionalization of **19** via various synthetic methods including, but not limited to, alkylation or Mitsunobu reaction, gives rise to compounds such as **20**. Deprotection of the dimethylpyrrole protecting group of **20** using one of a variety of conditions known to those skilled in the art gives rise to products **7**.

Scheme 8



Purification of intermediates and final products was carried out via either normal phase or reverse phase chromatography, or by preparative chiral SFC chromatography, where applicable. Normal phase chromatography was carried out using pre-packed silica cartridges, typically eluting with either gradients of hexanes and ethyl acetate or gradients of hexanes and acetone or gradients of hexanes and dichloromethane or gradients of dichloromethane and methanol or gradients of dichloromethane and acetone. Reverse

phase preparative HPLC purification was typically carried out using C18 or phenyl columns eluting with gradients of Solvent A (95% water, 5% acetonitrile, 0.1% TFA) and Solvent B (5% water, 95% acetonitrile, 0.1% TFA), or with gradients of Solvent A (95% water, 5% acetonitrile with 10 mM ammonium acetate) and Solvent B (95% acetonitrile, 5% water with 10 mM ammonium acetate). In the majority of examples, fraction collection was triggered by UV (220 nm) and MS (ESI +). In a minority of examples, fraction collection was triggered by UV (220 nm) only. Preparative chiral SFC chromatography was carried out using various preparative SFC columns described below, typically eluting with isocratic mixtures of various mobile phase pairs (defined as SFC Solvents) described below. Fraction collection was triggered by UV. Homochiral products labeled as "enantiomer 1" were the first of two enantiomers to elute from the preparative SFC column, and homochiral products labeled as "enantiomer 2" were the second of two enantiomers to elute from the preparative SFC column.

SFC Column 1: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 μm particles
SFC Column 2: Daicel Chiralpak AS-H, 30 mm x 250 mm, 5 μm particles
SFC Column 3: Regis Technologies Inc. Whelk-O 1 (S,S), 21 mm x 250 mm, 5 μm particles
SFC Column 4: Daicel Chiralpak IA, 30 mm x 250 mm, 5 μm particles
SFC Column 5: Daicel Chiralpak AD-H, 30 mm x 250 mm, 5 μm particles
SFC Column 6: Daicel Chiralpak OD-H, 30 mm x 250 mm, 5 μm particles
SFC Column 7: YMC Chiral ART Amylose-SA, 30 mm x 250 mm, 5 μm particles
SFC Column 8: Daicel Chiralpak IH, 21 mm x 250 mm, 5 μm particles
SFC Column 9: Daicel Chiralcel OB-H, 19 mm x 250 mm, 5 μm particles
SFC Column 10: Regis Technologies Inc. Whelk-O 1 (S,S), 19 mm x 250 mm, 5 μm particles

SFC Solvents 1: Solvent A = supercritical CO_2; Solvent B = MeOH with 0.1% DEA
SFC Solvents 2: Solvent A = supercritical CO_2; Solvent B = *i*-PrOH with 0.1% NH_4OH
SFC Solvents 3: Solvent A = supercritical CO_2; Solvent B = MeOH with 0.1% NH_4OH
SFC Solvents 4: Solvent A = supercritical CO_2; Solvent B = 1:1 Acetonitrile:MeOH
SFC Solvents 5: Solvent A = supercritical CO_2; Solvent B = *i*-PrOH with 0.1% DEA

SFC Solvents 6: Solvent A = supercritical CO_2; Solvent B = EtOH with 0.1% NH_4OH

In a majority of examples, the following analytical LCMS injection methods were used to determine product mass (m/z) and final purity:

Analytical LCMS Method TFA-01: Column: Waters XBridge C18, 2.1 x 50 mm, 1.7 µm particle size; Mobile phase A: 5:95 acetonitrile:water with 0.1% TFA; Mobile phase B: 95:5 acetonitrile:water with 0.1% TFA; Temperature: 50 °C; Gradient: 0-100% B over 3 min, then a 0.5 min hold at 100% B; Flow Rate: 1 mL/min; Detection: UV at 220 nm and MS (ESI +/-).

Analytical LCMS Method TFA-02: Column: Waters Acquity BEH C18, 2.1 x 50 mm, 1.7 µm particle size; Mobile phase A: 2:98 water:acetonitrile with 0.1% TFA; Mobile phase B: 98:2 acetonitrile:water with 0.1% TFA; Gradient: 0-100% B over 2 minutes with 1 min hold at 100% B; Flow Rate: 1 mL/min; Detection: UV at 220 nm and MS (ESI +/-).

Analytical LCMS Method TFA-03: Column: Waters XBridge C8, 50 x 4.6 mm, 5 µm particle size; Mobile phase A: 0.1% TFA in water; Mobile phase B: 0.1% TFA in acetonitrile; Flow Rate: 1.5 mL/min.

Analytical LCMS Method TFA-04: Column: Waters Aquity BEH C18, 50 x 3.0 mm, 1.7µm particle size; Mobile Phase A: 0.1% TFA in water; Mobile Phase B: 0.1% TFA in acetonitrile; Flow Rate: 1.0 mL/min.

Analytical LCMS Method TFA-05: Column: Phenomenex Kinetex XB- C18, 75 x 3mm, 2.6 µm particle size, Mobile phase A: 0.1% TFA in water, Mobile phase B: 0.1% TFA in acetonitrile; Flow Rate: 1.0 mL/min.

Analytical LCMS Method AA-01: Column: Waters XBridge C18, 2.1 x 50 mm, 1.7 µM particle size; Mobile phase A: 5:95 acetonitrile:water with 10 mM ammonium acetate; Mobile phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate; Temperature: 50 °C; Gradient: 0-100% B over 3 min, then a 0.5 min hold at 100% B; Flow Rate: 1 mL/min; Detection: UV at 220 nm and MS (ESI +/-).

Analytical LCMS Method AA-02: Column: Waters Acquity BEH C18, 2.1 x 50 mm, 1.7 µm particle size; Mobile phase A: 5:95 water:acetonitrile with 10 mM NH_4OAc; Mobile phase B: 95:5 acetonitrile:water with 10 mM ammonium acetate; Gradient: 0-100% B over 2 minutes with 1 min hold at 100% B; Flow Rate: 1 mL/min; Detection: UV at 220 nm and MS (ESI +/-).

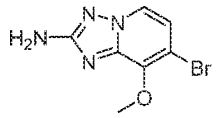
Analytical LCMS Method AA-03: Column: Waters XSelect CSH C18, 50 x 4.6 mm, 3.5 µm particle size, Mobile phase A: water with 10 mM ammonium acetate, Mobile phase B: acetonitrile; Flow Rate: 1 mL/min.

Analytical LCMS Method AF-01: Column: Phenomenex Kinetex XB - C18, 75 x 3.0 mm, 2.6 µm particle size; Mobile Phase A: 98:2 water:acetonitrile with 5mM ammonium formate; Mobile Phase B: 98:2 acetonitrile:water with 5mM ammonium formate; Flow Rate: 1.0 mL/min.

Analytical LCMS Method AF-02: Column: Waters Aquity BEH C18, 50 x 3.0 mm, 1.7µm particle size; Mobile Phase A: 98:2 water:acetonitrile with 5mM ammonium formate; Mobile Phase B: 98:2 acetonitrile:water with 5mM ammonium formate; Flow Rate: 0.7 mL/min.

EXAMPLES

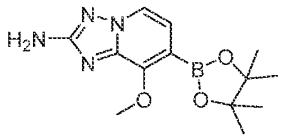
Intermediate 1: 7-bromo-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



To a stirred solution of 4-bromo-3-methoxypyridin-2-amine (500 mg, 2.46 mmol) in 1,4-dioxane (5 mL) was added ethoxycarbonyl isothiocyanate (388 mg, 2.96 mmol). The reaction mixture was stirred at RT for 12 h. To the reaction mixture was then added hydroxylamine hydrochloride (832 mg, 12.0 mmol), DIPEA (1.25 mL, 7.18 mmol) and EtOH (5 mL). The resulting mixture was stirred at 60 °C for 12 h. Solvent was evaporated and the residue was dissolved in 5 mL of DMSO and filtered. The crude filtrate was purified by reverse phase column chromatography (Teledyne Isco Redisep 80 g C18 column, eluting with 0.1% TFA in water/acetonitrile) to provide 7-bromo-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine TFA salt (500 mg, 1.33 mmol, 55.6 % yield) as a light grey solid.

LCMS (ESI, m/z) 245.0 $[M+3H]^+$

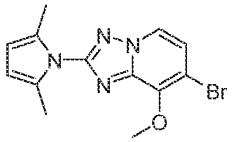
Intermediate 2: 8-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



In a 20 mL Chemglass reaction vial, to a stirred solution of 7-bromo-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine TFA salt (180 mg, 0.504 mmol) in dioxane (4 mL) was added bis(pinacolato)diboron (192 mg, 0.756 mmol) and potassium acetate (148 mg, 1.51 mmol). The reaction mixture was purged with nitrogen gas for 5 min and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (20.6 mg, 0.025 mmol) was added. The vial was sealed and the mixture was then stirred at 80 °C for 12 h. The crude mixture containing 8-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine was used directly in the next step without isolation or purification. A 100% yield was assumed.

LCMS (ESI, m/z) 291.0 $[M+H]^+$

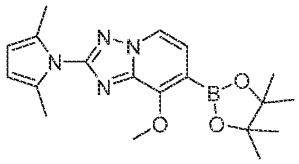
Intermediate 3: 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridine



To a stirred suspension of 7-bromo-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (1.70 g, 6.99 mmol) in toluene (30 mL) was added hexane-2,5-dione (4.79 g, 42.0 mmol). The reaction mixture was heated to 120 °C for 16 h using a Dean-Stark apparatus. Solvent was removed to yield crude material which was purified by column chromatography using silica gel (40 g) eluting with 0-20% of EtOAc/petroleum ether to afford 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridine (1.20 g, 2.40 mmol, 34.4 % yield) as a pink solid.

LCMS (ESI, m/z) 321.0 $[M+H]^+$

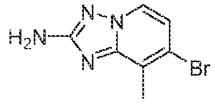
Intermediate 4: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine



In a Chemglass reaction vial, to a stirred solution of 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridine (600 mg, 1.87 mmol) in dioxane (10 mL) was added bis(pinacolato)diboron (569 mg, 2.24 mmol) and potassium acetate (550 mg, 5.60 mmol). The reaction mixture was purged with nitrogen gas and 1,1'-bis(diphenylphosphino)-ferrocenedichloro palladium(II) dichloromethane complex (153 mg, 0.187 mmol) was added. The vial was sealed and reaction mixture was then stirred at 100 °C for 1.5 h. Concentration of the mixture provided a crude residue which was purified by silica column chromatography, eluting with 20% of EtOAc/petroleum ether to afford 2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (350 mg, 0.931 mmol, 49.9 % yield).

LCMS (ESI, m/z) 368.8 $[M+H]^+$

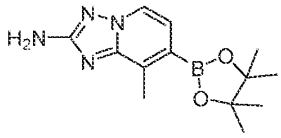
Intermediate 5: 7-bromo-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



In a 40 mL Chemglass reaction vial, to a stirred solution of 4-bromo-3-methylpyridin-2-amine (500 mg, 2.67 mmol) in 1,4-dioxane (5 mL) was added ethoxycarbonyl isothiocyanate (421 mg, 3.21 mmol). The reaction mixture was stirred at RT for 12 h. Then to the reaction mixture was added hydroxylamine hydrochloride (874 mg, 12.6 mmol), DIPEA (1.32 mL, 7.54 mmol) and EtOH (5 mL). The resulting mixture was stirred at 60 °C for 12 h. Solvent was evaporated and the residue was dissolved in 5 mL of DMSO and filtered. The filtrate was purified by reverse phase column chromatography (Teledyne Isco Redisep 80 g C18 column, eluting with 0.1% TFA in water/acetonitrile) to provide 7-bromo-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine TFA salt (500 mg, 1.32 mmol, 52.5 % yield) as a light grey solid.

LCMS (ESI, m/z) 229.0 $[M+2H]^+$

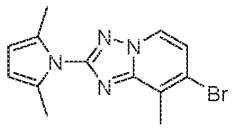
Intermediate 6: 8-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



In a Chemglass reaction vial, to a stirred solution of 7-bromo-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine TFA salt (180 mg, 0.528 mmol) in dioxane (4 mL) was added bis(pinacolato)diboron (201 mg, 0.792 mmol) and potassium acetate (155 mg, 1.58 mmol). The reaction mixture was purged with nitrogen gas for 5 min and then and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (21.6 mg, 0.0260 mmol) was added. The vial was sealed and the reaction mixture was stirred at 80 °C for 12 h. The crude mixture containing 8-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine was used directly in the next step without isolation or purification. A 100% yield was assumed.

LCMS (ESI, m/z) 275.2 $[M+H]^+$

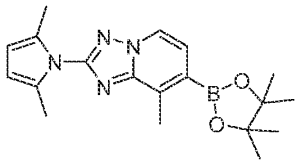
Intermediate 7: 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridine



To a stirred suspension of 7-bromo-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (1.00 g, 4.40 mmol) in toluene (30 mL) was added hexane-2,5-dione (3.02 g, 26.4 mmol). The reaction mixture was heated to 120 °C for 16 h using a Dean-Stark apparatus. Solvent was removed to yield crude material which was purified by column chromatography using silica gel (80 g) eluting with 0-50% of EtOAc/petroleum ether to afford 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridine (570 mg, 1.87 mmol, 42.4 % yield) as an off white solid.

LCMS (ESI, m/z) 304.9 $[M+H]^+$

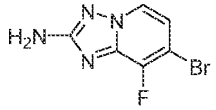
Intermediate 8: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine



In a Chemglass reaction vial, to a stirred solution of 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridine (560 mg, 1.84 mmol) in dioxane (10 mL) was added bis(pinacolato)diboron (559 mg, 2.20 mmol) and potassium acetate (540 mg, 5.50 mmol). The reaction mixture was purged with nitrogen gas for 2 min and 1,1'-bis(diphenylphosphino)-ferrocenedichloro palladium(II) dichloromethane complex (150 mg, 0.183 mmol) was added. The vial was sealed and the mixture was then stirred at 100 °C for 1.5 h. Solvent was evaporated and the crude residue was purified by column chromatography using silica gel, eluting with 0-20% of EtOAc/petroleum ether to yield 2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (550 mg, 1.423 mmol, 78 % yield) as a white solid.

LCMS (ESI, m/z) 353.2 $[M+H]^+$

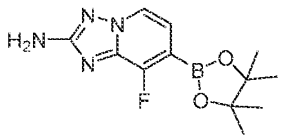
Intermediate 9: 7-bromo-8-fluoro-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



In a Chemglass reaction vial, to a stirred solution of 4-bromo-3-fluoropyridin-2-amine (500 mg, 2.62 mmol) in 1,4-dioxane (5 mL) was added ethoxycarbonyl isothiocyanate (412 mg, 3.14 mmol). The reaction mixture was stirred at RT for 12 h. Then to the reaction mixture was added hydroxylamine hydrochloride (863 mg, 12.4 mmol), DIPEA (1.30 mL, 7.45 mmol) and EtOH (5 mL). The vial was sealed and the resulting mixture was stirred at 60 °C for 12 h. Solvent was evaporated and the residue was dissolved in 5 mL of DMSO and filtered. The filtrate was purified by reverse phase column chromatography (Teledyne Isco Redisep C18 column, eluting with 0.1% ammonium formate in water/acetonitrile) to yield 7-bromo-8-fluoro-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (300 mg, 1.23 mmol, 49.7 % yield) as a light grey solid.

LCMS (ESI, m/z) 231.0 $[M+H]^+$

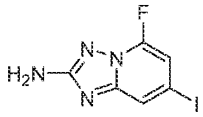
Intermediate 10: 8-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



In a Chemglass reaction vial, to a stirred solution of 7-bromo-8-fluoro-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (100 mg, 0.433 mmol) in dioxane (3 mL) was added bis(pinacolato)diboron (132 mg, 0.519 mmol) and potassium acetate (106 mg, 1.082 mmol). The reaction mixture was purged with nitrogen gas for 2 min and 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (35 mg, 0.043 mmol) was added. The vial was sealed and the reaction mixture was then stirred at 80 °C for 1.5 h. The crude mixture containing 8-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine was used directly in the next step without isolation or purification. A 100% yield was assumed.

LCMS (ESI, m/z) 279.0 $[M+H]^+$

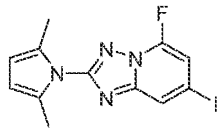
Intermediate 11: 5-fluoro-7-iodo-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



To a stirred solution of 6-fluoro-4-iodopyridin-2-amine (3.50 g, 14.7 mmol) in 1,4-dioxane (40 mL) was added ethoxycarbonyl isothiocyanate (2.08 mL, 17.6 mmol). The reaction mixture was stirred at RT for 16 h. Then to the reaction mixture was added hydroxylamine hydrochloride (3.39 g, 48.8 mmol), DIPEA (7.10 mL, 40.6 mmol) and EtOH (20 mL) and methanol (20 mL). The resulting mixture was stirred at 60 °C for 16 h. Solvent was evaporated and the residue was dissolved in 20 mL of DMSO and filtered through a pad of Celite. The filtrate was purified by reverse phase column chromatography (Teledyne Isco Redisep 80 g C18 column, eluting with 0.1% ammonium formate in water/acetonitrile) to yield 5-fluoro-7-iodo-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (1.20 g, 1.47 mmol, 18.0 % yield) as a pale brown solid.

LCMS (ESI, m/z) 279.0 $[M+H]^+$

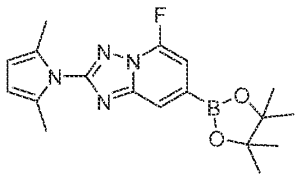
Intermediate 12 : 2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-fluoro-7-iodo-[1,2,4]triazolo[1,5-*a*]pyridine



To a solution of 5-fluoro-7-iodo-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (1.00 g, 3.60 mmol) in toluene (10 mL) was added hexane-2,5-dione (4.22 mL, 36.0 mmol) and acetic acid (1.03 mL, 18.0 mmol). The reaction mixture was heated in a microwave reactor at 140 °C for 16 h. Solvent was removed to yield crude material which was purified by column chromatography using silica gel and eluting with 0-20% of EtOAc/petroleum ether to afford 2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-fluoro-7-iodo-[1,2,4]triazolo[1,5-*a*]pyridine (911 mg, 2.43 mmol, 67.5 % yield) as a pale brown solid.

LCMS (ESI, m/z) 357.0 $[M+H]^+$.

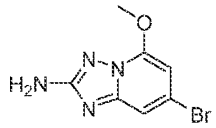
Intermediate 13: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine



In a Chemglass reaction vial, to a stirred solution of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-fluoro-7-iodo-[1,2,4]triazolo[1,5-*a*]pyridine (316 mg, 0.887 mmol) in dioxane (20 mL) was added bis(pinacolato)diboron (451 mg, 1.77 mmol) and potassium acetate (261 mg, 2.66 mmol). The reaction mixture was purged with nitrogen gas for 10 min and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (73 mg, 0.089 mmol) was added. The vial was sealed and the reaction mixture was then stirred at 100 °C for 10 h. The crude mixture containing 2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (316 mg, 0.887 mmol, quantitative yield) was used directly in the next step without isolation or purification.

LCMS (ESI, m/z) 247.0

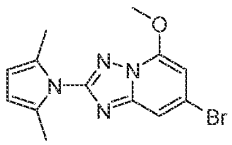
Intermediate 14 : 7-bromo-5-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



To a stirred solution of 4-bromo-6-methoxypyridin-2-amine (1.10 g, 5.42 mmol) in 1,4-dioxane (15 mL) was added ethoxycarbonyl isothiocyanate (0.853 g, 6.50 mmol). The reaction mixture was stirred at RT for 16 h. Then to the reaction mixture was added hydroxylamine hydrochloride (2.25 g, 32.3 mmol), DIPEA (5.64 mL, 32.3 mmol) and EtOH (15 mL) and methanol (15 mL). The resulting mixture was stirred at 60 °C for 16 h. Solvent was evaporated and the residue was dissolved in 15 mL of DMSO and filtered. The filtrate was purified by reverse phase column chromatography (Teledyne Isco Redisep 40 g C18 column, eluting with 5 mM ammonium formate in water/acetonitrile) to yield 7-bromo-5-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (1.20 g, 4.95 mmol, 92 % yield) as a pale brown solid.

LCMS (ESI, m/z): 245.0 $[M+2H]^+$

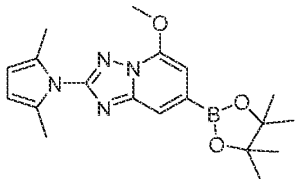
Intermediate 15: 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-methoxy-[1,2,4]triazolo[1,5-*a*]pyridine



To a mixture of 7-bromo-5-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (0.560 g, 2.30 mmol) in toluene (10 mL) was added hexane-2,5-dione (2.63 g, 23.0 mmol) and acetic acid (0.659 mL, 11.5 mmol). The reaction mixture was heated in a microwave reactor at 140 °C for 8 h. Solvent was removed to yield crude material which was purified by column chromatography using silica gel and eluting with 10-15% of EtOAc/hexane to afford 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-methoxy-[1,2,4]triazolo[1,5-*a*]pyridine (0.37 g, 1.13 mmol, 49.0 % yield) as a light brown solid.

LCMS (ESI, m/z) 323.0 $[M+2H]^+$

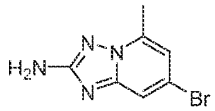
Intermediate 16: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine



To a stirred mixture of 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-methoxy-[1,2,4]triazolo[1,5-*a*]pyridine (700 mg, 2.18 mmol) in dioxane (15 mL) was added bis(pinacolato)diboron (1.10 g, 4.36 mmol) and potassium acetate (642 mg, 6.54 mmol). The reaction mixture was purged with nitrogen gas for 5 min and 1,1'-bis(diphenylphosphino)-ferrocenedichloro palladium(II) dichloromethane complex (178 mg, 0.218 mmol) was added. The reaction mixture was then stirred at 100 °C for 10 h. The mixture was diluted with EtOAc (20 mL), filtered through a bed of Celite and concentrated to yield crude 2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (803 mg, 2.18 mmol, 100 % yield) which was used directly in the next step without isolation or purification. A 100% yield was assumed.

LCMS (ESI, m/z) 369.2 $[M+H]^+$

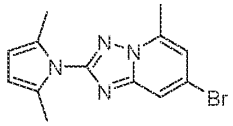
Intermediate 17: 7-bromo-5-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



In a Chemglass reaction vial, to a stirred solution of 4-bromo-6-methylpyridin-2-amine (1.50 g, 8.02 mmol) in 1,4-dioxane (15 mL) was added ethoxycarbonyl isothiocyanate (1.42 mL, 12.0 mmol). The reaction mixture was stirred at RT for 12 h. To the reaction mixture was added hydroxylamine hydrochloride (1.64 g, 23.6 mmol), DIPEA (2.47 mL, 14.1 mmol) and EtOH (10 mL). The vial was capped and the resulting mixture was stirred at 60 °C for 12 h. Solvent was evaporated and the residue was dissolved in 25 mL of DMSO and filtered through a pad of Celite. The filtrate was purified by reverse phase column chromatography (Teledyne Isco Redisep C18 column, eluting with 0.1% ammonium formate in water/acetonitrile) to yield 7-bromo-5-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (600 mg, 2.48 mmol, 52.7 % yield) as a yellow solid.

LCMS (ESI, m/z) 227.0 $[M+H]^+$

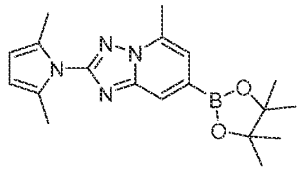
Intermediate 18: 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyridine



To a solution of 7-bromo-5-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (650 mg, 2.86 mmol) in toluene (10 mL) was added hexane-2,5-dione (1.96 g, 17.2 mmol) and acetic acid (0.819 mL, 14.3 mmol). The reaction mixture was heated in a microwave reactor at 140 °C for 8 h. Solvent was removed to yield crude material which was purified by column chromatography using silica gel and eluting with 0-20% of EtOAc/petroleum ether to afford 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyridine (300 mg, 0.811 mmol, 28.3 % yield) as a light brown solid.

LCMS (ESI, m/z) 323.0 $[M+2H]^+$

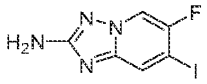
Intermediate 19: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine



In a Chemglass reaction vial, to a stirred solution of 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyridine (150 mg, 0.492 mmol) in dioxane (6 mL) was added bis(pinacolato)diboron (250 mg, 0.983 mmol) and potassium acetate (145 mg, 1.475 mmol). The reaction mixture was purged with nitrogen gas for 2 min and 1,1'-bis(diphenylphosphino)-ferrocenedichloro palladium(II) dichloromethane complex (40 mg, 0.049 mmol) was added. The vial was sealed and the reaction mixture was stirred at 100 °C for 2 h. The resulting mixture containing crude 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-methyl-[1,2,4]triazolo[1,5-a]pyridine (173 mg, 0.492 mmol, 100 % yield) was used directly in the next step without isolation or purification. A 100 % yield was assumed.

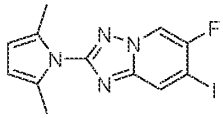
LCMS (ESI, m/z): 353.2 $[M+H]^+$

Intermediate 20: 6-fluoro-7-iodo-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



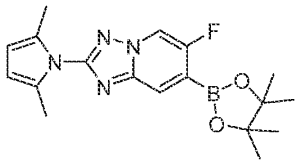
To a stirred solution of 5-fluoro-4-iodopyridin-2-amine (2.00 g, 8.40 mmol) in 1,4-dioxane (20 mL) was added ethoxycarbonyl isothiocyanate (1.18 mL, 10.1 mmol). The reaction mixture was stirred at RT for 3 h. To the reaction mixture was added hydroxylamine hydrochloride (2.92 g, 42.0 mmol), DIPEA (5.87 mL, 33.6 mmol) and EtOH (20 mL). The resulting mixture was stirred at 60 °C for 3 h. Solvent was evaporated and the residue was dissolved in 50 mL of DMSO and filtered through a pad of Celite. The filtrate was purified by reverse phase column chromatography (Teledyne Isco Redisep C18 column, eluting with 0.1% ammonium formate in water/acetonitrile) to yield 6-fluoro-7-iodo-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (2.00 g, 5.97 mmol, 71.1 % yield) as a white solid. LCMS (ESI, m/z) 279.0 $[M+H]^+$.

Intermediate 21: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-7-iodo-[1,2,4]triazolo[1,5-*a*]pyridine



To a solution of 6-fluoro-7-iodo-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (1.00 g, 3.60 mmol) in toluene (10 mL) was added hexane-2,5-dione (2.46 g, 21.6 mmol) and acetic acid (1.03 mL, 18.0 mmol). The reaction mixture was heated in a microwave reactor at 140 °C for 8 h. Solvent was removed to yield crude material which was purified by column chromatography using silica gel and eluting with 0-10% of EtOAc/petroleum ether to afford 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-7-iodo-[1,2,4]triazolo[1,5-*a*]pyridine (1.00 g, 1.16 mmol, 32.3 % yield) as a light yellow liquid.
LCMS (ESI, m/z) 357.0 $[M+H]^+$

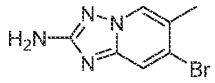
Intermediate 22: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine



In a Chemglass reaction vial, to a stirred solution of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-7-iodo-[1,2,4]triazolo[1,5-*a*]pyridine (500 mg, 1.40 mmol) in dioxane (5 mL) was added bis(pinacolato)diboron (713 mg, 2.81 mmol) and potassium acetate (413 mg, 4.21 mmol). The reaction mixture was purged with nitrogen gas for 2 min and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (115 mg, 0.140 mmol) was added. The vial was sealed and the reaction mixture was stirred at 100 °C for 2 h. The resulting crude mixture containing 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (500 mg, 1.40 mmol, 100 % yield) was used directly in the next step without isolation or purification. A 100 % yield was assumed.

LCMS (ESI, m/z) 274.9 $[M-82]^+$

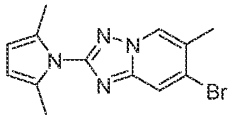
Intermediate 23: 7-bromo-6-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



To a stirred solution of 4-bromo-5-methylpyridin-2-amine (610 mg, 3.26 mmol) in 1,4-dioxane (15 mL) was added ethoxycarbonyl isothiocyanate (0.458 mL, 3.91 mmol). The reaction mixture was stirred at RT for 12 h. Then to the reaction mixture was added hydroxylamine hydrochloride (1.13 g, 16.3 mmol), DIPEA (2.28 mL, 13.1 mmol) and EtOH (10 mL). The resulting mixture was stirred at 60 °C for 3 h. The solvent was evaporated and the residue was dissolved in 10 mL of DMSO and filtered through a pad of Celite. The filtrate was purified by reverse phase column chromatography (Teledyne Isco Redisep C18 column, eluting with 0.1% ammonium formate in water/acetonitrile) to yield 7-bromo-6-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (260 mg, 0.475 mmol, 14.6 % yield) as a white solid.

LCMS (ESI, m/z) 227.0 $[M+H]^+$.

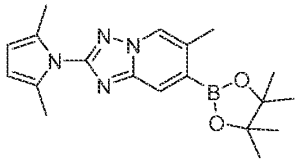
Intermediate 24: 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-methyl-[1,2,4]triazolo[1,5-*a*]pyridine



To a solution of 7-bromo-6-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (0.430 g, 1.89 mmol) in toluene (6 mL) was added hexane-2,5-dione (1.30 g, 11.4 mmol) and acetic acid (0.542 mL, 9.47 mmol). The reaction mixture was heated in a microwave reactor at 140 °C for 8 h. Solvent was removed to yield crude material which was purified by column chromatography using silica gel and eluting with 0-10% of EtOAc/petroleum ether to afford 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-methyl-[1,2,4]triazolo[1,5-*a*]pyridine (240 mg, 0.728 mmol, 38.4 % yield) as a light brown solid.

LCMS (ESI, m/z) 307.0 $[M+2H]^+$

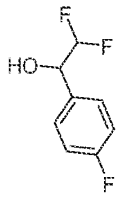
Intermediate 25: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine



In a Chemglass reaction vial, to a stirred solution of 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-methyl-[1,2,4]triazolo[1,5-*a*]pyridine (240 mg, 0.786 mmol) in dioxane (6 mL) was added bis(pinacolato)diboron (399 mg, 1.57 mmol) and potassium acetate (232 mg, 2.36 mmol). The reaction mixture was purged with nitrogen gas for 2 min and 1,1'-bis(diphenylphosphino)-ferrocenedichloro palladium(II) dichloromethane complex (64.2 mg, 0.079 mmol) was added. The vial was sealed and the reaction mixture was stirred at 100 °C for 2 h. The resulting crude mixture containing 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (277 mg, 0.786 mmol, 100 % yield) was used directly in the next step without isolation or purification. A 100 % yield was assumed.

LCMS (ESI, m/z) 353.2 $[M+H]^+$

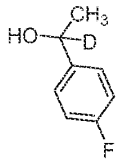
Intermediate 26: 2,2-difluoro-1-(4-fluorophenyl)ethan-1-ol



To a solution of (difluoromethyl)trimethylsilane (2.52 g, 20.3 mmol) and 4-fluorobenzaldehyde (1.26 g, 10.15 mmol) in DMF (33 mL) at RT was added cesium fluoride (0.210 g, 1.42 mmol), and the reaction mixture was stirerd at RT for 12 h. TBAF, 1M solution in THF (20.3 mL, 20.3 mmol) was added, and the reaction mixture was stirred at RT for 1 h. Water and diethyl ether were added and the aqueous layer was extracted with ether (x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was evaporated in vacuo to give the crude product. The crude product was purified by silica gel chromatography eluting with 0-50% ethyl acetate/hexanes to give 2,2-difluoro-1-(4-fluorophenyl)ethan-1-ol (1.45 g, 8.23 mmol, 81% yield).

^{1}H NMR (500 MHz, CDCl3) δ 7.43 (dd, *J*=8.7, 5.4 Hz, 2H), 7.17 - 7.06 (m, 2H), 5.94 - 5.59 (m, 1H), 4.84 (br d, *J*=4.6 Hz, 1H), 2.80 - 2.58 (m, 1H).

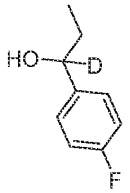
Intermediate 27: 1-(4-fluorophenyl)ethan-1-*d*-1-ol



To a solution of 1-(4-fluorophenyl)ethan-1-one (1.38 g, 9.99 mmol) in MeOH (33.3 mL) at 0 °C was added sodium borodeuteride (0.418 g, 9.99 mmol), and the reaction mixture was stirred at RT for 30 min. Water was added and the aqueous layer was extracted with ethyl acetate (x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was evaporated in vacuo to give 1-(4-fluorophenyl)ethan-1-*d*-1-ol (1.10 g, 7.79 mmol, 78% yield) as a colorless oil. This material was used in subsequent reactions without further purification.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.43 - 7.32 (m, 2H), 7.11 - 6.93 (m, 2H), 1.50 (d, *J*=0.7 Hz, 3H).

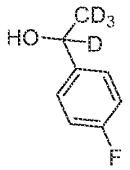
Intermediate 28: 1-(4-fluorophenyl)propan-1-*d*-1-ol



To a solution of 1-(4-fluorophenyl)propan-1-one (2.10 g, 13.8 mmol) in MeOH (46 mL) at 0 °C was added sodium borodeuteride (0.578 g, 13.8 mmol), and the reaction mixture was stirred at RT for 30 min. Water was added and the aqueous layer was extracted with ethyl acetate (x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was evaporated in vacuo to give 1-(4-fluorophenyl)propan-1-*d*-1-ol (1.97 g, 12.7 mmol, 92% yield) as a colorless oil.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.37 - 7.31 (m, 2H), 7.09 - 7.01 (m, 2H), 1.95 - 1.66 (m, 3H), 0.92 (t, *J*=7.4 Hz, 3H).

Intermediate 29 : 1-(4-fluorophenyl)ethan-1,2,2,2-d_4-1-ol



29A: 1-(4-fluorophenyl)ethan-1-one-2,2,2-d_3: In a 250 mL round bottom flask were combined 4-fluoro-*N*-methoxy-*N*-methylbenzamide (6.00 g, 32.8 mmol) and THF (100 mL). The mixture was cooled in an ice bath and was treated with methyl-d_3-magnesium iodide, 1.0M solution in diethyl ether (42.6 mL, 42.6 mmol). The resulting mixture was removed from the ice bath and was stirred at RT overnight. The reaction mixture was concentrated in vacuo to approximately 1/2 volume, then saturated aqueous ammonium chloride (50 mL) was added and the mixture was further concentrated in vacuo to remove remaining organic solvent. The residue was extracted with EtOAc (150 mL), and the EtOAc phase was washed three times with water (50 mL) and then with brine (30 mL). The organic was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to a crude light orange oil. The crude oil was diluted with 1 volume of hexanes and loaded onto a hexanes preequilibrated 120 g silica cartridge. Elution 100% hexanes for 1

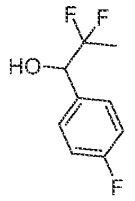
column colume, then gradient 100% hexanes to 100% DCM over 8 column volumes, then hold 100% DCM for 4 CV. Product eluted as a very large, very broad band beginning at approximately 65 %B and ending early in the 100% DCM hold. Like fractions were combined and concentrated in vacuo to give 1-(4-fluorophenyl)ethan-1-one-2,2,2-d_3 (3.63 g, 25.7 mmol, 78.0% yield) as a colorless oil.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.03 - 7.98 (m, 2H), 7.18 - 7.13 (m, 2H).

29: 1-(4-fluorophenyl)ethan-1,2,2,2-d_4-1-ol: To a solution of 1-(4-fluorophenyl)ethan-1-one-2,2,2-d_3 (1.65 g, 11.7 mmol) in MeOH (33 mL) at RT was added sodium borohydride (0.442 g, 11.7 mmol), and the reaction mixture was stirerd at RT for 30 min. Water was added and the aqueous layer was extracted with ethyl acetate (x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was evaporated in vacuo to give 1-(4-fluorophenyl)ethan-1,2,2,2-d_4-1-ol (1.60 g, 11.1 mmol, 95% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 - 7.32 (m, 2H), 7.11 - 7.01 (m, 2H).

Intermediate 30: 2,2-difluoro-1-(4-fluorophenyl)propan-1-ol



30A: 2,2-difluoro-1-(4-fluorophenyl)propan-1-one: To a solution of 2,2-difluoropropanenitrile (318 mg, 3.49 mmol) in THF (11.6 mL) at RT was added (4-fluorophenyl)magnesium bromide (3.84 mL, 3.84 mmol) and the reaction mixture was heated at 60 °C for 35 min. 10 mL (1 N) was added, and the aqueous layer was extracted with diethyl ether (x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was evaporated in vacuo to give 2,2-difluoro-1-(4-fluorophenyl)propan-1-one (650 mg, 3.45 mmol, 99% yield). This material was used directly in the next step as-is without purification.

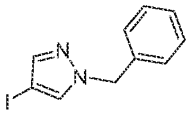
^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.29 - 8.13 (m, 2H), 7.19 (t, J=8.5 Hz, 2H), 1.95 - 1.87 (t, 3H, J = 19.2 Hz).

30: 2,2-difluoro-1-(4-fluorophenyl)propan-1-ol: To a solution of 2,2-difluoro-1-(4-fluorophenyl)propan-1-one (1.80 g, 9.57 mmol) in MeOH (31.7 mL) at 0 °C was added

sodium borohydride (0.471 g, 12.4 mmol) and the reaction mixture was stirred at RT for 20 min. Water was added and the aqueous layer was extracted with diethyl ether (x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was evaporated in vacuo to give the crude product. The crude product was purified by silica gel chromatography eluting with 0-40% ether/hexanes to give 2,2-difluoro-1-(4-fluorophenyl)propan-1-ol (1.20 g, 6.31 mmol, 66.0% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (dd, *J*=8.5, 5.6 Hz, 2H), 7.20 - 6.97 (m, 2H), 4.86 (td, *J*=9.3, 3.4 Hz, 1H), 1.52 (t, *J*=18.9 Hz, 3H).

Intermediate 31: 1-benzyl-4-iodo-1H-pyrazole

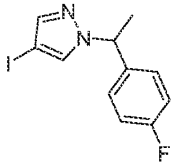


To a solution of 4-iodopyrazole (3.00 g, 15.5 mmol) in DMF (60 mL) was slowly added sodium hydride, 60% in oil (870 mg, 21.7 mmol). After the addition was complete, the reaction was stirred for 20 min, then the result was treated with benzyl bromide reagent grade 98% (3.0 mL, 25 mmol) and the mixture was stirred at room temp for 45 min. The reaction was quenched with water (50 mL) and diluted with EtOAc (400 mL). The organic layer was washed with water (4 x 25 mL), brine (1 x 25 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude product was purified via flash chromatography on silica gel, eluting with 0-30% gradient of ethyl acetate in hexanes to afford 1-benzyl-4-iodo-1H-pyrazole (4.40 g, 15.5 mmol, quantitative).

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.57 (s, 1H), 7.45 - 7.33 (m, 4H), 7.27 - 7.23 (m, 2H), 5.33 (s, 2H).

LCMS (ESI, m/z): 284.8 $[M+H]^+$

Intermediate 32: 1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole

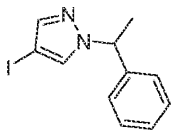


To a solution of 4-iodopyrazole (2.00 g, 10.3 mmol) in DMF (50 mL) was slowly added sodium hydride, 60% dispersion in mineral oil (0.500 g, 12.5 mmol) in several small

portions. The resulting mixture was stirred at RT for 20 min and was then treated with 1-(1-bromoethyl)-4-fluorobenzene (3.20 g, 15.8 mmol). The mixture was stirred overnight. The crude mixture was diluted with water (50 mL) and diethyl ether (400 mL) and the result was shaken and phases were separated. The organic phase was further washed with water (4 x 20 mL) and then brine (1 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to a residue. The residue was dissolved in hexane (7 mL) and applied to the head of a 40 g silica cartridge. Elution gradient 100% hexanes to 30% EtOAc in hexanes over 10 column volumes provided racemic 1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole (2.73 g, 8.64 mmol, 84% yield) as a colorless oil.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.57 (s, 1H), 7.43 (s, 1H), 7.22 (t, *J*=6.4 Hz, 2H), 7.05 (t, *J*=8.3 Hz, 2H), 5.51 (q, *J*=7.1 Hz, 1H), 1.89 (d, *J*=7.0 Hz, 3H).
MS ESI m/z 316.9 $(M+H)^+$

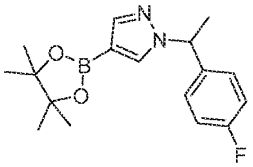
Intermediate 33: 4-iodo-1-(1-phenylethyl)-1H-pyrazole



Intermediate 33 was obtained via a similar procedure as described for the preparation of Intermediate 32, where (1-bromoethyl)benzene was substituted for 1-(1-bromoethyl)-4-fluorobenzene. The desired racemic 4-iodo-1-(1-phenylethyl)-1H-pyrazole (3.20 g, 10.3 mmol, quantitative) was obtained as a colorless oil.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.57 (s, 1H), 7.44 (s, 1H), 7.41 - 7.40 (m, 1H), 7.41 - 7.30 (m, 2H), 7.27 - 7.20 (m, 2H), 5.54 (q, *J*=7.1 Hz, 1H), 1.91 (d, *J*=7.0 Hz, 3H).
MS ESI m/z 298.8 $(M+H)^+$

Intermediate 34: 1-(1-(4-fluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

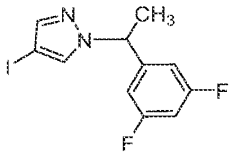


To a solution of pyrazole-4-boronic acid, pinacol ester (2.00 g, 10.3 mmol) in DMF (60 mL) was slowly added sodium hydride, 60% dispersion in mineral oil (0.500 g, 12.5 mmol) in several small portions. The resulting mixture was stirred at RT for 20 min and was then treated with 1-(1-bromoethyl)-4-fluorobenzene (3.20 g, 15.8 mmol). The mixture was stirred overnight. The crude mixture was concentrated under a gentle stream of nitrogen, then diluted with water (20 mL) and ethyl acetate (450 mL) and the result was shaken and phases were separated. The organic phase was further washed with water (8 x 25 mL) and then brine (1 x 25 mL), dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to a residue. The residue was dissolved in DCM (4 mL) and applied to the head of a 24 g silica cartridge. Elution gradient 100% DCM to 100% EtOAc over 10 column volumes provided racemic 1-(1-(4-fluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.29 g, 7.24 mmol, 70% yield) as a viscous yellow oil.

^{1}H NMR (600 MHz, CHLOROFORM-d) δ 7.85 (s, 1H), 7.74 (s, 1H), 7.21 (dd, *J*=8.4, 5.4 Hz, 2H), 7.11 - 6.98 (m, 2H), 5.65 - 5.46 (m, 1H), 1.90 (d, *J*=7.1 Hz, 3H), 1.43 - 1.24 (m, 12H).

MS ESI m/z 316.9 $(M+H)^+$

Intermediate 35: 1-(1-(3,5-difluorophenyl)ethyl)-4-iodo-1H-pyrazole

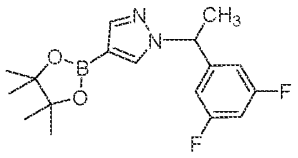


Intermediate 35 was obtained via the same procedure as described for the preparation of Intermediate 32, where 1-(1-bromoethyl)-3,5-difluorobenzene (1.0 g, 4.5 mmol) was substituted for 1-(1-bromoethyl)-4-fluorobenzene and the desired racemic 1-(1-bromoethyl)-3,5-difluorobenzene (1.0 g, 3.0 mmol, 97%) was obtained.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.59 (s, 1H), 7.50 (s, 1H), 6.81 - 6.67 (m, 3H), 5.49 (q, *J*=7.1 Hz, 1H), 1.89 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 344.6 $(M+H)^+$

Intermediate 36: 1-(1-(3,5-difluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

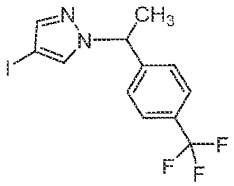


Intermediate 36 was obtained via the same procedure as described for the preparation of Intermediate 34, where 1-(1-bromoethyl)-3,5-difluorobenzene (1.0 g, 4.5 mmol) was substituted for 1-(1-bromoethyl)-4-fluorobenzene and the desired racemic 1-(1-(3,5-difluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (970 mg, 2.90 mmol, 64.2%) was obtained.

^{1}H NMR (600 MHz, CHLOROFORM-d) δ 7.88 (s, 1H), 7.81 (s, 1H), 6.73 (br d, *J*=6.9 Hz, 3H), 5.65 - 5.53 (m, 1H), 1.91 (d, *J*=7.1 Hz, 4H), 1.35 (s, 13H).

MS ESI m/z 334.8 $(M+H)^+$

Intermediate 37: 4-iodo-1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-pyrazole

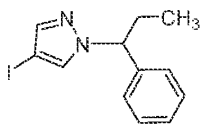


Intermediate 37 was obtained via the same procedure as described for the preparation of Intermediate 32, where 1-(1-bromoethyl)-4-(trifluoromethyl)benzene (1.0 g, 3.9 mmol) was substituted for 1-(1-bromoethyl)-4-fluorobenzene and the desired racemic 4-iodo-1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-pyrazole (1.11 g, 3.00 mmol, 84%) was obtained.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.62 (d, *J*=8.2 Hz, 2H), 7.59 (s, 1H), 7.51 (s, 1H), 7.32 (d, *J*=8.1 Hz, 2H), 5.58 (q, *J*=7.0 Hz, 1H), 1.93 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 366.7 $(M+H)^+$

Intermediate 38: 4-iodo-1-(1-phenylpropyl)-1H-pyrazole

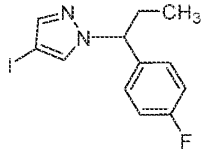


Intermediate 38 was obtained via the same procedure as described for the preparation of Intermediate 32, where (1-bromopropyl)benzene (0.6 mL, 3.9 mmol) was substituted for 1-(1-bromoethyl)-4-fluorobenzene and the desired racemic 4-iodo-1-(1-phenylpropyl)-1H-pyrazole (1.18 g, 3.78 mmol, 96.4%) was obtained.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.56 (s, 1H), 7.47 (s, 1H), 7.39 - 7.29 (m, 4H), 5.18 (t, *J*=7.7 Hz, 1H), 2.53 - 2.34 (m, 1H), 2.21 (dquin, *J*=14.1, 7.1 Hz, 1H), 0.94 (t, *J*=7.3 Hz, 3H).

MS ESI m/z 312.6 $(M+H)^+$

Intermediate 39: 1-(1-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole

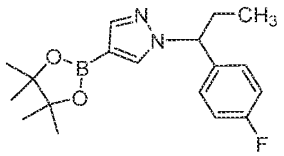


To a solution of 1-(4-fluorophenyl)propan-1-ol (200 mg, 1.30 mmol), 4-iodopyrazole (252 mg, 1.30 mmol) and triphenylphosphine (445 mg, 1.7 mmol) in anhydrous THF (10 mL) was added diisopropyl azodicarboxylate,98% (400 µL, 2.03 mmol) in a single portion over 40 seconds. The resulting bright yellow reaction was allowed to stir at room temp for 90 min. The reaction was diluted with ethyl acetate (225 mL) and water (10 mL) and the organic layer was washed with water (6 x 10 mL), brine (1 x 10 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude residue was purified by flash chromatography on silica gel, eluting with 0-50% gradient of ethyl acetate in hexanes to afford 1-(1-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole (179 mg, 54.4 mmol, 41.9%).

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.56 (s, 1H), 7.46 (s, 1H), 7.32 - 7.25 (m, 2H), 7.09 - 7.00 (m, 2H), 5.15 (dd, *J*=8.5, 7.0 Hz, 1H), 2.50 - 2.33 (m, 1H), 2.17 (dquin, *J*=14.2, 7.2 Hz, 1H), 0.93 (t, *J*=7.3 Hz, 3H).

MS ESI m/z 330.6 $(M+H)^+$

Intermediate 40: 1-(1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

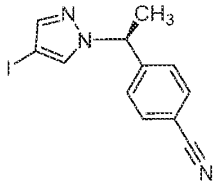


To a dry 75 mL pressure bottle under nitrogen was added 1-(1-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole (1.0 g, 3.0 mmol), bis(pinacolato)diboron (1.54 g, 6.06 mmol), potassium acetate (891 mg, 9.08 mmol), and anhydrous DMSO (30 mL). The reaction was purged well with argon and was then treated with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (250 mg, 0.306 mmol). The reaction was again purged very well with argon and the vessel was securely capped and heated at 80 °C for 2h. The reaction was diluted with ethyl acetate (450 mL) and water (20 mL) and the organic layer was washed with water (3 x 15 mL), brine (2 x 15 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude residue was purified by flash chromatography on silica gel, eluting with 0-100% gradient of ethyl acetate in hexanes to afford the title compound 1-(1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.08 g, 3.27 mmol, 108%) as a racemate.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.85 (s, 1H), 7.76 (s, 1H), 7.34 - 7.24 (m, 3H), 7.10 - 6.96 (m, 2H), 5.23 (dd, *J*=8.5, 7.0 Hz, 1H), 2.45 (ddd, *J*=13.9, 8.7, 7.3 Hz, 1H), 2.25 - 2.13 (m, 1H), 1.33 (s, 12H), 0.92 (t, *J*=7.3 Hz, 3H).

MS ESI m/z 331.0 $(M+H)^+$

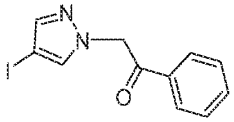
Intermediate 41: *(S)*-4-(1-(4-iodo-1H-pyrazol-1-yl)ethyl)benzonitrile



Following the general procedure as described for Intermediate 39, except using 4-[*(1R)*-1-hydroxyethyl]benzonitrile (100 mg, 0.679 mmol) and triphenylphosphine, polymer bound, Aldrich 93093-25G, 3 mmol/g load capacity (685 mg, 2.05 mmol), the title compound, *(S)*-4-(1-(4-iodo-1H-pyrazol-1-yl)ethyl)benzonitrile (376 mg, 1.16 mmol, 86.0%) was obtained.

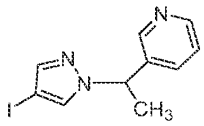
^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.67 - 7.63 (m, 2H), 7.60 (s, 1H), 7.52 (s, 1H), 7.33 - 7.26 (m, 3H), 5.58 (q, *J*=7.0 Hz, 1H), 1.92 (d, *J*=7.0 Hz, 3H).
MS ESI m/z 323.8 $(M+H)^+$

Intermediate 42: 2-(4-iodo-1H-pyrazol-1-yl)-1-phenylethan-1-one:



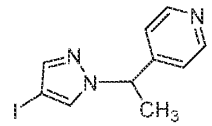
To a solution of 4-iodo-1H-pyrazole (1.0 g, 5.2 mmol) and potassium carbonate (1.75 g, 12.66 mmol) in acetone (25 mL) was added 2-bromoacetophenone (1.25 g, 6.28 mmol) and the reaction was stirred at room temp for 5 days. The reaction was filtered and the filtrate was evaporated to dryness. The crude residue was purified by flash chromatography on silica gel, eluting with 0-100% gradient of ethyl acetate in hexanes to afford the title compound, 2-(4-iodo-1H-pyrazol-1-yl)-1-phenylethan-1-one (395 mg, 1.27 mmol, 24.6%).
^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.06 - 7.97 (m, 2H), 7.70 - 7.64 (m, 1H), 7.61 (d, *J*=10.7 Hz, 2H), 7.58 - 7.52 (m, 2H), 5.63 (s, 2H).
MS ESI m/z 312.8 $(M+H)^+$

Intermediate 43: 3-(1-(4-iodo-1H-pyrazol-1-yl)ethyl)pyridine:



Intermediate 43 was obtained via the same procedure as described for the preparation of Intermediate 32, where 3-(1-bromoethyl)pyridine, HBr (575 mg, 2.15 mmol) was substituted for 1-(1-bromoethyl)-4-fluorobenzene to give the title compound, racemic 3-(1-(4-iodo-1H-pyrazol-1-yl)ethyl)pyridine (503 mg, 1.68 mmol, 93.0%).
^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.66 - 8.48 (m, 2H), 7.64 - 7.55 (m, 2H), 7.51 (s, 1H), 7.34 (dd, *J*=7.9, 4.8 Hz, 1H), 5.58 (q, *J*=7.1 Hz, 1H), 1.95 (d, *J*=7.2 Hz, 3H)
MS ESI m/z 299.8 $(M+H)^+$

Intermediate 44: 4-(1-(4-iodo-1H-pyrazol-1-yl)ethyl)pyridine:

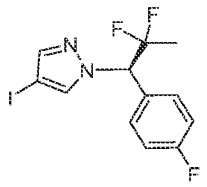


Intermediate 44 was obtained via the same procedure as described for the preparation of Intermediate 32, where 4-(1-bromoethyl)pyridine (500 mg, 2.69 mmol) was substituted for 1-(1-bromoethyl)-4-fluorobenzene to give the title compound, racemic 4-(1-(4-iodo-1H-pyrazol-1-yl)ethyl)pyridine (477 mg, 1.59 mmol, 71.9%).

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.67 - 8.54 (m, 2H), 7.61 (s, 1H), 7.54 (s, 1H), 7.14 - 7.03 (m, 2H), 5.53 (q, *J*=7.2 Hz, 1H), 1.92 (d, *J*=7.2 Hz, 3H).

MS ESI m/z 299.8 $(M+H)^+$

Intermediate 45: *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole



45A: 1-bromo-1-(4-fluorophenyl)propan-2-one: To a stirred solution of 1-(4-fluorophenyl) propan-2-one (20.0 g, 131 mmol) in toluene (200 mL) under a nitrogen atmosphere at 0 °C was slowly added bromine (6.77 mL, 131 mmol). After the addition was complete, the reaction was stirred at room temp for 60 min. The reaction mixture was diluted with ethyl acetate and the organic layer was washed with aqueous saturated sodium bisulfite (4 x 100 mL). The organic solvents were evaporated under reduced pressure to afford 1-bromo-1-(4-fluorophenyl) propan-2-one (30g, crude) which was used directly in the next step without further purification.

45B: 1-(4-fluorophenyl)-1-(4-iodo-1H-pyrazol-1-yl)propan-2-one: To a stirred solution of 4-iodo-1H-pyrazole (15.1 g, 77.9 mmol) in DMF (150 mL) at 0 °C under nitrogen atmosphere, was slowly added sodium hydride, 60% (3.89 g, 97.3 mmol). After the addition was complete, the reaction was stirred for 30 min and was then treated with crude 1-bromo-1-(4-fluorophenyl) propan-2-one material obtained from the previous step. The reaction was allowed to warm to room temp and was stirred for 12h. The reaction was

quenched with chilled water, diluted with ethyl acetate and the organic phase was washed with water, dried over anhydrous sodium sulfate, filtered and the solvents evaporated under reduced pressure. The crude material thus obtained was purified by flash chromatography on silica gel, eluting with 0-20% gradient of ethyl acetate in petroleum ether to afford 1-(4-fluorophenyl)-1-(4-iodo-1H-pyrazol-1-yl)propan-2-one (10 g, 29 mmol, 44%).

LCMS (ESI, m/z): 345.0 $[M+H]^+$.

45C: 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole racemate: To a stirred solution of 1-(4-fluorophenyl)-1-(4-iodo-1H-pyrazol-1-yl) propan-2-one (16 g, 46.5 mmol) in DCM (150 mL) at 0 °C under nitrogen atmosphere was slowly added DAST (18.4 mL, 139 mmol). After the addition was complete, the reaction was allowed to warm to room temp and was stirred for 12 hours. The reaction was quenched by the addition of chilled and saturated aqueous sodium bicarbonate and then diluted with DCM. The organic layer was dried over anhydrous sodium sulfate, filtered and the solvents evaporated from the filtrate under reduced pressure. The crude thus obtained was purified by flash chromatography on silica gel, eluting with 0-5% gradient of ethyl acetate in petroleum ether to afford racemic 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole (8.0 g, 21.9 mmol, 30.5 %) as a pale yellow liquid, contaminated with 1-(2-fluoro-1-(4-fluorophenyl)prop-1-en-1-yl)-4-iodo-1H-pyrazole.

LCMS (ESI, m/z): 367.0 $[M+H]^+$.

45: *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole: To a solution of material from the previous step containing racemic 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole and 1-(2-fluoro-1-(4-fluorophenyl)prop-1-en-1-yl)-4-iodo-1H-pyrazole (8.0 g, 23 mmol) in a mixture of DCM (200 mL) and sat. sodium bicarbonate solution (100 mL) at 25 °C under nitrogen atmosphere was added *meta*-chloroperoxybenzoic acid (7.54 g, 43.7 mmol). The mixture was then stirred at room temperature for 4 h or until the undesired 1-(2-fluoro-1-(4-fluorophenyl)prop-1-en-1-yl)-4-iodo-1H-pyrazole had been consumed. The reaction was diluted with saturated bicarbonate solution (100 mL) and extracted with DCM (2 x 300 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvents evaporated under reduced pressure. The crude thus obtained was purified by flash chromatography on silica gel, eluting with 0-5% gradient of ethyl acetate in petroleum ether to afford racemic 1-(2,2-

difluoro-1-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole. This racemic material was further separated into enantiomerically pure isomers via preparative chiral SFC chromatography with the following conditions: Column: Daicel Chiralpak IG, 30 mm x 250 mm, 5μm; Mobil Phase A: supercritical CO2; Mobile Phase B: *i*-PrOH; Elution gradient: isocratic 10%B over 10 min; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (220 nm). The *(S)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole enantiomer was the first enantiomer to elute off the column. Fractions containing the first eluting enantiomer were combined and dried to provide *(S)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole (5.3 g, 14.5 mmol, 29%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.83 - 7.57 (m, 3H), 7.35 - 7.19 (m, 2H), 6.19 (t, *J*=13.3 Hz, 1H), 1.59 (t, *J*=19.0 Hz, 3H).

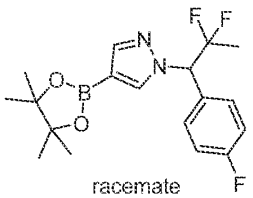
LCMS (ESI, m/z): 367.0 $[M+H]^+$.

The *(R)* enantiomer was the second enantiomer to elute from the chiral SFC column. Fractions containing the second eluting enantiomer were combined and dried to provide *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole (5.3 g, 14.5 mmol, 29%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.76 - 7.60 (m, 3H), 7.25 (t, *J*=9.0 Hz, 2H), 6.19 (t, *J*=13.3 Hz, 1H), 1.59 (t, *J*=19.0 Hz, 3H).

LCMS (ESI, m/z): 367.0 $[M+H]^+$.

Intermediate 46: 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

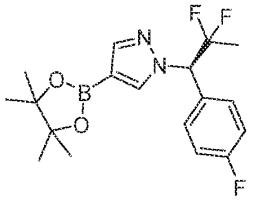


In a 40 mL Chemglass reaction vial with small magnetic stirbar and rubber septum installed, a solution of racemic 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole (516 mg, 1.41 mmol) in THF (10 mL) was placed under a blanket of nitrogen.

The vessel was placed in an ice-acetone bath and cooled to approximately -10 °C for 10 min. The cold mixture was treated by slow dropwise addition with isopropylmagnesium chloride, 2.0M in THF (0.810 mL, 1.62 mmol). Addition occurred over 5 min, approximately 1 drop every 4 seconds. The originally colorless mixture took on a very light yellow tinge of color as soon as addition commenced and did not darken appreciably over the next 45 min. The mixture was stirred cold for 45 min, then the mixture was treated with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.431 mL, 2.11 mmol) all at once. The cold bath was removed and the mixture was allowed to stir at RT for 1 h. The mixture was chilled in an ice bath, and to the cold mixture was added 1 mL of saturated aqueous ammonium chloride with stirring. The mixture was concentrated in vacuo to remove most of the organic solvent. The residue was dissolved in EtOAc (100 mL) and water (50 mL) and the resulting mixture was shaken and phases were separated. The organic was washed with more water (2 x 50 mL), then with brine (50 mL). The organic was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo, and placed under high vacuum for several hours. Thus was obtained racemic 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (591 mg, quantitative) as a yellow oil.

MS ESI m/z 366.9 $(M+H)^+$

Intermediate 47: *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole



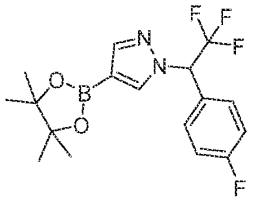
In a 75 mL Chemglass medium pressure vessel under a blanket of nitrogen gas were combined *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole (2.65 g, 7.24 mmol), bis(pinacolato)diboron (2.21 g, 8.69 mmol), potassium acetate (2.13 g, 21.7 mmol) and anhydrous DMSO (25 mL). The reaction mixture (a slightly yellow slurry) was purged well by bubbling vigorously with nitrogen gas with stirring for 5 min. The mixture was then treated with dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II)

dichloromethane (0.296 g, 0.362 mmol), and the mixture was again purged very well with nitrogen for 5 min. The vessel was securely sealed and placed in an 80 °C oil bath for 100 min with stirring. The mixture was then allowed to cool to RT and was poured into a separatory funnel containing water (100 mL) and diethyl ether (250 mL). The result was shaken and phases were separated. The organic phase was washed with water (2 x 75 mL). The combined aqueous washes was back-extracted with diethyl ether (100 mL). The back-extract was washed with water (50 mL). The combined organic was then dried over anhydrous magnesium sulfate, filtered and concentrated to a brown oil. The brown oil residue was dissolved in minimum 1:1 hexanes:DCM and was loaded atop a 220 g silica flash cartridge. Elution 100% hexanes for 0.5 column volumes, then gradient from 100% hexanes to 50% EtOAc in hexanes over 12 CV, hold 50% EtOAc in hexanes for 4 CV. Product fractions were pooled and concentrated in vacuo to give a yellow oil which was placed under high vacuum overnight to provide *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.19 g, 5.97 mmol, 82.0% yield) as a yellow oil.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.92 (s, 1H), 7.86 (s, 1H), 7.53 (dd, *J*=8.6, 5.2 Hz, 2H), 7.08 (t, *J*=7.8 Hz, 2H), 5.67 (dd, *J*=15.9, 9.5 Hz, 1H), 1.68 (t, *J*=18.8 Hz, 3H), 1.33 (s, 12H).

MS ESI m/z 367.0 $(M+H)^+$

Intermediate 48: 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazole



48A : 2,2,2-trifluoro-1-(4-fluorophenyl)ethan-1-ol: To an ice-cold 0 °C, clear, colorless solution of 2,2,2-trifluoro-1-(4-fluorophenyl)ethan-1-one (19.2 g, 100 mmol) in MeOH (200 mL) was slowly added, in five portions over 20 min, sodium borohydride (4.92 g, 130 mmol). Vigorous bubbling ensued. The mixture was stirred at RT overnight. The mixture was concentrated in vacuo to a thick cloudy residue which was taken up in EtOAc (350 mL) and the result was washed with water (4 x 100 mL) and then with brine (50 mL). The

organic was dried over anhydrous magnesium sulfate, filtered and concentrated to a very slightly yellow oil residue which was placed under high vacuum with stirring to provide 2,2,2-trifluoro-1-(4-fluorophenyl)ethan-1-ol (19.2 g, 98.7 mmol, 99% yield) as a clear, slightly yellow oil.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.50 (dd, *J*=8.6, 5.5 Hz, 2H), 7.16 - 7.10 (m, 2H), 5.05 (qd, *J*=6.5, 4.5 Hz, 1H), 2.61 (d, *J*=4.4 Hz, 1H).

48B: 2,2,2-trifluoro-1-(4-fluorophenyl)ethyl trifluoromethanesulfonate: In a 100 mL 2-neck round bottom flask fitted with a magnetic stir bar, a thermometer and a 50 mL addition funnel, and under a blanket of nitrogen, a solution of 2,2,2-trifluoro-1-(4-fluorophenyl)ethan-1-ol (5.02 g, 25.9 mmol) and 2,6-dimethylpyridine (4.43 g, 4.79 mL, 41.4 mmol) in dry cyclohexane (26 mL) was cooled in an ice-acetone bath to -10 °C. Trifluoromethanesulfonic anhydride (6.51 mL, 38.8 mmol) was added dropwise via addition funnel slowly over 20 min, maintaining the temperature below 0 °C throughout the addition. Color instantly changed from slightly yellow to salmon pink/orange upon addition of the first few drops of trifluoromethanesulfonic anhydride. The vessel was transferred to an ice/water bath and the salmon pink colored suspension mixture was stirred at 0 °C for 90 min. The mixture was then transferred to a separatory funnel and was diluted with cyclohexane (30 mL) and water (30 mL) was added. The mixture was shaken and phases were separated. The organic was washed with aqueous 1N HCl (1 x 30 mL, then 2 x 15 mL) and then with water (30 mL). The cyclohexane phase was dried over anhydrous sodium sulfate, filtered into a 250 mL round bottom flask, and concentrated in vacuo (25 °C setting on the rotary evaporator water bath) to a residue. The resulting yellow oil was placed under high vacuum with stirring for 15 min. The yellow oil thus obtained containing 2,2,2-trifluoro-1-(4-fluorophenyl)ethyl trifluoromethanesulfonate (7.66 g, 23.5 mmol, 91% yield) was carried directly into the next step without further manipulation.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.53 (dd, *J*=8.8, 5.1 Hz, 2H), 7.24 - 7.19 (m, 2H), 5.86 (q, *J*=5.8 Hz, 1H).

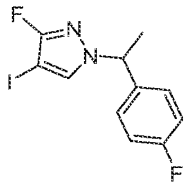
48: 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazole: In a 250 mL round bottom flask fitted with a magnetic stirbar and under a blanket of nitrogen gas, a mixture of 2,2,2-trifluoro-1-(4-fluorophenyl)ethyl trifluoromethanesulfonate (7.65 g, 23.45 mmol) and pyrazole-4-boronic acid, pinacol ester (6.37 g, 32.8 mmol) in cyclohexane (50 mL) was treated with potassium

carbonate (4.86 g, 35.2 mmol). The vessel was fitted with a waterless reflux condenser and the mixture was heated with stirring under nitrogen to 65 °C for 18.5 h. The mixture was transferred to a 250 mL separatory funnel with diethyl ether (100 mL) and water (50 mL). The mixture was shaken and phases were separated. The organic was washed with water (2 x 30 mL) and then with brine (30 mL). The combined aqueous washes were back-extracted with diethyl ether (50 mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to a orange oil residue which was loaded with minimal hexanes onto a hexanes preequilibrated 330 g silica cartridge. Elution (200 mL/min) gradient 100% hexanes to 60% EtOAc in hexanes. Product fractions were pooled and concentrated in vacuo to provide racemic 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazole (5.34 g, approx. 13.0 mmol, approx. 90% purity, approx. 55% yield) as a nearly colorless thick oil.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.88 (d, *J*=4.2 Hz, 2H), 7.50 (t, *J*=6.7 Hz, 2H), 7.12 (t, *J*=8.1 Hz, 2H), 5.96 (q, *J*=7.6 Hz, 1H), 1.34 (s, 12H).

MS ESI m/z 371.0 $(M+H)^+$

Intermediate 49: 3-fluoro-1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole



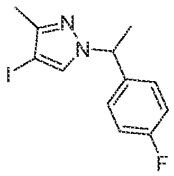
49A: 3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazole: To a solution of 3-fluoro-1H-pyrazole (317 mg, 3.68 mmol) in DMF (7.8 mL) at RT was added sodium hydride, 60% oil dispersion (192 mg, 4.79 mmol), and the reaction mixture was stirred at RT for 30 min. 1-(1-Bromoethyl)-4-fluorobenzene (0.774 mL, 5.52 mmol) was added, and the reaction mixture was stirred at RT for 1 h. Water was added, and the aqueous layer was extracted with ethyl acetate (x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was evaporated in vacuo to give the crude residue which was purified by silica gel chromatography eluting with 5-20% ethyl acetate/hexanes to give 3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazole (657 mg, 3.16 mmol, 86% yield) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15 - 7.09 (m, 3H), 7.02 - 6.84 (m, 2H), 5.70 (dd, *J*=6.0, 2.4 Hz, 1H), 5.22 (q, *J*=6.9 Hz, 1H), 1.76 (d, *J*=7.1 Hz, 3H).

49: 3-fluoro-1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole: A solution of 3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazole (657 mg, 3.16 mmol) and NIS (1.2 g, 5.1 mmol) in MeCN (15.7 mL) was heated at 80 °C for 12 h. MeCN was removed in vacuo, and the crude product was purified by silica gel chromatography eluting with 0-20% ethyl acetate/hexanes to give 3-fluoro-1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole (987 mg, 2.95 mmol, 94% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 - 7.21 (m, 3H), 7.13 - 7.00 (m, 2H), 5.32 (d, *J*=7.0 Hz, 1H), 1.84 (d, *J*=7.0 Hz, 3H).

Intermediate 50: 1-(1-(4-fluorophenyl)ethyl)-4-iodo-3-methyl-1H-pyrazole



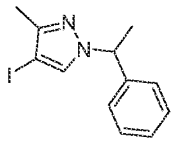
To a dry 250 mL round bottom flask under a blanket of nitrogen gas was added 4-iodo-5-methyl-1H-pyrazole (2.00 g, 9.62 mmol) and anhydrous DMF (50 mL). The resulting solution was treated slowly (in small portions) with sodium hydride, 60% dispersion in mineral oil (0.500 g, 12.5 mmol) over 15 min. The mixture was stirred at room temp for 25 min and was then treated with 1-(1-bromoethyl)-4-fluorobenzene (2.25 mL, 14.4 mmol) in a single portion. The mixture was stirred at RT overnight and was then quenched by slow addition of water (5 mL). The mixture was concentrated to 15 mL volume and was diluted with EtOAc (200 mL) and water (150 mL). The result was shaken and phases were separated. The organic phase was further washed with water (3 x 75 mL) and brine (50 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to a colorless oil. The crude residue was dissolved in DCM (100 mL) and Celite (20 g) was added, and the mixture was concentrated to provide a free-flowing powder. The dry-loaded material was purified via normal phase chromatography (120 g silica cartridge, elution gradient from 100% hexanes to 14% EtOAc/hexanes over 15 column volumes. Two products eluted from the column as somewhat broad peaks. Fractions containing the major product (second peak to elute) were pooled and concentrated in vacuo to give racemic 1-

(1-(4-fluorophenyl)ethyl)-4-iodo-3-methyl-1H-pyrazole (2.16 g, 6.55 mmol, 68.2% yield) as a colorless oil.

^{1}H NMR (600 MHz, CHLOROFORM-d) δ 7.35 (s, 1H), 7.20 (t, *J*=6.7 Hz, 2H), 7.11 - 6.99 (m, 2H), 5.44 (q, *J*=7.1 Hz, 1H), 2.34 - 2.21 (m, 3H), 1.85 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 330.9 $(M+H)^+$

Intermediate 51: 4-iodo-3-methyl-1-(1-phenylethyl)-1H-pyrazole

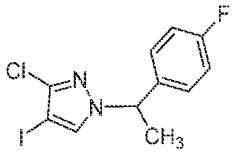


Intermediate 51 was obtained via a similar procedure as described for the preparation of Intermediate 50, where (1-bromoethyl)benzene was substituted for 1-(1-bromoethyl)-4-fluorobenzene. The desired racemic 4-iodo-3-methyl-1-(1-phenylethyl)-1H-pyrazole (2.09 g, 6.69 mmol, 69.6% yield) was obtained as a colorless oil.

^{1}H NMR (600 MHz, CHLOROFORM-d) δ 7.42 - 7.29 (m, 4H), 7.23 (d, *J*=7.3 Hz, 2H), 5.47 (q, *J*=7.1 Hz, 1H), 2.31 - 2.26 (m, 3H), 1.87 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 312.9 $(M+H)^+$

Intermediate 52: 3-chloro-1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole

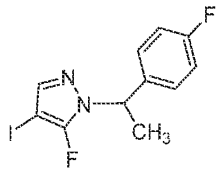


Intermediate 52 was obtained via the same procedure as described for the preparation of Intermediate 32, where 3-chloro-4-iodo-1H-pyrazole (2.0 g, 8.8 mmol) was substituted for 4-iodopyrazole to give the title compound, racemic 3-chloro-1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole (1.15 g, 3.28 mmol, 37.5%).

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.33 (s, 1H), 7.28 - 7.23 (m, 2H), 7.11 - 7.04 (m, 2H), 5.43 (q, *J*=7.0 Hz, 1H), 1.88 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 350.8, 352.8 $(M+H)^+$

Intermediate 53: 5-fluoro-1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole

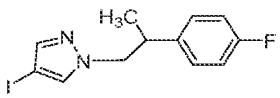


To a dry vial under nitrogen was added 1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole (200 mg, 0.633 mmol) and anhydrous THF (4 mL). The reaction was purged with argon and the mixture was cooled to -78C and then treated (over 30 sec) with lithium diisopropylamide, 1.0M solution in THF/hexanes (760 µL, 0.760 mmol). After the addition was complete, the reaction was stirred at -78 °C for 30 min, then a solution of N-fluorobenzenesulfonimide (400 mg, 1.27 mmol) in THF (1.0 mL) was added over 10 seconds. The reaction was stirred at -78 °C for 30 min, then allowed to warm to room temp over 18h. The reaction was quenched with saturated aqueous ammonium chloride (5 mL) and diluted with ethyl acetate (110 mL). The organic layer was washed with water (4 x 5 mL), brine (1 x 5 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude residue was purified by via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 20% B - 80% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 5-fluoro-1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole (88.9 mg, 0.270 mmol, 42.1%).

^{1}H NMR (600 MHz, CHLOROFORM-d) δ 7.41 (br s, 1H), 7.29 (br s, 2H), 7.05 (br d, *J*=6.0 Hz, 2H), 5.59 - 5.38 (m, 1H), 1.89 (br s, 3H).

LCMS (ESI, m/z): 335.0 $[M+H]^+$

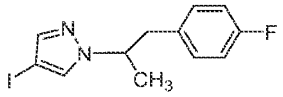
Intermediate 54: 1-(2-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole



Intermediate 54 was obtained via the same procedure as described for the preparation of Intermediate 32, where 1-(1-bromopropan-2-yl)-4-fluorobenzene (500 mg, 2.30 mmol)

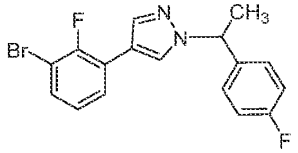
was substituted for 1-(1-bromoethyl)-4-fluorobenzene to give the title compound, racemic 1-(2-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole (411 mg, 0.320 mmol, 63.9%).
MS ESI m/z 330.7 $(M+H)^+$

Intermediate 55: 1-(1-(4-fluorophenyl)propan-2-yl)-4-iodo-1H-pyrazole



Intermediate 55 was obtained via the same procedure as described for the preparation of Intermediate 39, where 1-(4-fluorophenyl)propan-2-ol (300 mg, 1.95 mmol)) was substituted for 1-(4-fluorophenyl)propan-1-ol to give the title compound, racemic 1-(2-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole (105 mg, 1.24 mmol, 13.9%).
^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.52 (s, 1H), 7.13 (s, 1H), 7.11 - 7.06 (m, 2H), 7.04 - 6.98 (m, 2H), 4.30 - 4.13 (m, 2H), 3.44 - 3.30 (m, 1H), 1.28 (d, *J*=7.0 Hz, 3H).
MS ESI m/z 330.7 $(M+H)^+$

Intermediate 56: 4-(3-bromo-2-fluorophenyl)-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazole:

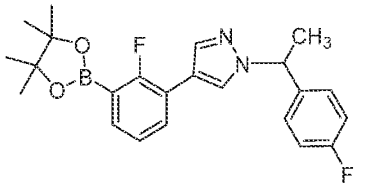


To a dry reaction vial under nitrogen was added 1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole (200 mg, 0.633 mmol), (3-bromo-2-fluorophenyl)boronic acid (145 mg, 0.663 mmol), dioxane (6 mL) and potassium phosphate tribasic, 2.0M in water (1.25 mL, 2.50 mmol). The reaction was purged well with argon and was treated with dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (30 mg, 0.040 mmol). The result was again purged well with argon and heated at a 90 °C for 2 hours 45 min. The reaction was diluted reaction with water (10 mL) and ethyl acetate (220 mL) and the organic layer was washed with water (5 x 10 mL), brine (1 x 10 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude residue was purified by flash chromatography on silica gel, eluting with 0-35% gradient of ethyl acetate in hexanes to afford racemic 4-(3-bromo-2-fluorophenyl)-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazole (136 mg, 375 mmol, 59.4%).

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.93 (s, 1H), 7.84 (d, *J*=2.5 Hz, 1H), 7.49 (ddd, *J*=7.9, 6.7, 1.5 Hz, 1H), 7.41 (ddd, *J*=8.0, 6.5, 1.7 Hz, 1H), 7.28 - 7.24 (m, 2H), 7.10 - 7.01 (m, 3H), 5.59 (q, *J*=7.1 Hz, 1H), 1.96 (d, *J*=7.2 Hz, 3H).

MS ESI m/z 362.7, 364.7(M+H)$^+$

Intermediate 57: 4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazole

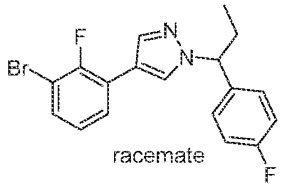


To a dry 150 mL pressure bottle under nitrogen was added 4-(3-bromo-2-fluorophenyl)-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazole (1.5 g, 4.1 mmol), bis(pinacolato)diboron (1.8 g, 7.1 mmol), potassium acetate (1.22 g, 12.4 mmol) and anhydrous dioxane (40 mL). The reaction was purged very well with argon and was then treated with dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (250 mg, 0.306 mmol). The reaction was purged again very well with argon, and the vessel was securely capped and heated at 90 °C for 5.5 hours. The reaction was treated with additional bis(pinacolato)diboron (210 mg, 0.827 mmol) and dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (57.8mg, 0.071 mmol), purged very well with argon, and the vessel was resealed and heated at 90 °C for 4 hours. The reaction was diluted with ethyl acetate (450 mL) and the organic layer was washed with water (6 x 15 mL), brine (20 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude residue was purified by flash chromatography on silica gel, eluting with 0-35% gradient of ethyl acetate in hexanes to afford racemic 4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazole (1.75 g, 4.27 mmol, quantitative).

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.99 - 7.89 (m, 2H), 7.68 (td, *J*=7.6, 1.4 Hz, 1H), 7.64 - 7.57 (m, 1H), 7.24 (dd, *J*=8.6, 5.2 Hz, 2H), 7.17 (t, *J*=7.5 Hz, 1H), 7.04 (t, *J*=8.6 Hz, 2H), 5.58 (br d, *J*=6.3 Hz, 1H), 1.94 (br d, *J*=6.4 Hz, 3H), 1.40 (s, 12H).

MS ESI m/z 411(M+H)$^+$

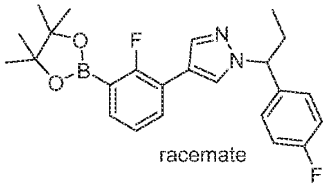
Intermediate 58: 4-(3-bromo-2-fluorophenyl)-1-(1-(4-fluorophenyl)propyl)-1H-pyrazole racemate



To a stirred mixture of racemic 1-(1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (500 mg, 1.51 mmol) and 1,3-dibromo-2-fluorobenzene (384 mg, 1.51 mmol) in 1,4-dioxane (5 mL) was added tripotassium phosphate (964 mg, 4.54 mmol). The reaction mixture was purged with nitrogen gas for 10 min and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (124 mg, 0.151 mmol) was added. The reaction mixture was then stirred at 80 °C for 16 h. The mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to yield racemic 4-(3-bromo-2-fluorophenyl)-1-(1-(4-fluorophenyl)propyl)-1H-pyrazole (500 mg, 0.87 mmol, 88 % yield) as a yellow solid.

LCMS (ESI, m/z) 377.0 $[M+H]^+$

Intermediate 59: 4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-(1-(4-fluorophenyl)propyl)-1H-pyrazole racemate

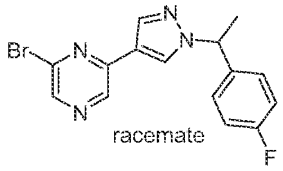


To a stirred solution of racemic 4-(3-bromo-2-fluorophenyl)-1-(1-(4-fluorophenyl)propyl)-1H-pyrazole (400 mg, 1.06 mmol) in dioxane (5 mL) was added bis(pinacolato)diboron (269 mg, 1.06 mmol) and potassium acetate (260 mg, 2.65 mmol). The reaction mixture was purged with nitrogen gas for 10 min and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (87.0 mg, 0.106 mmol) was added. The reaction mixture was then stirred at 80 °C for 2 h. The mixture was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous

sodium sulfate, filtered and evaporated to give crude material. The crude product was purified by column chromatography using silica gel, eluting with 0-20% ethyl acetate/petroleum ether to yield racemic 4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-(1-(4-fluorophenyl)propyl)-1H-pyrazole (300 mg, 0.707 mmol, 66.7 % yield) as a colorless liquid.

LCMS (ESI, m/z) 425.2 $[M+H]^+$

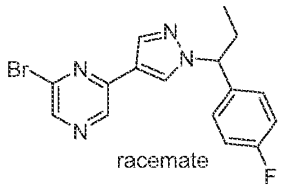
Intermediate 60: 2-bromo-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazine racemate



To a stirred mixture of racemic 1-(1-(4-fluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.00 g, 3.16 mmol) and 2,6-dibromopyrazine (940 mg, 3.95 mmol) in DME (10 mL) and water (3 mL) was added Cs_2CO_3 (2.06 g, 6.33 mmol). The reaction mixture was purged with nitrogen gas for 10 min and 1,1'-bis-(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (258 mg, 0.316 mmol) was added. The reaction mixture was then stirred at 80 °C for 16 h. The mixture was diluted with water and extracted with ethyl acetate. The combined organic phase was dried over anhydrous sodium sulphate, filtered and concentrated to yield crude material. The crude material was purified by column chromatography using silica gel, eluting with 0-30% ethyl acetate/petroleum ether to yield racemic 2-bromo-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazine (400 mg, 1.15 mmol, 36.4 % yield) as a yellow semi-solid.

LCMS (ESI, m/z) 349.0 $[M+2H]^+$

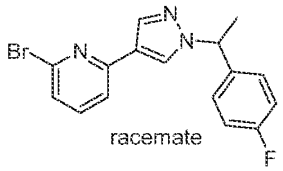
Intermediate 61: 2-bromo-6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazine racemate



To a stirred mixture of racemic 1-(1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (486 mg, 1.47 mmol) and 2,6-dibromopyrazine (500 mg, 2.10 mmol) in 1,4-dioxane (10 mL) was added tripotassium phosphate (1.34 g, 6.31 mmol). The reaction mixture was purged with nitrogen gas for 10 min and 1,1'-bis-(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (172 mg, 0.210 mmol) was added. The reaction mixture was then stirred at 80 °C for 16 h. The mixture was diluted with water and extracted with ethyl acetate. The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to yield crude material. The crude material was purified by column chromatography using silica gel, eluting with 0-30% ethyl acetate/petroleum ether to yield racemic 2-bromo-6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazine (500 mg, 1.38 mmol, 65.9 % yield) as an off-white semi solid.

LCMS (ESI, m/z) 363.0 $[M+2H]^+$

Intermediate 62: 2-bromo-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridine racemate

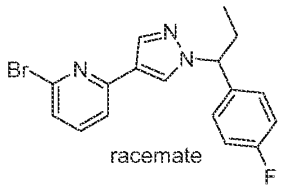


In a Chemglass reaction vial, to a stirred mixture of racemic 1-(1-(4-fluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.00 g, 3.16 mmol) and 2,6-dibromopyridine (0.899 g, 3.80 mmol) in dioxane (9 mL) and water (1 mL) was added tripotassium phosphate (2.01 g, 9.49 mmol). The reaction mixture was purged with nitrogen gas for 2 min and 1,1'-bis-(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (0.258 mg, 0.316 mmol) was added. The vial was sealed and the reaction mixture was stirred at 80 °C for 2 h. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was concentrated to yield

crude material which was purified by column chromatography using silica gel, eluting with 0-20% ethyl acetate/petroleum ether to yield racemic 2-bromo-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridine (600 mg, 1.61 mmol, 51.0 % yield) as a colorless liquid.

LCMS (ESI, m/z) 346.0 $[M+H]^+$

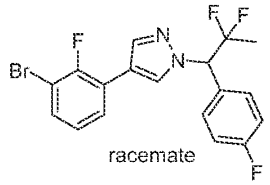
Intermediate 63: 2-bromo-6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridine racemate



In a Chemglass reaction vial, to a stirred mixture of racemic 1-(1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.00 g, 3.03 mmol) and 2,6-dibromopyridine (0.861 g, 3.63 mmol) in dioxane (9 mL) and water (1 mL) was added tripotassium phosphate (1.93 g, 9.09 mmol). The reaction mixture was purged with nitrogen gas for 2 min and 1,1'-bis-(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (0.247 mg, 0.303 mmol) was added. The vial was sealed and the reaction mixture was stirred at 80 °C for 2 h. The mixture was diluted with water (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was concentrated to yield crude material which was purified by column chromatography using silica gel, eluting with 0-20% ethyl acetate/petroleum ether to yield racemic 2-bromo-6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridine (600 mg, 1.48 mmol, 48.9 % yield) as a colorless liquid.

LCMS (ESI, m/z) 360.0 $[M+H]^+$

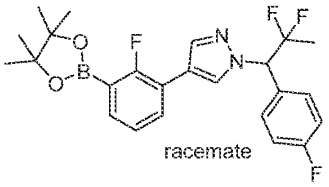
Intermediate 64: 4-(3-bromo-2-fluorophenyl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole racemate



In a Chemglass reaction vial, to a stirred mixture of racemic 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole (1.00 g, 2.73 mmol) and (3-bromo-2-fluorophenyl)boronic acid (0.598 g, 2.73 mmol) in DME (10 mL) and water (1 mL) was added cesium carbonate (2.67 g, 8.19 mmol) and tetrakis(triphenylphosphine)palladium (0.316 g, 0.273 mmol). The reaction mixture was purged with nitrogen gas for 10 min, then the vial was sealed and the mixture was stirred at 80 °C for 2 h. The mixture was filtered through a pad of Celite, eluting with a combination of DCM and methanol. The filtrate was concentrated and the crude material was purified by column chromatography using silica gel and eluting with 0-20% of ethyl acetate/hexane to yield racemic 4-(3-bromo-2-fluorophenyl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole (750 mg, 1.53 mmol, 55.8 % yield) as a brown semi-solid.

LCMS (ESI, m/z) 415.0 $[M+H]^+$

Intermediate 65: 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrazole racemate

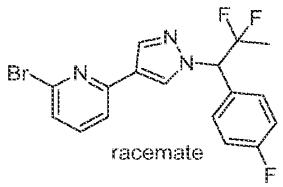


In a Chemglass reaction vial, to a stirred solution of racemic 4-(3-bromo-2-fluorophenyl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole (700 mg, 1.694 mmol) in dioxane (15 mL) were added bis(pinacolato)diboron (645 mg, 2.54 mmol) and potassium acetate (499 mg, 5.08 mmol). The reaction mixture was purged with nitrogen gas for 10 min and 1,1'-bis-(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (77.4 mg, 0.102 mmol) was added. The vial was sealed and the reaction mixture was stirred at 100 °C for 1 h. The mixture was filtered through a pad of Celite, eluting with a combination of DCM and methanol. The filtrate was concentrated and the crude material

was purified by the column chromatography using silica gel and eluting with 0-60% ethyl acetate/petroleum ether to yield racemic 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrazole (650 mg, 1.23 mmol, 72.5 % yield) as a brown semi-solid.

LCMS (ESI, m/z) 461.2 $[M+H]^+$

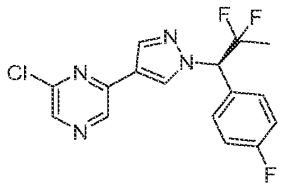
Intermediate 66: 2-bromo-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridine racemate



In a Chemglass reaction vial, to a stirred mixture of racemic 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (500 mg, 1.36 mmol) and 2,6-dibromopyridine (388 mg, 1.64 mmol) in 1,4-dioxane (9 mL) and water (1 mL) was added tripotassium phosphate (869 mg, 4.10 mmol). The reaction mixture was purged with nitrogen gas for 2 min and 1,1'-bis-(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (112 mg, 0.137 mmol) was added. The vial was sealed and the reaction mixture was stirred at 80 °C for 4 h. The mixture was diluted with ethyl acetate (10 mL) and washed with water (5 mL). The organic phase was concentrated and the resulting crude material was purified by column chromatography using silica gel and eluting with 0-20% of ethyl acetate/petroleum ether to yield racemic 2-bromo-6-(1-(2,2-difluoro-1-(4-fluorophenyl)-propyl)-1H-pyrazol-4-yl)pyridine (220 mg, 0.522 mmol, 38.2 % yield) as a colorless liquid.

LCMS (ESI, m/z) 396.0 $[M+H]^+$

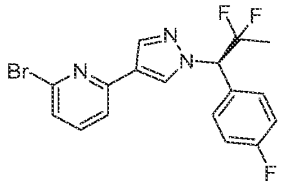
Intermediate 67: *(R)*-2-chloro-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazine



In a Chemglass reaction vial, to a stirred mixture of *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.500 g, 1.36 mmol) and 2-bromo-6-chloropyrazine (0.330 g, 1.71 mmol) in 1,4-dioxane (12 mL) and water (3 mL) was added tripotassium phosphate (0.869 g, 4.10 mmol). The reaction mixture was purged with nitrogen gas for 10 min and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (89.0 mg, 0.137 mmol) was added. The vial was sealed and the reaction mixture was stirred at 80 °C for 6 h. The mixture was diluted with EtOAc (40 mL) and washed with water (10 mL). The organic phase was concentrated to yield crude material which was purified by column chromatography using silica gel and eluting with 0-20% ethyl acetate/petroleum ether to yield *(R)*-2-chloro-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazine (470 mg, 1.26 mmol, 92.0 % yield) as a brown liquid.

LCMS (ESI, m/z) 353.0 $[M+H]^+$

Intermediate 68: *(R)*-2-bromo-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridine

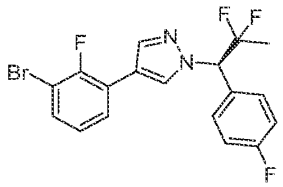


In a Chemglass reaction vial, to a stirred mixture of *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.0g, 2.73 mmol) and 2,6-dibromopyridine (0.776 g, 3.28 mmol) in 1,4-dioxane (16 mL) and water (4 mL) was added tripotassium phosphate (1.74 g, 8.19 mmol). The reaction mixture was purged with nitrogen gas for 2 min and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (223 mg, 0.273 mmol) was added. The vial was sealed and the reaction mixture was stirred at 80 °C for 2 h. The mixture was diluted with

ethyl acetate (40 mL) and washed with water (20 mL). The organic phase was concentrated to yield crude material which was purified by column chromatography using silica gel and eluting with 0-20% of ethyl acetate/petroleum ether to yield *(R)*-2-bromo-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridine (580 mg, 1.36 mmol, 49.7 % yield) as a colorless liquid.

LCMS (ESI, m/z) 396.0 $[M+H]^+$

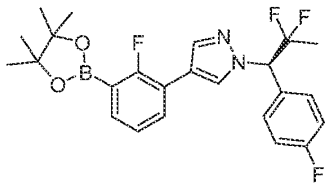
Intermediate 69: *(R)*-4-(3-bromo-2-fluorophenyl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole



In a Chemglass reaction vial, to a stirred mixture of *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole (1.00 g, 2.73 mmol) and (3-bromo-2-fluorophenyl)boronic acid (0.717 g, 3.28 mmol) in 1,4-dioxane (18 mL) and water (2 mL) was added tripotassium phosphate (1.74 g, 8.19 mmol). The reaction mixture was purged with nitrogen gas for 10 min and 1,1'-bis-(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (223 mg, 0.273 mmol) was added. The vial was sealed and the reaction mixture was then stirred at 80 °C for 2 h. The mixture was diluted with EtOAc (20 mL) and washed with water (10 mL). The organic phase was dried over sodium sulphate and concentrated to yield crude material which was purified by column chromatography using silica gel and eluting with 0-20% of ethyl acetate/petroleum ether to yield *(R)*-4-(3-bromo-2-fluorophenyl)-1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazole (1.0 g, 1.9 mmol, 69 % yield) as a brown liquid.

LCMS (ESI, m/z) 415.0 $[M+H]^+$

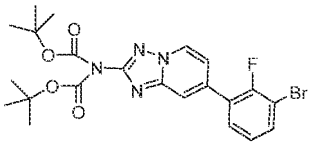
Intermediate 70: *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrazole



In a Chemglass reaction vial, to a stirred solution of *(R)*-4-(3-bromo-2-fluorophenyl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole (1.60 g, 3.87 mmol) in dioxane (20 mL) was added bis(pinacolato)diboron (1.28 g, 5.03 mmol) and potassium acetate (1.14 g, 11.6 mmol). The reaction mixture was purged with nitrogen gas for 10 min and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (316 mg, 0.387 mmol) was added. The vial was sealed and the reaction mixture was then stirred at 100 °C for 16 h. The mixture was filtered through a pad of Celite, eluting with EtOAc. The filtrate was concentrated and the crude material was purified by the column chromatography using 230-400 mesh silica gel and eluting with 0-20% ethyl acetate/petroleum ether to yield *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrazole (1.40 g, 2.92 mmol, 75.0 % yield) as a brown semi-solid.

LCMS (ESI, m/z) 461.2 $[M+H]^+$

Intermediate 71: *tert*-butyl (7-(3-bromo-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)(*tert*-butoxycarbonyl)carbamate



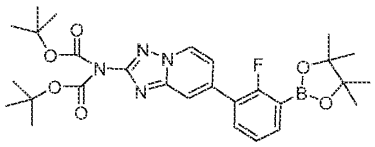
To a dry 150 mL round bottom flask under nitrogen was added *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (2.0 g, 4.3 mmol), 1-bromo-2-fluoro-3-iodobenzene (1.31 g, 4.34 mmol), dioxane (40 mL) and potassium phosphate tribasic, 2.0M in water (8.70 mL, 17.4 mmol). The reaction was purged very well with nitrogen, treated with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (350 mg, 0.429 mmol), purged with nitrogen again and heated at 65 °C for 5.5h. The reaction was diluted ethyl acetate (20 mL), filtered through a pad of Celite and the Celite

pad was rinsed with 1:1 ethyl acetate/dichloromethane mixture (200 mL). The solvent was removed *in vacuo* and the crude residue was purified by flash chromatography on silica gel, eluting with 0-25% gradient of ethyl acetate in dichloromethane to afford the title compound, *tert*-butyl (7-(3-bromo-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)(*tert*-butoxycarbonyl)carbamate (1.79 g, 3.53 mmol, 81.0%).

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.62 (d, *J*=7.2 Hz, 1H), 7.90 (br s, 1H), 7.69 (t, *J*=7.1 Hz, 1H), 7.48 (br t, *J*=6.1 Hz, 1H), 7.32 - 7.28 (m, 1H), 7.21 (br t, *J*=7.5 Hz, 1H), 1.52 (s, 18H).

MS ESI m/z 506.9, 508.9 $(M+H)^+$

Intermediate 72: *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate:

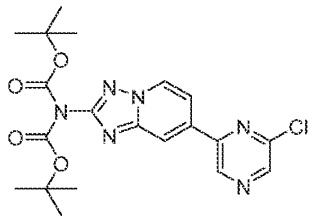


To a dry 40 mL reaction vial under nitrogen was added *tert*-butyl (7-(3-bromo-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)(*tert*-butoxycarbonyl)carbamate (850 mg, 1.67 mmol), bis(pinacolato)diboron (555 mg, 2.19 mmol), potassium acetate (495 mg, 5.04 mmol) and dioxane (12 mL). The reaction was purged well with argon, treated with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (100 mg, 0.122 mmol), purged well with argon again, and securely capped and heated at 95 °C for 2.5 hours. The reaction was treated with additional bis(pinacolato)diboron (148 mg, 0.583 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (24 mg, 0.030 mmol), flushed with argon and heated at 95 °C for 3.5 hours. The reaction was diluted with ethyl acetate, filtered through a pad of Celite and the crude residue was purified by flash chromatography on silica gel, eluting with 0-100% gradient of ethyl acetate in dichloromethane to afford the title compound, *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (841 mg, 1.52 mmol, 91.0%).

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.56 (dd, *J*=7.2, 0.8 Hz, 1H), 7.89 - 7.83 (m, 2H), 7.62 (td, *J*=7.6, 1.8 Hz, 1H), 7.36 - 7.30 (m, 2H), 1.41 (s, 12H), 1.29 (s, 16H).

MS ESI m/z 555.5 $(M+H)^+$

Intermediate 73: *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate

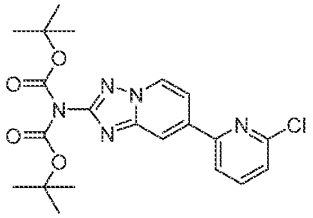


In a 150 mL Chemglass pressure vessel were combined *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (3.50 g, 7.60 mmol) and 2-bromo-6-chloropyrazine (1.47 g, 7.60 mmol) in 1,4-dioxane (70 mL). To the mixture was added potassium phosphate tribasic, 2M aqueous solution (11.4 mL, 22.8 mmol). The mixture was sparged with nitrogen by bubbling with rapid stirring for 5 min. Then, dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II) (0.297 g, 0.456 mmol) was added, and the mixture was sparged with a stream of nitrogen with stirring for 5 additional min. The vessel was sealed and the mixture was heated to 65 °C for 5.5 h. The crude mixture was concentrated in vacuo to a residue, and the residue was reconstituted in EtOAc (20 mL) and the resulting black suspension was filtered through a pad of Celite and rinsed through with 1:1 EtOAc:DCM. Concentration in vacuo gave a red oil which solidified upon standing. The residue was dissolved in minimum DCM (~20 mL) and loaded atop a hexanes preequilibrated 220 g silica cartridge. Elution gradient 100% hexanes to 100% EtOAc over 10 column volumes, hold 100% EtOAc for 4 CVs. Product eluted as a sharp peak around 55-60% EtOAc in hexanes. Product fractions were combined and concentrated in vacuo to a nearly white powder which was placed under high vacuum for several hours to provide *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (2.36 g, 5.29 mmol, 69.6% yield) as an off-white powder.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 9.07 (s, 1H), 8.70 - 8.67 (m, 2H), 8.37 (s, 1H), 7.83 (dd, *J*=7.3, 1.9 Hz, 1H), 1.51 (s, 18H).

MS ESI m/z 446.9 $(M+H)^+$

Intermediate 74: *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate

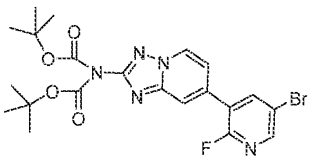


Intermediate 74 was obtained via a similar procedure as described for the preparation of Intermediate 73, where 2-chloro-6-iodopyridine was substituted for 2-bromo-6-chloropyrazine. The desired *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (0.448 g, 1.00 mmol, 93% yield) was obtained as an off-white powder.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.63 (d, *J*=7.2 Hz, 1H), 8.28 (s, 1H), 7.89 - 7.79 (m, 3H), 7.42 (dd, *J*=7.6, 1.0 Hz, 1H), 1.52 - 1.49 (m, 18H).

MS ESI m/z 446.0 $(M+H)^+$

Intermediate 75: *tert*-butyl (7-(5-bromo-2-fluoropyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)(*tert*-butoxycarbonyl)carbamate:

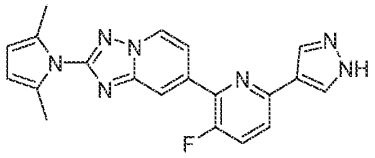


To a 40 mL reaction vial under nitrogen was added *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (500 mg, 1.09 mmol), 5-bromo-2-fluoro-3-iodopyridine (328 mg, 1.09 mmol), dioxane (10 mL) and potassium phosphate tribasic, 2.0 M in water (1.7 mL, 3.4 mmol). The reaction was purged well with argon, treated with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (44 mg, 0.05 mmol), purged again with argon, and the vessel was securely capped and heated at 70 °C for 2.5 h. The residue was dissolved in ethyl acetate (200 mL) and the organic layer was washed with water (3 x 10 mL), brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude residue was purified by flash

chromatography on silica gel, eluting with 0-50% gradient of ethyl acetate in hexanes to afford the title compound, *tert*-butyl (7-(5-bromo-2-fluoropyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)(*tert*-butoxycarbonyl)carbamate (340 mg, 0.67 mmol, 61.6%).

MS ESI m/z 508.2, 509.9 $(M+H)^+$

Intermediate 76: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(3-fluoro-6-(1H-pyrrol-3-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine



76A: 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine: In each of two separate 20 mL microwave reaction vessels was placed 7-bromo-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (2.00 g, 9.39 mmol). To both vessels was added toluene (12.5 mL), 2,5-hexanedione (2.20 mL, 18.8 mmol) and acetic acid (1.08 mL, 18.8 mmol). The vessels were sealed and placed in a microwave reactor at 155 °C for 12 h. The two reaction mixtures were combined and concentrated in vacuo to give a brown oil residue. The brown residue was diluted with DCM (5 mL) and loaded atop a hexanes preequilibrated 120 g silica cartridge. Elution gradient 100% hexanes to 100% DCM over 7 column volumes, hold 100% DCM for 5 CVs. Product fractions were combined and concentrated in vacuo to a residue. The material was placed under high vacuum overnight with stirring to provide 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (4.22 g, 14.6 mmol, 77% yield) as a thick, light amber oil.

MS ESI m/z 290.6, 292.6 $(M+H)^+$

76B: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine: In a 350 mL Chemglass pressure vessel with threaded stopper, fitted with a large magnetic stirbar to allow for efficient biphase stirring, were combined 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (4.15 g, 14.3 mmol), potassium acetate (4.20 g, 42.8 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (3.98 g, 15.7 mmol) in 1,4-dioxane (100 mL). The mixture was sparged with nitrogen gas with vigorous stirring for 10 min, then dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (0.582 g, 0.713 mmol) was added. The mixture was sparged for an additional 5 min with vigorous stirring, and

the vessel was sealed and heated to 100 degrees C for 1 h. The vessel was removed from heating and allowed to cool, opened, and a nitrogen sparge was immediately inserted into the vessel. A small aliquot of crude mixture was sampled by LCMS, which showed complete consumption of the bromide starting material and formation of a major product with m/z consistent with the molecular weight of the free boronic acid of the desired 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine. This crude black mixture was carried directly into the next step. A 100% yield was assumed.

MS ESI m/z 256.8 $(M+H)^+$

76C : 7-(6-chloro-3-fluoropyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine: While sparging with nitrogen gas and vigorously stirring, to the crude black mixture from the previous step containing 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (assumed 4.82 g, 14.3 mmol) was added freshly prepared, nitrogen pre-sparged potassium phosphate tribasic, 2M aqueous solution (100 mL, 200 mmol). The resulting mixture was sparged with nitrogen by bubbling with vigorous stirring for 5 min. To the mixture was added additional dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (0.291 g, 0.356 mmol). The mixture was sparged again with nitrogen by bubbling with vigorous stirring for 5 min, then the mixture was charged with an excess of 6-chloro-3-fluoro-2-iodopyridine (5.07 g, 19.7 mmol) and the mixture was sparged again with nitrogen by bubbling with vigorous stirring for 5 min. The vessel was sealed and the mixture was heated to 70 °C for 45 min. The vessel was removed from heating and allowed to cool, opened, and a nitrogen sparge was immediately inserted into the vessel. A small aliquot of crude mixture was sampled by LCMS, which showed complete consumption of the boronate starting material and formation of a major product with m/z consistent with the molecular weight of the desired 7-(6-chloro-3-fluoropyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine. This crude black mixture was carried directly into the next step. A 100% yield was assumed.

MS ESI m/z 342.0 $(M+H)^+$

76: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(3-fluoro-6-(1H-pyrrol-3-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine: To the crude, nearly black mixture from the previous step containing 7-(6-chloro-3-fluoropyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-

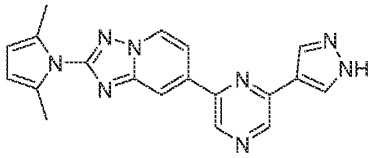
[1,2,4]triazolo[1,5-*a*]pyridine (assumed 4.87 g, 14.3 mmol), under a blanket of nitrogen, was added an excess of solid 1H-pyrazole-4-boronic acid (9.6 g, 86 mmol). The resulting mixture was sparged with nitrogen by bubbling with vigorous stirring for 10 min, during which time most but not all of the solids appeared to go into solution. The mixture was charged with more dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (0.291 g, 0.356 mmol) and was sparged with nitrogen for another 5 min. Then the vessel was sealed and the mixture was heated to 95 °C. After 90 min, the vessel was removed from heating, allowed to cool, opened, and a nitrogen sparge was immediately inserted. A small aliquot of crude mixture was sampled by LCMS which showed incomplete conversion of the 7-(6-chloro-3-fluoropyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine starting material. Additional 1H-pyrazole-4-boronic acid (9.6 g, 86 mmol) and more dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (0.291 g, 0.356 mmol) were added and the resulting mixture was sparged with nitrogen while vigorously stirring for 10 min. Most of the additional pyrazole-4-boronic acid dissolved during the sparging. The mixture was sealed and heated to 95 °C for 2 h. The vessel was again removed from heating, allowed to cool, opened, and a nitrogen sparge was immediately inserted. A small aliquot of crude mixture was sampled by LCMS which showed nearly complete conversion of the 7-(6-chloro-3-fluoropyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine starting material. Additional 1H-pyrazole-4-boronic acid (1.60 g, 1 eq, 14.5 mmol) was added and the resulting mixture was sparged with nitrogen while vigorously stirring for 10 min. The vessel was sealed and heated to 95 °C for 2 h. The mixture was removed from heating and allowed to come to RT. The reaction biphase was separated using a separatory funnel into aqueous and organic phases. The organic phase was concentrated to a brown solid. To the residue was added EtOAc (250 mL) and water (150 mL) and this mixture was shaken and the phases were separated. The organic was washed with water (3 x 150 mL) and was then filtered through a celite plug and rinsed through with EtOAc. The organic was concentrated in vacuo to a brown solid. The residue was dissolved by warming in 500 mL of dichloromethane. This solution was loaded atop a 330 g silica cartridge which had been preequilibrated with dichloromethane. Elution gradient 100% DCM to 100% acetone over 7 column volumes, hold 100% acetone for 4 CVs. The product eluted as a broad peak (light brown fractions) in the middle of the gradient. Product fractions were pooled and

concentrated in vacuo to give an off-white powder. The material was placed under high vacuum while warming the flask to 60-65 °C in a water bath for 8 h and then overnight at RT, a process which removed an undesired colorless solid from the desired material by sublimation. Thus was obtained 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(3-fluoro-6-(1H-pyrrol-3-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (4.66 g, 12.5 mmol, 88% yield over 3 steps) as a beige solid.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 13.24 - 13.03 (m, 1H), 9.11 (d, *J*=7.1 Hz, 1H), 8.51 - 8.07 (m, 3H), 8.01 - 7.83 (m, 3H), 5.90 (s, 2H), 2.31 (s, 6H).

MS ESI m/z 374.1 $(M+H)^+$

Intermediate 77: 7-(6-(1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine

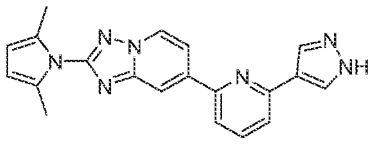


Intermediate 77 was obtained via a similar procedure as described for the preparation of Intermediate 76, where 2-bromo-6-chloropyrazine was substituted for 6-chloro-3-fluoro-2-iodopyridine in Step 76C. The desired 7-(6-(1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (3.72 g, 10.4 mmol, 71.6% yield over 3 steps) was obtained as a light brown powder.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 13.34 (br s, 1H), 9.32 (s, 1H), 9.15 (d, *J*=7.1 Hz, 1H), 9.10 (s, 1H), 8.80 (s, 1H), 8.17 (dd, *J*=7.2, 1.8 Hz, 1H), 5.91 (s, 2H), 2.32 (s, 6H).

MS ESI m/z 357.1 $(M+H)^+$

Intermediate 78: 7-(6-(1H-pyrazol-4-yl)pyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine



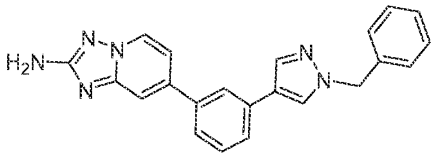
Intermediate 78 was obtained via a similar procedure as described for the preparation of Intermediate 76, where 2-chloro-6-iodopyridine was substituted for 6-chloro-3-fluoro-2-

iodopyridine in Step 76C. The desired 7-(6-(1H-pyrazol-4-yl)pyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (3.78 g, 10.6 mmol, 73.5% yield over 3 steps) was obtained as a light brown powder.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 13.16 (br s, 1H), 9.08 (d, *J*=7.2 Hz, 1H), 8.68 (d, *J*=1.0 Hz, 1H), 8.59 - 8.20 (m, 2H), 8.17 (dd, *J*=7.2, 1.8 Hz, 1H), 8.10 (d, *J*=7.5 Hz, 1H), 7.96 (t, *J*=7.8 Hz, 1H), 7.79 (d, *J*=7.7 Hz, 1H), 5.90 (s, 2H), 2.31 (s, 6H).

MS ESI m/z 356.1 $(M+H)^+$

Example 1: 7-(3-(1-benzyl-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



1A: 1-benzyl-4-(3-bromophenyl)-1H-pyrazole: To a dry reaction vial was added 1-benzyl-4-iodo-1H-pyrazole (100 mg, 0.352 mmol), 3-bromophenylboronic acid (74 mg, 0.37 mmol), dioxane (2 mL) and potassium phosphate tribasic, 2.0M in water (704 µL, 1.41 mmol). The reaction was flushed very well with argon, then treated with dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane, 99% (17 mg, 0.020 mmol). The reaction was again flushed very well with argon, and the vial was securely capped and heated at 90 °C for 2 hours. The reaction was diluted water (6 mL) and ethyl acetate (75 mL) and the organic layer was washed with water (3 x 5 mL), brine (1 x 5 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude residue was purified by flash chromatography on silica gel, eluting with 0-75% gradient of ethyl acetate in hexanes to afford 1-benzyl-4-(3-bromophenyl)-1H-pyrazole (76.5 mg, 0.240 mmol, 69.4%).

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.82 (d, *J*=0.7 Hz, 1H), 7.65 - 7.59 (m, 2H), 7.43 - 7.29 (m, 7H), 7.27 - 7.20 (m, 1H), 5.36 (s, 2H).

LCMS (ESI, m/z): 312.9, 314.9 $[M+H]^+$.

1B: *tert*-butyl (7-(3-(1-benzyl-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)(*tert*-butoxycarbonyl)carbamate: To a solution of 1-benzyl-4-(3-bromophenyl)-1H-pyrazole (76.5 mg, 0.244 mmol) and *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-

tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (120 mg, 0.261 mmol) in dioxane (2.5 mL) was added potassium phosphate tribasic, 2.0M in water (490 µL, 0.980 mmol). The reaction was flushed very well with argon, then treated with dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II), 99% (15 mg, 0.023 mmol). The reaction was again flushed very well with argon and the vessel was securely capped and heated at 65 °C for 5.5 hours. The reaction was diluted with water (15 mL) and ethyl acetate (100 mL) and the organic layer was washed with water (3 x 8 mL), brine (1 x 8 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude residue was purified by flash chromatography on silica gel, eluting with 0-75% gradient of ethyl acetate in dichloromethane to afford the title compound, *tert*-butyl (7-(3-(1-benzyl-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)(*tert*-butoxycarbonyl)carbamate (123 mg, 0.22 mmol, 89%)

LCMS (ESI, m/z): 567.3 $[M+H]^+$.

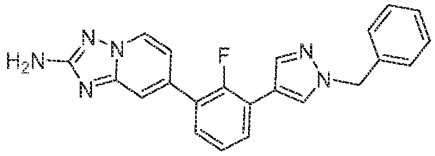
1: 7-(3-(1-benzyl-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine:

To a solution of *tert*-butyl (7-(3-(1-benzyl-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)(*tert*-butoxycarbonyl)carbamate (123 mg, 0.217 mmol) in dichloromethane (2.0 mL) was added TFA (0.017 mL, 0.217 mmol) with rapid swirling and the reaction was allowed to stand at room temp for 75 min. The volatiles were removed under a gentle stream of nitrogen and the crude product was purified by via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 15% B - 55% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give 7-(3-(1-benzyl-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (51 mg, 0.14 mmol, 64%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.59 (d, *J*=7.0 Hz, 1H), 8.45 (s, 1H), 8.07 (s, 1H), 8.01 (s, 1H), 7.74 (s, 1H), 7.63 (dd, *J*=13.4, 7.9 Hz, 2H), 7.51 - 7.43 (m, 1H), 7.41 - 7.34 (m, 2H), 7.33 - 7.26 (m, 4H), 6.02 (s, 2H), 5.37 (s, 2H).

LCMS (ESI, m/z): 367.1 $[M+H]^+$

Example 2: 7-(3-(1-benzyl-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine

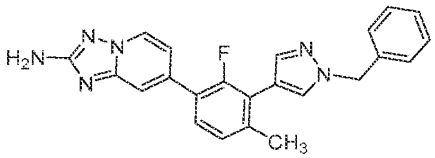


The title compound 7-(3-(1-benzyl-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine was prepared in a similar fashion as described for the preparation of Example 1, except 3-bromo-2-fluorophenylboronic acid (81 mg, 0.37 mmol) was used in place of 3-bromophenylboronic acid in the first step. The crude product prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 17% B - 57% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give 7-(3-(1-benzyl-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (29 mg, 0.075 mmol, 67%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 - 8.53 (m, 1H), 8.35 (s, 1H), 8.01 (s, 1H), 7.79 (br t, *J*=7.2 Hz, 1H), 7.53 (s, 1H), 7.46 (br t, *J*=7.4 Hz, 1H), 7.42 - 7.25 (m, 6H), 7.13 - 7.04 (m, 1H), 6.06 (s, 2H), 5.39 (s, 3H).

LCMS (ESI, m/z): 385.1 $[M+H]^+$.

Example 3: 7-(3-(1-benzyl-1H-pyrazol-4-yl)-2-fluoro-4-methylphenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



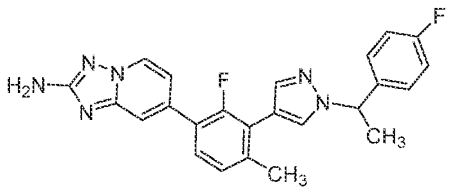
The title compound 7-(3-(1-benzyl-1H-pyrazol-4-yl)-2-fluoro-4-methylphenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine was prepared in a similar fashion as described for the preparation of Example 1, except (3-bromo-2-fluoro-6-methylphenyl)boronic acid (86 mg, 0.37 mmol) was used in place of 3-bromophenylboronic acid in the first step. The crude product prepared in the final synthetic step was purified via preparative LC/MS with the

following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 19% B - 59% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give 7-(3-(1-benzyl-1H-pyrazol-4-yl)-2-fluoro-4-methylphenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (41.7 mg, 0.105 mmol, 59.7%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 - 8.53 (m, 1H), 8.14 (s, 1H), 7.71 (s, 1H), 7.49 (s, 1H), 7.45 (br t, *J*=8.0 Hz, 1H), 7.40 - 7.34 (m, 2H), 7.34 - 7.23 (m, 4H), 7.05 (br d, *J*=7.0 Hz, 1H), 6.04 (s, 2H), 5.41 (s, 2H), 2.37 (s, 3H).

LCMS (ESI, m/z): 399.2 $[M+H]^+$

Example 4: 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-4-methylphenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

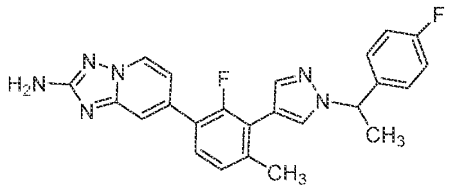
The title compound 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-4-methylphenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 was prepared in a similar fashion as described for the preparation of Example 1, where Intermediate 32 was used in place of 1-benzyl-4-iodo-1H-pyrazole and (3-bromo-2-fluoro-6-methylphenyl)boronic acid (86 mg, 0.37 mmol) was used in place of 3-bromophenylboronic acid in the first step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 24-64% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic (3-(1-benzyl-1H-pyrazol-4-yl)-2-fluoro-4-methylphenyl)-

[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralpax IC, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 40%B over 18 minutes; Flow Rate: 85 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (275 nm). Fractions containing the first isomer to elute from the chiral column were combined and dried via centrifugal evaporation to provide 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-4-methylphenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine, enantiomer 1 (23 mg, 0.054 mmol, 33%).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.62 - 8.54 (m, 1H), 8.19 - 8.12 (m, 1H), 7.71 (s, 1H), 7.53 - 7.41 (m, 2H), 7.35 (br t, *J*=6.3 Hz, 2H), 7.29 - 7.23 (m, 1H), 7.19 (dt, *J*=8.6, 4.4 Hz, 2H), 7.05 (br d, *J*=6.7 Hz, 1H), 6.04 (s, 2H), 5.78 - 5.65 (m, 1H), 2.36 (s, 3H), 1.86 (br d, *J*=7.0 Hz, 3H).

MS ESI m/z 431.1 $(M+H)^+$

Example 5: 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-4-methylphenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



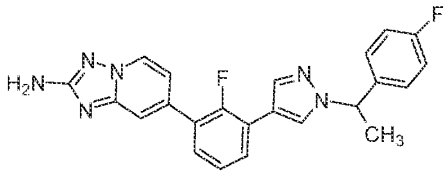
enantiomer 2

The title compound 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-4-methylphenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine, enantiomer 2 (25 mg, 0.059 mmol, 35%) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 4.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.59 (d, *J*=6.8 Hz, 1H), 8.15 (s, 1H), 7.71 (s, 1H), 7.52 - 7.41 (m, 2H), 7.35 (dd, *J*=8.3, 5.6 Hz, 2H), 7.25 (d, *J*=8.0 Hz, 1H), 7.22 - 7.14 (m, 2H), 7.05 (br d, *J*=7.0 Hz, 1H), 6.04 (s, 2H), 5.71 (q, *J*=7.0 Hz, 1H), 2.36 (s, 3H), 1.85 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 431.1 $(M+H)^+$

Example 6: 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

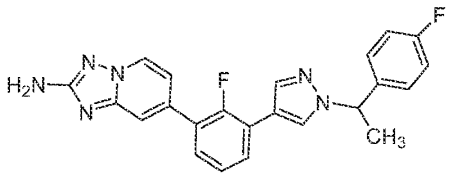
The title compound 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 was prepared in a similar fashion as described for the preparation of Example 1, where Intermediate 32 was used in place of 1-benzyl-4-iodo-1H-pyrazole and 3-bromo-2-fluorophenylboronic acid (76.3 mg, 0.349 mmol) was used in place of 3-bromophenylboronic acid in the first step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 20%B - 60% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralpak IC, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 30%B over 12 minutes; Flow Rate: 85 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (240 nm). Fractions containing the first isomer to elute from the chiral column were combined and dried via centrifugal evaporation to provide 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (19 mg, 0.046 mmol, 32%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.62 (d, *J*=7.0 Hz, 1H), 8.37 (d, *J*=1.4 Hz, 1H), 8.01 (s, 1H), 7.80 (td, *J*=7.3, 1.3 Hz, 1H), 7.54 (s, 1H), 7.47 (td, *J*=7.4, 1.5 Hz, 1H), 7.41 - 7.29

(m, 3H), 7.18 (t, *J*=8.9 Hz, 2H), 7.08 (d, *J*=7.0 Hz, 1H), 6.07 (s, 2H), 5.72 (q, *J*=7.1 Hz, 1H), 1.85 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 417.1 $(M+H)^+$

Example 7: 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



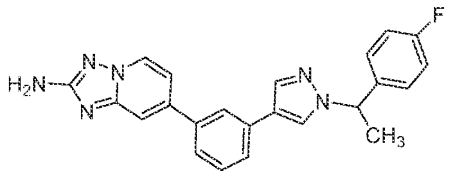
enantiomer 2

The title compound 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine, enantiomer 2 (19 mg, 0.046 mmol, 32%) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 6.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.62 (d, *J*=6.8 Hz, 1H), 8.37 (s, 1H), 8.01 (s, 1H), 7.84 - 7.75 (m, 1H), 7.53 (s, 1H), 7.47 (t, *J*=7.0 Hz, 1H), 7.41 - 7.30 (m, 3H), 7.18 (t, *J*=8.8 Hz, 2H), 7.08 (br d, *J*=7.0 Hz, 1H), 6.07 (s, 2H), 5.72 (q, *J*=6.8 Hz, 1H), 1.85 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 417.1 $(M+H)^+$

Example 8: 7-(3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



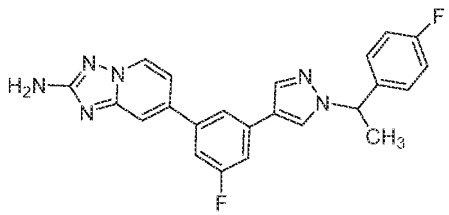
enantiomer 2

The title compound 7-(3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was prepared in a similar fashion as

described for the preparation of Example 1, where Intermediate 32 was used in place of 1-benzyl-4-iodo-1H-pyrazole in the first step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 20% B - 60% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralpak IC, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 55%B over 19 minutes; Flow Rate: 85 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (240 nm). The title compound was the second isomer to elute from the column. Fractions containing the second enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (23 mg, 0.059 mmol, 32%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.59 (d, *J*=7.0 Hz, 1H), 8.52 (s, 1H), 8.06 (s, 1H), 8.03 (s, 1H), 7.74 (s, 1H), 7.64 (dd, *J*=19.7, 7.8 Hz, 2H), 7.52 - 7.44 (m, 1H), 7.38 - 7.32 (m, 2H), 7.29 (dd, *J*=7.0, 1.9 Hz, 1H), 7.17 (t, *J*=8.9 Hz, 2H), 6.02 (s, 2H), 5.65 (q, *J*=7.0 Hz, 1H), 1.85 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 399.1 $(M+H)^+$

Example 9: 7-(3-fluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



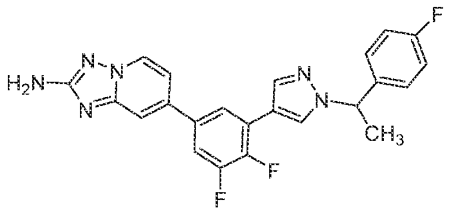
enantiomer 2

The title compound 7-(3-fluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was prepared in a similar fashion as described for the preparation of Example 1, where Intermediate 32 was used in place of 1-benzyl-4-iodo-1H-pyrazole and 3-bromo-5-fluorophenylboronic acid was used in place of 3-bromophenylboronic acid in the first step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 18-58% B over 20.5 minutes, then a 4-minute hold at 100% B; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(3-fluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 25%B over 22 minutes; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (240 nm). Fractions containing the second enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(3-fluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (20 mg, 0.049 mmol, 30%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.66 - 8.56 (m, 2H), 8.17 - 8.09 (m, 1H), 7.95 - 7.88 (m, 1H), 7.86 - 7.78 (m, 1H), 7.59 - 7.44 (m, 2H), 7.38 - 7.29 (m, 3H), 7.24 - 7.12 (m, 2H), 6.11 - 6.00 (m, 2H), 5.71 - 5.59 (m, 1H), 1.94 - 1.75 (m, 3H).

MS ESI m/z 417.0 $(M+H)^+$

Example 10: 7-(3,4-difluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



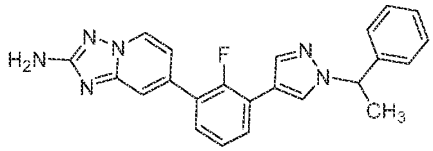
enantiomer 2

The title compound 7-(3,4-difluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was prepared in a similar fashion as described for the preparation of Example 1, where Intermediate 32 was used in place of 1-benzyl-4-iodo-1H-pyrazole and 5-bromo-2,3-difluorophenylboronic acid was used in place of 3-bromophenylboronic acid in the first step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 26-66% B over 20.5 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(3,4-difluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 μm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 30%B over 12.5 minutes; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (240 nm). Fractions containing the second isomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(3,4-difluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (14 mg, 0.033 mmol, 28%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.66 - 8.58 (m, 1H), 8.57 - 8.49 (m, 1H), 8.13 (br s, 1H), 7.99 (br d, *J*=1.2 Hz, 1H), 7.86 - 7.74 (m, 2H), 7.42 - 7.29 (m, 3H), 7.23 - 7.13 (m, 2H), 6.06 (br s, 2H), 5.79 - 5.68 (m, 1H), 1.87 (br d, *J*=7.0 Hz, 3H).

MS ESI m/z 435.0 $(M+H)^+$

Example 11: 7-(2-fluoro-3-(1-(1-phenylethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



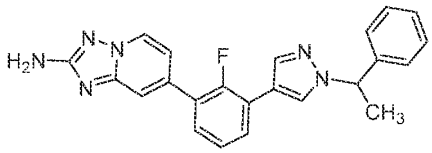
enantiomer 1

The title compound 7-(2-fluoro-3-(1-(1-phenylethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 was prepared in a similar fashion as described for the preparation of Example 1, where Intermediate 33 was used in place of 1-benzyl-4-iodo-1H-pyrazole and 3-bromo-2-fluorophenylboronic acid was used in place of 3-bromophenylboronic acid in the first step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 21-61% B over 20.5 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(2-fluoro-3-(1-(1-phenylethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 30%B over 11 minutes; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (240 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(2-fluoro-3-(1-(1-phenylethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (27 mg, 0.068 mmol, 34%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.61 (d, *J*=7.0 Hz, 1H), 8.37 (s, 1H), 8.00 (s, 1H), 7.84 - 7.77 (m, 1H), 7.53 (s, 1H), 7.50 - 7.42 (m, 1H), 7.39 - 7.24 (m, 6H), 7.08 (d, *J*=6.9 Hz, 1H), 6.07 (s, 2H), 5.70 (q, *J*=6.9 Hz, 1H), 1.86 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 399.1 $(M+H)^+$

Example 12: 7-(2-fluoro-3-(1-(1-phenylethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine enantiomer 2



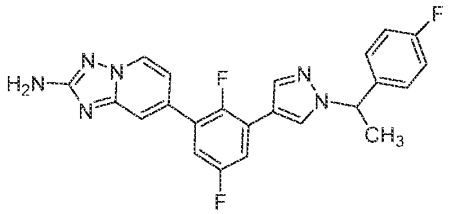
enantiomer 2

The title compound 7-(2-fluoro-3-(1-(1-phenylethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine, enantiomer 2 (27 mg, 0.069 mmol, 34%) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 11.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.61 (d, *J*=7.0 Hz, 1H), 8.37 (s, 1H), 8.00 (s, 1H), 7.80 (t, *J*=7.3 Hz, 1H), 7.53 (s, 1H), 7.50 - 7.41 (m, 1H), 7.38 - 7.23 (m, 6H), 7.08 (d, *J*=6.8 Hz, 1H), 6.07 (s, 2H), 5.69 (q, *J*=7.0 Hz, 1H), 1.86 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 399.1 $(M+H)^+$

Example 13: 7-(2,5-difluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

13A: 4-(3-bromo-2,5-difluorophenyl)-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazole: To a dry reaction vial under nitrogen was added 1,3-dibromo-2,5-difluorobenzene (200 mg, 0.736 mmol), 1-(1-(4-fluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (233 mg, 0.736 mmol), dioxane (8 mL) and potassium phosphate tribasic, 2.0M in water (1.5 mL, 3.0 mmol). The reaction was purged well with argon and was then treated with dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane, 99%

(45 mg, 0.060 mmol). The reaction was purged with argon again and the vessel was capped and heated at 90 °C for 3.5 hours. The reaction was diluted with water (10 mL) and ethyl acetate (200 mL). The organic layer was washed with water (3 x 5 mL), brine (1 x 5 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude obtained was purified by flash chromatography on silica gel, eluting with 0-100% gradient of ethyl acetate in dichloromethane to afford 4-(3-bromo-2,5-difluorophenyl)-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazole (89 mg, 0.23 mmol, 32 %).

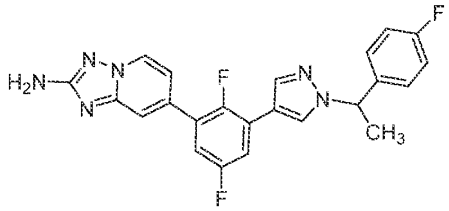
MS ESI m/z 380.9, 382.9 $(M+H)^+$

13: The title compound 7-(2,5-difluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 was prepared in a similar fashion as described for the preparation of Example 1, where 4-(3-bromo-2,5-difluorophenyl)-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazole was used in place of 1-benzyl-4-(3-bromophenyl)-1H-pyrazole in step 1B. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 25-65% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(2,5-difluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: 1:1 MeOH:ACN; Elution gradient: isocratic 25%B over 11 minutes; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (235 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(2,5-difluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (25 mg, 0.057 mmol, 19%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (d, *J*=7.0 Hz, 1H), 8.44 (s, 1H), 8.07 (s, 1H), 7.76 - 7.68 (m, 1H), 7.59 (s, 1H), 7.37 (br dd, *J*=8.0, 5.8 Hz, 3H), 7.18 (t, *J*=8.8 Hz, 2H), 7.10 (br d, *J*=7.0 Hz, 1H), 6.11 (s, 2H), 5.72 (q, *J*=6.8 Hz, 1H), 1.85 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 435.1 $(M+H)^+$

Example 14: 7-(2,5-difluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



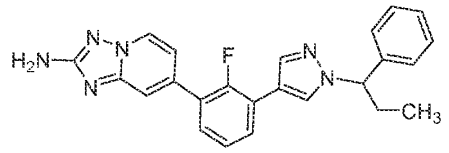
enantiomer 2

The title compound 7-(2,5-difluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (25 mg, 0.058 mmol, 19%) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 13.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (d, *J*=7.0 Hz, 1H), 8.44 (d, *J*=1.3 Hz, 1H), 8.07 (s, 1H), 7.72 (ddd, *J*=9.1, 5.6, 3.2 Hz, 1H), 7.59 (s, 1H), 7.43 - 7.31 (m, 3H), 7.23 - 7.14 (m, 2H), 7.10 (br d, *J*=7.0 Hz, 1H), 6.11 (s, 2H), 5.72 (q, *J*=7.0 Hz, 1H), 1.85 (d, *J*=7.0 Hz, 3H)

MS ESI m/z 435.1 $(M+H)^+$

Example 15: 7-(2-fluoro-3-(1-(1-phenylpropyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

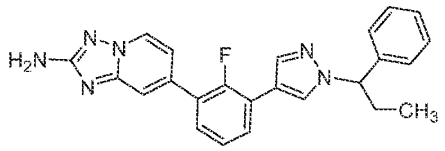
The title compound 7-(2-fluoro-3-(1-(1-phenylpropyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 was prepared in a similar fashion as described for the preparation of Example 1, where Intermediate 38 was used in place of 1-benzyl-4-iodo-1H-pyrazole and 3-bromo-2-fluorophenylboronic acid was used in place of

3-bromophenylboronic acid in the first step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 24-64% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(2-fluoro-3-(1-(1-phenylpropyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Whelk-O1 (S,S), 21 mm x 250 mm, 5 μm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% NH_4OH; Elution gradient: isocratic 45%B over 4 minutes; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (240 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(2-fluoro-3-(1-(1-phenylethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1. The material was further purified via preparative SFC with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 μm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 40%B over 7 minutes; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (240 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(2-fluoro-3-(1-(1-phenylethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (18 mg, 0.045 mmol, 25%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.62 (d, *J*=7.0 Hz, 1H), 8.39 (s, 1H), 8.02 (s, 1H), 7.84 - 7.77 (m, 1H), 7.54 (s, 1H), 7.49 - 7.43 (m, 1H), 7.43 - 7.38 (m, 2H), 7.37 - 7.26 (m, 4H), 7.08 (br d, *J*=7.0 Hz, 1H), 6.07 (s, 2H), 5.40 (dd, *J*=9.2, 6.5 Hz, 1H), 2.46 - 2.35 (m, 1H), 2.25 - 2.11 (m, 1H), 0.85 (t, *J*=7.2 Hz, 3H).

MS ESI m/z 413.2 $(M+H)^+$

Example 16: 7-(2-fluoro-3-(1-(1-phenylpropyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



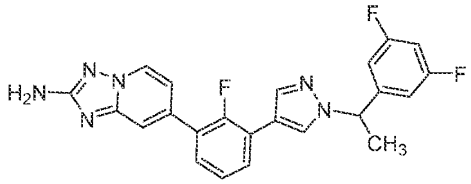
enantiomer 2

The title compound 7-(2,5-difluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (18 mg, 0.044 mmol, 25%) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 15.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.62 (d, *J*=6.9 Hz, 1H), 8.39 (s, 1H), 8.02 (s, 1H), 7.84 - 7.76 (m, 1H), 7.53 (s, 1H), 7.49 - 7.25 (m, 7H), 7.08 (d, *J*=7.0 Hz, 1H), 6.07 (s, 2H), 5.40 (dd, *J*=9.1, 6.1 Hz, 1H), 2.48 - 2.35 (m, 1H), 2.17 (dt, *J*=13.7, 6.8 Hz, 1H), 0.85 (t, *J*=7.2 Hz, 3H).

MS ESI m/z 413.1 $(M+H)^+$

Example 17: 7-(3-(1-(1-(3,5-difluorophenyl)ethyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

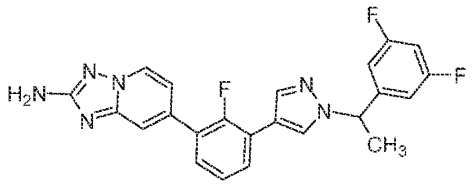
The title compound 7-(3-(1-(1-(3,5-difluorophenyl)ethyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 was prepared in a similar fashion as described for the preparation of Example 1, where Intermediate 35 was used in place of 1-benzyl-4-iodo-1H-pyrazole and 3-bromo-2-fluorophenylboronic acid was used in place of 3-bromophenylboronic acid in the first step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 25-65% B over 20 minutes;

Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(3-(1-(1-(3,5-difluorophenyl)ethyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralpak AD-H, 21 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 25%B over 50 minutes; Flow Rate: 75 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (240 nm). Fractions containing the first enantiomer to elute from the chiral SFC column were combined and dried via centrifugal evaporation to provide 7-(3-(1-(1-(3,5-difluorophenyl)ethyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (14 mg, 0.031 mmol, 21%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (d, *J*=6.9 Hz, 1H), 8.44 (s, 1H), 8.05 (s, 1H), 7.82 (t, *J*=6.8 Hz, 1H), 7.55 (s, 1H), 7.48 (t, *J*=6.8 Hz, 1H), 7.35 (t, *J*=7.7 Hz, 1H), 7.22 - 7.14 (m, 1H), 7.10 (br d, *J*=7.0 Hz, 1H), 7.03 (br d, *J*=6.5 Hz, 2H), 5.76 (q, *J*=7.2 Hz, 1H), 1.86 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 435.1 $(M+H)^+$

Example 18: 7-(3-(1-(1-(3,5-difluorophenyl)ethyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



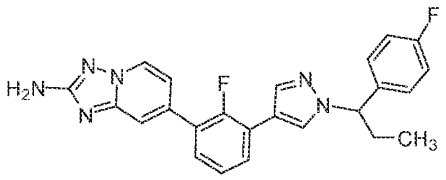
enantiomer 2

The title compound 7-(3-(1-(1-(3,5-difluorophenyl)ethyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (14 mg, 0.031 mmol, 21%) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 17.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (d, *J*=7.0 Hz, 1H), 8.44 (s, 1H), 8.05 (s, 1H), 7.86 - 7.78 (m, 1H), 7.55 (s, 1H), 7.48 (t, *J*=7.6 Hz, 1H), 7.34 (t, *J*=7.7 Hz, 1H), 7.22 - 7.13

(m, 1H), 7.09 (br d, *J*=7.0 Hz, 1H), 7.03 (br d, *J*=6.7 Hz, 2H), 5.76 (q, *J*=7.2 Hz, 1H), 1.86 (d, *J*=7.0 Hz, 3H).
MS ESI m/z 435.0 $(M+H)^+$

Example 19: 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

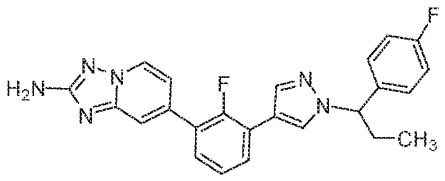
The title compound 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 was prepared in a similar fashion as described for the preparation of Example 1, where 1-(1-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole was used in place of 1-benzyl-4-iodo-1H-pyrazole and 3-bromo-2-fluorophenylboronic acid (73 mg, 0.33 mmol) was used in place of 3-bromophenylboronic acid in the first step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 26-66% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 20%B over 25 minutes; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (254 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(2-fluoro-3-(1-(1-(4-

fluorophenyl)propyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (17 mg, 0.039 mmol, 23%).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.62 (d, *J*=7.0 Hz, 1H), 8.40 (d, *J*=1.7 Hz, 1H), 8.02 (s, 1H), 7.80 (t, *J*=6.9 Hz, 1H), 7.54 (s, 1H), 7.47 (dd, *J*=8.6, 5.6 Hz, 3H), 7.33 (t, *J*=7.7 Hz, 1H), 7.18 (t, *J*=8.9 Hz, 2H), 7.08 (d, *J*=7.0 Hz, 1H), 6.07 (s, 2H), 5.42 (dd, *J*=9.5, 6.2 Hz, 1H), 2.39 (ddd, *J*=13.7, 9.2, 7.0 Hz, 1H), 2.15 (dt, *J*=14.0, 6.8 Hz, 1H), 0.83 (t, *J*=7.2 Hz, 3H).

MS ESI m/z 431.1 $(M+H)^+$

Example 20: 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



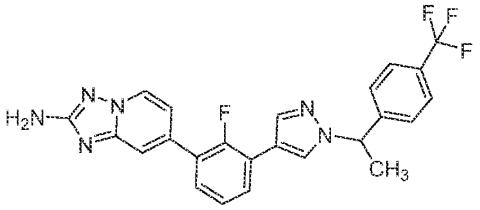
enantiomer 2

The title compound 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (17 mg, 0.039 mmol, 22%) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 19.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.62 (d, *J*=6.8 Hz, 1H), 8.40 (s, 1H), 8.02 (s, 1H), 7.85 - 7.75 (m, 1H), 7.54 (s, 1H), 7.51 - 7.43 (m, 3H), 7.33 (t, *J*=7.8 Hz, 1H), 7.18 (t, *J*=8.8 Hz, 2H), 7.08 (br d, *J*=7.0 Hz, 1H), 6.07 (s, 2H), 5.42 (dd, *J*=9.2, 6.4 Hz, 1H), 2.46 - 2.33 (m, 1H), 2.22 - 2.09 (m, 1H), 0.83 (t, *J*=7.2 Hz, 3H).

MS ESI m/z 431.1 $(M+H)^+$

Example 21: 7-(2-fluoro-3-(1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



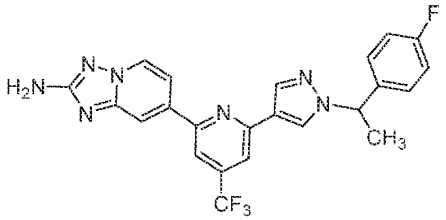
enantiomer 2

The title compound 7-(2-fluoro-3-(1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was prepared in a similar fashion as described for the preparation of Example 1, where 4-iodo-1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-pyrazole (100 mg, 0.273 mmol) was used in place of 1-benzyl-4-iodo-1H-pyrazole and 3-bromo-2-fluorophenylboronic acid (60 mg, 0.27 mmol) was used in place of 3-bromophenylboronic acid in the first step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 29-69% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(2-fluoro-3-(1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Whelk-O1 (S,S), 21 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 40%B over 13 minutes; Flow Rate: 75 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (254 nm). Fractions containing the second enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(2-fluoro-3-(1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (20 mg, 0.043 mmol, 27%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.62 (d, *J*=6.8 Hz, 1H), 8.44 (s, 1H), 8.05 (s, 1H), 7.85 - 7.79 (m, 1H), 7.73 (d, *J*=8.2 Hz, 2H), 7.57 - 7.44 (m, 4H), 7.34 (t, *J*=7.7 Hz, 1H), 7.08 (d, *J*=7.0 Hz, 1H), 6.07 (s, 2H), 5.84 (q, *J*=6.8 Hz, 1H), 1.89 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 467.0 $(M+H)^+$

Example 22: 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-4-(trifluoromethyl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



enantiomer 2

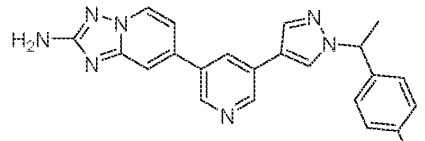
The title compound 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-4-(trifluoromethyl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was prepared in a similar fashion as described for the preparation of Example 13, where 2,6-dichloro-4-(trifluoromethyl)pyridine (143 mg, 0.664 mmol) was used in place of 1,3-dibromo-2,5-difluorobenzene in the first step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 27-67% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-4-(trifluoromethyl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 40%B over 13 minutes; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (254 nm). Fractions containing the second enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-4-

(trifluoromethyl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (14 mg, 0.030 mmol, 22%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.66 (d, *J*=7.0 Hz, 1H), 8.36 - 8.31 (m, 2H), 8.28 (s, 1H), 8.08 (s, 1H), 7.84 (dd, *J*=7.0, 1.7 Hz, 1H), 7.39 (dd, *J*=8.7, 5.6 Hz, 2H), 7.19 (t, *J*=8.8 Hz, 2H), 6.13 (s, 2H), 5.74 (q, *J*=6.9 Hz, 1H), 1.88 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 468.0 $(M+H)^+$

Example 23: 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



enantiomer 2

23A: 3-bromo-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridine: Under a blanket of nitrogen, a solution of (5-bromopyridin-3-yl)boronic acid (104 mg, 0.516 mmol), racemic 1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole (163 mg, 0.516 mmol), dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane, 99% (21 mg, 0.026 mmol) and potassium phosphate tribasic, 2M aqueous solution (0.77 mL, 1.5 mmol) in 1,4-dioxane (4 mL) was sparged with nitrogen gas for 5 min. The mixture was then heated to 75 °C for 60 min. This crude reaction mixture containing racemic 3-bromo-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridine was carried directly into the next step without workup or purification. A 100% yield was assumed.

MS ESI m/z 345.9 $(M+H)^+$

23B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: The crude reaction mixture from the preceeding step containing racemic 3-bromo-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridine (assumed 179 mg, 0.516 mmol) was treated with *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (261 mg, 0.568 mmol), and dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II) (17 mg, 0.026 mmol) was added. The mixture was sparged with nitrogen gas for 5 min. The vessel was sealed and the mixture was heated to 80 °C for 3 h and then stood at RT overnight. The crude mixture was concentrated via

nitrogen stream to a dry residue. The residue was dissolved by shaking with minimal DCM, and the resulting mixture was passed through a United Chemical Technologies Inc. Hydromatrix Clean-Up extraction column (750 mg, part number CUHYD7LR3, Lot number CE2A053). The cartridge was rinsed through several times with clean DCM (total DCM volume used was approximately 12 mL). The DCM mixture was then concentrated under a nitrogen stream to a residue. The residue was taken up in minimum DCM and loaded onto a DCM preequilibrated 12g silica cartridge. Elution 100% DCM for 1 column volume (CV), then gradient 100% DCM to 100% EtOAc over 8 CV, then hold 100% EtOAc for 4 CV. Desired material eluted near the end of the gradient as a broad band and as mixed fractions. Fractions containing product were combined and concentrated in vacuo to give a brown residue containing racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (242 mg, 0.355 mmol, 88% yield over 2 steps). No further purification of this material was performed. A portion of this material was carried forward into the next step as-is.

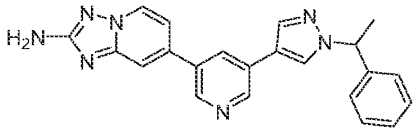
MS ESI m/z 600.2 $(M+H)^+$

23C: 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate: In a 1 dram vial with a PTFE-lined screw cap were combined racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (82 mg, 0.12 mmol) with a mixture of DCM (1 mL) and TFA (1.0 mL, 1.5 g, 13 mmol). The resulting solution was stirred at RT for 1 h, followed by concentration to a residue under a stream of nitrogen. The crude residue was dissolved in DMF (2 mL) to provide a sample which was purified via preparative LCMS with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 14-54% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV (220 nm wavelength) signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to afford racemic 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (29.7 mg, 0.074 mmol, 62% yield).

^{1}H NMR (500 MHz, DMSO-d6) δ 8.91 (d, *J*=2.0 Hz, 1H), 8.84 (d, *J*=2.2 Hz, 1H), 8.67 - 8.60 (m, 2H), 8.42 (d, *J*=2.1 Hz, 1H), 8.18 (s, 1H), 7.86 (s, 1H), 7.40 - 7.31 (m, 3H), 7.18 (t, *J*=8.4 Hz, 2H), 6.07 (s, 2H), 5.68 (q, *J*=7.1 Hz, 1H), 1.86 (d, *J*=7.0 Hz, 3H).
MS ESI m/z 400.1 $(M+H)^+$

23: 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2: The racemic 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (29.7 mg, 0.074 mmol) obtained in the previous step was further separated into individual enantiomers via preparative chiral SFC chromatography with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 μm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% DEA; Flow Rate: 100 mL/min; Elution: isocratic 30%B over 15 min; Column Temperature: 50 °C. Fraction collection was triggered by UV (220 nm). Fractions containing the second enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (8.4 mg, 0.021 mmol, 56% of the theoretical single isomer yield from preparative SFC).
1H NMR (500 MHz, DMSO-d6) δ 8.90 (d, *J*=1.9 Hz, 1H), 8.83 (d, *J*=2.1 Hz, 1H), 8.67 - 8.59 (m, 2H), 8.42 (t, *J*=2.0 Hz, 1H), 8.18 (s, 1H), 7.85 (d, *J*=1.2 Hz, 1H), 7.39 - 7.32 (m, 3H), 7.18 (t, *J*=8.9 Hz, 2H), 6.07 (s, 2H), 5.68 (q, *J*=7.0 Hz, 1H), 1.86 (d, *J*=7.1 Hz, 3H).
MS ESI m/z 400.2 $(M+H)^+$

Example 24: 7-(5-(1-(1-phenylethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



enantiomer 2

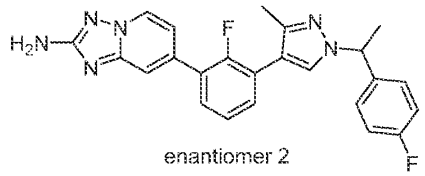
The title compound 7-(5-(1-(1-phenylethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained via a similar procedure as that described for Example 23, where 4-iodo-1-(1-phenylethyl)-1H-pyrazole was substituted for 1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole in step 23A. This

compound was the second enantiomer to elute from preparative SFC Column 1 where SFC Solvents 1 were the eluent.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.94 - 8.90 (m, 1H), 8.87 - 8.83 (m, 1H), 8.68 - 8.63 (m, 2H), 8.44 (s, 1H), 8.19 (s, 1H), 7.87 (s, 1H), 7.39 - 7.33 (m, 3H), 7.30 (br d, *J*=7.3 Hz, 3H), 6.08 (s, 2H), 5.67 (br q, *J*=6.8 Hz, 1H), 1.88 (br d, *J*=7.0 Hz, 3H).

MS ESI m/z 382.2 $(M+H)^+$

Example 25: 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-3-methyl-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



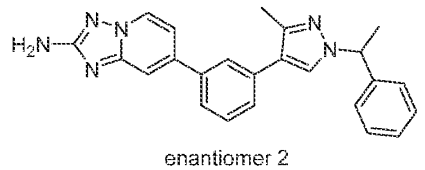
enantiomer 2

The title compound 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-3-methyl-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained via a similar procedure as that described for Example 23, where 1-(1-(4-fluorophenyl)ethyl)-4-iodo-3-methyl-1H-pyrazole was substituted for 1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole and where (3-bromo-2-fluorophenyl)boronic acid was substituted for (5-bromopyridin-3-yl)boronic acid in step 23A. This compound was the second enantiomer to elute from preparative SFC Column 5 where SFC Solvents 5 were the eluent.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.60 (d, *J*=6.9 Hz, 1H), 8.07 (s, 1H), 7.56 - 7.47 (m, 3H), 7.41 - 7.32 (m, 3H), 7.17 (t, *J*=8.8 Hz, 2H), 7.08 (br d, *J*=6.9 Hz, 1H), 6.05 (s, 2H), 5.60 (q, *J*=7.1 Hz, 1H), 2.25 (s, 3H), 1.81 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 431.1 $(M+H)^+$

Example 26: 7-(3-(3-methyl-1-(1-phenylethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



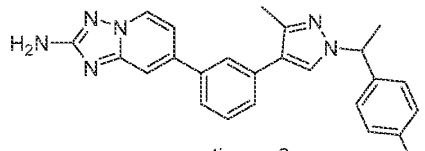
enantiomer 2

The title compound 7-(3-(3-methyl-1-(1-phenylethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained via a similar procedure as that described for Example 23, where 4-iodo-3-methyl-1-(1-phenylethyl)-1H-pyrazole was substituted for 1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole and where 3-bromophenylboronic acid was substituted for (5-bromopyridin-3-yl)boronic acid in step 23A. This compound was the second enantiomer to elute from preparative SFC Column 5 where SFC Solvents 5 were the eluent.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.59 (d, *J*=6.9 Hz, 1H), 8.30 (s, 1H), 7.84 (s, 1H), 7.70 (d, *J*=1.1 Hz, 1H), 7.67 - 7.62 (m, 1H), 7.52 (s, 2H), 7.38 - 7.24 (m, 6H), 6.02 (s, 2H), 5.54 (q, *J*=7.1 Hz, 1H), 2.36 (s, 3H), 1.84 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 395.1 $(M+H)^+$

Example 27: 7-(3-(1-(1-(4-fluorophenyl)ethyl)-3-methyl-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



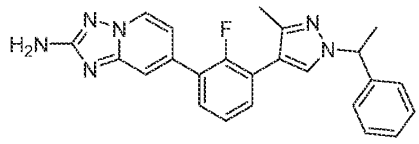
enantiomer 2

The title compound 7-(3-(1-(1-(4-fluorophenyl)ethyl)-3-methyl-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained via a similar procedure as that described for Example 23, where 1-(1-(4-fluorophenyl)ethyl)-4-iodo-3-methyl-1H-pyrazole was substituted for 1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole and where 3-bromophenylboronic acid was substituted for (5-bromopyridin-3-yl)boronic acid in step 23A. This compound was the second enantiomer to elute from preparative SFC Column 5 where SFC Solvents 5 were the eluent.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.59 (d, *J*=6.9 Hz, 1H), 8.28 (s, 1H), 7.83 (s, 1H), 7.70 (d, *J*=1.1 Hz, 1H), 7.65 (td, *J*=4.3, 1.8 Hz, 1H), 7.54 - 7.50 (m, 2H), 7.36 (dd, *J*=8.7, 5.5 Hz, 2H), 7.26 (dd, *J*=7.0, 1.9 Hz, 1H), 7.17 (t, *J*=8.9 Hz, 2H), 6.01 (s, 2H), 5.56 (q, *J*=7.0 Hz, 1H), 2.36 (s, 3H), 1.82 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 413.1 $(M+H)^+$

Example 28: 7-(2-fluoro-3-(3-methyl-1-(1-phenylethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



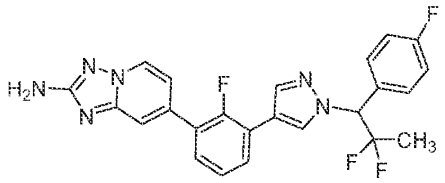
enantiomer 2

The title compound 7-(2-fluoro-3-(3-methyl-1-(1-phenylethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained via a similar procedure as that described for Example 23, where 4-iodo-3-methyl-1-(1-phenylethyl)-1H-pyrazole was substituted for 1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole and where (3-bromo-2-fluorophenyl)boronic acid was substituted for (5-bromopyridin-3-yl)boronic acid in step 23A. This compound was the second enantiomer to elute from preparative SFC Column 5 where SFC Solvents 5 were the eluent.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.60 (d, *J*=6.9 Hz, 1H), 8.06 (d, *J*=1.2 Hz, 1H), 7.55 - 7.46 (m, 3H), 7.39 - 7.25 (m, 6H), 7.09 (t, *J*=7.6 Hz, 1H), 6.05 (s, 2H), 5.57 (q, *J*=6.9 Hz, 1H), 2.25 (s, 3H), 1.82 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 413.0 $(M+H)^+$

Example 29: 7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

29A: 4-(3-bromo-2-fluorophenyl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole: To a dry reaction vial under nitrogen was added 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (70.0 mg, 0.191 mmol), 1-bromo-2-fluoro-3-iodobenzene (57.5 mg, 0.191 mmol), dioxane (3 mL) and potassium phosphate tribasic, 2.0M in water (300 µL, 0.600 mmol). The reaction

was flushed well with nitrogen and was then treated with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (10 mg, 0.012 mmol). The reaction was flushed very well with argon and the vial was securely capped and heated at 65 °C for 4.5 hours. The mixture was diluted with ethyl acetate (10 mL), filtered through a small pad of Celite and the pad was rinsed well with a 1:1 ethyl acetate / dichloromethane mixture (75 mL). The solvent was removed *in vacuo* and the crude residue was purified by flash chromatography on silica gel, eluting with 0-50% gradient of ethyl acetate in dichloromethane to afford 4-(3-bromo-2-fluorophenyl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole (35.9 mg, 0.0869 mmol, 45.4 %).

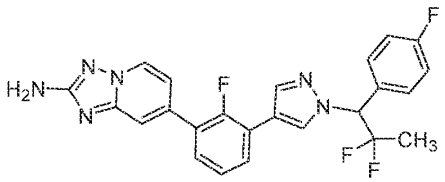
MS ESI m/z 412.7, 414.7 $(M+H)^+$

29B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: To a vial containing 4-(3-bromo-2-fluorophenyl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole (35.9 mg, 0.087 mmol) was added *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (43 mg, 0.093 mmol), dioxane (3 mL), and potassium phosphate tribasic, 2.0 M in water (150 µL, 0.300 mmol). The mixture was purged well with nitrogen and was then treated with dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II), 99% (6.0 mg, 9.2 µmol). The resulting mixture was purged well with nitrogen, securely capped and heated at 75 °C for 5.5 hours. The mixture was diluted with ethyl acetate (10 mL) and filtered through a small pad of Celite. The Celite pad was rinsed with a 1:1 dichloromethane / ethyl acetate mixture (50 mL), and evaporated to dryness to give *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (57.9 mg, 0.0869 mmol, quantitative) which was used directly in the next step without further purification.

29: 7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1: To a solution of *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (57.9 mg, 0.0869 mmol) was added neat trifluoroacetic acid (600 µL, 7.79 mmol) and the reaction was allowed to stand at room temp for 90 minutes. The volatiles were removed under a gentle stream of nitrogen and the crude product was purified via preparative LC/MS with the following conditions:

Column: Waters XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 29-69% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralpak IC, 30 mm x 250 mm, 5 μm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 30%B over 16 minutes; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (254 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide the title compound, 7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (6.6 mg, 0.014 mmol, 16%).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.61 (d, *J*=6.8 Hz, 1H), 8.43 (s, 1H), 8.15 (s, 1H), 7.83 (t, *J*=7.3 Hz, 1H), 7.75 (dd, *J*=8.5, 5.7 Hz, 2H), 7.54 (s, 1H), 7.49 (t, *J*=7.6 Hz, 1H), 7.35 (t, *J*=7.7 Hz, 1H), 7.27 (t, *J*=8.7 Hz, 2H), 7.09 (br d, *J*=7.0 Hz, 1H), 6.33 - 6.19 (m, 1H), 6.06 (s, 2H), 1.64 (t, *J*=19.1 Hz, 3H).
MS ESI m/z 467.1 $(M+H)^+$

Example 30: 7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine, enantiomer 2



enantiomer 2

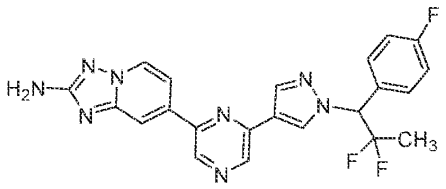
The title compound 7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (6.7 mg, 0.014 mmol,

16%) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 29.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.62 (d, *J*=7.0 Hz, 1H), 8.43 (s, 1H), 8.15 (s, 1H), 7.83 (br t, *J*=7.5 Hz, 1H), 7.75 (dd, *J*=8.5, 5.6 Hz, 2H), 7.54 (s, 1H), 7.52 - 7.46 (m, 1H), 7.35 (t, *J*=7.8 Hz, 1H), 7.27 (t, *J*=8.9 Hz, 2H), 7.09 (br d, *J*=6.9 Hz, 1H), 6.26 (br t, *J*=13.3 Hz, 1H), 6.07 (s, 2H), 1.65 (br t, *J*=19.1 Hz, 3H).

MS ESI m/z 467.0 $(M+H)^+$

Example 31: 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

31A: *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate:

To a dry reaction vial under nitrogen was added racemic 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (70.5 mg, 0.193 mmol), *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (92 mg, 0.21 mmol), dioxane (3 mL), and potassium phosphate tribasic, 2.0M in water (335 µL, 0.670 mmol). The reaction was purged well with argon, then treated with [1,1-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (15 mg, 0.020 mmol). The reaction was again purged very well with argon and the vial was securely capped and heated at 75 °C for 5.5 hours. The reaction was diluted with ethyl acetate and filtered through a small pad of Celite. The Celite pad was rinsed well with 1:1 ethyl acetate/dichloromethane mixture (100 mL) and the filtrate was evaporated to dryness to give racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-

yl)carbamate (125 mg, 0.19 mmol, quantitative) which was used directly in the next step without further purification.

MS ESI m/z 651.2 $(M+H)^+$

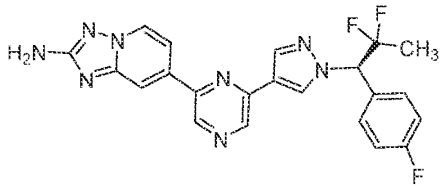
31: 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1: To a solution of *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (125 mg, 0.192 mmol) in dichloromethane (2.5 mL) was added TFA (1.0 mL, 13 mmol) and the resulting dark solution was allowed to stand at room temp for 75 minutes. The volatiles were removed under a gentle stream of nitrogen and the crude product was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 22-62% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative LC/MS with the following conditions Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 0.1% TFA; Mobile Phase B: 95:5 acetonitrile:water with 0.1% TFA; Gradient: 13-53% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative chiral SFC with the following conditions: Column: Regis Technologies Inc. Whelk-O1, 21 mm x 250 mm, 10 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 20%B over 36 minutes; Flow Rate: 75 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (254 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to

provide 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (9.3 mg, 0.021 mmol, 11%)

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.23 (s, 1H), 9.07 (s, 1H), 8.82 (s, 1H), 8.70 (d, *J*=7.0 Hz, 1H), 8.43 (s, 1H), 8.25 (d, *J*=0.9 Hz, 1H), 7.83 - 7.71 (m, 3H), 7.29 (t, *J*=8.9 Hz, 2H), 6.31 (t, *J*=13.2 Hz, 1H), 6.15 (s, 2H), 1.68 (t, *J*=19.1 Hz, 3H).

MS ESI m/z 451.0 $(M+H)^+$

Example 32: *(R)*-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine



32A: *tert*-butyl *(R)*-(*tert*-butoxycarbonyl)(7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate:

To a 40 mL reaction vial under nitrogen was added *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (300 mg, 0.819 mmol), *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (400 mg, 0.895 mmol), dioxane (8 mL) and potassium phosphate tribasic, 2.0M in water (1.25 mL, 2.50 mmol). The reaction was purged very well with nitrogen and was then treated with dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II), 99% (50 mg, 0.08 mmol). The reaction was again purged very well with nitrogen and the vial was securely capped and heated at 70 °C for 3 hours. The reaction was diluted with ethyl acetate (225 mL) and water (10 mL) and the organic layer was washed with water (5 x 10 mL), brine (1 x 10 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude material was purified by flash chromatography on silica gel, eluting with 0-100% gradient of ethyl acetate in hexanes to afford *tert*-butyl *(R)*-(*tert*-butoxycarbonyl)(7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate. This material was dissolved in ethyl acetate (220 mL) and the organic phase

was washed with aqueous 1.0M *N*-acetyl-L-cysteine (5 x 15 mL), water (2 x 10 mL), brine (1 x 10 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The material was further purified by flash chromatography on silica gel, eluting with 0-65% gradient of acetone in hexanes to afford *tert*-butyl *(R)*-(*tert*-butoxycarbonyl)(7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (831 mg, 1.28 mmol, quantitative).

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.97 (s, 1H), 8.84 (s, 1H), 8.70 (d, *J*=7.2 Hz, 1H), 8.50 (d, *J*=1.0 Hz, 1H), 8.34 (s, 1H), 8.23 (s, 1H), 7.87 (dd, *J*=7.2, 1.8 Hz, 1H), 7.63 (dd, *J*=8.8, 5.2 Hz, 2H), 7.21 - 7.09 (m, 2H), 5.76 (t, *J*=12.6 Hz, 1H), 1.77 (t, *J*=18.8 Hz, 3H), 1.52 (s, 20H).

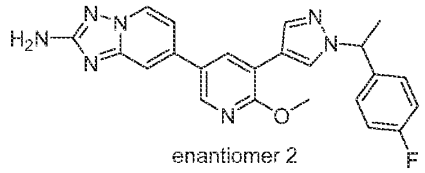
MS ESI m/z 651.4 $(M+H)^+$

32: *(R)*-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: To a solution of *tert*-butyl *(R)*-(*tert*-butoxycarbonyl)(7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (530 mg, 0.815 mmol) in anhydrous dichloromethane was added trifluoroacetic acid (1.0 mL, 13 mmol) and the reaction was allowed to stand at room temp for 100 min. The volatiles were removed under a gentle stream of nitrogen and the crude product was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 40-60% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give *(R)*-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (303 mg, 0.67 mmol, 82%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.23 (s, 1H), 9.07 (s, 1H), 8.82 (s, 1H), 8.70 (dd, *J*=7.0, 0.7 Hz, 1H), 8.43 (s, 1H), 8.25 (dd, *J*=1.9, 0.7 Hz, 1H), 7.83 - 7.71 (m, 3H), 7.29 (t, *J*=8.9 Hz, 2H), 6.31 (t, *J*=13.2 Hz, 1H), 60.6715 (s, 2H), 1.68 (t, *J*=19.1 Hz, 3H).

MS ESI m/z 451.3 $(M+H)^+$

Example 33: 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-6-methoxypyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



enantiomer 2

33A: 5-bromo-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-2-methoxypyridine: In a 8 mL Chemglass reaction vial were combined racemic 1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole (273 mg, 0.863 mmol) and 5-bromo-2-methoxypyridine-3-boronic acid (200 mg, 0.863 mmol) in 1,4-dioxane (5 mL). To the mixture was added potassium phosphate tribasic, 2M aqueous solution (1.29 mL, 2.59 mmol) followed by addition of dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (35.2 mg, 0.043 mmol). The mixture was sparged with a stream of nitrogen with stirring for 5 min, then the vial was capped and heated to 80 °C for 2 h. The mixture was diluted with EtOAc (10 mL) and the result was filtered through celite (20 mL), eluting with ethyl acetate. The filtered mixture was concentrated in vacuo to a brown residue. The residue was dissolved in minimum DCM and loaded atop a 24 g silica cartridge which was preequilibrated with hexanes. Elution gradient 100% hexanes to 35% EtOAc in hexanes over 12 column volumes, hold 35% EtOAc in hexanes for 5 CVs. Product eluted as a broad band in the middle of the gradient. Product-containing fractions were combined and concentrated in vacuo to provide racemic 5-bromo-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-2-methoxypyridine (165 mg, 0.439 mmol, 51.0% yield) as a yellow-brown residue.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.07 (d, *J*=2.4 Hz, 1H), 7.95 (s, 1H), 7.92 (s, 1H), 7.87 (d, *J*=2.4 Hz, 1H), 7.28 - 7.23 (m, 2H), 7.08 - 7.02 (m, 2H), 5.56 (q, *J*=7.0 Hz, 1H), 4.03 (s, 3H), 1.95 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 375.7 $(M+H)^+$

33B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-6-methoxypyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: In an 20 mL scintillation vial, racemic 5-bromo-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-2-methoxypyridine (74 mg, 0.20 mmol) and *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (100 mg, 0.216 mmol) were dissolved in 1,4-dioxane (2 mL). To the solution was added

potassium phosphate tribasic 2M aqueous solution (0.29 mL, 0.59 mmol) followed by addition of dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II) (6.4 mg, 9.8 μmol). The mixture was sparged with nitrogen gas for 5 min, then the vial was capped and the mixture was heated to 80 °C for 3 h. The crude mixture was concentrated via nitrogen stream. The residue was dissolved with shaking in DCM and the resulting mixture was passed through a United Chemical Technologies Inc. Hydromatrix Clean-Up extraction column (750 mg), part number CUHYD7LR3, lot number CE2A053. The cartridge was rinsed through several times with clean DCM (total DCM volume was approx 12 mL). The DCM mixture was then concentrated under nitrogen stream to a black residue. This crude residue containing racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-6-methoxypyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate was carried directly into the next step as-is without further purification. A 100% yield was assumed.

MS ESI m/z 630.3 $(M+H)^+$

33C: 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-6-methoxypyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate: A solution of the crude residue from the previous step containing racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-6-methoxypyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (assumed 124 mg, 0.197 mmol) in DCM (1 mL) was treated with TFA (1.0 mL, 1.5 g, 13 mmol) and the result was stirred for 30 min. The mixture was concentrated via nitrogen stream to a residue. The residue was dissolved in DMF and filtered to give a 2 mL sample which was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 μm particles; Mobile Phase A: 5:95 acetonitrile: water with 0.1% TFA; Mobile Phase B: 95:5 acetonitrile: water with 0.1% TFA; Gradient: 15-55% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). The material was further purified via preparative reverse phase with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 μm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 23-63% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were

combined and dried via centrifugal evaporation to provide racemic 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-6-methoxypyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (21.1 mg, 0.0491 mmol, 24.9% yield).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.61 (d, *J*=7.0 Hz, 1H), 8.50 (s, 2H), 8.46 (d, *J*=2.1 Hz, 1H), 8.21 (s, 1H), 7.81 (s, 1H), 7.38 - 7.32 (m, 3H), 7.22 - 7.14 (m, 2H), 5.71 (q, *J*=7.1 Hz, 1H), 4.04 (s, 3H), 1.86 (d, *J*=7.0 Hz, 3H).

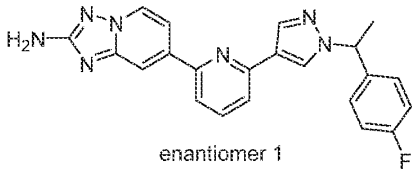
MS ESI m/z 430.0 $(M+H)^+$

33: 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-6-methoxypyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2: The racemic 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-6-methoxypyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (21.1 mg, 0.0491 mmol) obtained in the previous step was further separated into individual enantiomers via preparative chiral SFC chromatography with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 μm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution Gradient: isocratic 25%B over 25 min; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (254 nm). Fractions containing the second enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-6-methoxypyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (7.9 mg, 0.018 mmol, 75% of the theoretical single isomer yield from preparative SFC).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.61 (br d, *J*=6.9 Hz, 1H), 8.50 (s, 2H), 8.46 (d, *J*=2.1 Hz, 1H), 8.21 (s, 1H), 7.81 (s, 1H), 7.37 - 7.32 (m, 3H), 7.18 (t, *J*=8.8 Hz, 2H), 6.11 - 5.94 (m, 2H), 5.71 (q, *J*=6.3 Hz, 1H), 4.04 (s, 3H), 1.86 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 430.0 $(M+H)^+$

Example 34: 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

34A: 2-chloro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridine: In a 8 mL Chemglass reaction vial were combined racemic 1-(1-(4-fluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (150 mg, 0.474 mmol) and 2-chloro-6-iodopyridine (114 mg, 0.474 mmol) in 1,4-dioxane (3.2 mL). To the mixture was added potassium phosphate tribasic, 2M aqueous solution (0.71 mL, 1.4 mmol) followed by addition of dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (19 mg, 0.024 mmol). The mixture was sparged with a stream of nitrogen with stirring for 5 min, then the vial was capped and heated to 80 °C for 4 h. The mixture was concentrated via nitrogen stream to a residue, then to the residue was added EtOAc (4 mL) and saturated brine (1.5 mL) and the mixture was shaken and phases were separated. The aqueous was extracted with EtOAc (2 x 4 mL), and the combined organics were concentrated in vacuo to a brown residue. The residue was dissolved in minimum DCM and loaded atop a 12 g silica cartridge which was precquilibrated with hexanes. Elution gradient 100% hexanes to 50% EtOAc in hexanes over 12 column volumes, hold 50% EtOAc in hexanes for 5 CV. Product eluted as a broad band toward the end of the gradient. Product-containing fractions were combined and concentrated in vacuo to give racemic 2-chloro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridine (135 mg, 0.447 mmol, 94% yield) as a sticky colorless oil.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.05 (s, 1H), 7.98 (s, 1H), 7.61 (t, *J*=7.8 Hz, 1H), 7.41 - 7.33 (m, 1H), 7.30 - 7.22 (m, 2H), 7.13 (d, *J*=7.9 Hz, 1H), 7.08 - 7.01 (m, 2H), 5.56 (q, *J*=7.0 Hz, 1H), 1.94 (d, *J*=7.2 Hz, 3H).

MS ESI m/z 301.7 $(M+H)^+$

34B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: In a 4 mL Chemglass reaction vial, racemic 2-chloro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridine (50 mg, 0.17 mmol) and *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (84 mg, 0.18 mmol) were dissolved in 1,4-dioxane (2 mL). To the solution was added potassium phosphate tribasic, 2M aqueous solution (0.25 mL, 0.50 mmol) and dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II) (5.4 mg, 8.3 μmol). The mixture was sparged with nitrogen gas for 5 min, then the vial was capped and the mixture was heated to 80 °C for 2 h. The mixture was concentrated under nitrogen stream to provide a crude brown residue

containing racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate which was carried directly into the next step without further purification or manipulation. A 100% yield was assumed.

MS ESI m/z 600.2 $(M+H)^+$

34C: 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate: The crude mixture from the previous step containing racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (assumed 100 mg, 0.166 mmol) was combined with a mixture of DCM (2 mL) and TFA (2.0 mL, 3.0 g, 26 mmol). The resulting solution was stirred at RT for 2.5 h, followed by concentration to a residue under a stream of nitrogen. The crude residue was dissolved in MeOH (2 mL) to provide a sample which was purified via reverse phase preparative LCMS with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 19-59% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV (220 nm wavelength) signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to afford racemic 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (50.5 mg, 0.126 mmol, 76% yield).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 - 8.60 (m, 2H), 8.19 - 8.14 (m, 2H), 7.95 - 7.88 (m, 2H), 7.73 (d, *J*=7.1 Hz, 1H), 7.70 (d, *J*=7.4 Hz, 1H), 7.38 (dd, *J*=8.5, 5.7 Hz, 2H), 7.18 (t, *J*=8.7 Hz, 2H), 6.07 (s, 2H), 5.75 - 5.70 (m, 1H), 1.88 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 400.1 $(M+H)^+$

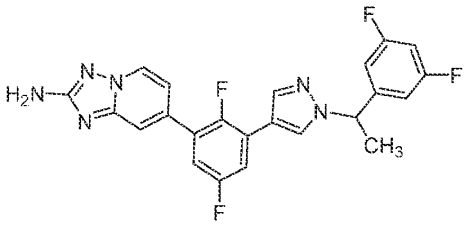
34: 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1: The racemic 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (50.5 mg, 0.126 mmol) obtained in the previous step was further separated into individual enantiomers via preparative chiral SFC chromatography with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Flow Rate: 100 mL/min; Elution Gradient:

isocratic 50%B over 6 min; Column Temperature: 40 °C. Fraction collection was triggered by UV (240 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (21.5 mg, 0.054 mmol, 85% of the theoretical single isomer yield from preparative SFC).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.64 - 8.61 (m, 2H), 8.18 (s, 1H), 8.15 (s, 1H), 7.96 - 7.88 (m, 2H), 7.72 (dd, *J*=13.8, 7.5 Hz, 2H), 7.38 (dd, *J*=8.5, 5.7 Hz, 2H), 7.18 (t, *J*=8.8 Hz, 2H), 6.10 - 6.04 (m, 2H), 5.76 - 5.71 (m, 1H), 1.88 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 400.2 $(M+H)^+$

Example 35: 7-(3-(1-(1-(3,5-difluorophenyl)ethyl)-1H-pyrazol-4-yl)-2,5-difluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

35A: 4-(3-bromo-2,5-difluorophenyl)-1-(1-(3,5-difluorophenyl)ethyl)-1H-pyrazole: This material was prepared by a similar procedure as described for Example 34, step 34A, where 2-chloro-6-iodopyridine was replaced with 1,3-dibromo-2,5-difluorobenzene and 1-(1-(4-fluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole was replaced with 1-(1-(3,5-difluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole to give the title compound, 4-(3-bromo-2,5-difluorophenyl)-1-(1-(3,5-difluorophenyl)ethyl)-1H-pyrazole (74 mg, 0.19 mmol, 31%).

MS ESI m/z 398.7, 400.7 $(M+H)^+$

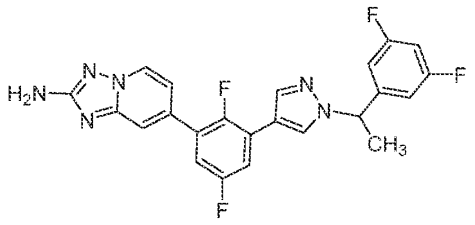
35 : The title compound 7-(3-(1-(1-(3,5-difluorophenyl)ethyl)-1H-pyrazol-4-yl)-2,5-difluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 was prepared in a similar fashion as described for the preparation of Example 1, where 4-(3-bromo-2,5-difluorophenyl)-1-(1-(3,5-difluorophenyl)ethyl)-1H-pyrazole was used in place of 1-

benzyl-4-(3-bromophenyl)-1H-pyrazole in step 1B. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 29-69% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(3-(1-(1-(3,5-difluorophenyl)ethyl)-1H-pyrazol-4-yl)-2,5-difluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralpak IA, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 40%B over 22 minutes; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (240 nm). The title compound was the first isomer to elute from the column. Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(3-(1-(1-(3,5-difluorophenyl)ethyl)-1H-pyrazol-4-yl)-2,5-difluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (26 mg, 0.057 mmol, 31%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (d, *J*=7.0 Hz, 1H), 8.49 (d, *J*=1.2 Hz, 1H), 8.10 (s, 1H), 7.74 (ddd, *J*=9.1, 5.5, 3.2 Hz, 1H), 7.59 (s, 1H), 7.38 (ddd, *J*=8.5, 5.5, 3.1 Hz, 1H), 7.21 - 7.14 (m, 1H), 7.11 (br d, *J*=7.0 Hz, 1H), 7.02 (br d, *J*=6.6 Hz, 2H), 6.10 (s, 2H), 5.75 (q, *J*=7.1 Hz, 1H), 1.86 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 453.0 $(M+H)^+$

Example 36: 7-(3-(1-(1-(3,5-difluorophenyl)ethyl)-1H-pyrazol-4-yl)-2,5-difluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



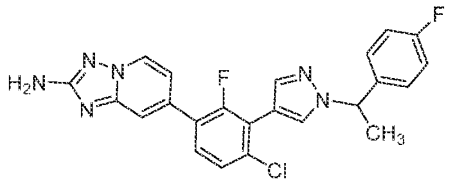
enantiomer 2

The title compound 7-(3-(1-(1-(3,5-difluorophenyl)ethyl)-1H-pyrazol-4-yl)-2,5-difluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (28 mg, 0.063 mmol, 34%) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 35.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.44 (d, *J*=7.0 Hz, 1H), 8.30 (s, 1H), 7.91 (s, 1H), 7.60 - 7.50 (m, 1H), 7.40 (s, 1H), 7.24 - 7.15 (m, 1H), 7.04 - 6.94 (m, 1H), 6.91 (br d, *J*=6.9 Hz, 1H), 6.83 (br d, *J*=6.6 Hz, 2H), 5.90 (s, 2H), 5.56 (q, *J*=6.9 Hz, 1H), 1.66 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 453.0 $(M+H)^+$

Example 37: 7-(4-chloro-2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



enantiomer 2

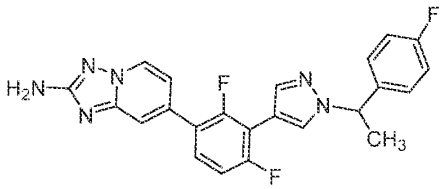
The title compound 7-(4-chloro-2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was prepared by a similar procedure as described for the preparation of Example 35, except 3-bromo-6-chloro-2-fluoroiodobenzene (106 mg, 0.316 mmol) was used in place of 1,3-dibromo-2,5-difluorobenzene. The crude product obtained in the final step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 27-

67% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(4-chloro-2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Whelk-O1 (S,S), 21 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 50%B over 12 minutes; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (220 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(4-chloro-2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine enantiomer 2 (9.0 mg, 0.020 mmol, 13%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (d, *J*=7.0 Hz, 1H), 8.49 (d, *J*=1.2 Hz, 1H), 8.10 (s, 1H), 7.74 (ddd, *J*=9.1, 5.5, 3.2 Hz, 1H), 7.59 (s, 1H), 7.38 (ddd, *J*=8.5, 5.5, 3.1 Hz, 1H), 7.21 - 7.14 (m, 1H), 7.11 (br d, *J*=7.0 Hz, 1H), 7.02 (br d, *J*=6.6 Hz, 2H), 6.10 (s, 2H), 5.75 (q, *J*=7.1 Hz, 1H), 1.86 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 451.2, 453.0 $(M+H)^+$

Example 38: 7-(2,4-difluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



enantiomer 2

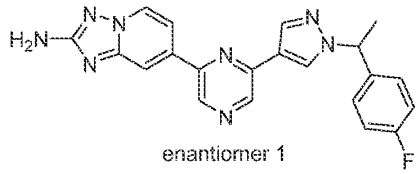
The title compound 7-(2,4-difluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained using a similar procedure as described for the preparation of Example 35, except 1-bromo-2,4-difluoro-3-iodobenzene (135 mg, 0.422 mmol) was used in place of 1,3-dibromo-2,5-difluorobenzene. The racemate obtained in the final synthetic step was separated into

individual enantiomers via preparative SFC which was performed with the following conditions: Column: Whelk-O1 (S,S), 21 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 50%B over 12 minutes; Flow Rate: 75 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (254 nm). Fractions containing the second enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(2,4-difluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (20 mg, 0.047 mmol, 22%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.62 (d, *J*=7.0 Hz, 1H), 8.36 (s, 1H), 7.99 - 7.91 (m, 1H), 7.59 - 7.50 (m, 2H), 7.43 - 7.37 (m, 2H), 7.32 (t, *J*=9.7 Hz, 1H), 7.23 - 7.15 (m, 2H), 7.07 (d, *J*=7.0 Hz, 1H), 6.08 (s, 2H), 5.78 (q, *J*=7.1 Hz, 1H), 1.86 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 435.0 $(M+H)^+$

Example 39: 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



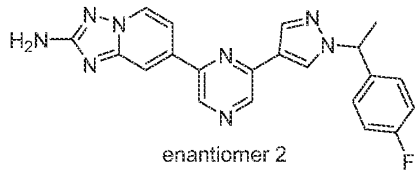
enantiomer 1

The title compound 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 was obtained via a similar procedure as that described for Example 34, where 2,6-dichloropyrazine was substituted for 2-chloro-6-iodopyridine in step 34A. This compound was the first enantiomer to elute from preparative SFC Column 1 where SFC Solvents 3 were the eluent.

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.20 - 9.17 (m, 1H), 9.01 (s, 1H), 8.78 (s, 1H), 8.69 - 8.66 (m, 1H), 8.30 (s, 1H), 8.25 (s, 1H), 7.75 (dd, *J*=7.0, 1.8 Hz, 1H), 7.39 (dd, *J*=8.4, 5.6 Hz, 2H), 7.19 (t, *J*=8.5 Hz, 2H), 6.14 (s, 2H), 5.75 (q, *J*=7.1 Hz, 1H), 1.89 (d, *J*=6.9 Hz, 3H).

MS ESI m/z 401.1 $(M+H)^+$

Example 40: 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



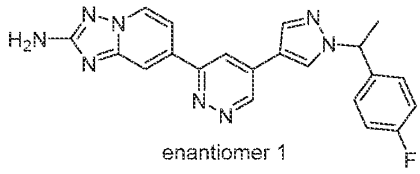
enantiomer 2

The title compound 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 39.

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.20 - 9.17 (m, 1H), 9.01 (s, 1H), 8.79 - 8.76 (m, 1H), 8.68 (d, *J*=6.7 Hz, 1H), 8.30 (s, 1H), 8.25 (s, 1H), 7.75 (d, *J*=7.1 Hz, 1H), 7.42 - 7.37 (m, 2H), 7.22 - 7.16 (m, 2H), 6.16 - 6.11 (m, 2H), 5.78 - 5.73 (m, 1H), 1.89 (br d, *J*=7.0 Hz, 3H).

MS ESI m/z 401.0 $(M+H)^+$

Example 41: 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

41A: 5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazin-3-ol: In a 8 mL Chemglass reaction vial were combined racemic 1-(1-(4-fluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (131 mg, 0.414 mmol) and 5-bromo-3-chloro-pyridazine (80 mg, 0.41 mmol) in 1,4-dioxane (3 mL). To the mixture was added potassium phosphate tribasic, 2M aqueous solution (0.620 mL, 1.24 mmol) followed by addition of dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (17 mg, 0.021 mmol). The mixture was sparged with a stream of nitrogen with stirring for 5 min, then the vial was capped and heated to 80 °C for 2 h. The mixture was diluted with EtOAc and poured directly through a pad of Celite and eluted with EtOAc. The crude brown solution was concentrated in vacuo to a residue. The residue was dissolved in minimum DCM and loaded atop a 24 g silica cartridge which was preequilibrated with DCM. Elution gradient 100% DCM to 100% EtOAc over 12 column volumes, hold 100% EtOAc for 10 CV. A broad peak eluting in the 100% EtOAc hold was collected, fractions

were combined and concentrated in vacuo to give a yellow-brown residue which contained racemic 5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazin-3-ol (50.6 mg, 0.178 mmol, 43.0% yield) This material was carried directly into the next step without further purification.

MS ESI m/z 284.7 $(M+H)^+$, 569.2 $(2M+H)^+$

41B: 3-chloro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazine: The material from the previous step containing containing racemic 5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazin-3-ol (50.6 mg, 0.178 mmol) was dissolved with heating in phosphorus(V) oxychloride (2.0 mL, 21 mmol). The resulting solution was stirred at 90 °C for 2 h. The mixture was concentrated in vacuo to a residue which contained racemic 3-chloro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazine (50.0 mg, 0.165 mmol, 94% yield). This material was used directly in the next step without purification.

MS ESI m/z 302.7 $(M+H)^+$

41C: *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate racemate: In an 20 mL scintillation vial, racemic 3-chloro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazine (50.0 mg, 0.165 mmol) and *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (84 mg, 0.18 mmol) were dissolved in 1,4-dioxane (2 mL). To the solution was added potassium phosphate tribasic, 2M aqueous solution (0.248 mL, 0.495 mmol) followed by addition of dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II) (5.4 mg, 8.3 µmol). The mixture was sparged with nitrogen gas for 5 min, then the vial was capped and the mixture was heated to 80 °C for 3 h. The crude mixture was concentrated via nitrogen stream. The residue was dissolved with shaking in DCM and the resulting mixture was passed through a United Chemical Technologies Inc. Hydromatrix Clean-Up extraction column (750 mg), part number CUHYD7LR3, lot number CE2A053. The cartridge was rinsed through several times with clean DCM (total DCM volume was approx 12 mL). The DCM mixture was then concentrated under nitrogen stream to a black residue. The crude black residue containing racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate was carried directly into the step as-is without further purification. A 100% yield was assumed.

MS ESI m/z 601.2 $(M+H)^+$

41D: 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate: The crude material from the previous step containing racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (assumed 99 mg, 0.165 mmol) was dissolved in DCM (1 mL) and the resulting solution was treated with TFA (1.0 mL, 1.5 g, 13 mmol). The mixture was stirred for 30 min and was then concentrated via nitrogen stream to a residue. The residue was dissolved in DMF and filtered to give a 2 mL sample which was purified via preparative Reverse Phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 11-51% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide racemic 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (24.5 mg, 0.0611 mmol, 36.3% yield).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.57 (d, *J*=1.9 Hz, 1H), 8.89 (s, 1H), 8.71 (d, *J*=7.0 Hz, 1H), 8.59 (d, *J*=1.9 Hz, 1H), 8.42 (s, 1H), 8.25 (s, 1H), 7.81 (dd, *J*=7.1, 1.7 Hz, 1H), 7.36 (dd, *J*=8.7, 5.5 Hz, 2H), 7.20 (t, *J*=8.8 Hz, 2H), 6.16 (s, 2H), 5.73 (q, *J*=7.2 Hz, 1H), 1.87 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 401.0 $(M+H)^+$

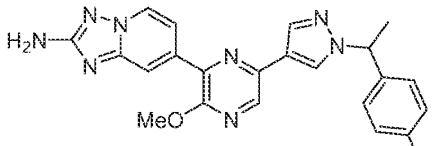
41: 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1: The racemic 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (24.5 mg, 0.0611 mmol) obtained in the previous step was further separated into individual enantiomers via preparative chiral SFC chromatography with the following conditions: Column: Daicel Chiralpak AS-H, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution Gradient: isocratic 35%B over 20 min; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (254 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide the desired 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-

yl)pyridazin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (9.0 mg, 0.023 mmol, 73% of the theoretical single isomer yield from preparative SFC).

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.57 (s, 1H), 8.88 (s, 1H), 8.72 (d, *J*=7.2 Hz, 1H), 8.59 (s, 1H), 8.43 - 8.41 (m, 1H), 8.26 (s, 1H), 7.82 (dd, *J*=6.9, 1.5 Hz, 1H), 7.36 (dd, *J*=8.5, 5.6 Hz, 2H), 7.23 - 7.17 (m, 2H), 5.73 (q, *J*=7.2 Hz, 1H), 1.87 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 400.9 $(M+H)^+$

Example 42: 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-3-methoxypyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



enantiomer 2

42A: 3-chloro-2-fluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazine: A mixture of 3,5-dichloro-2-fluoropyrazine (55.0 mg, 0.329 mmol), dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II) (13 mg, 0.020 mmol), potassium phosphate tribasic, 2M aqueous solution (494 µl, 0.988 mmol) and racemic 1-(1-(4-fluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (104 mg, 0.329 mmol) in 1,4-dioxane (2196 µl) was heated at 75 °C for 2 h. Water was added and the aqueous layer was extracted with ethyl acetate (x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was evaporated in vacuo to give the crude product. The crude product was purified by silica gel chromatography eluting with 0-10% ethyl acetate/hexanes to give racemic 3-chloro-2-fluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazine (54.0 mg, 0.168 mmol, 51.1% yield) as a white solid.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.22 (d, *J*=2.0 Hz, 1H), 8.13 (d, *J*=1.3 Hz, 1H), 7.95 (d, *J*=1.9 Hz, 1H), 7.32 - 7.23 (m, 2H), 7.14 - 6.90 (m, 2H), 5.59 (d, *J*=7.0 Hz, 1H), 1.97 (d, *J*=7.0 Hz, 3H).

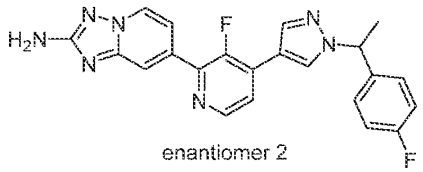
42: 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-3-methoxypyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2: A mixture of *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (95.0 mg, 0.206 mmol), racemic 3-chloro-2-fluoro-5-(1-(1-(4-

fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazine (60.0 mg, 0.187 mmol), dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II) (7.3 mg, 0.011 mmol) and potassium phosphate tribasic, 2M aqueous solution (281 µl, 0.561 mmol) in 1,4-dioxane (1.2 mL) was heated at 75 °C for 2 h. Water was added and the aqueous layer was extracted with ethyl acetate (x 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and filtered, and the filtrate was evaporated in vacuo to give the crude product, which was treated with HCl, 4.0M solution in 1,4-dioxane (468 µL, 1.87 mmol) in MeOH (1 mL) for 12 h. The solvents were removed, and the residue was purified via preparative reverse phase HPLC with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 20-60% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-3-methoxypyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. The racemate was further separated into individual enantiomers via preparative SFC with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% NH_4OH; Elution Gradient: isocratic 30%B over 15 min; Flow Rate: 85 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (230 nm). Fractions containing the second isomer to elute from the SFC column were combined and dried via centrifugal evaporation to give 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-3-methoxypyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (11.0 mg, 0.0256 mmol).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.80 (s, 1H), 8.65 (s, 1H), 8.61 (d, *J*=7.0 Hz, 1H), 8.30 (s, 1H), 8.11 (s, 1H), 7.68 (dd, *J*=7.0, 1.8 Hz, 1H), 7.46 - 7.35 (m, 2H), 7.18 (t, *J*=8.9 Hz, 2H), 5.79 (d, *J*=7.0 Hz, 1H), 4.09 (s, 3H), 1.88 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 431.2 $(M+H)^+$

Example 43: 7-(3-fluoro-4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



enantiomer 2

43A: 2-chloro-3-fluoro-4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridine: In a 40 mL Chemglass reaction vial were combined racemic 1-(1-(4-fluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (154 mg, 0.486 mmol) and 2-chloro-3-fluoro-4-iodopyridine (125 mg, 0.486 mmol) in 1,4-dioxane (5 mL). To the mixture was added potassium phosphate tribasic, 2M aqueous solution (0.728 mL, 1.46 mmol) followed by addition of dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (20 mg, 0.024 mmol). The mixture was sparged with a stream of nitrogen with stirring for 5 min, then the vial was capped and heated to 60 °C for 17 h. The crude mixture containing racemic 2-chloro-3-fluoro-4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridine was carried directly into the next step as-is. 100% yield was assumed.

MS ESI m/z 319.7 $(M+H)^+$

43B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-fluoro-4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: To the crude mixture from the previous step containing racemic 2-chloro-3-fluoro-4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridine (assumed 155 mg, 0.486 mmol) was added *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (224 mg, 0.486 mmol). Potassium phosphate tribasic, 2M aqueous solution (0.729 mL, 1.46 mmol) was then added, followed by addition of dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II) (19 mg, 0.029 mmol). The mixture was sparged with a stream of nitrogen with stirring for 5 min, then the vial was capped and the mixture was heated to 70 °C for 19 h. The mixture was concentrated via nitrogen stream to a residue. The crude mixture was reconstituted with 1:1 DCM:EtOAc (10 mL) and the resulting black susension was filtered through Celite and rinsed with 1:1 EtOAc:DCM. Concentration in vacuo gave a black oil residue which was dissolved in minimum DCM and loaded atop a DCM preequilibrated 24 g silica cartridge. Elution gradient 100% DCM to 100% EtOAc over 15 column volumes, hold 100% EtOAc for 6 CV. Fractions containing the desired racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-

fluoro-4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate were combined and concentrated in vacuo to an impure residue (213 mg, approx. 0.175 mmol, approx. 50% purity, approx. 36% yield) which was used in the next step as-is.

MS ESI m/z 618.2 $(M+H)^+$

43C: 7-(3-fluoro-4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate: The impure residue from the previous step containing racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-fluoro-4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (150 mg, approx. 50% purity, approx 0.124 mmol) dissolved in DCM (1 mL) was treated with TFA (0.24 mL, 0.36 g, 3.1 mmol) and the result was stirred for 75 min. The mixture was concentrated via nitrogen stream to a residue. The residue was dissolved in DMF and filtered to give a 2 mL sample which was purified via preparative reverse phase chromatography with the following conditions: Column: Waters Xbridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 19-59% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide racemic 7-(3-fluoro-4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (37.4 mg, 0.0895 mmol, 72.3% yield).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.66 (d, *J*=6.7 Hz, 1H), 8.61 (s, 1H), 8.51 (d, *J*=4.9 Hz, 1H), 8.19 (s, 1H), 7.88 - 7.84 (m, 2H), 7.45 (d, *J*=7.2 Hz, 1H), 7.39 (dd, *J*=8.2, 5.8 Hz, 2H), 7.19 (t, *J*=8.7 Hz, 2H), 6.13 (br s, 2H), 5.77 (q, *J*=7.1 Hz, 1H), 1.87 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 418.0 $(M+H)^+$

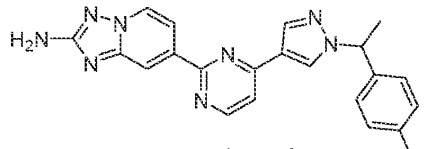
43: 7-(3-fluoro-4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2: The racemic 7-(3-fluoro-4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (37.4 mg, 0.0895 mmol) obtained in the previous step was further separated into individual enantiomers via preparative chiral SFC chromatography with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% NH_4OH; Flow Rate: 100 mL/min;

Elution Gradient: Isocratic 25%B over 16 min; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (254 nm). Fractions containing the second enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(3-fluoro-4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (13.9 mg, 0.0332 mmol, 74% of the theoretical single isomer yield from preparative SFC).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.66 (d, *J*=7.0 Hz, 1H), 8.61 (s, 1H), 8.50 (d, *J*=5.0 Hz, 1H), 8.19 (s, 1H), 7.88 - 7.84 (m, 2H), 7.46 - 7.37 (m, 3H), 7.22 - 7.16 (m, 2H), 6.13 (s, 2H), 5.79 - 5.75 (m, 1H), 1.87 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 418.1 $(M+H)^+$

Example 44: 7-(4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



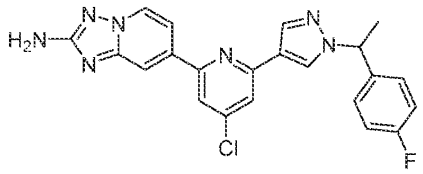
enantiomer 2

The title compound 7-(4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained via a similar procedure as that described for Example 43, where 4-bromo-2-chloropyrimidine was substituted for 2-chloro-3-fluoro-4-iodopyridine in step 43A. This compound was the second enantiomer to elute from preparative SFC Column 1 where SFC Solvents 3 were the eluent.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.89 (s, 1H), 8.85 (d, *J*=5.6 Hz, 1H), 8.66 (d, *J*=7.1 Hz, 1H), 8.39 (s, 1H), 8.35 (s, 1H), 7.92 (dd, *J*=7.0, 1.7 Hz, 1H), 7.74 (d, *J*=5.3 Hz, 1H), 7.40 (dd, *J*=8.5, 5.6 Hz, 2H), 7.19 (t, *J*=8.7 Hz, 2H), 6.14 (s, 2H), 5.76 (q, *J*=6.8 Hz, 1H), 1.89 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 401.1 $(M+H)^+$

Example 45: 7-(4-chloro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



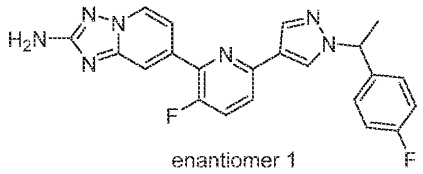
enantiomer 2

The title compound 7-(4-chloro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained via a similar procedure as that described for Example 43, where 2,6-dibromo-4-chloropyridine was substituted for 2-chloro-3-fluoro-4-iodopyridine in step 43A. This compound was the second enantiomer to elute from preparative SFC Column 1 where SFC Solvents 2 were the eluent.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.72 (s, 1H), 8.64 (d, *J*=7.1 Hz, 1H), 8.25 (s, 1H), 8.23 (s, 1H), 8.11 (s, 1H), 7.90 (d, *J*=1.3 Hz, 1H), 7.77 (dd, *J*=7.0, 1.7 Hz, 1H), 7.38 (dd, *J*=8.7, 5.5 Hz, 2H), 7.21 - 7.16 (m, 2H), 6.22 - 6.03 (m, 2H), 5.72 (q, *J*=7.0 Hz, 1H), 1.87 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 434.0 $(M+H)^+$

Example 46: 7-(3-fluoro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



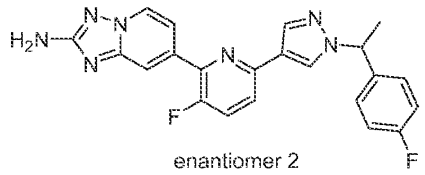
enantiomer 1

The title compound 7-(3-fluoro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 was obtained via a similar procedure as that described for Example 43, where 6-bromo-2-chloro-3-fluoropyridine was substituted for 2-chloro-3-fluoro-4-iodopyridine in step 43A. This compound was the first enantiomer to elute from preparative SFC Column 1 where SFC Solvents 3 were the eluent.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.66 (d, *J*=6.9 Hz, 1H), 8.58 (s, 1H), 8.14 (s, 1H), 7.95 (s, 1H), 7.88 (t, *J*=9.8 Hz, 1H), 7.83 - 7.79 (m, 1H), 7.56 (d, *J*=7.4 Hz, 1H), 7.37 (dd, *J*=8.5, 5.5 Hz, 2H), 7.21 - 7.15 (m, 2H), 6.12 (s, 2H), 5.75 - 5.69 (m, 1H), 1.86 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 418.1 $(M+H)^+$

Example 47: 7-(3-fluoro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



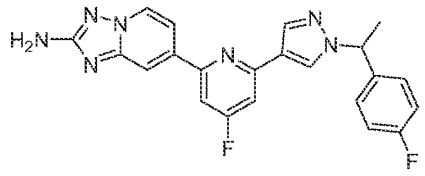
enantiomer 2

The title compound 7-(3-fluoro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 46.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.66 (d, *J*=7.1 Hz, 1H), 8.58 (s, 1H), 8.14 (s, 1H), 7.95 (s, 1H), 7.90 - 7.79 (m, 2H), 7.56 (d, *J*=8.1 Hz, 1H), 7.37 (t, *J*=6.6 Hz, 2H), 7.18 (t, *J*=8.5 Hz, 2H), 6.17 - 6.08 (m, 2H), 5.72 (q, *J*=6.9 Hz, 1H), 1.86 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 418.1 $(M+H)^+$

Example 48: 7-(4-fluoro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



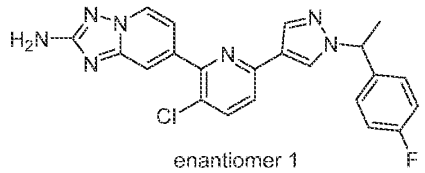
enantiomer 2

The title compound 7-(4-fluoro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained via a similar procedure as that described for Example 43, where 2,6-dibromo-4-fluoropyridine was substituted for 2-chloro-3-fluoro-4-iodopyridine in step 43A. This compound was the second enantiomer to elute from preparative SFC Column 1 where SFC Solvents 2 were the eluent.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.69 (s, 1H), 8.64 (d, *J*=7.0 Hz, 1H), 8.22 (br d, *J*=7.6 Hz, 2H), 7.95 - 7.91 (m, 1H), 7.76 (d, *J*=6.9 Hz, 1H), 7.67 (br d, *J*=10.2 Hz, 1H), 7.38 (t, *J*=6.7 Hz, 2H), 7.19 (t, *J*=8.7 Hz, 2H), 6.10 (s, 2H), 5.75 - 5.70 (m, 1H), 1.87 (d, *J*=6.9 Hz, 3H).

MS ESI m/z 418.1 $(M+H)^+$

Example 49: 7-(3-chloro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1

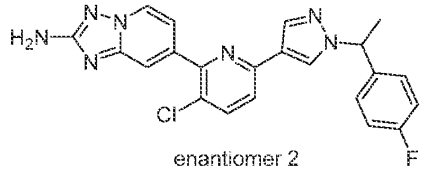


enantiomer 1

The title compound 7-(3-chloro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 was obtained via a similar procedure as that described for Example 43, where 6-bromo-2,3-dichloropyridine was substituted for 2-chloro-3-fluoro-4-iodopyridine in step 43A. This compound was the first enantiomer to elute from preparative SFC Column 2 where SFC Solvents 5 were the eluent. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.64 (d, *J*=6.8 Hz, 1H), 8.53 (s, 1H), 8.11 (s, 1H), 8.04 (d, *J*=8.4 Hz, 1H), 7.76 (d, *J*=8.4 Hz, 1H), 7.69 (s, 1H), 7.36 (dd, *J*=8.4, 5.6 Hz, 2H), 7.22 (dd, *J*=6.9, 1.5 Hz, 1H), 7.17 (t, *J*=8.9 Hz, 2H), 6.10 (s, 2H), 5.70 (q, *J*=7.0 Hz, 1H), 1.84 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 434.0 $(M+H)^+$

Example 50: 7-(3-chloro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



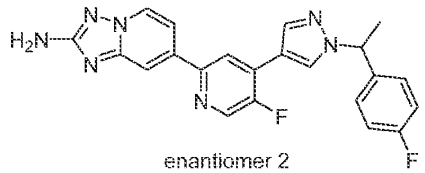
enantiomer 2

The title compound 7-(3-chloro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 49. After the initial preparative SFC chromatography, this material required repurification via an additional preparative SFC chromatography using SFC Column 6 with SFC Solvents 1 as the eluent to remove a minor impurity.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.63 (d, *J*=6.9 Hz, 1H), 8.51 (s, 1H), 8.10 (s, 1H), 8.03 (d, *J*=8.5 Hz, 1H), 7.76 (d, *J*=8.4 Hz, 1H), 7.68 (s, 1H), 7.36 (dd, *J*=8.6, 5.5 Hz, 2H), 7.22 (dd, *J*=6.9, 1.6 Hz, 1H), 7.16 (t, *J*=8.8 Hz, 2H), 6.09 (s, 2H), 5.69 (q, *J*=6.8 Hz, 1H), 1.83 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 434.0 $(M+H)^+$

Example 51: 7-(5-fluoro-4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



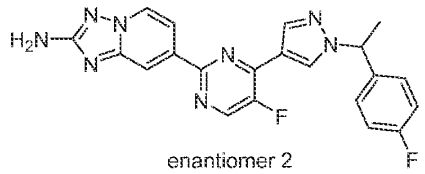
enantiomer 2

The title compound 7-(5-fluoro-4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained via a similar procedure as that described for Example 43, where 2-chloro-5-fluoro-4-iodopyridine was substituted for 2-chloro-3-fluoro-4-iodopyridine in step 43A. This compound was the second enantiomer to elute from preparative SFC Column 1 where SFC Solvents 1 were the eluent.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.70 (s, 1H), 8.68 (d, *J*=2.1 Hz, 1H), 8.63 (d, *J*=7.0 Hz, 1H), 8.51 (d, *J*=6.0 Hz, 1H), 8.30 (s, 1H), 8.17 (s, 1H), 7.69 (dd, *J*=7.0, 1.8 Hz, 1H), 7.39 (dd, *J*=8.6, 5.6 Hz, 2H), 7.19 (t, *J*=8.9 Hz, 2H), 6.08 (s, 2H), 5.77 (q, *J*=6.9 Hz, 1H), 1.88 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 418.1 $(M+H)^+$

Example 52: 7-(5-fluoro-4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



enantiomer 2

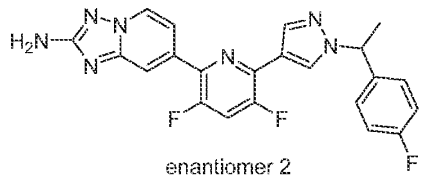
The title compound 7-(5-fluoro-4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained via a

similar procedure as that described for Example 43, where 4-bromo-2-chloro-5-fluoropyrimidine was substituted for 2-chloro-3-fluoro-4-iodopyridine in step 43A. This compound was the second enantiomer to elute from preparative SFC Column 1 where SFC Solvents 1 were the eluent.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.94 (d, *J*=2.7 Hz, 1H), 8.86 (s, 1H), 8.66 (d, *J*=7.2 Hz, 1H), 8.33 (br d, *J*=7.7 Hz, 2H), 7.87 (dd, *J*=7.0, 1.5 Hz, 1H), 7.43 (dd, *J*=8.5, 5.5 Hz, 2H), 7.18 (s, 1H), 7.23 - 7.17 (m, 1H), 6.15 (s, 2H), 5.84 (q, *J*=7.2 Hz, 1H), 1.90 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 419.1 $(M+H)^+$

Example 53: 7-(3,5-difluoro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



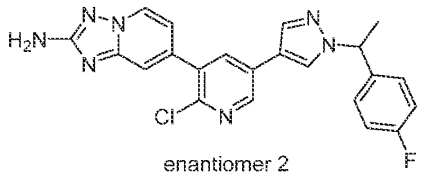
enantiomer 2

The title compound 7-(3,5-difluoro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained via a similar procedure as that described for Example 43, where 2,6-dibromo-3,5-difluoropyridine was substituted for 2-chloro-3-fluoro-4-iodopyridine in step 43A. This compound was the second enantiomer to elute from preparative SFC Column 1 where SFC Solvents 1 were the eluent.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.66 (d, *J*=7.1 Hz, 1H), 8.55 (s, 1H), 8.16 (s, 1H), 8.17 - 8.11 (m, 1H), 7.91 (s, 1H), 7.52 (d, *J*=7.0 Hz, 1H), 7.40 (dd, *J*=8.5, 5.6 Hz, 2H), 7.18 (t, *J*=8.9 Hz, 2H), 6.12 (s, 2H), 5.79 (q, *J*=7.1 Hz, 1H), 1.87 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 436.0 $(M+H)^+$

Example 54: 7-(2-chloro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



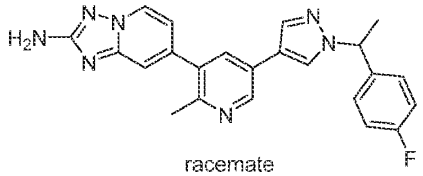
enantiomer 2

The title compound 7-(2-chloro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained via a similar procedure as that described for Example 43, where 3-bromo-2-chloro-5-iodopyridine was substituted for 2-chloro-3-fluoro-4-iodopyridine in step 43A. This compound was the second enantiomer to elute from preparative SFC Column 1 where SFC Solvents 1 were the eluent.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.76 (d, *J*=2.2 Hz, 1H), 8.65 (d, *J*=6.8 Hz, 1H), 8.60 (s, 1H), 8.22 (d, *J*=2.3 Hz, 1H), 8.14 (s, 1H), 7.52 (s, 1H), 7.33 (dd, *J*=8.4, 5.6 Hz, 2H), 7.17 (br t, *J*=8.9 Hz, 2H), 7.04 (dd, *J*=7.0, 1.4 Hz, 1H), 6.10 (s, 2H), 5.66 (q, *J*=6.8 Hz, 1H), 1.86 - 1.81 (m, 3H).

MS ESI m/z 434.0 $(M+H)^+$

Example 55 : 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-2-methylpyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate



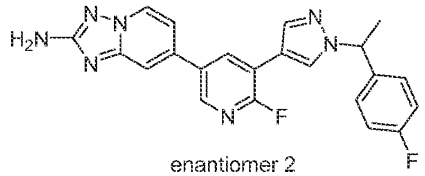
racemate

The title compound 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-2-methylpyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate was obtained via a similar procedure as that described for Example 43, where 5-bromo-3-chloro-2-methylpyridine was substituted for 2-chloro-3-fluoro-4-iodopyridine in step 43A.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.79 - 8.76 (m, 1H), 8.63 - 8.59 (m, 1H), 8.52 - 8.50 (m, 1H), 8.07 - 8.04 (m, 1H), 7.94 - 7.91 (m, 1H), 7.43 - 7.40 (m, 1H), 7.35 - 7.30 (m, 2H), 7.19 - 7.14 (m, 2H), 6.97 (dd, *J*=6.9, 1.7 Hz, 1H), 6.05 (s, 2H), 5.65 (q, *J*=6.9 Hz, 1H), 2.47 - 2.45 (m, 3H), 1.86 - 1.81 (m, 3H).

MS ESI m/z 414.1 $(M+H)^+$

Example 56: 7-(6-fluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



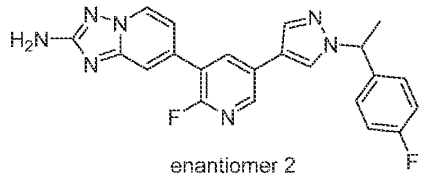
enantiomer 2

The title compound 7-(6-fluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained via a similar procedure as that described for Example 43, where 3-bromo-5-chloro-2-fluoropyridine was substituted for 2-chloro-3-fluoro-4-iodopyridine in step 43A. This compound was the second enantiomer to elute from preparative SFC Column 1 where SFC Solvents 1 were the eluent.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.72 - 8.62 (m, 2H), 8.53 (br d, *J*=17.9 Hz, 2H), 8.17 (s, 1H), 7.88 (s, 1H), 7.40 - 7.34 (m, 3H), 7.18 (t, *J*=8.3 Hz, 2H), 6.08 (s, 2H), 5.74 (q, *J*=7.0 Hz, 1H), 1.86 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 418.2 $(M+H)^+$

Example 57: 7-(2-fluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



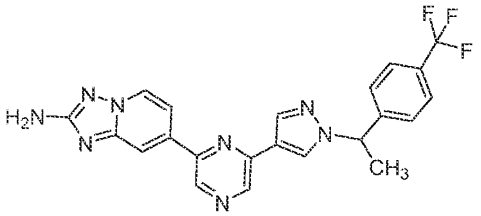
enantiomer 2

The title compound 7-(2-fluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained via a similar procedure as that described for Example 43, where 5-bromo-3-chloro-2-fluoropyridine was substituted for 2-chloro-3-fluoro-4-iodopyridine in step 43A. This compound was the second enantiomer to elute from preparative SFC Column 1 where SFC Solvents 1 were the eluent.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.67 (d, *J*=6.9 Hz, 1H), 8.58 (s, 1H), 8.56 (s, 1H), 8.46 (d, *J*=8.9 Hz, 1H), 8.14 (s, 1H), 7.71 (s, 1H), 7.34 (dd, *J*=8.1, 5.9 Hz, 2H), 7.21 - 7.16 (m, 3H), 6.12 (s, 2H), 5.67 (q, *J*=7.4 Hz, 1H), 1.85 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 418.1 $(M+H)^+$

Example 58: 7-(6-(1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



enantiomer 2

58A: *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate: To a dry reaction vial under nitrogen was added *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (60 mg, 0.13 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (41 mg, 0.16 mmol), potassium acetate (40 mg, 0.41 mmol) and dioxane (3 mL). The reaction was purged well with argon and was then treated with dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (10 mg, 0.012 mmol). The reaction was again purged well with argon and was securely capped and heated at 95 °C for 90 minutes. The reaction mixture containing crude *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate was used directly in the next reaction without purification or isolation. A 100% yield was assumed.

MS ESI m/z 457.0 $(M+H)^+$

58B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: To the crude reaction mixture from the previous step containing *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (assumed 72.3 mg, 0.134 mmol) was added 4-iodo-1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-pyrazole (52.0 mg, 0.142 mmol), potassium phosphate tribasic, 2.0M in water (200 µL, 0.400 mmol), dioxane (1.5 mL) and dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (11 mg, 0.013 mmol). The reaction was purged very well with argon and the vial was securely capped and heated

at 75 °C for 2 hours. The reaction was diluted with ethyl acetate (10 mL) and filtered through a small pad of Celite. The Celite pad was rinsed with a 1:1 dichloromethane/ethyl acetate mixture (100 mL) and the solvent was removed *in vacuo* to give *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (87 mg, 0.13 mmol, quantitative) which was used "as is" without further purification in the next step.

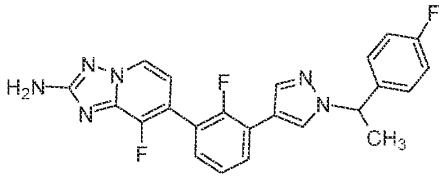
MS ESI m/z 651.2 $(M+H)^+$

58: 7-(6-(1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2: To the vial containing crude *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (87 mg, 0.13 mmol) was added neat TFA and the reaction was allowed to stand at room temp for 45 minutes. The volatiles were removed under a gentle stream of nitrogen and the crude product was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 47%B - 87% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(6-(1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 20%B over 22 minutes; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (254 nm). Fractions containing the second enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(6-(1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine, enantiomer 2 (5.9 mg, 0.013 mmol, 9.6%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.20 (s, 1H), 9.03 (s, 1H), 8.85 (s, 1H), 8.68 (d, *J*=7.0 Hz, 1H), 8.34 (s, 1H), 8.26 (d, *J*=1.2 Hz, 1H), 7.79 - 7.71 (m, 3H), 7.53 (d, *J*=8.1 Hz, 2H), 5.87 (q, *J*=7.4 Hz, 1H), 1.93 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 451.0 $(M+H)^+$

Example 59 : 8-fluoro-7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

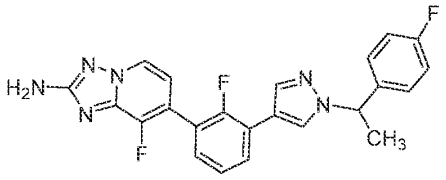
To a dry reaction vial under nitrogen was added 4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazole (50 mg, 0.12 mmol), 8-fluoro-7-iodo-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (37 mg, 0.13 mmol), dioxane (1.5 mL) and potassium phosphate tribasic, 2 M in water (305 µL, 0.610 mmol). The reaction mixture was purged well with argon, treated with dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (7.0 mg, 8.6 µmol), again purged well with argon, then the vial was securely capped and heated at 80 °C for 110 min. The crude mixture was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 24-64% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(6-(1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 15%B over 40 minutes; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (254 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide

8-fluoro-7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (10 mg, 0.024 mmol, 19%).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.55 (d, *J*=6.9 Hz, 1H), 8.37 (s, 1H), 8.01 (s, 1H), 7.92 - 7.82 (m, 1H), 7.41 - 7.33 (m, 4H), 7.17 (br t, *J*=8.9 Hz, 2H), 6.95 (t, *J*=6.6 Hz, 1H), 6.29 (s, 2H), 5.72 (q, *J*=6.9 Hz, 1H), 1.85 (br d, *J*=7.0 Hz, 3H).

MS ESI m/z 435.1 $(M+H)^+$

Example 60: 8-fluoro-7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



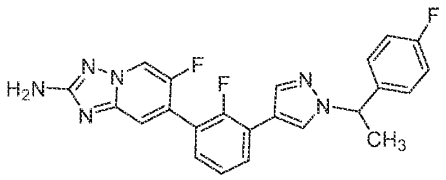
enantiomer 2

The title compound 8-fluoro-7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (11 mg, 0.025 mmol, 21%) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 59.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.55 (d, *J*=6.9 Hz, 1H), 8.37 (s, 1H), 8.01 (s, 1H), 7.87 (td, *J*=7.3, 2.5 Hz, 1H), 7.41 - 7.32 (m, 4H), 7.17 (t, *J*=8.8 Hz, 2H), 6.95 (t, *J*=6.6 Hz, 1H), 6.29 (s, 2H), 5.72 (q, *J*=7.2 Hz, 1H), 1.85 (d, *J*=7.0 Hz, 3H)

MS ESI m/z 435.1 $(M+H)^+$

Example 61: 6-fluoro-7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

61A: ethyl N-[[(5-fluoro-4-iodo-2-pyridinyl)amino]thioxomethyl]carbamate: To a 1000 mL round bottom flask under nitrogen was added 5-fluoro-4-iodopyridin-2-amine (17.2 g, 72.4 mmol), dioxane (200 mL) and dichloromethane (200 mL). The reaction was flushed briefly with nitrogen, then the mixture was treated with ethoxycarbonyl isothiocyanate (13.0 mL, 110 mmol) via an addition funnel over approximately 10 minutes, and the reaction mixture was allowed to stir at room temp for 18 days. The solvent was removed *in vacuo* and the crude residue was purified by flash chromatography on silica gel, eluting with 0-100% gradient of ethyl acetate in hexanes to afford ethyl *N*-[[(5-fluoro-4-iodo-2-pyridinyl)amino]thioxomethyl]carbamate (32.9 g, 89.1 mmol, quantitative).

MS ESI m/z 369.9 $(M+H)^+$

61B: 6-fluoro-7-iodo-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: To the flask containing ethyl N-[[(5-fluoro-4-iodo-2-pyridinyl)amino]thioxomethyl]carbamate (32.9 g, 89.1 mmol) was added ethanol (600 mL) and methanol (100 mL). The resulting pale orange suspension was then treated with hydroxylamine hydrochloride (31.0 g, 446 mmol), followed by *N,N*-diisopropylethylamine (47.0 mL, 269 mmol). The reaction was flushed briefly with nitrogen and was heated at 60 °C for 3 hours and was then stirred at room temperature for 18 hours. Most of the solvent was evaporated away until a thick slurry was present. The mixture was then diluted with water (800 mL) while stirring rapidly. After 90 minutes, solids were isolated by filtration and dried under high vacuum to give 6-fluoro-7-iodo-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (17.2 grams, 61.9 mmol, 69.4%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.94 (d, *J*=3.5 Hz, 1H), 7.92 (d, *J*=5.8 Hz, 1H), 6.13 (s, 2H).

MS ESI m/z 278.9 $(M+H)^+$

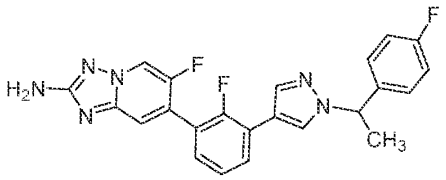
61: 6-fluoro-7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1: The title compound 6-fluoro-7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 was prepared via a similar procedure as described for the preparation of Example 59, where 6-fluoro-7-iodo-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (37 mg, 0.13 mmol) was used in place of 8-fluoro-7-iodo-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. The crude product was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5

acetonitrile:water with 10-mM ammonium acetate; Gradient: 24-64% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 6-fluoro-7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 μm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 40%B over 22 minutes; Flow Rate: 85 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (275 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 6-fluoro-7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (10 mg, 0.024 mmol, 20%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.03 (d, *J*=4.7 Hz, 1H), 8.36 (s, 1H), 8.00 (s, 1H), 7.93 - 7.82 (m, 1H), 7.49 (d, *J*=6.9 Hz, 1H), 7.44 - 7.31 (m, 4H), 7.17 (t, *J*=8.8 Hz, 2H), 6.14 (s, 2H), 5.71 (q, *J*=7.2 Hz, 1H), 1.84 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 435.1 $(M+H)^+$

Example 62: 6-fluoro-7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



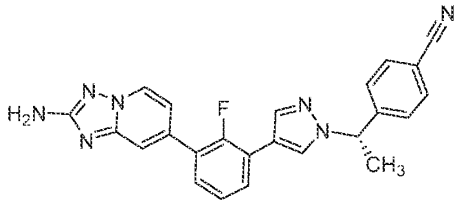
enantiomer 2

The title compound 6-fluoro-7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (11 mg, 0.025 mmol, 20%) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 61.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.03 (d, *J*=4.7 Hz, 1H), 8.36 (s, 1H), 8.00 (s, 1H), 7.92 - 7.81 (m, 1H), 7.49 (d, *J*=6.9 Hz, 1H), 7.43 - 7.30 (m, 4H), 7.17 (t, *J*=8.9 Hz, 2H), 6.14 (s, 2H), 5.71 (q, *J*=7.4 Hz, 1H), 1.84 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 435.2 $(M+H)^+$

Example 63: *(S)*-4-(1-(4-(3-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)-2-fluorophenyl)-1H-pyrazol-1-yl)ethyl)benzonitrile



63A: *tert*-butyl *(S)*-(*tert*-butoxycarbonyl)(7-(3-(1-(1-(4-cyanophenyl)ethyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: To a small reaction vial under nitrogen was added *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (40 mg, 0.070 mmol), *(S)*-4-(1-(4-iodo-1H-pyrazol-1-yl)ethyl)benzonitrile (33 mg, 0.10 mmol), dioxane (1 mL) and potassium phosphate tribasic, 2.0M in water (145 µL, 0.290 mmol). The reaction was purged well with argon and was then treated with dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (5.0 mg, 6.1 µmol). The mixture was purged with argon again and the vessel was securely capped and heated at 65 °C for 80 min. The reaction was diluted with ethyl acetate (10mL), filtered through a pad of Celite and the filtrated was evaporated to dryness to give *tert*-butyl *(S)*-(*tert*-butoxycarbonyl)(7-(3-(1-(1-(4-cyanophenyl)ethyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate which was used directly in the next step without further manipulation.

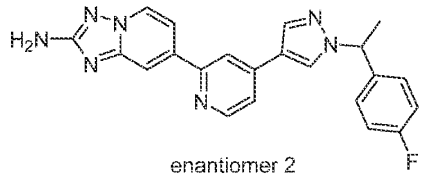
MS ESI m/z 624.1 $(M+H)^+$

63: *(S)*-4-(1-(4-(3-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)-2-fluorophenyl)-1H-pyrazol-1-yl)ethyl)benzonitrile: To a solution of *tert*-butyl *(S)*-(*tert*-butoxycarbonyl)(7-(3-(1-(1-(4-cyanophenyl)ethyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (45 mg, 0.070 mmol) in dichloromethane was added neat TFA (400 µL, 5.19 mmol) and the resulting dark solution was allowed to stand at room temp for

90 min. The volatiles were removed under a gentle stream of nitrogen and the crude product was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 14-54% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give *(S)*-4-(1-(4-(3-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)-2-fluorophenyl)-1H-pyrazol-1-yl)ethyl)benzonitrile (11 mg, 0.026 mmol, 35%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.62 (d, *J*=7.0 Hz, 1H), 8.44 (br s, 1H), 8.04 (s, 1H), 7.87 - 7.79 (m, 3H), 7.54 (s, 1H), 7.51 - 7.42 (m, 3H), 7.34 (t, *J*=7.7 Hz, 1H), 7.09 (br d, *J*=7.0 Hz, 1H), 5.88 - 5.77 (m, 1H), 1.87 (d, *J*=7.1 Hz, 3H).
MS ESI m/z 424.1 $(M+H)^+$

Example 64: 7-(4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



enantiomer 2

64A: 2-bromo-4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridine: In a 40 mL Chemglass reaction vial were combined racemic 1-(1-(4-fluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.100 g, 0.315 mmol) and 2-bromo-4-iodopyridine (0.089 g, 0.32 mmol) in 1,4-dioxane (3.5 mL). To the mixture was added potassium phosphate tribasic, 2M aqueous solution (0.473 mL, 0.945 mmol). The addition of the aqueous phosphate solution caused a color change fron light yellow to pink/orange. Then dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (0.013 g, 0.016 mmol) was added to the mixture. The mixture was sparged with a gentle stream of nitrogen with stirring for 5 min, then the vial was capped and heated to 65 °C for 16 h. This crude mixture containing racemic 2-bromo-4-(1-(1-(4-fluorophenyl)ethyl)-1H-

pyrazol-4-yl)pyridine was carried directly into the next step as-is. A 100% yield was assumed.

MS ESI m/z 345.7, 347.7 $(M+H)^+$

64B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: In a 40 mL Chemglass reaction vial were combined *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (145 mg, 0.315 mmol) and the crude reaction mixture from the previous step containing racemic 2-bromo-4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridine (assumed 109 mg, 0.315 mmol) in 1,4-dioxane (3.5 mL). To the mixture was added potassium phosphate tribasic, 2M aqueous solution (0.473 mL, 0.945 mmol) followed by addition of dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (13 mg, 0.016 mmol). The mixture was sparged with a gentle stream of nitrogen with stirring for 5 min, then the vial was capped and heated to 70 °C for 5 h. The mixture was allowed to cool to RT, was then sparged with nitrogen again for 10 min, and additional dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (13 mg, 0.016 mmol) was added. The resulting mixture was sparged with nitrogen for 5 more min, then the vessel was sealed and heated to 90 °C overnight. The crude mixture was diluted with 1:1 DCM:EtOAc (10 mL) and the resulting susension was filtered through a plug of Celite and rinsed through with 1:1 EtOAc:DCM. Concentration in vacuo gave a deep brown oil residue which was dissolved in minimum DCM and loaded atop a DCM preequilibrated 12 g silica cartridge. Elution gradient 100% DCM to 100% EtOAc over 15 column volumes, hold 100% EtOAc for 6 CV. Two broad major peaks eluted, one of which eluted well into the 100% EtOAc hold. Fractions containing m/z consistent with desired product as well as fractions with m/z consistent with desired material with loss of one or two N-Boc groups were combined and concentrated in vacuo to provide brown sticky oil containing the desired racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (206 mg, approx. 0.113 mmol, approx. 33% purity, approx. 36% yield). This impure material was carried forward into the next step as-is.

MS ESI m/z 600.1 $(M+H)^+$

64C: 7-(2-fluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate: A mixture of the impure material from the previous step containing racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(4-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (206 mg, approx. 0.113 mmol, approx. 33% purity) in DCM (1 mL) was treated with TFA (0.218 mL, 0.327 g, 2.83 mmol) and the result was stirred at RT for 1.5 h. The mixture was concentrated via nitrogen stream to a residue. The residue was dissolved in minimal DMF and filtered to give a 2 mL sample which was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 17-57% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide racemic 7-(2-fluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (15.6 mg, 0.0391 mmol, 34.5% yield).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.77 (s, 1H), 8.65 - 8.61 (m, 2H), 8.37 (s, 1H), 8.28 (s, 1H), 8.19 (s, 1H), 7.73 (dd, *J*=7.1, 1.5 Hz, 1H), 7.64 (d, *J*=5.0 Hz, 1H), 7.35 (dd, *J*=8.5, 5.5 Hz, 2H), 7.19 (t, *J*=8.9 Hz, 2H), 6.07 (s, 2H), 5.70 (q, *J*=6.9 Hz, 1H), 1.87 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 400.1 $(M+H)^+$

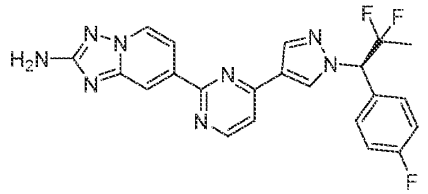
64: 7-(2-fluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2: The racemic 7-(2-fluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (15.6 mg, 0.0391 mmol) obtained in the previous step was further separated into individual enantiomers via preparative chiral SFC chromatography with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% DEA; Elution Gradient: Isocratic 25%B over 18 min; Flow Rate: 100.00 mL/min; Column Temperature: 50 °C. Fraction collection was triggered by PDA (210 nm - 600 nm). Fractions containing the second enantiomer to elute from the preparative SFC column were combined and dried via

centrifugal evaporation. Thus was obtained 7-(2-fluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (4.5 mg, 0.011 mmol, 58% of the theoretical single isomer yield from preparative SFC).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.62 (d, *J*=6.0 Hz, 2H), 8.35 (s, 1H), 8.27 (s, 1H), 8.17 (s, 1H), 7.73 (dd, *J*=7.0, 1.1 Hz, 1H), 7.64 (d, *J*=5.2 Hz, 1H), 7.35 (dd, *J*=8.5, 5.5 Hz, 2H), 7.18 (t, *J*=8.8 Hz, 2H), 6.06 (s, 2H), 5.69 (q, *J*=7.2 Hz, 1H), 1.86 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 400.0 $(M+H)^+$

Example 65: *(R)*-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



65A: *(R)*-2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidine: In a 40 mL Chemglass reaction vial were combined *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.160 g, 0.437 mmol) and 4-bromo-2-chloropyrimidine (0.0930 g, 0.481 mmol) in 1,4-dioxane (4 mL). The resulting solution was sparged with a gentle stream of nitrogen gas while stirring, and potassium phosphate tribasic, 2M aqueous (1.31 mL, 2.62 mmol) was introduced. The resulting mixture was sparged for 10 min with nitrogen gas, then dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (0.018 g, 0.022 mmol) was added and the mixture was again sparged with nitrogen for 5 min. The resulting dark brown mixture was heated with aggressive stirring to 70 °C for 30 min. This crude mixture containing *(R)*-2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidine was carried directly into the next step as-is. A 100% yield was assumed.

MS ESI m/z 352.9 $(M+H)^+$

65B: *tert*-butyl *(R)*-(*tert*-butoxycarbonyl)(7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: To the crude reaction mixture from the previous step containing *(R)*-2-

chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidine (assumed 0.154 g, 0.437 mmol) was added *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (0.221 g, 0.481 mmol) under nitrogen. The mixture was sparged with a gentle stream of nitrogen gas for 5 min while stirring. Then, dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (0.018 g, 0.022 mmol) was added and the mixture was sparged with nitrogen gas for 5 min. The vessel was sealed and the brown mixture was heated with aggressive stirring at 75 °C for 3 h. The crude mixture was passed through a pad of Celite (40 mL), rinsed through with EtOAc and concentrated in vacuo to a black residue. The residue was taken up in minimum DCM and loaded atop a hexanes preequilibrated 24 g silica cartridge. Elution 100% hexanes for 1 column volume, then gradient 100% hexanes to 100% EtOAc over 12 column volumes, then hold 100% EtOAc for 4 CV. Like fractions of the major peak were combined and concentrated in vacuo. The yellow oily material thus obtained was placed under high vacuum for 1 h to provide *tert*-butyl *(R)*-(*tert*-butoxycarbonyl)(7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (285 mg, 0.439 mmol, quantitative) as an off-white glassy foam.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.93 (s, 1H), 8.81 (d, *J*=5.2 Hz, 1H), 8.65 (d, *J*=7.1 Hz, 1H), 8.41 (s, 1H), 8.25 - 8.20 (m, 2H), 7.63 (dd, *J*=8.8, 5.2 Hz, 2H), 7.41 (d, *J*=5.2 Hz, 1H), 7.15 (t, *J*=8.1 Hz, 2H), 5.74 (t, *J*=12.5 Hz, 1H), 1.76 (t, *J*=18.8 Hz, 3H), 1.50 (s, 18H).

MS ESI m/z 651.5 $(M+H)^+$

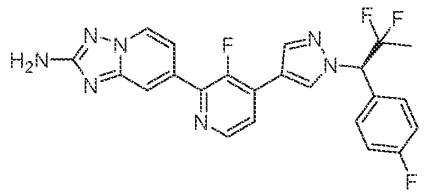
65: *(R)*-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: A solution of *tert*-butyl *(R)*-(*tert*-butoxycarbonyl)(7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (170 mg, 0.261 mmol) obtained in the previous step dissolved in DCM (1.5 mL) was treated with TFA (2.22 g, 1.50 mL, 19.5 mmol). The mixture was stirred at RT for 1 h. The mixture was concentrated under a gentle stream of nitrogen gas to a solid residue. The residue was dissolved in minimum DMF and filtered to provide a 2 mL sample which was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-

mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 23-58% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide *(R)*-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (70.2 mg, 0.156 mmol, 59.7% yield)

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.93 - 8.87 (m, 2H), 8.67 (d, *J*=7.0 Hz, 1H), 8.48 (s, 1H), 8.37 (s, 1H), 7.90 (dd, *J*=7.0, 1.7 Hz, 1H), 7.82 - 7.75 (m, 3H), 7.29 (t, *J*=8.9 Hz, 2H), 6.35 - 6.27 (m, 1H), 1.68 (br t, *J*=19.1 Hz, 3H).

MS ESI m/z 451.0 $(M+H)^+$

Example 66: *(R)*-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine

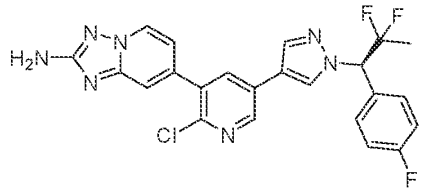


The title compound *(R)*-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine was obtained via a similar procedure as that described for Example 65, where 2-chloro-3-fluoro-4-iodopyridine was substituted for 4-bromo-2-chloropyrimidine in step 65A.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.69 - 8.63 (m, 2H), 8.53 (d, *J*=4.8 Hz, 1H), 8.33 (s, 1H), 7.90 (t, *J*=5.2 Hz, 1H), 7.88 (s, 1H), 7.77 (dd, *J*=8.4, 5.6 Hz, 2H), 7.46 (d, *J*=6.9 Hz, 1H), 7.29 (t, *J*=8.4 Hz, 2H), 6.34 (t, *J*=13.4 Hz, 1H), 6.21 - 6.06 (m, 2H), 1.66 (t, *J*=19.1 Hz, 3H).

MS ESI m/z 468.2 $(M+H)^+$

Example 67: *(R)*-7-(2-chloro-5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine

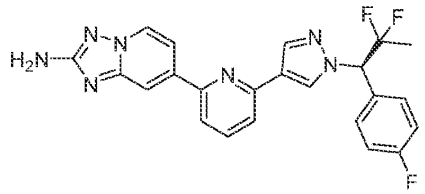


The title compound *(R)*-7-(2-chloro-5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine was obtained via a similar procedure as that described for Example 65, where 3-bromo-2-chloro-5-iodopyridine was substituted for 4-bromo-2-chloropyrimidine in step 65A.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.80 (s, 1H), 8.67 - 8.64 (m, 2H), 8.28 (d, *J*=2.4 Hz, 1H), 8.25 (s, 1H), 7.75 (dd, *J*=8.2, 5.4 Hz, 2H), 7.53 (s, 1H), 7.27 (t, *J*=8.4 Hz, 2H), 7.05 (dd, *J*=6.8, 1.7 Hz, 1H), 6.20 (br t, *J*=13.0 Hz, 1H), 6.13 - 6.09 (m, 2H), 1.65 (br t, *J*=19.1 Hz, 3H).

MS ESI m/z 484.2 $(M+H)^+$

Example 68: *(R)*-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine

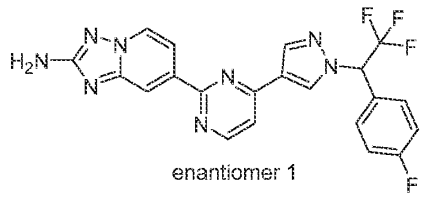


The title compound *(R)*-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine was obtained via a similar procedure as that described for Example 65, where 2-chloro-6-iodopyridine was substituted for 4-bromo-2-chloropyrimidine in step 65A.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.68 (s, 1H), 8.63 (d, *J*=6.9 Hz, 1H), 8.31 (s, 1H), 8.15 (d, *J*=1.1 Hz, 1H), 8.00 - 7.90 (m, 2H), 7.80 - 7.74 (m, 3H), 7.72 (dd, *J*=7.0, 1.9 Hz, 1H), 7.28 (t, *J*=8.5 Hz, 2H), 6.28 (t, *J*=13.3 Hz, 1H), 6.07 (s, 2H), 1.67 (t, *J*=19.1 Hz, 3H).

MS ESI m/z 450.1 $(M+H)^+$

Example 69: 7-(4-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

69A: 2-chloro-4-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidine: In a 40 mL Chemglass reaction vial were combined racemic 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazole (0.158 g, 0.384 mmol) and 4-bromo-2-chloropyrimidine (0.082 g, 0.423 mmol) in 1,4-dioxane (4 mL). The solution was gently sparged with nitrogen gas while stirring, and potassium phosphate tribasic, 2M aqueous (1.15 mL, 2.31 mmol) was introduced. The resulting mixture was gently sparged with nitrogen gas and stirring for 10 min, then dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (0.016 g, 0.019 mmol) was added and the mixture was nitrogen sparged for an additional 5 min. The resulting deep brown mixture was heated with aggressive stirring to 70 °C for 30 min. This crude mixture containing racemic 2-chloro-4-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidine was carried directly into the next step as-is. A 100% yield was assumed.

MS ESI m/z 356.9 $(M+H)^+$

69B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)yl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: To the crude reaction mixture from the previous step containing racemic 2-chloro-4-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidine (assumed 0.137 g, 0.384 mmol) was added *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (0.195 g, 0.423 mmol) under nitrogen. The mixture was gently sparged with nitrogen gas for 5 min while stirring. Then, dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (0.016 g, 0.019 mmol) was added and the mixture was sparged with nitrogen gas for 5 min. The vessel was sealed and the brown mixture was heated with aggressive stirring at 75 °C for 3 h. The crude mixture was passed through a pad of Celite (40 mL), rinsed through with EtOAc and concentrated in vacuo to a black residue. The residue was taken up in minimum DCM and loaded atop a hexanes preequilibrated 24 g silica cartridge. Elution 100% hexanes for 1 column volume, then gradient 100% hexanes to 100% EtOAc over 12 column volumes,

then hold 100% EtOAc for 4 CV. Like fractions of the major peak were combined and concentrated in vacuo. The yellow oily material thus obtained was placed under high vacuum for 1 h to provide racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(4-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (170.6 mg, 0.261 mmol, 67.8% yield) as an off-white glassy foam.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.91 (s, 1H), 8.82 (d, *J*=5.1 Hz, 1H), 8.64 (d, *J*=7.2 Hz, 1H), 8.36 (s, 1H), 8.26 - 8.20 (m, 2H), 7.61 (dd, *J*=8.7, 5.0 Hz, 2H), 7.41 (d, *J*=5.2 Hz, 1H), 7.19 (t, *J*=8.1 Hz, 2H), 6.03 (q, *J*=7.5 Hz, 1H), 1.50 (s, 18H).

MS ESI m/z 655.5 $(M+H)^+$

69C: 7-(4-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate: A mixture of *tert*-butyl (*tert*-butoxycarbonyl)(7-(4-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (168 mg, 0.257 mmol) in DCM (1.5 mL) was treated with TFA (2.22 g, 1.5 mL, 19.5 mmol). The mixture was stirred at RT for 1 h. The mixture was concentrated under a gentle stream of nitrogen overnight to a solid residue. The residue was dissolved in minimum DMF and filtered to provide a 2 mL sample which was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 24-59% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide racemic 7-(4-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (59.1 mg, 0.130 mmol, 46.8% yield).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.96 (s, 1H), 8.91 (d, *J*=5.1 Hz, 1H), 8.68 (d, *J*=6.9 Hz, 1H), 8.55 (s, 1H), 8.38 (s, 1H), 7.90 (d, *J*=7.1 Hz, 1H), 7.86 - 7.80 (m, 3H), 7.36 (t, *J*=8.8 Hz, 2H), 6.96 - 6.89 (m, 1H), 6.35 - 6.01 (m, 2H).

MS ESI m/z 455.1 $(M+H)^+$

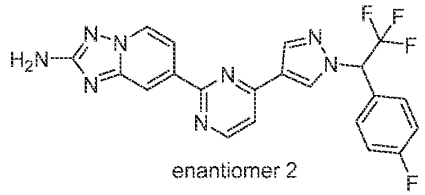
69: 7-(4-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1: The racemic 7-(4-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-

amine (59.1 mg, 0.130 mmol) obtained in the previous step was further separated into individual enantiomers via preparative chiral SFC chromatography with the following conditions: Column: Daicel Chiralpak IA, 30 mm x 250 mm, 5 μm particles; ; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution Gradient: Isocratic 40%B over 20 min; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (230 nm). Fractions containing the desired product were combined and dried via centrifugal evaporation. Thus was obtained 7-(4-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (16.7 mg, 0.0368 mmol, 56.5% of the theoretical single isomer yield from preparative SFC).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.96 (s, 1H), 8.91 (d, *J*=5.3 Hz, 1H), 8.68 (d, *J*=7.0 Hz, 1H), 8.55 (s, 1H), 8.37 (d, *J*=1.1 Hz, 1H), 7.91 - 7.80 (m, 4H), 7.36 (t, *J*=8.8 Hz, 2H), 6.96 - 6.89 (m, 1H), 6.16 (s, 2H).

MS ESI m/z 455.2 $(M+H)^+$

Example 70: 7-(4-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



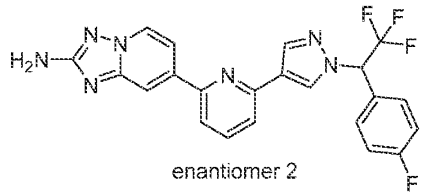
enantiomer 2

The title compound 7-(4-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (12.5 mg, 0.0275 mmol, 42.3% of the theoretical single isomer yield from preparative SFC) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 69.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.96 (s, 1H), 8.91 (d, *J*=5.3 Hz, 1H), 8.68 (d, *J*=7.1 Hz, 1H), 8.55 (s, 1H), 8.37 (s, 1H), 7.91 - 7.80 (m, 4H), 7.36 (t, *J*=8.9 Hz, 2H), 6.96 - 6.90 (m, 1H), 6.16 (s, 2H).

MS ESI m/z 455.2 $(M+H)^+$

Example 71: 7-(6-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2

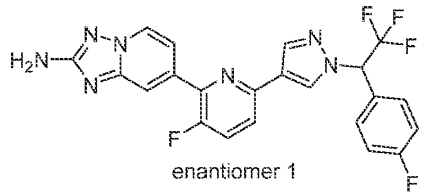


enantiomer 2

The title compound 7-(6-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained via a similar procedure as that described for Example 69, where 2-chloro-6-iodopyridine was substituted for 4-bromo-2-chloropyrimidine in step 69A. This compound was the second enantiomer to elute from preparative SFC Column 1 where SFC Solvents 5 were the eluent. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.72 (s, 1H), 8.64 (d, *J*=6.9 Hz, 1H), 8.38 (s, 1H), 8.15 (s, 1H), 8.00 (d, *J*=7.7 Hz, 1H), 7.94 (t, *J*=7.7 Hz, 1H), 7.84 (dd, *J*=8.8, 5.4 Hz, 2H), 7.77 (d, *J*=7.5 Hz, 1H), 7.72 (d, *J*=7.1 Hz, 1H), 7.35 (t, *J*=8.2 Hz, 2H), 6.89 (q, *J*=8.1 Hz, 1H), 6.08 (s, 2H).

MS ESI m/z 454.4 $(M+H)^+$

Example 72: 7-(3-fluoro-6-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



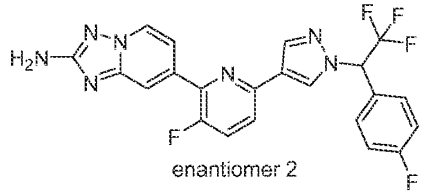
enantiomer 1

The title compound 7-(3-fluoro-6-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 was obtained via a similar procedure as that described for Example 69, where 6-bromo-2-chloro-3-fluoropyridine was substituted for 4-bromo-2-chloropyrimidine in step 69A. This compound was the first enantiomer to elute from preparative SFC Column 1 where SFC Solvents 3 were the eluent.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.70 - 8.64 (m, 2H), 8.34 (s, 1H), 7.95 - 7.87 (m, 3H), 7.82 (dd, *J*=8.6, 5.5 Hz, 2H), 7.54 (br d, *J*=6.7 Hz, 1H), 7.34 (t, *J*=8.9 Hz, 2H), 6.91 - 6.85 (m, 1H), 6.13 (s, 2H).

MS ESI m/z 472.1 $(M+H)^+$

Example 73: 7-(3-fluoro-6-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2

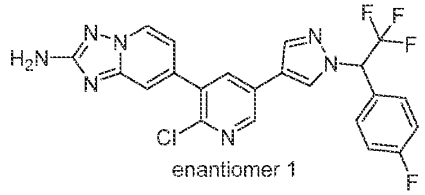


The title compound 7-(3-fluoro-6-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 72.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.69 - 8.66 (m, 2H), 8.34 (s, 1H), 7.96 - 7.87 (m, 3H), 7.83 (br dd, *J*=8.0, 5.6 Hz, 2H), 7.55 (br d, *J*=6.8 Hz, 1H), 7.34 (br t, *J*=8.8 Hz, 2H), 6.91 - 6.85 (m, 1H), 6.22 - 6.09 (m, 1H).

MS ESI m/z 472.2 $(M+H)^+$

Example 74: 7-(2-chloro-5-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



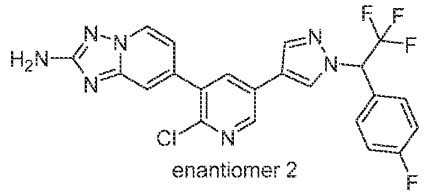
The title compound 7-(2-chloro-5-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 was obtained via a similar procedure as that described for Example 69, where 3-bromo-2-chloro-5-iodopyridine was substituted for 4-bromo-2-chloropyrimidine in step 69A. This

compound was the first enantiomer to elute from preparative SFC Column 8 where SFC Solvents 2 were the eluent.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.80 (d, *J*=2.4 Hz, 1H), 8.69 - 8.62 (m, 2H), 8.32 (s, 1H), 8.28 (d, *J*=2.4 Hz, 1H), 7.80 (dd, *J*=8.4, 5.5 Hz, 2H), 7.54 (s, 1H), 7.36 - 7.31 (m, 2H), 7.05 (dd, *J*=6.9, 1.8 Hz, 1H), 6.87 - 6.82 (m, 1H), 6.13 - 6.09 (m, 2H).

MS ESI m/z 488.1 $(M+H)^+$

Example 75: 7-(2-chloro-5-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2

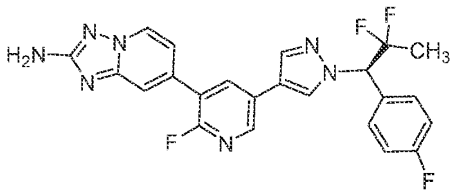


The title compound 7-(2-chloro-5-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 74.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.80 (d, *J*=2.4 Hz, 1H), 8.67 - 8.64 (m, 2H), 8.32 (s, 1H), 8.28 (d, *J*=2.4 Hz, 1H), 7.80 (dd, *J*=8.6, 5.4 Hz, 2H), 7.54 (d, *J*=1.1 Hz, 1H), 7.37 - 7.29 (m, 2H), 7.05 (dd, *J*=6.9, 1.8 Hz, 1H), 6.87 - 6.81 (m, 1H), 6.11 (s, 2H).

MS ESI m/z 488.4 $(M+H)^+$

Example 76: *(R)*-7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluoropyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



76A: 7-(5-chloro-2-fluoropyridin-3-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine: To a 350 mL pressure bottle under nitrogen was added 7-

bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (3.91 g, 13.4 mmol), bis(pinacolato)diboron (3.75 g, 14.8 mmol), potassium acetate (3.95 g, 40.2 mmol) and dioxane (100 mL). The reaction was purged with argon for 4 min, then treated with dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (670 mg, 0.820 mmol) and purged with argon again. The reaction was securely capped and heated at 100 °C for 1 hour. The crude product (with no isolation or purification) was treated with 3-bromo-5-chloro-2-fluoropyridine (2.82 g, 13.4 mmol), potassium phosphate tribasic, 2.0 M in water (67.0 mL, 134 mmol) and additional dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (670 mg, 0.820 mmol). The reaction was purged very well with argon and the vessel was securely capped and heated at 65 °C for 45 minutes. The aqueous phase from the crude reaction was removed via pipet and approximately two thirds of the volume of dioxane was removed under reduced pressure. The reaction was then diluted with ethyl acetate and filtered thru a pad of Celite. The organic layer was then washed with water (5 x 20 mL), brine (1 x 15 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude material was purified by flash chromatography on silica gel, eluting with 0-35% gradient of ethyl acetate in hexanes to afford 7-(5-chloro-2-fluoropyridin-3-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (2.41 g, 7.05 mmol, 52.5%).

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.68 (dd, *J*=7.2, 0.8 Hz, 1H), 8.29 (dd, *J*=2.5, 1.5 Hz, 1H), 8.00 (dd, *J*=8.2, 2.5 Hz, 1H), 7.98 - 7.94 (m, 1H), 7.36 - 7.24 (m, 1H), 5.96 (s, 2H), 2.41 (s, 6H).

MS ESI m/z 341.9, 343.7 $(M+H)^+$

76B: *(R)*-7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluoropyridin-3-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine: To a dry reaction vial under nitrogen was added *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (100 mg, 0.273 mmol), 7-(5-chloro-2-fluoropyridin-3-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (102.3 mg, 0.299 mmol), dioxane (3 mL) and potassium phosphate tribasic, 2.0M in water (415 µL, 0.830 mmol). The reaction was purged well with nitrogen, treated with dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II), 99% (20 mg, 0.031 mmol), purged again with nitrogen, and the vessel was securely capped and heated at 70 °C for 4 hours. The reaction was diluted with ethyl acetate and filtered through a small pad

of Celite. The Celite pad was rinsed with a mixture of ethyl acetate and dichloromethane (30 mL) and the solvent removed *in vacuo*. The crude material was purified by flash chromatography on silica gel, eluting with 0-50% gradient of ethyl acetate in hexanes, and the resulting isolated material was further purified by flash chromatography on silica gel, eluting with 0-65% gradient of acetone in hexanes to afford *(R)*-7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluoropyridin-3-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (111 mg, 0.203 mmol, 74.2%).

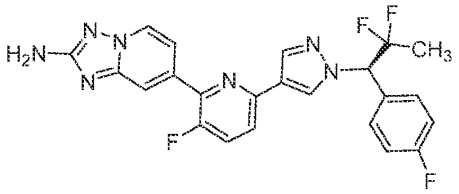
MS ESI m/z 546.4 $(M+H)^+$

76: *(R)*-7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluoropyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: To a solution of 7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluoropyridin-3-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (110.5 mg, 0.203 mmol) in a mixture of THF (1.6 mL) and water (0.5 mL) was added neat TFA (800 µL, 10.4 mmol). The vessel was securely capped and the mixture was heated at 70 °C for 6 hours. The crude reaction was then treated carefully with hydrazine hydrate (1.5 mL) and the result was heated at 70 °C for 2 hours. The reaction was diluted with ethyl acetate (100 mL) and water (5 mL) and the organic layer was washed with water (5 x 5 mL), brine (1 x 5 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude product was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 38% B - 62% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give *(R)*-7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluoropyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (32 mg, 0.069 mmol, 34%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 - 8.62 (m, 2H), 8.59 (s, 1H), 8.50 (br d, *J*=7.4 Hz, 1H), 8.24 (s, 1H), 7.79 - 7.69 (m, 3H), 7.32 - 7.25 (m, 2H), 7.22 - 7.17 (m, 1H), 6.27 - 6.16 (m, 1H), 6.12 (s, 2H), 1.66 (br t, *J*=18.9 Hz, 3H).

MS ESI m/z 468.2 $(M+H)^+$

Example 77: *(R)*-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



77A: *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloro-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: To a dry 150 mL pressure bottle under nitrogen was added 6-chloro-3-fluoro-2-iodopyridine (1.63 g, 6.33 mmol), *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (3.1 g, 6.7 mmol), dioxane (40 mL) and potassium phosphate tribasic, 2.0M in water (9.5 mL, 19 mmol). The reaction was purged very well with argon, then treated with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (500 mg, 0.612 mmol). The reaction was again purged very well with argon and the vessel was securely capped and heated at 85 °C for 1h 45 min. The reaction was diluted with ethyl acetate (400 mL) and water (35 mL) and the organic layer was washed with water (5 x 35 mL), brine (1 x 25 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude residue was purified by flash chromatography on silica gel, eluting with 0-75% gradient of ethyl acetate in hexanes to afford *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloro-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (2.36 g, 5.09 mmol, 76%).

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.64 (dd, *J*=7.2, 0.7 Hz, 1H), 8.45 (s, 1H), 7.88 (dd, *J*=7.3, 1.7 Hz, 1H), 7.59 (dd, *J*=10.1, 8.6 Hz, 1H), 7.42 (dd, *J*=8.5, 3.0 Hz, 1H), 1.50 (s, 18H).

MS ESI m/z 464.1, 466.1 $(M+H)^+$

77B: *tert*-butyl *(R)*-(*tert*-butoxycarbonyl)(7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: To a dry 150 mL pressure bottle under nitrogen was added *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (628 mg, 1.72 mmol), *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloro-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (875 mg, 1.89 mmol), dioxane (20 mL) and potassium phosphate tribasic, 2.0 M in water (2.6 mL, 5.2 mmol). The reaction was purged very well with argon, then treated with [1,1'-

bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (173 mg, 0.212 mmol). The reaction was again purged very well with argon and the vessel was securely capped and heated at 85 °C for 4.5 hours. The reaction was diluted with ethyl acetate (450 mL) and water (15 mL) and the organic layer was washed with water (4 x 15 mL), brine (3 x 15 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude material was purified by flash chromatography on silica gel, eluting with 0-100 % gradient of ethyl acetate in hexanes to afford *tert*-butyl *(R)*-(*tert*-butoxycarbonyl)(7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate. This material was dissolved in ethyl acetate and the organic layer was washed with 1.0M aq *N*-acetyl-L-cystine (4 x 20 mL), water (2 x 20 mL), brine (1 x 10 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The material was further purified by flash chromatography on silica gel, eluting with 0-70 % gradient of acetone in hexanes to afford *tert*-butyl *(R)*-(*tert*-butoxycarbonyl)(7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (897 mg, 1.34 mmol, 78%).

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.66 (d, *J*=7.2 Hz, 1H), 8.54 (s, 1H), 8.22 (s, 1H), 8.10 (s, 1H), 7.93 (dd, *J*=7.2, 1.1 Hz, 1H), 7.65 - 7.52 (m, 4H), 7.28 (s, 1H), 7.13 (t, *J*=8.6 Hz, 2H), 5.73 (dd, *J*=14.0, 11.3 Hz, 1H), 1.76 (t, *J*=18.8 Hz, 3H), 1.51 (s, 18H).

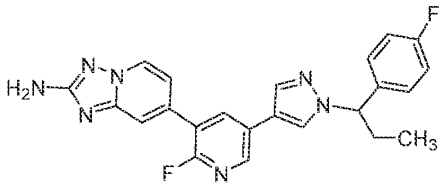
MS ESI m/z 668.3 $(M+H)^+$

77: *(R)*-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: To a solution of *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (897.4 mg, 1.344 mmol) in anhydrous dichloromethane (25 mL) was added neat TFA (3.0 mL, 39 mmol) and the reaction was allowed to stand at room temp for 1 hour. Additional TFA (1.5 mL, 19 mmol) was added and the reaction was allowed to stand at room temp for 2 hours 55 min. The volatiles were removed under a gentle stream of nitrogen and the crude product was purified via reverse phase chromatography using a Waters Sunfire™ Prep C18 OBD 10 micron, 50x250 mm column; Solvent pair: Solvent A: 95% water / 5% ACN/ 10 mmolar NH4OAc; Solvent B: 95% ACN / 5% water / 10 mmolar NH4OAc; Gradient: 15%B - 60%B over 33 min; Flow rate = 118.1 mL/min.; UV absorbance at 220 and 254 nm to afford *(R)*-7-(6-(1-

(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (501 mg, 1.07 mmol, 79%).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.67 (dd, *J*=7.1, 0.8 Hz, 1H), 8.63 (s, 1H), 8.27 (s, 1H), 7.97 - 7.84 (m, 3H), 7.76 (dd, *J*=8.8, 5.4 Hz, 2H), 7.55 (dt, *J*=6.3, 0.9 Hz, 1H), 7.28 (t, *J*=9.0 Hz, 2H), 6.28 (t, *J*=13.2 Hz, 1H), 6.13 (s, 2H), 1.66 (t, *J*=19.1 Hz, 3H).
MS ESI m/z 468.3 $(M+H)^+$

Example 78: 7-(2-fluoro-5-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

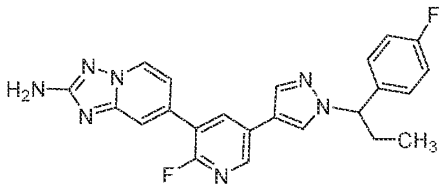
78A: *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-5-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: To a 20 mL reaction vial under nitrogen was added *tert*-butyl (7-(5-bromo-2-fluoropyridin-3-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)(*tert*-butoxycarbonyl)carbamate (125 mg, 0.246 mmol), 1-(1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (81 mg, 0.25 mmol), dioxane (4 mL) and potassium phosphate tribasic, 2.0M in water (370 µL, 0.740 mmol). The mixture was purged with argon and was treated with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (25.3 mg, 0.031 mmol). The mixture was purged with argon again and was then securely capped and heated at 70 °C in an oil bath for 4.5 h. The reaction was diluted with ethyl acetate, filtered through a pad of Celite, and the pad was rinsed with a 1:1 dichloromethane/ethyl acetate mixture and the solvent was removed *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 0-65% gradient of ethyl acetate in hexanes to afford racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-5-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (144 mg, 0.23 mmol, 93%).
LCMS (ESI, m/z): 632.3 $[M+H]^+$

78: 7-(2-fluoro-5-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1: To a solution of racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-5-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (144 mg, 0.228 mmol) in dichloromethane (4 mL) was added neat TFA (1.0 mL, 13 mmol) and the resulting tan solution was allowed to stand at room temp for 2.5 hours, and then the volatiles were removed under a gentle stream of nitrogen. The crude product was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 22-62% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(2-fluoro-5-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralpak IH, 21 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 30%B over 12 minutes; Flow Rate: 75 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (240 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(2-fluoro-5-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (27 mg, 0.063 mmol, 28%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (d, *J*=7.0 Hz, 1H), 8.58 - 8.50 (m, 2H), 8.42 (dd, *J*=9.5, 2.2 Hz, 1H), 8.12 (s, 1H), 7.69 (s, 1H), 7.43 (dd, *J*=8.5, 5.7 Hz, 2H), 7.22 - 7.13 (m, 3H), 6.09 (s, 2H), 5.35 (dd, *J*=8.8, 6.7 Hz, 1H), 2.44 - 2.24 (m, 1H), 2.14 (dt, *J*=14.1, 6.9 Hz, 1H), 0.84 (t, *J*=7.3 Hz, 3H).

MS ESI m/z 432.1 $(M+H)^+$

Example 79: 7-(2-fluoro-5-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



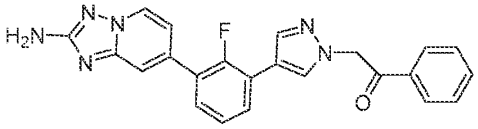
enantiomer 2

The title compound 7-(2-fluoro-5-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (28 mg, 0.066 mmol, 29%) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 78.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.64 (d, *J*=7.0 Hz, 1H), 8.54 (d, *J*=13.7 Hz, 2H), 8.46 - 8.38 (m, 1H), 8.12 (s, 1H), 7.69 (s, 1H), 7.43 (dd, *J*=8.6, 5.6 Hz, 2H), 7.24 - 7.12 (m, 3H), 6.09 (s, 2H), 5.35 (dd, *J*=9.0, 6.3 Hz, 1H), 2.44 - 2.27 (m, 1H), 2.14 (dt, *J*=13.7, 7.0 Hz, 1H), 0.84 (t, *J*=7.2 Hz, 3H).

MS ESI m/z 432.2 $(M+H)^+$

Example 80: 2-(4-(3-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)-2-fluorophenyl)-1H-pyrazol-1-yl)-1-phenylethan-1-one



80A: *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(1-(2-oxo-2-phenylethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: To a dry reaction vial under nitrogen was added 2-(4-iodo-1H-pyrazol-1-yl)-1-phenylethan-1-one (100 mg, 0.320 mmol), 3-bromo-2-fluorophenylboronic acid (74 mg, 0.34 mmol), dioxane (4 mL) and potassium phosphate tribasic, 2M in water (640 µL, 1.28 mmol). The mixture was purged well with argon and was treated with dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane, 99% (16 mg, 0.02 mmol). The mixture was again purged well with argon and then was securely capped and heated at 65 °C for 3.5h. The reaction was diluted with water (5 mL) and ethyl acetate (100 mL) and the organic layer was washed with water (4 x 5 mL), brine (1 x 5 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness to give crude 2-(4-(3-bromo-2-fluorophenyl)-1H-pyrazol-1-yl)-1-

phenylethan-1-one. This crude material was then treated with *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (190 mg, 0.413 mmol), dioxane (4 mL) and potassium phosphate tribasic, 2M in water (640 µL, 1.280 mmol). The resulting mixture was purged well with argon and was treated with dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II), 99% (209 mg, 0.320 mmol). The mixture was again purged well with argon and was securely capped and heated at 90 °C for 5.5 hours. The reaction was diluted with water (8 mL) and ethyl acetate (100 mL) and the organic layer was washed with water (4 x 5 mL), brine (1 x 5 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude product was purified by flash chromatography on silica gel, eluting with 0-100% gradient of ethyl acetate in dichloromethane to afford the title compound *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(1-(2-oxo-2-phenylethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (146 mg, 0.24 mmol, 74%).

LCMS (ESI, m/z): 613.2 $[M+H]^+$.

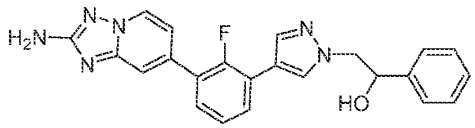
80: 2-(4-(3-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)-2-fluorophenyl)-1H-pyrazol-1-yl)-1-phenylethan-1-one: To a solution of *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(1-(2-oxo-2-phenylethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (30 mg, 0.050 mmol) in dichloromethane (4 mL) was added neat TFA (0.20 mL, 2.60 mmol) and the resulting solution was allowed to stand at room temp for 55 min. The volatiles were removed under a gentle stream of nitrogen. The crude product was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 12-52% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give 2-(4-(3-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)-2-fluorophenyl)-1H-pyrazol-1-yl)-1-phenylethan-1-one (12 mg, 0.029 mmol, 58%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (d, *J*=7.0 Hz, 1H), 8.26 (s, 1H), 8.11 - 8.04 (m, 3H), 7.83 (br t, *J*=7.5 Hz, 1H), 7.77 - 7.70 (m, 1H), 7.61 (t, *J*=7.7 Hz, 2H), 7.55 (s, 1H),

7.52 - 7.45 (m, 1H), 7.36 (t, *J*=7.7 Hz, 1H), 7.10 (br d, *J*=6.9 Hz, 1H), 6.07 (s, 2H), 5.93 (s, 2H).

MS ESI m/z 413.2 $(M+H)^+$

Example 81: 2-(4-(3-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)-2-fluorophenyl)-1H-pyrazol-1-yl)-1-phenylethan-1-ol enantiomer 1



enantiomer 1

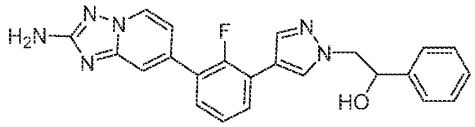
To a solution of *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(1-(2-oxo-2-phenylethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (110 mg, 0.180 mmol) in methanol (2 mL) was added sodium borohydride (16.1 mg, 0.426 mmol) and the reaction was allowed to stand at room temp for 80 min. The reaction was diluted with water (2 mL) and ethyl acetate (60 mL) and the organic layer was washed with water (4 x 4 mL), brine (1 x 4 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness to give crude racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(1-(2-hydroxy-2-phenylethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate. This crude material was dissolved in dichloromethane (2 mL) and treated with neat TFA (0.250 mL, 3.24 mmol) and the reaction was allowed to stand at room temp for 2 hours. The volatiles were removed under a gentle stream of nitrogen. The crude product was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 22-62% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 2-(4-(3-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)-2-fluorophenyl)-1H-pyrazol-1-yl)-1-phenylethan-1-ol. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralpak IC, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH/ACN (50:50); Elution gradient: isocratic 40%B over 22 minutes; Flow

Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (240 nm). The title compound was the first isomer to elute from the column. Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 2-(4-(3-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)-2-fluorophenyl)-1H-pyrazol-1-yl)-1-phenylethan-1-ol enantiomer 1 (12.3 mg, 0.030 mmol, 23.0%).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.61 (br d, *J*=6.6 Hz, 1H), 8.12 (br s, 1H), 7.97 (s, 1H), 7.76 (br t, *J*=6.8 Hz, 1H), 7.53 (s, 1H), 7.45 (br t, *J*=7.3 Hz, 1H), 7.40 - 7.30 (m, 5H), 7.29 - 7.24 (m, 1H), 7.09 (br d, *J*=7.0 Hz, 1H), 6.06 (s, 2H), 5.00 (br t, *J*=6.1 Hz, 1H), 4.29 (d, *J*=6.3 Hz, 2H).

MS ESI m/z 415.2 $(M+H)^+$

Example 82: 2-(4-(3-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)-2-fluorophenyl)-1H-pyrazol-1-yl)-1-phenylethan-1-ol enantiomer 2



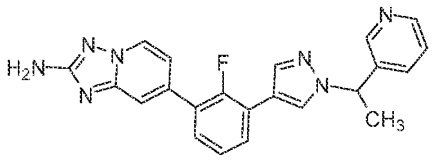
enantiomer 2

The title compound 2-(4-(3-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)-2-fluorophenyl)-1H-pyrazol-1-yl)-1-phenylethan-1-ol enantiomer 2 (13 mg, 0.030 mmol, 24%) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 81.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.61 (d, *J*=7.0 Hz, 1H), 8.12 (s, 1H), 7.97 (s, 1H), 7.76 (br t, *J*=7.2 Hz, 1H), 7.53 (s, 1H), 7.45 (br t, *J*=6.7 Hz, 1H), 7.40 - 7.30 (m, 5H), 7.30 - 7.24 (m, 1H), 7.09 (br d, *J*=6.6 Hz, 1H), 6.06 (s, 2H), 5.00 (t, *J*=6.2 Hz, 1H), 4.29 (d, *J*=6.3 Hz, 2H).

MS ESI m/z 415.0 $(M+H)^+$

Example 83: 7-(2-fluoro-3-(1-(1-(pyridin-3-yl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

83A: *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(1-(1-(pyridin-3-yl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: To a dry reaction vial under nitrogen was added 3-(1-(4-iodo-1H-pyrazol-1-yl)ethyl)pyridine (100 mg, 0.334 mmol), 3-bromo-2-fluorophenylboronic acid (77 mg, 0.35 mmol), dioxane (2 mL) and potassium phosphate tribasic, 2M in water (670 µL, 1.340 mmol). The reaction mixture was flushed very well with argon and was then treated with dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane, 99% (16 mg, 0.020 mmol). The resulting mixture was again flushed very well with argon and was securely capped and heated at 90 °C for 5 hours. The crude reaction was then treated with *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (208 mg, 0.452 mmol) and with dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II), 99% (16 mg, 0.025 mmol). The reaction mixture was purged with argon and was then heated at 90 °C for 3.5 hours. The reaction was diluted with water (5 mL) and ethyl acetate (100 mL) and the organic layer was washed with water (4 x 8 mL), brine (1 x 10 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude residue was purified by flash chromatography on silica gel, eluting with 0-100% gradient of acetone in hexanes to afford the title compound, racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(1-(1-(pyridin-3-yl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (130 mg, 0.22 mmol, 65%).

LCMS (ESI, m/z): 600.2 $[M+H]^+$.

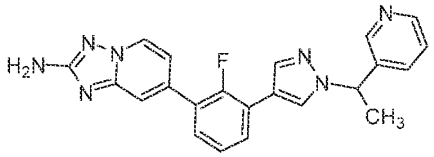
83: 7-(2-fluoro-3-(1-(1-(pyridin-3-yl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine enantiomer 1: To a solution of racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(1-(1-(pyridin-3-yl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (102 mg, 0.170 mmol) in dichloromethane (2 mL) was added neat TFA (0.75 mL, 13 mmol) and the resulting solution was allowed to stand at room temp for 55 min. The volatiles were removed under a gentle stream of nitrogen. The crude residue was purified via preparative LC/MS with the following

conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 10-50% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(2-fluoro-3-(1-(1-(pyridin-3-yl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralcel OD-H, 30 mm x 250 mm, 5 μm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% NH_4OH; Elution gradient: isocratic 25%B over 22 minutes; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (240 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(2-fluoro-3-(1-(1-(pyridin-3-yl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine, enantiomer 1 (28 mg, 0.071 mmol, 43%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.62 (d, *J*=6.9 Hz, 1H), 8.56 (d, *J*=1.9 Hz, 1H), 8.50 (dd, *J*=4.7, 1.5 Hz, 1H), 8.44 (s, 1H), 8.03 (s, 1H), 7.85 - 7.78 (m, 1H), 7.73 (dt, *J*=8.0, 1.8 Hz, 1H), 7.54 (s, 1H), 7.51 - 7.44 (m, 1H), 7.39 (dd, *J*=8.0, 4.7 Hz, 1H), 7.34 (t, *J*=7.7 Hz, 1H), 7.08 (d, *J*=7.0 Hz, 1H), 6.07 (s, 2H), 5.79 (q, *J*=7.1 Hz, 1H), 1.90 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 400.1 $(M+H)^+$

Example 84: 7-(2-fluoro-3-(1-(1-(pyridin-3-yl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



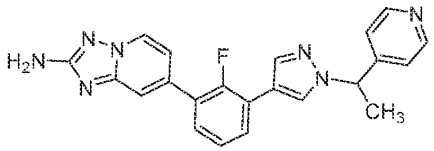
enantiomer 2

The title compound 7-(2-fluoro-3-(1-(1-(pyridin-3-yl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (26 mg, 0.066 mmol, 40%) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 83.

^{1}H NMR (500 MHz, DMSO-d6) δ 8.65 - 8.60 (m, 1H), 8.56 (d, *J*=1.3 Hz, 1H), 8.50 (dd, *J*=4.6, 1.4 Hz, 1H), 8.44 (br s, 1H), 8.03 (s, 1H), 7.81 (br t, *J*=7.2 Hz, 1H), 7.73 (br d, *J*=7.8 Hz, 1H), 7.54 (s, 1H), 7.50 - 7.45 (m, 1H), 7.39 (dd, *J*=7.9, 4.9 Hz, 1H), 7.34 (t, *J*=7.6 Hz, 1H), 7.08 (br d, *J*=6.8 Hz, 1H), 6.07 (s, 2H), 5.79 (q, *J*=6.9 Hz, 1H), 1.90 (br d, *J*=7.0 Hz, 3H).

MS ESI m/z 400.1 $(M+H)^+$

Example 85: 7-(2-fluoro-3-(1-(1-(pyridin-4-yl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 2

85A: 4-(1-(4-(3-bromo-2-fluorophenyl)-1H-pyrazol-1-yl)ethyl)pyridine: To a dry reaction vial under nitrogen was added 4-(1-(4-iodo-1H-pyrazol-1-yl)ethyl)pyridine (168 mg, 0.563 mmol), 3-bromo-2-fluorophenylboronic acid (130 mg, 0.594 mmol), dioxane (5 mL) and potassium phosphate tribasic, 2.0M in water (1.15 mL, 2.30 mmol). The reaction was purged well with argon and was then treated with dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane, 99% (25 mg, 0.031 mmol). The reaction was again flushed well with argon and the vial was securely capped and heated at 90 °C for 3.5 hours. The reaction was treated with additional 3-bromo-2-fluorophenylboronic acid (30.0 mg, 0.137 mmol) and catalyst (~10 mg), purged well with argon, securely capped and heated at 90 °C for 4 hours. The reaction was diluted with water (10 mL) and ethyl acetate (100 mL) and the organic layer was washed with water (3 x 8 mL), 1 x brine (1 x 8 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude residue was purified by flash chromatography on silica gel, eluting with 0-100% gradient of ethyl acetate in hexanes to afford 4-(1-(4-(3-bromo-2-fluorophenyl)-1H-pyrazol-1-yl)ethyl)pyridine (136 mg, 0.39 mmol, 69.7%).

MS ESI m/z 345.9, 347.8 $(M+H)^+$

85B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(1-(1-(pyridin-4-yl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: To a reaction vial containing 4-

(1-(4-(3-bromo-2-fluorophenyl)-1H-pyrazol-1-yl)ethyl)pyridine (136 mg, 0.392 mmol) was added *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (195 mg, 0.424 mmol), dioxane (5 mL) and potassium phosphate tribasic, 2.0M in water (790 µL, 1.58 mmol). The mixture was purged well with argon and was treated with dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II), 99% (15 mg, 0.023 mmol), purged with argon again, and the vial was securely capped and heated at 65 °C for 3.5 hours. The reaction was diluted with water (8 mL) and ethyl acetate (100 mL) and the organic layer was washed with water (4 x 8 mL), brine (1 x 10 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness to give *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(1-(1-(pyridin-4-yl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (309 mg, 0.52 mmol, quantitative). This crude material was used in subsequent reactions without further purification.

MS ESI m/z 600.3 $(M+H)^+$

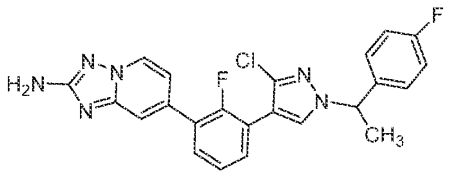
85: 7-(2-fluoro-3-(1-(1-(pyridin-4-yl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1: To a solution of *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(1-(1-(pyridin-4-yl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (309 mg, 0.515 mmol) in dichloromethane was added trifluoroacetic acid (750 µL, 9.73 mmol) and the resulting dark solution was allowed to stand at room temp for 75 minutes. The crude product was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 8%B – 48% B% B over 20.0 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(2-fluoro-3-(1-(1-(pyridin-4-yl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralpak AS-H, 30 mm x 250 mm, 20 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% NH_4OH; Elution gradient: isocratic 25%B over 20 minutes; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (240 nm). Fractions containing the first enantiomer to elute

from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(2-fluoro-3-(1-(1-(pyridin-4-yl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (27 mg, 0.068 mmol, 13%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.62 (d, *J*=7.1 Hz, 1H), 8.57 - 8.51 (m, 2H), 8.45 (s, 1H), 8.06 (s, 1H), 7.87 - 7.79 (m, 1H), 7.54 (s, 1H), 7.48 (t, *J*=7.2 Hz, 1H), 7.35 (t, *J*=7.8 Hz, 1H), 7.22 (d, *J*=6.0 Hz, 2H), 7.09 (d, *J*=7.0 Hz, 1H), 6.07 (s, 2H), 5.76 (q, *J*=7.2 Hz, 1H), 1.87 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 400.1 $(M+H)^+$

Example 86: 7-(3-(3-chloro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



enantiomer 2

86A: 3-chloro-1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole: To a dry 250 mL round bottom flask under nitrogen was added 3-chloro-4-iodo-1H-pyrazole (2.00 g, 8.76 mmol) and DMF (40 mL). The resulting solution was flushed briefly with nitrogen, then was slowly treated with sodium hydride, 60% in oil (0.420 g, 10.5 mmol) over 5 min. After the addition was complete, the reaction was stirred at room temp for 20 min and was then treated with 1-(1-bromoethyl)-4-fluorobenzene (1.85 mL, 13.2 mmol). The reaction vessel was sealed and the mixture was stirred at room temp for 4 days. The reaction was diluted with water (40 mL) and ethyl acetate (200 mL) and the organic layer was washed with water (8 x 15 mL), brine (1 x 10 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude residue was purified by flash chromatography on silica gel, eluting with 0-30% gradient of ethyl acetate in hexanes to afford 3-chloro-1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole (1.15 grams, 3.28 mmol, 37.5%).

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.33 (s, 1H), 7.28 - 7.23 (m, 2H), 7.11 - 7.04 (m, 2H), 5.43 (q, *J*=7.0 Hz, 1H), 1.88 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 350.8, 352.8 $(M+H)^+$

86B: 4-(3-bromo-2-fluorophenyl)-3-chloro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazole: To a dry reaction vial under nitrogen was added 3-chloro-1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole (200 mg, 0.571 mmol), (3-bromo-2-fluorophenyl)boronic acid (135 mg, 0.617 mmol), dioxane (6 mL) and potassium phosphate tribasic, 2.0M in water (1.15 mL, 2.30 mmol). The reaction was purged very well with argon and was then treated with dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (25 mg, 0.031 mmol). The reaction was again purged well with argon and the vial was securely capped and heated at 65 °C for 12 hours. The reaction was diluted with water (15 mL) and ethyl acetate (220 mL) and the organic phase was washed with water (4 x 15 mL), brine (1 x 10 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude residue was purified by flash chromatography on silica gel, eluting with 0-50% gradient of ethyl acetate in hexanes to afford 4-(3-bromo-2-fluorophenyl)-3-chloro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazole (110 mg, 0.28 mmol, 48.4%).

MS ESI m/z 396.7, 398.7 $(M+H)^+$

86C: *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-(3-chloro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: To a solution of 4-(3-bromo-2-fluorophenyl)-3-chloro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazole (160 mg, 0.402 mmol) and *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (220 mg, 0.478 mmol) in dioxane (4 mL) was added potassium phosphate tribasic, 2.0 M in water (800 µL, 1.60 mmol). The reaction was flushed well with argon and was then treated with dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II), 99% (20 mg, 0.031 mmol). The mixture was again purged well with argon and the vial was securely capped and heated at 65 °C for 5.5 hours. The reaction was diluted with water (8 mL) and EtOAc (100 mL) and the organic phase was washed with water (4 x 8 mL), brine (1 x 8 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude residue was purified by flash chromatography on silica gel, eluting with 0-25% gradient of ethyl acetate in dichloromethane to afford *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-(3-chloro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (57 mg, 0.088 mmol, 22%).

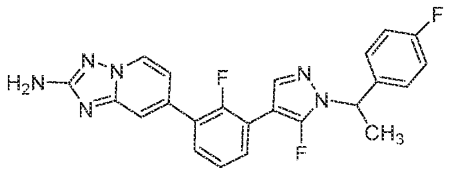
MS ESI m/z 651.1, 653.1 $(M+H)^+$

86: 7-(3-(3-chloro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2: To a solution of *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-(3-chloro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (57 mg, 0.088 mmol) in anhydrous dichloromethane (2.0 mL) was added neat TFA (2.0 mL, 26 mmol) and the reaction was allowed to stand at room temperature for 80 min. The volatiles were removed under a gentle stream of nitrogen and the crude product was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 28%B – 68%B over 20.0 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(3-(3-chloro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralpak IA, 30 mm x 250 mm, 20 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 50%B over 20 minutes; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (240 nm). Fractions containing the second enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(3-(3-chloro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (8.3 mg, 0.018 mmol, 21%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 - 8.59 (m, 1H), 8.38 - 8.28 (m, 1H), 7.70 - 7.59 (m, 2H), 7.57 - 7.52 (m, 1H), 7.48 - 7.36 (m, 3H), 7.28 - 7.17 (m, 2H), 7.08 (br d, *J*=7.0 Hz, 1H), 6.14 - 6.01 (m, 2H), 5.69 (q, *J*=6.8 Hz, 1H), 1.93 - 1.73 (m, 3H).

MS ESI m/z 451.1, 453.0 $(M+H)^+$

Example 87: 7-(2-fluoro-3-(5-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1

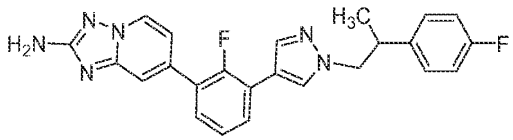


enantiomer 1

The title compound 7-(2-fluoro-3-(5-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 was prepared in a similar fashion as described for the preparation of Example 1, where 5-fluoro-1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole was used in place of 1-benzyl-4-iodo-1H-pyrazole and 3-bromo-2-fluorophenylboronic acid (61 mg, 0.28 mmol) was used in place of 3-bromophenylboronic acid in the first step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 32-72% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(2-fluoro-3-(5-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralpak IA, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 50%B over 14 minutes; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (240 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(2-fluoro-3-(5-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (3.9 mg, 0.0090 mmol, 22%).

MS ESI m/z 435.1 $(M+H)^+$

Example 88: 7-(2-fluoro-3-(1-(2-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



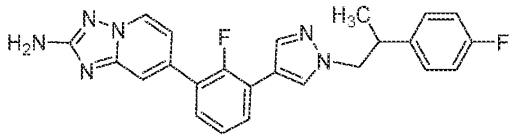
enantiomer 1

The title compound 7-(2-fluoro-3-(1-(2-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 was prepared in a similar fashion as described for the preparation of Example 1, where 1-(2-(4-fluorophenyl)propyl)-4-iodo-1H-pyrazole was used in place of 1-benzyl-4-iodo-1H-pyrazole and 3-bromo-2-fluorophenylboronic acid (73 mg, 0.33 mmol) was used in place of 3-bromophenylboronic acid in the first step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 17-57% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(2-fluoro-3-(1-(2-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralpak IA, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 50%B over 15 minutes; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (240 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(2-fluoro-3-(1-(2-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (8.8 mg, 0.020 mmol, 12%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.62 (d, *J*=6.9 Hz, 1H), 8.07 (d, *J*=1.8 Hz, 1H), 7.96 (s, 1H), 7.74 (t, *J*=6.8 Hz, 1H), 7.52 (s, 1H), 7.45 (t, *J*=7.6 Hz, 1H), 7.37 - 7.26 (m, 3H), 7.17 - 7.03 (m, 3H), 6.07 (s, 2H), 4.32 (d, *J*=7.6 Hz, 2H), 1.18 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 431.0 $(M+H)^+$

Example 89: 7-(2-fluoro-3-(1-(2-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



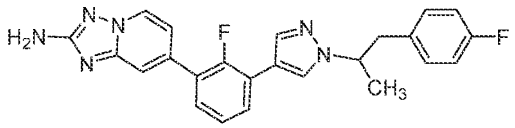
enantiomer 2

The title compound 7-(2-fluoro-3-(1-(2-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (7.3 mg, 0.017 mmol, 9.9%) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 88.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.62 (d, *J*=6.9 Hz, 1H), 8.07 (d, *J*=1.8 Hz, 1H), 7.96 (s, 1H), 7.78 - 7.69 (m, 1H), 7.52 (s, 1H), 7.48 - 7.41 (m, 1H), 7.37 - 7.25 (m, 3H), 7.17 - 7.03 (m, 3H), 6.07 (s, 2H), 4.32 (d, *J*=7.6 Hz, 2H), 1.18 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 431.2 $(M+H)^+$

Example 90: 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)propan-2-yl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

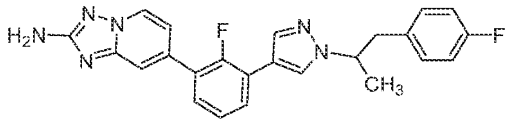
The title compound 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)propan-2-yl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 was prepared in a similar fashion as described for the preparation of Example 1, where 1-(1-(4-fluorophenyl)propan-2-yl)-4-iodo-1H-pyrazole was used in place of 1-benzyl-4-iodo-1H-pyrazole and 3-bromo-2-fluorophenylboronic acid (150 mg, 0.69 mmol) was used in place of 3-bromophenylboronic acid in the first step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water

with 10-mM ammonium acetate; Gradient: 20-60% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)propan-2-yl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralpak AD-H, 21 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 30%B over 30 minutes; Flow Rate: 75 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (254 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)propan-2-yl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (15 mg, 0.035 mmol, 19%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.59 (br d, *J*=7.0 Hz, 1H), 8.05 (br s, 1H), 7.94 (s, 1H), 7.72 (br t, *J*=7.2 Hz, 1H), 7.51 (s, 1H), 7.42 (br t, *J*=7.4 Hz, 1H), 7.35 - 7.26 (m, 1H), 7.12 - 7.05 (m, 3H), 7.05 - 6.94 (m, 2H), 6.04 (s, 2H), 4.82 - 4.51 (m, 1H), 3.13 (br d, *J*=9.1 Hz, 1H), 3.09 - 3.01 (m, 1H), 1.46 (d, *J*=6.6 Hz, 3H).

MS ESI m/z 431.0 $(M+H)^+$

Example 91: 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)propan-2-yl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



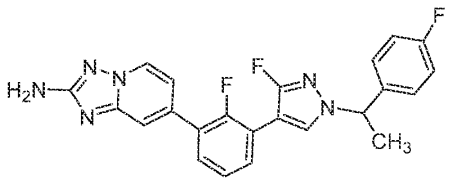
enantiomer 2

The title compound, 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)propan-2-yl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (12 mg, 0.028 mmol, 15%) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 90.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.59 (br d, *J*=7.0 Hz, 1H), 8.05 (br s, 1H), 7.94 (s, 1H), 7.72 (br t, *J*=7.3 Hz, 1H), 7.51 (s, 1H), 7.46 - 7.39 (m, 1H), 7.35 - 7.27 (m, 1H), 7.11 -

7.05 (m, 3H), 7.04 - 6.97 (m, 2H), 6.04 (s, 2H), 4.72 - 4.55 (m, 1H), 3.16 - 3.10 (m, 1H), 3.09 - 2.98 (m, 1H), 1.46 (d, *J*=6.6 Hz, 3H).
MS ESI m/z 431.0 $(M+H)^+$

Example 92: 7-(2-fluoro-3-(3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



enantiomer 2

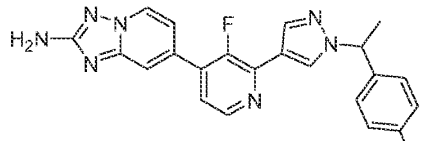
The title compound 7-(2-fluoro-3-(3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was prepared in a similar fashion as described for the preparation of Example 63, where racemic 3-fluoro-1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole (56 mg, 0.17 mmol) was used in place of *(S)*-4-(1-(4-iodo-1H-pyrazol-1-yl)ethyl)benzonitrile in the first step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 20-60% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(2-fluoro-3-(3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralpak IA, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 20%B over 30 minutes; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (254 nm). The title compound was the second isomer to elute from the column. Fractions containing the second enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to

provide 7-(2-fluoro-3-(3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (7.9 mg, 0.018 mmol, 12%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (d, *J*=7.0 Hz, 1H), 8.28 (s, 1H), 7.64 (t, *J*=7.4 Hz, 1H), 7.59 - 7.50 (m, 2H), 7.46 - 7.34 (m, 3H), 7.20 (t, *J*=8.9 Hz, 2H), 7.08 (br d, *J*=7.2 Hz, 1H), 6.08 (s, 2H), 5.68 - 5.54 (m, 1H), 1.80 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 435.1 $(M+H)^+$

Example 93: 7-(3-fluoro-2-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

93A: *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-chloro-3-fluoropyridin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: In a 40 mL Chemglass reaction vial were combined *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (224 mg, 0.486 mmol) and 2-chloro-3-fluoro-4-iodopyridine (125 mg, 0.486 mmol) in 1,4-dioxane (5 mL). To the mixture was added potassium phosphate tribasic, 2M aqueous solution (0.728 mL, 1.46 mmol) followed by addition of dichloro[1,1'-bis(di-*tert*-butylphosphino)ferrocene]palladium(II) (19 mg, 0.029 mmol). The mixture was sparged with a stream of nitrogen with stirring for 5 min, then the vial was capped and heated to 60 °C for 17 h. The crude mixture was carried directly into the next step as-is. 100% yield was assumed.

MS ESI m/z 463.9 $(M+H)^+$

93B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-fluoro-2-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: To the crude mixture from the previous step containing *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-chloro-3-fluoropyridin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (assumed 225 mg, 0.486 mmol) was added racemic 1-(1-(4-fluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (154 mg, 0.486 mmol). The resulting mixture was treated with potassium phosphate tribasic, 2M aqueous solution (0.73 mL, 1.5 mmol) and dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (20 mg, 0.024

mmol). The mixture was sparged with a stream of nitrogen with stirring for 5 min, then the vial was capped and heated to 70 °C for 19 h. The mixture was concentrated via nitrogen stream to a residue. The crude residue was reconstituted with 1:1 DCM:EtOAc (10 mL), and the resulting black suspension was filtered through a plug of Celite and rinsed through with 1:1 EtOAc:DCM. Concentration of the filtrate in vacuo gave a black oil. The black residue was dissolved in minimum DCM and loaded atop a DCM preequilibrated 24 g silica cartridge. Elution gradient 100% DCM to 100% EtOAc over 15 column volumes, hold 100% EtOAc for 6 CV. Individual fractions were checked by LCMS, and fractions containing desired m/z as either bis-N-Boc or mono-N-Boc protected material were combined and concentrated in vacuo to give a brown oil containing racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-fluoro-2-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (163 mg, 140 mmol, 29% yield). The resulting material was carried forward directly into the next step as-is.

MS ESI m/z 618.1 $(M+H)^+$

93C: 7-(3-fluoro-2-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate: A solution of *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-fluoro-2-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (163 mg, 0,140 mmol) in DCM (1 mL) was treated with TFA (0.27 mL, 0.40 g, 3.5 mmol) and the result was stirred for 75 min at RT. The mixture was concentrated via nitrogen stream to a residue. The residue was dissolved in DMF (2 mL) and filtered to provide a sample which was purified by preparative reverse phase LCMS with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 17-57% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide racemic 7-(3-fluoro-2-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (36 mg, 0.087 mmol, 62% yield).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.69 (d, *J*=6.9 Hz, 1H), 8.50 - 8.47 (m, 2H), 8.11 (s, 1H), 7.69 (s, 1H), 7.53 (t, *J*=5.3 Hz, 1H), 7.41 (dd, *J*=8.4, 5.7 Hz, 2H), 7.18 (br t, *J*=9.1 Hz, 3H), 6.16 (s, 2H), 5.80 - 5.75 (m, 1H), 1.87 (d, *J*=7.0 Hz, 3H).

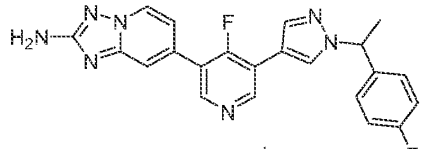
MS ESI m/z 418.0 $(M+H)^+$

93: 7-(3-fluoro-2-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1: The racemic 7-(3-fluoro-2-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (36 mg, 0.087 mmol) obtained in the previous step was further separated into individual enantiomers via preparative chiral SFC chromatography with the following conditions: Column: Daicel Chiralpak AS-H, 30 mm x 250 mm, 5 μm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% NH_4OH; Flow Rate: 100 mL/min; Elution Gradient: Isocratic 20%B over 18 min; Column Temperature: 40 °C. Fraction collection was triggered by UV (254 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(3-fluoro-2-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (11.1 mg, 0.027 mmol, 62% of the theoretical single isomer yield from preparative SFC).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.69 (d, *J*=7.1 Hz, 1H), 8.48 (d, *J*=6.4 Hz, 2H), 8.11 (s, 1H), 7.69 (s, 1H), 7.53 (t, *J*=5.5 Hz, 1H), 7.41 (t, *J*=6.5 Hz, 2H), 7.21 - 7.15 (m, 3H), 6.16 (s, 2H), 5.77 (q, *J*=7.4 Hz, 1H), 1.87 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 418.1 $(M+H)^+$

Example 94: 7-(4-fluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate

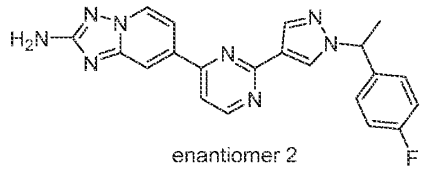


The title compound 7-(4-fluoro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate was obtained via a similar procedure as that described for Example 93, where 3,5-dichloro-4-fluoropyridine was substituted for 2-chloro-3-fluoro-4-iodopyridine in step 93A.

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.03 (d, *J*=9.5 Hz, 1H), 8.69 - 8.63 (m, 2H), 8.50 (s, 1H), 8.11 (s, 1H), 7.65 (s, 1H), 7.38 (dd, *J*=8.4, 5.6 Hz, 2H), 7.21 - 7.13 (m, 3H), 6.12 (s, 2H), 5.75 (q, *J*=7.0 Hz, 1H), 1.86 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 418.0 $(M+H)^+$

Example 95: 7-(2-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



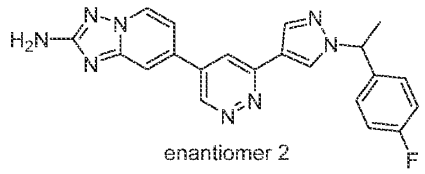
enantiomer 2

The title compound 7-(2-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained via a similar procedure as that described for Example 93, where 4-bromo-2-chloropyrimidine was substituted for 2-chloro-3-fluoro-4-iodopyridine in step 93A. This compound was the second enantiomer to elute from preparative SFC Column 1 where SFC Solvents 3 were the eluent.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.86 (d, *J*=5.3 Hz, 1H), 8.70 (d, *J*=5.2 Hz, 2H), 8.32 (s, 1H), 8.21 (s, 1H), 8.01 - 7.98 (m, 1H), 7.79 (dd, *J*=7.0, 1.8 Hz, 1H), 7.41 (dd, *J*=8.5, 5.5 Hz, 2H), 7.19 (t, *J*=8.9 Hz, 2H), 6.18 (s, 2H), 5.78 - 5.74 (m, 1H), 1.89 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 401.0 $(M+H)^+$

Example 96: 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



enantiomer 2

96A: *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloropyridazin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: In a 40 mL Chemglass reaction vial were combined *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (224 mg, 0.486 mmol) and 5-bromo-3-chloro-pyridazine (0.094 g, 0.49 mmol) in 1,4-dioxane (5 mL). To the mixture was added potassium phosphate tribasic, 2M aqueous solution (0.73 mL, 1.5 mmol) followed by addition of dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (0.020 g, 0.024 mmol). The mixture was sparged with a gentle stream of nitrogen with stirring for 5 min, then the

vial was capped and heated to 60 °C for 3 h. The crude mixture containing *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloropyridazin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate was carried forward as-is into the next step. A 100% yield was assumed.

MS ESI m/z 447.1 $(M+H)^+$

96B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: To the crude reaction mixture from the previous step containing (assumed 217 mg, 0.486 mmol) was added racemic 1-(1-(4-fluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (154 mg, 0.486 mmol). To the resulting mixture was added potassium phosphate tribasic, 2M aqueous solution (0.73 mL, 1.5 mmol) followed by addition of dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (20 mg, 0.024 mmol). The mixture was sparged with a stream of nitrogen with stirring for 5 min, then the vial was capped and heated to 80 °C for 16 h. The mixture was concentrated via nitrogen stream to a residue. The crude mixture was reconstituted with 1:1 DCM:EtOAc (10 mL) and the resulting black susension was filtered through Celite and rinsed through with 1:1 EtOAc:DCM. Concentration in vacuo gave a black oil residue which was dissolved in minimum DCM and loaded atop a hexanes preequilibrated 24 g silica cartridge. Elution gradient 100% hexanes to 100% EtOAc over 10 column vlumes, hold 100% EtOAc for 6 CV provided the desired racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (65.7 mg, approx. 0.044 mmol, approx. 41% purity) as an impure brown oil which was carried into the next step as-is without further purification.

MS ESI m/z 601.2 $(M+H)^+$

96C: 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate: A mixture of the material obtained in the previous step containing racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (65 mg, 0.044 mmol) in DCM (1 mL) was treated with TFA (0.085 mL, 0.126 g, 1.11 mmol) and the result was stirred for 75 min. The mixture was concentrated via nitrogen stream to a residue. The residue was dissolved in DMF and filtered to give a 2 mL sample which was purified via preparative reverse phase chromatography with the following conditions: Column: Waters Xbridge C18, 19 mm x 200 mm, 5 μm particles;

Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 10-50% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide racemic 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (15.2 mg, 0.038 mmol, 81% yield).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.57 (d, *J*=2.1 Hz, 1H), 8.78 (s, 1H), 8.75 (d, *J*=7.2 Hz, 1H), 8.42 (d, *J*=1.9 Hz, 1H), 8.34 (s, 1H), 8.12 (s, 1H), 7.53 (dd, *J*=7.0, 1.8 Hz, 1H), 7.39 (dd, *J*=8.4, 5.7 Hz, 2H), 7.20 (t, *J*=8.8 Hz, 2H), 6.32 - 6.10 (m, 2H), 5.78 - 5.73 (m, 1H), 1.89 (d, *J*=7.0 Hz, 3H).

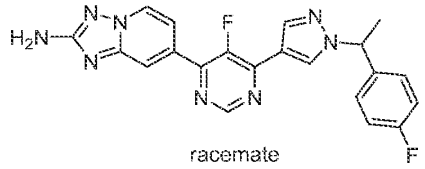
MS ESI m/z 401.0 $(M+H)^+$

96: 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2: The racemic 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (15.2 mg, 0.038 mmol) obtained in the previous step was further separated into individual enantiomers via preparative chiral SFC chromatography with the following conditions: Column: Chiralcel OJ-H, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% NH_4OH; Elution Gradient: isocratic 30%B over 22 min; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (254 nm). Fractions containing the second enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridazin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (2.5 mg, 0.0062 mmol, 33% of the theoretical single isomer yield from preparative SFC).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.57 (d, *J*=2.2 Hz, 1H), 8.78 (s, 1H), 8.75 (d, *J*=7.2 Hz, 1H), 8.42 (d, *J*=2.1 Hz, 1H), 8.34 (s, 1H), 8.11 (s, 1H), 7.52 (dd, *J*=6.9, 1.9 Hz, 1H), 7.39 (dd, *J*=8.6, 5.4 Hz, 2H), 7.20 (t, *J*=8.9 Hz, 2H), 6.19 (s, 2H), 5.75 (q, *J*=6.8 Hz, 1H), 1.89 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 401.2 $(M+H)^+$

Example 97: 7-(5-fluoro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate



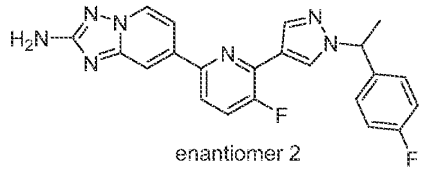
racemate

The title compound 7-(5-fluoro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate was obtained via a similar procedure as that described for Example 96, where 4,6-dichloro-5-fluoropyrimidine was substituted for 5-bromo-3-chloro-pyridazine in step 96A.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.02 (s, 1H), 8.74 (d, *J*=7.2 Hz, 1H), 8.72 (s, 1H), 8.24 (s, 1H), 8.03 (s, 1H), 7.55 (br d, *J*=6.5 Hz, 1H), 7.43 (dd, *J*=8.2, 5.9 Hz, 2H), 7.22 - 7.17 (m, 2H), 5.85 - 5.79 (m, 1H), 1.88 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 419.0 $(M+H)^+$

Example 98: 7-(5-fluoro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



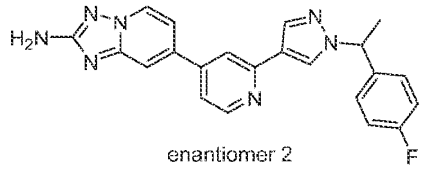
enantiomer 2

The title compound 7-(5-fluoro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained via a similar procedure as that described for Example 96, where 6-bromo-2-chloro-3-fluoropyridine was substituted for 5-bromo-3-chloro-pyridazine in step 96A. This compound was the second enantiomer to elute from preparative SFC Column 1 where SFC Solvents 3 were the eluent.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.64 - 8.59 (m, 2H), 8.18 (s, 1H), 8.13 (s, 1H), 8.08 - 8.03 (m, 1H), 7.90 - 7.85 (m, 1H), 7.73 - 7.69 (m, 1H), 7.41 (t, *J*=6.6 Hz, 2H), 7.22 - 7.16 (m, 2H), 6.07 (s, 2H), 5.81 (q, *J*=6.9 Hz, 1H), 1.89 (d, *J*=6.9 Hz, 3H).

MS ESI m/z 418.1 $(M+H)^+$

Example 99: 7-(2-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



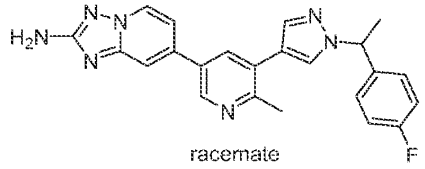
enantiomer 2

The title compound 7-(2-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained via a similar procedure as that described for Example 96, where 2-bromo-4-iodopyridine was substituted for 5-bromo-3-chloro-pyridazine in step 96A. This compound was the second enantiomer to elute from preparative SFC Column 1 where SFC Solvents 1 were the eluent.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.68 (br d, *J*=7.2 Hz, 1H), 8.64 - 8.57 (m, 2H), 8.20 (s, 1H), 8.15 (s, 1H), 7.96 (s, 1H), 7.64 (br d, *J*=4.3 Hz, 1H), 7.44 - 7.33 (m, 3H), 7.19 (br t, *J*=8.8 Hz, 2H), 5.73 - 5.67 (m, 1H), 1.87 (br d, *J*=6.9 Hz, 3H).

MS ESI m/z 400.1 $(M+H)^+$, 422.3 $(M+Na)^+$

Example 100: 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-6-methylpyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate



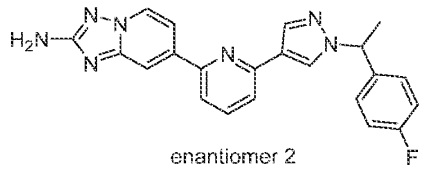
racemate

The title compound 7-(5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-6-methylpyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate was obtained via a similar procedure as that described for Example 96, where 5-bromo-3-chloro-2-methylpyridine was substituted for 5-bromo-3-chloro-pyridazine in step 96A.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.82 - 8.73 (m, 1H), 8.65 - 8.56 (m, 1H), 8.43 - 8.34 (m, 1H), 8.23 - 8.13 (m, 1H), 8.00 - 7.93 (m, 1H), 7.85 - 7.78 (m, 1H), 7.40 - 7.30 (m, 3H), 7.19 (t, *J*=8.4 Hz, 2H), 6.05 (s, 2H), 5.71 (q, *J*=6.8 Hz, 1H), 2.65 (s, 3H), 1.92 - 1.84 (m, 3H).

MS ESI m/z 414.0 $(M+H)^+$

Example 101: 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



enantiomer 2

101A: *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: In a 75 mL Chemglass pressure vessel were combined *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (2.00 g, 4.34 mmol) and 2-chloro-6-iodopyridine (1.04 g, 4.34 mmol) in 1,4-dioxane (30 mL). The solution was sparged with nitrogen gas with stirring, and potassium phosphate tribasic, 2M aqueous (13.0 mL, 26.1 mmol) was introduced. The resulting mixture was sparged with nitrogen gas with stirring for 10 min, then dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (0.177 g, 0.217 mmol) was added and the mixture was sparged for an additional 5 min with nitrogen gas. The resulting brown mixture was heated with aggressive stirring to 70 °C for 30 min. The crude reaction mixture containing *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate was carried directly into the next step as-is. A 100% yield was assumed.

MS ESI m/z 446.0 $(M+H)^+$

101B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: A solution containing racemic 1-(1-(4-fluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.44 g, 4.56 mmol) dissolved in 1,4-dioxane (5 mL) was gently sparged with nitrogen for 5 min with stirring. This solution was added via syringe under nitrogen to the crude reaction mixture from the previous step containing *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (assumed 1.94 g, 4.34 mmol). The resulting mixture was sparged with nitrogen gas for an additional 5 min while stirring. The vessel was sealed and the brown mixture was heated with aggressive stirring at 75 °C for 1 h. An additional 0.3 equivalents of racemic 1-(1-(4-fluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.412 g, 1.30 mmol) was dissolved in 1,4-dioxane (2 mL) and the resulting solution was sparged

with nitrogen gas for 5 min before being added via syringe to the reaction mixture. The mixture was reheated to 75C for 2.5 h. The crude mixture was removed from the heating bath and was concentrated in vacuo to a black residue. The residue was transferred to a separatory funnel using EtOAc (150 mL) and water (75 mL) and the mixture was shaken and phases were separated. The organic was washed with water (50 mL) and then with brine (30 mL). The organic was dried over anhydrous magnesuim sulfate, filtered and concentrated in vacuo to a black sticky oil. The residue was dissolved in minimum DCM and loaded onto a hexanes preequilibrated 120 g silica cartridge. Elution gradient 100% hexanes to 60% EtOAc in hexanes over 15 column volumes, hold 60% EtOAc in hexanes for 6 CV. Product eluted as a bell-shaped peak, eluting just before and into the 60% EtOAc hold. Clean fractions containing the desired material were combined and concentrated in vacuo to give a slightly off-white foam. Mixed fractions were resubjected to silica chromatography (100 g silica cartridge, same solvent conditions as used in the initial purification). Clean product fractions were combined and concentrated in vacuo. This repurified material was combined with the already purified material from the initial silica chromatography, and the result was concentrated in vacuo to an off-white foam solid which was placed under high vacuum overnight. Thus was obtained racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (2.031 g, 3.39 mmol, 78.0% yield).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.63 (d, *J*=7.1 Hz, 1H), 8.41 (s, 1H), 8.13 (s, 1H), 8.10 (s, 1H), 7.87 (d, *J*=7.1 Hz, 1H), 7.83 (t, *J*=7.7 Hz, 1H), 7.67 (d, *J*=7.5 Hz, 1H), 7.53 (dd, *J*=7.9, 0.7 Hz, 1H), 7.33 - 7.29 (m, 2H), 7.07 (t, *J*=8.1 Hz, 2H), 5.61 (q, *J*=7.2 Hz, 1H), 1.99 (d, *J*=7.2 Hz, 3H), 1.53 - 1.47 (m, 18H).

MS ESI m/z 600.3 $(M+H)^+$

101C: 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate: In a 40 mL Chemglass reaction vial fitted with a septum and under a blanket of nitrogen gas, a solution of racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (2.02 g, 3.38 mmol) in DCM (12 mL) was slowly treated with TFA (9.63 g, 6.50 mL, 84.0 mmol) over 1 min. Vigorous bubbling ensued, and the mixture warmed slightly. The mixture was stirred at RT for 2.5 h. The mixture was concentrated in vacuo to a thick beige oil. The material was transferred with

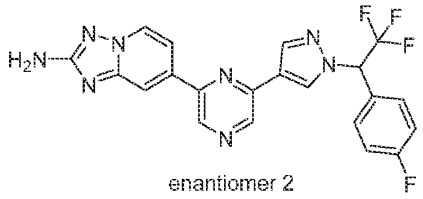
DCM into a 250 mL round bottom flask, diluted to 125 mL volume with DCM, and concentrated in vacuo to a residue. This dilution/evaporation was repeated once more. The resulting yellow sticky oil was redissolved in minimum DCM and 1,2-dichloroethane (50 mL) was added and the mixture was concentrated in vacuo, this time to provide an off-white powder. The resulting solid was redissolved in a mixture of DCM (10 mL) and 1,2-dichloroethane (50 mL) and the solution was again concentrated in vacuo to provide an off-white solid which was placed under high vacuum overnight. Thus was obtained 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate (2.168 g, 3.38 mmol, quantitative yield as a bis-TFA salt) as an off-white powder.

MS ESI m/z 400.0 $(M+H)^+$

101: 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2: The racemic 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (2.16 g, 3.38 mmol as a bis-TFA salt) obtained in the previous step was purified via preparative SFC chromatography with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 μm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% NH_4OH; Elution Gradient: isocratic 35%B over 15 min; Flow Rate: 90 mL/min; Column Temperature: 45 °C. Fraction collection was triggered by UV (220 nm). Fractions containing the second enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (615 mg, 1.54 mmol, 91.2% of the theoretical single isomer yield from preparative SFC).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.62 (d, *J*=8.3 Hz, 2H), 8.18 (s, 1H), 8.15 (s, 1H), 7.96 - 7.88 (m, 2H), 7.73 (br dd, *J*=7.0, 1.9 Hz, 1H), 7.71 (br d, *J*=7.5 Hz, 1H), 7.38 (t, *J*=6.6 Hz, 2H), 7.21 - 7.16 (m, 2H), 6.07 (s, 2H), 5.73 (q, *J*=7.0 Hz, 1H), 1.88 (d, *J*=7.0 Hz, 3H).

Example 102: 7-(6-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



enantiomer 2

102A: *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: In a 75 mL Chemglass pressure vessel were combined *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (1.40 g, 3.04 mmol) and 2-bromo-6-chloropyrazine (0.618 g, 3.19 mmol) in 1,4-dioxane (25 mL). The solution was gently sparged with nitrogen gas with stirring, and potassium phosphate tribasic, 2M aqueous (9.12 mL, 18.25 mmol) was introduced. The resulting mixture was sparged with nitrogen gas for 10 min, then dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (0.124 g, 0.152 mmol) was added and the mixture was sparged for an additional 5 min. The resulting deep brown/near black mixture was heated with aggressive stirring to 75 °C for 30 min to give a light orange solution. The crude reaction mixture containing *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate was carried directly into the next step as-is. A 100% yield was assumed.

MS ESI m/z 447.1 $(M+H)^+$

102B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: A solution containing racemic 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazole (1.501 g, 3.65 mmol) dissolved in 1,4-dioxane (5 mL) was gently sparged with nitrogen gas for 5 min with stirring. This solution was added via syringe under nitrogen to the crude reaction mixture from the previous step containing *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (assumed 1.36 g, 3.04 mmol). The resulting mixture was sparged with nitrogen gas for an additional 5 min while stirring. The mixture turned brown in color. Dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (0.124 g, 0.152 mmol) was added and the mixture was sparged with nitrogen gas for 5 more min. The vessel was sealed and the brown mixture was heated with aggressive stirring at 75 °C for 2.5 h at 75C. The mixture was transferred to a separatory funnel using EtOAc (200 mL) and water (100 mL) and the mixture was shaken and phases were separated. The organic

was washed with water (2 x 75 mL) and then with brine (30 mL). The combined aqueous phase was back-extracted with EtOAc (75 mL). The combined organic phase was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to a brown residue. The residue was dissolved in minimum DCM and loaded onto a hexanes preequilibrated 220 g silica cartridge. Elution gradient 100% hexanes to 100% EtOAc in hexanes over 12 column volumes, hold 100% EtOAc for 6 CV. Product eluted beginning approximately 65%B. Product fractions were combined and concentrated in vacuo to a slightly beige foam which was placed under high vacuum overnight to provide racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (1.00 g, 1.53 mmol, 50.4% yield) as a beige foam.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.98 (s, 1H), 8.85 (s, 1H), 8.69 (d, *J*=7.2 Hz, 1H), 8.46 (s, 1H), 8.28 (s, 1H), 8.26 (s, 1H), 7.84 (dd, *J*=7.2, 1.8 Hz, 1H), 7.61 (dd, *J*=8.7, 5.1 Hz, 2H), 7.19 (t, *J*=8.0 Hz, 2H), 6.03 (q, *J*=7.5 Hz, 1H), 1.52 (s, 18H).

MS ESI m/z 655.4 $(M+H)^+$

102C: 7-(6-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate: In a 40 mL Chemglass reaction vial were combined racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (1.00 g, 1.53 mmol) with DCM (4 mL). The stirred solution was placed under nitrogen and treated slowly with TFA (5.9 g, 4.0 mL, 52 mmol). Vigorous bubbling ensued immediately upon TFA addition. After 75 min, the mixture was concentrated via a gentle nitrogen stream overnight to a solid beige residue which was placed under high vacuum for several hours. Thus was obtained racemic 7-(6-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (1.03 g, 1.51 mmol, 99% yield as the bis-TFA salt).

MS ESI m/z 455.0 $(M+H)^+$

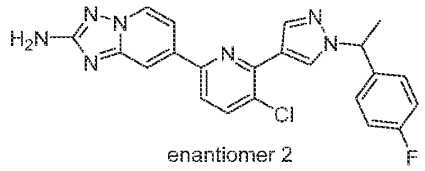
102: 7-(6-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2: The racemic 7-(6-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (1.03 g, 1.51 mmol as the bis-TFA salt) obtained in the previous step was purified via preparative SFC chromatography with the following conditions: Column: Daicel

Chiralcel OJ-H, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% NH_4OH; Elution Gradient: isocratic 25%B over 18 min; Flow Rate: 90 mL/min; Column Temperature: 45 °C. Fraction collection was triggered by UV (220 nm). Fractions containing the second enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(6-(1-(2,2,2-trifluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (248 mg, 0.546 mmol, 71.4% of the theoretical single isomer yield from preparative SFC).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.25 (s, 1H), 9.07 (s, 1H), 8.85 (s, 1H), 8.70 (d, *J*=6.9 Hz, 1H), 8.49 (s, 1H), 8.25 (d, *J*=1.2 Hz, 1H), 7.84 (dd, *J*=8.8, 5.4 Hz, 2H), 7.74 (dd, *J*=7.0, 1.9 Hz, 1H), 7.39 - 7.32 (m, 2H), 6.92 (q, *J*=8.1 Hz, 1H), 6.15 (s, 2H).

MS ESI m/z 455.2 $(M+H)^+$

Example 103: 7-(5-chloro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



enantiomer 2

103A: *tert*-butyl (*tert*-butoxycarbonyl)(7-(5,6-dichloropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: In a 40 mL Chemglass reaction vial were combined *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (200 mg, 0.435 mmol) and 6-bromo-2,3-dichloropyridine (99.0 mg, 0.435 mmol) in 1,4-dioxane (4.5 mL). To the mixture was added potassium phosphate tribasic, 2M aqueous solution (0.653 mL, 1.31 mmol) followed by addition of dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (18 mg, 0.022 mmol). The mixture was sparged with a gentle stream of nitrogen with stirring for 5 min, then the vial was capped and heated to 65 °C for 12 h. The crude mixture was diluted with EtOAc (5 mL) and filtered through a bed of celite, rinsing through with both EtOAc and DCM. The filtrate was concentrated in vacuo to a residue. The residue was dissolved in minimum DCM and loaded atop a 24 g silica cartridge. Elution gradient 100% DCM to 100% EtOAc over 15 column volumes. The product eluted in the middle of the gradient. Like fractions

were combined and concentrated in vacuo to provide *tert*-butyl (*tert*-butoxycarbonyl)(7-(5,6-dichloropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (178 mg, 0.371 mmol, 85% yield) as a yellow powder.

MS ESI m/z 479.9 $(M+H)^+$, 981.4 $(2M+Na)^+$

103B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-chloro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: In a 40 mL Chemglass reaction vial were combined racemic 1-(1-(4-fluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.044 g, 0.140 mmol) and *tert*-butyl (*tert*-butoxycarbonyl)(7-(5,6-dichloropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (0.067 g, 0.14 mmol) in 1,4-dioxane (1.5 mL). To the mixture was added potassium phosphate tribasic, 2M aqueous solution (0.21 mL, 0.42 mmol) followed by addition of dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (5.7 mg, 7.0 μmol). The mixture was sparged with a stream of nitrogen with stirring for 5 min, then the vial was capped and heated to 70 °C for 17 h. The crude mixture was diluted with EtOAc (5 mL) and the resulting black suspension was filtered through Celite and rinsed through with 1:1 EtOAc:DCM. Concentration under nitrogen stream gave a black oil residue containing racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-chloro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate. This crude material was carried forward directly into the next step without further purification. A 100% yield was assumed.

MS ESI m/z 634.1 $(M+H)^+$

103C: 7-(5-chloro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate: A mixture of the crude material obtained in the previous step containing racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-chloro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (89 mg, 0.140 mmol) in DCM (1 mL) was treated with TFA (0.27 mL, 0.40 g, 3.5 mmol) and the result was stirred at RT for 1.5 h. The mixture was concentrated via nitrogen stream to a residue. The residue was dissolved in minimum DMF and filtered to give a 2 mL sample which was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 μm particles; Mobile Phase A: 5:95 acetonitrile: water with 0.05% TFA; Mobile Phase B: 95:5 acetonitrile: water with 0.05% TFA; Gradient: 21-61% B over 20 min; Flow Rate: 20

mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide racemic 7-(5-chloro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (25.8 mg, 0.0390 mmol, 27.7% yield as a bis-TFA salt).

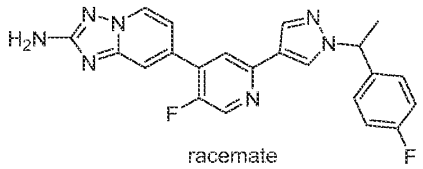
^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.74 (s, 1H), 8.70 (d, *J*=7.1 Hz, 1H), 8.33 (s, 1H), 8.21 (s, 1H), 8.07 (d, *J*=8.4 Hz, 1H), 8.02 (d, *J*=8.5 Hz, 1H), 7.82 (dd, *J*=7.1, 1.4 Hz, 1H), 7.42 (dd, *J*=8.6, 5.6 Hz, 2H), 7.19 (t, *J*=8.8 Hz, 2H), 5.80 (q, *J*=7.0 Hz, 1H), 1.88 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 434.2 $(M+H)^+$

103: 7-(5-chloro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2: The racemic 7-(5-chloro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (25.8 mg, 0.0390 mmol as a bis-TFA salt) obtained in the previous step was further separated into individual enantiomers via preparative chiral SFC chromatography with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% DEA; Elution Gradient: isocratic 25%B over 15 min; Flow Rate: 100 mL/min; Column Temperature: 50 °C. Fraction collection was triggered by UV (220 nm). Fractions containing the second enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide the title compound 7-(5-chloro-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (5.3 mg, 0.0012 mmol, 63% of the theoretical single isomer yield from preparative SFC).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.72 (s, 1H), 8.61 (d, *J*=7.0 Hz, 1H), 8.32 (s, 1H), 8.13 (s, 1H), 8.04 (d, *J*=8.4 Hz, 1H), 7.98 (d, *J*=8.5 Hz, 1H), 7.72 (dd, *J*=6.9, 1.3 Hz, 1H), 7.41 (dd, *J*=8.5, 5.6 Hz, 2H), 7.18 (t, *J*=8.8 Hz, 2H), 5.81 - 5.76 (m, 1H), 1.87 (d, *J*=7.0 Hz, 3H).
MS ESI m/z 434.1 $(M+H)^+$

Example 104: 7-(5-fluoro-2-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate



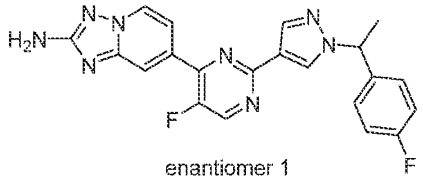
racemate

The title compound 7-(5-fluoro-2-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate was obtained via a similar procedure as that described for Example 103, where 2-chloro-5-fluoro-4-iodopyridine was substituted for 6-bromo-2,3-dichloropyridine in step 103A.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.70 (d, *J*=7.0 Hz, 1H), 8.61 (d, *J*=2.1 Hz, 1H), 8.55 (s, 1H), 8.13 (s, 1H), 8.03 (d, *J*=6.3 Hz, 1H), 7.76 (s, 1H), 7.36 (dd, *J*=8.5, 5.6 Hz, 2H), 7.23 - 7.16 (m, 3H), 6.17 (s, 2H), 5.69 (q, *J*=6.9 Hz, 1H), 1.85 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 418.1 $(M+H)^+$

Example 105: 7-(5-fluoro-2-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



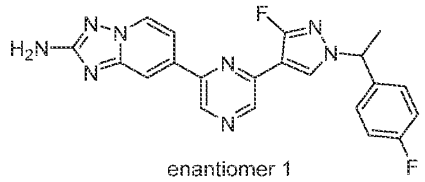
enantiomer 1

The title compound 7-(5-fluoro-2-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrimidin-4-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 was obtained via a similar procedure as that described for Example 103, where 4-bromo-2-chloro-5-fluoropyrimidine was substituted for 6-bromo-2,3-dichloropyridine in step 103A. This compound was the first enantiomer to elute from preparative SFC Column 2 where SFC Solvents 5 were the eluent.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.82 (d, *J*=3.5 Hz, 1H), 8.61 (d, *J*=7.0 Hz, 1H), 8.53 (s, 1H), 8.04 (s, 1H), 7.99 (s, 1H), 7.52 (br d, *J*=7.1 Hz, 1H), 7.29 (dd, *J*=8.5, 5.6 Hz, 2H), 7.07 (t, *J*=8.9 Hz, 2H), 6.12 (s, 2H), 5.64 (q, *J*=7.1 Hz, 1H), 1.76 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 419.0 $(M+H)^+$

Example 106: 7-(6-(3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

106A: *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: In a 8 mL Chemglass reaction vial, a mixture of *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (50 mg, 0.112 mmol), bis(pinacolato)diboron (34.1 mg, 0.134 mmol), potassium acetate (32.9 mg, 0.336 mmol), and dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (4.6 mg, 5.6 μmol) in 1,4-dioxane (0.93 mL) was gently sparged with a stream of nitrogen gas while stirring for 5 min. The vessel was then sealed and the mixture was stirred at 95 °C for 60 min. This crude reaction mixture containing *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate was taken directly into the next step as-is without purification. A 100% yield was assumed.

MS ESI m/z 457.0 $(M+H)^+$

106B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: The crude reaction mixture from the previous step containing *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (assumed 0.051 g, 0.112 mmol) was treated with racemic 3-fluoro-1-(1-(4-fluorophenyl)ethyl)-4-iodo-1H-pyrazole (0.041 g, 0.123 mmol). The resulting mixture was sparged with nitrogen by bubbling with rapid stirring for 5 min. To the mixture was added potassium phosphate tribasic, 2M aqueous solution (0.168 mL, 0.336 mmol). The mixture was sparged again with nitrogen by bubbling with rapid stirring for 5 min. Then, additional dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (4.6 mg, 5.6 μmol) was added, and the mixture was sparged with a stream of nitrogen with stirring for 5 additional min. The vial was capped and the nearly black mixture was heated to 75 °C for 2.5 h. This crude mixture containing racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(3-

fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate was concentrated via nitrogen stream to a black residue which was carried directly into the next step as-is without further manipulation. A 100% yield was assumed.

MS ESI m/z 619.2 $(M+H)^+$

106C: 7-(6-(3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate: To the crude residue from the previous step containing racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (assumed 0.0693 mg, 0.112 mmol) was added DCM (0.5 mL) followed by TFA (0.50 mL, 0.75 g, 6.5 mmol). The mixture was stirred at RT for 3 d. The crude mixture was concentrated via nitrogen stream to a residue. The residue was dissolved in 2 mL of DMF and filtered to provide a sample which was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 0.05% TFA; Mobile Phase B: 95:5 acetonitrile: water with 0.05% TFA; Gradient: 21-61% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide racemic 7-(6-(3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (25.3 mg, 0.0391 mmol, 34.2% yield as bis-TFA salt).

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.22 (br d, *J*=4.4 Hz, 1H), 8.83 (s, 1H), 8.73 (br d, *J*=2.9 Hz, 1H), 8.67 (d, *J*=7.2 Hz, 1H), 8.23 (br s, 1H), 7.73 (dd, *J*=7.0, 1.6 Hz, 1H), 7.42 (dd, *J*=8.5, 5.5 Hz, 2H), 7.23 - 7.17 (m, 2H), 5.62 (br d, *J*=6.8 Hz, 1H), 1.83 (br d, *J*=7.0 Hz, 3H).

MS ESI m/z 419.0 $(M+H)^+$

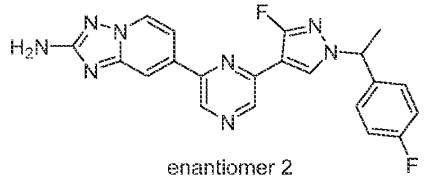
106: 7-(6-(3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1: The racemic 7-(6-(3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (25.3 mg, 0.0391 mmol as a bis-TFA salt) obtained in the previous step was further separated into individual enantiomers via preparative chiral SFC chromatography with the following conditions: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 µm particles; Mobile

Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% ammonium hydroxide; Elution Gradient: isocratic 40%B over 10 min; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (254 nm). Fractions were combined and dried via centrifugal evaporation. Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide the title compound 7-(6-(3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (6.3 mg, 0.015 mmol, 77% of the theoretical single isomer yield from preparative SFC).

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.27 - 9.24 (m, 1H), 8.84 (s, 1H), 8.77 (s, 1H), 8.71 - 8.68 (m, 1H), 8.26 (s, 1H), 7.74 (d, *J*=6.8 Hz, 1H), 7.43 (t, *J*=6.4 Hz, 2H), 7.23 - 7.19 (m, 2H), 6.15 (s, 2H), 5.66 - 5.61 (m, 1H), 1.84 (br d, *J*=6.9 Hz, 3H).

MS ESI m/z 419.0 $(M+H)^+$

Example 107: 7-(6-(3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



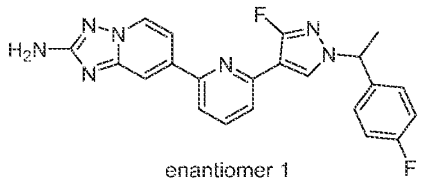
enantiomer 2

The title compound 7-(6-(3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (4.4 mg, 0.0105 mmol, 53.7% of the theoretical single isomer yield from preparative SFC) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 106.

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.26 (s, 1H), 8.84 (s, 1H), 8.77 (s, 1H), 8.70 (d, *J*=7.0 Hz, 1H), 8.26 (s, 1H), 7.74 (dd, *J*=7.1, 1.8 Hz, 1H), 7.43 (dd, *J*=8.6, 5.6 Hz, 2H), 7.21 (t, *J*=8.9 Hz, 2H), 6.24 - 6.07 (m, 2H), 5.64 (q, *J*=6.8 Hz, 1H), 1.84 (d, *J*=6.9 Hz, 3H).

MS ESI m/z 419.1 $(M+H)^+$

Example 108: 7-(6-(3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



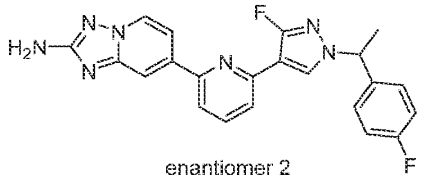
enantiomer 1

The title compound 7-(6-(3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 was obtained via a similar procedure as that described for Example 106, where *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate was substituted for *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate in step 106A. This compound was the first enantiomer to elute from preparative SFC Column 1 where SFC Solvents 2 were the eluent.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.67 - 8.61 (m, 2H), 8.18 (s, 1H), 8.03 - 7.93 (m, 2H), 7.74 (dd, *J*=7.0, 1.6 Hz, 1H), 7.58 (d, *J*=7.6 Hz, 1H), 7.43 (dd, *J*=8.6, 5.6 Hz, 2H), 7.24 - 7.17 (m, 2H), 6.20 - 5.98 (m, 2H), 5.65 - 5.60 (m, 1H), 1.84 (d, *J*=6.9 Hz, 3H).

MS ESI m/z 418.2 $(M+H)^+$

Example 109: 7-(6-(3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



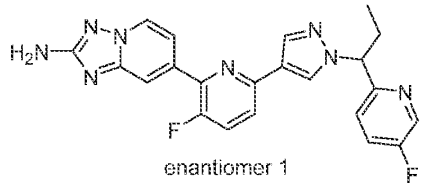
enantiomer 2

The title compound 7-(6-(3-fluoro-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 108.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.65 - 8.62 (m, 2H), 8.22 - 8.11 (m, 1H), 8.03 - 7.93 (m, 2H), 7.73 (dd, *J*=7.1, 1.8 Hz, 1H), 7.58 (d, *J*=7.9 Hz, 1H), 7.42 (t, *J*=6.6 Hz, 2H), 7.20 (t, *J*=8.3 Hz, 2H), 6.07 (s, 2H), 5.69 - 5.58 (m, 1H), 1.83 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 418.0 $(M+H)^+$

Example 110: 7-(3-fluoro-6-(1-(1-(5-fluoropyridin-2-yl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

110A: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(3-fluoro-6-(1-(1-(5-fluoropyridin-2-yl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine: In a 8 mL Chemglass reaction vial were combined 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(3-fluoro-6-(1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (100 mg, 0.268 mmol), racemic 1-(5-fluoropyridin-2-yl)propan-1-ol (108 mg, 0.696 mmol), triphenylphosphine (119 mg, 0.455 mmol) and anhydrous THF (2 mL) with stirring. The resulting light brown mixture was treated with di-*tert*-butyl azodicarboxylate (123 mg, 0.536 mmol) and the vial contents were stirred at RT for 2 h. The crude mixture was transferred to a 40 mL scintillation vial, then 1.5 g of Celite was added and the mixture was carefully concentrated in vacuo to provide a free-flowing powder. The dry-loaded material was purified by normal phase silica chromatography using a 24 g silica cartridge (elution 100% hexanes for 1 column volume (CV), then gradient 100% hexanes to 100% EtOAc over 14 CV, hold 100% EtOAc for 4 CV). Product eluted as the largest peak beginning at approximately 55% EtOAc in hexanes. The major peak fractions were combined and concentrated in vacuo to provide racemic 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(3-fluoro-6-(1-(1-(5-fluoropyridin-2-yl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (126 mg, 0.246 mmol, 92.0% yield) as a slightly yellow oil.

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.67 (d, *J*=7.6 Hz, 1H), 8.53 (s, 1H), 8.48 (d, *J*=2.7 Hz, 1H), 8.24 (s, 1H), 8.07 (s, 1H), 7.94 (dd, *J*=6.9, 1.4 Hz, 1H), 7.60 - 7.52 (m, 2H), 7.41 - 7.31 (m, 2H), 5.96 (s, 2H), 5.41 (dd, *J*=9.2, 6.4 Hz, 1H), 2.50 (dt, *J*=9.1, 7.0 Hz, 1H), 2.57 - 2.42 (m, 1H), 2.42 - 2.40 (m, 6H), 1.00 (t, *J*=7.3 Hz, 3H).

MS ESI m/z 511.5 $(M+H)^+$

110B: 7-(3-fluoro-6-(1-(1-(5-fluoropyridin-2-yl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate: A solution of racemic 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(3-fluoro-6-(1-(1-(5-fluoropyridin-2-yl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (124 mg, 0.243 mmol) in THF (3.9 mL) and

water (1 mL) was treated with TFA (0.94 mL, 1.4 g, 12 mmol). The mixture was heated to 70 °C for 5 h and was then allowed to stand at RT overnight. The mixture was concentrated in vacuo to remove most of the organic phase. The remaining deep brown residue was diluted with THF (3 mL) and then to the resulting mixture with stirring was very carefully and very slowly added hydrazine hydrate 50-60% aqueous solution. A very significant exotherm resulted. The resulting mixture was then heated with stirring to 70 °C for 100 min. The mixture was diluted with EtOAc (10 mL) and the result was shaken and phases were separated. The aqueous phase was set aside. The organic was washed with deionized water (5 mL), and this aqueous phase was combined with the aqueous phase from the first partition. The combined aqueous phases were extracted with EtOAc (10 mL). Organic phases were combined, dried over anhydrous magnesium sulfate, filtered and concentrated to a brown solid residue. The crude solid residue was dissolved in minimum DMF and filtered to make a 2 mL sample which was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 17-52% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide racemic 7-(3-fluoro-6-(1-(1-(5-fluoropyridin-2-yl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (31.3 mg, 0.0723 mmol, 29.8% yield).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.66 (d, *J*=7.0 Hz, 1H), 8.63 (s, 1H), 8.57 (d, *J*=3.0 Hz, 1H), 8.15 (s, 1H), 7.95 (s, 1H), 7.91 - 7.81 (m, 2H), 7.73 (td, *J*=8.7, 2.9 Hz, 1H), 7.58 (d, *J*=6.5 Hz, 1H), 7.40 (dd, *J*=8.8, 4.4 Hz, 1H), 6.24 - 6.02 (m, 2H), 5.53 (dd, *J*=9.4, 6.2 Hz, 1H), 2.44 - 2.28 (m, 2H), 0.87 (t, *J*=7.2 Hz, 3H).

MS ESI m/z 433.1 $(M+H)^+$

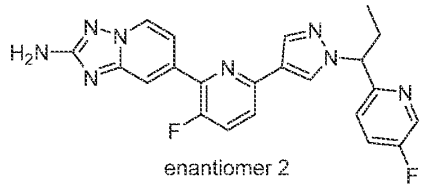
110: 7-(3-fluoro-6-(1-(1-(5-fluoropyridin-2-yl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1: The racemic 7-(3-fluoro-6-(1-(1-(5-fluoropyridin-2-yl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (31.3 mg, 0.0723 mmol) obtained in the previous step was further separated into individual enantiomers via preparative chiral SFC chromatography with the following conditions: Column: Daicel Chiralpak IH, 21 mm x 250 mm, 5 µm particles; Mobile Phase

A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% NH_4OH; Elution Gradient: isocratic 7%B over 50 min; Flow Rate: 75 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (230 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(3-fluoro-6-(1-(1-(5-fluoropyridin-2-yl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (9.7 mg, 0.022 mmol, 62.0% of the theoretical single isomer yield from preparative SFC).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.66 (d, *J*=7.1 Hz, 1H), 8.63 (s, 1H), 8.57 (d, *J*=2.8 Hz, 1H), 8.15 (s, 1H), 7.95 (s, 1H), 7.91 - 7.81 (m, 2H), 7.73 (td, *J*=8.8, 2.8 Hz, 1H), 7.57 (d, *J*=7.1 Hz, 1H), 7.40 (dd, *J*=8.7, 4.3 Hz, 1H), 6.12 (s, 2H), 5.53 (dd, *J*=9.0, 6.2 Hz, 1H), 2.43 - 2.28 (m, 2H), 0.87 (t, *J*=7.2 Hz, 3H).

MS ESI m/z 433.7 $(M+H)^+$

Example 111: 7-(3-fluoro-6-(1-(1-(5-fluoropyridin-2-yl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



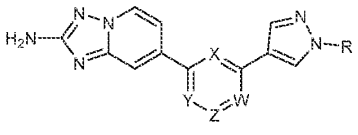
enantiomer 2

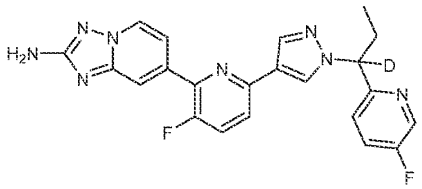
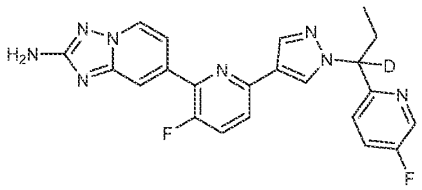
The title compound 7-(3-fluoro-6-(1-(1-(5-fluoropyridin-2-yl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (7.3 mg, 0.0169 mmol, 46.7% of the theoretical single isomer yield from preparative SFC) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 110.

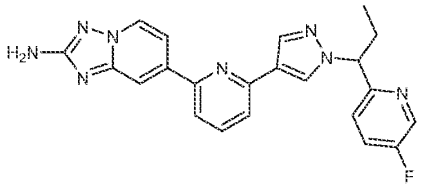
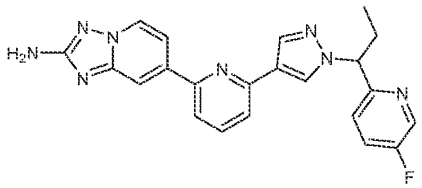
^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.66 (d, *J*=7.1 Hz, 1H), 8.63 (s, 1H), 8.57 (d, *J*=2.9 Hz, 1H), 8.15 (s, 1H), 7.95 (s, 1H), 7.91 - 7.81 (m, 2H), 7.73 (td, *J*=8.8, 3.0 Hz, 1H), 7.57 (d, *J*=6.9 Hz, 1H), 7.40 (dd, *J*=8.8, 4.3 Hz, 1H), 6.12 (s, 2H), 5.53 (dd, *J*=9.2, 6.0 Hz, 1H), 2.44 - 2.28 (m, 2H), 0.87 (t, *J*=7.4 Hz, 3H).

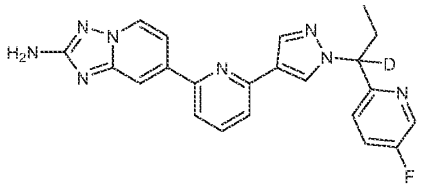
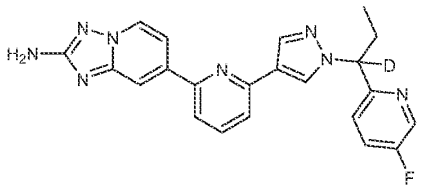
MS ESI m/z 433.2 $(M+H)^+$

Table 1: Compounds in Table 1 were prepared in a similar fashion to Examples 110 and 111.

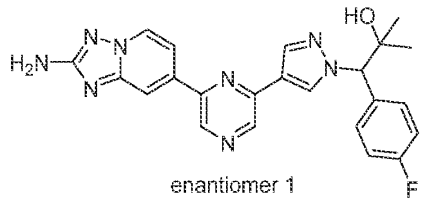


Ex No	Structure and Name	M+H+	Prep SFC Conditions if Applicable	1H NMR (500 MHz, DMSO-d6) δ
112	 7-(3-fluoro-6-(1-(1-(5-fluoropyridin-2-yl)propyl-1-*d*)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	434.2	Column 8 Solvents 3 First Eluted Isomer	1H NMR (500 MHz, DMSO-d6) δ 8.66 (d, *J*=6.9 Hz, 1H), 8.63 (s, 1H), 8.57 (d, *J*=2.6 Hz, 1H), 8.15 (s, 1H), 7.95 (s, 1H), 7.92 - 7.81 (m, 2H), 7.73 (td, *J*=8.9, 3.0 Hz, 1H), 7.57 (br d, *J*=7.7 Hz, 1H), 7.41 (dd, *J*=8.9, 4.3 Hz, 1H), 6.12 (s, 2H), 2.42 - 2.28 (m, 2H), 0.87 (t, *J*=7.2 Hz, 3H).
113	 7-(3-fluoro-6-(1-(1-(5-fluoropyridin-2-yl)propyl-1-*d*)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	434.2	Column 8 Solvents 3 Second Eluted Isomer	1H NMR (500 MHz, DMSO-d6) δ 8.66 (d, *J*=7.3 Hz, 1H), 8.63 (s, 1H), 8.57 (d, *J*=2.7 Hz, 1H), 8.15 (s, 1H), 7.95 (s, 1H), 7.91 - 7.81 (m, 2H), 7.73 (td, *J*=8.9, 3.0 Hz, 1H), 7.57 (br d, *J*=7.2 Hz, 1H), 7.41 (dd, *J*=8.5, 4.7 Hz, 1H), 6.12 (s, 2H), 2.42 - 2.28 (m, 2H), 0.87 (t, *J*=7.3 Hz, 3H).

Ex No	Structure and Name	M+H$^+$	Prep SFC Conditions if Applicable	^{1}H NMR (500 MHz, DMSO-d6) δ
114	 7-(6-(1-(1-(5-fluoropyridin-2-yl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	415.1	Column 1 Solvents 1 First Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.61 (d, *J*=7.2 Hz, 1H), 8.56 (d, *J*=2.8 Hz, 1H), 8.19 (s, 1H), 8.14 (s, 1H), 7.95 - 7.88 (m, 2H), 7.75 - 7.70 (m, 3H), 7.40 (dd, *J*=8.8, 4.5 Hz, 1H), 6.06 (s, 2H), 5.53 (dd, *J*=9.0, 6.5 Hz, 1H), 2.43 - 2.29 (m, 2H), 0.87 (t, *J*=7.2 Hz, 3H).
115	 7-(6-(1-(1-(5-fluoropyridin-2-yl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	415.1	Column 1 Solvents 1 Second Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.64 - 8.54 (m, 2H), 8.20 (s, 1H), 8.15 (s, 1H), 7.97 - 7.87 (m, 2H), 7.78 - 7.68 (m, 3H), 7.40 (dd, *J*=8.8, 4.5 Hz, 1H), 6.07 (s, 2H), 5.54 (dd, *J*=9.1, 6.2 Hz, 1H), 2.45 - 2.24 (m, 2H), 0.88 (t, *J*=7.2 Hz, 3H).

Ex No	Structure and Name	M+H$^+$	Prep SFC Conditions if Applicable	^{1}H NMR (500 MHz, DMSO-d6) δ
116	 7-(6-(1-(1-(5-fluoropyridin-2-yl)propyl-1-*d*)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	416.0	Column 1 Solvents 3 First Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.66 (s, 1H), 8.61 (d, *J*=6.9 Hz, 1H), 8.56 (d, *J*=2.8 Hz, 1H), 8.19 (s, 1H), 8.14 (s, 1H), 7.96 - 7.87 (m, 2H), 7.77 - 7.69 (m, 3H), 7.41 (dd, *J*=8.7, 4.3 Hz, 1H), 6.06 (s, 2H), 2.43 - 2.28 (m, 2H), 0.87 (t, *J*=7.3 Hz, 3H).
117	 7-(6-(1-(1-(5-fluoropyridin-2-yl)propyl-1-*d*)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	416.1	Column 1 Solvents 3 Second Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.68 (s, 1H), 8.62 (d, *J*=7.0 Hz, 1H), 8.57 (s, 1H), 8.20 (s, 1H), 8.15 (d, *J*=1.0 Hz, 1H), 8.01 - 7.84 (m, 2H), 7.79 - 7.66 (m, 3H), 7.41 (dd, *J*=8.7, 4.4 Hz, 1H), 6.07 (s, 2H), 2.44 - 2.29 (m, 2H), 0.88 (t, *J*=7.3 Hz, 3H).

Example 118: 1-(4-(6-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol enantiomer 1



enantiomer 1

118A: methyl 2-(4-(6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-2-(4-fluorophenyl)acetate racemate: In a 20 mL scintillation vial with PTFE-lined screwcap, a stirred mixture of 7-(6-(1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (358 mg, 1.01 mmol) and potassium carbonate (278 mg, 2.01 mmol) in acetonitrile (10 mL) was treated with racemic methyl 2-bromo-2-(4-fluorophenyl)acetate (298 mg, 1.21 mmol) and the result was heated to 80 °C for 85 min. The mixture was concentrated to approximately half of its original volume under a gentle stream of nitrogen. The crude mixture was taken up in EtOAc (75 mL) and washed with 1:1 water:saturated brine (1 x 30 mL), then the organic was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to an orange residue. The crude residue was dissolved in minimum DCM and loaded atop a hexanes preequilibrated 40 g silica cartridge. Elution 100% hexanes for 1 column volume, then gradient to 100% EtOAc over 16 CV, then hold 100% EtOAc for 5 CV. Product eluted as a large peak beginning at approximately 70% EtOAc in hexanes and continuing to just before 100% EtOAc was reached. Product fractions were combined and concentrated in vacuo to give an orange residue. The material was placed under high vacuum to give a foam solid. Thus was obtained racemic methyl 2-(4-(6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-2-(4-fluorophenyl)acetate (289 mg, 0.554 mmol, 55.1% yield).

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.96 (s, 1H), 8.81 (s, 1H), 8.70 (d, *J*=7.1 Hz, 1H), 8.46 (dd, *J*=1.8, 0.8 Hz, 1H), 8.24 (s, 1H), 8.15 (s, 1H), 7.83 (dd, *J*=7.2, 1.8 Hz, 1H), 7.50 (t, *J*=6.5 Hz, 2H), 7.20 (t, *J*=7.6 Hz, 2H), 6.30 (s, 1H), 5.96 (s, 2H), 3.90 (s, 3H), 2.42 (s, 6H).

MS ESI m/z 523.2 $(M+H)^+$

118B: 1-(4-(6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol: To an ice-cold solution of racemic methyl 2-(4-(6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-2-(4-

fluorophenyl)acetate (126 mg, 0.241 mmol) in anhydrous THF (2 mL) and under a blanket of nitrogen was slowly added methylmagnesium bromide in diethyl ether, 3.0M solution (0.402 mL, 1.21 mmol). Small gas bubbles formed and bubbled out of the mixture during addition of the MeMgBr to the brown solution. The solution became deeper brown in color over time. After addition was complete, the mixture was stirred at 0 °C for 20 min. Additional methylmagnesium bromide in diethyl ether, 3.0M solution (0.201 mL, 0.603 mmol) was then added and the resulting mixture was removed from the ice bath and stirred at RT for 25 min. The mixture was quenched by slow dropwise addition of glacial acetic acid. Each added drop of AcOH produced an exotherm and significant outgassing. Addition was stopped when outgassing ceased. The mixture was transferred to a 60 mL separatory funnel with EtOAc (30 mL) and water (20 mL). The mixture was shaken and phases were separated. The organic was washed with water (20 mL x 2), then with brine (15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to an orange residue. The crude residue was loaded in minimum DCM onto a hexanes preequilibrated 24 g silica cartridge. Elution 100% hexanes for 1 column volume, then gradient 100% hexanes to 100% EtOAc over 14 CV, hold 100% EtOAc for 4 CV. Product eluted as a very broad peak beginning approximately 70%B. Fractions containing the desired product were combined and concentrated in vacuo to give impure racemic 1-(4-(6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol (112.2 mg, approx. 0.12 mmol, approx. 57% purity, approx. 51% yield) as an orange glassy solid. The impure material was carried into the next step as-is without further purification.

MS ESI m/z 523.3 $(M+H)^+$

118C: 1-(4-(6-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol racemate: In a 2-5 mL Biotage microwave vial, a mixture of racemic 1-(4-(6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol (112 mg, approx. 0.12 mmol, approx. 57% purity) and hydroxylamine hydrochloride (298 mg, 4.29 mmol) in ethanol (1.4 mL) and water (0.70 mL) were heated in the microwave reactor with stirring for 3 h at 100 °C. The mixture then stood at RT overnight. The mixture was partially concentrated via a gentle nitrogen stream to reduce volume enough to be filtered in order to prepare a 2 mL sample which was purified via preparative reverse phase

chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 μm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 15-45% B over 25 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). The material obtained from this purification was further purified via preparative reverse phase with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 μm particles; Mobile Phase A: 5:95 acetonitrile: water with 0.05% TFA; Mobile Phase B: 95:5 acetonitrile: water with 0.05% TFA; Gradient: 9-49% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 1-(4-(6-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol (24 mg, 0.036 mmol, 28% yield as a bis-TFA salt).

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.19 (s, 1H), 9.04 (s, 1H), 8.84 (s, 1H), 8.70 (d, *J*=7.1 Hz, 1H), 8.32 (s, 1H), 8.23 (s, 1H), 7.76 - 7.68 (m, 3H), 7.22 - 7.15 (m, 2H), 6.28 - 6.02 (m, 2H), 5.49 (s, 1H), 5.16 - 5.00 (m, 1H), 1.20 - 1.09 (m, 6H).

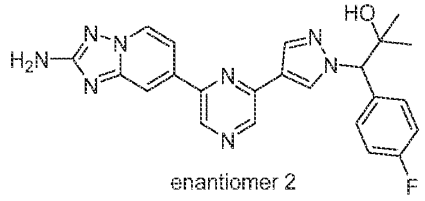
MS ESI m/z 445.2 $(M+H)^+$

118: 1-(4-(6-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol enantiomer 1: The racemic 1-(4-(6-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol (24 mg, 0.036 mmol as bis-TFA salt) obtained in the previous step was further separated into individual enantiomers via preparative chiral SFC chromatography with the following conditions: Column: Daicel Chiralpak IH, 21 mm x 250 mm, 5 μm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% NH_4OH; Elution Gradient: isocratic 20%B over 10 min; Flow Rate: 75 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (230 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 1-(4-(6-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol enantiomer 1 (7.7 mg, 0.017 mmol, 96% of the theoretical single isomer yield from preparative SFC).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.19 (s, 1H), 9.04 (s, 1H), 8.84 (s, 1H), 8.69 (d, *J*=6.7 Hz, 1H), 8.32 (s, 1H), 8.23 (s, 1H), 7.75 - 7.70 (m, 3H), 7.19 (t, *J*=8.9 Hz, 2H), 6.14 (s, 2H), 5.48 (s, 1H), 5.11 (s, 1H), 1.17 (s, 3H), 1.11 (s, 3H).

MS ESI m/z 445.2 $(M+H)^+$

Example 119: 1-(4-(6-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol enantiomer 2



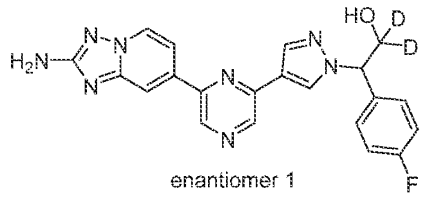
enantiomer 2

The title compound 1-(4-(6-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol enantiomer 2 (5.8 mg, 0.013 mmol, 72% of the theoretical single isomer yield from preparative SFC) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 118.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.19 (s, 1H), 9.04 (s, 1H), 8.84 (s, 1H), 8.69 (d, *J*=7.0 Hz, 1H), 8.32 (s, 1H), 8.23 (s, 1H), 7.76 - 7.70 (m, 3H), 7.19 (t, *J*=8.2 Hz, 2H), 6.14 (s, 2H), 5.48 (s, 1H), 5.11 (s, 1H), 1.17 (s, 3H), 1.11 (s, 3H).

MS ESI m/z 445.2 $(M+H)^+$

Example 120: 2-(4-(6-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-2-(4-fluorophenyl)ethan-1,1-*d*$_2$-1-ol enantiomer 1



enantiomer 1

120A: 2-(4-(6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-2-(4-fluorophenyl)ethan-1,1-*d*$_2$-1-ol: To a RT solution of racemic methyl 2-(4-(6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-2-(4-fluorophenyl)acetate (126 mg, 0.241 mmol) in

MeOH (4 mL) was added sodium borodeuteride (40.4 mg, 0.965 mmol). The solution immediately effervesced heavily, slowing to an end over approximately 3 min. The originally light brown solution became deep brown over this time. After stirring 10 min at RT, the mixture had become a light orange color. The mixture was quenched by very slow and cautious addition of acetic acid (0.5 mL). The quenched mixture was transferred to a 60 mL separatory funnel with EtOAc (30 mL) and water (20 mL). The mixture was shaken and phases were separated. The organic was washed with water (20 mL x 2), then with brine (15 mL), dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to an orange residue. The crude residue was loaded in minimum DCM onto a hexanes preerquilibrated 24 g silica cartridge. Elution 100% hexanes for 1 column volume, then gradient 100% hexanes to 100% EtOAc over 14 CV, hold 100% EtOAc for 4 CV. The desired material eluted during the 100%B hold and product fractions were combined and concentrated in vacuo to provide racemic 2-(4-(6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-2-(4-fluorophenyl)ethan-1,1-d_2-1-ol (87.8 mg, 0.177 mmol, 73.3% yield).

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.96 (s, 1H), 8.81 (s, 1H), 8.69 (d, *J*=7.2 Hz, 1H), 8.47 (s, 1H), 8.26 (s, 1H), 8.10 (s, 1H), 7.83 (dd, *J*=7.2, 1.9 Hz, 1H), 7.33 - 7.29 (m, 2H), 7.18 - 7.05 (m, 2H), 5.96 (s, 2H), 5.51 (s, 1H), 2.42 (s, 6H).

MS ESI m/z 497.3 $(M+H)^+$

120B: 2-(4-(6-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-2-(4-fluorophenyl)ethan-1,1-d_2-1-ol racemate: In a 2-5 mL Biotage microwave vessel, a mixture of racemic 2-(4-(6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-2-(4-fluorophenyl)ethan-1,1-d_2-1-ol (87.0 mg, 0.175 mmol) and hydroxylamine hydrochloride (244 mg, 3.50 mmol) in ethanol (2.5 mL) and water (0.65 mL) was heated in a microwave reactor for 6.5 h at 105 °C. The mixture then stood at RT overnight. The mixture was concentrated under a gentle nitrogen stream to a solid residue. The residue was dissolved in DMSO (1 mL) with warming until solution was achieved. The solution was filtered in order to prepare a 2 mL sample which was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 7-42% B over 20 min; Flow Rate: 20

mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide racemic 2-(4-(6-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-2-(4-fluorophenyl)ethan-1,1-d_2-1-ol (46.2 mg, 0.110 mmol, 58.1 % yield).

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.19 (s, 1H), 9.01 (s, 1H), 8.80 (s, 1H), 8.69 (d, *J*=7.0 Hz, 1H), 8.32 (s, 1H), 8.26 - 8.25 (m, 1H), 7.75 (dd, *J*=7.0, 1.8 Hz, 1H), 7.44 (dd, *J*=8.5, 5.5 Hz, 2H), 7.22 - 7.17 (m, 2H), 6.20 - 6.09 (m, 2H), 5.58 (s, 1H), 5.25 - 5.16 (m, 1H).

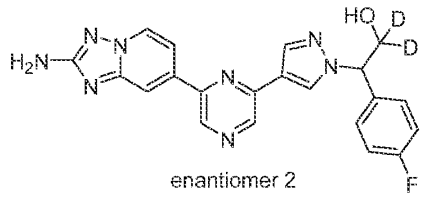
MS ESI m/z 419.2 $(M+H)^+$

120: 2-(4-(6-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-2-(4-fluorophenyl)ethan-1,1-d_2-1-ol enantiomer 1: The racemic 2-(4-(6-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-2-(4-fluorophenyl)ethan-1,1-d_2-1-ol (46.2 mg, 0.110 mmol) obtained in the previous step was further separated into individual enantiomers via preparative chiral SFC chromatography with the following conditions: Column: Daicel Chiralpak AS-H, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% DEA; Elution Gradient: isocratic 25%B over 25 min; Flow Rate: 100.00 mL/min; Column Temperature: 50 °C. Fraction collection was triggered by UV (220 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 2-(4-(6-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-2-(4-fluorophenyl)ethan-1,1-d_2-1-ol enantiomer 1 (8.7 mg, 0.021 mmol, 38% of the theoretical single isomer yield from preparative SFC).

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.19 (s, 1H), 9.01 (s, 1H), 8.80 (s, 1H), 8.68 (d, *J*=7.0 Hz, 1H), 8.32 (s, 1H), 8.25 (s, 1H), 7.77 - 7.73 (m, 1H), 7.48 - 7.40 (m, 2H), 7.20 (t, *J*=8.9 Hz, 2H), 6.14 (s, 2H), 5.58 (s, 1H), 5.23 (s, 1H).

MS ESI m/z 419.1 $(M+H)^+$

Example 121 : 2-(4-(6-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-2-(4-fluorophenyl)ethan-1,1-d_2-1-ol enantiomer 2



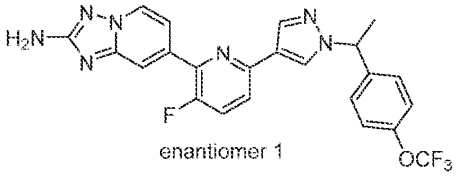
enantiomer 2

The title compound 2-(4-(6-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-2-(4-fluorophenyl)ethan-1,1-d_2-1-ol enantiomer 2 (8.8 mg, 0.021 mmol, 38% of the theoretical single isomer yield from preparative SFC) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 120.

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.18 (s, 1H), 9.01 (s, 1H), 8.80 (s, 1H), 8.68 (d, *J*=7.0 Hz, 1H), 8.32 (s, 1H), 8.25 (s, 1H), 7.75 (dd, *J*=7.0, 1.9 Hz, 1H), 7.47 - 7.41 (m, 2H), 7.19 (t, *J*=8.9 Hz, 2H), 6.14 (s, 2H), 5.58 (s, 1H), 5.23 (s, 1H).

MS ESI m/z 419.0 $(M+H)^+$

Example 122: 7-(3-fluoro-6-(1-(1-(4-(trifluoromethoxy)phenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

122A: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(3-(1-(1-(4-(trifluoromethoxy)phenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridine: In a 8 mL Chemglass reaction vial, under a blanket of nitrogen, were combined 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(3-fluoro-6-(1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (100 mg, 0.268 mmol), racemic 1-[4-(trifluoromethoxy)phenyl]ethan-1-ol (166 mg, 0.803 mmol), triphenylphosphine, polymer bound (Aldrich, catalog number 93093-25G, 3 mmol/g loading capacity) (357 mg, 1.07 mmol) and anhydrous THF (2 mL) with stirring. The resulting light brown mixture was treated with solid di-*tert*-butyl azodicarboxylate (216 mg, 0.937 mmol). The vial was agitated at RT for 3 h. The vial was then placed in a heated block at 80 degrees C for 5.5 h. The mixture then stood overnight at RT. The liquid was carefully pipetted out of the vial and filtered into a clean scintillation vial, leaving the PS-triphenylphosphine resin in the original reaction vial. To the reaction vial containing the

residual PS-triphenylphosphine was added THF (2 mL) and the contents were shaken for 10 min to rinse the resin. Again, the liquid was carefully removed, filtered and added to the original reaction liquid. Then, to the reaction vial was added additional THF (2 mL) and the contents were shaken for 10 min to rinse the resin again. The liquid was carefully removed, filtered and added to the original reaction liquid. The resin was discarded. The combined organics were concentrated via nitrogen stream to a residue. The crude residue containing racemic 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(3-(1-(1-(4-(trifluoromethoxy)phenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridine (110 mg, 0.196 mmol, 73% yield) was carried forward into the next step as-is without further purification.

MS ESI m/z 562.2 $(M+H)^+$

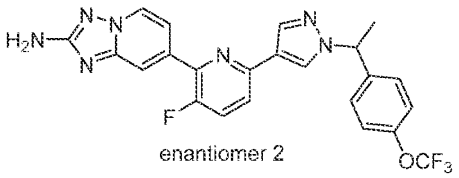
122: 7-(3-fluoro-6-(1-(1-(4-(trifluoromethoxy)phenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1: In an 8 mL Chemglass reaction vial, the crude mixture from the previous step containing racemic 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(3-fluoro-6-(1-(1-(4-(trifluoromethoxy)phenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (110 mg, 0.196 mmol) was dissolved in a mixture of THF (1 mL) and water (0.333 mL) and TFA (0.75 mL, 1.11 g, 9.73 mmol). The mixture was stirred at 60 °C for 6 h. The mixture was allowed to cool to RT, and the vial cap was carefully and slowly opened to vent any pressure. The crude mixture was concentrated via nitrogen stream to a residue overnight. The residue was redissolved in minimum DMF and filtered to give a 2 mL sample for purification. The crude material was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 29-69% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide racemic 7-(3-fluoro-6-(1-(1-(4-(trifluoromethoxy)phenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine which was then further purified via preparative SFC with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% NH_4OH; Elution Gradient:

isocratic 40%B over 12 min; Flow Rate: 85 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (230 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(3-fluoro-6-(1-(1-(4-(trifluoromethoxy)phenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (14.1 mg, 0.0291 mmol, 29.7% of the theoretical single isomer yield from preparative SFC).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.66 (d, *J*=7.0 Hz, 1H), 8.62 (s, 1H), 8.15 (s, 1H), 7.95 (s, 1H), 7.91 - 7.86 (m, 1H), 7.83 - 7.80 (m, 1H), 7.57 (d, *J*=7.9 Hz, 1H), 7.43 (d, *J*=8.7 Hz, 2H), 7.35 (d, *J*=8.1 Hz, 2H), 6.12 (s, 2H), 5.77 (q, *J*=6.7 Hz, 1H), 1.88 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 484.1 $(M+H)^+$

Example 123: 7-(3-fluoro-6-(1-(1-(4-(trifluoromethoxy)phenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



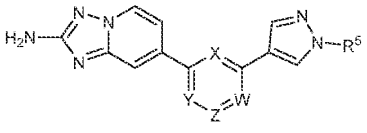
enantiomer 2

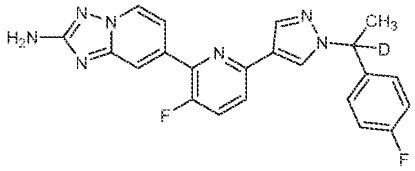
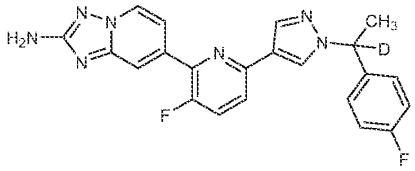
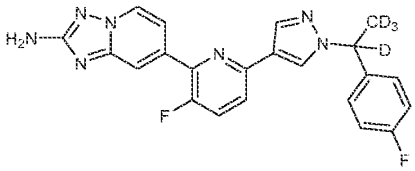
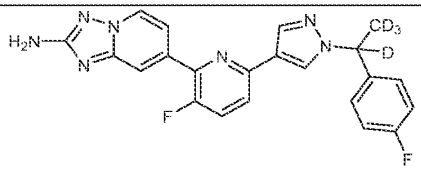
The title compound 7-(3-fluoro-6-(1-(1-(4-(trifluoromethoxy)phenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (12.4 mg, 0.0256 mmol, 26.1% of the theoretical single isomer yield from preparative SFC) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 122.

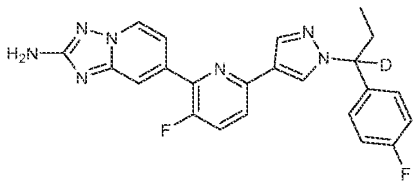
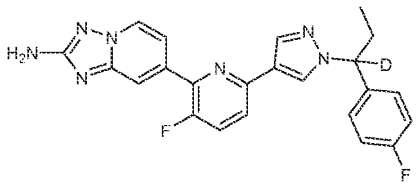
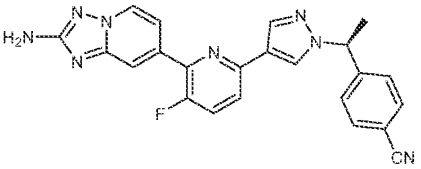
^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.66 (d, *J*=7.0 Hz, 1H), 8.62 (s, 1H), 8.15 (s, 1H), 7.95 (s, 1H), 7.91 - 7.80 (m, 2H), 7.57 (d, *J*=7.0 Hz, 1H), 7.44 (d, *J*=8.8 Hz, 2H), 7.35 (d, *J*=8.2 Hz, 2H), 6.13 (br s, 2H), 5.77 (q, *J*=7.1 Hz, 1H), 1.88 (d, *J*=7.0 Hz, 3H).

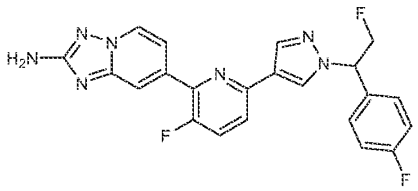
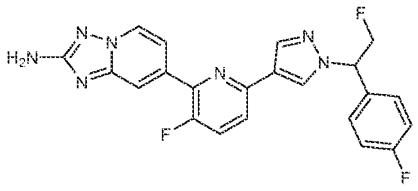
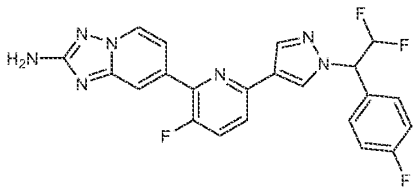
MS ESI m/z 484.3 $(M+H)^+$

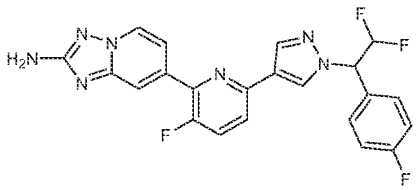
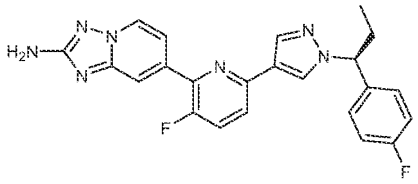
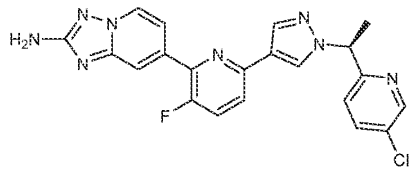
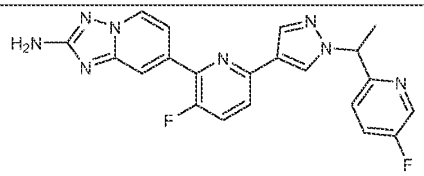
Table 2: Compounds in Table 2 were prepared in a similar fashion to Examples 122 and 123.

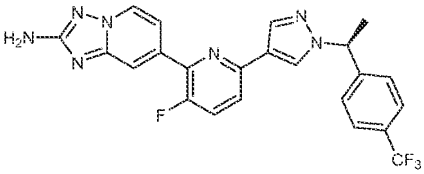
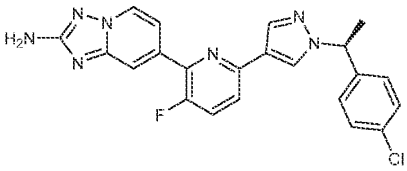
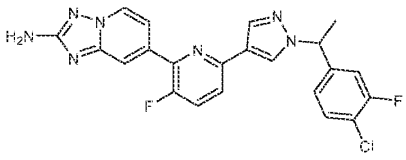


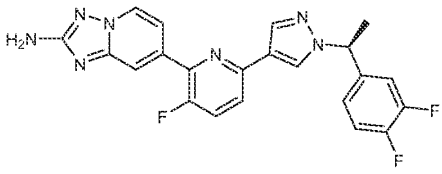
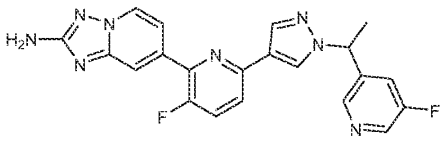
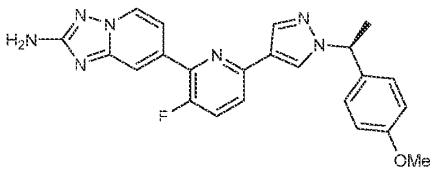
Ex No	Structure and Name	M+H+	Prep SFC Conditions if Applicable	^{1}H NMR (500 MHz, DMSO-d6) δ
124	 7-(3-fluoro-6-(1-(1-(4-fluorophenyl)ethyl-1-*d*)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	419.2	Column 1 Solvents 3 First Eluted Isomer	8.66 (d, *J*=7.0 Hz, 1H), 8.57 (s, 1H), 8.13 (s, 1H), 7.95 (s, 1H), 7.90 - 7.79 (m, 2H), 7.57 (d, *J*=7.9 Hz, 1H), 7.38 (t, *J*=6.6 Hz, 2H), 7.18 (t, *J*=7.9 Hz, 2H), 1.85 (s, 3H).
125	 7-(3-fluoro-6-(1-(1-(4-fluorophenyl)ethyl-1-*d*)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	419.0	Column 1 Solvents 3 Second Eluted Isomer	8.66 (d, *J*=7.2 Hz, 1H), 8.57 (s, 1H), 8.13 (s, 1H), 7.94 (s, 1H), 7.90 - 7.78 (m, 2H), 7.56 (d, *J*=7.0 Hz, 1H), 7.38 (t, *J*=6.5 Hz, 2H), 7.18 (t, *J*=8.0 Hz, 2H), 6.12 (s, 2H), 1.85 (s, 3H).
126	 7-(3-fluoro-6-(1-(1-(4-fluorophenyl)ethyl-1,2,2,2-d_4)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	422.1	Column 1 Solvents 2 First Eluted Isomer	8.66 (d, *J*=7.0 Hz, 1H), 8.57 (s, 1H), 8.13 (s, 1H), 7.95 (s, 1H), 7.88 (dd, *J*=11.6, 8.5 Hz, 1H), 7.82 - 7.79 (m, 1H), 7.56 (d, *J*=7.1 Hz, 1H), 7.37 (t, *J*=6.6 Hz, 2H), 7.18 (t, *J*=8.3 Hz, 2H), 6.12 (s, 2H).
127	 7-(3-fluoro-6-(1-(1-(4-fluorophenyl)ethyl-1,2,2,2-d_4)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	422.0	Column 1 Solvents 2 Second Eluted Isomer	8.66 (d, *J*=7.6 Hz, 1H), 8.57 (s, 1H), 8.13 (s, 1H), 7.95 (s, 1H), 7.91 - 7.85 (m, 1H), 7.82 - 7.79 (m, 1H), 7.56 (d, *J*=7.5 Hz, 1H), 7.37 (t, *J*=6.7 Hz, 2H), 7.18 (t,

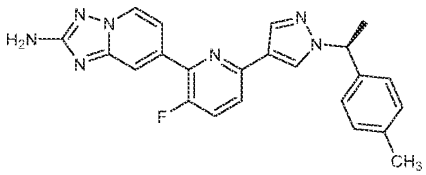
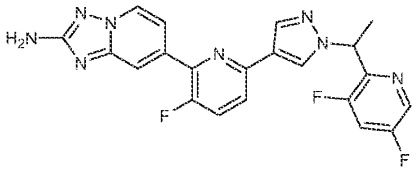
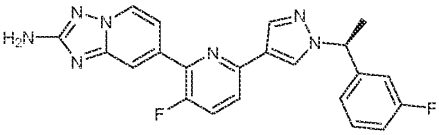
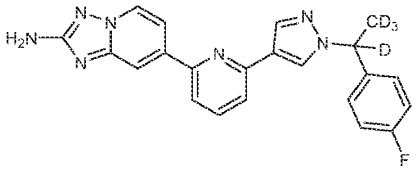
				J=8.5 Hz, 2H), 6.12 (s, 2H).
128	 7-(3-fluoro-6-(1-(1-(4-fluorophenyl)propyl-1-*d*)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	433.1	Column 1 Solvents 3 First Eluted Isomer	8.66 (d, *J*=6.8 Hz, 1H), 8.59 (s, 1H), 8.14 (s, 1H), 7.95 (s, 1H), 7.90 - 7.84 (m, 1H), 7.81 - 7.78 (m, 1H), 7.56 (d, *J*=7.0 Hz, 1H), 7.47 (t, *J*=6.4 Hz, 2H), 7.18 (t, *J*=8.4 Hz, 2H), 6.16 - 6.07 (m, 2H), 2.43 - 2.08 (m, 2H), 0.84 (t, *J*=7.3 Hz, 3H).
129	 7-(3-fluoro-6-(1-(1-(4-fluorophenyl)propyl-1-*d*)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	432.9	Column 1 Solvents 3 Second Eluted Isomer	8.66 (d, *J*=7.0 Hz, 1H), 8.59 (s, 1H), 8.14 (s, 1H), 7.95 (s, 1H), 7.90 - 7.85 (m, 1H), 7.80 (dd, *J*=8.7, 3.2 Hz, 1H), 7.57 (d, *J*=7.4 Hz, 1H), 7.47 (t, *J*=6.5 Hz, 2H), 7.18 (t, *J*=8.2 Hz, 2H), 6.21 - 6.05 (m, 2H), 2.43 - 2.09 (m, 2H), 0.84 (t, *J*=7.3 Hz, 3H).
130	 (*S*)-4-(1-(4-(6-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)-5-fluoropyridin-2-yl)-1H-pyrazol-1-yl)ethyl)benzonitrile	424.9		8.67 - 8.63 (m, 2H), 8.17 (s, 1H), 7.95 (s, 1H), 7.92 - 7.86 (m, 1H), 7.85 - 7.80 (m, 3H), 7.57 (d, *J*=7.6 Hz, 1H), 7.46 (d, *J*=8.3 Hz, 2H), 6.12 (s, 2H), 5.83 (q, *J*=6.9 Hz, 1H), 1.89 (d, *J*=7.1 Hz, 3H).

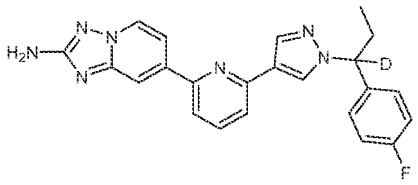
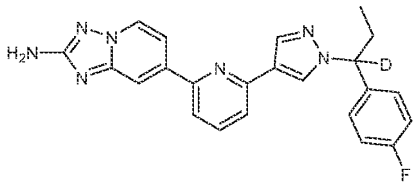
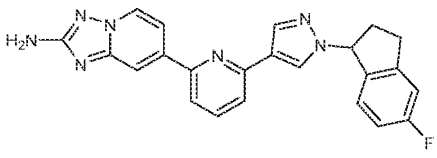
131	 7-(3-fluoro-6-(1-(2-fluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	436.1	Column 1 Solvents 2 First Eluted Isomer	8.69 - 8.63 (m, 2H), 8.23 (s, 1H), 7.95 (s, 1H), 7.92 - 7.80 (m, 2H), 7.56 (d, *J*=7.7 Hz, 1H), 7.48 (dd, *J*=8.7, 5.5 Hz, 2H), 7.23 (t, *J*=8.3 Hz, 2H), 6.12 (s, 2H), 6.02 (ddd, *J*=13.3, 9.0, 4.5 Hz, 1H), 5.39 - 5.22 (m, 1H), 5.08 - 4.91 (m, 1H).
132	 7-(3-fluoro-6-(1-(2-fluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	436.0	Column 1 Solvents 2 Second Eluted Isomer	8.70 - 8.64 (m, 2H), 8.23 (s, 1H), 7.95 (s, 1H), 7.89 (dd, *J*=11.4, 8.7 Hz, 1H), 7.84 - 7.81 (m, 1H), 7.56 (d, *J*=7.1 Hz, 1H), 7.48 (dd, *J*=8.7, 5.4 Hz, 2H), 7.23 (t, *J*=8.4 Hz, 2H), 6.12 (s, 2H), 6.02 (ddd, *J*=13.0, 8.9, 4.2 Hz, 1H), 5.40 - 5.20 (m, 1H), 5.08 - 4.90 (m, 1H).
133	 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	454.2	Column 3 Solvents 2 First Eluted Isomer	8.63 (s, 1H), 8.27 (s, 1H), 7.94 (s, 1H), 7.92 - 7.87 (m, 1H), 7.85 - 7.82 (m, 1H), 7.68 (t, *J*=6.6 Hz, 2H), 7.54 (d, *J*=7.0 Hz, 1H), 7.31 - 7.26 (m, 2H), 7.07 - 6.82 (m, 1H), 6.17 - 6.11 (m, 3H).

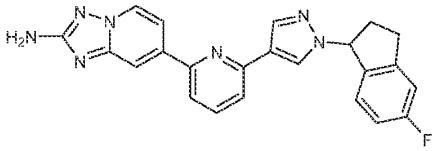
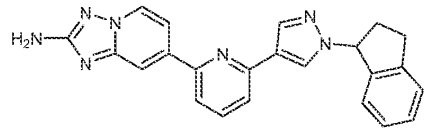
134	 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	454.1	Column 3 Solvents 2 Second Eluted Isomer	8.68 - 8.62 (m, 2H), 8.27 (s, 1H), 7.95 - 7.82 (m, 3H), 7.67 (t, *J*=6.6 Hz, 2H), 7.54 (d, *J*=8.0 Hz, 1H), 7.29 (t, *J*=8.3 Hz, 2H), 7.10 - 6.79 (m, 1H), 6.22 - 6.07 (m, 3H).
135	 (*S*)-7-(3-fluoro-6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	432.1		8.66 (d, *J*=7.2 Hz, 1H), 8.59 (s, 1H), 8.15 (s, 1H), 7.95 (s, 1H), 7.90 - 7.84 (m, 1H), 7.82 - 7.78 (m, 1H), 7.56 (d, *J*=7.2 Hz, 1H), 7.47 (dd, *J*=8.4, 5.6 Hz, 2H), 7.18 (t, *J*=8.9 Hz, 2H), 6.12 (s, 2H), 5.45 - 5.40 (m, 1H), 2.44 - 2.35 (m, 1H), 2.15 (dt, *J*=13.9, 7.0 Hz, 1H), 0.84 (t, *J*=7.1 Hz, 3H).
136	 (*S*)-7-(6-(1-(1-(5-chloropyridin-2-yl)ethyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	435.0		8.71 (d, *J*=6.9 Hz, 1H), 8.64 - 8.59 (m, 2H), 8.15 (s, 1H), 8.00 (s, 1H), 7.96 - 7.83 (m, 3H), 7.66 (br d, *J*=6.0 Hz, 1H), 7.21 (d, *J*=8.5 Hz, 1H), 5.78 (q, *J*=6.9 Hz, 1H), 1.90 (d, *J*=7.1 Hz, 3H).
137	 7-(3-fluoro-6-(1-(1-(5-fluoropyridin-2-yl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-	419.1	Column 1 Solvents 2 Second Eluted Isomer	8.65 (d, *J*=7.0 Hz, 1H), 8.60 (d, *J*=1.9 Hz, 1H), 8.57 - 8.52 (m, 1H), 8.13 (s, 1H), 7.95 (s, 1H), 7.90 - 7.80 (m, 2H),

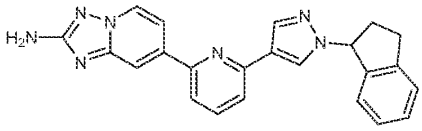
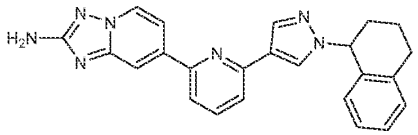
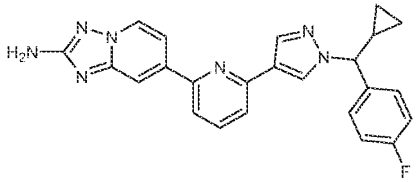
	[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2			7.74 - 7.68 (m, 1H), 7.58 (d, *J*=7.2 Hz, 1H), 7.27 (dd, *J*=8.7, 4.4 Hz, 1H), 6.11 (s, 2H), 5.78 (q, *J*=6.7 Hz, 1H), 1.89 (d, *J*=7.0 Hz, 3H).
138	 (*S*)-7-(3-fluoro-6-(1-(1-(4-(trifluoromethyl)phenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	468.1		8.72 (d, *J*=7.0 Hz, 1H), 8.64 (s, 1H), 8.18 (s, 1H), 8.02 (s, 1H), 7.93 - 7.83 (m, 2H), 7.74 - 7.66 (m, 3H), 7.50 (d, *J*=8.1 Hz, 2H), 5.83 (q, *J*=7.2 Hz, 1H), 1.90 (d, *J*=7.0 Hz, 3H).
139	 (*S*)-7-(6-(1-(1-(4-chlorophenyl)ethyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	434.0		8.66 (d, *J*=6.9 Hz, 1H), 8.59 (s, 1H), 8.14 (s, 1H), 7.95 (s, 1H), 7.90 - 7.79 (m, 2H), 7.57 (d, *J*=6.9 Hz, 1H), 7.42 (d, *J*=8.5 Hz, 2H), 7.33 (d, *J*=8.5 Hz, 2H), 6.12 (s, 2H), 5.72 (q, *J*=6.9 Hz, 1H), 1.86 (d, *J*=7.0 Hz, 3H).
140	 7-(6-(1-(1-(4-chloro-3-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	452.2	Column 1 Solvents 2 Second Eluted Isomer	8.66 (d, *J*=7.0 Hz, 1H), 8.61 (s, 1H), 8.16 (s, 1H), 7.95 (s, 1H), 7.91 - 7.85 (m, 1H), 7.83 - 7.80 (m, 1H), 7.59 - 7.55 (m, 2H), 7.38 (dd, *J*=10.6, 1.9 Hz, 1H), 7.15 (d, *J*=8.3 Hz, 1H), 6.12 (s, 2H), 5.75 (q, *J*=7.0 Hz, 1H), 1.87 (d, *J*=7.1 Hz, 3H).

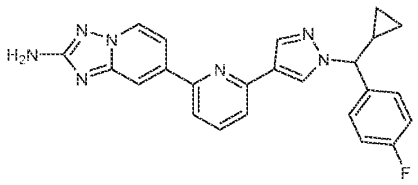
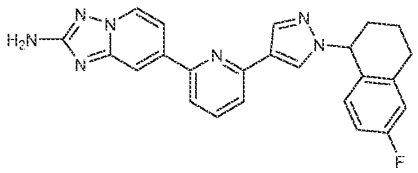
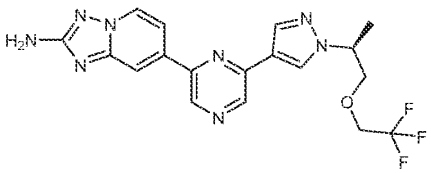
141	 (*S*)-7-(6-(1-(1-(3,4-difluorophenyl)ethyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	436.2		8.66 (d, *J*=7.0 Hz, 1H), 8.60 (s, 1H), 8.15 (s, 1H), 7.95 (s, 1H), 7.88 (dd, *J*=11.3, 8.8 Hz, 1H), 7.83 - 7.80 (m, 1H), 7.57 (d, *J*=7.1 Hz, 1H), 7.45 - 7.39 (m, 2H), 7.17 - 7.14 (m, 1H), 6.12 (s, 2H), 5.73 (q, *J*=6.8 Hz, 1H), 1.86 (d, *J*=7.0 Hz, 3H).
142	 7-(3-fluoro-6-(1-(1-(5-fluoropyridin-3-yl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	419.1	Column 3 Solvents 2 Second Eluted Isomer	8.68 - 8.62 (m, 2H), 8.52 (d, *J*=2.8 Hz, 1H), 8.44 (s, 1H), 8.17 (s, 1H), 7.95 (s, 1H), 7.91 - 7.78 (m, 2H), 7.70 (dt, *J*=9.8, 2.1 Hz, 1H), 7.60 - 7.54 (m, 1H), 6.12 (s, 2H), 5.85 (q, *J*=7.5 Hz, 1H), 1.92 (d, *J*=7.1 Hz, 3H).
143	 (*S*)-7-(3-fluoro-6-(1-(1-(4-methoxyphenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	430.1		8.65 (d, *J*=7.0 Hz, 1H), 8.51 (s, 1H), 8.11 (s, 1H), 7.94 (s, 1H), 7.90 - 7.77 (m, 2H), 7.56 (dd, *J*=6.9, 1.0 Hz, 1H), 7.27 (d, *J*=8.7 Hz, 2H), 6.90 (d, *J*=8.7 Hz, 2H), 6.12 (s, 2H), 5.63 (q, *J*=7.2 Hz, 1H), 3.73 (s, 3H), 1.84 (d, *J*=7.1 Hz, 3H).

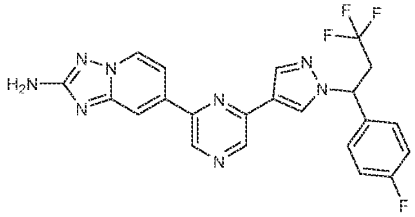
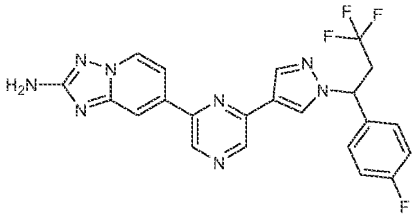
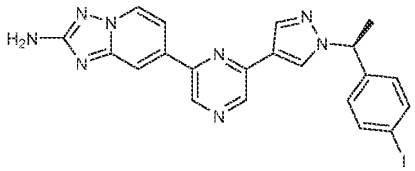
144	 (*S*)-7-(3-fluoro-6-(1-(1-(p-tolyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	414.1		8.65 (d, *J*=7.2 Hz, 1H), 8.53 (s, 1H), 8.11 (s, 1H), 7.94 (s, 1H), 7.89 - 7.84 (m, 1H), 7.82 - 7.78 (m, 1H), 7.56 (d, *J*=7.6 Hz, 1H), 7.20 (d, *J*=8.2 Hz, 2H), 7.15 (d, *J*=8.2 Hz, 2H), 6.12 (s, 2H), 5.64 (q, *J*=7.4 Hz, 1H), 2.27 (s, 3H), 1.85 (d, *J*=7.1 Hz, 3H).
145	 7-(6-(1-(1-(3,5-difluoropyridin-2-yl)ethyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	437.0	Column 1 Solvents 2 Second Eluted Isomer	8.66 (d, *J*=6.9 Hz, 1H), 8.57 (s, 1H), 8.53 (d, *J*=2.1 Hz, 1H), 8.07 (s, 1H), 8.00 - 7.93 (m, 2H), 7.90 - 7.81 (m, 2H), 7.57 (d, *J*=6.8 Hz, 1H), 6.12 (s, 2H), 6.05 - 6.00 (m, 1H), 1.90 (d, *J*=6.9 Hz, 3H).
146	 (*S*)-7-(3-fluoro-6-(1-(1-(3-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	418.1		8.71 (d, *J*=7.2 Hz, 1H), 8.61 (s, 1H), 8.16 (s, 1H), 8.01 (s, 1H), 7.89 (t, *J*=9.3 Hz, 1H), 7.84 (d, *J*=8.3 Hz, 1H), 7.67 (br d, *J*=6.9 Hz, 1H), 7.42 - 7.37 (m, 1H), 7.15 - 7.10 (m, 3H), 5.74 (q, *J*=6.7 Hz, 1H), 1.87 (d, *J*=7.1 Hz, 3H).
147		404.1	Column 1 Solvents 3 Second Eluted Isomer	8.65 - 8.59 (m, 2H), 8.18 (s, 1H), 8.15 (s, 1H), 7.94 (d, *J*=7.8 Hz, 1H), 7.90 (t, *J*=7.4 Hz, 1H), 7.73 (td, *J*=7.0, 1.8 Hz,

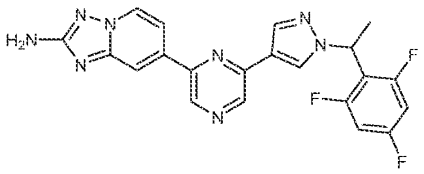
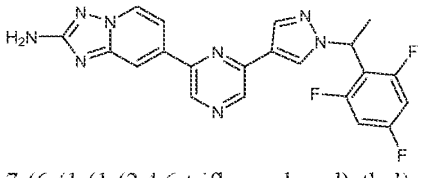
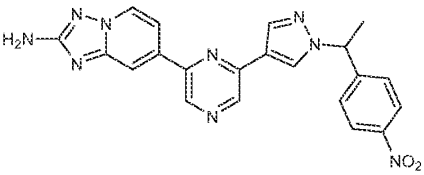
	7-(6-(1-(1-(4-fluorophenyl)ethyl-1,2,2,2-d_4)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2			1H), 7.70 (d, *J*=7.5 Hz, 1H), 7.41 - 7.36 (m, 2H), 7.18 (t, *J*=8.4 Hz, 2H), 6.07 (s, 2H).
148	 7-(6-(1-(1-(4-fluorophenyl)propyl-1-*d*)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	414.9	Column 1 Solvents 3 First Eluted Isomer	8.65 - 8.60 (m, 2H), 8.18 (s, 1H), 8.14 (s, 1H), 7.93 (d, *J*=8.0 Hz, 1H), 7.90 (d, *J*=7.4 Hz, 1H), 7.73 (d, *J*=7.1 Hz, 1H), 7.69 (d, *J*=7.4 Hz, 1H), 7.48 (dd, *J*=8.6, 5.6 Hz, 2H), 7.18 (t, *J*=8.7 Hz, 2H), 6.16 - 5.98 (m, 2H), 2.41 (dd, *J*=14.1, 7.6 Hz, 1H), 2.19 - 2.12 (m, 1H), 0.85 (t, *J*=7.2 Hz, 3H).
149	 7-(6-(1-(1-(4-fluorophenyl)propyl-1-*d*)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	415.2	Column 1 Solvents 3 Second Eluted Isomer	8.65 - 8.60 (m, 2H), 8.20 - 8.13 (m, 2H), 7.94 - 7.87 (m, 2H), 7.74 - 7.68 (m, 2H), 7.48 (t, *J*=6.6 Hz, 2H), 7.18 (t, *J*=8.8 Hz, 2H), 6.06 (s, 2H), 2.45 - 2.35 (m, 1H), 2.20 - 2.11 (m, 1H), 0.85 (t, *J*=7.2 Hz, 3H).
150	 7-(6-(1-(5-fluoro-2,3-dihydro-1H-inden-1-yl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	412.1	Column 1 Solvents 3 First Eluted Isomer	8.62 (d, *J*=7.0 Hz, 1H), 8.53 (s, 1H), 8.17 (s, 1H), 8.14 (s, 1H), 7.94 (d, *J*=7.8 Hz, 1H), 7.89 (t, *J*=7.7 Hz, 1H), 7.72 (d, *J*=6.9 Hz, 1H), 7.70 (d, *J*=7.4 Hz, 1H), 7.20 (d, *J*=9.0 Hz, 1H),

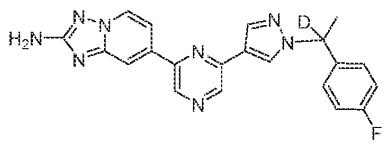
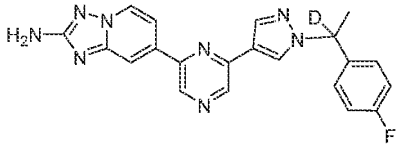
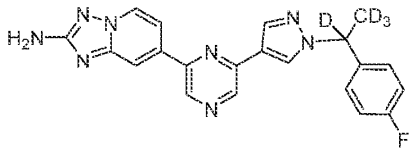
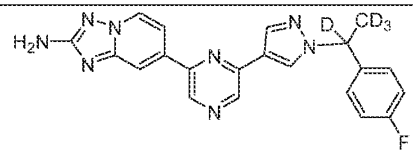
				7.16 (t, *J*=7.0 Hz, 1H), 7.01 (td, *J*=8.9, 2.2 Hz, 1H), 6.07 (s, 2H), 5.98 (t, *J*=7.1 Hz, 1H), 3.27 - 3.16 (m, 2H), 3.04 - 2.95 (m, 1H), 2.75 - 2.67 (m, 1H).
151	 7-(6-(1-(5-fluoro-2,3-dihydro-1H-inden-1-yl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	412.1	Column 1 Solvents 3 Second Eluted Isomer	8.62 (d, *J*=7.1 Hz, 1H), 8.53 (s, 1H), 8.17 (s, 1H), 8.14 (s, 1H), 7.94 (d, *J*=7.8 Hz, 1H), 7.89 (t, *J*=7.8 Hz, 1H), 7.75 - 7.67 (m, 2H), 7.20 (d, *J*=9.0 Hz, 1H), 7.16 (t, *J*=6.8 Hz, 1H), 7.01 (td, *J*=8.9, 2.6 Hz, 1H), 6.07 (s, 2H), 5.98 (t, *J*=6.9 Hz, 1H), 3.27 - 3.14 (m, 2H), 3.04 - 2.94 (m, 1H), 2.76 - 2.66 (m, 1H).
152	 7-(6-(1-(2,3-dihydro-1H-inden-1-yl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	394.1	Column 4 Solvents 4 First Eluted Isomer	8.63 (d, *J*=6.9 Hz, 1H), 8.53 (s, 1H), 8.18 - 8.14 (m, 2H), 7.96 - 7.88 (m, 2H), 7.78 - 7.67 (m, 2H), 7.37 (d, *J*=7.4 Hz, 1H), 7.30 (t, *J*=7.4 Hz, 1H), 7.24 - 7.17 (m, 1H), 7.15 - 7.09 (m, 1H), 6.01 (t, *J*=7.1 Hz, 1H), 3.26 - 3.17 (m, 2H), 3.03 - 2.95 (m, 1H), 2.72 - 2.64 (m, 1H).

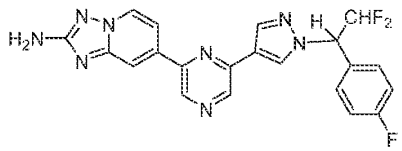
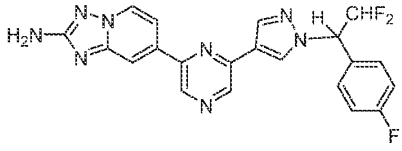
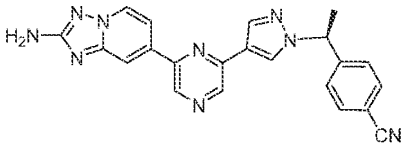
153	 7-(6-(1-(2,3-dihydro-1H-inden-1-yl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	394.0	Column 4 Solvents 4 Second Eluted Isomer	8.66 - 8.60 (m, 1H), 8.56 - 8.50 (m, 1H), 8.19 - 8.13 (m, 2H), 7.97 - 7.87 (m, 2H), 7.76 - 7.69 (m, 2H), 7.37 (d, *J*=7.4 Hz, 1H), 7.32 - 7.11 (m, 3H), 6.01 (t, *J*=7.2 Hz, 1H), 3.25 - 3.17 (m, 2H), 3.03 - 2.94 (m, 1H), 2.74 - 2.63 (m, 1H).
154	 7-(6-(1-(1,2,3,4-tetrahydronaphthalen-1-yl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	408.0	Column 4 Solvents 2 Second Eluted Isomer	8.61 (d, *J*=7.1 Hz, 1H), 8.43 (s, 1H), 8.19 (s, 1H), 8.12 (s, 1H), 7.95 - 7.87 (m, 2H), 7.71 (t, *J*=6.3 Hz, 2H), 7.24 - 7.19 (m, 2H), 7.16 - 7.04 (m, 1H), 6.80 (d, *J*=7.7 Hz, 1H), 6.06 (s, 2H), 5.74 - 5.65 (m, 1H), 2.98 - 2.91 (m, 1H), 2.86 - 2.79 (m, 1H), 2.34 - 2.21 (m, 2H), 2.12 - 1.95 (m, 1H), 1.92 - 1.78 (m, 1H).
155	 7-(6-(1-(cyclopropyl(4-fluorophenyl)methyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	426.2	Column 1 Solvents 3 First Eluted Isomer	8.69 (s, 1H), 8.62 (d, *J*=6.9 Hz, 1H), 8.17 (s, 1H), 8.15 (s, 1H), 7.98 - 7.87 (m, 2H), 7.73 (t, *J*=7.1 Hz, 2H), 7.44 (t, *J*=6.8 Hz, 2H), 7.22 - 7.16 (m, 2H), 6.07 (s, 2H), 4.80 (d, *J*=10.0 Hz, 1H), 1.92 - 1.84 (m, 1H), 0.77 - 0.66 (m,

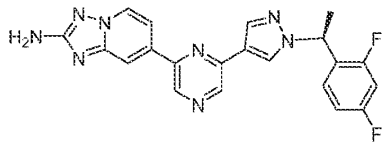
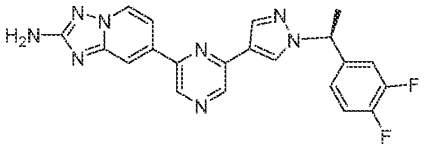
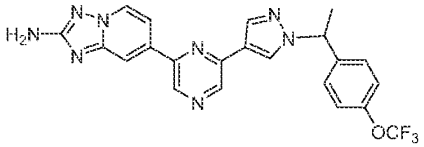
				2H), 0.57 - 0.45 (m, 2H).
156	 7-(6-(1-(cyclopropyl(4-fluorophenyl)methyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	426.2	Column 1 Solvents 3 Second Eluted Isomer	8.69 (s, 1H), 8.62 (d, *J*=7.0 Hz, 1H), 8.17 (s, 1H), 8.15 (s, 1H), 7.96 - 7.88 (m, 2H), 7.73 (t, *J*=7.1 Hz, 2H), 7.44 (t, *J*=6.6 Hz, 2H), 7.22 - 7.17 (m, 2H), 6.06 (s, 2H), 4.80 (d, *J*=10.0 Hz, 1H), 1.91 - 1.84 (m, 1H), 0.77 - 0.66 (m, 2H), 0.56 - 0.45 (m, 2H).
157	 7-(6-(1-(6-fluoro-1,2,3,4-tetrahydronaphthalen-1-yl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate	426.0		8.67 (d, *J*=7.0 Hz, 1H), 8.44 (s, 1H), 8.20 - 8.17 (m, 2H), 7.98 - 7.89 (m, 2H), 7.80 (br d, *J*=7.1 Hz, 1H), 7.72 (d, *J*=7.3 Hz, 1H), 7.28 - 6.93 (m, 3H), 6.90 - 6.83 (m, 1H), 5.67 (br t, *J*=6.8 Hz, 1H), 3.00 - 2.78 (m, 3H), 2.33 - 2.15 (m, 2H), 1.98 (dt, *J*=8.2, 5.1 Hz, 1H), 1.91 - 1.80 (m, 1H).
158	 (*S*)-7-(6-(1-(1-(2,2,2-trifluoroethoxy)propan-2-yl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	419.0		^{1}H NMR (500 MHz, DMSO-d_6) δ 9.18 (s, 1H), 9.00 (s, 1H), 8.70 - 8.64 (m, 2H), 8.29 (s, 1H), 8.25 (s, 1H), 7.75 (dd, *J*=7.1, 1.8 Hz, 1H), 6.14 (s, 2H), 4.74 - 4.68 (m, 1H), 4.11 - 3.91

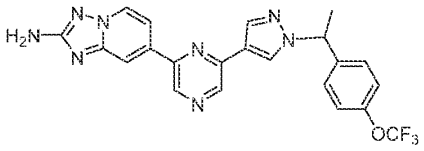
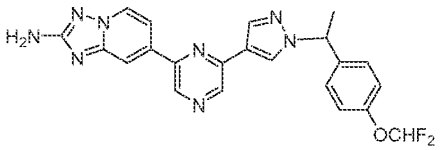
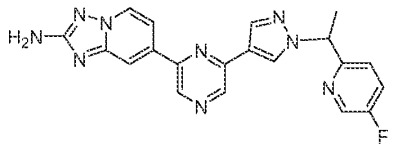
				(m, 4H), 1.47 (d, *J*=6.8 Hz, 3H).
159	 7-(6-(1-(3,3,3-trifluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	469.1	Column 2 Solvents 3 First Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.20 (s, 1H), 8.99 (s, 1H), 8.89 (s, 1H), 8.69 (d, *J*=7.1 Hz, 1H), 8.35 (s, 1H), 8.24 (s, 1H), 7.74 (dd, *J*=7.0, 1.8 Hz, 1H), 7.61 (t, *J*=6.5 Hz, 2H), 7.23 (t, *J*=8.3 Hz, 2H), 6.14 (s, 2H), 6.03 (dd, *J*=9.5, 5.1 Hz, 1H).
160	 7-(6-(1-(3,3,3-trifluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	469.1	Column 2 Solvents 3 Second Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.20 (s, 1H), 8.99 (s, 1H), 8.88 (s, 1H), 8.69 (d, *J*=6.9 Hz, 1H), 8.35 (s, 1H), 8.24 (s, 1H), 7.74 (dd, *J*=7.1, 1.8 Hz, 1H), 7.61 (dd, *J*=8.7, 5.4 Hz, 2H), 7.26 - 7.21 (m, 2H), 6.14 (s, 2H), 6.03 (dd, *J*=9.8, 4.6 Hz, 1H).
161	 (*S*)-7-(6-(1-(1-(4-iodophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	509.0		^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.20 (s, 1H), 9.02 (s, 1H), 8.78 (s, 1H), 8.71 (d, *J*=7.0 Hz, 1H), 8.32 - 8.26 (m, 2H), 7.79 (dd, *J*=7.1, 1.7 Hz, 1H), 7.73 (d, *J*=8.5 Hz, 2H), 7.13 (d, *J*=8.4 Hz, 2H), 5.71 (q, *J*=7.3 Hz, 1H),

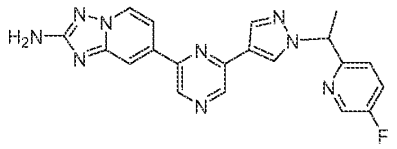
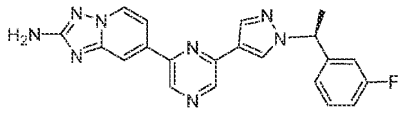
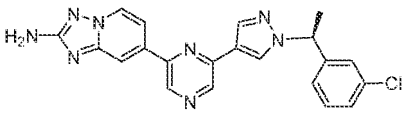
				1.87 (d, *J*=6.9 Hz, 3H).
162	 7-(6-(1-(1-(2,4,6-trifluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	437.1	Column 7 Solvents 6 First Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.19 (s, 1H), 9.05 (s, 1H), 8.81 (s, 1H), 8.68 (d, *J*=7.0 Hz, 1H), 8.26 (s, 2H), 7.76 (dd, *J*=7.1, 1.8 Hz, 1H), 7.24 (t, *J*=8.6 Hz, 2H), 6.18 - 6.10 (m, 2H), 5.97 - 5.92 (m, 1H), 2.01 (d, *J*=7.0 Hz, 3H).
163	 7-(6-(1-(1-(2,4,6-trifluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	437.1	Column 7 Solvents 6 Second Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.20 (s, 1H), 9.05 (s, 1H), 8.81 (s, 1H), 8.68 (d, *J*=6.8 Hz, 1H), 8.26 (s, 2H), 7.76 (dd, *J*=7.1, 1.9 Hz, 1H), 7.24 (t, *J*=9.0 Hz, 2H), 6.14 (s, 2H), 5.94 (q, *J*=7.2 Hz, 1H), 2.01 (d, *J*=7.2 Hz, 3H).
164	 7-(6-(1-(1-(4-nitrophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	428.0	Column 1 Solvents 2 Second Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.20 (s, 1H), 9.03 (s, 1H), 8.86 (s, 1H), 8.68 (d, *J*=6.9 Hz, 1H), 8.35 (s, 1H), 8.27 - 8.22 (m, 3H), 7.76 (dd, *J*=7.0, 1.8 Hz, 1H), 7.57 (d, *J*=8.8 Hz, 2H), 6.14 (s, 2H), 5.95 - 5.90 (m, 1H), 1.93 (d, *J*=7.0 Hz, 3H).

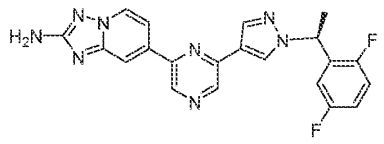
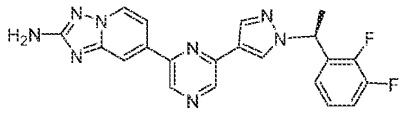
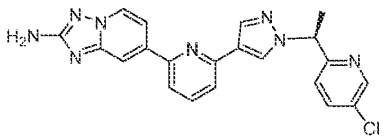
165	 7-(6-(1-(1-(4-fluorophenyl)ethyl-1-*d*)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	402.0	Column 1 Solvents 2 First Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ δ 9.19 (s, 1H), 9.01 (s, 1H), 8.78 (s, 1H), 8.68 (d, *J*=7.0 Hz, 1H), 8.30 (s, 1H), 8.25 (s, 1H), 7.75 (dd, *J*=7.0, 1.8 Hz, 1H), 7.46 - 7.34 (m, 2H), 7.19 (t, *J*=8.9 Hz, 2H), 6.14 (s, 1H), 1.88 (s, 3H).
166	 7-(6-(1-(1-(4-fluorophenyl)ethyl-1-*d*)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	402.0	Column 1 Solvents 2 Second Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.19 (s, 1H), 9.01 (s, 1H), 8.78 (s, 1H), 8.68 (d, *J*=7.0 Hz, 1H), 8.30 (s, 1H), 8.25 (d, *J*=1.0 Hz, 1H), 7.75 (dd, *J*=7.0, 1.8 Hz, 1H), 7.49 - 7.37 (m, 2H), 7.26 - 7.13 (m, 2H), 1.88 (s, 3H).
167	 7-(6-(1-(1-(4-fluorophenyl)ethyl-1,2,2,2-*d*$_4$)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	405.1	Column 1 Solvents 2 First Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.26 - 9.16 (m, 1H), 9.01 (s, 1H), 8.77 (s, 1H), 8.68 (d, *J*=7.1 Hz, 1H), 8.30 (s, 1H), 8.25 (s, 1H), 7.75 (dd, *J*=7.0, 1.8 Hz, 1H), 7.49 - 7.33 (m, 2H), 7.19 (t, *J*=8.9 Hz, 2H).
168	 7-(6-(1-(1-(4-fluorophenyl)ethyl-1,2,2,2-*d*$_4$)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	405.1	Column 1 Solvents 2 Second Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 10.02 - 10.01 (m, 1H), 9.19 (s, 1H), 9.01 (s, 1H), 8.78 (s, 1H), 8.68 (d, *J*=7.1 Hz, 1H), 8.30 (s, 1H), 8.25 (s, 1H), 7.75 (dd,

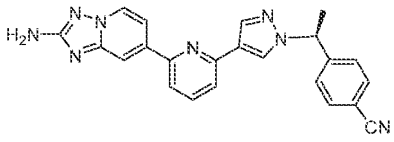
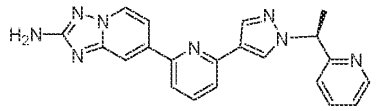
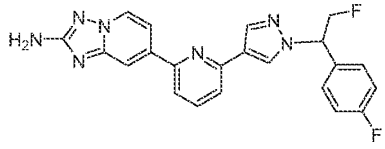
				J=7.1, 1.8 Hz, 1H), 7.44 - 7.35 (m, 2H), 7.19 (t, *J*=8.9 Hz, 2H).
169	 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	437.2	Column 2 Solvents 2 First Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.22 (s, 1H), 9.04 (s, 1H), 8.82 (s, 1H), 8.69 (d, *J*=7.0 Hz, 1H), 8.43 (s, 1H), 8.24 (d, *J*=0.9 Hz, 1H), 7.80 - 7.64 (m, 3H), 7.30 (t, *J*=8.9 Hz, 2H), 7.16 - 6.80 (m, 1H), 6.29 - 6.11 (m, 3H).
170	 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	437.2	Column 2 Solvents 2 Second Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.22 (s, 1H), 9.03 (s, 1H), 8.81 (s, 1H), 8.69 (d, *J*=6.9 Hz, 1H), 8.43 (s, 1H), 8.24 (s, 1H), 7.81 - 7.65 (m, 3H), 7.30 (t, *J*=8.8 Hz, 2H), 7.12 - 6.81 (m, 1H), 6.34 - 6.07 (m, 3H).
171	 (*S*)-4-(1-(4-(6-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)ethyl)benzonitrile	408.1		^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.20 (s, 1H), 9.02 (s, 1H), 8.84 (s, 1H), 8.68 (br d, *J*=6.5 Hz, 1H), 8.34 (s, 1H), 8.26 (s, 1H), 7.89 - 7.81 (m, 2H), 7.76 (dd, *J*=7.0, 1.8 Hz, 1H), 7.48 (d, *J*=8.2 Hz, 2H), 6.26 - 6.07 (m, 1H), 5.86 (br d, *J*=6.7 Hz, 1H), 1.91 (br d, *J*=7.0 Hz, 3H).

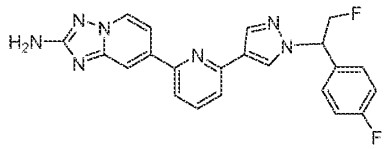
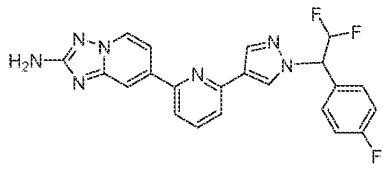
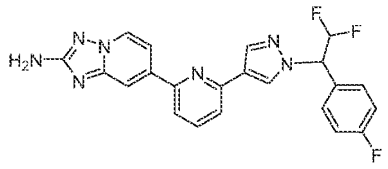
172	 (*S*)-7-(6-(1-(1-(2,4-difluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	419.1		^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.19 (s, 1H), 9.02 (s, 1H), 8.79 (s, 1H), 8.68 (br d, *J*=6.7 Hz, 1H), 8.30 (s, 1H), 8.25 (br s, 1H), 7.75 (dd, *J*=7.0, 1.7 Hz, 1H), 7.39 (td, *J*=8.5, 6.8 Hz, 1H), 7.33 - 7.21 (m, 1H), 7.17 - 7.04 (m, 1H), 5.95 (br d, *J*=7.0 Hz, 1H), 1.89 (br d, *J*=7.0 Hz, 3H).
173	 (*S*)-7-(6-(1-(1-(3,4-difluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	419.1		^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.19 (s, 1H), 9.01 (s, 1H), 8.79 (s, 1H), 8.68 (br d, *J*=6.8 Hz, 1H), 8.31 (s, 1H), 8.25 (br s, 1H), 7.76 (dd, *J*=7.0, 1.8 Hz, 1H), 7.51 - 7.37 (m, 2H), 7.20 - 7.15 (m, 1H), 5.76 (br d, *J*=6.9 Hz, 1H), 1.88 (br d, *J*=7.0 Hz, 3H).
174	 7-(6-(1-(1-(4-(trifluoromethoxy)phenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	467.1	Column 1 Solvents 2 First Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.19 (s, 1H), 9.02 (s, 1H), 8.82 (s, 1H), 8.68 (d, *J*=7.0 Hz, 1H), 8.32 (s, 1H), 8.26 (d, *J*=1.0 Hz, 1H), 7.75 (dd, *J*=7.0, 1.9 Hz, 1H), 7.46 (d, *J*=8.8 Hz, 2H), 7.36 (d, *J*=8.2 Hz, 2H), 6.14 (s, 1H), 5.80 (d, *J*=7.1 Hz,

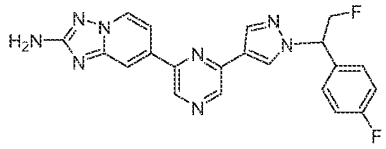
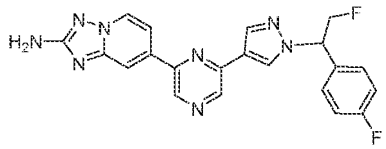
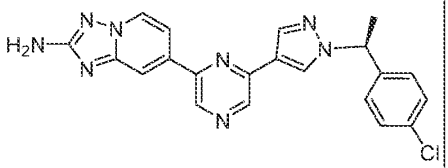
				1H), 1.90 (d, *J*=7.0 Hz, 3H).
175	 7-(6-(1-(1-(4-(trifluoromethoxy)phenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	467.1	Column 1 Solvents 2 Second Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.19 (s, 1H), 9.02 (s, 1H), 8.82 (s, 1H), 8.68 (d, *J*=7.0 Hz, 1H), 8.32 (s, 1H), 8.26 (d, *J*=1.0 Hz, 1H), 7.75 (dd, *J*=7.0, 1.8 Hz, 1H), 7.46 (d, *J*=8.7 Hz, 1H), 7.36 (br d, *J*=8.3 Hz, 1H), 6.14 (s, 1H), 5.80 (br d, *J*=7.0 Hz, 1H), 1.90 (d, *J*=7.0 Hz, 1H).
176	 7-(6-(1-(1-(4-(difluoromethoxy)phenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate	449.0		^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.19 (s, 1H), 9.03 - 8.98 (m, 1H), 8.79 (s, 1H), 8.68 (d, *J*=7.1 Hz, 1H), 8.32 - 8.23 (m, 2H), 7.75 (dd, *J*=7.0, 1.8 Hz, 1H), 7.40 (d, *J*=8.7 Hz, 2H), 7.23 - 7.15 (m, 3H), 5.75 (d, *J*=7.0 Hz, 1H), 1.89 (d, *J*=7.0 Hz, 3H).
177	 7-(6-(1-(1-(5-fluoropyridin-2-yl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	402.1	Column 1 Solvents 3 First Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.20 (s, 1H), 9.03 (s, 1H), 8.81 (s, 1H), 8.68 (d, *J*=7.0 Hz, 1H), 8.56 (d, *J*=2.9 Hz, 1H), 8.30 (s, 1H), 8.26 (d, *J*=1.1 Hz, 1H), 7.83 - 7.63 (m, 2H), 7.31 (dd, *J*=8.7, 4.4 Hz, 1H), 6.14 (s, 2H),

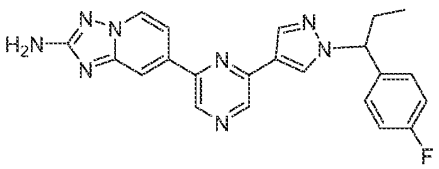
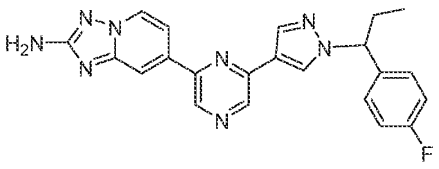
				5.83 (d, *J*=7.0 Hz, 1H), 1.92 (d, *J*=7.1 Hz, 3H).
178	 7-(6-(1-(1-(5-fluoropyridin-2-yl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	402.1	Column 1 Solvents 3 2nd Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.20 (s, 1H), 9.03 (s, 1H), 8.81 (s, 1H), 8.68 (d, *J*=7.2 Hz, 1H), 8.56 (d, *J*=2.9 Hz, 1H), 8.30 (s, 1H), 8.26 (d, *J*=1.2 Hz, 1H), 7.84 - 7.68 (m, 2H), 7.32 (dd, *J*=8.7, 4.4 Hz, 1H), 6.14 (s, 2H), 5.83 (d, *J*=7.1 Hz, 1H), 1.92 (d, *J*=7.1 Hz, 3H).
179	 (*S*)-7-(6-(1-(1-(3-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	401.0		^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.20 (s, 1H), 9.02 (s, 1H), 8.81 (s, 1H), 8.68 (d, *J*=7.0 Hz, 1H), 8.32 (s, 1H), 8.26 (s, 1H), 7.76 (dd, *J*=7.0, 1.6 Hz, 1H), 7.50 - 7.36 (m, 1H), 7.24 - 7.07 (m, 3H), 5.77 (br d, *J*=7.2 Hz, 1H), 1.90 (d, *J*=7.0 Hz, 3H).
180	 (*S*)-7-(6-(1-(1-(3-chlorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	416.9		^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.19 (s, 1H), 9.02 (s, 1H), 8.82 (s, 1H), 8.68 (br d, *J*=6.8 Hz, 1H), 8.32 (s, 1H), 8.25 (s, 1H), 7.76 (dd, *J*=7.0, 1.9 Hz, 1H), 7.44 – 7.34 (m, 3H), 7.29 (br d, *J*=7.5 Hz, 1H), 6.14 (s, 1H), 5.77 (br d, *J*=6.9 Hz,

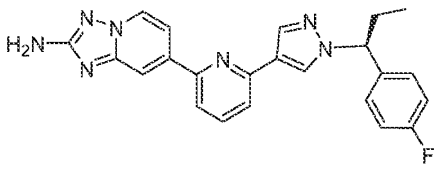
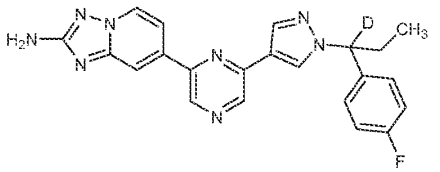
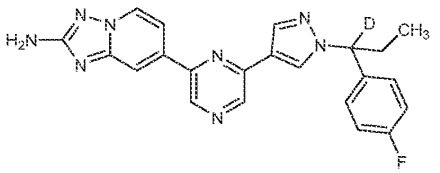
				1H), 1.89 (d, *J*=7.0 Hz, 3H).
181	 (*S*)-7-(6-(1-(1-(2,5-difluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	419.0		^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.20 (s, 1H), 9.03 (s, 1H), 8.82 (s, 1H), 8.68 (d, *J*=7.1 Hz, 1H), 8.32 (s, 1H), 8.26 (s, 1H), 7.76 (dd, *J*=7.0, 1.8 Hz, 1H), 7.31 (td, *J*=9.3, 4.4 Hz, 1H), 7.27 – 7.19 (m, 1H), 7.15 (ddd, *J*=9.0, 5.7, 3.1 Hz, 1H), 5.97 (br d, *J*=7.0 Hz, 1H), 1.90 (d, *J*=7.0 Hz, 3H).
182	 (*S*)-7-(6-(1-(1-(2,3-difluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	419.0		^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.20 (s, 1H), 9.03 (s, 1H), 8.83 (s, 1H), 8.68 (d, *J*=7.1 Hz, 1H), 8.32 (s, 1H), 8.26 (d, *J*=1.1 Hz, 1H), 7.76 (dd, *J*=7.0, 1.8 Hz, 1H), 7.40 (br d, *J*=8.8 Hz, 1H), 7.28 - 7.18 (m, 1H), 7.12 (br t, *J*=7.0 Hz, 1H), 6.03 (d, *J*=7.0 Hz, 1H), 1.92 (d, *J*=7.1 Hz, 3H).
183	 (*S*)-7-(6-(1-(1-(5-chloropyridin-2-yl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	417.0		^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.69 - 8.65 (m, 1H), 8.63 - 8.59 (m, 2H), 8.20 (s, 1H), 8.15 (s, 1H), 8.00 - 7.85 (m, 3H), 7.77 - 7.66 (m, 2H), 7.20 (d, *J*=8.5 Hz, 1H), 5.79 (br d, *J*=7.0

				Hz, 1H), 1.91 (d, *J*=7.0 Hz, 3H).
184	 (*S*)-4-(1-(4-(6-(2-amino-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyridin-2-yl)-1H-pyrazol-1-yl)ethyl)benzonitrile	407.2		^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.69 (s, 1H), 8.62 (d, *J*=7.3 Hz, 1H), 8.22 (s, 1H), 8.16 (d, *J*=1.1 Hz, 1H), 7.97 - 7.87 (m, 2H), 7.84 (d, *J*=8.4 Hz, 2H), 7.76 - 7.70 (m, 2H), 7.47 (d, *J*=8.3 Hz, 2H), 6.07 (s, 2H), 5.84 (d, *J*=7.0 Hz, 1H), 1.90 (d, *J*=7.0 Hz, 3H).
185	 (*S*)-7-(6-(1-(1-(pyridin-2-yl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	383		^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.69 - 8.48 (m, 3H), 8.19 (s, 1H), 8.14 (s, 1H), 7.97 - 7.87 (m, 2H), 7.82 - 7.69 (m, 3H), 7.32 (dd, *J*=7.3, 4.9 Hz, 1H), 7.14 (d, *J*=8.1 Hz, 1H), 6.06 (s, 2H), 5.76 (br d, *J*=7.2 Hz, 1H), 1.92 (br d, *J*=7.0 Hz, 3H).
186	 7-(6-(1-(2-fluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	418.2	Column 1 Solvents 3 First Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.72 (s, 1H), 8.62 (d, *J*=7.0 Hz, 1H), 8.27 (s, 1H), 8.16 (d, *J*=0.9 Hz, 1H), 8.00 - 7.95 (m, 1H), 7.94 - 7.88 (m, 1H), 7.78 - 7.67 (m, 2H), 7.49 (dd, *J*=8.7, 5.4 Hz, 2H), 7.24 (t, *J*=8.9 Hz, 2H), 6.10 - 5.95 (m,

				3H), 5.43 - 5.21 (m, 1H), 5.13 - 4.90 (m, 1H).
187	 7-(6-(1-(2-fluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	418.2	Column 1 Solvents 3 Second Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.72 (s, 1H), 8.63 (d, *J*=7.2 Hz, 1H), 8.27 (s, 1H), 8.16 (d, *J*=1.1 Hz, 1H), 8.01 - 7.89 (m, 2H), 7.79 - 7.69 (m, 2H), 7.49 (dd, *J*=8.7, 5.5 Hz, 2H), 7.24 (t, *J*=8.9 Hz, 2H), 6.17 - 5.96 (m, 3H), 5.44 - 5.23 (m, 1H), 5.11 - 4.92 (m, 1H).
188	 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	436.1	Column 1 Solvents 3 First Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.77 - 8.58 (m, 2H), 8.31 (s, 1H), 8.04 - 7.85 (m, 2H), 7.80 - 7.61 (m, 4H), 7.29 (br t, *J*=8.6 Hz, 2H), 7.14 - 6.78 (m, 1H), 6.27 - 5.97 (m, 3H).
189	 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	436.1	Column 1 Solvents 3 First Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.69 (s, 1H), 8.63 (d, *J*=7.0 Hz, 1H), 8.31 (s, 1H), 8.15 (d, *J*=0.7 Hz, 1H), 8.01 - 7.88 (m, 2H), 7.77 - 7.63 (m, 4H), 7.29 (t, *J*=8.8 Hz, 2H), 7.10 - 6.82 (m, 1H), 6.22 - 6.12 (m, 1H), 6.08 (s, 2H).

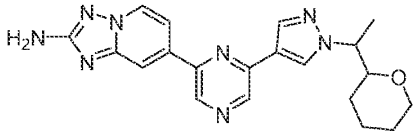
190	 7-(6-(1-(2-fluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	419.1	Column 2 Solvents 3 First Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.21 (s, 1H), 9.03 (s, 1H), 8.86 (s, 1H), 8.70 (d, *J*=7.1 Hz, 1H), 8.39 (s, 1H), 8.26 (s, 1H), 7.76 (dd, *J*=7.0, 1.7 Hz, 1H), 7.50 (dd, *J*=8.7, 5.5 Hz, 2H), 7.25 (t, *J*=8.8 Hz, 2H), 6.06 (ddd, *J*=13.1, 9.1, 4.3 Hz, 1H), 5.42 - 5.21 (m, 1H), 5.12 - 4.92 (m, 1H).
191	 7-(6-(1-(2-fluoro-1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	419.1	Column 2 Solvents 3 Second Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d_6) δ 9.21 (s, 1H), 9.03 (s, 1H), 8.86 (s, 1H), 8.70 (d, *J*=7.0 Hz, 1H), 8.39 (s, 1H), 8.26 (s, 1H), 7.76 (dd, *J*=7.0, 1.8 Hz, 1H), 7.50 (dd, *J*=8.6, 5.5 Hz, 2H), 7.25 (t, *J*=8.9 Hz, 2H), 6.05 (br dd, *J*=8.5, 4.6 Hz, 1H), 5.44 - 5.22 (m, 1H), 5.12 - 4.91 (m, 1H).
192	 (*S*)-7-(6-(1-(1-(4-chlorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	417.1		^{1}H NMR (500 MHz, DMSO-d_6) δ 9.25 - 9.14 (m, 1H), 9.06 - 8.95 (m, 1H), 8.79 (s, 1H), 8.68 (br d, *J*=6.3 Hz, 1H), 8.30 (s, 1H), 8.25 (s, 1H), 7.75 (dd, *J*=6.7, 1.3 Hz, 1H), 7.46 - 7.39 (m, 2H), 7.35 (br

				d, *J*=8.5 Hz, 2H), 5.75 (br d, *J*=7.1 Hz, 1H), 1.88 (br d, *J*=7.0 Hz, 3H).
193	 7-(6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1	415.2	Column 10 Solvents 2 First Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.19 (s, 1H), 9.01 (s, 1H), 8.79 (s, 1H), 8.69 (d, *J*=7.0 Hz, 1H), 8.31 (s, 1H), 8.25 (s, 1H), 7.75 (dd, *J*=7.0, 1.7 Hz, 1H), 7.49 (dd, *J*=8.6, 5.6 Hz, 2H), 7.20 (t, *J*=8.8 Hz, 2H), 5.46 (dd, *J*=9.2, 6.4 Hz, 1H), 2.43 (dt, *J*=16.3, 7.1 Hz, 1H), 2.26 - 2.11 (m, 1H), 0.86 (t, *J*=7.2 Hz, 3H).
194	 7-(6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2	415.0	Column 10 Solvents 2 Second Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.19 (s, 1H), 9.00 (s, 1H), 8.79 (s, 1H), 8.69 (d, *J*=7.1 Hz, 1H), 8.31 (s, 1H), 8.25 (d, *J*=0.9 Hz, 1H), 7.75 (dd, *J*=7.0, 1.7 Hz, 1H), 7.49 (dd, *J*=8.7, 5.5 Hz, 2H), 7.20 (t, *J*=8.8 Hz, 2H), 5.46 (dd, *J*=9.4, 6.3 Hz, 1H), 2.43 (dt, *J*=16.2, 7.1 Hz, 1H), 2.24 - 2.13 (m, 1H), 0.86 (t, *J*=7.2 Hz, 3H).

195	 *(S)*-7-(6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	414.2		^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.66 - 8.59 (m, 2H), 8.19 (s, 1H), 8.15 (s, 1H), 7.97 - 7.86 (m, 2H), 7.77 - 7.67 (m, 2H), 7.52 - 7.44 (m, 2H), 7.19 (t, *J*=8.9 Hz, 2H), 5.43 (dd, *J*=9.4, 6.2 Hz, 1H), 2.47 - 2.31 (m, 1H), 2.25 - 2.11 (m, 1H), 0.85 (t, *J*=7.3 Hz, 3H).
196	 7-(6-(1-(1-(4-fluorophenyl)propyl-1-d)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine enantiomer 1, (10.3 mg, 19.5%)	416.2	Column BV1 Solvents BV2 First Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.21 - 9.14 (m, 1H), 9.00 (s, 1H), 8.79 (s, 1H), 8.69 (d, *J*=7.1 Hz, 1H), 8.31 (s, 1H), 8.25 (s, 1H), 7.76 (dd, *J*=7.0, 1.8 Hz, 1H), 7.53 - 7.44 (m, 2H), 7.19 (t, *J*=8.9 Hz, 2H), 2.42 (br dd, *J*=13.8, 7.0 Hz, 1H), 2.17 (br dd, *J*=13.8, 7.3 Hz, 1H), 0.85 (t, *J*=7.2 Hz, 3H).
197	 7-(6-(1-(1-(4-fluorophenyl)propyl-1-d)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine enantiomer 2, (11 mg, 20.8%)	416.0	Column BV1 Solvents BV2 Second Eluted Isomer	^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.19 (s, 1H), 9.00 (s, 1H), 8.79 (s, 1H), 8.69 (d, *J*=7.0 Hz, 1H), 8.31 (s, 1H), 8.25 (d, *J*=1.1 Hz, 1H), 7.76 (dd, *J*=7.0, 1.8 Hz, 1H), 7.54 - 7.44 (m, 2H), 7.19 (t, *J*=8.9 Hz, 2H), 2.42 (br dd, *J*=14.0, 7.1 Hz,

				1H), 2.17 (dd, *J*=13.8, 7.3 Hz, 1H), 0.85 (t, *J*=7.2 Hz, 3H).

Example 198: 7-(6-(1-(1-(tetrahydro-2H-pyran-2-yl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

198A: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(1-(tetrahydro-2H-pyran-2-yl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine: In a 8 mL Chemglass reaction vial were combined 7-(6-(1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (120 mg, 0.337 mmol), 1-(oxan-2-yl)ethan-1-ol (132 mg, 1.01 mmol), triphenylphosphine, polymer bound, (Aldrich 93093-25G, 3 mmol/g load capacity, 449 mg, 1.35 mmol) and anhydrous THF (2.5 mL) with stirring. The resulting light brown mixture was treated with di-*tert*-butyl azodicarboxylate (271 mg, 1.18 mmol) and the vial was agitated overnight. The liquid was carefully pipetted out of the vial, leaving the triphenylphosphine resin in the vial. The liquid was filtered into a clean 8 mL scintillation vial. To the reaction vial was added DCM (2 mL) and the contents were shaken for 10 min to rinse the resin. Again, the liquid was carefully removed, filtered and added to the original reaction liquid. Then to the reaction vial was added THF (2 mL) and the contents were shaken for 10 min to rinse the resin. Again, the liquid was carefully removed, filtered and added to the original reaction liquid. The resin was discarded. The combined organics were concentrated via nitrogen stream to a residue. This crude residue containing 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(1-(tetrahydro-2H-pyran-2-yl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine as a diastereomeric mixture was carried into the next step as-is. A 30% yield of the desired material was assumed based on analytical LCMS peak integration.

MS ESI m/z 469.1 $(M+H)^+$

198B: 7-(6-(1-(1-(tetrahydro-2H-pyran-2-yl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate 1: The crude mixture from the previous step containing diastereomeric 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(1-(tetrahydro-

2H-pyran-2-yl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (assumed 0.047 g, 0.101 mmol) was dissolved in a mixture of THF (1.7 mL) and water (0.56 mL) and TFA (1.3 mL, 1.9 g, 17 mmol). The mixture was heated to 70C with stirring overnight. The mixture was concentrated under a gentle stream of nitrogen to a residue which was redissolved in minimal DMF and filtered to provide a 2 mL sample which was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 9-49% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Two individual peaks with m/z consistent with the desired product were visible in the preparative HPLC purification, but only the fractions from the first of the two peaks to elute from the prep HPLC column with the desired product m/z were combined and dried via centrifugal evaporation to provide 7-(6-(1-(1-(tetrahydro-2H-pyran-2-yl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate 1 (25.3 mg, 0.0648 mmol, approx. 64% yield) as a racemic mixture of two diastereomers.

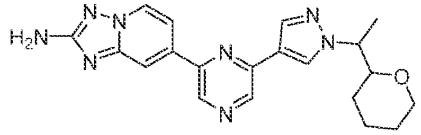
^{1}H NMR (500 MHz, DMSO-d_6) δ 9.18 (s, 1H), 9.00 (s, 1H), 8.68 (d, *J*=6.9 Hz, 1H), 8.56 (s, 1H), 8.25 (s, 1H), 8.23 (s, 1H), 7.75 (dd, *J*=7.1, 1.8 Hz, 1H), 6.14 (s, 2H), 4.39 (t, *J*=7.0 Hz, 1H), 3.84 (br dd, *J*=10.8, 2.1 Hz, 1H), 3.64 - 3.58 (m, 1H), 1.84 - 1.77 (m, 1H), 1.70 - 1.63 (m, 1H), 1.52 - 1.35 (m, 6H), 1.20 - 1.12 (m, 1H).

MS ESI m/z 391.2 $(M+H)^+$

198: 7-(6-(1-(1-(tetrahydro-2H-pyran-2-yl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1: The racemic 7-(6-(1-(1-(tetrahydro-2H-pyran-2-yl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (25.3 mg, 0.0648 mmol) obtained in the previous step was further separated into individual enantiomers via preparative chiral SFC chromatography with the following conditions: Column: Daicel Chiralcel OB-H, 19 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% ammonium hydroxide; Elution Gradient: isocratic 6%B over 26 min; Flow Rate: 70 mL/min; Column Temperature: 45 °C. Fraction collection was triggered by UV (220 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(6-(1-(1-(tetrahydro-2H-pyran-2-

yl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (8.1 mg, 0.0207 mmol, 64% of the theoretical single isomer yield from preparative SFC). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.18 - 9.16 (m, 1H), 9.00 (s, 1H), 8.68 (br d, *J*=6.8 Hz, 1H), 8.55 (s, 1H), 8.25 - 8.22 (m, 2H), 7.75 (dd, *J*=7.0, 1.8 Hz, 1H), 6.14 (s, 2H), 4.42 - 4.36 (m, 1H), 3.86 - 3.81 (m, 1H), 3.63 - 3.57 (m, 1H), 3.32 - 3.23 (m, 1H), 1.83 - 1.78 (m, 1H), 1.66 (br d, *J*=12.2 Hz, 1H), 1.53 - 1.35 (m, 6H), 1.20 - 1.11 (m, 1H).
MS ESI m/z 391.1 $(M+H)^+$

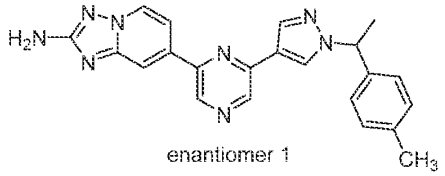
Example 199: 7-(6-(1-(1-(tetrahydro-2H-pyran-2-yl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



enantiomer 2

The title compound 7-(6-(1-(1-(tetrahydro-2H-pyran-2-yl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (8.1 mg, 0.0207 mmol, 64% of the theoretical single isomer yield from preparative SFC) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 198. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.18 - 9.16 (m, 1H), 9.00 (s, 1H), 8.68 (d, *J*=6.8 Hz, 1H), 8.55 (s, 1H), 8.25 - 8.22 (m, 2H), 7.75 (dd, *J*=7.0, 1.8 Hz, 1H), 6.14 (s, 2H), 4.39 (t, *J*=6.9 Hz, 1H), 3.86 - 3.81 (m, 1H), 3.63 - 3.57 (m, 1H), 3.31 - 3.25 (m, 1H), 1.83 - 1.78 (m, 1H), 1.69 - 1.64 (m, 1H), 1.52 - 1.36 (m, 6H), 1.20 - 1.11 (m, 1H).
MS ESI m/z 391.3 $(M+H)^+$

Example 200: 7-(6-(1-(1-(*p*-tolyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

200A: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(1-(*p*-tolyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine: A stirred solution of 7-(6-(1H-pyrazol-4-

yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (80 mg, 0.224 mmol) in THF (2 mL) was treated with NaH, 60% dispersion in mineral oil (13.5 mg, 0.337 mmol) at RT. Heavy effervescence occured. The resulting orange, cloudy mixture was stirred for 10 min and was then treated with racemic 1-(1-bromoethyl)-4-methylbenzene (53.6 mg, 0.269 mmol) all at once. The resulting cloudy mixture was stirred at RT for 45 min and was then heated to 65 °C overnight. The mixture was quenched by addition of 4 drops of saturated aqueous ammonium chloride. The mixture was stirred for 10 min and then concentrated via nitrogen stream to a residue. The crude residue containing racemic 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(1-(*p*-tolyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine was carried forward to the next step as-is. A 100% yield was assumed.

MS ESI m/z 475.2 $(M+H)^+$

200B: 7-(6-(1-(1-(*p*-tolyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate: The crude residue from the previous step containing racemic 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(1-(*p*-tolyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (assumed 106 mg, 0.224 mmol) was dissolved in a mixture of THF (1.1 mL) and Water (0.37 mL) and TFA (863 µl, 1.28 g, 11.2 mmol). The resulting mixture was heated to 70 °C for 30 min. The mixture was then concentrated via nitrogen stream to a residue. The residue was redissolved in minimum DMF and filtered to provide a 2 mL sample which was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 0.05% TFA; Mobile Phase B: 95:5 acetonitrile: water with 0.05% TFA; Gradient: 14-54% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(6-(1-(1-(*p*-tolyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (6.9 mg, 0.017 mmol, 7.6 % yield).

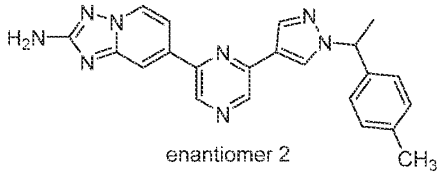
^{1}H NMR (500 MHz, DMSO-d_6) δ 9.20 (s, 1H), 9.02 (s, 1H), 8.76 - 8.72 (m, 2H), 8.28 (s, 2H), 7.82 (dd, *J*=6.9, 1.5 Hz, 1H), 7.24 - 7.20 (m, *J*=8.1 Hz, 2H), 7.19 - 7.14 (m, *J*=8.0 Hz, 2H), 5.68 (q, *J*=6.7 Hz, 1H), 2.27 (s, 3H), 1.87 (d, *J*=7.0 Hz, 3H).

MS ESI m/z 397.1 $(M+H)^+$

200: 7-(6-(1-(1-(*p*-tolyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1: The racemic 7-(6-(1-(1-(*p*-tolyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (6.9 mg, 0.017 mmol) obtained in the previous step was further separated into individual enantiomers via preparative chiral SFC chromatography with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% ammonium hydroxide; Elution Gradient: isocratic 30%B over 35 min; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (254 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(6-(1-(1-(*p*-tolyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (0.7 mg, 0.0018 mmol, 20% of the theoretical single isomer yield from preparative SFC).

MS ESI m/z 397.2 $(M+H)^+$

Example 201: 7-(6-(1-(1-(*p*-tolyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2

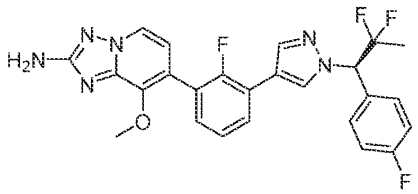


enantiomer 2

The title compound 7-(6-(1-(1-(*p*-tolyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (0.7 mg, 0.0018 mmol, 20% of the theoretical single isomer yield from preparative SFC) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 200.

MS ESI m/z 397.2 $(M+H)^+$

Example 202: *(R)*-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



202A: *(R)*-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridine: In a Chemglass reaction vial, a mixture of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (200 mg, 0.543 mmol), *(R)*-4-(3-bromo-2-fluorophenyl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole (224 mg, 0.543 mmol) and tripotassium phosphate (217 mg, 1.022 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was treated with 1,1'-bis-(diphenylphosphino)ferrocenedichloro palladium (II) dichloromethane complex (35 mg, 0.054 mmol). The reaction mixture was purged with nitrogen gas for 5 min, the vial was sealed, and the mixture was stirred at 100 °C for 16 h. The mixture was diluted with ethyl acetate and filtered through a plug of Celite. The filtrate was concentrated and the crude residue was purified by silica gel column chromatography using 40 g silica and eluting with 0-50% EtOAc/petroleum ether to yield *(R)*-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridine (100 mg, 0.174 mmol, 32.0 % yield) as a light yellow semi-solid.

LCMS (ESI, m/z): 575.2 $[M+H]^+$

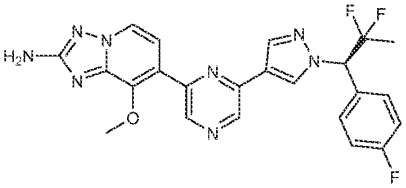
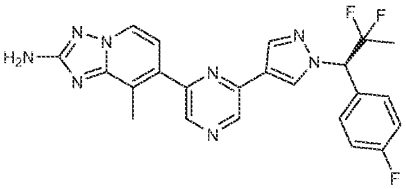
202: *(R)*-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: In a Chemglass reaction vial, to a stirred solution of *(R)*-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridine (100 mg, 0.174 mmol) in THF (3 mL) and water (1 mL) was added TFA (0.670 mL, 8.70 mmol). The vial was sealed and the reaction mixture was stirred at 70 °C for 12 h. The mixture was concentrated and the crude residue was purified by preparative HPLC with the following conditions: Diluent: THF:water:acetonitrile (50:10:40); Column: Waters XSelect C18 (19 x 150 mm, 5 micron particle size); Mobile phase A: 0.15% TFA in water; Mobile phase B: acetonitrile:water (90:10). Fractions containing the desired material were combined and concentrated to yield *(R)*-7-(3-(1-(2,2-

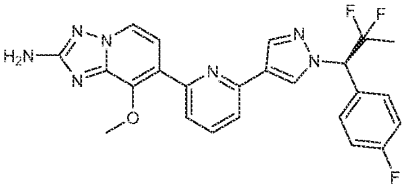
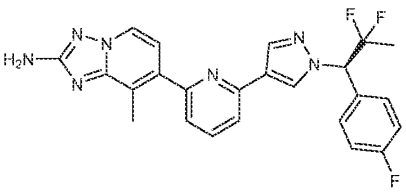
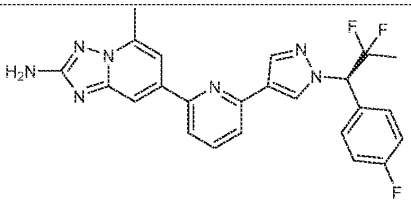
difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine TFA salt (9.0 mg, 0.015 mmol, 8.4 % yield) as a brown semi-solid.

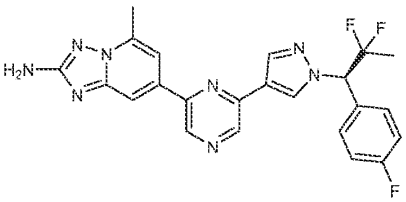
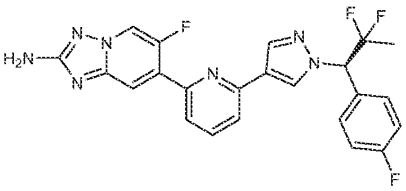
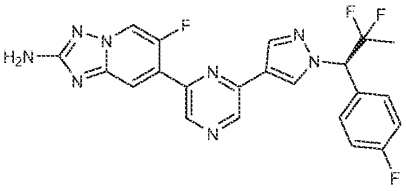
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (d, *J* = 6.80 Hz, 2H), 8.13 (s, 1H), 7.79-7.83 (m, 1H), 7.73-7.76 (m, 2H), 6.95-7.34 (m, 4H), 6.81 (d, *J* = 6.80 Hz, 1H), 6.27 (t, *J* = 26.40 Hz, 1H), 4.07 (s, 3H), 1.64 (s, 3H).

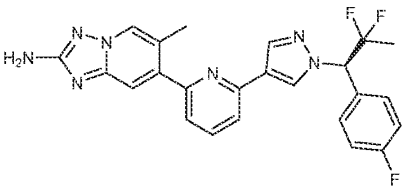
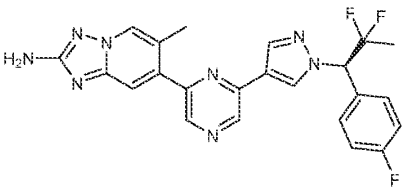
LCMS (ESI, m/z) 497.2 $[M+H]^+$

Table 3: Compounds in Table 3 were prepared in a similar fashion as detailed for the preparation of Example 202, where appropriate predescribed boronate intermediats were substituted in place of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine in step 202A. All examples were purified by various reverse phase preparative HPLC conditions in the final step.

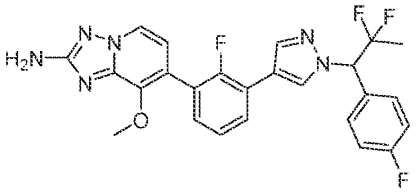
Ex No	Structure and Name	M+H$^+$	^{1}H NMR
203	 *(R)*-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	481.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (s, 1H), 9.00 (s, 1H), 8.73 (s, 1H), 8.43 (d, *J* = 6.80 Hz, 1H), 8.36 (s, 1H), 7.74-7.78 (m, 2H), 7.40 (s, 1H), 7.26-7.30 (m, 2H), 6.31 (t, *J* = 13.20 Hz, 1H), 6.17 (s, 2H), 4.25 (s, 3H), 1.66 (t, *J* = 19.20 Hz, 3H).
204	 *(R)*-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	465.2	^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.72 (d, *J* = 5.20 Hz, 2H), 8.52 (d, *J* = 6.80 Hz, 1H), 8.35 (s, 1H), 7.74-7.77 (m, 2H), 7.25-7.30 (m, 2H), 7.09 (d, *J* = 6.80 Hz, 1H), 6.27-6.33 (m, 1H), 6.09 (s, 2H), 2.53 (s, 3H), 1.66 (t, *J* = 18.80 Hz, 3H).

Ex No	Structure and Name	M+H$^+$	^{1}H NMR
205	 *(R)*-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	480.0	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.59 (s, 1H), 8.38 (d, *J* = 7.20 Hz, 1H), 8.25 (s, 1H), 7.90 (t, *J* = 7.60 Hz, 1H), 7.71-7.82 (m, 4H), 7.41 (d, *J* = 6.80 Hz, 1H), 7.25-7.30 (m, 2H), 6.28 (t, *J* = 13.60 Hz, 1H), 6.11 (s, 2H), 4.17 (s, 3H).
206	 *(R)*-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	464.2	^{1}H NMR (400 MHz, DMSO-d6) δ 8.45-8.45 (m, 2H), 8.20-8.23 (m, 1H), 7.90-7.93 (m, 1H), 7.72-7.76 (m, 3H), 7.44-7.46 (m, 1H), 7.24-7.29 (m, 2H), 7.01 (d, *J* = 6.80 Hz, 1H), 6.22-6.29 (m, 1H), 6.02 (s, 2H), 2.07 (s, 3H), 1.60-1.69 (m, 3H).
207	 *(R)*-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	464.0	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.68 (s, 1H), 8.34 (s, 1H), 8.02 (s, 1H), 7.90-7.96 (m, 2H), 7.74-7.80 (m, 3H), 7.64 (s, 1H), 7.29 (t, *J* = 18.00 Hz, 2H), 6.28 (t, *J* = 26.40 Hz, 1H), 6.09 (s, 2H), 2.69 (s, 3H), 1.63-1.72 (m, 3H).

Ex No	Structure and Name	M+H$^+$	^{1}H NMR
208	 *(R)*-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	465.0	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.19 (s, 1H), 9.05 (s, 1H), 8.81 (s, 1H), 0.00 (s, 1H), 8.12 (d, *J* = 1.20 Hz, 1H), 7.78 (dd, *J* = 5.60, 8.80 Hz, 2H), 7.68 (d, *J* = 0.80 Hz, 1H), 7.25-7.31 (m, 2H), 6.19-6.34 (m, 2H), 2.69 (s, 3H), 1.67 (t, *J* = 19.20 Hz, 3H).
209	 *(R)*-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	468.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.04 (d, *J* = 6.00 Hz, 1H), 8.65 (s, 1H), 8.29 (s, 1H), 7.95 (t, *J* = 7.60 Hz, 2H), 7.74-7.81 (m, 3H), 7.68 (dd, *J* = 1.60, 7.80 Hz, 1H), 7.27 (t, *J* = 8.80 Hz, 2H), 6.27 (t, *J* = 13.60 Hz, 1H), 6.15 (s, 2H), 1.68 (t, *J* = 19.20 Hz, 3H).
210	 *(R)*-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	469.3	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.12 (t, *J* = 5.60 Hz, 2H), 8.88 (d, *J* = 2.40 Hz, 1H), 8.80 (s, 1H), 8.41 (s, 1H), 8.00 (d, *J* = 6.80 Hz, 1H), 7.75-7.79 (m, 2H), 7.25-7.30 (m, 2H), 6.30 (t, *J* = 13.60 Hz, 1H), 1.62-1.76 (m, 3H).

Ex No	Structure and Name	M+H$^+$	^{1}H NMR
211	 *(R)*-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-6-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	464.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.56 (s, 1H), 8.52 (d, *J* = 0.80 Hz, 1H), 8.22 (s, 1H), 7.91 (t, *J* = 7.60 Hz, 1H), 7.72-7.76 (m, 3H), 7.47 (dd, *J* = 0.80, 7.60 Hz, 1H), 7.41 (s, 1H), 7.24-7.29 (m, 2H), 6.25 (t, *J* = 13.60 Hz, 1H), 5.96 (s, 2H), 1.64 (t, *J* = 19.20 Hz, 3H).
212	 *(R)*-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-6-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	465.0	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.08 (s, 1H), 8.72 (d, *J* = 6.80 Hz, 1H), 8.58 (s, 1H), 8.34 (s, 1H), 7.74-7.77 (m, 2H), 7.56 (s, 1H), 7.24-7.30 (m, 2H), 6.29 (t, *J* = 13.20 Hz, 1H), 6.02 (s, 2H), 2.35 (s, 3H), 1.65 (t, *J* = 19.20 Hz, 3H).

Example 213: 7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate



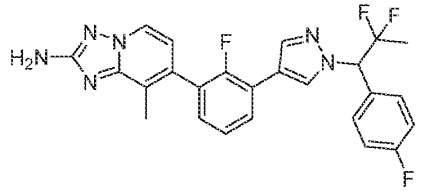
In a Chemglass reaction vial, to a stirred mixture of racemic 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrazole (151 mg, 0.329 mmol) and 7-bromo-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (80.0 mg, 0.329 mmol) in 1,4-dioxane (10 mL) was added potassium phosphate, tribasic (210 mg, 0.987 mmol). The reaction mixture was purged with nitrogen gas for 10

min and [1,1-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (21 mg, 0.033 mmol) was added. The vial was sealed and the reaction mixture was then stirred at 100 °C for 12 h. The mixture was filtered through a pad of Celite and eluted with a combination of DCM and methanol. The organic filtrate was concentrated to yield crude material which was purified by preparative reverse phase HPLC under the following conditions: Diluent: THF:water:acetonitrile (50:20:30); Column: Waters XSelect C18 (19 x 150 mm, 5 micron particle size); Mobile phase A: 10mM ammonium acetate in water; Mobile phase B: acetonitrile. Fractions containing desired material were pooled and concentrated to yield racemic 7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (45 mg, 0.090 mmol, 27 % yield) as an off white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 8.37-8.40 (m, 2H), 8.14 (s, 1H), 7.73-7.84 (m, 3H), 7.25-7.34 (m, 4H), 6.81 (d, *J* = 6.80 Hz, 1H), 6.24-6.31 (m, 1H), 6.11 (s, 2H), 4.09 (s, 3H), 1.65 (t, *J* = 19.20 Hz, 3H).

LCMS (ESI, m/z) 497.2 $[M+H]^+$

Example 214: 7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate



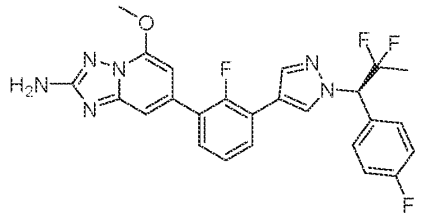
To a stirred mixture of racemic 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrazole (203 mg, 0.440 mmol) and 7-bromo-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (100 mg, 0.440 mmol) in 1,4-dioxane (5 mL) was added potassium phosphate tribasic (280 mg, 1.32 mmol). The reaction mixture was purged with nitrogen gas for 10 min and [1,1-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (29 mg, 0.044 mmol) was added. The reaction mixture was then stirred at 80 °C for 12 h. The mixture was diluted with EtOAc and the result was filtered through a pad of Celite. The organic filtrate was dried over anhydrous sodium sulfate and concentrated to yield crude material. The crude material was purified using preparative reverse phase HPLC with the following conditions: Diluent:

THF:water:acetonitrile (50:20:30); Column: waters XSelect C18 (19 x 150 mm, 5 micron particle size); Mobile phase A: 5 mM ammonium formate in water; Mobile phase B: acetonitrile. Fractions containing desired material were pooled and concentrated to yield racemic 7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (22 mg, 0.044 mmol, 10 % yield) as a white solid.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.45 (d, *J* = 6.80 Hz, 1H), 8.41 (d, *J* = 2.00 Hz, 1H), 8.15 (s, 1H), 7.84-7.88 (m, 1H), 7.73-7.76 (m, 2H), 7.35 (t, *J* = 15.60 Hz, 1H), 7.25-7.29 (m, 3H), 6.79 (d, *J* = 6.80 Hz, 1H), 6.27 (t, *J* = 26.40 Hz, 1H), 6.04 (s, 2H), 2.25 (s, 3H), 1.60-1.69 (m, 3H).

LCMS (ESI, m/z) 497.2 $[M+H]^+$

Example 215: *(R)*-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-5-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



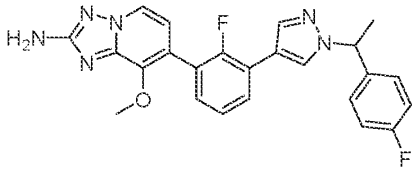
To a stirred mixture of *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrazole (113 mg, 0.246 mmol) and 7-iodo-5-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (65.0 mg, 0.224 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was added potassium phosphate, tribasic (143 mg, 0.672 mmol). The reaction mixture was purged with nitrogen gas for 5 min and 1,1'-bis-(diphenylphosphino)ferrocenedichloro palladium(II) (16.4 mg, 0.022 mmol) was added. The reaction mixture was then stirred at 80 °C for 2 h. The mixture was diluted with EtOAc and the result was filtered through a pad of Celite. The organic filtrate was dried over anhydrous sodium sulfate and concentrated to yield crude material. The crude material was purified using preparative reverse phase column chromatography with the following conditions: Diluent: THF:water:acetonitrile (50:20:30); Column: Teledyne Isco Redisep 80 g C18, 20-40 micron; Mobile phase A: 5mM ammonium formate in water; Mobile phase B: acetonitrile. Fractions containing desired material were pooled and concentrated to yield

(R)-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-5-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (56.0 mg, 0.112 mmol, 49.8 % yield) as an off white solid.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.43 (d, *J* = 2.0 Hz, 1H), 8.15 (s, 1H), 7.83 (t, *J* = 7.2 Hz, 1H), 7.76-7.73 (m, 2H), 7.53-7.49 (m, 1H), 7.34 (t, *J* = 8.8 Hz, 1H), 7.26 (t, *J* = 8.8 Hz, 2H), 7.14 (s, 1H), 6.58 (s, 1H), 6.28 (t, *J* = 13.2 Hz, 1H), 6.00 (s, 2H), 4.10 (s, 3H), 1.65 (t, *J* = 13.2 Hz, 3H).

LCMS (ESI, m/z) 497.0 $[M+H]^+$

Example 216: 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate

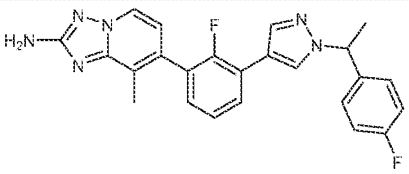
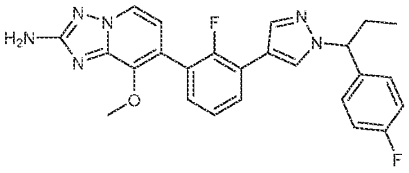


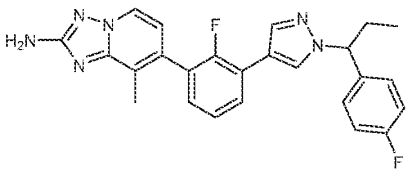
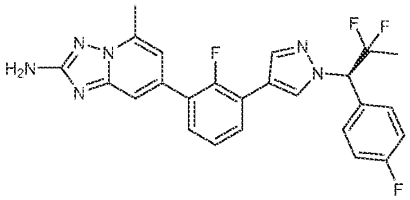
In a Chemglass reaction vial, to a stirred mixture of racemic 4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazole (138 mg, 0.336 mmol), 7-bromo-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine TFA salt (100 mg, 0.280 mmol) and tripotassium phosphate (178 mg, 0.840 mmol) in 1,4-dioxane (4 mL) was added 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (20.5 mg, 0.0280 mmol). The reaction mixture was purged with nitrogen gas, then the vial was sealed and the mixture was stirred at 100 °C for 12 h. The mixture was diluted with ice cold water (5 mL) and the result was extracted with ethyl acetate (2 x 10 mL). The organic layer was concentrated to yield crude material which was purified by reverse phase preparative HPLC under the following conditions: Diluent: THF:water:acetonitrile (50:20:30); Column: Waters Sunfire C18 (20 x 250 mm, 5 micron particle size); Mobile phase A: 10mM ammonium acetate in water; Mobile phase B: acetonitrile. Fractions containing desired material were pooled and concentrated to yield racemic 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (19 mg, 0.042 mmol, 15 % yield) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 8.37 (d, *J* = 6.80 Hz, 1H), 8.33 (d, *J* = 1.60 Hz, 1H), 7.98 (d, *J* = 0.80 Hz, 1H), 7.77 (dt, *J* = 1.60, 10.53 Hz, 1H), 7.34-7.38 (m, 2H), 7.23-7.31 (m, 2H), 7.14-7.19 (m, 2H), 6.79 (d, *J* = 6.80 Hz, 1H), 6.10 (s, 2H), 5.71 (q, *J* = 6.80 Hz, 1H), 1.84 (d, *J* = 7.20 Hz, 3H).

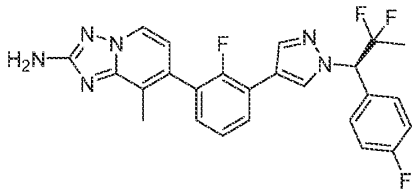
LCMS (ESI, m/z) 447.2 $[M+H]^+$.

Table 4: Compounds in Table 4 were prepared in a similar fashion as detailed for the preparation of Example 216, where appropriate predescribed halide intermediates were substituted in place of 7-bromo-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine TFA salt, and appropriate predescribed boronate intermediates were substituted in place of 4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-(1-(4-fluorophenyl)ethyl)-1H-pyrazole. All examples were purified by various reverse phase preparative HPLC conditions.

Ex No	Structure and Name	M+H	1H NMR
217	 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)phenyl)-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate	431.2	^{1}H-NMR (400 MHz, DMSO-d6) δ 8.44 (dd, *J* = 0.40, 6.80 Hz, 1H), 8.34 (d, *J* = 1.60 Hz, 1H), 7.99 (s, 1H), 7.81 (dt, *J* = 1.60, 10.53 Hz, 1H), 7.30-7.38 (m, 3H), 7.14-7.25 (m, 3H), 6.77 (d, *J* = 6.80 Hz, 1H), 6.03 (s, 2H), 5.70 (q, *J* = 7.20 Hz, 1H), 2.24 (s, 3H).
218	 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)phenyl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate	461.2	^{1}H NMR (400 MHz, MeO) δ 8.26 (d, *J* = 6.80 Hz, 1H), 8.21 (d, *J* = 1.60 Hz, 1H), 7.99 (d, *J* = 0.80 Hz, 1H), 7.74-7.76 (m, 1H), 7.40-7.44 (m, 2H), 7.29 (dd, *J* = 0.80, 5.00 Hz, 2H), 7.06-7.11 (m, 2H), 6.89 (d, *J* = 7.60 Hz, 1H), 5.33-5.37 (m, 1H), 4.01 (s, 3H), 2.42-2.51 (m, 1H), 2.20-2.30 (m,

Ex No	Structure and Name	M+H	1H NMR
			1H), 0.95 (t, *J* = 7.20 Hz, 3H).
219	 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)phenyl)-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate	445.2	^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.45 (dd, *J* = 0.40, 6.80 Hz, 1H), 8.37 (d, *J* = 1.60 Hz, 1H), 8.01 (s, 1H), 7.82-7.82 (m, 1H), 7.44-7.47 (m, 2H), 7.31-7.34 (m, 1H), 7.15-7.25 (m, 3H), 6.78 (d, *J* = 6.80 Hz, 1H), 6.04 (s, 2H), 5.41-5.42 (m, 1H), 2.33-2.42 (m, 1H), 2.25 (s, 3H), 2.08-2.19 (m, 1H), 0.83 (t, *J* = 7.20 Hz, 3H).
220	 *(R)*-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	481	^{1}H-NMR (400 MHz, DMSO-d$_6$): δ 8.44 (s, 1H), 8.15 (s, 1H), 7.81-7.85 (m, 1H), 7.73-7.76 (m, 2H), 7.46-7.50 (m, 1H), 7.42 (s, 1H), 7.34 (t, *J* = 8.00 Hz, 1H), 7.25-7.29 (m, 2H), 7.03 (s, 1H), 6.27 (t, *J* = 13.20 Hz, 1H), 2.64 (s, 3H), 1.65 (t, *J* = 18.80 Hz, 3H).

Example 221: *(R)*-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



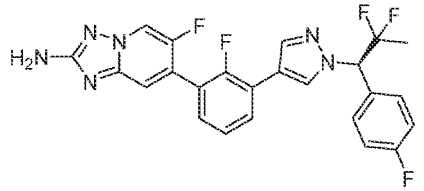
In a Chemglass reaction vial, to a stirred mixture of *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrazole (150 mg, 0.326 mmol) and 7-bromo-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (111 mg, 0.489 mmol) in 1,4-dioxane (8 mL) and water (2 mL) was added potassium phosphate, dibasic (142 mg, 0.815 mmol). The reaction mixture was purged with

nitrogen gas for 10 min and 1,1'-bis-(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (27 mg, 0.033 mmol) was added. The vial was sealed and the reaction mixture was then stirred at 100 °C for 12 h. The mixture was filtered through a pad of Celite, and the filtrate was concentrated to give a crude residue. The crude material was purified by reverse phase preparative HPLC with the following conditions: Diluent: THF:water:acetonitrile (50:20:30); Column: Waters Xbridge C18 (19 x 250 mm, 5 micron particle size); Mobile phase A: 5 mM ammonium formate in water; Mobile phase B: acetonitrile. Fractions containing the desired material were combined and concentrated to yield *(R)*-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (49 mg, 0.10 mmol, 31 % yield) as an off white solid.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.45 (d, *J* = 6.80 Hz, 1H), 8.40 (d, *J* = 2.00 Hz, 1H), 8.15 (s, 1H), 7.86-7.88 (m, 1H), 7.73-7.76 (m, 2H), 7.33-7.37 (m, 1H), 7.25-7.29 (m, 3H), 6.96 (d, *J* = 6.80 Hz, 1H), 6.23-6.30 (m, 1H), 6.04 (s, 2H), 2.25 (s, 3H), 1.60-1.69 (m, 3H).

LCMS (ESI, m/z): 481.2 $[M+H]^+$

Example 222: *(R)*-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-6-fluoro-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



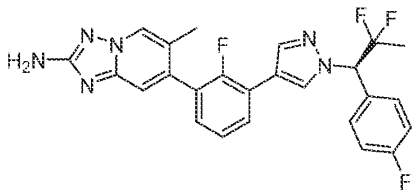
In a Chemglass reaction vial, to a stirred mixture of *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrazole (150 mg, 0.326 mmol), 6-fluoro-7-iodo-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (109 mg, 0.391 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was added tripotassium phosphate (208 mg, 0.978 mmol). The reaction mixture was purged with nitrogen gas for 2 min and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (27 mg, 0.033 mmol) was added. The vial was sealed and the reaction mixture was then stirred at 100 °C for 3 h. The mixture was diluted with EtOAc (20 mL) and washed with water (10 mL). The organic phase was concentrated to yield crude material which was purified by reverse phase column chromatography with the following

conditions: Diluent: THF:water:acetonitrile (50:20:30); Column: Teledyne Isco Redisep 40 g C18, 20-40 micron; Mobile phase A: 5 mM Ammonium formate in water; Mobile phase B: acetonitrile. Fractions containing the desired material were combined and concentrated to yield *(R)*-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-6-fluoro-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (100 mg, 0.200 mmol, 61.4 % yield) as an off white solid.

^{1}H NMR (400 MHz, DMSO-d$_6$) δ 9.04 (d, *J* = 4.80 Hz, 1H), 8.42 (d, *J* = 2.40 Hz, 1H), 8.03 (d, *J* = 97.60 Hz, 1H), 7.72-7.90 (m, 3H), 7.50 (d, *J* = 6.80 Hz, 1H), 7.35-7.42 (m, 2H), 7.24-7.29 (m, 2H), 6.27 (m, 2H), 6.13 (s, 1H), 1.64 (t, *J* = 19.20 Hz, 3H).

LCMS (ESI, m/z) 485.0 $[M+H]^+$

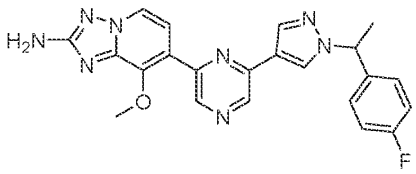
Example 223: *(R)*-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-6-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



In a Chemglass reaction vial, to a stirred mixture of *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrazole (223 mg, 0.484 mmol) and 7-bromo-6-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (110 mg, 0.484 mmol) in 1,4-dioxane (4 mL) and water (1 mL) was added tripotassium phosphate (308 mg, 1.45 mmol). The reaction mixture was purged with nitrogen gas for 2 min and then 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (39.6 mg, 0.48 mmol) was added. The vial was sealed and the reaction mixture was then stirred at 80 °C for 3 h. The mixture was diluted with ethyl acetate (40 mL) and washed with water (20 mL). The organic phase was concentrated to yield crude material which was purified by column chromatography using silica gel (24 g) and eluting with 80% of EtOAc/petroleum ether to yield *(R)*-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-6-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (135 mg, 0.273 mmol, 56.3 % yield) as an off white solid.

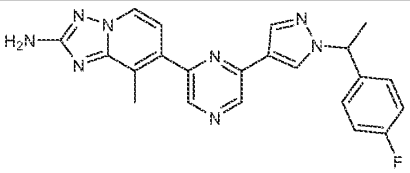
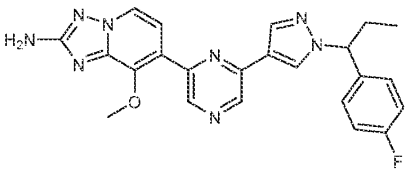
^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.55 (s, 1H), 8.40 (s, 1H), 8.14 (s, 1H), 7.83-7.87 (m, 1H), 7.72-7.76 (m, 2H), 7.32-7.35 (m, 1H), 7.23-7.28 (m, 4H), 6.26 (t, *J* = 26.40 Hz, 1H), 5.96 (s, 2H), 2.07 (s, 3H), 1.64 (t, *J* = 38.40 Hz, 3H).
LCMS (ESI, m/z) 481.0 $[M+H]^+$

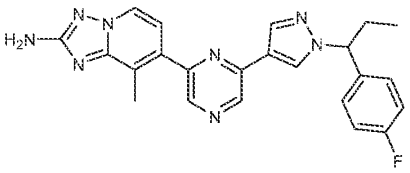
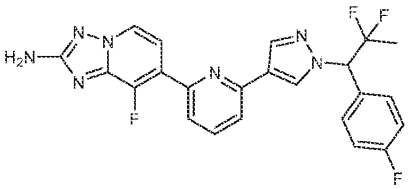
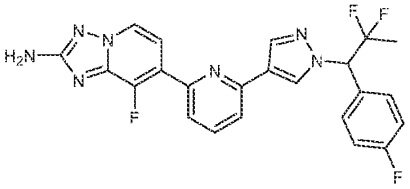
Example 224: 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate

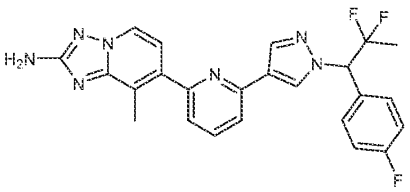
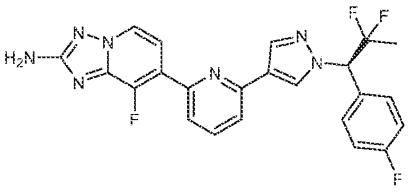
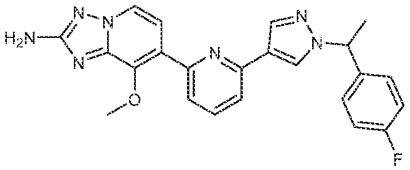


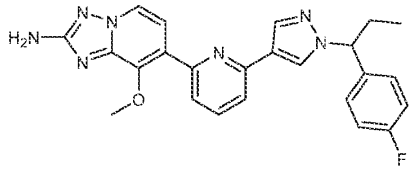
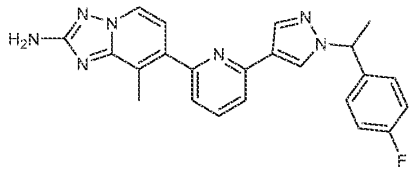
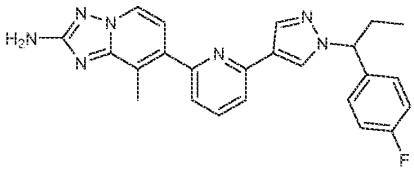
In a Chemglass reaction vial, to a crude reaction mixture prepared as described in the preparation of Intermediate 2 containing 8-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (140 mg, 0.483 mmol) was added racemic 2-bromo-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazine (168 mg, 0.483 mmol), tripotassium phosphate (205 mg, 0.965 mmol) and 1,4-dioxane (1 mL). To the reaction mixture was then added [1,1-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (31.4 mg, 0.048 mmol). The resulting mixture was purged with nitrogen gas, the vial was sealed, and the mixture was stirred at 100 °C for 16 h. The mixture was diluted with ice cold water (4 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic phase was dried over anhydrous sodium sulfate and concentrated to yield crude material. The crude material was purified by reverse phase preparative HPLC with the following conditions: Diluent: THF:water:acetonitrile (50:20:30); Column: Waters Sunfire C18 (20 x 250 mm, 5 micron particle size); Mobile phase A: 5 mM ammonium formate in water; Mobile phase B: acetonitrile. Fractions containing desired material were pooled and concentrated to yield racemic 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (28 mg, 0.064 mmol, 13 % yield) as an off white solid.
^{1}H-NMR (400 MHz, DMSO-d$_6$): δ 8.98 (dd, *J* = 3.20, 5.80 Hz, 2H), 8.69 (s, 1H), 8.42 (d, *J* = 6.80 Hz, 1H), 8.24 (d, *J* = 0.40 Hz, 1H), 7.37-7.43 (m, 3H), 7.16-7.22 (m, 2H), 6.17 (s, 2H), 5.75 (q, *J* = 7.20 Hz, 1H), 4.25 (s, 3H), 1.87 (d, *J* = 7.20 Hz, 3H).
LCMS (ESI, m/z) 431.0 $[M+H]^+$

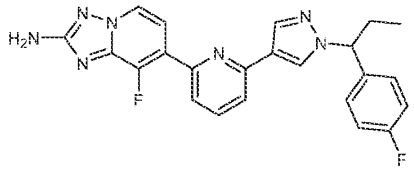
Table 5: Compounds in Table 5 were prepared in a similar fashion as detailed for the preparation of Example 224, where crude mixtures containing appropriate predescribed boronate intermediates were substituted in place of the crude mixture containing 8-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine, and appropriate predescribed halide intermediates were substituted in place of 2-bromo-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazine. All examples were purified by various reverse phase preparative HPLC conditions.

Ex No	Structure and Name	M+H	^{1}H NMR
225	 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate	415.2	^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 9.02 (s, 1H), 8.67 (d, *J* = 8.80 Hz, 2H), 8.52 (dd, *J* = 0.80, 7.00 Hz, 1H), 8.22 (s, 1H), 7.36-7.40 (m, 2H), 7.16-7.21 (m, 2H), 7.09 (d, *J* = 6.80 Hz, 1H), 6.09 (s, 2H), 5.74 (q, *J* = 6.80 Hz, 1H), 2.50 (s, 3H).
226	 7-(6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate	445.2	^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 8.97 (d, *J* = 4.80 Hz, 2H), 8.70 (d, *J* = 0.40 Hz, 1H), 8.43 (d, *J* = 6.80 Hz, 1H), 8.25 (s, 1H), 7.46-7.49 (m, 2H), 7.42 (d, *J* = 6.80 Hz, 1H), 7.17-7.21 (m, 2H), 6.18 (s, 2H), 5.46 (q, *J* = 6.00 Hz, 1H), 4.25 (s, 3H), 2.33-2.43 (m, 1H), 2.08-2.22 (m, 1H), 0.85 (t, *J* = 7.20 Hz, 3H).

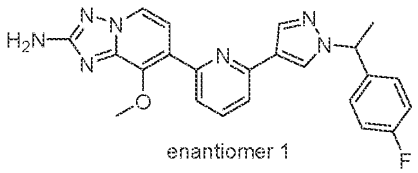
Ex No	Structure and Name	M+H	^{1}H NMR
227	 7-(6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate	429.2	^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 9.01 (s, 1H), 8.67 (d, *J* = 0.80 Hz, 2H), 8.51 (d, *J* = 0.80 Hz, 1H), 8.23 (s, 1H), 7.45-7.48 (m, 2H), 7.16-7.21 (m, 2H), 7.08 (d, *J* = 6.80 Hz, 1H), 6.08 (s, 2H), 5.44 (q, *J* = 6.40 Hz, 1H), 2.36-2.43 (m, 1H), 2.10-2.20 (m, 1H), 0.8 (m, 3H).
228	 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate	468.2	^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 8.60 (s, 1H), 8.53 (d, *J* = 8.00 Hz, 1H), 8.28 (s, 1H), 8.96 (t, *J* = 12.00 Hz, 1H), 7.73-7.80 (m, 4H), 7.55 (t, *J* = 12.00 Hz, 1H), 7.27 (t, *J* = 16.00 Hz, 2H), 6.28 (t, *J* = 14.00 Hz, 3H), 1.66 (t, *J* = 18.00 Hz, 3H).
229	 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate	480.2	^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 8.58 (s, 1H), 8.37-8.39 (m, 1H), 8.25 (s, 1H), 7.71-7.91 (m, 5H), 7.39-7.41 (m, 1H), 7.25-7.29 (m, 2H), 6.30-6.51 (m, 1H), 6.10-6.27 (m, 2H), 4.16 (s, 3H), 1.60-1.70 (m, 3H).

Ex No	Structure and Name	M+H	^{1}H NMR
230	 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate	464.2	^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 8.55 (s, 1H), 8.45 (d, *J* = 8.00 Hz, 1H), 8.22 (s, 1H), 7.91 (t, *J* = 16.00 Hz, 1H), 7.60-7.70 (m, 3H), 7.44-7.46 (m, 1H), 7.24-7.28 (m, 2H), 7.01 (d, *J* = Hz, 1H), 6.25 (t, *J* = 12.00 Hz, 1H), 6.02 (s, 2H), 1.64 (t, *J* = 20.00 Hz, 3H).
231	 *(R)*-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine	468.0	^{1}H-NMR (400 MHz, DMSO-d6) δ 8.63 (s, 1H), 8.53 (d, *J* = 7.20 Hz, 1H), 8.28 (s, 1H), 7.96 (t, *J* = 7.60 Hz, 1H), 7.73-7.80 (m, 4H), 7.55 (t, *J* = 6.80 Hz, 1H), 7.25-7.29 (m, 2H), 6.28 (t, *J* = 13.60 Hz, 1H), 1.66 (t, *J* = 18.80 Hz, 3H).
232	 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate	430.2	^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 8.50 (s, 1H), 8.37 (d, *J* = 8.00 Hz, 1H), 8.12 (s, 1H), 7.87 (t, *J* = 12.00 Hz, 1H), 7.78 (t, *J* = 8.00 Hz, 1H), 7.67 (dd, *J* = 8.00, Hz, 1H), 7.40 (dd, *J* = 24.00, Hz, 1H), 7.20-7.36 (m, 2H), 7.17 (t, *J* = 12.00 Hz, 2H), 6.10 (s, 2H), 5.72 (t, *J* = 4.00 Hz, 1H), 4.10 (s, 3H), 1.86 (d, *J* = 8.00 Hz, 3H).

Ex No	Structure and Name	M+H	^{1}H NMR
233	 7-(6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate	444.2	^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 8.53 (s, 1H), 8.37 (d, *J* = 6.80 Hz, 1H), 8.13 (s, 1H), 7.86 (t, *J* = 8.00 Hz, 1H), 7.77 (dd, *J* = 0.80, 7.60 Hz, 1H), 7.66 (dd, *J* = 0.80, 7.60 Hz, 1H), 7.41-7.48 (m, 3H), 7.14-7.20 (m, 2H), 6.10 (s, 2H), 5.40-5.44 (m, 1H), 4.15 (s, 3H), 2.38-2.42 (m, 1H), 2.13-2.16 (m, 1H), 0.84 (t, *J* = 7.20 Hz, 3H).
234	 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate	414.2	^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 8.44-8.49 (m, 2H), 8.09 (s, 1H), 7.89 (t, *J* = 7.60 Hz, 1H), 7.69-7.70 (m, 1H), 7.34-7.42 (m, 3H), 7.14-7.20 (m, 2H), 7.01 (d, *J* = 7.20 Hz, 1H), 6.02 (s, 2H), 5.67-5.73 (m, 1H), 2.49 (s, 3H), 1.84 (d, *J* = 6.80 Hz, 3H).
235	 7-(6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate	428.2	^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 8.51 (s, 1H), 8.46 (d, *J* = 6.80 Hz, 1H), 8.11 (s, 1H), 7.89 (t, *J* = 8.00 Hz, 1H), 7.68-7.70 (m, 1H), 7.41-7.48 (m, 3H), 7.16-7.20 (m, 2H), 7.01 (d, *J* = 6.80 Hz, 1H), 6.02 (s, 2H), 5.40-5.43 (m, 1H), 2.36-2.43 (m, 1H), 2.08-2.20 (m, 1H), 2.49 (s, 3H), 0.83 (t, *J* = 7.60 Hz, 3H).

Ex No	Structure and Name	M+H	^{1}H NMR
236	 8-fluoro-7-(6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate	432.2	^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 8.59 (s, 1H), 8.53 (d, *J* = 6.80 Hz, 1H), 8.17 (s, 1H), 7.94 (t, *J* = 7.60 Hz, 1H), 7.73-7.77 (m, 2H), 7.58 (s, 1H), 7.45-7.49 (m, 2H), 7.18-7.21 (m, 2H), 5.41-5.45 (m, 1H), 2.33-2.43 (m, 1H), 2.12-2.21 (m, 1H), 0.85 (t, *J* = 7.20 Hz, 3H).

Example 237: 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1

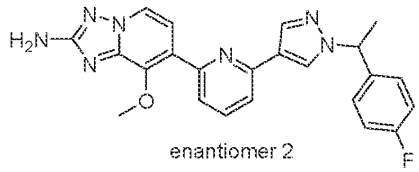


237A: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridine: In a Chemglass reaction vial, to a mixture of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (300 mg, 0.815 mmol) and 2-bromo-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridine (310 mg, 0.896 mmol) in 1,4-dioxane (10 mL) and water (0.5 mL) was added dipotassium phosphate (426 mg, 2.44 mmol). The resulting mixture was purged with nitrogen gas for 10 min and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (40 mg, 0.049 mmol) was added. The vial was sealed and the reaction mixture was stirred at 100 °C for 12 h. The mixture was filtered through a pad of Celite and eluted with EtOAc. The filtrate was concentrated to a crude residue which was purified by silica gel column chromatography, eluting with 0-20% EtOAc/petroleum ether to yield 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridine (300 mg, 0.461 mmol, 56.6 % yield) as a brown semi-solid. LCMS (ESI, m/z) 508.2 [M+H]+

237: 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1: In a Chemglass reaction vial, to a stirred solution of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridine (300 mg, 0.591 mmol) in THF (10 mL) and water (1 mL) was added TFA (2.28 mL, 29.6 mmol). The vial was sealed and the reaction mixture was stirred at 70 °C for 12 h. Solvents were evaporated and the residue was redissolved in 4:1 DCM:MeOH. Residual TFA was neutralized by addition of approximately 100 mg of sodium carbonate with stirring for 1 h. The mixture was filtered to remove solids, and the filtrate was concentrated in vacuo to a residue. The crude material was purified by silica gel column chromatography, eluting with 0-80% EtOAc/petroleum ether. The material thus obtained was further purified by the reverse phase column chromatography with the following conditions: Diluent: THF:water:acetonitrile (50:20:30); Column: Teledyne Isco Redisep 40 g C18 , 20-40 micron particle size; Mobile phase A: 5 mM ammonium formate in water; Mobile phase B: acetonitrile. Fractions containing desired material were pooled and concentrated to yield racemic 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (40 mg). The racemate was separated into individual enantiomers by preparative chiral SFC chromatography with the following conditions: Column: (R,R) WHELK-O1 (4.6 x 250 mm, 5 micron particle size); Solvent A: supercritical CO_2; Solvent B: Methanol; Flowrate : 3.0 mL/min, Elution: Isocratic 50.0 %B, Oven Temperature: 40 °C. Fractions containing the first enantiomer to elute from the preparative SFC column were combined and concentrated to give 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methoxy [1,2,4]triazolo[1,5-*a*] pyridin-2-amine enantiomer 1 (7.0 mg, 0.016 mmol, 2.7 % yield) as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 8.52 (s, 1H), 8.36 (d, J = 6.80 Hz, 1H), 8.12 (s, 1H), 7.76-7.88 (m, 2H), 7.66-7.68 (m, 1H), 7.42 (d, J = 6.80 Hz, 1H), 7.35-7.38 (m, 2H), 7.17 (t, J = 9.20 Hz, 2H), 6.10 (s, 2H), 5.68-5.74 (m, 1H), 4.16 (s, 3H), 1.86 (s, 3H).
LCMS (ESI, m/z) 430.0 $[M+H]^+$

Example 238: 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



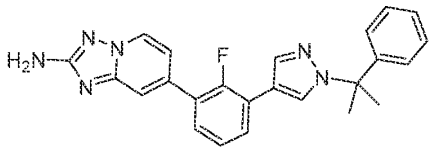
enantiomer 2

The title compound 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (7.0 mg, 0.016 mmol, 2.7 % yield) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 237 as a pale yellow solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 8.52 (s, 1H), 8.36 (d, J = 6.80 Hz, 1H), 8.12 (s, 1H), 7.76-7.88 (m, 2H), 7.66-7.68 (m, 1H), 7.42 (d, J = 6.80 Hz, 1H), 7.35-7.38 (m, 2H), 7.17 (t, J = 9.20 Hz, 2H), 6.10 (s, 2H), 5.68-5.74 (m, 1H), 4.16 (s, 3H), 1.86 (s, 3H).

LCMS (ESI, m/z) 430.0 $[M+H]^+$

Example 239: 7-(2-fluoro-3-(1-(2-phenylpropan-2-yl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



239A: 4-iodo-1-(2-phenylpropan-2-yl)-1H-pyrazole: (Following a procedure as outlined in *Organic Letters*, **2020**, *vol 22*, 7594-7598) To a ElectraSyn vial (10 mL) with a stir bar were combined 4-iodo-1H-pyrazole (100 mg, 0.516 mmol), 2-methyl-2-phenylpropionic acid (255 mg, 1.55 mmol), tetrabutylammonium hexafluorophosphate, 98% (150 mg, 0.387 mmol), 4A mol sieves (200 mg, 0.516 mmol), dichloromethane (5 mL) and 2,4,6-trimethylpyridine (68 µL, 0.516 mmol). The mixture was electrolyzed at a constant current of 10 mA for 2.5 h. Additional dichloromethane (5 mL) was added and the mixture was electrolyzed at a constant current of 10 mA for another 5.5 h. The mixture was diluted with ethyl acetate (100 mL) and water (5 mL) and the organic layer was washed with water (3 x 5 mL), brine (1 x 5 mL), dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude residue was purified by flash chromatography on silica gel, eluting with 0-75% gradient of ethyl acetate in hexanes to afford the title compound, 4-iodo-1-(2-phenylpropan-2-yl)-1H-pyrazole (39.0 mg, 0.125 mmol, 24.2%).

MS ESI m/z 312.8 $(M+H)^+$

239B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(1-(2-phenylpropan-2-yl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: To a solution of 4-iodo-1-(2-phenylpropan-2-yl)-1H-pyrazole (15 mg, 0.048 mmol) in dioxane (500 µL) was added a solution of *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (40 mg, 0.072 mmol) in dioxane (500 µL) and a solution of potassium phosphate tribasic, 2.0 M in water (75 µL, 0.15 mmol). The reaction was purged well with argon and was then treated with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (4.0 mg, 4.9 µmol). The reaction was again purged very well with argon and the vessel was securely capped and heated at 80 °C for 140 min. The mixture was diluted with ethyl acetate and filtered through a small pad of Celite. The Celite pad was rinsed with a 1:1 ethyl acetate:dichloromethane mixture and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel to afford the title compound *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(1-(2-phenylpropan-2-yl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (18 mg, 0.029 mmol, 61%).

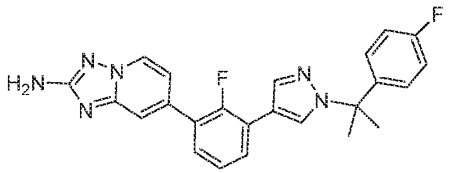
MS ESI m/z 613.4 $(M+H)^+$

239: 7-(2-fluoro-3-(1-(2-phenylpropan-2-yl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: To a solution of *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(1-(2-phenylpropan-2-yl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (18 mg, 0.029 mmol) in anhydrous dichloromethane (3 mL) was added neat TFA (150 µL, 1.95 mmol) and the reaction was allowed to stand at room temperature for 75 min. The volatiles were removed under a gentle stream of nitrogen and the crude residue was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 25-65% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give the title compound, 7-(2-fluoro-3-(1-(2-phenylpropan-2-yl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (6.9 mg, 0.017 mmol, 57%).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.60 (d, *J*=6.9 Hz, 1H), 8.35 (s, 1H), 8.02 (s, 1H), 7.89 - 7.80 (m, 1H), 7.53 (s, 1H), 7.46 (t, *J*=7.6 Hz, 1H), 7.37 - 7.19 (m, 4H), 7.10 (br d, *J*=6.9 Hz, 1H), 7.04 (d, *J*=7.3 Hz, 2H), 6.05 (s, 2H), 1.97 (s, 6H).

MS ESI m/z 413.2 $(M+H)^+$

Example 240: 7-(2-fluoro-3-(1-(2-(4-fluorophenyl)propan-2-yl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



240A: 1-(2-(4-fluorophenyl)propan-2-yl)-4-iodo-1H-pyrazole: (Following a procedure as outlined in *Organic Letters*, 2020, *vol 22*, 7594-7598) With no precautions to exclude air or moisture, an ElectraSyn vial (5 mL) with a stir bar was charged with 4-iodopyrazole (40.0 mg, 0.206 mmol), 2-(4-fluorophenyl)-2-methylpropanoic acid (109 mg, 0.600 mmol), tetrabutylammonium hexafluorophosphate (58 mg, 0.15 mmol), silver perchlorate (73.0 mg, 0.352 mmol), 3Å molecular sieves (100 mg powder, freshly dried), 2,4,6-collidine (24 mg, 28 µL, 0.20 mmol) and dichloromethane (3.0 mL). The ElectraSyn vial cap, equipped with anode (graphite) and cathode (Ni), were inserted into the mixture. After pre-stirring for 10 minutes, the reaction mixture was electrolyzed at a constant current of 10 mA for 2.5 hours. Note: this reaction was run 6 individual times, each time using the same amounts of reagents. The individual crude reaction mixtures were combined and the solvent was removed under a gentle stream of nitrogen. The resulting mixture was diluted with ethyl acetate (100 mL) and water (8 mL) and the organic layer was washed with water (5 x 8 mL), brine (1 x 10 mL), dried over sodium sulfate, filtered and evaporated to dryness. The crude residue was purified by flash chromatography on silica gel, eluting with 0-50% gradient of ethyl acetate in hexanes to afford the title compound, 1-(2-(4-fluorophenyl)propan-2-yl)-4-iodo-1H-pyrazole (168 mg, 0.508 mmol, 41%).

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 7.59 (s, 1H), 7.50 (s, 1H), 7.10 - 6.98 (m, 5H), 1.96 (s, 6H).

MS ESI m/z 331.0 $(M+H)^+$

240B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(1-(2-(4-fluorophenyl)propan-2-yl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: To a solution of 1-(2-(4-fluorophenyl)propan-2-yl)-4-iodo-1H-pyrazole (25 mg, 0.076 mmol) in dioxane (500 µL) was added a solution of *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (55 mg, 0.099 mmol) in dioxane (1000 µL) and potassium phosphate tribasic, 2.0 M in water (120 µL, 0.240 mmol). The mixture was purged well with argon and was then treated with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (7.0 mg, 8.6 µmol). The mixture was again purged very well with argon and the vessel was securely capped and heated at 80 °C for 3 h. The mixture was diluted with ethyl acetate (15 mL) and filtered through a small pad of Celite. The Celite pad was rinsed with a 1:1 ethyl acetate:dichloromethane mixture (50 mL) and the filtrate was concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel eluting with 0-100% gradient of ethyl acetate in hexanes to afford the title compound, *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(1-(2-(4-fluorophenyl)propan-2-yl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (17.7 mg, 0.028 mmol, 37.1%).

MS ESI m/z 631.5 $(M+H)^+$

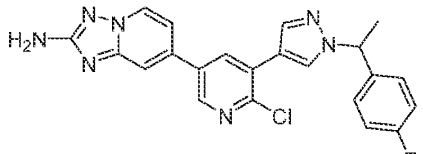
240: 7-(2-fluoro-3-(1-(2-(4-fluorophenyl)propan-2-yl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: To a solution of *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(1-(2-(4-fluorophenyl)propan-2-yl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (17.7 mg, 0.028 mmol) in anhydrous dichloromethane was added neat TFA (100 µL, 1.30 mmol) and the reaction was allowed to stand at room temp for 2.5 h. The volatiles were removed under a gentle stream of nitrogen and the crude residue was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 26-61% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give the title compound, 7-(2-fluoro-3-(1-(2-(4-

fluorophenyl)propan-2-yl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (6.7 mg, 0.0155 mmol, 55.5%).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.66 - 8.54 (m, 1H), 8.36 (s, 1H), 8.02 (s, 1H), 7.84 (t, *J*=7.5 Hz, 1H), 7.53 (s, 1H), 7.50 - 7.43 (m, 1H), 7.34 (t, *J*=7.7 Hz, 1H), 7.20 - 7.00 (m, 5H), 6.05 (s, 2H), 3.17 (d, *J*=5.2 Hz, 6H).

MS ESI m/z 431.1 $(M+H)^+$

Example 241: 7-(6-chloro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



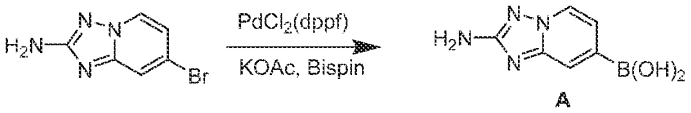
enantiomer 2

The title compound 7-(6-chloro-5-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 was obtained via a similar procedure as that described for Example 103, where 3-bromo-2-chloro-5-iodopyridine was substituted for 6-bromo-2,3-dichloropyridine in step 103A. This compound was the second enantiomer to elute from preparative SFC Column 1 where SFC Solvents 1 were the eluent.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.73 (d, *J*=2.1 Hz, 1H), 8.66 (d, *J*=6.9 Hz, 1H), 8.58 (s, 1H), 8.46 (d, *J*=2.1 Hz, 1H), 8.16 (s, 1H), 7.91 (s, 1H), 7.42 - 7.37 (m, 3H), 7.19 (t, *J*=8.8 Hz, 2H), 6.09 (s, 1H), 5.74 (q, *J*=6.9 Hz, 1H), 1.87 (d, *J*=7.1 Hz, 3H).

MS ESI m/z 434.1 $(M+H)^+$

Intermediate 79: (2-amino-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid

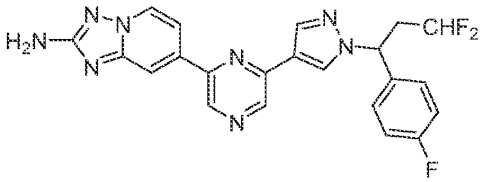


A

79: A mixture of 7-bromo-[1,2,4]triazolo[1,5-a]pyridin-2-amine (10 g, 46.9 mmol), bis(pinacolato)diboron (14.30 g, 56.3 mmol), potassium acetate (13.82 g, 141 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), (1.717 g, 2.347 mmol) in

1,4-dioxane (100 mL) was purged with N2 and stirred at 100 °C for 2 h. LCMS showed that the reaction was complete. The reaction mixture was set aside and used as was.

Example 242: 7-(6-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine enantimer 1



242A: 3,3-difluoro-1-(4-fluorophenyl)propan-1-ol: 1-fluoro-4-vinylbenzene (98 mg, 0.8 mmol), difluoromethanesulfinic acid sodium (166 mg, 1.200 mmol), tetrabutylammonium tetrafluoroborate (65.9 mg, 0.200 mmol), and acetone (7.2 mL)/water (0.8 mL) were added to a 10 mL vial equipped with a graphite anode (Graphite SK-50, 8 mm × 52 mm × 2 mm, immersion length is 25 mm) and a stainless-steel cathode (8 mm × 52 mm × 2 mm, immersion length is 25 mm). The mixture was purged with N_2 before applying electricity. The electrochemical reactor was operated under 5mA, 3.5 F/mol (2.5 mA/cm for 7.5 h) constant current mode at room temperature under magnetic stirring (800 rpm). The mixture was concentrated and purified via silica gel chromatography (4g, hexanes-100%EtOAc) to give 3,3-difluoro-1-(4-fluorophenyl)propan-1-ol (115 mg, 0.605 mmol, 76 % yield).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.37 (dd, *J*=8.5, 5.3 Hz, 2H), 7.12 - 7.05 (m, 2H), 6.17 - 5.86 (m, 1H), 4.97 (dd, *J*=9.7, 3.8 Hz, 1H), 2.42 - 2.26 (m, 1H), 2.23 - 2.09 (m, 1H), 2.04 - 1.91 (br, 1H)

242B: 4-bromo-1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole: To a solution of 4-bromo-1H-pyrazole (52.2 mg, 0.355 mmol), 3,3-difluoro-1-(4-fluorophenyl)propan-1-ol (45 mg, 0.237 mmol) and Ph_3P (150 mg, 0.572 mmol) in THF (1.5 mL) was added DIAD (0.100 mL, 0.515 mmol) dropwise. The mixture was stirred at rt for 30 min. The mixture was concentrated and purified via silica gel chromatography (4g, hexanes-50% EtOAc) to give the first eluting peak as desired 4-bromo-1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole (45 mg, 0.141 mmol, 59.6 % yield).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.56 (s, 1H), 7.32 - 7.28 (m, 2H), 7.11 - 7.04 (m, 2H), 5.86 - 5.53 (m, 1H), 5.43 (dd, *J*=9.8, 5.4 Hz, 1H), 3.23 - 3.05 (m, 1H), 2.67 - 2.53 (m, 1H)

MS ESI m/z 318.6 $(M+H)^+$

242C: tert-butyl (tert-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate: To a solution of 2-bromo-6-chloropyrazine (1.994 g, 10.31 mmol), (2-(bis(tert-butoxycarbonyl)amino)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid (4.52 g, 11.95 mmol), and 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (0.576 g, 0.884 mmol) in dioxane (30 mL) was added tripotassium phosphate (17.93 mL, 35.9 mmol). The mixture was stirred at 70 °C for 1 h. Water was added and extracted with 2x EtOAc. The organic layer was concentrated and purified via silica gel chromatography (80 g, hexanes-100%EtOAc) to give tert-butyl (tert-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (3.6 g, 8.06 mmol, 67.4 % yield).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 9.07 (s, 1H), 8.70 - 8.65 (m, 2H), 8.37 (dd, *J*=1.9, 0.9 Hz, 1H), 7.83 (dd, *J*=7.2, 2.0 Hz, 1H), 1.51 (s, 18H)

MS ESI m/z 447.1 $(M+H)^+$

242D: tert-butyl (tert-butoxycarbonyl)(7-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate: To a solution of tert-butyl (tert-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (0.197 g, 0.44 mmol), bispin (0.134 g, 0.528 mmol), and $PdCl_2$(dppf) (0.016 g, 0.022 mmol) in dioxane (5 mL) was added potassium acetate (0.108 g, 1.100 mmol). The mixture was vacuumed, and nitrogen filled three times, then stirred at 85 °C for 1 h. The reaction mixture was used as the crude tert-butyl (tert-butoxycarbonyl)(7-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate for the next step.

242E: tert-butyl (tert-butoxycarbonyl)(7-(6-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate: To the crude tert-butyl (tert-butoxycarbonyl)(7-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (114 mg, 0.212 mmol) was added 4-bromo-1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole (45 mg, 0.141

mmol), tripotassium phosphate (0.212 mL, 0.423 mmol) and $PdCl_2(dppf)$ (5.16 mg, 7.05 μmol). The mixture was stirred at 85 °C for 1.5 h. Water was added and extracted with 2x EtOAc. The organic layer was concentrated and purified via silica gel chromatography (4 g, hexanes-100%EtOAc) to give tert-butyl (tert-butoxycarbonyl)(7-(6-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (85 mg, 0.131 mmol, 93 % yield).

MS ESI m/z 651.4 $(M+H)^+$

242: 7-(6-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine: To a solution of tert-butyl (tert-butoxycarbonyl)(7-(6-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (85 mg, 0.131 mmol) in DCM (1 mL) was added TFA (0.5 mL, 6.49 mmol). The mixture was stirred at rt for 4 h, then concentrated. The residue was purified via preparative reverse phase chromatography with the following conditions: Column: XBridge C18, 19 mm x 200 mm, 5 μm particles; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation. The material was further purified via preparative SFC with the following conditions: Column: Chiralpak AS-H, 30 mm x 250mm, 5 Âμm particles; Flow Rate: 100.00 mL/min; Column Temperature: 50 °C. Fraction collection was triggered by PDA (220
nm). Fractions containing the desired product were combined and dried via centrifugal evaporation. The first eluting isomer 7-(6-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (10.8 mg, 0.024 mmol, 18.35 % yield) and the second eluting isomer 7-(6-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (9.6 mg, 0.021 mmol, 16.20 % yield) were obtained.

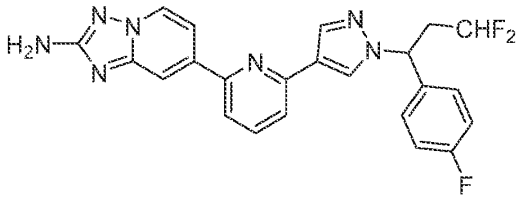
242, the first eluting isomer, ^1H NMR (500 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.99 (s, 1H), 8.85 (s, 1H), 8.68 (d, *J*=7.0 Hz, 1H), 8.35 (s, 1H), 8.24 (s, 1H), 7.74 (dd, *J*=7.1, 1.8 Hz, 1H), 7.54 (dd, *J*=8.7, 5.4 Hz, 2H), 7.22 (t, *J*=8.9 Hz, 2H), 6.14 (s, 2H), 6.11 - 5.84 (m, 2H), 3.26 - 3.12 (m, 1H), 2.86 - 2.72 (m, 1H)

MS ESI m/z 451.0 $(M+H)^+$

243, the second eluting isomer, ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.99 (s, 1H), 8.84 (s, 1H), 8.68 (d, *J*=6.9 Hz, 1H), 8.35 (s, 1H), 8.24 (s, 1H), 7.76 - 7.72 (m, 1H), 7.54 (dd, *J*=8.4, 5.6 Hz, 2H), 7.22 (t, *J*=8.8 Hz, 2H), 6.14 (s, 2H), 6.11 - 5.85 (m, 2H), 3.25 - 3.12 (m, 1H), 2.87 - 2.72 (m, 1H)

MS ESI m/z 451.0 $(M+H)^+$

Example 244: 7-(6-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine



244A: 1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole: To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (214 mg, 1.104 mmol), 3,3-difluoro-1-(4-fluorophenyl)propan-1-ol (140 mg, 0.736 mmol) and Ph_3P (251 mg, 0.957 mmol) in THF (3 mL) was dropwise added DIAD (0.186 mL, 0.957 mmol) at 0 °C under N_2. The mixture was allowed to warm up to rt over 1 h. Another 1 eq. of Ph_3P was added followed dropwise 1 eq. of DIAD. The mixture was stirred at rt for 30 min. The mixture was concentrated and purified via silica gel chromatography (12g, hexanes-40%EtOAc) to give 1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (170 mg, 0.464 mmol, 63.1 % yield).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.87 (s, 1H), 7.72 (s, 1H), 7.34 - 7.26 (m, 2H), 7.10 - 6.99 (m, 2H), 5.79 - 5.46 (m, 2H), 3.24 - 3.06 (m, 1H), 2.68 - 2.54 (m, 1H), 1.32 (s, 12H)

MS ESI m/z 366.8 $(M+H)^+$

244B: tert-butyl (tert-butoxycarbonyl)(7-(6-chloropyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate: To a solution of 2-chloro-6-iodopyridine (2.117 g, 8.84 mmol) in dioxane (30 mL) was added tert-butyl (tert-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (3.7 g, 8.04 mmol), dichloro[1,1'-bis(di-t-butylphosphino)ferrocene]palladium(II) (0.419 g, 0.643 mmol) and

tripotassium phosphate (12.06 mL, 24.11 mmol). The mixture was stirred at 70 °C for 1 h. Water was added and extracted with 2xEtOAc. The organic layer was concentrated. The residue was purified via silica gel chromatography (120g, hexanes-50%EtOAc) to give tert-butyl (tert-butoxycarbonyl)(7-(6-chloropyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (2.2 g, 4.93 mmol, 61.4 % yield).

MS ESI m/z 446.0 $(M+H)^+$

244C: tert-butyl (tert-butoxycarbonyl)(7-(6-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate: To a solution of tert-butyl (tert-butoxycarbonyl)(7-(6-chloropyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (146 mg, 0.328 mmol), 1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (100 mg, 0.273 mmol), and XPhos Pd G4 (11.76 mg, 0.014 mmol) in dioxane (1.5 mL) was added tripotassium phosphate (0.410 mL, 0.819 mmol). The mixture was stirred at 85 °C for 1 h. Water was added and extracted with 2xEtOAc. The organic layer was concentrated and purified via silica gel chromatography (12g, hexanes-100%EtOAc) to give tert-butyl (tert-butoxycarbonyl)(7-(6-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (170 mg, 0.262 mmol, 96 % yield).

MS ESI m/z 650.5 $(M+H)^+$

244 and **245:** Prepared in a similar fashion to **242** and **243** using **244C** as the starting material.

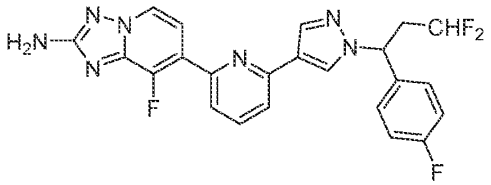
244, the first eluting isomer, ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.40 - 8.34 (m, 1H), 7.98 (s, 1H), 7.91 (br s, 1H), 7.72 - 7.62 (m, 2H), 7.51 - 7.41 (m, 2H), 7.32 - 7.25 (m, 2H), 7.01 - 6.93 (m, 2H), 5.83 (br s, 2H), 5.75 - 5.56 (m, 2H), 3.01 - 2.87 (m, 1H), 2.59 - 2.46 (m, 1H)

MS ESI m/z 450.3 $(M+H)^+$

245, the second eluting isomer, ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.48 (s, 1H), 8.43 - 8.36 (m, 1H), 8.01 (d, J=1.9 Hz, 1H), 7.94 (s, 1H), 7.74 - 7.63 (m, 2H), 7.52 - 7.43 (m, 2H), 7.34 - 7.27 (m, 2H), 7.03 - 6.94 (m, 2H), 5.90 - 5.60 (m, 4H), 2.96 - 2.88 (m, 1H), 2.62 - 2.52 (m, 1H)

MS ESI m/z 450.2 $(M+H)^+$

Example 246: 7-(6-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-fluoro-[1,2,4]triazolo-[1,5-a]pyridin-2-amine



246A: 7-(6-chloropyridin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine: To a solution of 8-fluoro-7-iodo-[1,2,4]triazolo[1,5-a]pyridin-2-amine (278 mg, 1.0 mmol), 2-chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (287 mg, 1.200 mmol) and $PdCl_2$(dppf)-DCM adduct (40.8 mg, 0.050 mmol) in dioxane (4.0 mL) was added tripotassium phosphate (1.000 mL, 3.00 mmol). The mixture was stirred at 95 °C for 1 h. Another 0.2 eq. of boronate and 0.02 eq. of $PdCl_2$(dppf) were added. After stirring at 100 °C for 30 min, water was added and extracted with 5x EtOAc to get most of product out of the aqueous layer. The organic layer was dried over Na_2SO_4 then concentrated to give a crude 7-(6-chloropyridin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (250 mg, 0.948 mmol, 95 % yield). The material was used without further purification for the next step.

MS ESI m/z 263.7 $(M+H)^+$

246 and **247**: To a solution of the crude 7-(6-chloropyridin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (60.5 mg, 0.229 mmol), 1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (70 mg, 0.191 mmol), and XPhos Pd G4 (8.23 mg, 9.56 µmol) in dioxane (1.5 mL) was added tripotassium phosphate (0.287 mL, 0.573 mmol). The mixture was stirred at 85 °C for 1 h. Water was added and extracted with 2x EtOAc. The organic layer was dried over Na_2SO_4, and concentrated. The residue was purified via preparative reverse phase chromatography with the following conditions: Column: XBridge C18, 19 mm x 200 mm, 5µm particles; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation. The material was further purified via preparative SFC with the following conditions: Column: Chiralpak IA, 30 mm x 250 mm, 5 µm particles; Flow Rate: 100 mL/min; Column Temperature: 35 °C. Fraction collection was triggered by UV (220 - 300) and MS (ESI +). Fractions containing the desired product

were combined and dried via centrifugal evaporation. The first eluting isomer 7-(6-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (2.5 mg, 5.26 µmol, 2.75 % yield) and the second eluting isomer 7-(6-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (2.7 mg, 5.72 µmol, 2.99 % yield) were obtained.

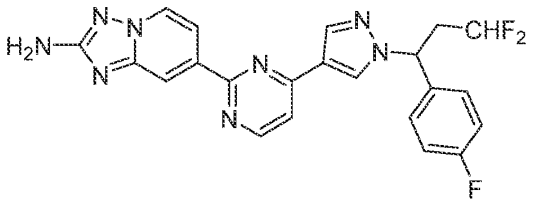
246, the first eluting isomer, ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.52 (d, *J*=7.2 Hz, 1H), 8.21 (s, 1H), 7.96 - 7.92 (m, 1H), 7.76 (d, *J*=6.9 Hz, 1H), 7.73 (d, *J*=7.9 Hz, 1H), 7.57 (t, *J*=7.0 Hz, 1H), 7.52 (dd, *J*=8.7, 5.4 Hz, 2H), 7.21 (t, *J*=8.8 Hz, 2H), 6.27 (s, 2H), 6.09 - 5.82 (m, 2H), 3.18 - 3.09 (m, 1H), 2.79 - 2.69 (m, 1H)

MS ESI m/z 467.9 $(M+H)^+$

247, the second eluting isomer, ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.50 (d, *J*=7.1 Hz, 1H), 8.20 (s, 1H), 7.95 - 7.92 (m, 1H), 7.76 (br d, *J*=7.3 Hz, 1H), 7.72 (d, *J*=7.8 Hz, 1H), 7.57 (t, *J*=6.9 Hz, 1H), 7.51 (dd, *J*=8.6, 5.7 Hz, 2H), 7.20 (t, *J*=9.0 Hz, 2H), 6.25 (s, 2H), 6.09 - 5.81 (m, 2H), 3.16 - 3.09 (m, 1H), 2.80 - 2.72 (m, 1H)

MS ESI m/z 468.0 $(M+H)^+$

Example 248: 7-(4-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-pyrimidin-2-yl)-[1,2,4]-triazolo[1,5-a]pyridin-2-amine



248A: 2-chloro-4-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidine: To a solution of 1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (110 mg, 0.300 mmol), 4-bromo-2-chloropyrimidine (105 mg, 0.541 mmol) and $PdCl_2$(dppf)-DCM adduct (12.27 mg, 0.015 mmol) in dioxane (2 mL) was added tripotassium phosphate (0.451 mL, 0.901 mmol). The mixture was stirred at 70 °C for 30 min. EtOAc was added, washed with water then concentrated. The residue was purified via silica gel chromatography (4 g, hexanes-100%EtOAc) to give 2-chloro-4-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidine (90 mg, 0.255 mmol, 85 % yield).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.51 (d, *J*=5.2 Hz, 1H), 8.16 (s, 1H), 8.11 (s, 1H), 7.40 - 7.33 (m, 2H), 7.31 (d, *J*=5.2 Hz, 1H), 7.12 - 7.05 (m, 2H), 5.89 - 5.57 (m, 1H), 5.54 (dd, *J*=9.7, 5.6 Hz, 1H), 3.27 - 3.11 (m, 1H), 2.74 - 2.59 (m, 1H)

MS ESI m/z 353.0 $(M+H)^+$

248 and **249:** To a solution of 2-chloro-4-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidine (90 mg, 0.255 mmol) in dioxane (1.0 mL) was added a crude (2-amino-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid (68.1 mg, 0.383 mmol), Xphos Pd G4 (21.98 mg, 0.026 mmol) and tripotassium phosphate (0.383 mL, 0.765 mmol). The mixture was stirred at 105 °C for 1 h. Water was added and extracted with 3x EtOAc. The organic layer was dried over Na_2SO_4 then concentrated. The residue was purified via preparative reverse phase chromatography with the following conditions: Column: XBridge C18, 19 mm x 200 mm, 5

µm particles; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation. The material was further purified via preparative SFC with the following conditions: Column: Chiralpak AS-H, 30 mm x 250 mm, 5 Âµm particles; Flow Rate: 100.00 mL/min; Column Temperature: 50 °C. Fraction collection was triggered by UV (220 nm). Fractions containing the desired product were combined and dried via centrifugal evaporation. The first eluting isomer 7-(4-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (7.9 mg, 0.018 mmol, 6.87 % yield), and the second eluting isomer 7-(4-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (12.6 mg, 0.027 mmol, 10.58 % yield) were obtained.

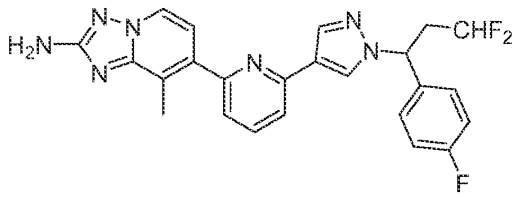
248, the first eluting isomer, ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.96 (s, 1H), 8.85 (d, *J*=5.3 Hz, 1H), 8.66 (d, *J*=7.0 Hz, 1H), 8.41 - 8.37 (m, 2H), 7.91 (dd, *J*=7.0, 1.8 Hz, 1H), 7.72 (d, *J*=5.3 Hz, 1H), 7.54 (dd, *J*=8.6, 5.5 Hz, 2H), 7.22 (t, *J*=8.9 Hz, 2H), 6.13 - 5.85 (m, 2H), 3.29 - 3.11 (m, 1H), 2.87 - 2.73 (m, 1H)

MS ESI m/z 451.1 $(M+H)^+$

249, the second eluting isomer, ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.95 (s, 1H), 8.85 (d, *J*=5.3 Hz, 1H), 8.65 (d, *J*=7.0 Hz, 1H), 8.39 (d, *J*=5.0 Hz, 2H), 7.91 (dd, *J*=6.9, 1.6 Hz, 1H), 7.71 (d, *J*=5.3 Hz, 1H), 7.54 (dd, *J*=8.5, 5.4 Hz, 2H), 7.22 (t, *J*=8.8 Hz, 2H), 6.14 (s, 2H), 6.12 - 5.86 (m, 2H), 3.23 - 3.14 (m, 1H), 2.84 - 2.74 (m, 1H)

MS ESI m/z 450.9 $(M+H)^+$

Example 250: 7-(6-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine



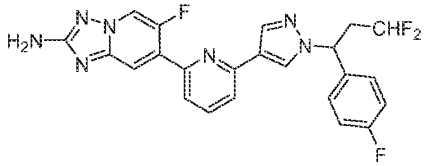
250 and **251:** Prepared in a similar fashion to **246** and **247.**

250A: 7-(6-chloropyridin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine: MS ESI m/z 259.8 $(M+H)^+$

250, the first eluting isomer, ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.45 (d, *J*=6.8 Hz, 1H), 8.15 (s, 1H), 7.92 - 7.88 (m, 1H), 7.68 (d, *J*=8.0 Hz, 1H), 7.54 - 7.48 (m, 2H), 7.42 (d, *J*=7.6 Hz, 1H), 7.20 (br t, *J*=8.9 Hz, 2H), 7.01 (d, *J*=6.9 Hz, 1H), 6.01 (s, 2H), 5.97 - 5.79 (m, 2H), 3.19 - 3.10 (m, 1H), 2.79 - 2.69 (m, 1H), 2.48 (s, 3H)
MS ESI m/z 464.1 $(M+H)^+$

251, the second eluting isomer, ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.45 (d, *J*=6.8 Hz, 1H), 8.15 (s, 1H), 7.92 - 7.88 (m, 1H), 7.68 (d, *J*=7.9 Hz, 1H), 7.51 (dd, *J*=8.6, 5.6 Hz, 2H), 7.42 (d, *J*=7.8 Hz, 1H), 7.20 (t, *J*=8.9 Hz, 2H), 7.01 (d, *J*=6.9 Hz, 1H), 6.01 (s, 2H), 5.96 - 5.80 (m, 2H), 3.20 - 3.08 (m, 1H), 2.81 - 2.69 (m, 1H), 2.48 (s, 3H)
MS ESI m/z 464.1 $(M+H)^+$

Example 252: 7-(6-(1-(3,3-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine



252 and **252:** Prepared in a similar fashion to **246** and **247.**

252A: 7-(6-chloropyridin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine: MS ESI m/z 263.7 $(M+H)^+$

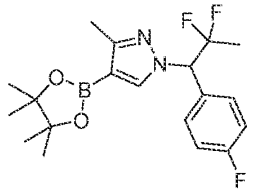
252, the first eluting isomer, ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.09 - 9.05 (m, 1H), 8.68 (s, 1H), 8.23 - 8.20 (m, 1H), 8.01 - 7.97 (m, 1H), 7.96 - 7.91 (m, 1H), 7.75 (br d, *J*=7.8 Hz, 1H), 7.70 - 7.65 (m, 1H), 7.56 - 7.50 (m, 2H), 7.25 - 7.18 (m, 2H), 6.09 - 5.82 (m, 2H), 3.25 - 3.11 (m, 1H), 2.84 - 2.70 (m, 1H)

MS ESI m/z 468.1 $(M+H)^+$

253, the second eluting isomer, ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.02 (br d, *J*=6.0 Hz, 1H), 8.67 (s, 1H), 8.21 (s, 1H), 7.97 - 7.90 (m, 2H), 7.74 (br d, *J*=7.9 Hz, 1H), 7.66 (br d, *J*=7.1 Hz, 1H), 7.56 - 7.50 (m, 2H), 7.21 (br t, *J*=8.4 Hz, 2H), 6.10 - 5.81 (m, 2H), 3.23 - 3.10 (m, 1H), 2.83 - 2.69 (m, 1H)

MS ESI m/z 468.1 $(M+H)^+$

Intermediate 80: 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole



Intermediate 80A: 1-bromo-1-(4-fluorophenyl)propan-2-one (**Intermediate 45A**) To a solution of 1-(4-fluorophenyl)propan-2-one (8.15 g, 53.6 mmol) in toluene (80 mL) at 0°C was added dibromine (2.76 mL, 53.6 mmol) dropwise. The reaction mixture was stirred at rt for 1h. It was diluted with EtOAc, quenched with 10% sodium thiosulfate, extracted with EtOAc, washed with water and brine, and dried over sodium sulfate. Filtration and concentration gave the crude product which was used for the next step without further purification.

Intermediate 80B: 1-(4-fluorophenyl)-1-(4-iodo-3-methyl-1H-pyrazol-1-yl)propan-2-one: To a solution of 4-iodo-3-methyl-1H-pyrazole (6.3 g, 30.3 mmol) in DMF (40 mL) at 0°C under nitrogen was added sodium hydride (60% dispersion in mineral oil) (1.454 g, 36.3 mmol) in portions. The reaction mixture was stirred at 0°C for 10 min and at rt for 15 min. It was cooled to 0°C and 1-bromo-1-(4-fluorophenyl)propan-2-one (9.10 g, 39.4 mmol) was added dropwise. The reaction mixture was stirred at 0°C for 30 min and at rt overnight. It was quenched with sat'd ammonium chloride, extracted with EtOAc, washed with brine, and dried over sodium sulfate. The crude product was purified by silica gel

chromatography, eluting with a gradient from 0 - 25% EtOAc in hexanes. Fractions containing the product were combined and evaporated to afford 1-(4-fluorophenyl)-1-(4-iodo-3-methyl-1H-pyrazol-1-yl)propan-2-one (2.8 g, 7.82 mmol, 25.8 % yield).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.39 - 7.34 (m, 2H), 7.29 (s, 1H), 7.16 (s, 2H), 6.09 (s, 1H), 2.26 (s, 3H), 2.23 (s, 3H).

LCMS (ESI, m/z): 358.6 $[M+H]^+$.

Intermediate 80C: 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-iodo-3-methyl-1H-pyrazole: To a solution of 1-(4-fluorophenyl)-1-(4-iodo-3-methyl-1H-pyrazol-1-yl)propan-2-one (790 mg, 2.206 mmol) in DCM (8 mL) at 0°C was added DAST (0.874 mL, 6.62 mmol) dropwise. The reaction mixture was stirred at rt overnight. It was quenched with ice-water, extracted with DCM, washed with sat'd sodium bicarbonate and brine, and dried over sodium sulfate. The crude product was purified by silica gel chromatography (40 g RediSep® column, eluting with a gradient from 0 - 20% EtOAc in. hexanes, 12 cv). Fractions containing the product were combined and evaporated to afford 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-iodo-3-methyl-1H-pyrazole (280 mg, 0.737 mmol, 33.4 % yield).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.60 (s, 1H), 7.53 - 7.46 (m, 2H), 7.13 - 7.06 (m, 2H), 5.64 - 5.48 (m, 1H), 2.27 (s, 3H), 1.77 - 1.60 (m, 3H).

LCMS (ESI, m/z): 380.6 $[M+H]^+$.

Intermediate 80, racemic: 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

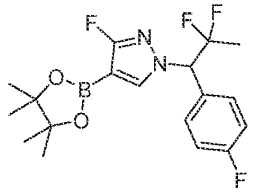
To a pressure vial were added 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-iodo-3-methyl-1H-pyrazole (224 mg, 0.589 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (224 mg, 0.884 mmol), potassium acetate (173 mg, 1.768 mmol), and DMSO (3 mL). It was purged with nitrogen and $PdCl_2$(dppf)-CH_2Cl_2 adduct (72.2 mg, 0.088 mmol) was added. The reaction mixture was heated at 75°C for 1h. It was cooled to rt, quenched with water, extracted with EtOAc. The combined organic layer was washed with brine and dried over sodium sulfate. The crude product was purified by silica gel chromatography (40 g RediSep® column, eluting with a gradient from 0 - 30% EtOAc in. hexanes, 15 cv). Fractions containing the product were combined and evaporated to afford 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole racemate (180 mg, 0.473 mmol, 80 % yield) as a tan oil.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.88 - 7.77 (m, 1H), 7.56 - 7.44 (m, 2H), 7.13 - 7.00 (m, 2H), 5.69 - 5.52 (m, 1H), 2.41 (s, 3H), 1.68 (t, *J*=18.8 Hz, 3H), 1.28 (s, 12H). LCMS (ESI, m/z): 380.8 $[M+H]^+$.

Intermediate 80, chiral: (R)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole: To a pressure vial were added (R)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-iodo-3-methyl-1H-pyrazole (500 mg, 1.315 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (480 mg, 1.841 mmol), potassium acetate (323 mg, 3.29 mmol), and DMSO (8 mL). It was purged with nitrogen and $PdCl_2$(dppf)-CH_2Cl_2 adduct (107 mg, 0.132 mmol) was added. The reaction mixture was heated at 75°C for 1h. It was cooled to rt, quenched with water, extracted with EtOAc. The combined organic layer was washed with brine and dried over sodium sulfate. The crude product was purified by silica gel chromatography (40 g RediSep® column, eluting with a gradient from 0 - 30% EtOAc in. hexanes, 15 cv). Fractions containing the product were combined and evaporated to afford (R)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (415 mg, 1.091 mmol, 83 % yield) as a tan oil.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.88 - 7.77 (m, 1H), 7.56 - 7.44 (m, 2H), 7.13 - 7.00 (m, 2H), 5.69 - 5.52 (m, 1H), 2.41 (s, 3H), 1.68 (t, *J*=18.8 Hz, 3H), 1.28 (s, 12H). LCMS (ESI, m/z): 380.8 $[M+H]^+$.

Intermediate 81: 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole



Intermediate 81A: 1-(3-fluoro-1H-pyrazol-1-yl)-1-(4-fluorophenyl)propan-2-one: To a solution of 3-fluoro-1H-pyrazole (330 mg, 3.83 mmol) in DMF (6 mL) at 0°C was added NaH (60% dispersion in mineral oil) (184 mg, 4.60 mmol). It was stirred at rt for 10 min and cooled to 0°C, 1-bromo-1-(4-fluorophenyl)propan-2-one (1063 mg, 4.60 mmol) was added dropwise. The reaction mixture was stirred at rt overnight. It was quenched with sat'd NH4Cl, extracted with EtOAc, washed with brine, and dried over sodium sulfate. The crude

product was purified by silica gel chromatography (40 g RediSep® column, eluting with a gradient from 0 - 30% EtOAc in. hexanes, 15 cv). Fractions containing the product were combined and evaporated to afford 1-(3-fluoro-1H-pyrazol-1-yl)-1-(4-fluorophenyl)propan-2-one (470 mg, 1.990 mmol, 51.9 % yield).

LCMS (ESI, m/z): 236.8 $[M+H]^+$.

Intermediate 81B: 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-1H-pyrazole: To a solution of 1-(3-fluoro-1H-pyrazol-1-yl)-1-(4-fluorophenyl)propan-2-one (350 mg, 1.482 mmol) in DCM (6 mL) at 0°C was added DAST (0.587 mL, 4.44 mmol) dropwise. The reaction mixture was stirred at rt overnight. It was quenched with ice-water and extracted with DCM. The combined organic layer was washed with sat'd sodium bicarbonate, brine, and dried over sodium sulfate. The crude product was purified by silica gel chromatography (40 g RediSep® column, eluting with a gradient from 0 - 20% EtOAc in. hexanes, 12 cv). Fractions containing the product were combined and evaporated to afford 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-1H-pyrazole (180 mg, 47%).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.60 - 7.49 (m, 2H), 7.43 (t, *J*=2.5 Hz, 1H), 7.17 - 7.04 (m, 2H), 5.89 (dd, *J*=5.9, 2.5 Hz, 1H), 5.46 - 5.35 (m, 1H), 1.70 (t, *J*=18.9 Hz, 3H).

LCMS (ESI, m/z): 258.8 $[M+H]^+$.

Intermediate 81C: 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-4-iodo-1H-pyrazole: To a solution of 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-1H-pyrazole (180 mg, 0.697 mmol) in acetonitrile (6 mL) was added NIS (157 mg, 0.697 mmol). The reaction mixture was heated at 65°C for 4h and rt overnight. It was cooled to rt and concentrated. The crude product was purified by silica gel chromatography (40 g RediSep® column, eluting with a gradient from 0 - 20% EtOAc in. hexanes, 15 cv). Fractions containing the product were combined and evaporated to afford 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-4-iodo-1H-pyrazole (212 mg, 0.552 mmol, 79 % yield).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.57 - 7.50 (m, 2H), 7.49 - 7.46 (m, 1H), 7.16 - 7.06 (m, 2H), 5.38 (s, 1H), 1.80 - 1.65 (m, 3H).

LCMS (ESI, m/z): 384.7 $[M+H]^+$.

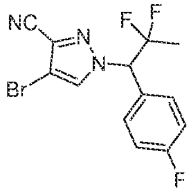
Intermediate 81: 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole racemate: To a pressure vial were added 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-4-iodo-1H-pyrazole (200 mg, 0.521

mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (159 mg, 0.625 mmol), potassium acetate (128 mg, 1.302 mmol), and DMSO (6 mL). It was purged with nitrogen and $PdCl_2$(dppf)-CH_2Cl_2 adduct (42.5 mg, 0.052 mmol) was added. The reaction mixture was heated at 75°C for 1h. It was cooled to rt and added ice-water, extracted with EtOAc. The combined organic layer was washed with brine and dried over sodium sulfate. The crude product was purified by silica gel chromatography (40 g RediSep® column, eluting with a gradient from 0 - 25% EtOAc in. hexanes, 15 cv). Fractions containing the product were combined and evaporated to afford 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole racemate (119 mg, 0.310 mmol, 59.5 % yield).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.74 - 7.65 (m, 1H), 7.58 - 7.48 (m, 2H), 7.15 - 7.04 (m, 2H), 5.47 - 5.34 (m, 1H), 1.79 - 1.64 (m, 3H), 1.33 (s, 12H).

LCMS (ESI, m/z): 384.7 $[M+H]^+$.

Intermediate 82: 4-bromo-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole-3-carbonitrile



Intermediate 82A: 1-chloro-1-(4-fluorophenyl)propan-2-one: To a solution of 1-(4-fluorophenyl)propan-2-one (5 g, 32.9 mmol) in DCM (30 mL) at 0°C was added sulfuryl chloride (3.21 mL, 39.4 mmol) dropwise. The reaction mixture was stirred at rt for 4h. The reaction mixture was diluted with DCM, washed with water, sat'd sodium bicarbonate, and brine. Filtration and concentration gave the crude product which was used for the next step without further purification.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.51 - 7.34 (m, 2H), 7.17 - 6.93 (m, 3H), 5.35 (s, 1H), 2.24 (s, 3H).

Intermediate 82B: 4-bromo-1-(1-(4-fluorophenyl)-2-oxopropyl)-1H-pyrazole-3-carbonitrile: To a solution of 4-bromo-1H-pyrazole-3-carbonitrile (1.01 g, 5.87 mmol) in acetonitrile (25 mL) was added potassium carbonate (1.623 g, 11.75 mmol) at 0°C. The suspension was stirred at rt for 30 min. 1-Chloro-1-(4-fluorophenyl)propan-2-one (1.096 g,

5.87 mmol) was added dropwise. The reaction mixture was stirred at rt for 2h. It was quenched with water, extracted with EtOAc. The organic layer was washed with brine and dried over sodium sulfate. The crude product was purified by silica gel chromatography (24 g RediSep® column, eluting with a gradient from 5 - 25% EtOAc in. hexanes, 13 cv). Fractions containing the product were combined and evaporated to afford 4-bromo-1-(1-(4-fluorophenyl)-2-oxopropyl)-1H-pyrazole-3-carbonitrile (1.13 g, 3.51 mmol, 59.7 % yield).

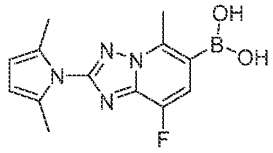
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.47 (s, 1H), 7.43 - 7.36 (m, 2H), 7.25 - 7.16 (m, 2H), 6.31 - 6.17 (m, 1H), 2.29 (s, 3H).

LCMS (ESI, m/z): 319.7/321.6 $[M+H]^+$.

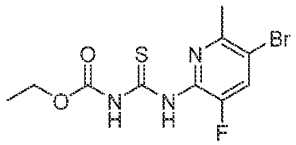
Intermediate 82: 4-bromo-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole-3-carbonitrile racemate: To a solution of 4-bromo-1-(1-(4-fluorophenyl)-2-oxopropyl)-1H-pyrazole-3-carbonitrile (580 mg, 1.80 mmol)in DCN (20 mL) at 0°C was added DAST (0.714 mL, 5.40 mmol) dropwise. The reaction mixture was stirred at 0°C for 30 min and then rt overnight. It was concentrated. It was quenched with ice-water, extracted with DCM. The combined organic layer was washed with sodium carbonate, brine, and dried over sodium sulfate. The crude product was purified by silica gel chromatography (40 g RediSep® column, eluting with a gradient from 0 - 30% EtOAc in. hexanes, 13 cv). Fractions containing the product were combined and evaporated to afford 4-bromo-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole-3-carbonitrile racemate (450 mg, 1.308 mmol, 72.6 % yield).

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.81 - 7.66 (m, 1H), 7.60 - 7.43 (m, 2H), 7.21 - 7.05 (m, 2H), 5.71 - 5.52 (m, 1H), 1.80 - 1.65 (m, 3H).

Intermediate 83: (2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-5-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)boronic acid



Intermediate 83A: O-ethyl N-((3-fluoro-6-methyl-5-bromopyridin-2-yl)carbamothioyl)carbamate



To a solution of 5-bromo-3-fluoro-6-methylpyridin-2-amine (1.04 g, 5.07 mmol) in dioxane (12 mL) was added O-ethyl carbonisothiocyanatidate (0.699 g, 5.33 mmol) dropwise. The reaction mixture was stirred at rt overnight and concentrated. The solid was triturated with small amount of ethanol to remove the dark color. The solid was dried and used for the next step.

LCMS (ESI, m/z): 335.8/337.7 $[M+H]^+$.

Intermediate 83B: 6-bromo-8-fluoro-5-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine: To a suspension of thiourea (1.704 g, 5.07 mmol) in ethanol (15 mL) were added hydroxylamine hydrochloride (2.1g, 30.2 mmol) and Hunig'sbase (3.10 mL, 17.75 mmol). It was heated at 70°C for 2h and RT overnight. It was concentrated and the residue was suspended in small amount of ethanol and the solid was collected by filtration. It was dried to give 6-bromo-8-fluoro-5-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.87 g, 3.55 mmol, 70.0 % yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (d, *J*=10.1 Hz, 1H), 2.66 (d, *J*=1.1 Hz, 3H).

LCMS (ESI, m/z): 244.8/246.8 $[M+H]^+$.

Intermediate 83C: 6-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-5-methyl-[1,2,4]triazolo[1,5-a]pyridine: The reaction mixture of 6-bromo-8-fluoro-5-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (315 mg, 1.285 mmol), hexane-2,5-dione (734 mg, 6.43 mmol), and acetic acid (0.29 mL, 5.14 mmol) in toluene were heated at 130°C overnight. It was cooled to rt and concentrated. The crude product was purified by silica gel chromatography (40 g RediSep® column, eluting with a gradient from 0 - 40% EtOAc in. hexanes, 13 cv). Fractions containing the product were combined and evaporated to afford 6-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-5-methyl-[1,2,4]triazolo[1,5-a]pyridine (220 mg, 0.680 mmol, 53 % yield).

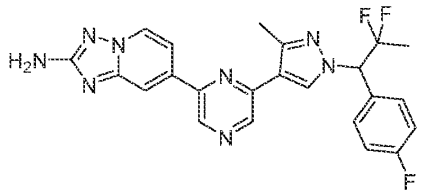
LCMS (ESI, m/z): 322.9/324.7 $[M+H]^+$.

Intermediate 83: (2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-5-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)boronic acid: The title compound (2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-5-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)boronic acid was obtained in a similar fashion as described for the preparation of **intermediate** 80 where 6-

bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-5-methyl-[1,2,4]triazolo[1,5-a]pyridine was used in place of 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-iodo-3-methyl-1H-pyrazole.

LCMS (ESI, m/z): 288.8 $[M+H]^+$.

Example 254: 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine



254A: tert-butyl (tert-butoxycarbonyl)(7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate

To a pressure vial were added 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (65 mg, 0.171 mmol), tert-butyl (tert-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (76 mg, 0.171 mmol), potassium phosphate (2 M water solution) (0.214 mL, 0.427 mmol), and dioxane (2 mL). The reaction mixture was purged with nitrogen and 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (11.14 mg, 0.017 mmol) was added. It was heated at 70°C for 1h and cooled to rt. The reaction was diluted water and ethyl acetate. The layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude residue was used for next step without further purification.

LCMS (ESI, m/z): 665.0 $[M+H]^+$.

254: 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine racemate

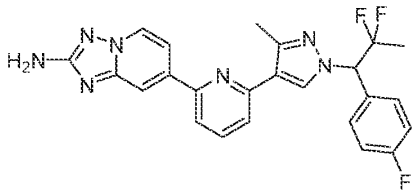
A solution of the crude residue from the previous step containing racemic tert-butyl (tert-butoxycarbonyl)(7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (assumed 114 mg, 0.171 mmol) in DCM (1 mL) was treated with TFA (1.0 mL) and the reaction mixture was stirred for 2 h. The mixture was concentrated via nitrogen stream to a residue. The residue was

dissolved in DMF and filtered to give a 2 mL sample which was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 21 - 51% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide racemic 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine racemate (21.3 mg, 0.046 mmol, 27% yield). This racemic material was then further purified via preparative SFC with the following conditions: Column: Whelk-O1 (R,R), 21 mm x 250 mm, 5 µm particles; Flow Rate:75.00 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (230 nm). Fractions containing the first isomer to elute from the chiral column were combined and dried via centrifugal evaporation to provide 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine, enantiomer 1 (9 mg, 0.019 mmol, 11.4%).

254, the first eluting enantiomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.26 - 9.15 (m, 1H), 9.02 - 8.93 (m, 1H), 8.78 - 8.64 (m, 2H), 8.24 - 8.14 (m, 1H), 7.78 (br dd, *J*=8.3, 5.7 Hz, 2H), 7.70 (dd, *J*=6.9, 1.6 Hz, 1H), 7.28 (t, *J*=8.9 Hz, 2H), 6.23 - 6.14 (m, 1H), 1.67 (br t, *J*=19.0 Hz, 3H).

LCMS (ESI, m/z): 465.2 $[M+H]^+$.

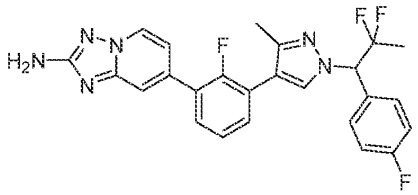
Example 255: 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine



The title compound 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine enantiomer was obtained as the first eluting enantiomer from the preparative SFC column in a similar fashion as described for the preparation of example **254** where tert-butyl (tert-butoxycarbonyl)(7-(6-

chloropyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate was used in place of tert-butyl (tert-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate in the first step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 26-56% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Whelk-O1 (R,R), 21 mm x 250 mm, 5 μm particles; Flow Rate:75.00 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (230 nm). Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 40%B over 18 minutes; Flow Rate: 85 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (275 nm). Fractions containing the first isomer to elute from the chiral column were combined and dried via centrifugal evaporation to provide 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine, enantiomer 1 (10.2 mg, 12.7%). **255**, the first eluting enantiomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 - 8.61 (m, 1H), 8.58 - 8.54 (m, 1H), 8.13 - 8.08 (m, 1H), 7.99 - 7.88 (m, 2H), 7.80 - 7.73 (m, 2H), 7.71 - 7.65 (m, 2H), 7.32 - 7.24 (m, 2H), 6.20 - 6.09 (m, 1H), 2.62 (s, 3H), 1.77 - 1.59 (m, 3H).
LCMS (ESI, m/z): 464.2 $[M+H]^+$.

Example 256: 7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine

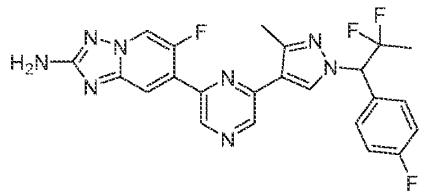


The title compound 7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine enantiomer 1 was obtained as the first eluting enantiomer from the preparative SFC column in a similar fashion as described for the preparation of example **254** where tert-butyl (7-(3-bromo-2-fluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)(tert-butoxycarbonyl)carbamate was used in place of tert-butyl (tert-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate in the first step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 27-57% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Whelk-O1 (R,R), 21 mm x 250 mm, 5 μm particles; Flow Rate:75.00 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (230 nm). Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 40%B over 18 minutes; Flow Rate: 85 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (275 nm). Fractions containing the first isomer to elute from the chiral column were combined and dried via centrifugal evaporation to provide 7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine enantiomer 1 (13.8 mg, 17.8%). 256

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 - 8.50 (m, 1H), 8.20 - 8.07 (m, 1H), 7.79 - 7.69 (m, 2H), 7.60 - 7.45 (m, 3H), 7.43 - 7.33 (m, 1H), 7.31 - 7.21 (m, 2H), 7.17 - 7.03 (m, 1H), 6.18 - 5.87 (m, 3H), 2.27 (s, 3H), 1.63 (br t, *J*=19.1 Hz, 3H).

LCMS (ESI, m/z): 481.1 $[M+H]^+$.

Example 257: 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine

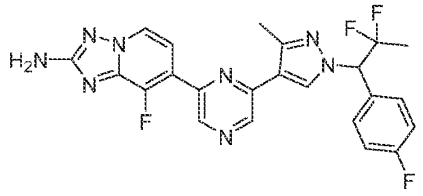


The title compound 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine, enantiomer 1 (9.1 mg, 12.5%) was obtained as the first eluting enantiomer from the preparative SFC column in a similar fashion as described for the preparation of example **254** where tert-butyl (tert-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate was used in place of tert-butyl (tert-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate in the first step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 24-64% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Whelk-O1 (R,R), 21 mm x 250 mm, 5 μm particles; Flow Rate:75.00 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (230 nm). Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 40%B over 18 minutes; Flow Rate: 85 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (275 nm). Fractions containing the first isomer to elute from the chiral column were combined and dried via centrifugal evaporation to provide 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine enantiomer 1 (9.1 mg, 12.5%).

257, the first eluting enantiomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.06 - 8.99 (m, 2H), 8.88 - 8.84 (m, 1H), 8.73 - 8.68 (m, 1H), 7.93 (br d, *J*=7.0 Hz, 1H), 7.83 - 7.66 (m, 2H), 7.26 (br t, *J*=8.9 Hz, 2H), 6.32 - 6.05 (m, 3H), 2.57 (s, 3H), 1.75 - 1.55 (m, 3H).

LCMS (ESI, m/z): 483.2 $[M+H]^+$.

Example 258: 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine

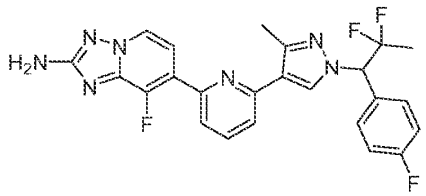


The title compound 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine racemate was obtained in a similar fashion as described for the preparation of example **254** where tert-butyl (tert-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate was used in place of tert-butyl (tert-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate in the first step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 22-52% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (20.7 mg, 51.1%).

258, racemic: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.04 - 9.00 (m, 1H), 8.99 - 8.95 (m, 1H), 8.73 (s, 1H), 8.67 - 8.53 (m, 1H), 7.77 (dd, *J*=8.4, 5.7 Hz, 2H), 7.50 (t, *J*=6.8 Hz, 1H), 7.36 - 7.15 (m, 2H), 6.42 - 6.29 (m, 2H), 6.25 - 6.07 (m, 1H), 1.67 (br t, *J*=19.1 Hz, 3H).

LCMS (ESI, m/z): 483.1 $[M+H]^+$.

Example 259: 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine

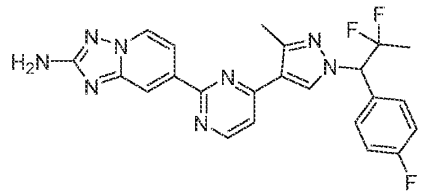


The title compound 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine racemate was obtained in a similar fashion as described for the preparation of example **254** where tert-butyl (tert-butoxycarbonyl)(8-fluoro-7-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate was used in place of tert-butyl (tert-butoxycarbonyl)(7-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate in the first step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 25-55% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 77-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (10 mg, 27.5%).

259, racemic: ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.61 - 8.47 (m, 2H), 7.91 (s, 1H), 7.83 - 7.69 (m, 4H), 7.58 - 7.47 (m, 1H), 7.27 (t, *J*=8.9 Hz, 2H), 6.32 - 6.24 (m, 2H), 6.21 - 6.03 (m, 1H), 1.81 - 1.53 (m, 3H).

LCMS (ESI, m/z): 482.2 $[M+H]^+$.

Example 260: 7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine



260A: 2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidine: To a pressure vial were added 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (290 mg, 0.763 mmol), 2,4-dichloropyrimidine (114 mg, 0.763 mmol), potassium phosphate (2 M water solution) (1.14 mL, 2.29 mmol), and dioxane (2 mL). The reaction mixture was purged with nitrogen and $PdCl_2(dppf)$-CH_2Cl_2 adduct (62 mg, 0.076 mmol) was added. It was heated at 80°C for 90 min. and cooled to rt. The reaction was diluted water and ethyl acetate. The layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude residue was used for next step without further purification. The crude product was purified by silica gel chromatography (40 g RediSep® column, eluting with a gradient from 0 - 50% EtOAc in. hexanes). Fractions containing the product were combined and evaporated to afford 2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidine (250 mg, 0.682 mmol, 89 % yield) as a colorless foam.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.60 - 8.47 (m, 1H), 8.30 - 8.21 (m, 1H), 7.65 - 7.51 (m, 2H), 7.36 - 7.32 (m, 1H), 7.12 (t, *J*=8.6 Hz, 2H), 5.71 - 5.43 (m, 1H), 2.65 - 2.56 (m, 3H), 1.83 - 1.66 (m, 3H).

LCMS (ESI, m/z): 366.9/368.7 $[M+H]^+$.

260B: tert-butyl (tert-butoxycarbonyl)(7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate: To a pressure vial were added 2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidine (35 mg, 0.095 mmol), tert-butyl (tert-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (48.3 mg, 0.105 mmol), potassium phosphate (2 M water solution) (0.14 mL, 0.286 mmol), and dioxane (2 mL). The reaction mixture was purged with nitrogen and 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (6.2 mg, 0.01 mmol) was added. It was heated at 70°C for 90 min. and cooled to rt. The reaction was diluted water and ethyl acetate. The layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude residue was used for next step without further purification.

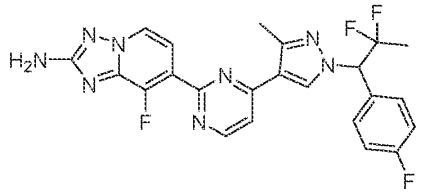
LCMS (ESI, m/z): 665.4 $[M+H]^+$.

260: 7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine: The title compound 7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine, racemate (21.7 mg, 71.5%) was obtained in a similar fashion as described for the preparation of example **254** where tert-butyl (tert-butoxycarbonyl)(7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate was used in place of tert-butyl (tert-butoxycarbonyl)(7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate in the second step. The crude racemate prepared in the final synthetic step was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 25-55% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give racemic 7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Whelk-O1 (R,R), 21 mm x 250 mm, 5 µm particles; Flow Rate:75.00 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (230 nm). Mobile Phase A: supercritical CO_2; Mobile Phase B: *i*-PrOH with 0.1% NH_4OH; Elution gradient: isocratic 40%B over 18 minutes; Flow Rate: 85 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (275 nm). Fractions containing the first isomer to elute from the chiral column were combined and dried via centrifugal evaporation to provide 7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine, enantiomer 1 (10.4 mg, 44.4%).

260, first eluting enantiomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 - 8.84 (m, 1H), 8.84 - 8.80 (m, 1H), 8.73 - 8.62 (m, 1H), 8.34 - 8.26 (m, 1H), 7.88 - 7.84 (m, 1H), 7.80 - 7.71 (m, 3H), 7.32 - 7.25 (m, 2H), 6.26 - 6.15 (m, 1H), 6.15 - 6.12 (m, 2H), 2.67 (s, 3H), 1.68 (br t, *J*=19.1 Hz, 3H).

LCMS (ESI, m/z): 465.2 $[M+H]^+$.

Example 261: 7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine

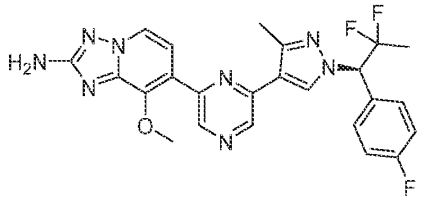


The title compound 7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine, racemate (4.7 mg, 32.5%) was obtained in a similar fashion as described for the preparation of example **260** where tert-butyl (tert-butoxycarbonyl)(8-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate was used in place of tert-butyl (tert-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate in the first step.

261, racemic: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.95 - 8.84 (m, 1H), 8.81 - 8.71 (m, 1H), 8.59 - 8.44 (m, 1H), 7.82 - 7.70 (m, 3H), 7.62 - 7.53 (m, 1H), 7.35 - 7.19 (m, 2H), 6.36 - 6.27 (m, 2H), 6.27 - 6.11 (m, 1H), 1.76 - 1.57 (m, 3H).

LCMS (ESI, m/z): 483.1 $[M+H]^+$.

Example 262: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine



262A: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine

To a pressure vial were added 7-(6-chloropyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (40 mg, 0.113 mmol), (R)-1-(2,2-difluoro-1-(4-

fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (47 mg, 0.124 mmol), potassium phosphate (2 M water solution) (0.17 mL, 0.338 mmol), and dioxane (2 mL). The reaction mixture was purged with nitrogen and 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (7.2 mg, 0.011 mmol) was added. It was heated at 70°C for 1h and cooled to rt. The reaction was diluted with water and ethyl acetate. The layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water, brine, and dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residue was dissolved in DMF and filtered to give a 2 mL sample which was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 32-100% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide : (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (33 mg, 51%). LCMS (ESI, m/z): 573.2 $[M+H]^+$.

262: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine

A solution of (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine

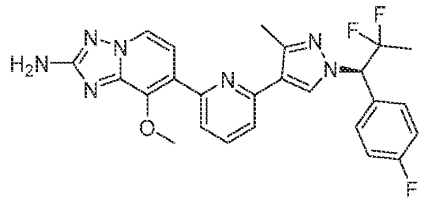
(32 mg, 0.056 mmol) in THF (1 mL), water (0.5 mL), and TFA (1 mL) was heated at 70°C in a sealed pressure vial overnight. The mixture was concentrated via nitrogen stream to a residue. The residue was dissolved in DMF and filtered to give a 2 mL sample which was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 32 - 60% B over 24 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via

centrifugal evaporation to provide (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine (8 mg, 28.5%).

262, chiral: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.01 (s, 1H), 8.93 (s, 1H), 8.68 (s, 1H), 8.51 - 8.34 (m, 1H), 7.84 - 7.70 (m, 2H), 7.45 - 7.34 (m, 1H), 7.32 - 7.21 (m, 2H), 6.24 - 6.06 (m, 3H), 4.25 (s, 3H), 2.57 (s, 3H), 1.66 (m, 3H).

LCMS (ESI, m/z): 495.2 $[M+H]^+$.

Example 263: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine

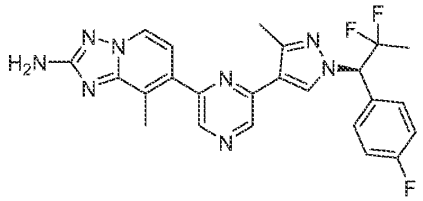


The title compound (R)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (3.5 mg, 7.4%) was obtained in a similar fashion as described for the preparation of **Example 262** where 7-(6-chloropyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine was used in place of 7-(6-chloropyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine in the first step.

263, chiral: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56 - 8.46 (m, 1H), 8.43 - 8.33 (m, 1H), 7.92 - 7.70 (m, 4H), 7.66 - 7.56 (m, 1H), 7.47 - 7.37 (m, 1H), 7.33 - 7.20 (m, 2H), 6.20 - 6.06 (m, 3H), 4.16 (s, 3H), 2.58 - 2.54 (m, 3H), 1.75 - 1.58 (m, 3H).

LCMS (ESI, m/z): 494.2 $[M+H]^+$.

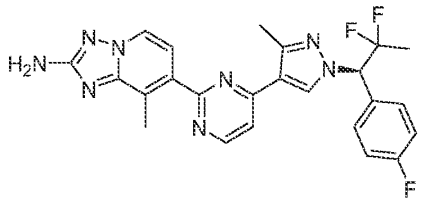
Example 264: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine



The title compound (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (5.1 mg, 9.0%) was obtained in a similar fashion as described for the preparation of **Example 262** where (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine was used in place of (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine.

264, chiral ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.06 - 8.92 (m, 1H), 8.77 - 8.62 (m, 2H), 8.57 - 8.47 (m, 1H), 7.86 - 7.65 (m, 2H), 7.37 - 7.21 (m, 2H), 7.16 - 7.03 (m, 1H), 6.25 - 6.11 (m, 1H), 2.54 (s, 3H), 1.80 - 1.58 (m, 3H).
LCMS (ESI, m/z): 479.3 $[M+H]^+$.

Example 265: (R)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine



265A: (R)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine

The title compound (R)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine was obtained in a similar fashion as described for the preparation of **Intermediate 262** where 2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine was used in

place of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine and (R)-2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidine was used in place 2-chloro-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazine. The crude racemate prepared was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 0-100% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give (R)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine.

LCMS (ESI, m/z): 557.2 $[M+H]^+$.

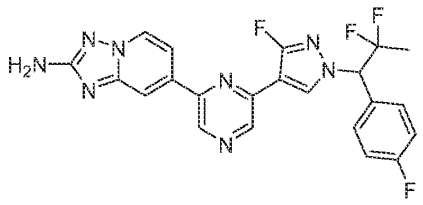
265: (R)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine

The title compound (R)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (23.6 mg, 51.2%) was obtained in a similar fashion as described for the preparation of example **262** where (R)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine was used in place of (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine.

265, chiral: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.86 (d, *J*=5.4 Hz, 1H), 8.75 - 8.64 (m, 1H), 8.52 - 8.37 (m, 1H), 7.83 - 7.63 (m, 3H), 7.43 - 7.35 (m, 1H), 7.34 - 7.18 (m, 2H), 6.23 - 6.10 (m, 1H), 6.07 - 5.96 (m, 2H), 3.19 (s, 1H), 2.74 - 2.58 (s, 3H), 1.73 - 1.57 (m, 3H).

LCMS (ESI, m/z): 479.2 $[M+H]^+$.

Example 266: 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine

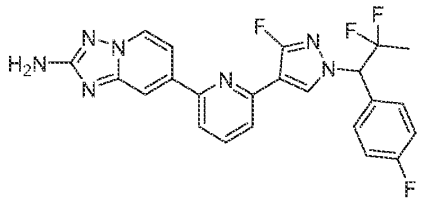


The title compound 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine, racemate (25.9 mg, 17.8%) was obtained in a similar fashion as described for the preparation of example **254** where 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-4-(3,3,4,4-tetramethylborolan-1-yl)-1H-pyrazole was used in place of 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in the first step.

266, racemic: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.37 - 9.24 (m, 1H), 8.99 - 8.85 (m, 1H), 8.83 - 8.66 (m, 2H), 8.35 - 8.19 (m, 1H), 7.87 - 7.66 (m, 3H), 7.45 - 7.25 (m, 2H), 6.31 - 6.11 (m, 3H), 1.83 - 1.56 (m, 3H).

LCMS (ESI, m/z): 469.1 $[M+H]^+$.

Example 267: 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine

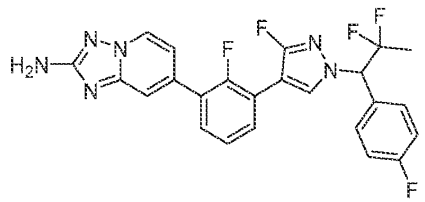


The title compound 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine, enantiomer 1 (13.4 mg, 15.2%) was obtained in a similar fashion as described for the preparation of example **255** where 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole was used in place of 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in the first step.

267, first eluting enantiomer: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.71 - 8.59 (m, 2H), 8.20 - 8.12 (m, 1H), 8.09 - 7.91 (m, 2H), 7.79 - 7.52 (m, 4H), 7.37 - 7.18 (m, 2H), 6.26 - 6.12 (m, 1H), 1.67 (br t, *J*=19.1 Hz, 3H).

LCMS (ESI, m/z): 468.1 $[M+H]^+$.

Example 268: 7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine

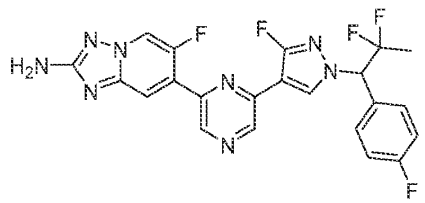


The title compound 7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-1H-pyrazol-4-yl)-2-fluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine, enantiomer 2 (9.4 mg, 13.1%) was obtained in a similar fashion as described for the preparation of example **256** where 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole was used in place of 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in the first step.

268, chiral: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.69 - 8.57 (m, 1H), 8.41 - 8.26 (m, 1H), 7.82 - 7.72 (m, 2H), 7.72 - 7.51 (m, 3H), 7.47 - 7.24 (m, 3H), 7.15 - 7.03 (m, 1H), 6.25 - 6.13 (m, 1H), 1.65 (br t, *J*=19.0 Hz, 3H).

LCMS (ESI, m/z): 485.1 $[M+H]^+$.

Example 269: 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-1H-pyrazol-4-yl)pyrazin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine



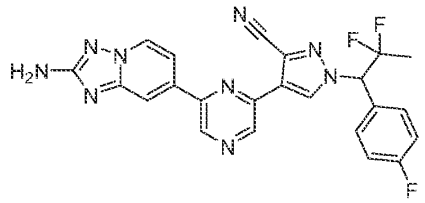
The title compound 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-1H-pyrazol-4-yl)pyrazin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine, racemate (8.5 mg, 12.5%) was obtained in a similar fashion as described for the preparation of example **257** where 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole was used in place of 1-(2,2-difluoro-1-(4-

fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in the first step.

269, racemic: ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.11 - 9.04 (m, 1H), 8.93 - 8.83 (m, 1H), 8.80 - 8.57 (m, 1H), 8.01 - 7.92 (m, 1H), 7.81 - 7.66 (m, 2H), 7.37 - 7.06 (m, 2H), 6.31 - 6.07 (m, 3H), 1.66 (br t, *J*=19.1 Hz, 3H).

LCMS (ESI, m/z): 487.0 $[M+H]^+$.

Example 270: 4-(6-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole-3-carbonitrile

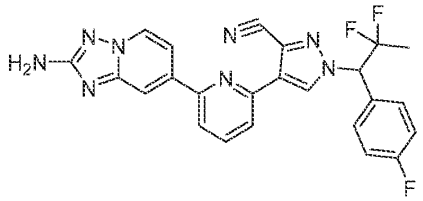


The title compound 4-(6-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole-3-carbonitrile, racemate (16.2 mg, 19.1%) was obtained in a similar fashion as described for the preparation of example **254** where tert-butyl (tert-butoxycarbonyl)(7-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate was used in place of 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole and 4-bromo-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole-3-carbonitrile was used in place of tert-butyl (tert-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate in the first step.

270, racemic: ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.38 - 9.25 (m, 1H), 9.11 (s, 1H), 9.06 (s, 1H), 8.70 (d, *J*=7.0 Hz, 1H), 8.33 (s, 1H), 7.94 - 7.70 (m, 3H), 7.30 (br t, *J*=8.8 Hz, 2H), 6.57 - 6.21 (m, 1H), 1.84 - 1.56 (m, 3H).

LCMS (ESI, m/z): 476.2 $[M+H]^+$.

Example 271: 4-(6-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyridin-2-yl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole-3-carbonitrile



271A : 4-(6-chloropyridin-2-yl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole-3-carbonitrile: The title compound 4-(6-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyridin-2-yl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole-3-carbonitrile (101 mg, 88%) was obtained in a similar fashion as described for the preparation of **260A** where 4-bromo-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole-3-carbonitrile was used in place of 2,4-dichloropyrimidine and 2-chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine was used in place of 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole.

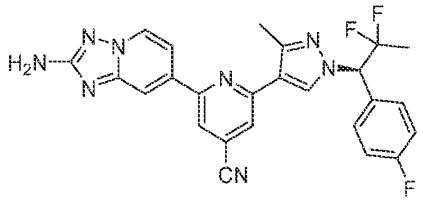
LCMS (ESI, m/z): 376.8/378.6 $[M+H]^+$.

271: The title compound 4-(6-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole-3-carbonitrile, racemate (12.1 mg, 23.1%) was obtained in a similar fashion as described for the preparation of example **258** where 4-(6-chloropyridin-2-yl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole-3-carbonitrile was used in place of 2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidine in the first step.

271, racemic: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.03 - 8.92 (m, 1H), 8.70 - 8.54 (m, 1H), 8.33 - 8.24 (m, 1H), 8.21 - 8.12 (m, 1H), 8.09 - 8.00 (m, 1H), 7.96 - 7.75 (m, 4H), 7.40 - 7.18 (m, 2H), 6.51 - 6.32 (m, 1H), 1.69 (br t, *J*=19.1 Hz, 3H).

LCMS (ESI, m/z): 475.2 $[M+H]^+$.

Example 272: (R)-2-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-7-yl)-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)isonicotinonitrile

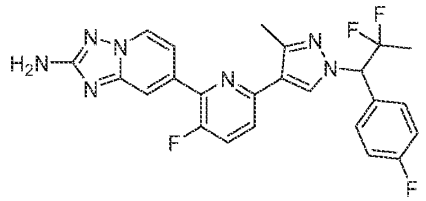


The title compound (R)-2-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-7-yl)-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)isonicotinonitrile (20.2 mg, 43.6%) was obtained in a similar fashion as described for the preparation of **example 254** where tert-butyl (tert-butoxycarbonyl)(7-(6-chloro-4-cyanopyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate was used in place of tert-butyl (tert-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate and (R)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole was used in place of 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in the first step.

272, chiral: ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.73 (s, 1H), 8.67 (d, *J*=7.0 Hz, 1H), 8.48 - 8.38 (m, 1H), 8.19 (br d, *J*=5.1 Hz, 2H), 7.85 - 7.61 (m, 3H), 7.28 (br t, *J*=8.8 Hz, 2H), 6.26 - 6.01 (m, 1H), 2.62 (s, 3H), 1.67 (br t, *J*=19.1 Hz, 3H).

LCMS (ESI, m/z): 489.2 $[M+H]^+$.

Example 273: 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine

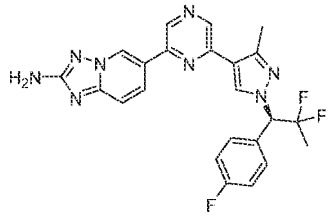


The title compound 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine, racemate (34.2 mg, 67.6%) was obtained in a similar fashion as described for the preparation of example **260** where 2-chloro-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)-3-fluoropyridine was used in place of 2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidine in the first step.

273, racemic ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.68 (d, *J*=7.0 Hz, 1H), 8.54 (s, 1H), 7.96 - 7.85 (m, 2H), 7.82 - 7.71 (m, 3H), 7.53 (d, *J*=7.4 Hz, 1H), 7.33 - 7.18 (m, 2H), 6.20 - 6.08 (m, 3H), 1.66 (br t, *J*=19.1 Hz, 3H).

LCMS (ESI, m/z): 482.3 $[M+H]^+$.

Example 274: (R)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine

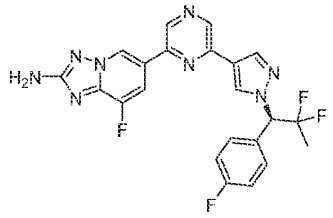


The title compound (*R*)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (7.3 mg, 16.1%) was obtained in a similar fashion as described for the preparation of example **254** where tert-butyl (tert-butoxycarbonyl)(6-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate was used in place of tert-butyl (tert-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate and (R)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole was used in place of 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in the first step.

274, chiral: ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.35 (s, 1H), 9.11 (s, 1H), 8.90 (s, 1H), 8.72 (s, 1H), 8.25 (br d, *J*=9.0 Hz, 1H), 7.77 (br dd, *J*=8.4, 5.8 Hz, 2H), 7.52 (d, *J*=9.1 Hz, 1H), 7.28 (br t, *J*=8.7 Hz, 2H), 6.32 - 6.06 (m, 3H), 2.61 (s, 3H), 1.78 - 1.51 (m, 3H).

LCMS (ESI, m/z): 465.2 $[M+H]^+$.

Example 275: (R)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine



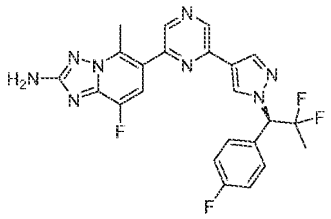
The title compound : (R)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (3.5 mg, 8.7%) was obtained in a similar fashion as described for the preparation of example **254** where 6-(6-chloropyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-[1,2,4]triazolo[1,5-

a]pyridine was used in place of 7-(6-chloropyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine and (R)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole was used in place of 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazolein the first step.

275, chiral: ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.43 - 9.33 (m, 1H), 9.19 - 9.07 (m, 1H), 8.99 (s, 1H), 8.88 - 8.80 (m, 1H), 8.45 (s, 1H), 8.26 (dd, *J*=11.7, 1.1 Hz, 1H), 7.78 (dd, *J*=8.7, 5.5 Hz, 2H), 7.38 - 7.21 (m, 2H), 6.42 (s, 2H), 6.35 - 6.17 (m, 1H), 1.74 (br d, *J*=5.0 Hz, 3H).

LCMS (ESI, m/z): 469.1 $[M+H]^+$.

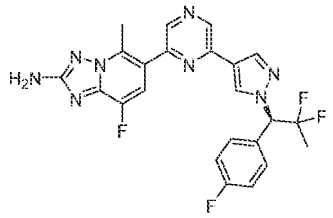
Example 276: (R)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-fluoro-5-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine



276A: (R)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-5-methyl-[1,2,4]triazolo[1,5-a]pyridine: The title compound (R)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-5-methyl-[1,2,4]triazolo[1,5-a]pyridine (30 mg, 37.8%) was obtained in a similar fashion as described for the preparation of **260A** where (2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-5-methyl-[1,2,4]triazolo[1,5-a]pyridin-6-yl)boronic acid was used in place of tert-butyl (tert-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate and (R)-2-chloro-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazine was used in place of 2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidine. The crude material prepared was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM

ammonium acetate; Gradient: 0-100% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give (R)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-5-methyl-[1,2,4]triazolo[1,5-a]pyridine.

Example 276: (R)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-fluoro-5-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine

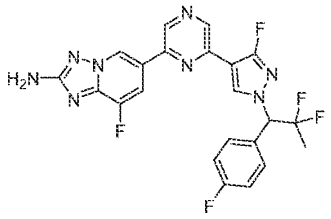


The title compound (R)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-fluoro-5-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (2.4 mg, 9.1%) was obtained in a similar fashion as described for the preparation of example **262** where (R)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-5-methyl-[1,2,4]triazolo[1,5-a]pyridine was used in place of (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine.

276, chiral: ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.71 (d, *J*=3.1 Hz, 2H), 8.35 (s, 1H), 7.86 - 7.60 (m, 3H), 7.27 (t, *J*=8.9 Hz, 2H), 6.36 (s, 2H), 6.31 - 6.14 (m, 1H), 3.55 (s, 3H), 2.72 (s, 3H), 1.69 - 1.61 (m, 3H).

LCMS (ESI, m/z): 483.2 $[M+H]^+$.

Example 277: 6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-1H-pyrazol-4-yl)pyrazin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine



277A : 6-(6-chloropyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridine: To a pressure vial were added 2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (677 mg, 1.9 mmol), 2-bromo-6-chloropyrazine (368 mg, 1.9 mmol), potassium phosphate (2 M water solution) (2.85 mL, 5.7 mmol), and dioxane (12 mL). The reaction mixture was purged with nitrogen and 1,1'-bis(di-tert-butylphosphino)ferrocene palladium dichloride (124 mg, 0.19 mmol) was added. It was heated at 70°C for 1h and cooled to rt. The reaction was diluted water and ethyl acetate. The layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water, brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The crude product was purified by silica gel chromatography (40 g Rerise® column, eluting with a gradient from 0 - 30% EtOAc in. hexanes, 15 cv). Fractions containing the product were combined and evaporated to afford 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (370 mg, 56.8 % yield).

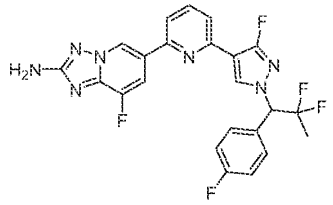
^{1}H NMR (400 MHz, CHLOROFORM-d) δ 9.20 (d, *J*=0.9 Hz, 1H), 8.97 (s, 1H), 8.66 (s, 1H), 8.10 - 7.90 (m, 1H), 5.96 (s, 2H), 2.45 (s, 6H).

LCMS (ESI, m/z): 342.9/344.7 $[M+H]^+$.

277: 6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-1H-pyrazol-4-yl)pyrazin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine: The title compound 6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-1H-pyrazol-4-yl)pyrazin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (2.6 mg, 7.5%) was obtained in a similar fashion as described for the preparation of example **276** 6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridine was used in place of (R)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-5-methyl-[1,2,4]triazolo[1,5-a]pyridine.

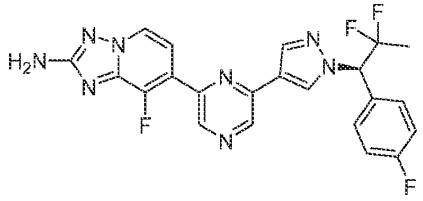
277, racemic: ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.43 - 9.33 (m, 1H), 9.27 - 9.15 (m, 1H), 8.86 - 8.69 (m, 2H), 8.26 - 8.16 (m, 1H), 7.83 - 7.68 (m, 2H), 7.39 - 7.19 (m, 2H), 6.49 - 6.36 (m, 2H), 6.25 - 6.11 (m, 1H), 1.80 - 1.60 (m, 3H).
LCMS (ESI, m/z): 487.1 $[M+H]^+$.

Example 278: 6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-1H-pyrazol-4-yl)pyridin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine



The title compound 6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-1H-pyrazol-4-yl)pyridin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (3.9 mg, 14.6%) was obtained in a similar fashion as described for the preparation of example **276** where 6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-1H-pyrazol-4-yl)pyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridine was used in place of (R)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-5-methyl-[1,2,4]triazolo[1,5-a]pyridine.
278, racemic: ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.27 (d, *J*=1.2 Hz, 1H), 8.72 (d, *J*=1.7 Hz, 1H), 8.30 - 8.16 (m, 1H), 8.06 - 7.86 (m, 2H), 7.86 - 7.70 (m, 2H), 7.55 (d, *J*=7.5 Hz, 1H), 7.30 (br t, *J*=8.9 Hz, 2H), 6.36 (s, 2H), 6.25 - 6.08 (m, 1H), 1.67 (br t, *J*=19.1 Hz, 3H).
LCMS (ESI, m/z): 486.1 $[M+H]^+$.

Example 279: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine

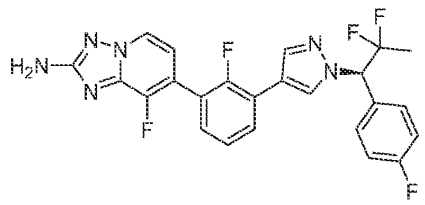


The title compound (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (7.1 mg, 11.1%) was

obtained in a similar fashion as described for the preparation of example **260** where (R)-2-chloro-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazine was used in place of 2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidine and tert-butyl (tert-butoxycarbonyl)(8-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate was used in place tert-butyl (tert-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate in the first step. **279**, chiral: ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.11 (s, 1H), 8.98 (d, *J*=1.9 Hz, 1H), 8.78 (s, 1H), 8.65 - 8.56 (m, 1H), 8.40 (s, 1H), 7.77 (dd, *J*=8.5, 5.6 Hz, 3H), 7.59 - 7.50 (m, 1H), 7.29 (br t, *J*=8.8 Hz, 2H), 6.42 - 6.24 (m, 1H), 1.82 - 1.59 (m, 3H).

LCMS (ESI, m/z): 469.1 $[M+H]^+$.

Example 280: (R)-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine

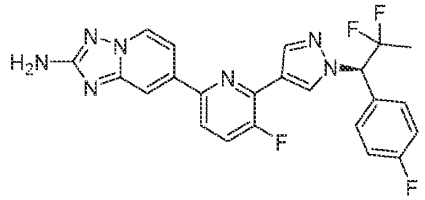


The title compound (R)-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (14.7 mg, 31.1%) was obtained in a similar fashion as described for the preparation of example **260** where 4-(3-bromo-2-fluorophenyl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-fluoro-1H-pyrazole was used in place of 2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrimidine and tert-butyl (tert-butoxycarbonyl)(8-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate was used in place tert-butyl (tert-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate in the first step.

280, chiral: ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.56 (d, *J*=6.9 Hz, 1H), 8.48 - 8.38 (m, 1H), 8.20 - 8.10 (m, 1H), 7.91 (td, *J*=7.4, 1.8 Hz, 1H), 7.75 (dd, *J*=8.6, 5.6 Hz, 2H), 7.50 - 7.35 (m, 2H), 7.35 - 7.23 (m, 2H), 7.04 - 6.91 (m, 1H), 6.38 - 6.18 (m, 3H), 1.65 (t, *J*=19.0 Hz, 3H).

LCMS (ESI, m/z): 485.2 $[M+H]^+$.

Example 281: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-5-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine

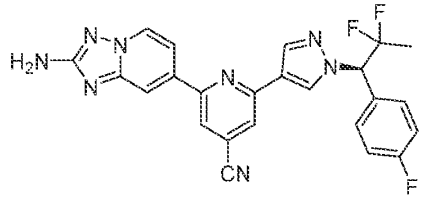


The title compound (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-5-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (47.7 mg, 76%) was obtained in a similar fashion as described for the preparation of **example 254** where tert-butyl (tert-butoxycarbonyl)(7-(6-chloro-5-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate was used in place of tert-butyl (tert-butoxycarbonyl)(7-(6-chloropyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate in the first step.

281, chiral: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.64 (d, *J*=7.0 Hz, 1H), 8.38 - 8.25 (m, 1H), 8.13 (s, 1H), 8.11 - 8.06 (m, 1H), 7.90 (t, *J*=9.6 Hz, 1H), 7.77 (dd, *J*=8.2, 5.7 Hz, 2H), 7.70 (d, *J*=7.0 Hz, 1H), 7.29 (t, *J*=8.7 Hz, 2H), 6.38 (s, 1H), 6.10 (s, 2H), 1.67 (s, 3H).

LCMS (ESI, m/z): 475.2 $[M+H]^+$.

Example 282: (R)-2-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-7-yl)-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)isonicotinonitrile

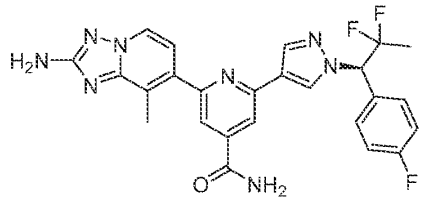


The title compound (R)-2-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-7-yl)-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)isonicotinonitrile (5.2 mg, 17%) was obtained in a similar fashion as described for the preparation of **example 254** where tert-butyl (tert-butoxycarbonyl)(7-(6-chloro-4-cyanopyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate was used in place of tert-butyl (tert-butoxycarbonyl)(7-(6-chloropyrazin-2-

yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate and (R)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole was used in place of 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole in the first step.

281, chiral: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.83 - 8.75 (m, 1H), 8.70 - 8.61 (m, 1H), 8.49 - 8.33 (m, 2H), 8.32 - 8.16 (m, 2H), 7.86 - 7.68 (m, 3H), 7.28 (br t, *J*=8.9 Hz, 2H), 6.37 - 6.21 (m, 1H), 6.18 - 6.05 (m, 2H), 1.66 (br t, *J*=19.1 Hz, 3H).
LCMS (ESI, m/z): 475.2 $[M+H]^+$.

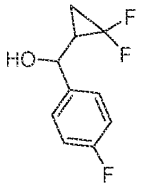
Example 283: (R)-2-(2-amino-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)isonicotinamide



The title compound (R)-2-(2-amino-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)isonicotinamide (6.8 mg, 14.4%) was obtained in a similar fashion as described for the preparation of **example 263** where (R)-2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)isonicotinamide was used in place of 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-3-methyl-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine.

283, chiral: ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 - 8.58 (m, 1H), 8.54 - 8.41 (m, 1H), 8.37 - 8.19 (m, 2H), 8.17 - 8.07 (m, 1H), 7.86 - 7.70 (m, 4H), 7.33 - 7.23 (m, 2H), 7.13 - 7.00 (m, 1H), 6.36 - 6.18 (m, 1H), 6.13 - 5.93 (m, 2H), 2.55 (s, 3H), 1.71 - 1.59 (m, 3H).
LCMS (ESI, m/z): 507.3 $[M+H]^+$.

Intermediate 84: (2,2-difluorocyclopropyl)(4-fluorophenyl)methanol



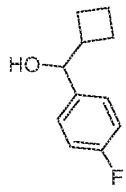
Step 1: To a solution of 2,2-difluorocyclopropane-1-carboxylic acid (1060 mg, 8.68 mmol) in DCM (4342 µl) at 0 °C was added N,O-dimethylhydroxylamine, HCl (1016 mg, 10.42 mmol), followed successively by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2497 mg, 13.03 mmol) and triethylamine (1816 µl, 13.03 mmol). The mixture was allowed to stir at rt overnight. LC/MS shows the desired material. The reaction was quenched with $NaHCO_3$ (sat'd), and extracted twice into DCM, and the combined organic layers were washed with water, 1M HCl, and brine. The solution was then dried over $MgSO_4$, filtered, and concentrated in vacuo. ^{1}H NMR (400 MHz, chloroform-d) δ 3.78 (s, 3H), 3.27 (s, 3H), 3.03 - 2.88 (m, 1H), 2.23 - 2.12 (m, 1H), 1.70 (dddd, *J*=12.0, 10.9, 7.4, 4.8 Hz, 1H).

Step 2: To a solution of 2,2-difluoro-*N*-methoxy-*N*-methylcyclopropane-1-carboxamide from the previous step (898 mg, 5.44 mmol) in tetrahydrofuran (5438 µl) at 0 °C was added 1 M 4-fluorophenylmagnesium bromide solution in THF (8157 µl, 8.16 mmol) dropwise. The ice bath was removed, and stirring was continued at rt. The mixture was quenched with MeOH, then concentrated. The residue was taken up in EtOAc, then washed with saturated NH_4Cl solution. The aqueous phase was back-extracted with EtOAc, then the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was taken forward as-is into the next step. ^{1}H NMR (400 MHz, chloroform -d) δ 8.11 - 8.02 (m, 2H), 7.21 (m, 2H), 3.36 (ddd, *J*=13.4, 10.4, 7.9 Hz, 1H), 2.45 (dtd, *J*=12.2, 7.7, 5.9 Hz, 1H), 1.93 - 1.78 (m, 1H).

Step 3: To a solution of crude (2,2-difluorocyclopropyl)(4-fluorophenyl)methanone (1089 mg, 5.44 mmol) in methanol was added sodium borohydride (103 mg, 2.72 mmol). Bubbling was noticed. After 20 min, TLC (10% EtOAc/Hexane) showed the disappearance of starting material and the development of a lower Rf spot. Solvents were removed, and the residue purified on a 40 g SG cartridge, eluting from 0 to 25% EtOAc/hexane over 10 CV to afford (2,2-difluorocyclopropyl)(4-fluorophenyl)methanol (982.8 mg, 4.86 mmol, 89 % yield). ^{1}H NMR (400 MHz, chloroform -d) δ 7.45 - 7.38

(m, 2H), 7.09 (t, *J*=8.1 Hz, 2H), 4.48 (d, *J*=9.0 Hz, 1H), 2.05 - 1.96 (m, 1H), 1.55 - 1.44 (m, 1H), 1.28 - 1.21 (m, 1H).

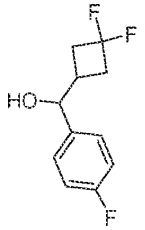
Intermediate 85: (cyclobutyl)(4-fluorophenyl)methanol



The above intermediate was made using the method described for Intermediate **84** but utilizing cyclobutanecarboxylic acid.

^{1}H NMR (400 MHz, chloroform -d) δ 7.35 - 7.25 (m, 2H), 7.03 (t, *J*=8.2 Hz, 2H), 4.57 (br d, *J*=8.0 Hz, 1H), 2.61 (sxt, *J*=8.0 Hz, 1H), 2.14 - 1.75 (m, 6H).

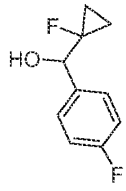
Intermediate 86: (3,3-difluorocyclobutyl)(4-fluorophenyl)methanol



The above intermediate was made using the method described for Intermediate **84** but utilizing 3,3-difluorocyclobutanecarboxylic acid.

^{1}H NMR (400 MHz, chloroform -d) δ 7.37 - 7.25 (m, 2H), 7.07 (t, *J*=8.2 Hz, 2H), 4.65 (dd, *J*=6.5, 2.9 Hz, 1H), 2.75 - 2.57 (m, 2H), 2.54 - 2.27 (m, 3H).

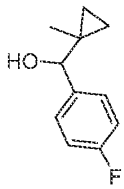
Intermediate 87: (1-fluorocyclopropyl)(4-fluorophenyl)methanol



The above intermediate was made using the method described for Intermediate **84** but utilizing 1-fluorocyclopropanecarboxylic acid.

^{1}H NMR (400 MHz, chloroform -d) δ 7.44 (dd, *J*=8.6, 5.6 Hz, 2H), 7.08 (t, *J*=8.2 Hz, 2H), 4.84 (d, *J*=16.9 Hz, 1H), 2.49 - 2.30 (br s, 1H), 1.20 - 1.02 (m, 2H), 0.87 - 0.66 (m, 2H).

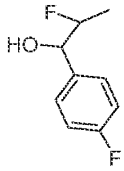
Intermediate 88: (1-methylcyclopropyl)(4-fluorophenyl)methanol



The above intermediate was made using the method described for Intermediate **84** but utilizing 1-methylcyclopropanecarboxylic acid.

^{1}H NMR (400 MHz, chloroform -d) δ 7.41 - 7.33 (m, 2H), 7.08 - 7.00 (m, 2H), 4.17 (s, 1H), 2.03 (br s, 1H), 0.94 (s, 3H), 0.74 - 0.67 (m, 1H), 0.65 - 0.59 (m, 1H), 0.47 - 0.35 (m, 2H).

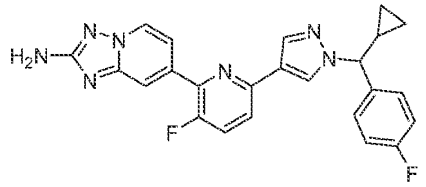
Intermediate 89: 2-fluoro-1-(4-fluorophenyl)propan-1-ol



Step 1: To a solution of 1-fluoro-4-(prop-1-en-1-yl)benzene (1.34 g, 9.84 mmol) in dioxane (24.60 ml) was added 1,10-phenanthroline-5,6-dione (0.155 g, 0.738 mmol) and *N*-fluorobenzenesulfonimide (9.31 g, 29.5 mmol). Next, palladium(II) chloride (0.087 g, 0.492 mmol) was added, and the mixture sonicated. Finally, trichloroacetic acid (8.04 g, 49.2 mmol) was added, and the mixture was heated at 30 °C for 5 h. After cooling to rt, the mixture was diluted in DCM and washed twice with water. The organic layer was dried over $MgSO_4$, filtered, and concentrated. To the resulting liquid/solid mixture was added a little DCM, then 10% EtOAc/hexane was added. The remaining solid was filtered off (Buchner/paper), and the solid rinsed with more 10% EtOAc/hexane. The filtrate was concentrated to an oil, which was purified by SG chromatography (220 g, 0 to 6% EtOAc/hexane over 9 CV). The fractions were a mix of *cis* and *trans*.

Step 2: To a solution of 2-fluoro-1-(4-fluorophenyl)propyl 2,2,2-trichloroacetate (390.4 mg, 1.229 mmol) in tetrahydrofuran (6147 µl) was added methanol (1.24E+04 µl, 307 mmol) and pyridine (2486 µl, 30.7 mmol). Solvents were removed., and the residue was purified by flash chromatography to produce 2-fluoro-1-(4-fluorophenyl)propan-1-ol. ^{1}H NMR (400 MHz, chloroform -d) δ 7.38 (t, *J*=6.6 Hz, 2H), 7.09 (t, *J*=8.1 Hz, 2H), 4.94 - 4.84 (m, 1H), 4.79 - 4.61 (m, 1H), 1.32 - 1.22 (m, 3H).

Example 284: 7-(3-fluoro-6-(1-(cyclopropyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



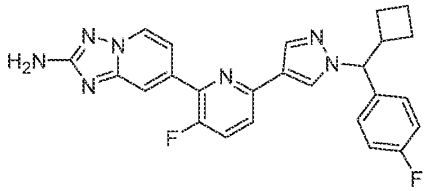
284A: 7-(6-(1-(cyclopropyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine: To a solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(3-fluoro-6-(1*H*-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (Intermediate 76) and cyclopropyl(4-fluorophenyl)methanol (111 mg, 0.671 mmol) in THF (1669 µl) was added triphenylphosphine resin (298 mg, 0.894 mmol), then solid di-tert-butyl diazene-1,2-dicarboxylate (180 mg, 0.783 mmol). The mixture was agitated at rt overnight. LC/MS showed conversion to the desired 7-(6-(1-(cyclopropyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine and the undesired by-product *tert*-butyl 4-(6-(2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)-5-fluoropyridin-2-yl)-1*H*-pyrazole-1-carboxylate. The resin was filtered off, and then rinsed with additional THF. Concentration of the filtrate yielded a product mixture which was taken forward together for deprotection.

MS ESI m/z $(M+H)^+$ 522.2.

284: 7-(3-fluoro-6-(1-(cyclopropyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: To a solution of 7-(6-(1-(cyclopropyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine **284A** (117 mg, 0.224 mmol) in ethanol (2240 µl) was added 5 M hydroxylamine hydrochloride (896 µl, 4.48 mmol) in water. The mixture was

heated for 16 h in the microwave at 100 °C. LC/MS contained the desired m/z for the desired product. Solvents were removed, and the residue was taken up in DCM. The DCM solution was separated from a wet, solid material, then the solid was again triturated with DCM. The combined DCM solutions were concentrated, taken up in DMF, filtered, and concentrated. The compound was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 20-55% B over 25 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). The resulting racemic compound was further resolved by chiral chromatography with the following conditions: Column: Whelk-O1 (R,R), 21 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% ammonium hydroxide; Elution Gradient: isocratic 30 %B over 16 min; Flow Rate: 75 mL/min; column temperature: 45 °C. Fraction collection was triggered by UV (235 nm). Both enantiomers of 7-(3-fluoro-6-(1-(cyclopropyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine were isolated (**284**, 3.1 mg and **285**, 2.8 mg). MS ESI m/z $(M+H)^+$ 444.1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.48 - 8.39 (m, 2H), 7.96 - 7.89 (m, 1H), 7.77 - 7.71 (m, 1H), 7.70 - 7.63 (m, 1H), 7.62 - 7.57 (m, 1H), 7.39 - 7.32 (m, 1H), 7.26 - 7.16 (m, 2H), 7.02 - 6.92 (m, 2H), 5.96 - 5.84 (m, 2H), 4.62 - 4.51 (m, 1H), 1.68 - 1.59 (m, 1H), 0.54 - 0.42 (m, 2H), 0.34 - 0.20 (m, 2H).

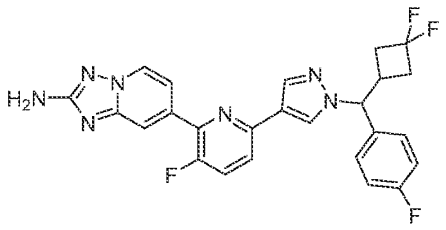
Example 286: 7-(6-(1-(cyclobutyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



286A: 7-(6-(1-(cyclobutyl(4-fluorophenyl)methyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine: The above intermediate was made using Intermediate **85** as described for the synthesis of **284A**. MS ESI m/z $(M+H)^+$ 536.4.

286: 7-(6-(1-(cyclobutyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: **286A** was reacted in the manner described for Example **284** to afford the title compound **286**. The compound was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 22-54% B over 25 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). The resulting racemic compound was further resolved by chiral chromatography with the following conditions: Column: Whelk-O1 (R,R), 21 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% ammonium hydroxide; Elution Gradient: isocratic 30 %B over 16 min; Flow Rate: 75 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (230 nm). Both enantiomers of 7-(6-(1-(cyclobutyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine were isolated (**286**, 10 mg and **287**, 9.7 mg). MS ESI m/z $(M+H)^+$ 458.2. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 - 8.63 (m, 1H), 8.57 - 8.52 (m, 1H), 8.13 - 8.07 (m, 1H), 7.99 - 7.93 (m, 1H), 7.91 - 7.83 (m, 1H), 7.82 - 7.74 (m, 1H), 7.61 - 7.53 (m, 1H), 7.50 - 7.42 (m, 2H), 7.22 - 7.13 (m, 2H), 6.17 - 6.07 (m, 2H), 5.52 - 5.43 (m, 1H), 3.47 - 3.33 (m, 1H), 2.06 - 1.95 (m, 1H), 1.93 - 1.84 (m, 3H), 1.82 - 1.71 (m, 2H).

Example 288: 7-(6-(1-((3,3-difluorocyclobutyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine

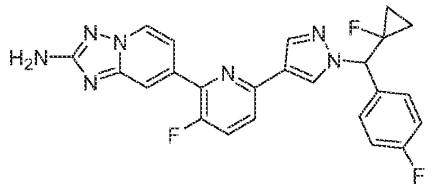


288A: 7-(6-(1-(3,3-difluorocyclobutyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine

The above intermediate was made made using Intermediate **86** as described for the synthesis of **284A**. MS ESI m/z $(M+H)^+$ 572.4.

288: 7-(6-(1-((3,3-difluorocyclobutyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: **288A** was reacted in the manner described for Example **284** to afford the title compound **288**. The compound was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 26-56% B over 22 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS (ESI +). The resulting racemic compound was further resolved by chiral chromatography with the following conditions: Column: Whelk-O1 (R,R), 21 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% ammonium hydroxide; Elution Gradient: isocratic 20 %B over 22 min; Flow Rate: 75 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (230 nm). Both enantiomers of 7-(6-(1-((3,3-difluorocyclobutyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine were isolated (**288**, 9.8 mg and **289**,11.8 mg).
MS ESI m/z $(M+H)^+$ 494.2.
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 - 8.64 (m, 1H), 8.62 - 8.56 (m, 1H), 8.18 - 8.12 (m, 1H), 7.98 - 7.93 (m, 1H), 7.91 - 7.84 (m, 1H), 7.83 - 7.76 (m, 1H), 7.60 - 7.49 (m, 3H), 7.25 - 7.15 (m, 2H), 6.18 - 6.06 (m, 2H), 5.64 - 5.55 (m, 1H), 3.44 - 3.35 (m, 1H), 2.74 - 2.56 (m, 2H), 2.48 - 2.34 (m, 2H).

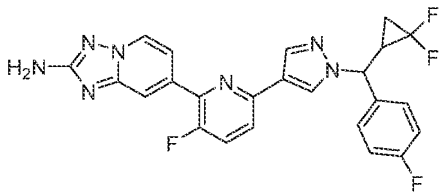
Example 290: 7-(6-(1-((1-fluorocyclopropyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



290A: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(3-fluoro-6-(1-((1-fluorocyclopropyl)(4-fluorophenyl)-methyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine
The above intermediate was made made using Intermediate **87** as described for the synthesis of **284A**. MS ESI m/z $(M+H)^+$ 540.2.

290: 7-(6-(1-((1-fluorocyclopropyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: **290A** was reacted in the manner described for Example **284** to afford the title compound **290**. The compound was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 20-60% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS (ESI +). The resulting racemic compound was further resolved by chiral chromatography with the following conditions: Column: Whelk-O1 (R,R), 21 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% ammonium hydroxide; Elution Gradient: isocratic 30 %B over 12.5 min; Flow Rate: 75 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (230 nm). Both enantiomers of 7-(6-(1-((1-fluorocyclopropyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine were isolated (**290**, 13.5 mg and **291**, 16.6 mg). MS ESI m/z $(M+H)^+$ 462.2. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.69 - 8.64 (m, 1H), 8.56 - 8.52 (m, 1H), 8.24 - 8.20 (m, 1H), 7.93 (s, 1H), 7.92 - 7.88 (m, 2H), 7.57 - 7.53 (m, 1H), 7.48 - 7.40 (m, 2H), 7.28 - 7.19 (m, 2H), 6.16 - 6.09 (m, 2H), 5.81 - 5.72 (m, 1H), 1.31 - 1.22 (m, 2H), 1.16 - 1.08 (m, 1H), 0.94 - 0.86 (m, 1H).

Example 292: 7-(6-(1-((2,2-difluorocyclopropyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine

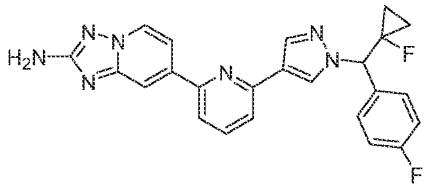


292A: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(3-fluoro-6-(1-((2,2-difluorocyclopropyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine

The above intermediate was made made using Intermediate **84** as described for the synthesis of **284A**. MS ESI m/z $(M+H)^+$ 558.2.

Example 292: 7-(6-(1-((2,2-difluorocyclopropyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: **292A** was reacted in the manner described for Example **284** to afford the title compound **292**. The compound was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 μm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 20-60% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS (ESI +). The resulting mixture of 4 compounds was further resolved by chiral chromatography with the following conditions: Column: Chiralpak IH, 21 mm x 250 mm, 5 μm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% ammonium hydroxide; Elution Gradient: isocratic 10 %B over 32 min; Flow Rate: 75 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (230 nm). Two fractions (*R* and *S* at the benzylic center), each racemic on the cyclopropyl ring, were obtained. 7-(6-(1-((2,2-difluorocyclopropyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine were isolated (**292**, 4.1 mg and **293**, 5.0 mg).
MS ESI m/z $(M+H)^+$ 480.2
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.71 (s, 1H), 8.66 (d, *J*=7.0 Hz, 1H), 8.20 (s, 1H), 7.96 (s, 1H), 7.89 (dd, *J*=11.4, 8.7 Hz, 1H), 7.80 (dd, *J*=8.6, 3.2 Hz, 1H), 7.56 (d, *J*=7.0 Hz, 1H), 7.41 (t, *J*=6.6 Hz, 2H), 7.25 (t, *J*=8.4 Hz, 2H), 6.12 (s, 2H), 5.37 (d, *J*=10.7 Hz, 1H), 3.01 - 2.92 (m, 1H), 1.89 - 1.79 (m, 1H), 1.68 - 1.60 (m, 1H), 1.24 (s, 1H).

Example 294: 7-(6-(1-((1-fluorocyclopropyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-y)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



294A: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl-7-(6-(1-(1-fluorocyclopropyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-pyridin-2-yl)-)-[1,2,4]triazolo[1,5-*a*]pyridine

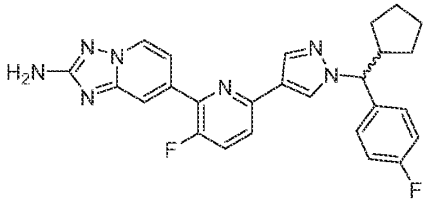
The above intermediate was made using the method described for **284A** but utilizing 7-(6-(1*H*-pyrazol-4-yl)pyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (intermediate 78) and Intermediate **87**. MS ESI m/z $(M+H)^+$ 522.2.

294: 7-(6-(1-((1-fluorocyclopropyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-y)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: **294A** was reacted in the manner described for Example **284** to afford the title compound **294**. The compound was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 20-60% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS (ESI +). The resulting racemic mixture was further resolved by chiral chromatography with the following conditions: Column: Chiralpak WHELKO1, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% DEA; Elution Gradient: isocratic 35 %B over 25 min; Flow Rate: 100 mL/min; Column Temperature: 50 °C. Fraction collection was triggered by PDA (220 nm). Both enantiomers of 7-(6-(1-((1-fluorocyclopropyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-pyridin-2-yl)-[1,2,4]-triazolo[1,5-*a*]pyridin-2-amine were isolated (**294**, 6.8 mg and **295**, 6.7 mg).

MS ESI m/z $(M+H)^+$ 444.1.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.61 (br d, *J*=6.7 Hz, 1H), 8.57 (s, 1H), 8.25 (s, 1H), 8.11 (s, 1H), 7.98 - 7.88 (m, 2H), 7.77 (br d, *J*=7.3 Hz, 1H), 7.72 (br d, *J*=6.9 Hz, 1H), 7.44 (br t, *J*=6.3 Hz, 2H), 7.27 - 7.18 (m, 2H), 6.05 (s, 2H), 5.74 (d, *J*=24.1 Hz, 1H), 1.33 - 1.19 (m, 2H), 1.12 (br m, 1H), 0.90 (m, 1H).

Example 296: 7-(6-(1-((cyclopentyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine

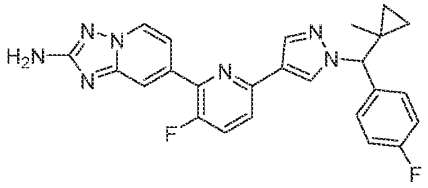


296A: 7-(6-(1-(cyclopentyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl-[1,2,4]triazolo[1,5-*a*]pyridine

The above intermediate was made made using cyclopentyl(4-fluorophenyl)methanol as described for the synthesis of **284A**. MS ESI m/z $(M+H)^+$ 550.3.

296: 7-(6-(1-((cyclopentyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: **296A** was reacted in the manner described for Example **284** to afford the title compound **296**. The compound was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 33-73% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS (ESI +). Racemic 7-(6-(1-((1-cyclopentyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine was isolated (**296**, 16.0 mg). MS ESI m/z $(M+H)^+$ 472.2. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.66 (d, *J*=7.0 Hz, 1H), 8.59 (s, 1H), 8.10 (s, 1H), 7.94 (s, 1H), 7.88 - 7.83 (m, 1H), 7.77 (dd, *J*=8.6, 3.3 Hz, 1H), 7.61 (dd, *J*=8.6, 5.6 Hz, 2H), 7.55 (d, *J*=8.0 Hz, 1H), 7.18 (t, *J*=8.8 Hz, 2H), 6.11 (s, 2H), 5.20 (d, *J*=11.3 Hz, 1H), 3.11-3.01 (m, 1H), 1.91 - 1.14 (m, 8H).

Example 297: 7-(6-(1-((1-methylcyclopropyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



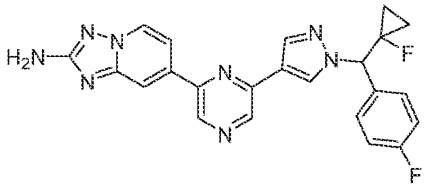
297A 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(3-fluoro-6-(1-((1-methylcyclopropyl)(4-fluorophenyl)-methyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine

The above intermediate was made made using Intermediate **88** as described for the synthesis of **284A**. MS ESI m/z $(M+H)^+$ 536.3.

297: 7-(6-(1-((1-methylcyclopropyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: **297A** was reacted in the manner described for Example **284** to afford the title compound **297**. The compound was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile:

water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 30-60% B over 25 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS (ESI +). The resulting racemic compound was further resolved by chiral chromatography with the following conditions: Column: Whelk-O1 (R,R), 21 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% ammonium hydroxide; Elution Gradient: isocratic 30 %B over 14 min; Flow Rate: 75 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (230 nm). Both enantiomers of 7-(6-(1-((1-methylcyclopropyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine were isolated (**297**, 11.7 mg and **298**, 5.5 mg). MS ESI m/z $(M+H)^+$ 458.2. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (d, *J*=7.0 Hz, 1H), 8.53 (s, 1H), 8.19 (s, 1H), 7.98 - 7.82 (m, 3H), 7.56 (br d, *J*=6.9 Hz, 1H), 7.41 - 7.34 (m, 2H), 7.20 (br t, *J*=8.7 Hz, 2H), 6.12 (s, 2H), 5.36 (s, 1H), 1.14 (s, 3H), 0.75 - 0.43 (m, 4H).

Example 299: 7-(6-(1-((1-fluorocyclopropyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-y)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine

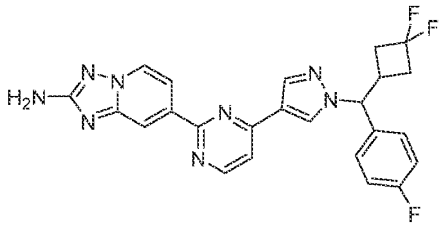


299A: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl-7-(6-(1-(1-fluorocyclopropyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-pyrazin-2-yl)-)-[1,2,4]triazolo[1,5-*a*]pyridine The above intermediate was made using the method described for **284A** but utilizing 7-(6-(1*H*-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (intermediate 77) and Intermediate **87**. MS ESI m/z $(M+H)^+$ 523.5.

299: 7-(6-(1-((1-fluorocyclopropyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-y)pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: **299A** was reacted in the manner described for Example **284** to afford the title compound **299**. The compound was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge phenyl, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM

ammonium acetate; Gradient: 16-46% B over 24 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS (ESI +). Further purification was achieved purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 18-47% B over 22 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm). The resulting racemic mixture was further resolved by chiral chromatography with the following conditions: Column: Chiralpak WHELK-O1 (R,R), 21 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% ammonium hydroxide; Elution Gradient: isocratic 30 %B over 22 min; Flow Rate: 75 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (230 nm). The 2 enantiomers of 7-(6-(1-((1-fluorocyclopropyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-pyrazin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine were isolated (**299**, 2.5 mg and **300**, 3.5 mg). MS ESI m/z $(M+H)^+$ 445.1. ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.22 (s, 1H), 9.10 (s, 1H), 8.73 (s, 1H), 8.71 - 8.66 (m, *J*=7.2 Hz, 1H), 8.38 (s, 1H), 8.24 (s, 1H), 7.77 - 7.72 (m, *J*=7.1 Hz, 1H), 7.46 (br dd, *J*=8.3, 5.5 Hz, 2H), 7.25 (br t, *J*=8.9 Hz, 2H), 6.14 (s, 2H), 5.80 (d, *J*=24.7 Hz, 1H), 1.35 - 1.21 (m, 2H), 1.18 - 1.10 (m, 1H), 0.96 - 0.87 (m, 1H).

Example 301: 7-(4-(1-((3,3-difluorocyclobutyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



301A: 7-(4-(1*H*-pyrazol-4-yl)pyrimidin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl-[1,2,4]triazolo-[1,5-*a*]pyridine

Step 1: To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (11.7 g, 60.3 mmol) and Boc-anhydride (15.40 ml, 66.3 mmol) in DCM (183 ml) was added Et_3N (12.61 ml, 90 mmol), and the resulting solution was stirred at rt. The reaction mixture was washed twice with water, then with brine. The organic phase was then dried

over $MgSO_4$, filtered, and concentrated in vacuo. A portion of the material solidified over time. *Tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole-1-carboxylate (15.52 g, 52.8 mmol, 88 % yield) was obtained. MS ESI m/z $(M+H\text{-}Boc)^+$ 194.9; m/z $(M+H\text{-}t\text{Bu})^+$ 238.8.

Step 2: To a solution of tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole-1-carboxylate (1.2232 g, 4.16 mmol) and 2,4-dichloropyrimidine (0.619 g, 4.16 mmol) in dioxane (35.6 ml) was added a solution of Cs_2CO_3 (2.71 g, 8.32 mmol) in water (5.94 ml). The mixture was sparged with N_2, then 1,1'-Bis(diphenylphosphino)ferrocene dichloropalladium (II) (0.304 g, 0.416 mmol) was added. The mixture was sealed and heated at 70 °C overnight. Solvents were removed (some residual water was present), then water and EtOAc were added. The layers were partitioned, and the aqueous layer was extracted twice more with EtOAc. The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and concentrated. The residue was applied to a 40 g SG column and eluted with a 0 to 100% EtOAc/hexane gradient over 10 CV to obtain *tert*-butyl 4-(2-chloropyrimidin-4-yl)-1*H*-pyrazole-1-carboxylate (649.3 mg, 2.313 mmol, 55.6 % yield). MS ESI m/z $(M+H)^+$ 281.1. ^1H NMR (400 MHz, CHLOROFORM-d) δ 8.77 (d, *J*=0.7 Hz, 1H), 8.62 (d, *J*=5.2 Hz, 1H), 8.27 (d, *J*=0.7 Hz, 1H), 7.43 (d, *J*=5.2 Hz, 1H), 1.71 (s, 9H).

Step 3: Dioxane (7565 µl) was sparged with N_2 for 5 min, then solid 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (352 mg, 1.040 mmol) and *tert*-butyl 4-(2-chloropyrimidin-4-yl)-1*H*-pyrazole-1-carboxylate (265.45 mg, 0.946 mmol) were quickly added to form a free solution. 1,1'-Bis(di-tert-butylphosphino)-ferrocene palladium dichloride (61.6 mg, 0.095 mmol) and pre-sparged 2M K_3PO_4 (1418 µl, 2.84 mmol) were then added in rapid succession, and the headspace of the flask quickly flushed with nitrogen. After sealing the flask, is was placed into a 70 °C oil bath for 75 min. After cooling to rt, LC/MS showed the desired. The mixture was diluted with EtOAc and separated the organic layer from the aqueous (and precipitated salt). The solid was washed twice more with EtOAc, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The material was added to a 24 g SG cartridge and eluted with a 0 to 100% EtOAc/hexane gradient over 10 CV to afford *tert*-butyl 4-(2-(2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrimidin-4-yl)-1*H*-pyrazole-1-carboxylate (315.7 mg, 0.692 mmol, 73.1

% yield). The material was initially an oil, but solidified when a small amount of pure EtOAc was added. A little hexane was then added and the solvents were removed again in vacuo to obtain the solid material. MS ESI m/z $(M+H)^+$ 457.2. ^{1}H NMR (400 MHz, chloroform -d) δ 8.98 (dd, *J*=1.7, 0.9 Hz, 1H), 8.89 (d, *J*=5.2 Hz, 1H), 8.85 (d, *J*=0.7 Hz, 1H), 8.69 (dd, *J*=7.2, 0.9 Hz, 1H), 8.39 (d, *J*=0.7 Hz, 1H), 8.30 - 8.25 (m, 1H), 7.49 (d, *J*=5.2 Hz, 1H), 5.96 (s, 2H), 2.43 (s, 6H), 1.75 (s, 9H).

Step 4: To a solution of *tert*-butyl 4-(2-(2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-7-yl)pyrimidin-4-yl)-1*H*-pyrazole-1-carboxylate (307.75 mg, 0.674 mmol) in CH2Cl2 (1.05E+04 µl) was added TFA (1039 µl, 13.48 mmol). A yellow color instantly appeared. Solvents were removed, leaving a rose-colored oil. MeOH was added to produce a white material. MS ESI m/z $(M+H)^+$ 357.0.

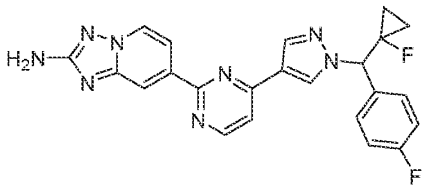
301B: 7-(6-(1-(3,3-difluorocyclobutyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine

The above intermediate was made using the method described for Intermediate **284A** but utilizing 7-(4-(1*H*-pyrazol-4-yl)pyrimidin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl-[1,2,4]triazolo[1,5-*a*]pyridine and Intermediate **86**.

301: 7-(4-(1-((3,3-difluorocyclobutyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: **301B** was reacted in the manner described for Example **284** to afford the title compound **301**. The compound was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 25-55% B over 22 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS (ESI +). The resulting racemic compound was further resolved by chiral chromatography with the following conditions: Column: Whelk-O1 (R,R), 21 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% ammonium hydroxide; Elution Gradient: isocratic 30 %B over 14 min; Flow Rate: 75 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (235 nm). Both enantiomers of 7-(4-(1-((3,3-difluorocyclobutyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine were isolated (**301**, 4.5 mg and **302**, 4.2 mg). MS ESI m/z $(M+H)^+$ 477.2. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.66 (s, 1H), 8.62 (d, *J*=7.0 Hz,

1H), 8.19 (s, 1H), 8.15 (s, 1H), 7.96 - 7.88 (m, 2H), 7.74 - 7.68 (m, 2H), 7.55 (dd, *J*=8.5, 5.6 Hz, 2H), 7.21 (m, 1H), 6.07 (s, 2H), 5.59 (d, *J*=10.7 Hz, 1H), 2.75 - 2.34 (m, 5H).

Example 303: 7-(4-(1-((1-fluorocyclopropyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



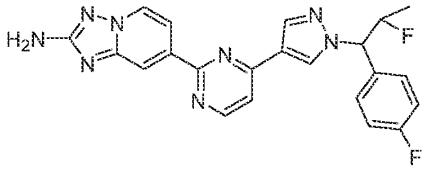
303A: 7-(6-(1-(1-fluorocyclopropyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-3-fluoropyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine

The above intermediate was made using the method described for **284A** but utilizing 7-(4-(1*H*-pyrazol-4-yl)pyrimidin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl-[1,2,4]triazolo[1,5-*a*]pyridine (**301A**) and Intermediate **87**. MS ESI m/z $(M+H)^+$ 523.2.

303: 7-(4-(1-((1-fluorocyclopropyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: **303A** was reacted in the manner described for Example **284** to afford the title compound **303**. The compound was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 15-47% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS (ESI +) and UV (220 nm). The resulting racemic compound was further resolved by chiral chromatography with the following conditions: Column: Whelk-O1 (S,S), 10 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1% ammonium hydroxide; Elution Gradient: isocratic 35 %B over 18 min; Flow Rate: 10 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (230 nm). Both enantiomers of 7-(4-(1-((1-fluorocyclopropyl)(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)-pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine were isolated (**303**, 4.2 mg and **304**, 3.1 mg). MS ESI m/z $(M+H)^+$ 445.2. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.87 (d, *J*=5.3 Hz, 1H), 8.82 (s, 1H), 8.66 (d, *J*=6.7 Hz, 1H), 8.44 (s, 1H), 8.37 (s, 1H), 7.91 (dd, *J*=7.1, 1.8 Hz, 1H), 7.84

(d, *J*=5.3 Hz, 1H), 7.46 (dd, *J*=8.7, 5.6 Hz, 2H), 7.25 (t, *J*=8.9 Hz, 2H), 6.14 (s, 2H), 5.80 (d, *J*=24.5 Hz, 1H), 1.33 - 1.22 (m, 2H), 1.18 - 1.10 (m, 1H), 0.96 - 0.88 (m, 1H).

Example 305: 7-(4-(1-(2-fluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine

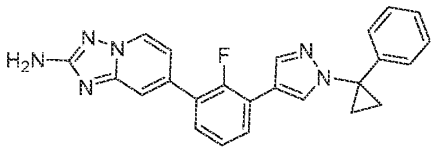


305A: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(4-(1-(2-fluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine

The above intermediate was made using the method described for **284A** but utilizing 7-(4-(1*H*-pyrazol-4-yl)pyrimidin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl-[1,2,4]triazolo[1,5-*a*]pyridine (**301A**) and Intermediate **89**. MS ESI m/z $(M+H)^+$ 511.2.

305: 7-(4-(1-(2-fluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: **305A** was reacted in the manner described for Example **284** to afford the title compound **305**. The compound was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 15-35% B over 25 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by MS (ESI +). 7-(4-(1-(2-fluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine was isolated as a mixture of 4 diasteriomers (7.2 mg). MS ESI m/z $(M+H)^+$ 433.1. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.18 (s, 1H), 9.00 (s, 1H), 8.84 - 8.63 (m, 2H), 8.38 - 8.33 (m, 1H), 8.22 (s, 1H), 7.78 - 7.71 (m, 1H), 7.68 - 7.61 (m, 2H), 7.28 - 7.21 (m, 2H), 6.13 (s, 2H), 5.76 - 5.50 (m, 2H), 1.36 - 1.17 (m, 3H).

Example 306: 7-(2-fluoro-3-(1-(1-phenylcyclopropyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine



306A: 1-(1-(4-fluorophenyl)cyclobutyl)-4-iodo-1H-pyrazole:

Followed the procedure as outlined in *Organic Letters*, **2020**, *vol 22*, 7594-7598.

To a 5 mL ElectroSyn vial was added 4-iodo-1h-pyrazole (40 mg, 0.206 mmol), 1-(4-fluorophenyl)cyclobutanecarboxylic acid (120 mg, 0.618 mmol), silver perchlorate (75 mg, 0.362 mmol), tetrabutylammonium hexafluorophosphate (60 mg, 0.155 mmol), 3A mol sieves (100 mg), CH2Cl2 (3.0 mL) and 2,4,6-trimethylpyridine (27 µL, 0.206 mmol). The ElectroSyn vial cap, equipped with an anode (graphite) and cathode (Ni) was inserted into the reaction and the reaction was stirred at room temp for 10 min. The reaction mixture was then electrolyzed at a constant current of 10 mA for 2.5 hours. The solvent was then removed under a gentle stream of nitrogen.

Note: this reaction was repeated six (6) times using the exact same conditions as described above.

The residue from all six reactions was combined, dissolved in ethyl acetate (100 mL) and filtered thru a small pad of Celite to remove all the inorganic material. The organic layer was washed with water (4 x 10 mL), brine (1 x 10 mL), dried over sodium sulfate, filtered and evaporated to dryness. The crude residue was purified by flash chromatography on silica gel, eluting with 0-100% gradient of ethyl acetate in hexane, to afford the title compound, 1-(1-(4-fluorophenyl)cyclobutyl)-4-iodo-1H-pyrazole (189 mg, 0.552 mmol, 44.7%)

MS ESI m/z 343.0 $(M+H)^+$

306B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(1-(1-(4-fluorophenyl)cyclobutyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate

To the vial containing 1-(1-(4-fluorophenyl)cyclobutyl)-4-iodo-1H-pyrazole (52.8 mg, 0.154 mmol) was added *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (86 mg, 0.154 mmol), potassium phosphate tribasic, 2.0M in water (230 µL, 0.460 mmol), and Dioxane (2 mL). The reaction was stirred and sonnicated until all solids dissolved, then it was purged very well with argon. The reaction was then treated with[1,1'-

bis(diphenylphosphino)-ferrocene]dichloropalladium(ii), complex with dichloromethane (12 mg, 0.015 mmol), purged with argon again, securely capped and heated at 80 °C for 4 hours. The reaction was diluted with ethyl acetate, filtered thru a small pad of celite and the pad was rinsed with a 1:1 ethyl acetate:dichloromethane mixture (50 mL) and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography on silica gel, eluting with 0-100% gradient of ethyl acetate in hexane, to afford the title compound *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(1-(1-(4-fluorophenyl)cyclobutyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (46.3 mg, 0.072 mmol, 46.7%)

MS ESI m/z 643.6 $(M+H)^+$

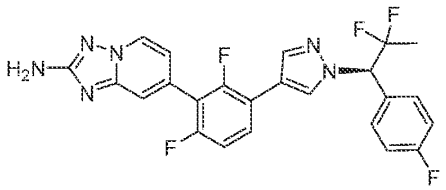
306: 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)cyclobutyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine

To a solution of compound *tert*-butyl (*tert*-butoxycarbonyl)(7-(2-fluoro-3-(1-(1-(4-fluorophenyl)cyclobutyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (46.3 mg, 0.072 mmol) in dichloromethane (2.0 mL) was added neat trifluoroacetic acid (200 mlit, 2.60 mmol) and the resulting solution was allowed to stand at room temp for 90 min. Additional trifluoroacetic acid (200 mlit, 2.60 mmol) and the resulting solution was allowed to stand at room for 4 hours and 40 minutes. The volatiles were removed under a gentle stream of nitrogen and the crude residue was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 30-70% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give the title compound, 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)cyclobutyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (19 mg, 0.043 mmol, 57.5%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.83 - 2.15 (m, 2 H) 2.76 - 2.94 (m, 2 H) 3.00 - 3.18 (m, 2 H) 6.07 (s, 2 H) 7.07 (br d, *J*=6.72 Hz, 1 H) 7.18 (t, *J*=8.87 Hz, 2 H) 7.32 (t, *J*=7.67 Hz, 1 H) 7.36 - 7.42 (m, 2 H) 7.46 (br t, *J*=6.84 Hz, 1 H) 7.53 (s, 1 H) 7.81 (br t, *J*=6.80 Hz, 1 H) 8.02 (s, 1 H) 8.32 (s, 1 H) 8.61 (d, *J*=6.97 Hz, 1 H)

MS ESI m/z 443.16 $(M+H)^+$

Example 307: (R)-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,6-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine



307A: *tert*-butyl (7-(3-bromo-2,6-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)(*tert*-butoxycarbonyl)carbamate:

To a 40 mL reaction vial under nitrogen was added *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (360 mg, 0.782 mmol), 1-bromo-2,4-difluoro-3-iodobenzene (249 mg, 0.782 mmol), dioxane (8 mL) and potassium phosphate tribasic (1.2 mL, 2.400 mmol). The reaction was purged well with argon, then treated with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (75 mg, 0.092 mmol). The reaction was again purged well with argon, securely capped and heated at 80 °C for 2 hours. The reaction was diluted with ethyl acetate, filtered thru a small pad of celite and the pad was rinsed with a 1:1 ethyl acetate:dichloromethane mixture (50 mL) and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography on silica gel, eluting with 0-100% gradient of ethyl acetate in hexane, to afford the title compound, *tert*-butyl (7-(3-bromo-2,6-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)(*tert*-butoxycarbonyl)carbamate (262.6 mg, 0.500 mmol, 63.9%)

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.64 (d, *J*=7.2 Hz, 1H), 7.86 (s, 1H), 7.65 (ddd, *J*=9.0, 7.6, 5.7 Hz, 1H), 7.16 (dd, *J*=7.1, 1.4 Hz, 1H), 7.03 (td, *J*=8.9, 1.7 Hz, 1H), 1.52 (s, 18H)

MS ESI m/z 525.1, 527.0 $(M+H)^+$

307B : *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,6-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (chirally pure)

To the vial containing , *tert*-butyl (7-(3-bromo-2,6-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)(*tert*-butoxycarbonyl)carbamate (125.7 mg, 0.239 mmol) was added chirally

pure 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (88 mg, 0.239 mmol), dioxane (3 mL) and potassium phosphate tribasic, 2.0 M in water (360 µL, 0.720 mmol). The reaction was purged well with argon, then treated with [1,1`-bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (19 mg, 0.023 mmol). The reaction was again purged well with argon, securely capped and heated at 80 °C 80C for 9 hours. The reaction was treated with additional [1,1`-Bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (19 mg, 0.023 mmol), purged well with argon again and heated at 80 °C oil bath for 8 hours. The reaction was diluted with ethyl acetate (75 mL), filtered thru a small pad of celite and the pad was rinsed with a 1:1 ethyl acetate:dichloromethane mixture (75 mL) and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography on silica gel, eluting with 0-100% gradient of ethyl acetate in hexane, to afford the chirally pure title compound, *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,6-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (122.2 mg, 0.178 mmol, 67.1%).

MS ESI m/z 685.4 $(M+H)^+$

307 : (R)-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,6-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine

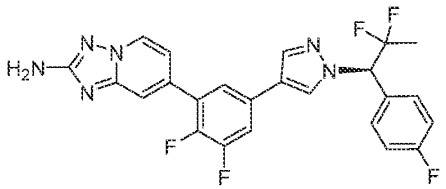
To a solution of chirally pure *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,6-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (122.1 mg, 0.178 mmol) in anhydrous CH2Cl2 (4 mL) was added neat TFA (1.0 mL, 12.98 mmol) and the resulting pale yellow solution was allowed to stand at room temp for 1 hour 25 min. The volatiles were removed under a gentle stream of nitrogen and the crude residue was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 28-63% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give the title compound, (R)-7-(3-(1-(2,2-difluoro-1-(4-

fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,6-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (57 mg, 0.118 mmol, 65.5%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.64 (t, J=19.03 Hz, 3 H) 6.26 (t, J=13.27 Hz, 1 H) 6.99 (br d, J=6.55 Hz, 1 H) 7.22 - 7.39 (m, 3 H) 7.52 (s, 1 H) 7.74 (dd, J=8.50, 5.51 Hz, 2 H) 7.88 (td, J=8.58, 6.39 Hz, 1 H) 8.12 (s, 1 H) 8.39 (s, 1 H) 8.66 (d, J=7.30 Hz, 1 H)

MS ESI m/z 485.2 $(M+H)^+$

Example 308: (R)-7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,3-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine



308A: *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-chloro-2,3-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate

To a dry 20 mL reaction vial under nitrogen was added *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (110 mg, 0.239 mmol), 1-bromo-5-chloro-2,3-difluorobenzene (54.3 mg, 0.239 mmol), potassium phosphate tribasic, 2.0M in water (360 µL, 0.720 mmol) and dioxane (2 mL). The reaction was purged well with argon, then treated with [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (17 mg, 0.021 mmol). The reaction was again purged well with argon, securely capped and heated at 80 °C for 2.5 hours. The reaction was diluted with ethyl acetate and filtered thru a small pad of Celite. The Celite pad was rinsed well with 1:1 dichloromethane:ethyl acetate mixture and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography on silica gel, eluting with 0-60% gradient of ethyl acetate in hexane, to afford the title compound, *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-chloro-2,3-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (75 mg, 0.156 mmol, 65.3%)

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.64 (d, J=7.0 Hz, 1H), 7.91 (br s, 1H), 7.38 - 7.30 (m, 2H), 7.25 (br d, J=6.6 Hz, 1H), 1.52 (s, 19H)

MS ESI m/z 481.3, 483.0 $(M+H)^+$

309B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,3-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (chirally pure)

To the vial containing *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-chloro-2,3-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (75 mg, 0.156 mmol) was added chirally pure 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (57.1 mg, 0.156 mmol), dioxane (2 mL) and potassium phosphate tribasic, 2.0 M in water (235 µL, 0.470 mmol). The reaction was purged well with argon, then treated with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (12 mg, 0.015 mmol). The reaction was again purged well with argon, securely capped heated at 80 °C for 18 hours. The reaction was treated with additional 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (57.1 mg, 0.156 mmol) and [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (10 mg, 0.015 mmol), purged well with argon, securely capped and heated at 95 °C for 15 hours. The reaction was treated with additional [1,1'-Bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (10 mg, 0.015 mmol), purged well with argon and heated at 95 °C for 24h. The reaction was diluted with ethyl acetate (20 mL) and filtered thru a small pad of celite. The celite pad was rinsed with a 1:1 dichloromethane:ethyl acetate mixture (100 mL) and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography on silica gel, eluting with 0-100% gradient of ethyl acetate in hexane, to afford the title compound, chirally pure *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,3-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (100.2 mg, 0.146 mmol, 94%)

MS ESI m/z 685.2 $(M+H)^+$

308 : (R)-7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,3-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine

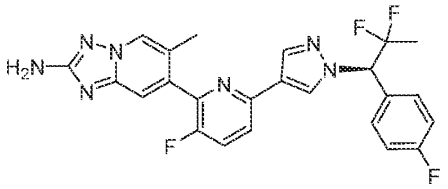
To a solution of *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,3-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (100.2 mg, 0.146 mmol) in CH2Cl2 (2 mL) was added neat TFA (300 µL, 3.89 mmol) and reaction was allowed to stand at room temp for 100 minutes. The reaction was treated with additional neat TFA (300 µL, 3.89 mmol) and allowed to stand at room

temp for 130 minutes. The volatiles were removed under a gentle stream of nitrogen and the crude residue was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 30-70% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give the title compound, (R)-7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,3-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (29.2 mg, 0.060 mmol, 41.2%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.65 (t, J=19.16 Hz, 3 H) 6.06 - 6.24 (m, 3 H) 7.15 (br d, J=6.88 Hz, 1 H) 7.27 (t, J=8.83 Hz, 2 H) 7.65 (s, 1 H) 7.71 - 7.80 (m, 3 H) 7.81 - 7.92 (m, 1 H) 8.19 (s, 1 H) 8.58 (s, 1 H) 8.66 (d, J=6.47 Hz, 1 H)

MS ESI m/z 485.1 $(M+H)^+$

Example 309 : (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-6-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine



309A: *tert*-butyl (*tert*-butoxycarbonyl)(6-fluoro-7-iodo-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate

To a suspension of 6-fluoro-7-iodo-[1,2,4]triazolo[1,5-a]pyridin-2-amine (80 mg, 0.288 mmol) in acetonitrile (1.5 mL) and CH2Cl2 (1.5 mL) was added di-*tert*-butyl pyrocarbonate (160 mg, 0.733 mmol), followed by 4-(4-(dimethylamino)pyridine (14.5 mg, 0.119 mmol). The resulting light tan suspension was allowed to stir at room temp for 5.5 hours. The reaction was treated with additional di-*tert*-butyl dicarbonate (80 mg, 0.37 mmol) and allowed to stir at room temp for 18 hours. The solvent was removed *in vacuo* and the crude residue was purified by flash chromatography on silica gel, eluting with 0-50% gradient of ethyl acetate in hexane, to afford the title compound, *tert*-butyl (*tert*-

butoxycarbonyl)(6-fluoro-7-iodo-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (112.9 mg, 0.236 mmol, 82%).

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.49 (d, *J*=2.3 Hz, 1H), 8.23 (d, *J*=5.7 Hz, 1H), 1.49 (s, 18H)

MS ESI m/z 479.1 $(M+H)^+$

309B: *tert*-butyl (*tert*-butoxycarbonyl)(6-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate

To the vial containing *tert*-butyl (*tert*-butoxycarbonyl)(6-fluoro-7-iodo-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (112.9 mg, 0.236 mmol) was added bis(pinacolato)diboron (90 mg, 0.354 mmol), potassium acetate,99%,100g (70 mg, 0.713 mmol), DMSO (2.5 mL) and dioxane (2.5 mL). The reaction was purged well with nitrogen, then treated with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (20 mg, 0.024 mmol). The reaction was again purged well with nitrogen, securely capped and heated at 90 °C for 2 hours. LC/MS analysis indicated incomplete reaction. The solvent was removed under a gentle stream of nitrogen. The reaction was treated with additional bis(pinacolato)diboron (90 mg, 0.354 mmol), potassium acetate,99%,100g (70 mg, 0.713 mmol) and DMSO (2.5 mL). The reaction was purged very will with nitrogen and then treated with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (20 mg, 0.024 mmol). The reaction was again purged very well with nitrogen, securely capped and heated at 85 °C for 4 hours. The reaction was diluted with ethyl acetate (100 mL) and water (8 mL) and the organic layer was washed with water (6 x 10 mL), brine (1 x 10 mL), dried over sodium sulfate, filtered and evaporated to dryness. The crude residue was purified by flash chromatography on silica gel, eluting with 0-100% gradient of ethyl acetate in hexane, to afford the title compound, *tert*-butyl (*tert*-butoxycarbonyl)(6-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (81.1 mg, 0.170 mmol, 71.8%).

MS ESI m/z 397.0 $(M+H)^+$ (as the boronic acid adduct).

309C: *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloro-3-fluoropyridin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate

To the reaction vial containing *tert*-butyl (*tert*-butoxycarbonyl)(6-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (81 mg, 0.169 mmol) was added 6-chloro-3-fluoro-2-iodopyridine (53.8 mg, 0.209 mmol), dioxane

(3 mL) and potassium phosphate tribasic, 2.0 M in water (255 µL, 0.510 mmol). The reaction was purged very well with nitrogen, then treated with [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (13 mg, 0.016 mmol). The reaction was again purged very well with nitrogen, securely capped and heated at 85C for 2 hours. The reaction was diluted ethyl acetate (75 mL) and filtered thru a small pad of Celite. The Celite pad was rinsed with a 1:1 ethyl acetate:dichloromethane mixture (50 mL) and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography on silica gel, eluting with 0-75% gradient of ethyl acetate in hexane, to afford the title compound, *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloro-3-fluoropyridin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (27.3 mg, 0.057 mmol, 33.5%).

MS ESI m/z 482.10 $(M+H)^+$

309D: *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate

To the reaction vial containing *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-chloro-3-fluoropyridin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (27.3 mg, 0.057 mmol) was added chirally pure 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (41 mg, 0.112 mmol), dioxane (4 mL) and potassium phosphate tribasic, 2.0 m in water (85 µL, 0.170 mmol). The reaction was purged well with nitrogen, then treated with [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (5 mg, 6.12 µmol). The reaction was again purged very well with nitrogen, securely capped and heated at 85 °C for 4.5 hours. The reaction was diluted with ethyl acetate (35 mL) and filtered thru a small pad of celite. The Celite pad was rinsed pad with 1:1 ethyl acetate:CH2Cl2 mixture (60 mL) and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography on silica gel, eluting with 0-100% gradient of ethyl acetate in hexane, to afford the title compound, *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (32 mg, 0.045 mmol, 82%)

MS ESI m/z 686.4 $(M+H)^+$

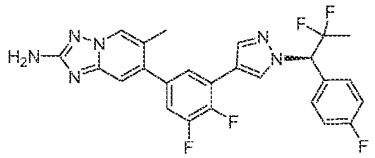
309: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-6-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine

To a solution of *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (32 mg, 0.047 mmol) in dichloromethane (3 mL) was added neat TFA (125 µL, 1.622 mmol) and the resulting clear, colorless solution was allowed to stand at room temp for 90 min. The reaction was treated with additional TFA (500 milt, 6.49 mmol) and the reaction was allowed to stand at room temp for 1 hour. The reaction was treated with additional TFA (500 milt, 6.49 mmol) and the reaction was allowed to stand at room temp for 3 hours. The volatiles were removed under a gentle stream of nitrogen and the crude residue was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 27-65% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give the title compound, (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3-fluoropyridin-2-yl)-6-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (11.5 mg, 0.024 mmol, 50.8%).

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.65 (br t, *J*=19.11 Hz, 3 H) 6.15 - 6.32 (m, 3 H) 7.27 (t, *J*=8.87 Hz, 2 H) 7.63 (d, *J*=6.63 Hz, 1 H) 7.74 (dd, *J*=8.33, 5.51 Hz, 2 H) 7.88 - 7.98 (m, 2 H) 8.22 (s, 1 H) 8.56 (s, 1 H) 9.07 (d, *J*=4.89 Hz, 1 H).

MS ESI m/z 486.4 $(M+H)^+$

Example 310: (R)-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-4,5-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine



310A. chirally pure 4-(5-chloro-2,3-difluorophenyl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole

To a dry 20 mL reaction vial under nitrogen was added chirally pure 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (110 mg, 0.300 mmol), 1-bromo-5-chloro-2,3-difluorobenzene (68.3 mg, 0.300 mmol), potassium phosphate tribasic, 2.0M in water (360 µL, 0.720 mmol) and dioxane (2 mL). The reaction was purged well with argon, treated with [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(ii), complex with dichloromethane (17 mg, 0.021 mmol), purged well with argon again, securely capped and heated at 80 °C for 2.5 hours. The reaction was diluted with ethyl acetate and filtered thru a small pad of Celite. The Celite pad was rinsed well with 1:1 dichloromethane:ethyl acetate mixture and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography on silica gel, eluting with 0-25% gradient of ethyl acetate in hexane, to afford the title compound, chirally pure 4-(5-chloro-2,3-difluorophenyl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole (62.7 mg, 0.162 mmol, 54%)

^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.03 (s, 1H), 7.94 (s, 1H), 7.59 (dd, *J*=8.7, 5.2 Hz, 2H), 7.35 - 7.25 (m, 1H), 7.17 - 7.02 (m, 3H), 5.75 - 5.60 (m, 1H), 1.73 (t, *J*=18.8 Hz, 4H)

MS ESI m/z 486.4 $(M+H)^+$ 387.0, 388.7

310B: chirally pure *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-4,5-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate

To the reaction vial containing chirally pure 4-(5-chloro-2,3-difluorophenyl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole (58 mg, 0.150 mmol) was added *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (74 mg, 0.161 mmol), dioxane (2 mL) and potassium phosphate tribasic, 2.0M in water (225 µL, 0.450 mmol). The reaction was purged well with argon, then treated with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (12 mg, 0.015 mmol). The reaction was again purged well with argon, securely capped and heated at 85 °C for 18 hours. Added [1,1-Bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (15 mg, 0.023 mmol), flush reaction well with argon, securely cap and heatred at 95 °C for 18 hours. Added additional *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-

a]pyridin-2-yl)carbamate (25 mg, 0.05 mmol) and additional [1,1'-bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (15 mg, 0.023 mmol). Purged reaction well with argon, securely capped and heated at 95 °C for 18 hours. Diluted reaction with ethyl acetate (30 mL) and filtered thru a small pad of Celite. The Celite pad was rinsed with 1:1 dichloromethane:ethyl acetate mixture (75 mL) and solvent was removed *in* vacuo. The crude residue was purified by flash chromatography on silica gel, eluting with 0-100% gradient of ethyl acetate in hexane, to afford the title compound, chirally pure *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-4,5-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (28.5 mg, 0.042 mmol, 27.8%).

MS ESI m/z 486.4 $(M+H)^+$ 685.2

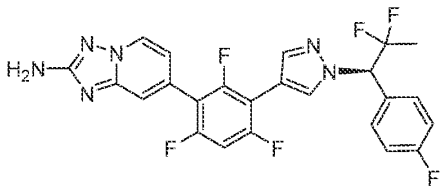
310: (R)-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-4,5-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine

To a solution of chirally pure *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-4,5-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (28.5 mg, 0.042 mmol) in CH2Cl2 (3 mL) was added neat TFA (75 µL, 0.973 mmol) and the reaction was allowed to stand at room temp for 100 minutes. The reaction was trerated with additional TFA (75 µL, 0.973 mmol) and the reaction was allowed to stand at room temp for 90 minutes. The volatiles were removed under a gentle stream of nitrogen and the crude residue was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 30-70% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give the title compound, (R)-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-4,5-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (12.6 mg, 0.026 mmol, 62.5%).

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.66 (br t, *J*=19.11 Hz, 3 H) 6.06 (s, 2 H) 6.29 (br t, *J*=12.94 Hz, 1 H) 7.28 (t, *J*=8.67 Hz, 2 H) 7.32 - 7.37 (m, 1 H) 7.73 - 7.89 (m, 4 H) 7.99 - 8.05 (m, 1 H) 8.30 (s, 1 H) 8.58 (s, 1 H) 8.62 (d, *J*=7.05 Hz, 1 H)

MS ESI m/z 486.4 $(M+H)^+$ 485.2

Example 311: (R)-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine



311A: *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-chloro-2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate

To a dry 40 mL reaction vial under nitrogen was added *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (350 mg, 0.760 mmol), 2-bromo-4-chloro-1,3,5-trifluorobenzene (187 mg, 0.760 mmol), dioxane (7 mL) and potassium phosphate tribasic, 2.0M in water (0.380 mL, 0.760 mmol). The reaction was purged well with argon, then treated with [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (50 mg, 0.061 mmol). The reaction was again purged well with argon, securely capped and heated at 100 °C for 4 hours. The reaction was diluted with ethyl acetate (75 mL) and filtered thru a small pad of Celite. The Celite pad was rinsed 1:1 ethyl acetate/dichloromethane mixture (80 mL) and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography on silica gel, eluting with 0-75% gradient of ethyl acetate in hexane, to afford the title compound, *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-chloro-2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (220.1 mg, 0.441 mmol, 58%)

MS ESI m/z $(M+H)^+$ 499.1, 501.1

311B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate

To a dry reaction vial under nitrogen was added *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-chloro-2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (82 mg, 0.164 mmol), chirally pure 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (54.8 mg, 0.150 mmol), dioxane (2 mL) and Potassium phosphate tribasic, 2.0 M in water (250 µL, 0.500 mmol). The reaction was flushed very well with nitrogen, then treated with [1,1'-

Bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (10 mg, 0.012 mmol). The reaction was again purged well with nitrogen, securely capped and heated at 85 °C for 6 hours. The reaction was treated with additional [1,1-Bis(di-*tert*-butylphosphino)ferrocene]dichloropalladium(II) (11 mg, 0.017 mmol), flushed well with nitrogen, securely capped and heated at 85 °C for 18 hours. The reaction was diluted with ethyl acetate (50 mL) and filtered thru a small pad of Celite. The Celite pad was rinsed with 1:1 dichloromethane/ ethyl acetate mixture (75 mL) and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography on silica gel, eluting with 0-75% gradient of ethyl acetate in hexane to afford the title compound, *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (58.8 mg, 0.084 mmol, 50.9%)

MS ESI m/z $(M+H)^+$ 703.3

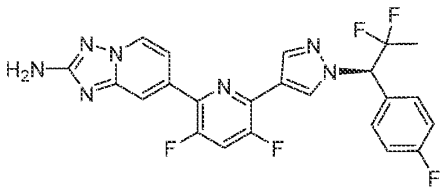
311: (R)-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine

To a solution of , *tert*-butyl (*tert*-butoxycarbonyl)(7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,4,6-trifluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (58.8 mg, 0.084 mmol) in CH2Cl2 (4 mL) was added neat TFA (6.45 µl, 0.084 mmol) and the light tan solution was allowed to stand at room temp for 100 minutes. The volatiles were removed under a gentle stream of nitrogen and the crude residue was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 29-59% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give the title compound, (R)-7-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-4,5-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (24.4 mg, 0.049 mmol, 58%).

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.64 (t, *J*=19.03 Hz, 3 H) 6.11 (s, 1 H) 6.33 (br t, *J*=12.85 Hz, 1 H) 6.98 (d, *J*=7.05 Hz, 1 H) 7.27 (t, *J*=8.83 Hz, 2 H) 7.44 - 7.58 (m, 2 H) 7.74 (dd, *J*=8.25, 5.85 Hz, 2 H) 8.02 (s, 1 H) 8.41 (s, 1 H) 8.66 (d, *J*=6.88 Hz, 1 H)

MS ESI m/z $(M+H)^+$ 503.3

Example 312: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3,5-difluoropyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine



312A: *tert*-butyl (7-(6-bromo-3,5-difluoropyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)(*tert*-butoxycarbonyl)carbamate

To a 40 mL reaction vial under nitrogen was added 2,6-Dibromo-3,5-difluoropyridine (301.4 mg, 1.105 mmol), *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (508 mg, 1.105 mmol), dioxane (15 mL) and potassium phosphate tribasic, 2.0M in water (1.7 mL, 3.40 mmol). The reaction was purged well with argon, then treated with [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (90 mg, 0.110 mmol). The reaction was again purged well with argon, securely capped and heated at 75 °C for 4.5 hours. The reaction was diluted with ethyl acetate (75 mL) and filtered thru a pad of Celite. The Celite pad was rinsed with 1:1 ethyl acetate/dichloromethane mixture (150 mL) and the solvent removed *in vacuo*. The crude residue was purified by flash chromatography on silica gel, eluting with 0-100% gradient of ethyl acetate in hexane to afford the title compound, di-*tert*-butyl ((3,5-difluoropyridine-2,6-diyl)bis([1,2,4]triazolo[1,5-a]pyridine-7,2-diyl))bis((*tert*-butoxycarbonyl)carbamate (191.2 mg, 0.363 mmol, 32.9%).

MS ESI m/z $(M+H)^+$ 526.2, 528

312B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3,5-difluoropyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate

To a dry reaction vial under nitrogen was added di-*tert*-butyl ((3,5-difluoropyridine-2,6-diyl)bis([1,2,4]triazolo[1,5-a]pyridine-7,2-diyl))bis((*tert*-butoxycarbonyl)carbamate (80 mg, 0.152 mmol), chirally pure 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (67.5 mg, 0.184 mmol), dioxane (2 mL) and potassium phosphate tribasic, 2.0 M in water (230 µL, 0.460 mmol). The reaction was

purged well with nitrogen, then treated with [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (12 mg, 0.015 mmol). The reaction was again purged very well with nitrogen, securely capped and heated at 80 °C for 5 hours. The reaction was diluted with ethyl acetate (50 mL) and filtered thru a small pad of Celite. The Celite pad was rinsed with 1:1 ethyl acetate/CH2Cl2 mixture (75 mL) and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography on silica gel, eluting with 0-75% gradient of ethyl acetate in hexane to afford the title compound, chirally pure *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3,5-difluoropyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (118.8 mg, 0.166 mmol, quantitative yield)

MS ESI m/z $(M+H)^+$ 686.5

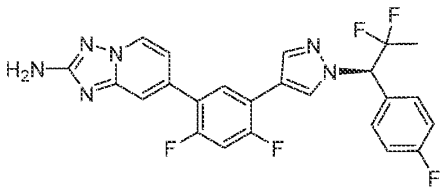
312: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3,5-difluoropyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine

To a solution of chirally pure *tert*-butyl (*tert*-butoxycarbonyl)(7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3,5-difluoropyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (118.8 mg, 0.173 mmol) in anhydrous CH2Cl2 (4 mL) was added neat TFA (500 µL, 6.49 mmol) and the resulting light tan solution was allowed to stand at room temp for 130 minutes. The volatiles were removed under a gentle stream of nitrogen and the crude residue was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 25-63% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give the title compound, (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3,5-difluoropyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (44.5 mg, 0.092 mmol, 52.5%).

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.66 (t, *J*=19.16 Hz, 3 H) 6.36 (br t, *J*=12.94 Hz, 1 H) 7.28 (t, *J*=8.87 Hz, 2 H) 7.51 (d, *J*=6.80 Hz, 1 H) 7.76 (dd, *J*=8.54, 5.56 Hz, 2 H) 7.90 (s, 1 H) 8.17 (t, *J*=10.49 Hz, 1 H) 8.26 (s, 1 H) 8.62 (s, 1 H) 8.67 (d, *J*=7.05 Hz, 1 H)

MS ESI m/z $(M+H)^+$ 486.1

Example 313: (R)-7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,4-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine



313A : *tert*-butyl (7-(5-bromo-2,4-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)(*tert*-butoxycarbonyl)carbamate

To a dry reaction vial under nitrogen was added *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (200 mg, 0.434 mmol), 1,5-Dibromo-2,4-difluorobenzene (118 mg, 0.434 mmol), dioxane (5 mL) and potassium phosphate tribasic, 2.0M in water (650 µL, 1.300 mmol). The reaction was purged well with nitrogen, then treated with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (35 mg, 0.043 mmol). The reaction was again purged well with nitrogen, securely capped and heated at 80 °C for four hours. The reaction was diluted with ethyl acetate (40 mL) and filtered thru a small pad of Celite. The Celite pad was rinsed with 1:1 ethyl acetate/dichloromethane mixture (100 mL) and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography on silica gel, eluting with 0-75% gradient of ethyl acetate in hexane to afford the title compound, *tert*-butyl (7-(5-bromo-2,4-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)(*tert*-butoxycarbonyl)carbamate (62.6 mg, 0.119 mmol, 27.4%).

MS ESI m/z $(M+H)^+$ 525.1, 527.0

313B: *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,4-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate

To the vial containing *tert*-butyl (7-(5-bromo-2,4-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)(*tert*-butoxycarbonyl)carbamate (62.6 mg, 0.119 mmol) was added chirally pure 1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (43.6 mg, 0.119 mmol), dioxane (2 mL) and potassium phosphate tribasic, 2.0 M in water (180 µL, 0.360 mmol). The reaction was purged well with nitrogen,

then treated with [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (97 mg, 0.119 mmol). The reaction was again purged very well with nitrogen, securely capped and heated at 80 °C for 4 hours. The reaction was diluted with ethyl acetate (40 mL) and filtered thru a small pad of Celite. The Celite pad was rinsed with 1:1 dichloromethane:ethyl acetate mixture (100 mL) and the solvent was removed *in* vacuo. evaporate to dryness. The crude residue was purified by flash chromatography on silica gel, eluting with 0-100% gradient of ethyl acetate in hexane to afford the title compound, chirally pure *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,4-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (49.6 mg, 0.072 mmol, 73%).

MS ESI m/z $(M+H)^+$ 685.4

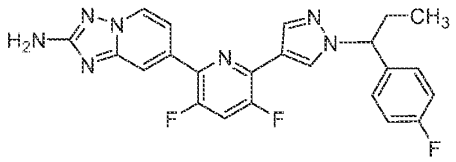
313: (R)-7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,4-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine

To a solution of chirally pure *tert*-butyl (*tert*-butoxycarbonyl)(7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,4-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (49.6 mg, 0.072 mmol) in anhydrous CH2Cl2 (2 mL) was added neat TFA (500 µL, 6.49 mmol) and the reaction was allowed to stand at room temp for 100 minutes. The volatiles were removed under a gentle stream of nitrogen and the crude residue was purified via preparative LC/MS with the following conditions: Column: Waters XBridge C18, 200 mm x 19 mm, 5-µm particles; Mobile Phase A: 5:95 acetonitrile:water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile:water with 10-mM ammonium acetate; Gradient: 30-68% B over 20 minutes; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to give the title compound, (R)-7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2,4-difluorophenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (22 mg, 0.045 mmol, 62.7%)

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.65 (t, *J*=19.16 Hz, 3 H) 6.08 (s, 1 H) 6.26 (br t, *J*=13.23 Hz, 1 H) 7.11 (br d, *J*=6.88 Hz, 1 H) 7.27 (t, *J*=8.91 Hz, 2 H) 7.51 (t, *J*=10.90 Hz, 1 H) 7.61 (s, 1 H) 7.75 (dd, *J*=8.50, 5.60 Hz, 2 H) 8.04 (t, *J*=8.67 Hz, 1 H) 8.19 (s, 1 H) 8.47 (d, *J*=1.41 Hz, 1 H) 8.63 (d, *J*=7.05 Hz, 1 H)

MS ESI m/z $(M+H)^+$ 485.0

Example 314: 7-(3,5-difluoro-6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine, enantiomer 1



enantiomer 1

314A: Racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(3,5-difluoro-6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate

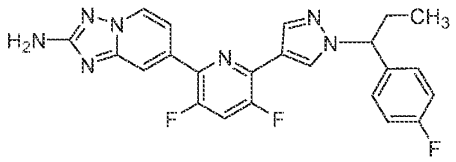
To a dry reaction vial under nitrogen was added *tert*-butyl (*tert*-butoxycarbonyl)(7-(3,5-difluoro-6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (80 mg, 0.152 mmol), racemic 1-(1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (110 mg, 0.333 mmol), dioxane (2 mL) and potassium phosphate tribasic, 2.0M in water (230 µL, 0.460 mmol). The reaction was purged very well with nitrogen, then treated with [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(ii), complex with dichloromethane (12 mg, 0.015 mmol). The reaction was again flushed well with nitrogen, securely capped and heated at 80 °C for 5 hours. The reaction was diluted with ethyl acetate and filtered thru a small pad of Celite. The Celite pad was rinsed with a 1:1 dichloromethane:ethyl acetate mixture (50 mL) and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography on silica gel, eluting with 0-75% gradient of ethyl acetate in hexane to afford the title compound, racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(3,5-difluoro-6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (136.6 mg, 0.210 mmol, quantitative yield) MS ESI m/z $(M+H)^+$ 650.2

314: 7-(3,5-difluoro-6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine, enantiomer 1

To a solution of racemic *tert*-butyl (*tert*-butoxycarbonyl)(7-(3,5-difluoro-6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-yl)carbamate (136.6 mg, 0.210 mmol) in anhydrous CH2Cl2 (3. mL) was added neat TFA (0.016 mL, 0.210 mmol) and the reaction was allowed to stand at room temp for 45 minutes.

The volatiles were removed under a gentle stream of nitrogen and the residue was purified via preparative LCMS with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5-μm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 30-60% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 C. Fraction collection was triggered by MS and UV (220 nm wavelength) signals. Fractions containing the desired product were combined and dried via centrifugal evaporation to afford racemic 7-(3,5-difluoro-6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine. This racemic material was then further purified via preparative SFC with the following conditions: Column: Whelk-O1 (R,R), 21 mm x 250 mm, 5 μm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: Methanol with 0.1% NH_4OH; Elution gradient: isocratic 20%B over 20 minutes; Flow Rate: 75 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (232 nm). Fractions containing the first enantiomer to elute from the preparative SFC column were combined and dried via centrifugal evaporation to provide 7-(3,5-difluoro-6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine, enantiomer 1 (15.8 mg, 0.035 mmol, 16.6%)
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.84 (br t, J=7.20 Hz, 3 H) 2.09 - 2.26 (m, 2 H) 2.36 - 2.47 (m, 2 H) 5.47 - 5.57 (m, 1 H) 6.08 - 6.16 (m, 2 H) 7.19 (t, J=8.87 Hz, 2 H) 7.46 - 7.55 (m, 2 H) 7.91 (s, 1 H) 8.09 - 8.20 (m, 2 H) 8.59 (s, 1 H) 8.67 (d, J=6.96 Hz, 1 H)
MS ESI m/z $(M+H)^+$ 450.1

Example 315: 7-(3,5-difluoro-6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine, enantiomer 2



enantiomer 2

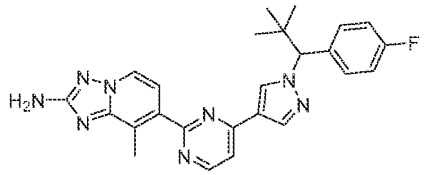
The title compound 7-(3,5-difluoro-6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine, enantiomer 2 (18.0 mg, 0.040

mmol, 18.9%) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of **Example 314.**

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.84 (br t, J=7.15 Hz, 3 H) 2.09 - 2.24 (m, 1 H) 2.36 - 2.46 (m, 1 H) 5.51 (br dd, J=9.30, 6.53 Hz, 1 H) 6.13 (s, 2 H) 7.19 (br t, J=8.68 Hz, 2 H) 7.46 - 7.61 (m, 2 H) 7.91 (s, 1 H) 8.08 - 8.24 (m, 2 H) 8.58 (s, 1 H) 8.67 (d, J=7.06 Hz, 1 H)

MS ESI m/z $(M+H)^+$ 450.2

Example 316: 7-(4-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine



316A: 1-(4-fluorophenyl)-2,2-dimethylpropan-1-ol:

In a 250 mL two neck RBF, to a well stirred solution of pivalaldehyde (5 g, 58 mmol) in THF (50 mL) was added (4-fluorophenyl)magnesium bromide (69.7 mL, 69.7 mmol, 1M) slowly at 0°C under nitrogen atmosphere. Then, the reaction mixture was allowed to warm up to room temperature and stirred for 2 h. Upon completion of the reaction, the reaction mixture was quenched with water and the compound was extracted by using ethyl acetate. The organic layers were separated, dried over anhydrous sodium sulphate and concentrated to yield crude product. The crude materia was purified by silica gel column chromatography 0-40% EtOAc/petrol ether to yield 1-(4-fluorophenyl)-2,2-dimethylpropan-1-ol (4.7 g, 25.8 mmol, 44.4 % yield) as a brown liquid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.30 (dd, J = 6.00, 8.40 Hz, 2H), 7.08-7.13 (m, 2H), 5.18 (d, J = 4.00 Hz, 1H), 4.24 (d, J = 4.40 Hz, 1H), 0.82 (s, 9H).

316B: 2-chloro-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)pyrimidine:

In a 250 mL seal tube 2,4-dichloropyrimidine (8.03 g, 53.8 mmol), 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (10 g, 36 mmol), [1,1`Bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (2.94 g, 3.6 mmol) and potassium phosphate (22.89 g, 108 mmol) were placed and the tube flushed with nitrogen. Then, 1,4-dioxane/water (4:1) (100 mL) was

added and the reaction mixture was purged with nitrogen and heated at 80 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the reaction mixture was quenched with water and compound was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvent evaporated to yield crude product, which was purified using silica gel column chromatography using 0-100% of EtOAc/petrol ether to afford 2-chloro-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)pyrimidine (9 g, 32.6 mmol, 91% yield) as a brown semisolid. MS ESI M/Z (ESI, m/z): 265.0 $[M+H]^+$.

316C: 2-chloro-4-(1H-pyrazol-4-yl)pyrimidine:

In a 250 mL two neck RBF, to a well stirred solution of 2-chloro-4-(1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-4-yl)pyrimidine (9 g, 34 mmol) in dichloromethane (DCM) (100 mL) was added trifluoroacetic acid (TFA) (52.4 mL, 680 mmol) at room temperature and the reaction mixture was stirred for 3 h. Upon completion of the reaction, reaction mixture was quenched with saturated solution of $NaHCO_3$ with maintained pH 7, and compound was extracted with ethyl acetate. The organic layers were separated, dried over anhydrous sodium sulphate, filtered and the filtrate was concentrated to yield crude product. The crude material was purified by silica gel column chromatography 0-100% of EtOAc/petrol ether to yield 2-chloro-4-(1H-pyrazol-4-yl)pyrimidine (4 g, 18.8 mmol, 55.4 % yield) as a white solid. MS ESI M/Z (ESI, m/z): 181.0 $[M+H]^+$.

316D: 2-chloro-4-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1H-pyrazol-4-yl)pyrimidine:

In a 40 mL vial, 2-chloro-6-(1H-pyrazol-4-yl)pyrazine (0.5 g, 2.77 mmol), 1-(4-fluorophenyl)-2,2-dimethylpropan-1-ol (1.51 g, 8.31 mmol) and triphenylphosphine (3.63 g, 13.84 mmol) were placed, THF (15 mL) was added and the reaction mixture was purged with nitrogen, under constant stirring, for 5 minutes. Then, di-tert-butyl azodicarboxylate (3.18 g, 13.84 mmol) was added and the reaction mixture was stirred for 16 h at room temperature under nitrogen atmosphere. Upon completion of the reaction, the reaction mixture was concentrated to yield crude product, which was purified using silica gel column chromatography using 0-12% EtOAc/petrol ether to afford 2-chloro-4-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1H-pyrazol-4-yl)pyrimidine (1 g, 2.32 mmol, 84% yield) as a brown gum. MS ESI M/Z (ESI, m/z): 345.0 $[M+H]^+$.

316E: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(4-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine:

In a 40 mL vial, (2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid (0.376 g, 1.39 mmol), 2-chloro-4-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1H-pyrazol-4-yl)pyrimidine (0.4 g, 1.16 mmol), [1,1'bis(diphenylphosphino)ferrocene]-dichloropalladium (II) complex with dichloromethane (0.95 g, 0.116 mmol) and potassium phosphate (0.739 g, 3.48 mmol) were placed, and the vial was flushed with nitrogen. Then, 1,4-dioxane/water (4:1) (10 mL) was added and the reaction mixture was purged with nitrogen and heated at 80°C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the reaction mixture was quenched with water and compound was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvent evaporated to yield crude material, which was purified using silica gel column chromatography using 0-10% EtOAc/petrol ether to afford 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(4-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-8-methyl-[1,2,4]-triazolo[1,5-a]pyridine (0.18 g, 0.239 mmol, 20.61% yield) as a pale brown solid. MS ESI M/Z (ESI, m/z): 535.2 $[M+H]^+$.

316: 7-(4-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine; Peak 1 and Peak 2:

To a well stirred solution of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(4-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.13 g, 0.243 mmol) in THF (2 mL) and water (0.5 mL) was added TFA (0.93 mL, 12.07 mmol) and the reaction mixture was stirred at 70°C for 16 h. Upon completion of the reaction, the solvent was evaporated. Excess TFA was quenched with 10 mL of saturated $NaHCO_3$ solution and the mixture was extracted with DCM (30 mL x 2). The organic layer was dried over anhydrous sodium sulphate, filtered and solvent evaporated. The crude material was purified by preparative HPLC to yield 65 mg of 7-(4-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine as a racemate. The racemate was purified further by SFC to separate enantiomer 1 and enantiomer 2.

Preparative HPLC method: Diluent: THF:WATER:ACN(30:30:40); Column: XBridge Prep C8 (19x250mm) 5µ; Temperature: Ambient; Mobile phase A: 5mM Ammonium Formate in Water; Mobile phase B: Acetonitrile; Flow:15mL/min; Time/Grad : 0/60,10/90.

SFC method: Column/dimensions: Chiralpak IJ (250 X 4.6)mm,5 μm; % CO_2: 70%; % Co solvent: 30% of 5 mm Ammonium acetate ACN-MeOH; Total Flow: 3.0g/min; Back Pressure: 100bar; Temperature : 40°C; UV: 220 nm.

316, enantiomer 1:

7-(4-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.028 g, 0.061 mmol, 16.9 % yield) (Peak 1) as a reddish brown solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 1H), 9.00 (s, 1H), 8.68-8.72 (m, 2H), 8.38 (s, 1H), 8.23 (q, J = 0.80 Hz, 1H), 7.72-7.76 (m, 3H), 7.21 (t, J = 8.80 Hz, 2H), 6.14 (s, 2H), 5.46 (s, 1H), 1.01 (s, 9H).

Note: 3H of Me group is merged with DMSO-d_6 solvent.

MS ESI M/Z (ESI, m/z): 457.3 $[M+H]^+$.

Chiral purity: 99.19% ee; RT value: 3.05 min.

SFC Method: Chiralcel-OJ-H (250X4.6)mm 5μ_Methanol_40_5.lcd; Flowrate : 3.0000 mL/min; Co-Solvent : 40.0 %; Make up Pump Flow : 0.5000 mL/min; Oven-A Temperature : 40°C; BPR Pressure : 100.0 bar; BPR Temperature : 50°C.

317, enantiomer 2:

7-(4-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.026 g, 0.056 mmol, 15.56 % yield) (Peak 2) as a reddish brown solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 1H), 9.00 (s, 1H), 8.68-8.72 (m, 2H), 8.38 (s, 1H), 8.23 (q, J = 0.80 Hz, 1H), 7.72-7.76 (m, 3H), 7.21 (t, J = 8.80 Hz, 2H), 6.14 (s, 2H), 5.46 (s, 1H), 1.01 (s, 9H).

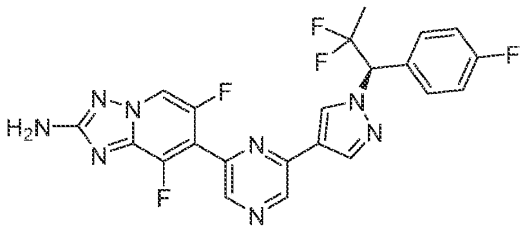
Note: 3H of Me group is merged with DMSO-d_6 solvent.

MS ESI m/z 457.3 $(M+H)^+$.

Chiral purity: 100% ee; RT value: 4.18 min.

SFC Method: Chiralcel-OJ-H (250X4.6)mm 5μ_Methanol_40_5.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 40.0 %; Make up Pump Flow: 0.5000 mL/min; Oven-A Temperature: 40°C; BPR Pressure: 100.0 bar; BPR Temperature : 50°C.

Example 318: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-6,8-difluoro-[1,2,4]triazolo[1,5-a]-pyridin-2-amine :



318A: 4-bromo-3,5-difluoropyridin-2-amine:

In a 250 mL RBF, to a stirred solution of 3,5-difluoropyridin-2-amine (4 g, 30.75 mmol) in THF (50 mL), was added LDA (46.13 mL, 92.26 mmol) at -78°C under nitrogen atmosphere. The reaction mixture was stirred for 1 h at -78°C. After 1 h, a solution of 1,2-dibromo-tetrafluoroethane (14.65 mL, 122.7 mmol) in THF (20 mL) was added to the stirring solution of 3,5-difluoropyridin-2-amine and LDA in THF slowly at -78°C and the reaction mixture was stirred for at -78 °C 1 h. Upon completion of the reaction, the mixture was quenched with saturated solution of NH_4Cl and the compound was extracted with ethyl acetate. The organic layer was dried over sodium sulphate and evaporated to yield crude material, which was purified using silica gel column chromatography with 0-8% of EtOAc/petrol ether to afforded 4-bromo-3,5-difluoropyridin-2-amine (5 g, 23.29 mmol, 62.2% yield) as a pale brown solid. MS ESI m/z 209.1 $(M+H)^+$.

318B: *O*-methyl N-((4-bromo-3,5-difluoropyridin-2-yl)carbamothioyl)carbamate

In a 250 mL RBF, to a stirred solution of 4-bromo-3,5-difluoropyridin-2-amine (5 g, 23.92 mmol) in 1,4-dioxane was added O-ethyl carbonisothiocyanatidate (3.08 mL, 26.1 mmol) at room temperature. The reaction mixture was stirred at room temperature for 16 h. Upon completion of the reaction, the mixture was filtered through a celite pad and the celite pad was washed with 1,4-dioxane. The filtrate was concentrated to give 8 g of **11b'** as crude oil, which was used for for next step without purification.

MS ESI m/z 342.2 $(M+H)^+$.

318C: 7-bromo-6,8-difluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 250 mL RBF, to a stirred solution of **318B** (8g, 23.52 mmol) in ethanol (80 mL) was added DIPEA (16.43 mL, 94 mmol) and hydroxylamine hydrochloride (8.17 g, 118 mmol). The reaction mixture was heated to 60°C for 3 h. Upon completion of the reaction, ethanol was removed under vacuum to give a brown residue. The residue was dissolved in a minimum amount of DMSO and purified by reverse phase flash chromatography to obtain

5 g of 7-bromo-6,8-difluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (5 g, 20.07 mmol, 85.3% yield) as a brown solid. MS ESI m/z 251.0 $(M+H)^+$.

318D: 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6,8-difluoro-[1,2,4]triazolo[1,5-a]pyridine:

In a 30 mL microwave vial, to the stirred solution of 7-bromo-6,8-difluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (1.5 g, 6.02 mmol) in toluene (15 mL) were added hexane-2,5-dione (3.53 mL, 30.1 mmol) and acetic acid (1.724 mL, 30.1 mmol). The reaction mixture was heated to 120°C, under microwave irradiation for 12 h. Upon completion of the reaction, toluene was removed under reduced pressure to yield brown crude material, which was purified using silica gel column chromatography with 0-20% of EtOAc/petrol ether to afforded 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6,8-difluoro-[1,2,4]triazolo[1,5-a]pyridine (1 g, 2.93 mmol, 48.7 % yield) as a pale brown solid. MS ESI m/z 329.0 $(M+H)^+$.

318E (*R*)-2-chloro-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazine:

In a 40 mL vial, (*R*)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2 g, 5.46 mmol), 2-bromo-6-chloropyrazine (1.268 g, 6.55 mmol), 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex (0.044 g, 0.546 mmol) and tripotassium phosphate (3.48 g, 16.38 mmol) were placed, and the vial was flushed with nitrogen. Then, 1,4-dioxane/water (5:1) (18 mL) was added to the vial and reaction mixture was purged with nitrogen and heated to 80 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvent evaporated from the filtrate under reduced pressure to yield crude material, which was purified using silica gel column chromatography with 0-100% of EtOAc/petrol ether to afforded (*R*)-2-chloro-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazine (1.5 g, 4.25 mmol, 78 % yield) as a off white solid. MS ESI m/z 353.1 $(M+H)^+$.

318F: (*R*)-2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-6-(trimethylstannyl)pyrazine

In a hot air dried 20 mL microwave reaction vial, to a stirred solution of (*R*)-2-chloro-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazine (0.3 g, 0.850 mmol) in

1,4-dioxane (5 mL) hexamethylditin (0.882 mL, 4.25 mmol) was added. The reaction mixture was purged with nitrogen gas for 2 min. Then, tetrakis(triphenylphosphine)palladium(0) (0.098 g, 0.085 mmol) was added and the reaction mixture was stirred at 100 °C for 1 h under microwave irradiation. Upon completion of the reaction, the mixture was diluted with ethyl acetate and filtered through celite. The filtrate was concentrated to yield crude material, which was purified using silica gel column chromatography with 0-100% of EtOAc/petrol ether to afforded (*R*)-2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-6-(trimethylstannyl)pyrazine (0.245 g, 0.509 mmol, 59.9 % yield) as a colorless semi-solid. MS ESI m/z 483.1 $(M+H)^+$.

318G: (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6,8-difluoro-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL reaction vial, to a stirred solution of 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6,8-difluoro-[1,2,4]triazolo[1,5-a]pyridine (0.17 g, 0.520 mmol) in 1,4-dioxane (4 mL), (*R*)-2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-6-(trimethylstannyl)pyrazine (0.2 g, 0.416 mmol) was added. The reaction mixture was purged with nitrogen gas for 2 min and chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II) (0.032 g, 0.042 mmol) was added. The mixture was heated at 80°C for 12 h. Upon completion of the reaction, the mixture was diluted with ethyl acetate and filtered through celite. The filtrate was concentrated to yield crude material, which was purified using silica gel column chromatography with 0-50% of EtOAc/petrol ether to afforded (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6,8-difluoro-[1,2,4]triazolo[1,5-a]pyridine (0.15 g, 0.266 mmol, 63.9 % yield) as a colorless semi-solid.

MS ESI m/z 565.4 $(M+H)^+$.

318: (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-6,8-difluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

To a well stirred solution of (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6,8-difluoro-[1,2,4]triazolo[1,5-a]-pyridine (0.14 g, 0.248 mmol) in THF (2 mL) and water (0.5 mL) was added TFA (0.955 mL, 12.40 mmol). The mixture was stirred at 70°C for 16 h. Upon completion of the reaction, the solvent was evaporated, excess TFA was quenched with 10

mL of saturated $NaHCO_3$ solution and extracted with DCM (30 mL x 2). The organic layer was dried over anhydrous sodium sulphate, filtered and solvent evaporated to yield crude material. The crude residue was purified by the preparative HPLC and the required fraction was lyophilized to yield (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-6,8-difluoro-[1,2,4]-triazolo[1,5-a]pyridin-2-amine (0.023 g, 0.047 mmol, 18.82 % yield) as an off white solid.

Preparative HPLC method:

Diluent: Water:THF:ACN(10:60:30); Column: X-Select C18 (250 x19)mm, 5micron; Temperature: Ambient; Mobile phase A: 5Mm ammonium acetate in water; Mobile phase B: acetonitrile; Flow: 15mL/min; Time/Grad: 0/20, 9/60.

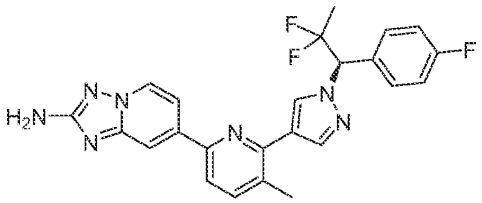
^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 9.18 (s, 1H), 9.10 (q, J = 0.80 Hz, 1H), 8.76 (s, 1H), 8.71 (s, 1H), 8.34 (s, 1H), 7.75 (q, J = 5.60 Hz, 2H), 7.26-7.31 (m, 2H), 6.41 (s, 2H), 6.31 (t, J = 13.20 Hz, 1H), 1.66 (t, J = 19.20 Hz, 3H).

MS ESI m/z 487.1 $(M+H)^+$.

Chiral purity: 100% ee; RT value: 4.459 min.

SFC Method: YMC Cellulose-SC(250mmX4.6X5u)_0.1% NH_4OH in methanol_40_16.lcd; Flowrate : 3.0000 mL/min; Co-Solvent :40.0 %; Oven-B Temperature: 40°C; Oven B Column Position:2; BPR Pressure : 100.0 bar; BPR Temperature: 50 C.

Example 319: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-5-methylpyridin-2-yl)-[1,2,4]triazolo[1,5-a]-pyridin-2-amine



319A: (2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid:

In a 350 mL sealed tube, to a stirred solution of 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (5 g, 17.17 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (8.72 g, 34.3 mmol) in 1,4-dioxane (50 mL) was added potassium acetate (5.06 g, 51.5 mmol) and the reaction mixture was purged with nitrogen gas for 10 minutes. [1,1'Bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with

dichloromethane (1.4 g, 1.71 mmol) was added and the reaction mixture was purged with nitrogen gas for 2 min and allowed to stir at 100°C for 2 h. Upon completion of the reaction, the reaction mixture was filtered through celite and the celite was washed with ethyl acetate. The filtrate was concentrated to give crude material, which was subjected to reverse phase chromatography for purification to obtain 7 g of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid (7 g, 16.56 mmol, 96% yield) as a brown solid. MS ESI m/z 257.2 $(M+H)^+$.

319B: 7-(6-chloro-5-methylpyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine:

Into a 40 mL vial, (2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid (1.5 g, 3.10 mmol), 2,6-dichloro-3-methylpyridine (0.754 g, 4.66 mmol), tetrakis(triphenylphosphine)palladium(0) (0.359 g, 0.31 mmol) and sodium carbonate (0.987 g, 9.31mmol) were added, and the vial was flushed with nitrogen. Then, 1,4-dioxane/water (4:1) (10 mL) was added, the reaction mixture was purged with nitrogen and heated at 80 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvent evaporated to yield crude material, which was purified using silica gel column chromatography with 0-10% of EtOAc/petrol ether to afford 7-(6-chloro-5-methylpyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]-pyridine (0.28 g, 0.622 mmol, 20.02% yield) as a pale brown gum. MS ESI m/z 338.2 $(M+H)^+$.

319C (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-5-methylpyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine:

Into 20 mL vial, 7-(6-chloro-5-methylpyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]-triazolo[1,5-a]pyridine (0.284 g, 0.841 mmol), (*R*)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.28 g, 0.76 mmol), [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (0.049 g, 0.076 mmol) and potassium phosphate (0.4 g, 2.294 mmol) were added, and the vial was flushed with nitrogen. Then, 1,4-dioxane/water (5:1) (5 mL) was added, the reaction mixture was purged with nitrogen and heated at 80 °C for 3 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium

sulphate, filtered and solvent evaporated to yield crude material, which was purified using silica gel column chromatography with 0-60% of EtOAc/petrol ether to afford (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)-propyl)-1H-pyrazol-4-yl)-5-methylpyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]-triazolo[1,5-a]pyridine (0.2 g, 0.277 mmol, 36.2% yield) as a pale brown gum. MS ESI m/z 542.2 $(M+H)^+$.

319: (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-5-methylpyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

To a well stirred solution of (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-5-methylpyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.2 g, 0.369 mmol) in THF (3 mL) and water (0.8 mL), TFA (1.42 mL, 18.46 mmol) was added and the reaction mixture was allowed to stir at 70°C for 16 h. Upon completion of the reaction, the solvent was evaporated, excess TFA was quenched with saturated solution of $NaHCO_3$ and extracted with DCM. The organic layer was dried using sodium sulphate and evaporated to yield crude material, which was purified by the preparative HPLC. The required fraction was lyophilized to yield (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-5-methylpyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.015 g, 0.032 mmol, 8.73 % yield) as an off white solid.

Preparative HPLC method:

Diluent: THF:ACN:WATER(50:30:20); Column : X Bridge C18(150 x19)mm, 5micron Temperature: Ambient; Mobile phase A: 10mM Ammoium acetate in water; Mobile phase B: acetonitrile; Flow: 15mL/min; Time/Grad: 0/30,14/70.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.59-8.62 (m, 2H), 8.26 (s, 1H), 8.11 (d, J = 1.20 Hz, 1H), 7.94 (d, J = 8.00 Hz, 1H), 7.77-7.81 (m, 3H), 7.69-7.72 (m, 1H), 7.26-7.31 (m, 2H), 6.32 (t, J = 13.60 Hz, 1H), 6.05 (s, 2H), 1.68 (t, J = 19.20 Hz, 3H) .

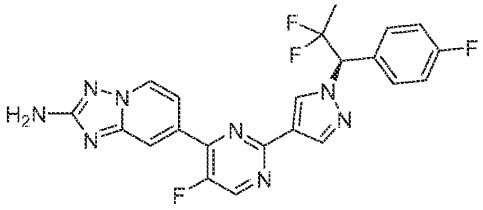
Note: 3H of Me group is merged with DMSO-d_6 solvent.

MS ESI m/z 464.0 $(M+H)^+$.

Chiral purity: 100% ee; RT value: 2.83 min.

SFC Method: Chiralcel OD-H(250mmX4.6X5u)_IPA_40_45.lcd; Flowrate: 3.0000 mL/min; Co-Solvent:40.0 %; Oven-B Temperature: 40°C; Oven B Column Position:6; BPR Pressure: 100.0 bar; BPR Temperature: 50°C.

Example 320: (R)-7-(2-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-4-yl)-5-fluoropyrimidin-4-yl)-[1,2,4]triazolo-[1,5-a]-pyridin-2-amine



320A: 7-(2-chloro-5-fluoropyrimidin-4-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine:

To a 20 mL vial containing a well stirred solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.7 g, 1.449 mmol) and 2,4-dichloro-5-fluoropyrimidine (0.484 g, 2.90 mmol) in 1,4-dioxane (7 mL) in water (1.5 mL), Cs_2CO_3 (1.416 g, 4.35 mmol) was added and the reaction mixture was purged with nitrogen for 10 minutes. [1,1`Bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (0.118 g, 0.145 mmol) was added to the reaction mixture and the mixture was heated at 80°C for 2 h under nitrogen atmosphere. Upon completion of the reaction, water was added and extracted with ethyl acetate (100 mL). The organic layer was dried over $MgSO_4$, filtered and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography using 0-8% of EtOAc/petrol ether to give 7-(2-chloro-5-fluoropyrimidin-4-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.32 g, 0.747 mmol, 51.6 % yield) as pale brown viscous liquid.

MS ESI m/z 343.02 $(M+H)^+$.

320B: (*R*)-7-(2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoropyrimidin-4-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine:

To a 20 mL vial containing a well stirred solution of 7-(2-chloro-5-fluoropyrimidin-4-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.309 g, 0.901 mmol) and (*R*)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.3 g, 0.819 mmol) in a mixture of 1,4-dioxane (4 mL) and water (1 mL), potassium phosphate, tribasic (0.428 g, 2.458 mmol) was added and the reaction mixture was purged with nitrogen for 8 minutes. Then, [1,1'-bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II) (0.053 g, 0.082 mmol) was added and the mixture was heated at 80 °C for 3 h under nitrogen atmosphere. Upon completion of the reaction, water was added and extracted with ethyl acetate (70 mL). The organic layer was

dried over $MgSO_4$, filtered and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography using 0-60% of EtOAc/petrol ether to give (*R*)-7-(2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoropyrimidin-4-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.3 g, 0.516 mmol, 63.0 % yield) as pale brown gummy liquid. MS ESI m/z 547.12 $(M+H)^+$.

320: (*R*)-7-(2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoropyrimidin-4-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

To a 20 mL vial containing a well stirred solution of (*R*)-7-(2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoropyrimidin-4-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.3 g, 0.549 mmol) in a mixture of THF (4 mL) and water (1 mL), TFA (2.114 mL, 27.4 mmol) was slowly added at room temperature. The reaction mixture was heated to 70°C and stirred for 16 h. Upon completion of the reaction, TFA was removed under vacuum, the residue was neutralized with saturated solution of sodium bicarbonate and compound was extracted with DCM. The organic layer was dried over anhydrous sodium sulphate, filtered and the filtrate was concentrated under vacuum. The residue was purified by prep-HPLC to obtain (*R*)-7-(2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoropyrimidin-4-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.065 g, 0.138 mmol, 25.2 % yield) as off white solid.

Preparative HPLC method:

Diluent: THF:WATER:ACN(30:30:40); Column: XBridge Prep C8 (19x250mm) 5µ; Temperature : Ambient; Mobile phase A: 5mM Ammonium formate in water; Mobile phase B: Acetonitrile; Flow: 15mL/min; Time/Grad: 0/30,17/70.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.97 (d, J = 3.60 Hz, 1H), 8.73-8.75 (m, 1H), 8.70 (s, 1H), 8.28 (s, 1H), 8.09 (d, J = 2.00 Hz, 1H), 7.74-7.78 (m, 2H), 7.61-7.63 (m, 1H), 7.26-7.30 (m, 2H), 6.32 (t, J = 13.20 Hz, 1H), 6.24 (s, 2H), 1.66 (t, J = 19.20 Hz, 3H).

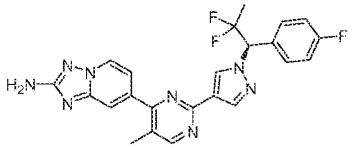
MS ESI m/z 469.0 $(M+H)^+$.

Chiral purity: 100% ee; RT: 2.323 min.

SFC Method:

Chiralcel OD-H(250mmX4.6X5u)_IPA_40_46.lcd; Flowrate : 3.0000 mL/min; Co-Solvent: 40.0 %; Oven-B Temperature: 40°C; Oven B Column Position:6; BPR Pressure: 100.0 bar; BPR Temperature: 50°C.

Example 321: (R)-7-(2-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-4-yl)-5-methylpyrimidin-4-yl)-[1,2,4]triazolo-[1,5-a]pyridin-2-amine



321A: 7-(2-chloro-5-methylpyrimidin-4-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]-triazolo[1,5-a]pyridine

In an 8 mL vial, to the solution of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.1 g, 0.207 mmol) and 2,4-dichloro-5-methylpyrimidine (50.6 mg, 0.310 mmol) in a mixture of 1,4-dioxane (1 mL) and water (0.05 mL), potassium phosphate, tribasic (0.108 g, 0.621 mmol)) was added. The reaction mixture was purged with nitrogen for 10 minutes and [1,1'Bis(diphenylphosphino)ferrocene]-dichloropalladium (II), complex with dichloromethane (0.016 g, 0.021 mmol) was added. The reaction mixture was heated at 80 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was filtered through celite, washed with ethyl acetate, dried over $MgSO_4$ and concentrated to yield crude material which was taken to the next step without further purification. MS ESI m/z 339.8 $(M+H)^+$.

321B: (*R*)-7-(2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-methylpyrimidin-4-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, to a solution of 7-(2-chloro-5-methylpyrimidin-4-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.153 g, 0.451 mmol) and (*R*)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.15 g, 0.410 mmol) in 1,4-dioxane (5 mL) and water (0.5 mL), potassium phosphate, tribasic (214 mg, 1.229 mmol) was added. The reaction mixture was purged with nitrogen for 8 minutes and [1,1'-bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II) (0.0267 g, 0.041 mmol) was added. The reaction mixture was heated at 80°C for 2 h under nitrogen atmosphere. Upon completion of reaction, the mixture was diluted with water and extracted with ethyl acetate. The aqueous layer was separated, and dried over $MgSO_4$, filtered and the filtrate was concentrated to yield crude material, which was purified by silica gel column chromatography using 0-60% of EtOAc/petrol ether to give (*R*)-7-(2-(1-(2,2-difluoro-1-(4-fluorophenyl)-propyl)-1*H*-pyrazol-4-yl)-5-methylpyrimidin-4-yl)-2-(2,5-

dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]-triazolo[1,5-a]pyridine (0.19 g, 0.290 mmol, 70.7 % yield).

MS ESI m/z 543.30 $(M+H)^+$.

321: (*R*)-7-(2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-methyl-pyrimidin-4-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

To a 20 mL vial containing a well stirred solution of (*R*)-7-(2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-5-methylpyrimidin-4-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.19 g, 0.350 mmol) in a mixture of THF (2 mL) and water (0.5 mL), TFA (1.349 mL, 17.51 mmol) was added slowly at room temperature. The reaction mixture was heated to 70°C and stirred for 16 h. Upon completion of the reaction, TFA was removed under vacuum, the residue was neutralized with saturated solution of sodium bicarbonate and extracted with DCM. The organic layer was dried over anhydrous sodium sulphate, filtered and the filtrate was concentrated under vacuum. The residue was purified by prep-HPLC to obtain (*R*)-7-(2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-5-methylpyrimidin-4-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.025 g, 0.053 mmol, 15.26 % yield) as off-white solid.

Preparative HPLC method:

Diluent: Water:THF:ACN(10:60:30); Column: X-Select C18 (250 x19)mm, 5micron; Temperature: Ambient; Mobile phase A: 5mM Ammonium Formate; Mobile phase B: acetonitrile; Flow:15mL/min; Time/Grad: 0/20, 9/60.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.74 (s, 1H), 8.74 (s, 1H), 8.66-8.68 (m, 1H), 8.61 (s, 1H), 8.22 (s, 1H), 7.72-7.76 (m, 2H), 7.68-7.69 (m, 1H), 7.25-7.29 (m, 2H), 7.19-7.22 (m, 1H), 6.29 (t, J = 13.20 Hz, 1H), 6.12 (s, 2H), 2.39 (s, 3H), 1.60-1.69 (m, 3H).

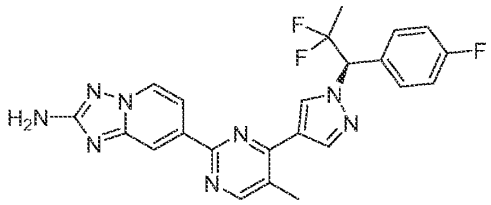
MS ESI m/z 465.0 $(M+H)^+$.

Chiral purity: 100% ee; RT value: 2.323 min.

SFC Method:

Cellulose-1(250mmX4.6X5u)_0.1% NH_4OH in methanol_40_4.lcd; Flowrate: 3.0000; mL/min; Co-Solvent : 40.0 %; Make up Pump Flow : 0.5000 mL/min; Oven-B Temperature : 40°C; Oven-B Column Position :1; BPR Pressure : 100.0 bar; BPR Temperature : 50°C.

Example 322: (R)-7-(4-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-4-yl)-5-methylpyrimidin-2-yl)-[1,2,4]triazolo-[1,5-a]pyridin-2-amine



322A: (*R*)-2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-methylpyrimidine:

In a 40 mL vial, to a solution of (*R*)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (1 g, 2.73 mmol) and 2,4-dichloro-5-methylpyrimidine (0.668 g, 4.10 mmol) in 1,4-dioxane (10 mL) and water (2 mL), was added potassium phosphate, tribasic (1.427 g, 8.19 mmol)) and the reaction mixture was purged with nitrogen for 10 minutes. [1,1`Bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (0.223 g, 0.273 mmol) was added and the mixture was heated at 80°C for 2 h under nitrogen atmosphere. Upon completion of the reaction, water was added to the reaction mixture and extracted with ethyl acetate (200 mL). The organic layer was dried over $MgSO_4$, filtered and the filtrate was concentrated under vacuum. The crude material was purified by silica gel column chromatography using 0-8% of EtOAc/petrol ether to give (*R*)-2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-5-methylpyrimidine (0.73 g, 1.194 mmol, 43.7 % yield) as pale brown solid. MS ESI m/z 367.10 $(M+H)^+$.

322B: (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-methyl-pyrimidin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, to a solution of (*R*)-2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-methylpyrimidine (0.253 g, 0.689 mmol) and 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.333 g, 0.689 mmol) in 1, 4-dioxane (4 mL) and water (0.8 mL), potassium phosphate tribasic (360 mg, 2.068 mmol)) was added. The reaction mixture was purged with nitrogen for 10 minutes and [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (0.056 g, 0.069 mmol) was added to the reaction. The mixture was heated at 80°C for 2 h under nitrogen atmosphere. Upon completion, the mixture was diluted with water and extracted with ethyl acetate. The aqueous layer was separated, and the organic fraction was dried over $MgSO_4$, filtered and the filtrate was

concentrated. The residue was purified by silica gel column chromatography using 0-60% of EtOAc/petrol ether to yield (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-methylpyrimidin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.2 g, 0.181 mmol, 26.2 % yield) as pale brown viscous liquid. MS ESI m/z 543.31 $(M+H)^+$.

322: (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-methylpyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to a solution of (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-methylpyrimidin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (200 mg, 0.369 mmol) in THF (1.5 mL) and water (0.3 mL), was added TFA (1420 µl, 18.43 mmol) slowly at room temperature. The reaction mixture was heated at 70ºC for 16 h. Upon completion of the reaction, TFA was removed under vacuum, the residue was neutralized with saturated solution of sodium bicarbonate and extracted with DCM. The organic layer was dried over anhydrous sodium sulphate, filtered and the filtrate was concentrated under vacuum. The residue was purified by prep-HPLC to obtain (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-methylpyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.005 g, 10.69 µmol, 2.90 % yield) as pale pink solid.

Preparative HPLC method:

Diluent: Water:THF:ACN(10:60:30); Column: X-Select C18 (250 x19)mm, 5micron; Temperature: Ambient; Mobile phase A: 5mM Ammonium Formate; Mobile phase B: Acetonitrile; Flow :15mL/min; Time/Grad : 0/20, 12/70.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.84 (s, 1H), 8.76 (d, J = 0.40 Hz, 1H), 8.64-8.66 (m, 1H), 8.45 (s, 1H), 8.34-8.34 (m, 1H), 7.88-7.90 (m, 1H), 7.77-7.81 (m, 2H), 7.27-7.32 (m, 2H), 6.36 (t, J = 12.80 Hz, 3H), 6.13 (s, 2H), 1.63-1.73 (m, 3H).

Note: 3H of Me group is merged with DMSO-d_6 solvent

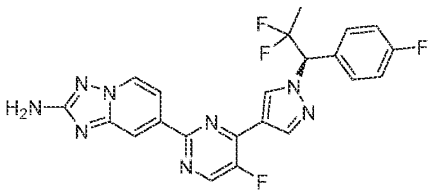
MS ESI m/z 465.1 $(M+H)^+$

Chiral purity: 100% ee; RT:2.965 min.

SFC Method:

Cellulose-1(250mmX4.6X5u)_0.1% NH_4OH in methanol_40_4.lcd; Flowrate : 3.0000 mL/min; Co-Solvent: 40.0 %; Make up Pump Flow: 0.5000 mL/min; Oven-B Temperature: 40°C; Oven-B Column Position: 1; BPR Pressure: 100.0 bar; BPR Temperature: 50°C.

Example 323: (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-4-yl)-5-fluoropyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]-pyridin-2-amine



323A (*R*)-2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoropyrimidine:

In a 40 mL sealed tube, to a solution of (*R*)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1g, 2.73 mmol) and 2,4-dichloro-5-fluoropyrimidine (0.684 g, 4.10 mmol) in 1,4-dioxane (10 mL) and water (2 mL), potassium phosphate (1.427 g, 8.19 mmol)) was added. The reaction mixture was purged with nitrogen for 10 minutes and [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (0.223 g, 0.273 mmol) was added. The mixture was heated at 80°C for 3 h under nitrogen atmosphere. Upon completion of the reaction, water was added and extracted with ethyl acetate (100 mL). The organic layer was dried over $MgSO_4$, filtered and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography using 0-8% of EtOAc/petrol ether to give (*R*)-2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoropyrimidine (0.86 g, 2.204 mmol, 81 % yield) as pale brown solid.

MS ESI m/z 371.11 $(M+H)^+$.

323B: (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoropyrimidin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, to a solution of (*R*)-2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-5-fluoropyrimidine (0.253 g, 0.683 mmol) and 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.33 g, 0.683 mmol) in 1, 4-dioxane (4 mL) and water (0.8 mL), potassium phosphate (0.357 g, 2.049 mmol) was added. The reaction mixture was purged with nitrogen for 10 minutes and [1,1'bis-(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (0.055 g, 0.068 mmol) was added. The mixture was heated

at 80 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, water was added and the mixture was extracted with ethyl acetate (100 mL). The organic layer was dried over $MgSO_4$, filtered and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography using 0-60% of EtOAc/petrol ether to give (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-5-fluoropyrimidin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.16 g, 0.085 mmol, 12.43 % yield) as pale brown gummy liquid.

MS ESI m/z 547.20l $(M+H)^+$.

323: (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoro-pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to a solution of (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoropyrimidin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.16 g, 0.293 mmol) in THF (1.5 mL) and water (0.3 mL) slowly TFA (1.128 mL, 14.64 mmol) was added at room temperature. The reaction mixture was heated at 70°C for 16 h. Upon completion of the reaction, TFA was removed under vacuum, the residue was neutralized with saturated solution of sodium bicarbonate and extracted with DCM. The organic layer was dried over anhydrous sodium sulphate, filtered and the filtrate was concentrated under vacuum. The residue was purified by prep-HPLC to obtain (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoropyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.010 g, 0.021 mmol, 7.14 % yield) as pale brown solid.

Preparative HPLC method:

Diluent: Water:THF:ACN(10:60:30); Column: X-Select C18 (250 x19)mm, 5micron; Temperature: Ambient; Mobile phase A: 5mM Ammonium Formate in water; Mobile phase B: Acetonitrile; Flow:15mL/min; Time/Grad : 0/20, 12/70,13/70.

^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 8.99 (d, J = 3.20 Hz, 1H), 8.90 (d, J = 0.80 Hz, 1H), 8.67-8.69 (m, 1H), 8.48 (s, 1H), 8.32-8.33 (m, 1H), 7.85-7.87 (m, 1H), 7.76-7.80 (m, 2H), 7.28-7.32 (m, 2H), 6.38-6.45 (m, 1H), 6.16 (s, 2H),1.63-1.73 (m, 3H).

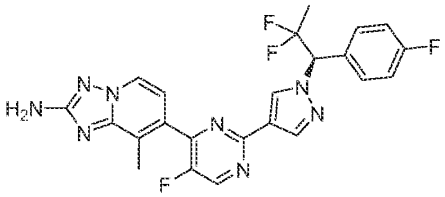
MS ESI m/z 469.1 $(M+H)^+$

Chiral purity: 98.6% ee; RT:3.7 min.

SFC Method:

Chiralcel OD-H(250mmX4.6X5u)_0.2% Ammonia in methanol_40_12.lcd; Flowrate: 3.0000 mL/min; Co-Solvent:40.0 %; Oven-B Temperature: 40°C; Oven B Column Position:1; BPR Pressure : 100.0 bar; BPR Temperature : 50°C.

Example 324: (R)-7-(2-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-4-yl)-5-fluoropyrimidin-4-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine



324A: (2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid

Into a 150 mL sealed tube, to a stirred solution of 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (400 mg, 1.311 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.666 g, 2.62 mmol) in 1,4-dioxane (50 mL) was added potassium acetate (0.386 g, 3.93 mmol) and the reaction mixture was purged with nitrogen gas for 10 minutes. Then, [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (0.107 g, 0.131 mmol) was added. The reaction mixture was purged with nitrogen gas for 2 min and allowed to stir at 100°C for 1 h. Upon completion of the reaction, the mixture was filtered through celite and the celite pad was washed with ethyl acetate. The filtrate was concentrated to give crude product (0.462 g), which was used for the next step without purification. MS ESI m/z 353.2 $(M+H)^+$.

324B: 7-(2-chloro-5-fluoropyrimidin-4-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine:

In a 40 mL vial, 2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.4 g, 1.136 mmol), 2,4-dichloro-5-fluoropyrimidine (0.19 g, 1.136 mmol), [1,1'bis(diphenylphosphino)-ferrocene]dichloropalladium (II), complex with dichloromethane (0.95 g, 0.116 mmol) and potassium phosphate (0.73 g, 3.41 mmol) were added. The vial was flushed with nitrogen. Then, 1,4-dioxane/water (4:1) (10 mL) was added and the reaction mixture was purged with nitrogen and heated at 80 °C for 2 h under nitrogen atmosphere. Upon completion of

the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated to yield crude maaterial, which was purified by silica gel column chromatography using 0-100% of EtOAc/petrol ether to afford 7-(2-chloro-5-fluoropyrimidin-4-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.16 g, 0.377 mmol, 33.2 % yield) as a light yellow semisolid. MS ESI m/z 357.1 $(M+H)^+$.

324C: (*R*)-7-(2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-5-fluoropyrimidin-4-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine:

In a 40 mL vial, 7-(2-chloro-5-fluoropyrimidin-4-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.15 g, 0.420 mmol), (*R*)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (intermediate 47, 0.154 g, 0.420 mmol), [1,1'bis(diphenylphosphino)ferrocene]-dichloropalladium (II), complex with dichloromethane (0.034 g, 0.042 mmol) and potassium phosphate (0.268 g, 1.26 mmol) were placed. The vial was flushed with nitrogen. Then, 1,4-dioxane/water (4:1) (5 mL) was added and the reaction mixture was purged with nitrogen and heated at 80 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the reaction mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated to yield crude material, which was purified using silica gel column chromatography using 0-100% of EtOAc/petrol ether to afford (*R*)-7-(2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-5-fluoropyrimidin-4-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.13 g, 0.204 mmol, 48.5% yield) as a light brown liquid.

MS ESI m/z 561.2 $(M+H)^+$.

324: (*R*)-7-(2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-5-fluoropyrimidin-4-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to a well stirred solution of (*R*)-7-(2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-5-fluoropyrimidin-4-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.12 g, 0.214 mmol) in THF (5 mL) and water (1.25 mL) was added TFA (0.825 mL, 10.70 mmol) and the mixture was allowed

to stirred at 70 °C for 16 h. Upon completion of the reaction, solvent was evaporated, excess TFA was quenched with 10 mL of saturated $NaHCO_3$ solution and compound was extracted with DCM (30 mL X 2). The organic layer was dried over anhydrous sodium sulphate, filtered and solvent evaporated to yield crude material. The crude residue was purified by the preparative HPLC and the required fraction was lyophilized to yield (*R*)-7-(2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-5-fluoropyrimidin-4-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.019 g, 0.039 mmol, 18.21% yield) as an off white solid.

Preparative HPLC method:

Diluent : THF:ACN:WATER(50:30:20); Column : Biphenyl C18(21.2 x250)mm; 5micron, Temperature : Ambient, Mobile phase A: 5mM Ammonium formate in water; Mobile phase B: ACETONITRILE; Flow :15mL/min, Time/Grad : 0/20 ,20/60 ,24/60.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.98 (d, J = 2.00 Hz, 1H), 8.61 (s, 1H), 8.56 (dd, J = 0.40, 6.80 Hz, 1H), 8.21 (s, 1H), 7.74 (dd, J = 5.20, 8.80 Hz, 2H), 7.25-7.30 (m, 2H), 7.00 (t, J = 6.40 Hz, 1H), 6.31 (t, J = 13.20 Hz, 1H), 6.16 (s, 2H), 2.40 (d, J = 0.80 Hz, 3H), 1.65 (t, J = 19.20 Hz, 3H).

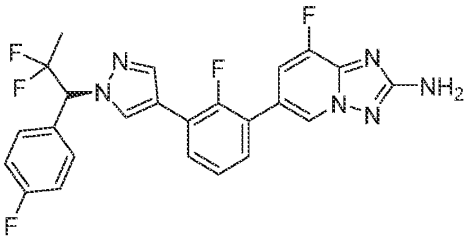
MS ESI m/z 483.0 $(M+H)^+$.

LC-MS method: Column: Kinetex XB - C18 (75 x 3.0)mm, 2.6µm; Mobile Phase A: 5mm Ammonium formate pH 3.3:ACN (98:02); Mobile Phase B: ACN: Buffer (98:02); Flow Rate: 1.0 ml/min.

Chiral purity: 97.8% ee; RT value: 4.267 min.

SFC Method: Column/dimensions: (S,S)-WHELK-O1(150X4.6)mm 5µm_0.2% ammonia in methanol_25_3.lcd, flowrate: 3.0000 mL/min; co-Solvent: 25.0 %; Make up Pump Flow: 0.5000 mL/min; Oven-A Temperature : 40°C; Oven A Column Position: 4; BPR Pressure: 100.0 bar; BPR Temperature : 50 C.

Example 325: (R)-6-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine



325A: (*R*)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrazole:

In a 40 mL vial, (*R*)-4-(3-bromo-2-fluorophenyl)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazole (0.3 g, 0.726 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.369 g, 1.45 mmol), [1,1`bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (0.059 g, 0.073 mmol) and potassium acetate (0.214 g, 2.178 mmol) were placed. The vial was flushed with nitrogen. Then, 1,4-dioxane (7 mL) was added and the reaction mixture was purged with nitrogen and heated at 100 °C for 1 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was filtered through celite and the celite pad was washed with ethyl acetate. The filtrate was concentrated to give crude material(0.398 g), which was used for next step without further purification. MS ESI m/z 461.3 $(M+H)^+$.

325: (R)-6-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 40 mL vial, (*R*)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1H-pyrazole (0.398 g, 0.866 mmol), 6-bromo-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.2 g, 0.866 mmol), [1,1`bis(diphenyl-phosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (0.07 g, 0.087 mmol) and potassium phosphate (0.551 g, 2.6 mmol) were placed. The vial was flushed with nitrogen. Then, 1,4-dioxane/water (4:1) (6 mL) was added and the reaction mixture was purged with nitrogen and heated at 80 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The crude residue was purified by the preparative HPLC and the required fraction was lyophilized to yield (*R*)-6-(3-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-8-fluoro-

[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.045 g, 0.092 mmol, 10.59% yield) as an off white solid.

Preparative HPLC method:

Diluent : Water:THF:ACN(20:50:30); Column : X-Select Prep C18 (250 x19)mm, 5 micron; Temperature: Ambient; Mobile phase A: 5Mm ammonium formate in water; Mobile phase B: ACN; Flow: 15mL/min; Time/Grad: 0/40, 12/80, 15/80.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.74 (s, 1H), 8.43 (d, J = 2.00 Hz, 1H), 8.15 (s, 1H), 7.84-7.80 (m, 1H), 7.79-7.68 (m, 3H), 7.52-7.47 (m, 1H), 7.34 (t, J = 7.60 Hz, 1H), 7.30-7.25 (m, 2H), 6.28-6.25 (m, 3H), 1.65 (t, J = 19.20 Hz, 3H).

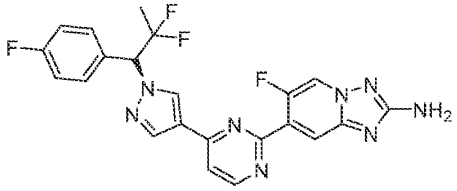
MS ESI m/z 485.1 $(M+H)^+$.

LC-MS method: Column: Kinetex XB- C18 (75x3mm) 2.6 µm; Mobile phase A :0.1% TFA in H_2O; Mobile phase B: 0.1% TFA in ACN; Flow Rate: 1.0ml/min.

Chiral purity: 100% ee; RT value: 2.357 min.

SFC Method: Column/dimensions: Cellulose-SC (250X4.6)mm 5µ_ACN_IPA(50_50)_40_67.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 40.0 %; Make up Pump Flow: 0.5000 mL/min; Oven-B Temperature: 40°C;Oven-B Column Position:1; BPR Pressure: 100.0 bar; BPR Temperature : 50°C.

Example 326: (R)-7-(4-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-4-yl)-pyrimidin-2-yl)-6-fluoro-[1,2,4]-triazolo[1,5-a]-pyridin-2-amine



326A: (*R*)-2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidine

In a 40 mL vial, (*R*)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.5 g, 4.10 mmol), 2,4-dichloropyrimidine (0.915 g, 6.14 mmol), [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (0.335 g, 0.41 mmol) and potassium phosphate (2.61 g, 12.29 mmol) were placed. The vial was flushed with nitrogen. Then, 1,4-dioxane/H_2O (4:1) (15 mL) was added and the reaction mixture was purged with nitrogen and heated at 80 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched

with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated to yield crude material, which was purified by silica gel column chromatography using 0-30% of EtOAc/petrol ether to afford (*R*)-2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidine (1.2 g, 3.22 mmol, 79 % yield) as a colourless liquid. MS ESI m/z 353.2 $(M+H)^+$.

326B: (2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid:

In a 20 mL vial, 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-7-iodo-[1,2,4]triazolo[1,5-a]-pyridine (0.3 g, 0.842 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.428 g, 1.65 mmol), [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (0.069 g, 0.084 mmol) and potassium acetate (0.248 g, 2.53 mmol) were placed. The vial was flushed with nitrogen. Then, 1,4-dioxane (10 mL) was added and the reaction mixture was purged with nitrogen and heated at 100 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was filtered through celite and the celite pad was washed with ethyl acetate. The filtrate was concentrated to give crude product (0.231 g), which was used for next step without purification. MS ESI m/z 275.2 $(M+H)^+$.

326C: (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, (*R*)-2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidine (0.296 g, 0.839 mmol), (2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid (0.230 g, 0.839 mmol), [1,1'bis-(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (0.068 g, 0.084 mmol) and potassium phosphate (0.534 g, 2.52 mmol) were placed The vial was flushed with nitrogen. Then, 1,4-dioxane/H_2O (4:1) (10 mL) was added to the vial and the reaction mixture was purged with nitrogen and heated at 80 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated to yield crude product, which was purified by silica gel column chromatography using 0-100% of EtOAc/petrol ether to afford (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-

yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridine (0.23 g, 0.404 mmol, 48.1 % yield) as a brown colored semisolid. MS ESI m/z 547.4 $(M+H)^+$.

326: (R)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to a well stirred solution of (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridine (0.23 g, 0.421 mmol) in THF (6 mL) and water (1.5 mL) was added TFA (1.621 mL, 21.04 mmol) and the mixture was allowed to stirr at 70 °C for 16 h. Upon completion of the reaction, the solvents were evaporated, excess TFA was quenched with 20 mL of saturated $NaHCO_3$ solution and compound was extracted with ethyl acetate (30 mL X 2). The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated from the filtrate. The crude residue was purified by the reverse phase preparative HPLC and the required fraction was lyophilized to yield (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.041 g, 0.086 mmol, 20.38 % yield) as a white solid.

Reverse phase preparative HPLC method:

Diluent: THF:Water:ACN(50:20:30); Column: Redisep 80g C18, 20-40 micron; Mobile phase A: 5mM Ammonium formate in water; Mobile phase B: Acetonitrile; Instrument 1D: Teledyne Isco-Combi flash; Compound elution (%): 55%Acetonitrile/ 5mM Ammonium formate in water; Flow Rate: 40ml/min.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.03 (dd, J = 0.40, 6.00 Hz, 1H), 8.90 (d, J = 5.20 Hz, 1H), 8.82 (s, 1H), 8.41 (s, 1H), 8.01 (d, J = 7.20 Hz, 1H), 7.84 (d, J = 5.20 Hz, 1H), 7.76 (dd, J = 5.60, 8.80 Hz, 2H), 7.26-7.30 (m, 2H), 6.33 (t, J = 13.20 Hz, 1H), 6.21 (s, 2H), 1.66 (t, J = 19.20 Hz, 3H).

MS ESI m/z 469.0 $(M+H)^+$.

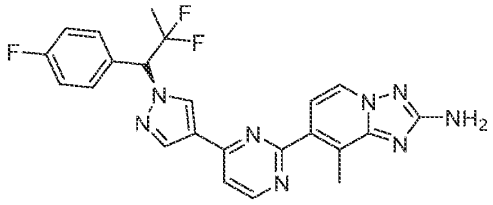
LC-MS method: Column: Kinetex XB - C18 (75 x 3.0)mm, 2.6µm; Mobile Phase A:5mm Ammonium formate pH 3.3:ACN (98:02); Mobile Phase B: ACN: Buffer (98:02); Flow Rate: 1.0 ml/min.

Chiral purity: 100% ee; RT value: 4.597 min.

SFC Method: Column/dimensions: B746755_Cellulose-SC (250X4.6)mm 5µ_Methanol_40_12.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 40.0 %; Make up Pump Flow: 0.5000

mL/min; Oven-A Temperature: 40°C; Oven A Column Position: 1; BPR Pressure: 100.0 bar; BPR Temperature: 50°C.

Example 327: (R)-7-(4-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-4-yl)-pyrimidin-2-yl)-8-methyl-[1,2,4]-triazolo[1,5-a]-pyridin-2-amine



327A: (2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid:

In a 20 mL vial, 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]-pyridine (0.3 g, 0.983 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.499 g, 1.96 mmol), [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (0.080 g, 0.098 mmol) and potassium acetate (0.289 g, 2.95 mmol) were placed. The vial was flushed with nitrogen. Then, 1,4-dioxane (10 mL) was added to the vial and the mixture was purged with nitrogen and heated at 100 °C for 1 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was filtered through celite and the celite pad was washed with ethyl acetate. The filtrate was concentrated to give crude product (0.346 g), which was used for next step without further purification. MS ESI m/z 353.2 $(M+H)^+$.

327B: (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, (*R*)-2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidine (0.346 g, 0.982 mmol), (2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid (0.346 g, 0.982 mmol), [1,1'bis(diphenyl-phosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (0.08 g, 0.098 mmol) and potassium phosphate (0.626 g, 2.95 mmol) were placed. The vial was flushed with nitrogen. Then, 1,4-dioxane/H_2O (4:1) (10 mL) was added and the reaction mixture was purged with nitrogen and heated at 80 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated to yield crude product, which was purified by

silica gel column chromatography using 0-100% of EtOAc/petrol ether to afford (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.29 g, 0.481 mmol, 49% yield) as a light brown liquid. MS ESI m/z 543.0 $(M+H)^+$.

327: (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to a well stirred solution of (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (290 mg, 0.534 mmol)in THF (6 mL) and water (1.5 mL) was added TFA (2.059 mL, 26.7 mmol) and the mixture was allowed to stirred at 70 °C for 16 h. Upon completion of the reaction, solvent was evaporated, excess TFA was quenched with 20 mL of saturated $NaHCO_3$ solution and compound was extracted with ethyl acetate (30 mL X 2). The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated from the filtrate. The crude material was purified by the reverse phase preparative HPLC and the required fraction was lyophilized to yield (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]-pyridin-2-amine (40 mg, 0.084 mmol, 15.79 % yield) as an off white solid.

Reverse phase preparative HPLC method:

Diluent: THF:Water:ACN(50:20:30); Column: Redisep 80g C18, 20-40 micron; Mobile phase A: 5mM Ammonium formate in water; Mobile phase B: Acetonitrile; Instrument 1D: Teledyne Isco-Combi flash; Compound elution (%): 45%Acetonitrile/5mM Ammonium formate in water; Flow Rate: 40ml/min.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.90 (d, J = 5.20 Hz, 1H), 8.80 (s, 1H), 8.48 (dd, J = 0.80, 7.00 Hz, 1H), 8.41 (s, 1H), 7.74-7.81 (m, 3H), 7.44 (d, J = 6.80 Hz, 1H), 7.26-7.31 (m, 2H), 6.33 (t, J = 13.20 Hz, 1H), 6.07 (s, 2H), 2.73 (d, J = Hz, 3H), 1.66 (t, J = 18.80 Hz, 3H)..

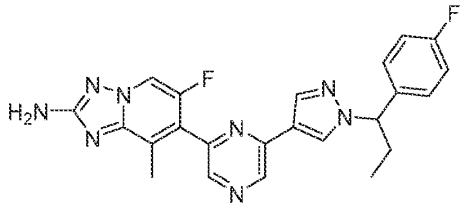
MS ESI m/z 465.0 $(M+H)^+$.

Chiral purity: 100% ee; RT value: 5.361 min.

SFC Method: Column/dimensions: Chiralpak IF (250X4.6)mm 5µ_5 mM NH_4OAc in ACN_MeOH(1_1)_40_10.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 40.0 %; Make up

Pump Flow: 0.5000 mL/min; Oven-A Temperature: 40°C; Oven A Column Position: 2; BPR Pressure: 100.0 bar; BPR Temperature: 50°C.

Example 328: 6-fluoro-7-(6-(1-(1-(4-fluorophenyl)-propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methyl-[1,2,4]-triazolo[1,5-a]-pyridin-2-amine



328A: 4-bromo-2-chloro-5-fluoro-3-methylpyridine:

In a 250 mL RBF, to a stirred solution of 2-chloro-5-fluoro-3-methylpyridine (10 g, 68.7 mmol) in THF (100 mL), was added lithium diisopropylamide (37.8 mL, 76 mmol) at -78 °C under nitrogen atmosphere. Reaction mixture was stirred for 1.5 h at -78 °C. After 1.5 h, solution of 1,2-dibromotetrafluoroethane (9.01 mL, 76 mmol) in THF (20 mL) was added to a stirring solution of 2-chloro-5-fluoro-3-methylpyridine and lithium diisopropylamide in THF slowly at -78 °C. The mixture was stirred for at -78 °C 1.5 h. Upon completion of the reaction, the mixture was quenched with saturated solution of NH_4Cl and compound was extracted by using ethyl acetate. The organic layer was dried over sodium sulphate and evaporated to yield crude product, which was purified by silica gel column chromatography using 0-5% of EtOAc/petrol ether to afforded 4-bromo-2-chloro-5-fluoro-3-methylpyridine (7.7 g, 27.0 mmol, 39.3% yield) as a colourless liquid. MS ESI m/z 226.0 $(M+H)^+$.

328B: *N*-(4-bromo-5-fluoro-3-methylpyridin-2-yl)-1,1-diphenylmethanimine:

In a 150 mL sealed tube, 4-bromo-2-chloro-5-fluoro-3-methylpyridine (5.0 g, 22.28 mmol), benzophenone imine (3.74 mL, 22.28 mmol), sodium tert-butoxide (4.28 g, 44.6 mmol), BINAP (2.081 g, 3.34 mmol) and tris(dibenzylideneacetone)dipalladium ($Pd_2(dba)_3$) (1.020 g, 1.114 mmol) were placed. The vial was flushed with nitrogen. Then, toluene (10 mL) was added and the mixture was purged with nitrogen and heated at 80 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was filtered through celite and the celite pad was washed with ethyl acetate. The filtrate was concentrated to give crude product (5 g), which was used for the next step without purification. MS ESI m/z 371.0 $(M+H)^+$.

328C: 4-bromo-5-fluoro-3-methylpyridin-2-amine:

In a 250 mL RBF, to a stirred solution of *N*-(4-bromo-5-fluoro-3-methylpyridin-2-yl)-1,1-diphenylmethanimine (5 g, 13.54 mmol) in THF (50 mL), was added HCl (13.54 mL, 20.31 mmol) (1.5 N) at room temperature and the mixture was stirred for 2 h. Upon completion of the reaction, the mixture was quenched with saturated solution of $NaHCO_3$ and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated to yield crude product, which was purified by silica gel column chromatography using 0-30% of EtOAc/petrol ether to afford 4-bromo-5-fluoro-3-methylpyridin-2-amine (1.9 g, 7.32 mmol, 54.1% yield) as a yellow solid. MS ESI m/z 207.0 $(M+H)^+$.

328D: *O*-ethyl N-((4-bromo-5-fluoro-3-methylpyridin-2-yl)carbamothioyl)carbamate

In a 250 mL RBF, to a stirred solution of 4-bromo-5-fluoro-3-methylpyridin-2-amine (1.9 g, 9.27 mmol) in 1,4-dioxane (20 mL) was added O-ethyl carbonisothiocyanatidate (1.642 mL, 13.90 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 h. Upon completion of the reaction, the mixture was filtered through celite and the celite pad was washed with 1,4-dioxane. The filtrate was concentrated to give 1.9 g of **47e** as crude oil, which was used for for next step without further purification.
MS ESI m/z 338.0 $(M+H)^+$.

328E: 7-bromo-6-fluoro-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 250 mL RBF, to a stirred solution of **318D** (1.9 g, 5.65 mmol) in ethanol (20 mL) was added DIPEA (3.95 mL, 22.61 mmol) and hydroxylamine hydrochloride (1.964 g, 28.3 mmol). The reaction mixture was heated at 60 °C for 2 h. Upon completion of reaction, ethanol was removed under vacuum to give a brown residue. Theresidue was dissolved in a minimum amount of DMSO and purified by reverse phase flash chromatography to obtain 7-bromo-6-fluoro-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (1.0 g, 3.26 mmol, 57.8 % yield) as a pale yellow solid. MS ESI m/z 247.0 $(M+H)^+$.

328F: 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-8-methyl-[1,2,4]triazolo[1,5-a]-pyridine:

In a 30 mL microwave vial, to the stirred solution of 7-bromo-6-fluoro-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (1.0 g, 4.08 mmol) in toluene (10 mL) were added hexane-2,5-dione (3.11 mL, 24.48 mmol) and acetic acid (1.168 mL, 20.40 mmol). The reaction mixture was heated at 120 °C, under microwave irradiation for 8 h. Upon completion of reaction, toluene was removed under reduced pressure to yield a brown

residue, which was purified by silica gel column chromatography using 0-10% of EtOAc/petrol ether to afforded 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.9 g, 2.73 mmol, 66.9 % yield) as an off white solid. MS ESI m/z 325.0 $(M+H)^+$.

328G: 2-chloro-6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazine:

In a 40 mL vial, 2-bromo-6-chloropyrazine (0.469 g, 2.423 mmol), 1-(1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.8 g, 2.423 mmol), [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.198 g, 0.242 mmol) and potassium phosphate (1.54 g, 7.27 mmol) were placed. The vial was flushed with nitrogen. Then, 1,4-dioxane/water (4:1) (5 mL) was added to the vial and reaction mixture was purged with nitrogen and heated at 80 °C for 12 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated under reduced pressure to yield crude material, which was purified using silica gel column chromatography using 0-100% of EtOAc/petrol ether to afford 2-chloro-6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazine (0.6 g, 1.824 mmol, 75% yield) as a light brown liquid. MS ESI m/z 317.2 $(M+H)^+$.

328H: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-8-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-8-methyl-[1,2,4]-triazolo[1,5-a]pyridine (0.2 g, 0.619 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.314 g, 1.23 mmol), [1,1'bis(diphenylphosphino)ferrocene]-dichloropalladium (II), complex with DCM (0.050 g, 0.062 mmol) and potassium acetate (0.182 g, 1.85 mmol) were placed. The vial was flushed with nitrogen. Then, 1,4-dioxane (5 mL) was added and the mixture was purged with nitrogen and heated at 100 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was filtered through celite and the celite pad was washed with ethyl acetate. The filtrate was concentrated to give crude material (0.229 g), which was used for next step without further purification. MS ESI m/z 371.2 $(M+H)^+$.

328I: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-7-(6-(1-(1-(4-fluorophenyl)-propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, 2-chloro-6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazine (0.196 g, 0.619 mmol), 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-8-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.229 g, 0.619 mmol), [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.05 g, 0.062 mmol) and potassium phosphate (0.394 g, 1.85 mmol) were placed. The vial was flushed with nitrogen. Then, 1,4-dioxane/H_2O (4:1) (6 mL) was added and the mixture was purged with nitrogen and heated at 80 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified by silica gel column chromatography using 0-100% of EtOAc/petrol ether to afford 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-7-(6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.3 g, 0.452 mmol, 73% yield) as a colourless liquid. MS ESI m/z 525.2 $(M+H)^+$.

328: 6-fluoro-7-(6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine :

In a 20 mL vial, to a well stirred solution of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-7-(6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (300 mg, 0.572 mmol) in THF (5 mL) and water (1.25 mL) was added TFA (2.203 mL, 28.6 mmol) and the mixture was allowed to stirr at 70 °C for 16 h. Upon completion of the reaction, solvent was evaporated, excess TFA was quenched with 20 mL of saturated $NaHCO_3$ solution and compound was extracted with ethyl acetate (30 mL X 2). The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The crude residue was purified by preparative HPLC and the required fraction was lyophilized to yield 6-fluoro-7-(6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.018 g, 0.039 mmol, 6.89 % yield) as a white solid.

Preparative HPLC method:

Diluent: THF:water:ACN(40:20:40); Column: Sunfire C18 (250 x19)mm, 5micron; Temperature: Ambient; Mobile phase A: 5mM Ammonium Formate in water; Mobile phase B: ACN; Flow: 15mL/min; Time/Grad: 0/40,10/80.

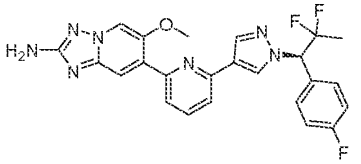
^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.07 (s, 1H), 8.92 (dd, J = 0.40, 4.80 Hz, 1H), 8.67 (d, J = 0.40 Hz, 1H), 8.59 (d, J = 1.60 Hz, 1H), 8.22 (s, 1H), 7.44-7.48 (m, 2H), 7.19-7.17 (m, 2H), 6.15 (s, 2H), 5.43 (dd, J = 6.40, 9.20 Hz, 1H), 2.34 (d, J = 0.40 Hz, 4H), 2.12-2.19 (m, 1H), 2.07 (s, 1H), 0.83 (t, J = 7.20 Hz, 3H).

MS ESI m/z 447.2 $(M+H)^+$.

Chiral purity: 100% ee; RT value: 3.317 min.

SFC Method: Column/dimensions: Cellulose-1(250mmX4.6X5u)_0.1% NH_4OH in methanol_40_10.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 40.0 %; Make up Pump Flow: 0.5000 mL/min; Oven-B Temperature: 40°C; Oven-B Column Position: 1; BPR Pressure: 100.0 bar; BPR Temperature : 50°C.

Example 329: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-6-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine



329A: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-methoxy-[1,2,4]triazolo[1,5-a]pyridine (0.4 g, 1.245 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.633 g, 2.49 mmol), [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.102 g, 0.125 mmol) and potassium acetate (0.367 g, 3.74 mmol)were placed. The vial was flushed with nitrogen. Then, 1,4-dioxane (7 mL) was added and the reaction mixture was purged with nitrogen and heated at 100 °C for 1 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was filtered through celite and the celite pad was washed with ethyl acetate. The filtrate was concentrated to give crudematerial, which was purified by reverse phase HPLC to obtain (2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-methoxy-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid (0.1 g, 0.329 mmol, 26.4% yield). MS ESI m/z 287.2 $(M+H)^+$.

329B: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-pyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-methoxy-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, (2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-methoxy-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid (0.1 g, 0.350 mmol), (R)-2-bromo-6-(1-(2,2-difluoro-1-(4-fluorophenyl)-propyl)-1H-pyrazol-4-yl)pyridine (0.138 g, 0.350 mmol) [1,1'bis(diphenylphosphino)-ferrocene]dichloropalladium (II), complex with DCM (0.028 g, 0.035 mmol) and potassium phosphate (0.223 g, 1.049 mmol) were placed. The vial was flushed with nitrogen. Then, 1,4-dioxane/H_2O (4:1) (6 mL) was added and the mixture was purged with nitrogen and heated at 80 °C for 12 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified by silica gel column chromatography using 0-100% of EtOAc/petrol ether to afford (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-methoxy-[1,2,4]triazolo[1,5-a]pyridine (0.12 g, 0.172 mmol, 49.1% yield) as a light brown liquid. MS ESI m/z 558.2 $(M+H)^+$.

329: (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-6-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to a well stirred solution of (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-methoxy-[1,2,4]triazolo[1,5-a]pyridine (100 mg, 0.179 mmol) in THF (5 mL) and water (1.25 mL) was added TFA (0.691 mL, 8.97 mmol) and the mixture was allowed to stirred at 70 °C for 16 h. Upon completion of the reaction, solvent was evaporated, excess TFA was quenched with 20 mL of saturated $NaHCO_3$ solution and compound was extracted with DCM (30 mL X 2). The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The crude residue was purified by the preparative HPLC and the required fraction was lyophilized to yield (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-6-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.006 g, 0.012 mmol, 6.70% yield) as a white solid.

Preparative HPLC method:

Diluent : THF:water:ACN(40:20:40); Column: X Select CSH C18 (250 x19)mm, 5micron Temperature: Ambient; Mobile phase A: 5mM Ammonium gormate in water; Mobile phase B: ACN; Flow: 15mL/min; Time/Grad : 0/40 ,7/80, 10/80.

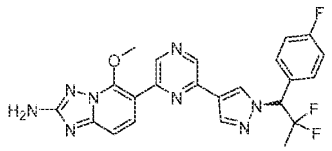
^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 8.61 (s, 1H), 8.48 (s, 1H), 8.26 (s, 1H), 7.87 (t, J = 8.00 Hz, 1H), 7.75-7.73 (m, 5H), 7.28 (t, J = 8.80 Hz, 2H), 6.27 (t, J = 13.60 Hz, 1H), 5.93 (s, 2H), 3.88 (s, 3H), 1.66 (t, J = 19.20 Hz, 3H).

MS ESI m/z 480.2 $(M+H)^+$.

Chiral purity: 98.05% ee; RT value: 4.683 min.

SFC Method: Column/dimensions: Chiralcel OZ-H(250mmX4.6X5u)_0.1% NH_4OH in methanol_40_6.lcd; Run Time: 10.00; Flowrate: 3.0000 mL/min; Co-Solvent: 40.0 %; Make up Pump Flow: 0.5000 mL/min; Oven-A Temperature: 40°C; Column Number: 6; Oven-B Temperature: 40°C; Column Number: 1; BPR Pressure: 100.0 bar; BPR Temperature: 50°C.

Example 330: (R)-6-(6-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine



330A: (*R*)-2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-6-(trimethylstannyl)pyrazine:

In a hot air dried 20 mL microwave reaction vial, to a stirred solution of (*R*)-2-chloro-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazine (0.3 g, 0.850 mmol) in 1,4-dioxane (6 mL) hexamethylditin (0.882 mL, 4.25 mmol) was added. The reaction mixture was purged with nitrogen gas for 2 min. Then, tetrakis(triphenylphosphine)palladium(0) (0.098 g, 0.085 mmol) was added and the reaction mixture was stirred at 100 °C for 1 h under microwave irradiation. Upon completion of reaction, the mixture was diluted with ethyl acetate and filtered through celite. The filtrate was concentrated and purified by silica gel column chromatography using 0-100% of EtOAc/petrol ether to afford (*R*)-2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-6-(trimethylstannyl)pyrazine (0.27 g, 0.528 mmol, 62.0 % yield) as a colorless liquid. MS ESI m/z 483.0 $(M+H)^+$.

330: (R)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 20 mL reaction vial, to a stirred solution of 6-bromo-5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.076 g, 0.312 mmol) in 1,4-dioxane (4 mL) was added (*R*)-2-(1-(2,2-

difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-6-(trimethylstannyl)pyrazine (0.15 g, 0.312 mmol). The reaction mixture was purged with nitrogen gas for 2 min and [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.012 g, 0.016 mmol) was added and heated at 80 °C for 12 h. Upon completion of reaction, the mixture was diluted with ethyl acetate and filtered through celite. The filtrate was concentrated and the residue was purified by the preparative HPLC to yield (*R*)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-5-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine (19 mg, 0.039 mmol, 12.56 % yield) as a light brown solid.

Preparative HPLC method:

Diluent: Water:THF:ACN(30:30:40); Column: Kinetex Biphenyl(250 x 21.2)mm, 5micron; Temperature: Ambient; Mobile phase A: 5mM Ammonium formate; Mobile phase B: ACN; Flow: 15mL/min; Time/Grad: 0/40, 15/70.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.98 (s, 1H), 8.92 (s, 1H), 8.74 (s, 1H), 8.37 (s, 1H), 8.09 (d, J = 9.20 Hz, 1H), 7.77 (dd, J = 5.60, 8.80 Hz, 2H), 7.31-7.28 (m, 3H), 6.31 (t, J = 14.40 Hz, 3H), 4.24 (s, 3H), 1.67 (t, J = 18.80 Hz, 3H).

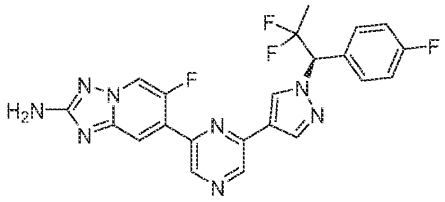
MS ESI m/z 481.2 $(M+H)^+$.

Chiral purity: 99.53% ee; RT value: 3.541 min.

SFC Method: Column/dimensions: Chiralpak IJ(250mmX4.6X5u)_0.1% NH_4OH in methanol_40_6.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 40.0 %; Oven-B Temperature: 40°C; Oven B Column Position:1

BPR Pressure : 100.0 bar; BPR Temperature : 50°C.

Example 331: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine



331A: (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.149 g, 0.544 mmol), (*R*)-2-(1-(2,2-

difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-6-(trimethylstannyl)pyrazine (0.16 g, 0.45 mmol), [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.037 g, 0.045 mmol) and potassium phosphate (0.289 g, 1.361 mmol) were placed. The vial was flushed with nitrogen. Then, 1,4-dioxane/H_2O (4:1) (6 mL) was added and the mixture was purged with nitrogen and heated at 80 °C for 4 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvent evaporated. The residue was purified by silica gel column chromatography using 0-50% of EtOAc/petrol ether to afford (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridine (0.15 g, 0.222 mmol, 49% yield) as a light brown liquid. MS ESI m/z 547.0 $(M+H)^+$.

331: (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-pyrazin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to a well stirred solution of (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridine (150 mg, 0.274 mmol) in THF (5 mL) and water (1.25 mL) was added TFA (1.057 mL, 13.72 mmol). The mixture was allowed to stirred at 70 °C for 16 h. Upon completion of the reaction, the solvent was evaporated, excess TFA was quenched with 20 mL of saturated $NaHCO_3$ solution and compound was extracted with DCM (30 mL X 2). The organic layer was dried over anhydrous sodium sulphate, filtered and solvent evaporated. The crude residue was purified by the preparative HPLC to yield (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-6-fluoro-[1,2,4]triazolo-[1,5-a]pyridin-2-amine (0.03 g, 0.064 mmol, 23.27% yield) as an off white solid.

Preparative HPLC method:

Diluent: THF:water:ACN(40:10:40); Column: X-Select-C18l (250 x19)mm, 5micron; Temperature: Ambient; Mobile phase A: 5mM Ammonium Formate in water; Mobile phase B: Acetonitrile; Flow: 15mL/min; Time/Grad: 0/40,10/80.

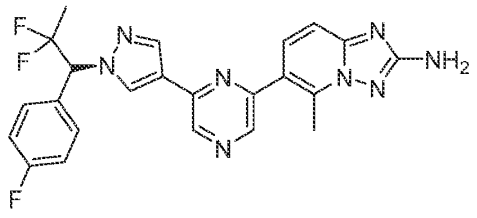
^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.11 (s, 1H), 9.10 (s, 1H), 8.88 (d, J = 2.40 Hz, 1H), 8.80 (s, 1H), 8.41 (s, 1H), 8.00 (d, J = 7.20 Hz, 1H), 7.77 (dd, J = 5.20, 8.60 Hz, 2H), 7.26-7.30 (m, 2H), 6.30 (t, J = 13.20 Hz, 1H), 6.22 (s, 2H), 1.67 (t, J = 19.20 Hz, 3H).

MS ESI m/z 469.0 $(M+H)^+$.

Chiral purity: 99.69% ee; RT value: 5.168 min.

SFC Method: Column/dimensions: Chiralpak-IC(250X4.6)mm 5µ_0.2% NH_3 in ACN MeOH(50_50)_35_5.lcd; Run Time: 10.00; Flowrate: 3.0000 mL/min; Co-Solvent:35.0 %; Make up Pump Flow: 0.5000 mL/min; Oven-A Temperature: 40°C; Column Number: 1; Oven-B Temperature: 40°C; Column Number: 6; BPR Pressure: 100.0 bar; BPR Temperature : 50°C.

Example 332: (R)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-5-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine



332A: 6-bromo-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-methyl-[1,2,4]triazolo[1,5-a]pyridine: In a 30 mL microwave vial, to a stirred solution of 6-bromo-5-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (1 g, 4.40 mmol) in toluene (10 mL) was added hexane-2,5-dione (5.03 g, 44.0 mmol) and acetic acid (0.252 mL, 4.40 mmol). The reaction mixture was heated at 140 °C in a microwave for 6 h. Upon completion of the reaction, toluene was removed under vacuum to yield a brown residue, which was purified by silica gel column chromatography using 0-10% of EtOAc/petrol ether to afford 6-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.6 g, 1.966 mmol, 44.6% yield) as an off white solid. MS ESI m/z 305.02 $(M+H)^+$.

332B: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine:

To a stirred solution of 6-bromo-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.2 g, 0.655 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.333 g, 1.311 mmol) in 1,4-dioxane (5 mL) was added potassium acetate (0.193 g, 1.966 mmol). The reaction mixture was purged with nitrogen gas for 10 minutes. Then [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with DCM (0.053 g, 0.066 mmol) was added. The reaction mixture was purged with nitrogen gas for 2 min and allowed to stir at 100 °C for 2 h. Upon completion of the reaction,

the mixture was filtered through celite and the celite pad was washed with ethyl acetate. The filtrate was concentrated to give crude product, which was directly used for the next step without further purification. MS ESI m/z 353.2 $(M+H)^+$.

332C: 6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-methyl-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, to a solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.231 g, 0.656 mmol) and 2-chloro-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazine (0.2 g, 0.567 mmol) in 1,4-dioxane (6 mL) and water (1.5 mL) was added tripotassium phosphate (0.361 g, 1.701 mmol). The reaction mixture was degassed for 10 minutes and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with DCM (0.046 g, 0.057 mmol) was added. The mixture was heated to 80 °C and stirred for 2 h until complete consumption of starting material as monitored by UPLC. Aqueous layer was separated, and organic fraction was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography using 0-30% EA/petrol ether to yield 6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.15 g, 0.212 mmol, 37.4% yield) as brown liquid.

MS ESI m/z 543.21 $(M+H)^+$.

332: (R)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-pyrazin-2-yl)-5-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine :

In a 20 mL vial, to the solution of 6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.15 g, 0.276 mmol) in THF (6 mL) and water (1.5 mL) was added TFA (1.065 mL, 13.82 mmol) slowly at room temperature. The reaction mixture was heated to 70 °C and stirred for 16 h until all the starting materials get consumed as monitored by UPLC. After completion of the reaction, TFA was removed under vacuum and the residue was neutralized with saturated solution of sodium bicarbonate (5 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over sodium sulphate and concentrated under vacuum. This residue was purified by reverse phase column chromatography and chiral SFC to afford (*R*)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-

yl)pyrazin-2-yl)-5-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.024 g, 0.050 mmol, 18.09 % yield) as off-white solid.

RP Flash purification method:

Diluent: Water:THF:ACN(50:20:30); Column: Redisep 80gm C18, 20-40 micron; Temperature: Ambient; Mobile phase A: 5mM Ammonium Formate; Mobile phase B: Acetonitrile; Flow: 30mL/min;.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.03 (s, 1H), 8.71 (s, 2H), 8.35 (s, 1H), 7.72-7.77 (m, 2H), 7.69 (s, 1H), 7.38 (d, J = 8.80 Hz, 1H), 7.27 (dd, J = 2.00, 12.60 Hz, 2H), 6.29 (t, J = 13.20 Hz, 1H), 6.17 (s, 2H), 2.76 (s, 3H), 1.66 (t, J = 19.20 Hz, 3H).

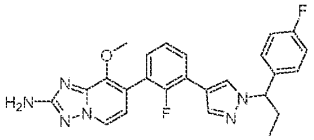
MS ESI m/z 465.1 $(M+H)^+$

Chiral purity: 100% ee; RT:2.115 min.

SFC Method:

Chiralpak IH(250X4.6)mm 5µ_Methanol_50_6.lcd; Flowrate: 3.0000 mL/min; Co-Solvent : 50.0 %; Make up Pump Flow: 0.5000 mL/min; Oven-A Temperature: 40°C; Oven-A Column Position:1; BPR Pressure: 100.0 bar; BPR Temperature: 50°C.

Example 333: (R)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-5-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine



333A: 4-(3-bromo-2-fluorophenyl)-1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazole:

In a 40 mL vial, to a solution of (3-bromo-2-fluorophenyl)boronic acid (0.994 g, 4.54 mmol) and 1-(1-(4-fluorophenyl)propyl)-4-iodo-1*H*-pyrazole (1.5 g, 4.54 mmol) in dioxane (15 mL) and water (1.8 mL) was added tripotassium phosphate (2.89 g, 13.63 mmol). The reaction mixture was degassed for 10 minutes and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with DCM (0.371 g, 0.454 mmol) was added. The mixture was heated to 80 °C and stirred for 2 hours until complete consumption of starting material as monitored by UPLC. The aqueous layer was separated, and the organic fraction was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography using 0-30% EA/petrol ether to yield 4-(3-bromo-

2-fluorophenyl)-1-(1-(4-fluorophenyl)propyl)-1H-pyrazole (0.5 g, 1.282 mmol, 28.2% yield) as colourless liquid. MS ESI m/z 377.05 $(M+H)^+$.

333B: 4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazole:

In a 350 mL sealed tube, to a stirred solution of 4-(3-bromo-2-fluorophenyl)-1-(1-(4-fluorophenyl)propyl)-1H-pyrazole (0.5 g, 1.325 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.673 g, 2.65 mmol) in 1,4-dioxane (7 mL) was added potassium acetate (0.39 g, 3.98 mmol). The reaction mixture was purged with nitrogen gas for 10 minutes. Then 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) DCM complex (0.097 mg, 0.133 mmol) was added. The mixture was purged with nitrogen gas for 2 min and allowed to stir at 80 °C for 6 h. Upon completion of the reaction, the mixture was filtered through celite and the celite pad was washed with ethyl acetate. The filtrate was concentrated and the crude material was then purified by flash column chromtography on silica gel eluting with 0-30% ethyl acetate in petroleum ether to afford 4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-(1-(4-fluorophenyl)propyl)-1H-pyrazole (0.37 g, 0.784 mmol, 59.1% yield) as colourless liquid. MS ESI m/z 425.2 $(M+H)^+$.

333: 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)phenyl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to a solution of 4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-(1-(4-fluorophenyl)propyl)-1H-pyrazole (0.15 g, 0.354 mmol) and 7-bromo-8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.086 g, 0.354 mmol) in 1,4-dioxane (6 mL) and water (1.5 mL) was added tripotassium phosphate (0.225 g, 1.061 mmol). The reaction mixture was degassed for 10 minutes and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) DCM complex (0.029 g, 0.035 mmol) was added. The mixture was heated to 80 °C and stirred for 2 h until complete consumption of starting material as monitored by UPLC. The aqueous layer was separated, and the organic fraction was dried over $MgSO_4$ and concentrated. The residue was purified using preparative HPLC to afford 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)phenyl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.021 g, 0.044 mmol, 12.35% yield) as off-white solid.

Preparative HPLC method:

Diluent: Water:THF:ACN(30:30:40); Column: Kinetix biphenyl (250 x19)mm, 5micron; Temperature: Ambient; Mobile phase A: 5mM Ammonium Formate; Mobile phase B: Acetonitrile; Flow: 15mL/min; Time/Grad: 0/40, 12/80.

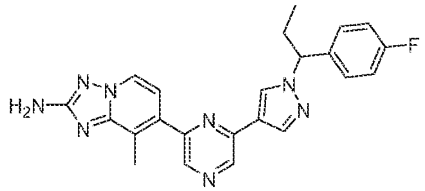
^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.36 (t, J = 3.20 Hz, 2H), 7.99 (s, 1H), 7.77 (d, J = 2.00 Hz, 1H), 7.44-7.47 (m, 2H), 7.24-7.29 (m, 2H), 7.17 (t, J = 8.80 Hz, 2H), 6.79 (d, J = 6.80 Hz, 1H), 6.10 (s, 2H), 5.41 (d, J = 2.80 Hz, 1H), 4.07 (s, 3H), 2.34-2.40 (m, 1H), 2.10-2.17 (m, 1H), 0.82 (t, J = 8.40 Hz, 3H), MS ESI m/z 461.1 $(M+H)^+$

Chiral purity: 100% ee; RT: 2.112 min.

SFC Method:

Chiralpak IH(250X4.6)mm 5µ_Methanol_50_5.lcd; Flowrate : 3.0000 mL/min; Co-Solvent : 50.0 %; Make up Pump Flow: 0.5000 mL/min; Oven-A Temperature: 40°C; Oven-A Column Position: 1; BPR Pressure: 100.0 bar; BPR Temperature: 50°C.

Example 334: 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)-propyl)-1H-pyrazol-4-yl)phenyl)-8-methyl-[1,2,4]-triazolo[1,5-a]-pyridin-2-amine



334A 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, to the solution of 2-chloro-6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazine (0.18 g, 0.568 mmol) and 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.2 g, 0.568 mmol) in 1,4-dioxane (4 mL) and water (1.000 mL) was added tripotassium phosphate (0.362 g, 1.703 mmol). The reaction mixture was degassed for 10 minutes and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with DCM (0.046 g, 0.057 mmol) was added. The mixture was heated to 80 °C and stirred for 3 h until complete consumption of starting material as monitored by UPLC. The aqueous layer was separated, and the organic fraction was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography, eluting in 0-60% EA/petrol ether to yield 2-(2,5-dimethyl-1H-

pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methyl-[1,2,4]-triazolo[1,5-a]pyridine (0.13 g, 0.222 mmol, 39% yield) as brown liquid.

MS ESI m/z 507.2 $(M+H)^+$.

334: 7-(6-(1-(1-(4-fluorophenyl) propyl)-1*H*-pyrazol-4-yl) pyrazin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to a solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.13 g, 0.257 mmol) in THF (6 mL) and water (1.5 mL) was added TFA (0.989 mL, 12.83 mmol) slowly at room temperature. The reaction mixture was heated to 70 °C and stirred for 16 h until all the starting material was consumed as monitored by UPLC. After completion of the reaction, TFA was removed under vacuum and the residue was neutralized with saturated solution of sodium bicarbonate (5 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over sodium sulphate and concentrated under vacuum. The residue was purified by prep HPLC to afford 7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.05 g, 0.115 mmol, 44.7% yield) as off-white solid.

Preparative HPLC method:

Diluent: THF:water:ACN(40:20:40); Column: Sunfire C18 (250 x19)mm, 5micron; Temperature: Ambient; Mobile phase A: 5mM Ammonium Formate; Mobile phase B: Acetonitrile; Flow: 15mL/min; Time/Grad: 0/50, 10/80.

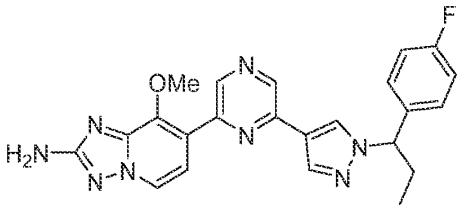
^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.01 (s, 1H), 8.67 (d, J = 1.20 Hz, 2H), 8.52 (dd, J = 0.40, 7.00 Hz, 1H), 8.23 (s, 1H), 7.45-7.48 (m, 2H), 7.19 (dd, J = 2.40, 5.60 Hz, 2H), 7.11 (t, J = 6.80 Hz, 1H), 6.10 (s, 2H), 5.44 (dd, J = 6.00, 9.40 Hz, 1H), 2.44-2.51 (m, 3H), 2.36-2.41 (m, 1H), 2.12-2.19 (m, 1H), 0.83 (t, J = 7.20 Hz, 3H). MS ESI m/z 429.2 $(M+H)^+$

Chiral purity: 97.1% ee; RT:6.223 min.

SFC Method:

Cellulose-1(250mmX4.6X5u) _Methanol_30_10.lcd; Flowrate: 3.0000 mL/min; Co-Solvent : 30.0 %; Make up Pump Flow: 0.5000 mL/min; Oven-B Temperature: 40°C; Oven-B Column Position: 1; BPR Pressure: 100.0 bar; BPR Temperature: 50°C.

Example 335: 7-(6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methoxy-[1,2,4]-triazolo[1,5-a]-pyridin-2-amine



335A: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, to a solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.344 g, 0.934 mmol) and 2-chloro-6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazine (0.207 g, 0.654 mmol) in 1,4-dioxane (12 mL) and water (3 mL), was added potassium phosphate (0.595 g, 2.80 mmol). The reaction mixture was degassed for 10 minutes and $PdCl_2(dppf)$-CH_2Cl_2 complex (0.076 g, 0.093 mmol) was added. The mixture was heated to 80 °C and stirred for 2 h until complete consumption of starting material as monitored by UPLC. After completion of the reaction water was added and the mixture was extracted with ethyl acetate (200 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by column chromatography, eluting in 0-30% EA/petrol ether to give 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (0.21 g, 0.342 mmol, 36.6% yield) as colourless liquid. MS ESI m/z 523.2 $(M+H)^+$.

335: 7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-8-methoxy-[1,2,4]-triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to a solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (210 mg, 0.402 mmol) in THF (6 mL) and water (2 mL) was added TFA (1.548 mL, 20.09 mmol) slowly at room temperature. The reaction mixture was heated to 70 °C and stirred for 16 hours until all the starting material was consumed as monitored by UPLC. After completion of the reaction, TFA was removed under vacuum and the residue was neutralized with saturated solution of sodium bicarbonate (5 mL) and extracted with ethyl acetate (30 mL). The organic layer was dried over sodium sulphate and concentrated under vacuum. The residue was purified by reverse phase column chromatography to afford 7-

(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine (25 mg, 0.055 mmol, 13.58 % yield) as off-white solid.

RP Flash purification method:

Diluent: Water:THF:ACN(50:20:30); Column: Redisep 80gm C18, 20-40 micron; Temperature: Ambient; Mobile phase A: 5mM Ammonium Formate; Mobile phase B: Acetonitrile; Flow: 30mL/min; Time/Grad: 0/20, 12/70.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.96 (d, J = 4.20 Hz, 2H), 8.69 (s, 1H), 8.42 (d, J = 7.20 Hz, 1H), 8.25 (s, 1H), 7.45-7.49 (m, 2H), 7.42 (d, J = 7.20 Hz, 1H), 7.16-7.21 (m, 2H), 6.17 (s, 2H), 5.45 (dd, J = 6.40, 9.20 Hz, 1H), 4.24 (s, 3H), 2.41-2.37 (m, 1H), 2.13-2.20 (m, 1H), 0.84 (t, J = 7.2, 3H).

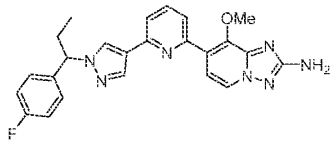
MS ESI m/z 445.1 $(M+H)^+$

Chiral purity: 100% ee; RT: 6.400 min.

SFC Method:

Chiralpak ASH(250mmX4.6X5u)_ACN IPA(50_50)_20_2.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 20.0 %; Make up Pump Flow: 0.5000 mL/min; Oven-B Temperature: 40°C; Oven-B Column Position:1; BPR Pressure: 100.0 bar; BPR Temperature: 50°C.

Example 336: 7-(6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-pyridin-2-yl)-8-methoxy-[1,2,4]-triazolo[1,5-a]-pyridin-2-amine



336A: 2-bromo-6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridine:

To a stirred solution of 7 1-(1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.8 g, 2.423 mmol), 2,6-dibromopyridine (0.574 g, 2.423 mmol) in 1,4-dioxane (8 mL) and water (2 mL) was added tripotassium phosphate (1.543 g, 7.27 mmol). The reaction mixture was purged with nitrogen gas for 5 minutes. Then [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with DCM (0.198 g, 0.242 mmol) was added. The reaction mixture was purged with nitrogen gas for 2 min and allowed to stir at 80 °C for 2 h. Upon completion of the reaction, as monitored by UHPLC-MS, the reaction mixture was diluted with ice cold water and extracted with ethyl acetate. The organic layer was dried over sodium sulphate and passed through a pad of

silica gel to yield crude 2-bromo-6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridine (0.5 g, 1.388 mmol, 57.3% yield), which was taken to the next step without further purification. MS ESI m/z 360.01 $(M+H)^+$.

336B: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, to a solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.344 g, 0.934 mmol) and 2-bromo-6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridine (0.202 g, 0.560 mmol) in 1,4-dioxane (6 mL) and water (1.5 mL) was added tripotassium phosphate (0.595 g, 2.80 mmol). The reaction mixture was degassed for 10 minutes and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with DCM (0.076 g, 0.093 mmol) was added. The mixture was heated to 80 °C and stirred for 2 h until complete consumption of starting material as monitored by UPLC. The aqueous layer was separated, and the organic fraction was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography, with 0-100% EA/petrol ether to yield 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]-pyridine (0.185 g, 0.326 mmol, 34.9% yield) as colourless liquid.

MS ESI m/z 522.2 $(M+H)^+$.

336: 7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]-triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to a solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (0.185 g, 0.355 mmol) in THF (6 mL) and water (2 mL) was added TFA (1.366 mL, 17.73 mmol) slowly at room temperature. The reaction mixture was heated to 70 °C and stirred for 16 h until all the starting material was consumed as monitored by UPLC. After completion of the reaction, TFA was removed under vacuum and the residue was neutralized with saturated solution of sodium bicarbonate (5 mL) and extracted with ethyl acetate (50 mL). The organic layer was dried over sodium sulphate and concentrated under vacuum. The residue was purified by reverse phase preparative HPLC to afford 7-(6-(1-(1-(4-fluorophenyl) propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.042 g, 0.094 mmol, 26.4% yield) as off-white solid.

Reverse phase preparative HPLC purification method:

Diluent: Water:THF:ACN(50:20:30); Column: Redisep 80gm C18, 20-40 micron; Temperature : Ambient; Mobile phase A: 5mM Ammonium Formate; Mobile phase B: Acetonitrile; Flow: 30mL/min; Time/Grad: 0/20, 12/70.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.53 (d, J = 0.40 Hz, 1H), 8.36 (d, J = 7.20 Hz, 1H), 8.13 (s, 1H), 7.86 (t, J = 8.00 Hz, 1H), 7.77 (dd, J = 0.80, 8.00 Hz, 1H), 7.66 (dd, J = 1.20, 7.80 Hz, 1H), 7.41-7.48 (m, 3H), 7.17-7.20 (m, 2H), 6.10 (s, 2H), 5.42 (dd, J = 6.00, 9.20 Hz, 1H), 4.15 (s, 3H), 2.36-2.43 (m, 1H), 2.14 (t, J = 7.60 Hz, 1H), 0.84 (t, J = 7.20 Hz, 3H).

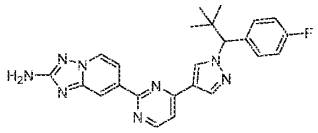
MS ESI m/z 444.1 $(M+H)^+$

Chiral purity: 99.6% ee; RT:4.523 min.

SFC Method:

(R,R)WHELK-O1(250X4.6)mm,5u)_0.1% TEA in Methanol_40_6.lcd; Flowrate : 3.0000 mL/min; Co-Solvent: 40.0 %; Make up Pump Flow: 0.5000 mL/min; Oven-B Temperature: 40°C; Oven-B Column Position: 3; BPR Pressure: 100.0 bar; BPR Temperature: 50°C.

Example 337: 7-(4-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1H-pyrazol-4-yl)-pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]-pyridin-2-amine



337A: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(4-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 40 mL vial, to a solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.49 g, 1.450 mmol) and 2-chloro-4-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)pyrimidine (0.5 g, 1.450 mmol) in 1,4-dioxane (10 mL) and water (2 mL), was added tripotassium phosphate (0.923 g, 4.35 mmol). The reaction mixture was degassed for 10 minutes and [1,1'bis(diphenylphosphino)-ferrocene]dichloropalladium (II), complex with DCM (0.118 g, 0.145 mmol) was added. The mixture was heated to 80 °C and stirred for 2 h until complete consumption of starting material as monitored by UPLC. The aqueous layer was separated, and the organic fraction was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography, with 0-30% EA/petrol ether to yield 2-(2,5-

dimethyl-1*H*-pyrrol-1-yl)-7-(4-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.53 g, 0.916 mmol, 63.2% yield) as pale brown solid.

MS ESI m/z 521.2 $(M+H)^+$.

337: 7-(4-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl) pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine; Peak-1 & Peak-2:

In a 20 mL vial, to a solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(4-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.53 g, 1.018 mmol) in THF (5 mL) and water (1 mL), was added TFA (3.92 mL, 50.9 mmol) slowly at room temperature. The reaction mixture was heated to 70 °C and stirred for 16 h until all the starting material was consumed as monitored by UPLC. After completion of the reaction, TFA was removed under vacuum and the residue was neutralized with saturated solution of sodium bicarbonate (15 mL) and extracted with DCM (50 mL). The organic layer was dried over sodium sulphate and concentrated under vacuum. The crude was directly submitted for enantiomeric separation by chiral SFC to yield enantiomer-1 and enantiomer-2.

SFC method:

Column/dimensions: YMC Cellulose-SC(250mmX4.6X5u)_ACN IPA(50_50)_50_23.lcd, Co solvent: 50%, Flowrate : 3.0000 mL/min; Back Pressure: 100bar; Temperature : 50°C;

337, enantiomer 1 :

7-(4-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]-triazolo[1,5-a]pyridin-2-amine (55 mg, 0.121 mmol, 11.93 % yield) (Peak 1) as an off-white solid. ^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 8.83-8.86 (m, 2H), 8.67 (dd, J = 0.80 Hz, 6.8 Hz, 1H), 8.43 (s, 1H), 8.37 (q, J = 0.80 Hz, 1H), 7.90 (dd, J = 2.00 Hz, 7.2 Hz, 1H), 7.72-7.76 (m, 3H), 7.21 (t, J = 8.80 Hz, 2H), 6.17 (br s, 2H), 5.47 (s, 1H), 1.00 (s, 9H). MS ESI m/z 443.2 $(M+H)^+$.

Chiral purity: 99.2% ee; RT value: 3.509 min.

SFC Method: YMC Cellulose-SC(250mmX4.6X5u)_ACN IPA(50_50)_ 50_4.lcd, Co solvent: 50%, Flowrate : 3.0000 mL/min; Back Pressure: 100bar; Temperature : 50°C;

338 enantiomer 2:

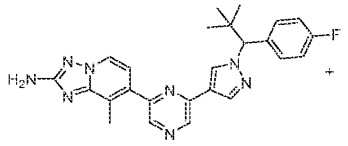
7-(4-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]-triazolo[1,5-a]pyridin-2-amine (55 mg, 0.121 mmol, 11.93 % yield) (Peak 2) as an

off-white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.83-8.86 (m, 2H), 8.67 (dd, J = 0.80 Hz, 6.8 Hz, 1H), 8.43 (s, 1H), 8.37 (q, J = 0.80 Hz, 1H), 7.90 (dd, J = 2.00 Hz, 7.2 Hz, 1H), 7.72-7.76 (m, 3H), 7.21 (t, J = 2.00 Hz, 2H), 6.16 (br s, 2H), 5.47 (s, 1H), 1.00 (s, 9H). MS ESI m/z 443.2 $(M+H)^+$.

Chiral purity: 99.2% ee; RT value: 4.971 min.

SFC Method: YMC Cellulose-SC(250mmX4.6X5u)_ACN IPA(50_50)_ 50_3.lcd, Co solvent: 50%, Flowrate : 3.0000 mL/min; Back Pressure: 100bar; Temperature : 50 °C.

Example 339: 7-(6-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine



339A: 2-chloro-6-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)pyrazine:

In a 250 mL sealed tube, to a solution of 1-(tetrahydro-2H-pyran-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (5 g, 17.98 mmol) and 2-bromo-6-chloropyrazine (3.48 g, 17.98 mmol) in 1,4-dioxane (60 mL) and water (15 mL), was added tripotassium phosphate (11.45 g, 53.9 mmol). The reaction mixture was degassed for 10 minutes and [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (1.468 g, 1.798 mmol) was added to the reaction. The above reaction mixture was heated to 80 °C and stirred for 2 h until complete consumption of starting material as monitored by UPLC. The aqueous layer was separated, and the organic fraction was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography, whith 0-30% EA/petrol ether to yield of 2-chloro-6-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl) pyrazine (3 g, 11.33 mmol, 63% yield) as brown gummy liquid. MS ESI m/z 265.01 $(M+H)^+$.

339B: 2-chloro-6-(1*H*-pyrazol-4-yl) pyrazine:

In a 250 mL two neck RBF, to a well stirred solution of 2-chloro-6-(1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-pyrazol-4-yl)pyrazine (8.6 g, 32.5 mmol) in DCM (60 mL),was added TFA (50.1 mL, 650 mmol) at room temperature and reaction mixture was stirred for 3 h. Upon completion of the reaction, the mixture was quenched with saturated solution of $NaHCO_3$ maintaining pH 7, and compound was extracted by using ethyl acetate. The organic layers were separated, dried over sodium sulphate and concentrated. The residue was purified by

silica gel column chromatography with 0-100% of EtOAc/eetrol ether to yield 2-chloro-6-(1*H*-pyrazol-4-yl)pyrazine (3 g, 14.95 mmol, 46% yield) as a white solid. MS ESI m/z 181.0 $(M+H)^+$.

339C: 2-chloro-6-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)pyrazine:

In a 40 mL vial, to a solution of 2-chloro-6-(1*H*-pyrazol-4-yl) pyrazine (0.5 g, 2.77 mmol) and 1-(4-fluorophenyl)-2,2-dimethylpropan-1-ol (1.514 g, 8.31 mmol) in THF (15 mL), was added triphenylphosphine (3.631 g, 13.84 mmol). Then, di-tert-butyl azodicarboxylate (3.188 g, 13.84 mmol) was added and the mixture was stirred for 16 h at room temperature under nitrogen atmosphere. Upon completion of the reaction, the mixture was concentrated. The residue was purified by silica gel column chromatography using 0-12% of EtOAc/petrol ether to afford 2-chloro-6-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)pyrazine (1 g, 2.320 mmol, 84% yield) as a brown gummy liquid. MS ESI m/z 345.0 $(M+H)^+$.

339D: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, to a solution of (2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid (0.376 g, 1.392 mmol) and 2-chloro-6-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)pyrazine (0.4 g, 1.160 mmol) in 1,4-dioxane (8 mL) and water (2 mL) was added tripotassium phosphate (0.739 g, 3.48 mmol). The reaction mixture was degassed for 10 minutes and [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II), complex with DCM (0.095 g, 0.116 mmol) was added. The mixture was heated to 80 °C and stirred for 2 h until complete consumption of starting material as monitored by UPLC. The aqueous layer was separated, and the organic fraction was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography, with 0-30% EA/petrol ether to yield 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.13 g, 0.175 mmol, 15.09% yield) as brown liquid.

MS ESI m/z 535.2 $(M+H)^+$.

339: 7-(6-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine; Peak 1 and Peak 2:

In an 8 mL vial, to a solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-8-methyl [1,2,4]triazolo[1,5-a]pyridine (0.13 g, 0.243 mmol) in THF (2 mL) and water (0.5 mL), was added TFA (0.937 mL, 12.16 mmol) slowly at room temperature. The reaction mixture was heated to 70 °C and stirred for 16 h until all the starting material was consumed as monitored by UPLC. After completion of the reaction, TFA was removed under vacuum and the residue was neutralized with saturated solution of sodium bicarbonate (10 mL) and extracted with DCM (20 mL). The organic layer was dried over sodium sulphate and concentrated under vacuum. The residue was directly submitted for enantiomeric separation by chiral SFC to yield enantiomer-1 and enantiomer-2.

SFC method:

Column/dimensions: Chiralpak IH (250 X 4.6) mm,5 µm; ACN_IPA(50_50)_40_12.lcd, Co solvent: 40%, Flowrate : 3.0000 mL/min; Back Pressure: 100bar; Temperature : 50°C;

339, Enantiomer 1:

7-(6-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (17 mg, 0.036 mmol, 14.81 % yield) (Peak 1) as an off-white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.01 (s, 1H), 8.68 (s, 1H), 8.61 (s, 1H), 8.52 (t, J = 6.40 Hz, 1H), 8.31 (s, 1H), 7.71-7.75 (m, 2H), 7.20 (t, J = 8.80 Hz, 2H), 7.09 (d, J = 7.20 Hz, 1H), 6.09 (s, 2H), 5.45 (s, 1H), 0.99 (s, 9H). MS ESI m/z 457.2 $(M+H)^+$.

Note: 3 protons (3H) are merged with DMSO-d_6 peak.

Chiral purity: 99.5% ee; RT value: 2.101 min.

SFC Method: Chiralpak IH (250 X 4.6) mm,5 µm; ACN_IPA(50_50)_40_3.lcd, Co solvent: 40%, Flowrate : 3.0000 mL/min; Back Pressure: 100bar; Temperature : 50°C;

340, Enantiomer 2:

7-(6-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl) pyrazin-2-yl)-8-methyl-[1,2,4] triazolo[1,5-a]pyridin-2-amine (23 mg, 0.049 mmol, 20.25 % yield) (Peak 2) as an off-white solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.01 (s, 1H), 8.68 (s, 1H), 8.61 (s, 1H), 8.51-8.53 (m, 1H), 8.31 (s, 1H), 7.71-7.75 (m, 2H), 7.20 (t, J = 8.80 Hz, 2H), 7.08 (d, J = 6.80 Hz, 1H), 6.09 (s, 2H), 5.45 (s, 1H), 0.99 (s, 9H).

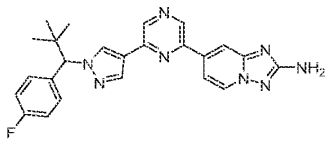
Note: 3 protons (3H) are merged with DMSO-d_6 peak.

MS ESI m/z 457.2 $(M+H)^+$.

Chiral purity: 93.5% ee; RT value: 2.475 min.

SFC Method: Chiralpak IH (250 X 4.6) mm,5 µm; ACN_IPA (50_50)_40_3.lcd, Co solvent: 40%, Flowrate : 3.0000 mL/min; Back Pressure: 100bar; Temperature : 50 °C.

Example 341: 7-(6-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]-triazolo[1,5-a]-pyridin-2-amine



341A: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, 7-(6-(1*H*-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.3 g, 0.842 mmol), 1-(4-fluorophenyl)-2,2-dimethylpropan-1-ol (1.534 g, 8.42 mmol), triphenylphosphine (1.104 g, 4.21 mmol) and di-tert-butyl azodicarboxylate (0.969 g, 4.21 mmol) were placed. The vial was flushed with nitrogen. Then, THF (10 mL) was added. The reaction mixture was purged with nitrogen and stirred at room temperature for 16 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified by silica gel column chromatography using 0-25% of EtOAc/petrol ether to afford 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.12 g, 0.207 mmol, 24.64% yield) as a pale brown liquid. MS ESI m/z 522.2 $(M+H)^+$.

341: 7-(6-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine; Peak 1 and Peak 2:

In a 20 mL vial, to a well stirred solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]-pyridine (0.12 g, 0.230 mmol) in THF (2 mL) and water (0.5 mL) was added TFA (0.888 mL, 11.52 mmol) and the reaction mixture was allowed to stir at 70 °C for 16 h. Upon completion of the reaction, the solvents were evaporated, quenched excess TFA with 10 mL of saturated $NaHCO_3$ solution and compound was extracted with DCM (30 mL X 2). The organic layer was dried over anhydrous sodium sulphate, filtered and solvents

evaporated. The residue was purified by the preparative HPLC to yield 0.034 g of 7-(6-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine as a racemate. The racemate was purified by SFC to yield enantiomer 1 and enantiomer 2.

Preparative HPLC method:

Diluent: THF:WATER:ACN(30:30:40); Column : XBridge Prep C8 (19x250mm) 5µ; Temperature : Ambient; Mobile phase A: 5mM Ammonium Formate in Water; Mobile phase B: Acetonitrile; Flow :15mL/min; Time/Grad : 0/60,10/90.

SFC method:

Column/dimensions: Chiralcel OJ-H(250 X 30)mm,5 µm; % CO2: 75%; % Co solvent: 25% of ACN-MeOH (1:1); Total Flow: 100.0g/min; Back Pressure: 100 bar; Temperature : 40°C;

UV: 220 nm.

341, Enantiomer 1:

7-(6-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.015 g, 0.034 mmol, 14.55% yield) (Peak 1) as a off white solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 1H), 9.00 (s, 1H), 8.68-8.72 (m, 2H), 8.38 (s, 1H), 8.23 (q, J = 0.80 Hz, 1H), 7.72-7.76 (m, 3H), 7.21 (t, J = 8.80 Hz, 2H), 6.14 (s, 2H), 5.46 (s, 1H), 1.01 (s, 9H).

MS ESI m/z 443.0 $(M+H)^+$.

Chiral purity: 98.13% ee; RT value: 3.819 min.

SFC Method: Column/dimensions: Chiralpak IJ(250mmX4.6X5u)_5mM NH_4OAc in ACN_MEOH(1_1)_30_4.lcd; Flowrate : 3.0000 mL/min; Co-Solvent :30.0 %; Oven-A Temperature : 40; Oven A Column Position: 4; BPR Pressure : 100.0 bar; BPR Temperature : 50 C.

342, Enantiomer 2:

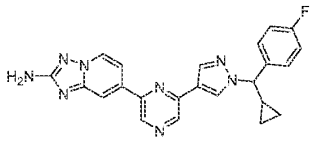
7-(6-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.015 g, 0.033 mmol, 14.49% yield) (Peak 2) as a off white solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 1H), 9.00 (s, 1H), 8.68-8.72 (m, 2H), 8.38 (s, 1H), 8.23 (q, J = 0.80 Hz, 1H), 7.72-7.76 (m, 3H), 7.21 (t, J = 8.80 Hz, 2H), 6.14 (s, 2H), 5.46 (s, 1H), 1.01 (s, 9H). MS ESI m/z 443.0 $(M+H)^+$.

Chiral purity: 94.78% ee; RT value: 4.203 min.

SFC Method: Column/dimensions: Chiralpak IJ (250mmX4.6X5u)_5mM NH_4OAc in ACN_MeOH(1_1)_30_3.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 30.0 %; Oven-A Temperature: 40; Oven A Column Position: 4; BPR Pressure: 100.0 bar; BPR Temperature: 50 C.

Example 343: 7-(6-(1-(cyclopropyl-(4-fluorophenyl)-methyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine



343A: cyclopropyl(4-fluorophenyl)methanol:

In a 250 mL two neck RBF, to a well stirred solution of cyclopropyl(4-fluorophenyl)methanone (4.37 mL, 30.5 mmol) in MeOH (50 mL) was added $NaBH_4$ (2.88 g, 76 mmol) slowly at 0 °C under nitrogen atmosphere. The reaction mixture was allowed warm up to room temperature and stirred for 2 h. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using DCM. The organic layers were separated, dried over anhydrous sodium sulphate and concentrated to yield crude product (5 g) which was used for the next step without further purification.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.16-7.43 (m, 2H), 7.09-7.15 (m, 2H), 5.19 (d, J = 4.40 Hz, 1H), 0.00 (dd, J = 4.40, 7.40 Hz, 1H), 0.99-1.03 (m, 1H), 0.30-0.46 (m, 4H).

343B: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)-2,2-dimethylpropyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, 7-(6-(1*H*-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.8 g, 2.24 mol), cyclopropyl(4-fluorophenyl)methanol (3.73 g, 22.45 mmol), triphenylphosphine (2.94 g, 11.22 mol) and di-tert-butyl azodicarboxylate (2.58 g, 11.22 mmol) were placed. The vial was flushed with nitrogen. Then, THF (10 mL) was added and the mixture was purged with nitrogen and stirred at room temperature for 16 h under nitrogen atmosphere. Upon completion of the reaction,

the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified by silica gel column chromatography using 0-25% of EtOAc/petrol ether to afford 7-(6-(1-(cyclopropyl(4-fluorophenyl)methyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (1.5 g, 0.713 mmol, 31.8% yield) as a pale brown liquid. MS ESI m/z 505.2.2 $(M+H)^+$.

343: 7-(6-(1-(cyclopropyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine; Peak 1 and Peak 2:

In a 20 mL vial, to a well stirred solution of 7-(6-(1-(cyclopropyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (1.5 g, 0.713 mmol) in THF (10 mL) and water (2 mL) was added TFA (2.75 mL, 35.7 mmol) and the reaction mixture was allowed to stir at 70 °C for 16 h. Upon completion of the reaction, the solvents were evaporated, quenched excess TFA with 10 mL of saturated $NaHCO_3$ solution and compound was extracted with DCM (30 mL X 2). The organic layer was dried over anhydrous sodium sulphate, filtered and solvent was evaporated. The residue was purified by preparative HPLC to yield 0.038 g of 7-(6-(1-(cyclopropyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine as a racemate. The racemate was purified by SFC to separate enantiomer 1 and enantiomer 2.

Preparative HPLC method:

Diluent: Water:THF:ACN(10:60:30); Column: Ymc Triart C18 (250 x21.2)mm, 5micron; Temperature: Ambient; Mobile phase A: 0.1% Formic acid in water; Mobile phase B: Acetonitrile; Flow: 15mL/min; Time/Grad: 0/35,18/70.

SFC method:

Column/dimensions: Chiralcel OJ-H(250 X 30)mm,5 µm; % CO_2: 65%; % Co solvent: 35 % of acetonitrile:MeOH(50:50); Total Flow: 100.0g/min; Back Pressure: 120 bar; Temperature: 40°C; UV: 231 nm.

343, Enantiomer 1:

7-(6-(1-(cyclopropyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.017 g, 0.039 mmol, 5.48 % yield) (Peak 1) as an off white solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 1H), 9.02 (s, 1H), 8.84 (s, 1H), 8.68 (t, J = 0.40 Hz, 1H), 8.29 (s, 1H), 8.25 (d, J = 1.20 Hz, 1H), 7.73-7.76 (m, 1H), 7.42-7.46 (m, 2H), 7.19-7.22 (m, 2H), 6.13 (s, 2H), 4.82 (d, J = 10.00 Hz, 1H), 1.86-1.89 (m, 1H), 0.54-0.57 (m, 2H), 0.46-0.49 (m, 2H).

MS ESI m/z 427.0 $(M+H)^+$.

Chiral purity: 100% ee; RT value: 3.072 min.

SFC Method: Column/dimensions: Chiralpak IJ (250mmX4.6X5u) _ACN MeOH(50_50)_35_3.lcd; Flowrate: 3.0000 mL/min; Co-Solvent:35.0 %; Oven-A Temperature: 40; Oven A Column Position: 4; BPR Pressure: 100.0 bar;BPR Temperature: 50 C.

344, Enantiomer 2 :

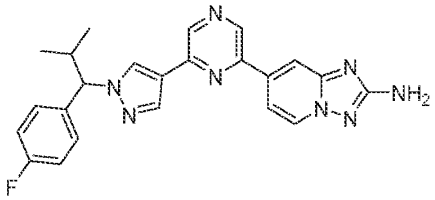
7-(6-(1-(cyclopropyl(4-fluorophenyl)methyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.017 g, 0.039 mmol, 5.42 % yield) (Peak 2) as an off white solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 1H), 9.02 (s, 1H), 8.84 (s, 1H), 8.68 (t, J = 0.40 Hz, 1H), 8.29 (s, 1H), 8.25 (d, J = 1.20 Hz, 1H), 7.73-7.76 (m, 1H), 7.42-7.46 (m, 2H), 7.19-7.22 (m, 2H), 6.13 (s, 2H), 4.82 (d, J = 10.00 Hz, 1H), 1.86-1.89 (m, 1H), 0.54-0.57 (m, 2H), 0.46-0.49 (m, 2H). MS ESI m/z 427.0 $(M+H)^+$.

Chiral purity: 98.62% ee; RT value: 3.584 min.

SFC Method: Column/dimensions: Chiralpak IJ (250mmX4.6X5u)_ACN MeOH(50_50)_35_4.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 35.0 %; Oven-A Temperature : 40; Oven A Column Position: 4; BPR Pressure: 100.0 bar; BPR Temperature: 50 C.

Example 345: 7-(6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo-[1,5-a]pyridin-2-amine



345A: 1-(4-fluorophenyl)-2-methylpropan-1-ol:

In a 250 mL two neck RBF, to a well stirred solution of isobutyraldehyde (6.33 mL, 69.3 mmol) in THF (50 mL) was added (4-fluorophenyl)magnesium bromide (83 mL, 83 mmol) slowly at 0 °C under nitrogen atmosphere. The reaction mixture was allowed to warm up to room temperature and stirred for 2 h. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layers were separated, dried over anhydrous sodium sulphate and concentrated. The residue was purified by silica gel column chromatography with 0-40% EtOAc/petrol ether to yield 1-(4-fluorophenyl)-2-methylpropan-1-ol (5 g, 29.7 mmol, 42.9% yield) as a pale brown liquid.

^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 7.30 (dd, J = 2.00, 6.00 Hz, 2H), 7.10-7.14 (m, 2H), 5.12 (d, J = 4.40 Hz, 1H), 4.25 (dd, J = 4.80, 6.00 Hz, 1H), 1.75-1.80 (m, 1H), 0.84 (d, J = 6.80 Hz, 3H), 0.73 (d, J = 6.80 Hz, 3H).

345B: 1-(1-chloro-2-methylpropyl)-4-fluorobenzene:

In a 100 mL two neck RBF, to a well stirred solution of 1-(4-fluorophenyl)-2-methylpropan-1-ol (5 g, 29.7 mmol) in DCM (30 mL) was added thionyl chloride (10.85 mL, 149 mmol) slowly at 0 °C under nitrogen atmosphere. The reaction mixture was allowed to warm up to room temperature and stirred for 4 h. Upon completion of the reaction, the reaction mixture was quenched with saturated solution of $NaHCO_3$ and compound was extracted by using ethyl acetate. The organic layers were separated, dried over anhydrous sodium sulphate and concentrated. The residue was purified by silica gel column chromatography with 0-10% EtOAc/petrol ether to yield 1-(1-chloro-2-methylpropyl)-4-fluorobenzene (3.8 g, 20.36 mmol, 68.5% yield) as a pale brown liquid.

^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 7.43-7.48 (m, 2H), 7.18-7.23 (m, 2H), 4.95 (d, J = 8.00 Hz, 1H), 2.17-2.24 (m, 1H), 1.05 (d, J = 6.40 Hz, 3H), 0.79 (d, J = 6.80 Hz, 3H).

345C: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 40 mL vial, to a stirring solution of 7-(6-(1*H*-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.85 g, 2.003 mmol) and 1-(1-chloro-2-methylpropyl)-4-fluorobenzene (3.739 g, 20.03 mmol) in DMF (10 mL) was added K_2CO_3 (2.215 g, 16.03 mmol) and the mixture was heated at 80 °C for 16 h. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium

sulphate, filtered and solvents evaporated. The residue was purified by silica gel column chromatography using 0-25% of EtOAc/petrol ether to afford 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.14 g, 0.249 mmol, 12.41% yield) as a pale brown liquid. MS ESI m/z 507.2 $(M+H)^+$.

345: 7-(6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]-triazolo[1,5-a]pyridin-2-amine; Peak 1 and Peak 2:

In a 20 mL vial, to a well stirred solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.14 g, 0.276 mmol) in THF (2.5 mL) and water (0.2 mL) was added TFA (1.065 mL, 13.82 mmol) and the reaction mixture was allowed to stir at 70 °C for 16 h. Upon completion of the reaction, the solvents were evaporated, quenched excess TFA with 20 mL of saturated $NaHCO_3$ solution and compound was extracted with ethyl acetate (30 mL X 2). The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified by preparative HPLC to yield 0.050 g of 7-(6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine as a racemate. The racemate was purified by SFC to separate enantiomer 1 and enantiomer 2.

Preparative HPLC method:

Diluent: Water:THF:ACN(30:40:30); Column: X-SELECT CSH C8 (250 x19)mm, 5µ; Temperature: Ambient; Mobile phase A: 5Mm ammonium formate in water; Mobile phase B: acetonitrile; Flow: 15mL/min; Time/Grad: 0/35, 12/70,15/70.

SFC method:

Column/dimensions: Chiralcel OJ-H(250 X 30)mm,5 µm; % CO_2: 65%; % Co solvent: 35 % of acetonitrile:MeOH(50:50); Total Flow: 100.0g/min; Back Pressure: 125 bar; Temperature : 40°C; UV: 231 nm.

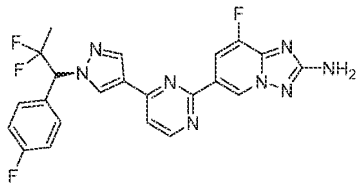
345, Enantiomer 1:

7-(6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.025 g, 0.058 mmol, 20.87 % yield) (Peak 1) as an off white solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.18 (s, 1H), 8.99 (s, 1H), 8.78 (s, 1H), 8.68-8.70 (m, 1H), 8.30 (s, 1H), 8.24 (s, 1H), 7.73-7.75 (m, 1H), 7.63-7.67 (m, 2H), 7.21 (t, J = 8.80 Hz, 2H), 6.14 (s, 2H), 5.11 (d, J = 10.80 Hz, 1H), 2.74-2.84 (m, 1H), 0.80-0.85 (m, 6H).
MS ESI m/z 429.0 $(M+H)^+$.
Chiral purity: 99.6% ee; RT value: 2.143 min.
SFC Method: Column/dimensions: Chiralcel-OJ-H (250X4.6) mm 5µ_5 mM NH_4OAc in ACN_MeOH(1_1)_40_4.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 40.0 %; Make up Pump Flow: 0.5000 mL/min; Oven-A Temperature: 40°C; Oven A Column Position: 3; BPR Pressure: 100.0 bar; BPR Temperature: 50°C.

346, Enantiomer 2:
7-(6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.02 g, 0.046 mmol, 16.71% yield) (Peak 2) as an off white solid.
^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.18 (s, 1H), 8.99 (s, 1H), 8.78 (s, 1H), 8.68-8.70 (m, 1H), 8.30 (s, 1H), 8.24 (s, 1H), 7.73-7.75 (m, 1H), 7.63-7.67 (m, 2H), 7.21 (t, J = 8.80 Hz, 2H), 6.14 (s, 2H), 5.11 (d, J = 10.80 Hz, 1H), 2.74-2.84 (m, 1H), 0.80-0.85 (m, 6H). MS ESI m/z 429.0 $(M+H)^+$.
Chiral purity: 95.95% ee; RT value: 2.394 min.
SFC Method: Column/dimensions: Chiralcel-OJ-H (250X4.6)mm 5µ_5 mM NH4OAc in ACN_MeOH(1_1)_40_3.lcd; Flowrate : 3.0000 mL/min; Co-Solvent : 40.0 %; Make up Pump Flow: 0.5000 mL/min; Oven-A Temperature: 40°C; Oven A Column Position: 3; BPR Pressure: 100.0 bar; BPR Temperature: 50°C.

Example 347: (*R*)-6-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-8-fluoro-[1,2,4]-triazolo[1,5-a]-pyridin-2-amine



347A: 6-bromo-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridine:
In a 30 mL microwave vial, to a stirred solution of 6-bromo-8-fluoro-[1,2,4]triazolo[1,5-a]-pyridin-2-amine (1.5 g, 6.49 mmol) in toluene (7 mL) were added hexane-2,5-dione

(3.71 g, 32.5 mmol) and acetic acid (1.858 mL, 32.5 mmol). The reaction mixture was heated to 120 °C, under microwave irradiation for 12 h. Upon completion of the reaction, toluene was removed under reduced pressure to yield a brown residue, which was purified by silica gel column chromatography using 0-10% of EtOAc/petrol ether to afforded 6-bromo-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridine (1.8 g, 5.61 mmol, 86% yield) as a light pink solid. MS ESI m/z 309.0 $(M+H)^+$.

347B: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, 6-bromo-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridine (300 mg, 0.970 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.493 g, 1.94 mmol), [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.079 g, 0.097 mmol) and potassium acetate (0.286 g, 2.91 mmol) were placed, and the vial was flushed with nitrogen. Then, 1,4-dioxane (5 mL) was added and the mixture was purged with nitrogen and heated at 100 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was filtered through celite and the celite pad was washed with ethyl acetate. The filtrate was concentrated to give crude product (0.35 g), which was used for next step without further purification. MS ESI m/z 375.2 (275.1 boronic acid mass) $(M+H)^+$.

347C: (*R*)-6-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrimidin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]-pyridine:

In a 20 mL vial, 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.35 g, 0.983 mmol), (*R*)-2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrimidine (0.347 g, 0.983 mmol), [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.05 g, 0.062 mmol) and potassium phosphate (0.513 g, 2.95 mmol) were placed, and the vial was flushed with nitrogen. Then, 1,4-dioxane/H_2O (5:1) (5 mL) was added and the mixture was purged with nitrogen and heated at 80 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified using silica gel column chromatography using 0-10% of EtOAc/petrol ether to afford (*R*)-6-(4-(1-(2,2-difluoro-1-

(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrimidin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-fluoro-[1,2,4]triazolo-[1,5-a]pyridine (0.32 g, 0.539 mmol, 54.8 % yield) as a pale brown solid. MS ESI m/z 547.2 $(M+H)^+$.

347: (*R*)-6-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrimidin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine;:

In a 20 mL vial, to a well stirred solution of (*R*)-6-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrimidin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridine (0.3 g, 0.549 mmol) in THF (4 mL) and water (0.5 mL) was added TFA (2.114 mL, 27.4 mmol) and the mixture was allowed to stirr at 70 °C for 16 h. Upon completion of the reaction, solvents were evaporated, excess TFA was quenched with 20 mL of saturated $NaHCO_3$ solution and compound was extracted with ethyl acetate (30 mL X 2). The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified by the reverse phase preparative HPLC to yield (*R*)-6-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrimidin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.4 g, 0.085 mmol, 15.42% yield) as an off white solid.

Reverse phase preparative HPLC method:

Diluent: THF: Acetonitrile (50:50); Column: Redisep 80g C18, 20-40 micron; Mobile phase A : 5mM Ammonium formate in water; Mobile phase B: Acetonitrile; Instrument 1D: Teledyne Isco-Combi flash; Compound elution (%): 60%Acetonitrile/ 5mM Ammonium formate in water; Flow Rate: 40mL/min.

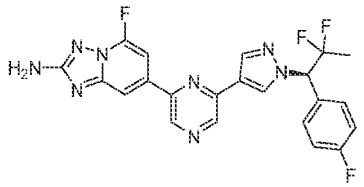
^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.33 (d, J = 1.20 Hz, 1H), 8.95 (s, 1H), 8.82 (d, J = 5.20 Hz, 1H), 8.51 (s, 1H), 8.25-8.28 (m, 1H), 7.74-7.79 (m, 3H), 7.29 (t, J = 9.20 Hz, 2H), 6.44 (s, 2H), 6.28 (t, J = 13.20 Hz, 1H), 1.67 (t, J = 19.20 Hz, 3H).

MS ESI m/z 469.1 $(M+H)^+$.

Chiral purity: 99.34% ee; RT value: 3.316 min.

SFC Method: Column/dimensions: Chiralpak IK (250X4.6)mm 5µ_5 mM NH_4OAc in ACN_MeOH(1_1)_30_43.lcd; Flowrate: 4.0000 mL/min; Co-Solvent: 30.0 %; Make up Pump Flow: 0.5000 mL/min; Oven-B Temperature: 40°C; Oven-B Column Position: 5; BPR Pressure: 100.0 bar; BPR Temperature: 50°C.

Example 348: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-5-fluoro-[1,2,4]-triazolo[1,5-a]-pyridin-2-amine



348A: 6-fluoro-4-iodopyridin-2-amine:

In a 75 mL sealed tube, to a stirring solution of 2,6-difluoro-4-iodopyridine (2 g, 8.30 mmol), and sodium tert-butoxide (4.28 g, 44.6 mmol) in DMSO (10 mL) was added ammonium hydroxide (5 mL, 38.5 mmol) and the mixture was heated at 120 °C for 16 h. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified by silica gel column chromatography using 0-100% of EtOAc/petrol ether to afford 4-bromo-5-fluoro-3-methylpyridin-2-amine (1.9 g, 7.32 mmol, 54.1% yield) as a off white solid. MS ESI m/z 239.2 $(M+H)^+$.

348B: *O*-ethyl N-((6-fluoro-4-iodopyridin-2-yl)carbamothioyl)carbamate

In a 100 mL RBF, to a stirred solution of 6-fluoro-4-iodopyridin-2-amine (3.5 g, 14.71 mmol) in 1,4-dioxane (20 mL) was added O-ethyl carbonisothiocyanatidate (2.081 mL, 17.65 mmol) at room temperature. The mixture was stirred at room temperature for 16 h. Upon completion of the reaction, the mixture was filtered through celite and the celite pad was washed with 1,4-dioxane. The filtrate was concentrated to give 3 g of **348B** as pale brown solid, which was used for for the next step without further purification.

MS ESI m/z 370.1 $(M+H)^+$.

348C: 5-fluoro-7-iodo-[1,2,4] triazolo[1,5-a]pyridin-2-amine:

In a 250 mL RBF, to a stirred solution of **348B** (3 g, 8.13 mmol) in MeOH (10 mL)/Ethanol (10 mL) was added DIPEA (7.10 mL, 40.6 mmol) and hydroxylamine hydrochloride (3.39 g, 48.8 mmol) and reaction mixture was heated at 50 °C for 16 h. Upon completion of reaction, ethanol was removed under vacuum to give a brown residue. The residue was dissolved in minimum amount of DMSO and purified by reverse phase flash chromatography to obtain 5-fluoro-7-iodo-[1,2,4]triazolo[1,5-a]pyridin-2-amine (1.2 g, 1.467 mmol, 18.06% yield) as a pale brown solid. MS ESI m/z 279.0 $(M+H)^+$.

348D: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-fluoro-7-iodo-[1,2,4] triazolo[1,5-a]pyridine:

In a 30 mL microwave vial, to a stirred solution of 5-fluoro-7-iodo-[1,2,4] triazolo[1,5-a]-pyridin-2-amine (1 g, 3.60 mmol) in toluene (20 mL) were added hexane-2,5-dione (4.22 mL, 36.0 mmol) and acetic acid (1.030 mL, 17.98 mmol). The reaction mixture was heated to 140 °C, under microwave irradiation for 16 h. Upon completion of the reaction, toluene was removed under reduced pressure. The residue was purified by silica gel column chromatography using 0-20% of EtOAc/petrol ether to afford 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-fluoro-7-iodo-[1,2,4] triazolo[1,5-a]pyridine (0.911 g, 2.426 mmol, 67.5% yield) as a pale brown solid. MS ESI m/z 357.0 $(M+H)^+$.

348E: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 40 mL vial, 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-fluoro-7-iodo-[1,2,4]triazolo[1,5-a]-pyridine (0.45 g, 1.264 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.642 g, 2.53 mmol), [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.103 g, 0.126 mmol) and potassium acetate (0.372 g, 3.79 mmol) were placed, and the vial was flushed with nitrogen. Then, 1,4-dioxane (15 mL) was added and the reaction mixture was purged with nitrogen and heated at 100 °C for 8 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was filtered through celite and the celite pad was washed with ethyl acetate. The filtrate was concentrated to give crude product (0.4 g), which was used for the next step without further purification. MS ESI m/z)375.2 (275.1 boronic acid mass) $(M+H)^+$.

348F: (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-fluoro-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.35 g, 0.874 mmol), (*R*)-2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrimidine (0.339 g, 0.962 mmol), [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.074 g, 0.087 mmol) and potassium phosphate (0.457 g, 2.62 mmol) were placed, and the vial was flushed with nitrogen. Then, 1,4-dioxane/H_2O (5:1) (10 mL) was added and the reaction mixture was purged with nitrogen and heated at 80 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified by

silica gel column chromatography using 0-40% of EtOAc/petrol ether to afford (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-fluoro-[1,2,4]triazolo[1,5-a]pyridine (0.64 g, 0.867 mmol, 99% yield) as a pale brown liquid. MS ESI m/z 547.2 $(M+H)^+$.

348: (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-5-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to a well stirred solution of (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-5-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.64 g, 0.867 mmol) in THF (12 mL) and water (4 mL) was added TFA (3.34 mL, 43.3 mmol) and the mixture was allowed to stirr at 70 °C for 16 h. Upon completion of the reaction, the solvents were evaporated, excess TFA was quenched with 20 mL of saturated $NaHCO_3$ solution and compound was extracted with DCM (30 mL X 2). The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified by preparative HPLC to yield (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-5-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.0098 g, 0.020 mmol, 2.3% yield) as an off white solid.

Preparative HPLC method:

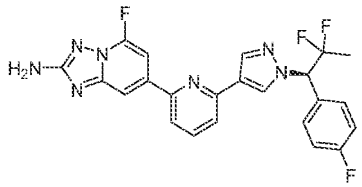
Diluent: THF:Water:ACN(50:20:30); Column: Xbridge C18 (150 x 19)mm, 5micron; Mobile phase A: 5mM Ammonium formate in water; Mobile phase B: Acetonitrile.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.26 (s, 1H), 9.09 (s, 1H), 8.85 (s, 1H), 8.46 (s, 1H), 8.18 (d, J = 1.60 Hz, 1H), 7.78 (dd, J = 5.60, 8.80 Hz, 2H), 7.71 (dd, J = 1.60, 6.40 Hz, 1H), 7.26-7.31 (m, 2H), 6.41 (s, 2H), 6.29 (t, J = 13.20 Hz, 1H), 1.67 (t, J = 19.20 Hz, 3H). MS ESI m/z) 469.0 $(M+H)^+$.

Chiral purity: 100% ee; RT value: 5.216 min.

SFC Method: Column/dimensions: Chiralcel-OJ-H (250X4.6)mm 5µ_ACN_IPA(50_50)_25_2.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 25.0 %; Make up Pump Flow: 0.5000 mL/min; Oven-A Temperature: 40°C; Oven A Column Position: 3; BPR Pressure: 100.0 bar; BPR Temperature: 50°C.

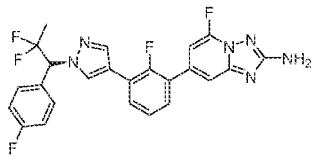
Example 349: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-5-fluoro-[1,2,4]-triazolo[1,5-a]-pyridin-2-amine



The target compound was prepared following the methods described in **example 348** using 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-5-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.316 g, 0.887 mmol) and (*R*)-2-bromo-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridine (0.351 g, 0.887 mmol).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.72 (s, 1H), 8.34 (s, 1H), 8.07 (d, J = 1.60 Hz, 1H), 8.02 (dd, J = 0.80, 8.00 Hz, 1H), 7.94 (t, J = 7.60 Hz, 1H), 7.75-7.79 (m, 3H), 7.67 (dd, J = 1.60, 6.40 Hz, 1H), 7.26-7.30 (m, 2H), 6.35 (s, 2H), 6.26 (t, J = 13.60 Hz, 1H), 1.66 (t, J = 19.20 Hz, 3H). MS ESI m/z 468.0 $(M+H)^+$.

Example 350: (R)-7-(3-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-4-yl)-2-fluorophenyl)-5-fluoro-[1,2,4]triazolo-[1,5-a]pyridin-2-amine



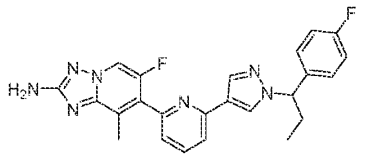
The target compound was prepared following the methods described in **example 348** using (*R*)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazole (0.225 g, 0.327 mmol), 5-fluoro-7-iodo-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.07 g, 0.252 mmol).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.44 (d, J = 2.00 Hz, 1H), 8.16 (s, 1H), 7.86 (dt, J = 1.60, 10.67 Hz, 1H), 7.75 (dd, J = 5.60, 8.80 Hz, 2H), 7.52 (dt, J = 1.60, 10.27 Hz, 1H), 7.47 (s, 1H), 7.36 (t, J = 8.00 Hz, 1H), 7.25-7.30 (m, 2H), 7.12 (d, J = 6.00 Hz, 1H), 6.35 (s, 2H), 7.28 (t, J = 13.20 Hz, 1H), 1.65 (t, J = 19.20 Hz, 3H). MS ESI m/z 485.0 $(M+H)^+$.

Chiral purity: 100% ee; RT value: 5.184 min.

SFC Method: Column/dimensions: Cellulose-4(250X4.6) mm,5µm_0.1% NH_4OH in methanol_40_4.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 40.0 %; Oven-B Temperature: 40°C; Oven B Column Position: 1; BPR Pressure: 100.0 bar; BPR Temperature: 50°C.

Example 351: 6-fluoro-7-(6-(1-(1-(4-fluorophenyl)-propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methyl-[1,2,4]-triazolo[1,5-a]-pyridin-2-amine



351A: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-6-fluoro-8-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL seal tube, to a stirred solution of 6-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-5-fluoro-7-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.2 g, 0.619 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.314 g, 1.23 mmol) in 1,4-dioxane (5 mL) was added potassium acetate (0.182 g, 1.857 mmol) and the reaction mixture was purged with nitrogen gas for 10 minutes. Then, [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.05 g, 0.062 mmol) was added, the reaction mixture was purged with nitrogen gas for further 2 min and allowed to stir at 100 °C for 4 h. Upon completion of the reaction, the mixture was filtered through celite and the celite pad was washed with ethyl acetate. The filtrate was concentrated to give crude product (0.229 g), which was used for next step without further purification. MS ESI m/z 371.2 $(M+H)^+$.

351B: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-6-fluoro-7-(6-(1-(1-(4-fluorophenyl)-propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, (2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-6-fluoro-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid (0.229 g, 0.795 mmol), 2-bromo-6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridine (0.252 g, 0.795 mmol), [1,1'bis(diphenylphosphino)ferrocene]-dichloropalladium (II), complex with DCM (0.0.58 g, 0.079 mmol) and potassium phosphate (0.506 g, 2.385 mmol) were placed, and the vial was flushed with nitrogen. Then, 1,4-dioxane/water (4:1) (6 mL) was added and the mixture was purged with nitrogen and heated at 80 °C for 4 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified by silica gel column chromatography using 0-40% of EtOAc/PE to afford 2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-pyridin-2-

yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.16 g, 0.305 mmol, 38.4% yield) as a light yellow semisolid. MS ESI m/z 524.2 $(M+H)^+$.

351: 6-fluoro-7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to a well stirred solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-6-fluoro-7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]-pyridine (0.15 g, 0.286 mmol) in THF (3 mL) and water (1 mL) was added TFA (1.104 mL, 14.32 mmol) and the mixture was allowed to stirred at 70 °C for 12 h. Upon completion of the reaction, the solvents were evaporated, excess TFA was quenched with 10 mL of saturated $NaHCO_3$ solution and compound was extracted with EtOAc (30 mL X 2). The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified by preparative HPLC to yield 6-fluoro-7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.04 g, 0.090 mmol, 31.3% yield) as an off white solid.

Preparative HPLC method:

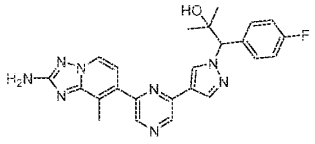
Diluent: THF:Water:ACN(40:10:40; Column: XBridge-C18(150 x19)mm, 5micron; Temperature: Ambient; Mobile phase A: 5mM Ammonium Formate in Water; Mobile phase B: Acetonitrile; Flow: 15mL/min; Time/Grad: 0/80,7/80.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.85 (dd, J = 0.80, 4.60 Hz, 1H), 8.50 (d, J = 0.00 Hz, 1H), 8.09 (s, 1H), 7.92 (t, J = 8.00 Hz, 1H), 7.74 (dd, J = 0.80, 8.00 Hz, 1H), 7.45 (dt, J = 2.40, 9.20 Hz, 2H), 7.33 (d, J = 7.60 Hz, 1H), 7.14-7.19 (m, 2H), 6.09 (s, 2H), 5.39-5.40 (m, 1H), 2.35-2.42 (m, 1H), 2.30 (d, J = 0.40 Hz, 3H), 2.10-2.16 (m, 1H), 0.82 (t, J = 7.60 Hz, 3H). MS ESI m/z 446.2 $(M+H)^+$.

Chiral purity: 97.8% ee; RT value: 4.896 min.

SFC Method: Column/dimensions: Cellulose-4 (250X4.6) mm, 5µm_0.2% Ammonia in methanol_40_10.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 40.0 %; Oven-B Temperature: 40°C; Oven B Column Position: 1; BPR Pressure: 100.0 bar; BPR Temperature: 50°C.

Example 352: 1-(4-(6-(2-amino-8-methyl-[1,2,4]-triazolo[1,5-a]-pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-1-(4-fluoro-phenyl)-2-methyl-propan-2-ol



352A: Methyl 2-(4-fluorophenyl)acetate:

In a 250 mL two neck RBF, to a well stirred solution of 2-(4-fluorophenyl)acetic acid (10 g, 64.9 mmol) in MeOH (100 mL) was added sulfuric acid (0.173 mL, 3.24 mmol) slowly at room temperature. The reaction mixture was heated at 80 °C for 6 h. Upon completion of the reaction, the mixture was quenched with saturated solution of $NaHCO_3$, diluted with water and compound was extracted by using DCM. The organic layers were separated, dried over anhydrous sodium sulphate and concentrated. The residue was purified by silica gel column chromatography with 0-40% of EtOAc/PE to yield methyl 2-(4-fluorophenyl)acetate (9 g, 53.5 mmol, 82% yield) as a colourless liquid, which was used directly in the next step.

352B: methyl 2-bromo-2-(4-fluorophenyl)acetate:

In a 250 mL two neck RBF, to a well stirred solution of methyl 2-(4-fluorophenyl)acetate (8.5 g, 50.5 mmol) in $CHCl_3$ (85 mL) was added *N*-bromosuccinimide (10.80 g, 60.7 mmol) and AIBN (0.830 g, 5.05 mmol) at room temperature. The reaction mixture was heated at 60 °C for 1.5 h. Upon completion of the reaction, the mixture was quenched with saturated solution of $NaHCO_3$ and compound was extracted by using DCM. The organic layers were separated, dried over anhydrous sodium sulphate and concentrated. The residue was purified by silica gel column chromatography with 0-30% of EtOAc/PE to yield methyl 2-bromo-2-(4-fluorophenyl)acetate (12 g, 48.6 mmol, 96% yield) as a colourless liquid, which was used directly in the next step.

352C: methyl 2-(4-fluorophenyl)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)acetate:

In a 500 mL two neck RBF, to a well stirred solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (7.54 g, 38.9 mmol) in ACN (160 mL) was added K_2CO_3 (13.43 g, 97 mmol) at room temperature. Methyl 2-bromo-2-(4-fluorophenyl)acetate (8 g, 32.4 mmol) was added and the mixture was heated at 80 °C for 5 h. Upon completion of the reaction, the mixture was quenched with ice water and compound was extracted by using DCM. The organic layers were separated, dried over anhydrous sodium sulphate and

concentrated. The residue was purified by silica gel column chromatography with 0-20% of EtOAc/PE to yield methyl 2-(4-fluorophenyl)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)acetate (7 g, 19.43 mmol, 60% yield) as a colourless semisolid. MS ESI m/z 361.2 $(M+H)^+$.

352D: 7-(6-chloropyrazin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo-[1,5-a]pyridine:

In a 40 mL vial, 2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (1.0 g, 2.84 mmol), 2-bromo-6-chloropyrazine (0.824 g, 4.26 mmol), [1,1'bis(diphenylphosphino)ferrocene]-dichloropalladium (II), complex with DCM (0.208 g, 0.284 mmol) and potassium phosphate (1.8 g, 8.52 mmol) were placed, and the vial was flushed with nitrogen. Then, 1,4-dioxane/water (20:1) (10 mL) was added and the mixture was purged with nitrogen and heated at 80 °C for 3 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified by silica gel column chromatography using 0-40% of EtOAc/PE to afford 7-(6-chloropyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.9 g, 2.444 mmol, 86% yield) as a white solid. MS ESI m/z 339.2 $(M+H)^+$.

352E: methyl 2-(4-(6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo-[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1*H*-pyrazol-1-yl)-2-(4-fluorophenyl)acetate:

In a 40 mL vial, methyl 2-(4-fluorophenyl)-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazol-1-yl)acetate (0.35 g, 0.972 mmol), 7-(6-chloropyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.3 g, 0.885 mmol), [1,1'bis-(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.034 g, 0.042 mmol) and potassium phosphate (0.619 g, 2.92 mmol) were placed, and the vial was flushed with nitrogen. Then, 1,4-dioxane/water (4:1) (10 mL) was added and the mixture was purged with nitrogen and heated at 80 °C for 4 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified by silica gel column chromatography using 0-100% of EtOAc/PE to afford methyl 2-(4-(6-(2-(2,5-dimethyl-

1*H*-pyrrol-1-yl)-8-methyl-[1,2,4]-triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1*H*-pyrazol-1-yl)-2-(4-fluorophenyl)acetate (0.35 g, 0.652 mmol, 67.1% yield) as an off white solid. MS ESI m/z 537.2 $(M+H)^+$.

352F: 1-(4-(6-(2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1*H*-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol:

In a 25 mL two neck RBF, to a well stirred solution of methyl 2-(4-(6-(2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-2-(4-fluorophenyl)acetate (0.2 g, 0.373 mmol) in THF (4 mL) was added methylmagnesium bromide (1.24 mL, 3.72 mmol) slowly at 0 °C under nitrogen atmosphere. The reaction mixture was allowed to warm up to room temperature and stirred for 1 h. Upon completion of the reaction, the mixture was quenched with acetic acid and diluted with water, and compound was extracted by using ethyl acetate. The organic layers were separated, dried over anhydrous sodium sulphate and concentrated. The residue was purified by silica gel column chromatography with 0-100% of EtOAc/PE to yield 1-(4-(6-(2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1*H*-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol (0.15 g, 0.280 mmol, 75% yield) as a light yellow semisolid. MS ESI m/z 537.2 $(M+H)^+$.

352: 1-(4-(6-(2-amino-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol; Peak 1 and Peak 2:

In a 20 mL microwave vial, to a well stirred solution of 1-(4-(6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1*H*-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol (0.15 g, 0.280 mmol) in EtOH (3 mL) and water (1 mL) was added hydroxylamine hydrochloride (0.388 g, 5.59 mmol) and the reaction mixture was allowed to stir at 100 °C for 4 h in the microwave. Upon completion of the reaction, the mixture was concentrated to half under nitrogen stream and submitted for preparative HPLC purification to yield 0.052 g of 1-(4-(6-(2-amino-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1*H*-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol as a racemate. The racemate was purified by SFC to separate enantiomer 1 and enantiomer 2.

Preparative HPLC method:

Diluent: THF:water:ACN(40:20:40); Column: Sunfire C18 (250 x19)mm, 5micron; Temperature: Ambient; Mobile phase A: 5mM Ammonium formate; Mobile phase B: ACN; Flow: 15mL/min; Time/Grad : 0/30, 15/70.

SFC method:

Column/dimensions: (R,R)WHELK-O1(250X4.6)mm,5u)_ACN IPA(50_50)_40_4.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 40.0 %; Oven-A Temperature: 40; Oven A Column Position: 1; BPR Pressure: 100.0 bar; BPR Temperature : 50 C.

352, Enantiomer 1:

1-(4-(6-(2-amino-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol (0.017 g, 0.037 mmol, 13.09 % yield) (Peak 1) as an off white solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.05 (s, 1H), 8.74 (s, 1H), 8.69 (s, 1H), 8.52 (dd, J = 0.40, 6.80 Hz, 1H), 8.25 (s, 1H), 7.70 (dt, J = 2.40, 9.20 Hz, 2H), 7.15-7.20 (m, 2H), 7.09 (d, J = 7.20 Hz, 1H), 6.09 (s, 2H), 5.47 (s, 1H), 5.07 (s, 1H), 2.53 (s, 3H), 1.13 (d, J = 24.80 Hz, 6H). MS ESI m/z 459.1 $(M+H)^+$.

Chiral purity: 100% ee; RT value: 4.416 min.

SFC Method: Column/dimensions: (R,R)WHELK-O1(250X4.6)mm,5u)_ACN IPA(50_50)_40_7.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 40.0 %; Oven-A Temperature: 40; Oven A Column Position: 1; BPR Pressure: 100.0 bar; BPR Temperature: 50 C.

353, Enantiomer 2:

1-(4-(6-(2-amino-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol (0.017 g, 0.036 mmol, 12.97 % yield) (Peak 2) as an off white solid.

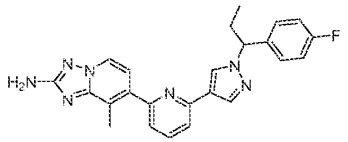
^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.04 (s, 1H), 8.74 (s, 1H), 8.68 (s, 1H), 8.52 (dd, J = 6.80, Hz, 1H), 8.24 (s, 1H), 7.68-7.71 (m, 2H), 7.15-7.19 (m, 2H), 7.08 (d, J = 7.20 Hz, 1H), 6.09 (s, 2H), 5.47 (s, 1H), 5.07 (s, 1H), 2.52 (s, 3H), 1.12 (d, J = 24.40 Hz, 6H). MS ESI m/z 459.2 $(M+H)^+$.

Chiral purity: 98.69% ee; RT value: 5.493 min.

SFC Method: Column/dimensions: (R,R)WHELK-O1(250X4.6)mm,5u)_ACN IPA(50_50)_40_6.lcd Flowrate: 3.0000 mL/min; Co-Solvent: 40.0 %; Oven-A

Temperature: 40; Oven A Column Position: 1; BPR Pressure: 100.0 bar; BPR Temperature: 50 C.

Example 354: 7-(6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methyl-[1,2,4]-triazolo[1,5-a]-pyridin-2-amine



354A: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, 2-bromo-6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridine (0.19 g, 0.527 mmol), 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.223 g, 0.633 mmol), [1,1'bis-(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.038 g, 0.053 mmol) and potassium phosphate (0.336 g, 1.582 mmol) were placed, and the vial was flushed with nitrogen. Then, 1,4-dioxane/water (4:1) (5 mL) was added and the mixture was purged with nitrogen and heated at 80 °C for 3 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified by reverse phase column chromatography to afford 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.15 g, 0.172 mmol, 32.6% yield) as a light brown semisolid. MS ESI m/z 506.2 $(M+H)^+$.

354: 7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-8-methyl-[1,2,4]-triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to a well stirred solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.15 g, 0.297 mmol) in THF (3 mL) and water (1mL) was added TFA (1.143 mL, 14.83 mmol) and the mixture was allowed to stirred at 70 °C for 12 h. Upon completion of the reaction, the solvents were evaporated, excess TFA was quenched with 20 mL of saturated $NaHCO_3$ solution and compound was extracted with ethyl acetate (30 mL X 2).

The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated.. The crude was purified by preparative HPLC to yield 7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.008 g, 0.018 mmol, 6.18 % yield) as an off white solid.

Preparative HPLC method:

Diluent: THF:water:ACN(50:10:40); Column: X-SELECT-C18 (250 x 19)mm, 5micron; Mobile phase A: 5mM AF in water; Mobile phase B: ACN; Flow: 13mL/min.

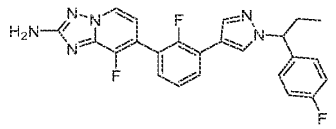
^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.51 (d, J = 0.40 Hz, 1H), 8.45 (dd, J = 0.80, 6.80 Hz, 1H), 8.11 (s, 1H), 7.89 (t, J = 7.60 Hz, 1H), 7.69 (dd, J = 0.80, 8.00 Hz, 1H), 7.40-7.46 (m, 3H), 7.15-7.19 (m, 2H), 7.01 (d, J = 6.80 Hz, 1H), 6.02 (s, 2H), 5.39-5.43 (m, 1H), 2.32-2.41 (m, 1H), 2.10-2.17 (m, 1H), 0.83 (t, J = 7.20 Hz, 3H).

Note: 3H of Me group is merged with DMSO-d_6 solvent. MS ESI m/z 428.2 $(M+H)^+$.

Chiral purity: 99.13% ee; RT value: 4.619 min.

SFC Method: Column/dimensions: Chiralpak IJ (250mmX4.6X5u)_0.2% NH_3 in IPA_30_2.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 30.0 %; Oven-B Temperature: 40°C; Oven B Column Position:1; BPR Pressure: 100.0 bar; BPR Temperature: 50 C.

Example 355: 8-fluoro-7-(2-fluoro-3-(1-(1-(4-fluoro-phenyl)propyl)-1H-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine



In a 20 mL vial, 4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-(1-(4-fluorophenyl)propyl)-1H-pyrazole (0.084 g, 0.198 mmol), 7-bromo-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.055 g, 0.238 mmol), [1,1'bis(diphenylphosphino)-ferrocene]dichloropalladium (II), complex with DCM (0.014 g, 0.02 mmol) and potassium phosphate (0.126 g, 0.595 mmol) were placed, and the vial was flushed with nitrogen. Then, 1,4-dioxane/water (4:1) (5 mL) was added and the mixture was purged with nitrogen and heated at 80 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified by the reverse phase preparative HPLC to yield 8-fluoro-7-(2-

fluoro-3-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)phenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.027 g, 0.057 mmol, 28.8% yield) as a white solid.

Reverse phase preparative HPLC method:

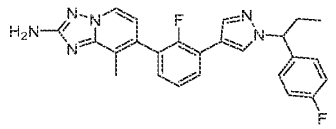
Diluent: THF:water:ACN(50:20:30); Column: Redisep 40gm C18, 20-40 micron; Mobile phase A: 5mM Ammonium formate in water; Mobile phase B: ACN; Instrument 1D: Teledyne Isco-Combi flash; Compound elution (%): 49% Acetonitrile/ 5mM Ammonium formate in water; Flow Rate: 20 ml/min.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.55 (d, J = 7.20 Hz, 1H), 8.39 (d, J = 2.00 Hz, 1H), 8.02 (s, 1H), 7.84-7.89 (m, 1H), 7.43-7.48 (m, 2H), 7.34-7.38 (m, 2H), 7.15-7.20 (m, 2H), 6.95 (t, J = 6.80 Hz, 1H), 6.29 (s, 2H), 5.42 (q, J = 6.40 Hz, 1H), 2.33-2.43 (m, 1H), 2.08-2.19 (m, 1H), 0.81-0.84 (m, 3H). MS ESI m/z 449.2 $(M+H)^+$.

Chiral purity: 99.75% ee; RT value: 6.861 min.

SFC Method: Column/dimensions: Chiralcel-OJ-H (250X4.6)mm 5µ_Methanol_25_4.lcd; Run Time: 6.00; Flowrate: 3.0000 mL/min; Co-Solvent:25.0 %; Make up Pump Flow: 0.5000 mL/min; Oven-A Temperature: 40°C; Column Number: 3; Oven-B Temperature: 40°C; Column Number: 1; BPR Pressure: 100.0 bar; BPR Temperature: 50 C.

Example 356: 7-(2-fluoro-3-(1-(1-(4-fluorophenyl)-propyl)-1H-pyrazol-4-yl)phenyl)-8-methyl-[1,2,4]-triazolo[1,5-a]-pyridin-2-amine



In a 20 mL vial, 4-(2-fluoro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazole (0.086 g, 0.202 mmol), 7-bromo-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.055 g, 0.242 mmol), [1,1'bis(diphenylphosphino)-ferrocene]dichloropalladium (II), complex with DCM (0.014 g, 0.02 mmol) and potassium phosphate (0.129 g, 0.606 mmol) were placed, and the vial was flushed with nitrogen. Then, 1,4-dioxane/water (4:1) (5 mL) was added and the mixture was purged with nitrogen and heated at 80 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified by the reverse phase preparative HPLC to yield 7-(2-fluoro-3-(1-

(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)phenyl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.011 g, 0.024 mmol, 11.65 % yield) as a white solid.

Reverse phase preparative HPLC method:

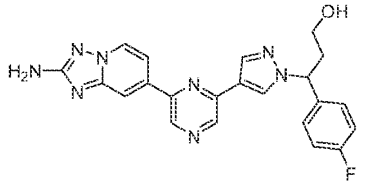
Diluent: THF:water:ACN(50:20:30); Column: Redisep 40gm C18, 20-40 micron; Mobile phase A: 5mM Ammonium formate in water; Mobile phase B: ACN; Instrument 1D: Teledyne Isco-Combi flash; Compound elution (%): 46% Acetonitrile/ 5mM Ammonium formate in water; Flow Rate: 20 ml/min.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.44 (dd, J = 0.40, 6.80 Hz, 1H), 8.36 (d, J = 2.00 Hz, 1H), 8.00 (s, 1H), 7.81-7.81 (m, 1H), 7.45 (dd, J = 5.60, 8.80 Hz, 2H), 7.30-7.34 (m, 1H), 7.15-7.23 (m, 3H), 6.77 (d, J = 6.80 Hz, 1H), 6.030 (s, 2H), 5.41 (q, J = 6.40 Hz, 1H), 2.32-2.42 (m, 1H), 2.24 9s, 3H), 2.08-2.19 (m, 1H), 0.82 (t, J = 7.60 Hz, 3H). MS ESI m/z 445.0 $(M+H)^+$.

Chiral purity: 99.75% ee; RT value: 5.751 min.

SFC Method: Column/dimensions: Chiralcel-OJ-H (250X4.6)mm 5µ_Methanol_25_3.lcd; Run Time : 6.00; Flowrate : 3.0000 mL/min; Co-Solvent :25.0 %; Make up Pump Flow : 0.5000 mL/min; Oven-A Temperature : 40°C; Column Number: 3; Oven-B Temperature : 40°C; Column Number: 1; BPR Pressure : 100.0 bar; BPR Temperature : 50°C.

Example 357: 3-(4-(6-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-3-(4-fluorophenyl)-propan-1-ol



357A: 1-(4-fluorophenyl)but-3-en-1-ol:

In a 250 mL two neck RBF, to a well stirred solution of 4-fluorobenzaldehyde (5 g, 40.3 mmol) in THF (100 mL) was added allylmagnesium bromide (40.3 mL, 40.3 mmol) slowly at -78 °C under nitrogen atmosphere. The reaction mixture was allowed to warm up to room temperature and stirred for 2 h. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layers were separated, dried over anhydrous sodium sulphate and concentrated. The residue was

purified by silica gel column chromatography 0-50% of EtOAc/Pet ether to yield 1-(4-fluorophenyl)but-3-en-1-ol (5 g, 30.1 mmol, 74.7 % yield) as a colourless liquid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.32-7.37 (m, 2H), 7.09-7.15 (m, 2H), 5.71-5.78 (m, 1H), 5.28 (d, J = 4.40 Hz, 1H), 4.94-5.00 (m, 2H), 4.60 (d, J = 4.80 Hz, 1H), 2.35-2.39 (m, 2H).

357B: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)but-3-en-1-yl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 150 mL sealed tube, 7-(6-(1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (1 g, 2.81 mmol), triphenylphosphine (3.68 g, 14.03 mmol), 1-(4-fluorophenyl)but-3-en-1-ol (4.66 g, 28.1 mmol) were taken, THF (50 mL) was added to the vial and reaction mixture was purged with nitrogen, with constant stirring, for 5 minutes. Then, Di-tert-butyl azodicarboxylate (3.23 g, 14.03 mmol) was added to the reaction mixture and reaction mixture was heated at 70 °C for 16 h under nitrogen atmosphere. Upon completion of the reaction, the reaction mixture was concentrated to yield crude, which was purified using silica gel column chromatography using 0-30% of EtOAc/Pet ether to afford 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)but-3-en-1-yl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.785 g, 1.167 mmol, 41.6 % yield) as a colourless liquid. MS ESI m/z 505.2 $(M+H)^+$.

357C: 4-(4-(6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-4-(4-fluorophenyl)butane-1,2-diol:

In a 150 mL seal tube, to a stirring solution of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)but-3-en-1-yl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (780 mg, 1.546 mmol) in acetone (40 mL) was added osmium tetroxide (0.040 mL, 0.031 mmol) and 4-methylmorpholine 4-oxide (0.572 mL, 2.78 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 16 h under nitrogen atmosphere. After 16 h, aqueous solution of $NaHSO_3$ (39%, 10 mL) was added and stirred at room temperature for 2 h. Upon completion of the reaction, the mixture was diluted with water and compound was extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4, filtered and solvents evaporated to yield crude material (0.6 g), which was used for next step without further purification. MS ESI m/z 539.2 $(M+H)^+$.

357D: 4 3-(4-(6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-3-(4-fluorophenyl)propanal:

In a 40 mL vial, to a stirring solution of 4-(4-(6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-4-(4-fluorophenyl)butane-1,2-diol (0.6 g, 1.114 mmol) in THF/H_2O (4:1) (20 mL) was added sodium periodate (429 mg, 2.005 mmol) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 16 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was diluted with water and compound was extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4, filtered and solvents evaporated to yield 3-(4-(6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-3-(4-fluorophenyl)-ropanal (0.215 g, 0.424 mmol, 38.1 % yield) as white solid. MS ESI m/z 507.2 $(M+H)^+$.

357E: 3-(4-(6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-3-(4-fluorophenyl)propan-1-ol:

In a 100 mL two neck RBF, to a well stirred solution of 3-(4-(6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-3-(4-fluorophenyl)-propanal (0.21 g, 0.415 mmol) in MeOH (30 mL) was added sodium borohydride (0.826 g, 21.83 mmol) slowly at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 1 h. Upon completion of the reaction, the reaction mixture was quenched with water, and compound was extracted by using DCM. The organic layers were separated, dried over anhydrous sodium sulphate and concentrated. The residue was purified by silica gel column chromatography with 0-50% of EtOAc/Pet ether to yield 3-(4-(6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-3-(4-fluorophenyl)propan-1-ol (0.1 g, 0.197 mmol, 47.4 % yield) as a white solid.

MS ESI m/z 509.2 $(M+H)^+$.

357: 3-(4-(6-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-3-(4-fluorophenyl)propan-1-ol (Racemate):

In a 20 mL vial, to a well stirred solution of 3-(4-(6-(2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-3-(4-fluorophenyl)propan-1-ol (100 mg, 0.197 mmol) in THF (5 mL) and water (1mL) was added TFA (0.75 mL, 9.83 mmol) and the mixture was allowed to stir at 70 °C for 16 h. Upon completion of the reaction, the solvents were evaporated, excess TFA was quenched with 10 mL of saturated $NaHCO_3$ solution and compound was extracted with DCM (30 mL

X 2). The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified by the preparative HPLC to yield 3-(4-(6-(2-amino-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyrazin-2-yl)-1H-pyrazol-1-yl)-3-(4-fluorophenyl)propan-1-ol (0.008 g, 0.018 mmol, 9.41 % yield) as a white solid.

Preparative HPLC method:

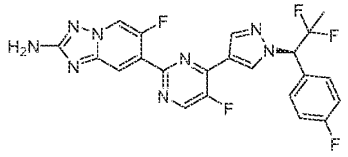
Diluent: THF:ACN:water(50:30:20); Column : X Select C18(250 x19)mm, 5micron; Temperature : Ambient; Mobile phase A: 10mM Ammoium Acetate in water; Mobile phase B: ACN; Flow :15mL/min; Time/Grad : 0/20,14/60.

SFC Method: Column/dimensions: Chiralcel-OJ-H (250X4.6)mm 5µ_0.1% NH_4OH in Methanol_40_8.lcd; Flowrate : 3.0000 mL/min; Co-Solvent : 40.0 %; Make up Pump Flow : 0.5000 mL/min; Oven-A Temperature : 40°C; Oven A Column Position: 3; BPR Pressure : 100.0; BPR Temperature: 50 C.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 1H), 9.00 (s, 1H), 8.81 (s, 1H), 8.68 (dd, J = 0.80, 7.20 Hz, 1H), 8.31 (s, 1H), 8.25 (dd, J = 0.80, 1.80 Hz, 1H), 7.75 (dd, J = 2.00, 6.80 Hz, 1H), 7.47-7.51 (m, 2H), 7.18-7.23 (m, 2H), 6.13 (s, 2H), 5.72 (dd, J = 6.00, 9.00 Hz, 2H), 4.70 (t, J = 4.80 Hz, 1H), 2.56-2.65 (m, 1H), 2.30 (t, J = 6.00 Hz, 1H).

Note: 2H of CH_2 is merging with DMSO-d_6. MS ESI m/z 431.0 $(M+H)^+$.

Example 358: (R)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-5-fluoropyrimidin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine



358A: (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoro-pyrimidin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridine :

In a 20 mL vial, to a solution of (2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid (0.222 g, 0.809 mmol) and (*R*)-2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoropyrimidine (0.200 g, 0.539 mmol) in 1,4-dioxane (8.0 mL) and H_2O (2.0 mL) was added potassium phosphate (0.344 g, 1.618 mmol). The reaction mixture was degassed for 10 minutes and [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.044 g, 0.054 mmol) was added to the reaction. The mixture was heated to 80 ºC and stirred for

2 hours until complete consumption of starting material as monitored by UPLC. The reaction mixture was diluted with EtOAc (40.0 mL) and water (10.0 mL). Aqueous layer was separated, and organic fraction was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (230:400 silica gel), with 0-30% EA/Pet Ether to yield (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoropyrimidin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridine (0.160 g, 0.263 mmol, 48.8 % yield) as white solid. MS ESI m/z 565.2 $(M+H)^+$.

358: (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoropyrimidin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to the solution of (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoropyrimidin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-6-fluoro-[1,2,4]-triazolo[1,5-a]pyridine (0.160 g, 0.283 mmol) in THF (3 mL) and water (1 mL) was added TFA (1.092 mL, 14.17 mmol) slowly at room temperature. The reaction mixture was heated to 70 °C and stirred for 16 hours until all the starting materials get consumed as monitored by UPLC. After completion of the reaction, TFA was removed under vacuum and the residue was neutralized with saturated solution of sodium bicarbonate (15 mL) and extracted with DCM (100 mL). The organic layer was dried over sodium sulphate and concentrated under vacuum. The residue was purified by prep HPLC to afford (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoropyrimidin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.025 g, 0.051 mmol, 17.95 % yield) as white solid.

Preparative HPLC method:

Diluent: THF:water:ACN(50:20:30); Column: X Bridge C18(19 x150)mm, 5micron; Temperature : Ambient; Mobile phase A: 0.1% formic acid; Mobile phase B: Acetonitrile; Flow :15mL/min; Time/Grad : 0/40,13/80.

^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 9.02-9.06 (m, 2H), 8.82 (s, 1H), 8.38 (s, 1H), 8.01 (d, J = 7.20 Hz, 1H), 7.75-7.78 (m, 2H), 7.27-7.32 (m, 2H), 6.43 (t, J = 13.20 Hz, 1H), 6.22 (s, 2H), 1.67 (t, J = 18.80 Hz, 3H).

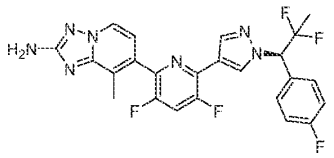
MS ESI m/z 487.1 $(M+H)^+$.

Chiral purity: 98.5% ee; RT:6.223 min.

SFC Method:

(R,R)WHELK-O1(250X4.6)mm,5u)_0.1% NH_4OH in methanol_40_20.lcd; Flowrate : 3.0000 mL/min; Co-Solvent : 40.0 %; Make up Pump Flow : 0.5000 mL/min; Oven-B Temperature : 40°C; Oven-B Column Position :1; BPR Pressure : 100.0 bar; BPR Temperature: 50 C.

Example 359: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-4-yl)-3,5-difluoropyridin-2-yl)-8-methyl-[1,2,4]-triazolo[1,5-a]pyridin-2-amine



359A: (*R*)-2-bromo-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-3,5-difluoropyridine:

In a 40 mL vial, to the solution of (*R*)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (1.0 g, 2.73 mmol) and 2,6-dibromo-3,5-difluoropyridine (0.894 g, 3.28 mmol), in 1,4-dioxane (12.0 mL)and H_2O (3.0 mL), was added potassium phosphate (1.739 g, 8.19 mmol). The reaction mixture was degassed for 10 minutes and [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.223 g, 0.273 mmol) was added. The mixture was heated to 80 °C and stirred for 2 hours until complete consumption of starting material as monitored by UPLC. Water was added and the mixture was extracted with ethyl acetate (200 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (230:400 silica gel) and 20% EA/Pet ether to give (*R*)-2-bromo-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-3,5-difluoropyridine (0.31 g, 0.488 mmol, 17.86 % yield) as colorless liquid. MS ESI m/z 432.0 $(M+H)^+$.

359B: (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-3,5-difluoropyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, to a solution of (2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid (0.141 g, 0.521 mmol) and (*R*)-2-bromo-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3,5-difluoropyridine (0.150 g, 0.347 mmol), in 1,4-dioxane (8.0 mL) and H_2O (2.0 mL) was added potassium

phosphate (0.221 g, 1.041 mmol). The reaction mixture was degassed for 10 minutes and [1,1'bis(diphenylphosphino)ferrocene]-dichloropalladium (II), complex with DCM (0.028 g, 0.035 mmol) was added. The mixture was heated to 80 °C and stirred for 2 h. Upon completion of reaction, the mixture was diluted with EtOAc and water. The organic layer was separated, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography with 0-30% EA/Pet Ether to yield (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-3,5-difluoropyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.146 g, 0.202 mmol, 58.3 % yield) as white solid. MS ESI m/z 578.2 $(M+H)^+$.

359: (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-3,5-difluoropyridin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to a solution of (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-3,5-difluoropyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-methyl-[1,2,4]-triazolo[1,5-a]pyridine (0.136 g, 0.235 mmol) in THF (3 mL), H_2O (1 mL) was added TFA (0.907 mL, 11.77 mmol) slowly at room temperature. The reaction mixture was heated to 70 °C and stirred for 16 hours until all the starting materials got consumed as monitored by UPLC. After completion of the reaction, TFA was removed under vacuum. The residue was neutralized with saturated solution of sodium bicarbonate (15 mL) and extracted with DCM (100 mL). The organic layer was dried over sodium sulphate and concentrated under vacuum. The residue was purified by prep HPLC to afford (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoropyrimidin-2-yl)-6-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.025 g, 0.051 mmol, 17.95 % yield) as white solid.

Preparative HPLC method:

Diluent: THF:water:ACN(50:20:30); Column: X Bridge C18(19 x150)mm, 5micron; Temperature : Ambient; Mobile phase A: 10mM Ammonium acetate in water; Mobile phase B: Acetonitrile; Flow :15mL/min; Time/Grad : 0/40,12/80.

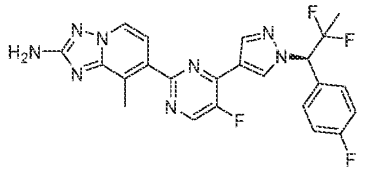
^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.49-8.54 (m, 2H), 8.16-8.21 (m, 2H), 7.72-7.75 (m, 2H), 7.25-7.29 (m, 2H), 6.92 (d, J = 6.00 Hz, 1H), 6.34 (t, J = 13.20 Hz, 1H), 6.09 (s, 2H), 2.33 (s, 3H), 1.65 (t, J = 19.20 Hz, 3H). MS ESI m/z 500.1 $(M+H)^+$.

Chiral purity: 96.9% ee; RT:3.200 min.

SFC Method:

Cellulose-4(250mmX4.6X5u) _0.1% NH_4OH in Methanol_40_27.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 40.0 %; Make up Pump Flow: 0.5000 mL/min; Oven-B Temperature : 40°C; Oven-B Column Position :6; BPR Pressure : 100.0 bar; BPR Temperature: 50 C.

Example 360: (R)-7-(4-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-4-yl)-5-fluoro-pyrimidin-2-yl)-8-methyl-[1,2,4]triazolo-[1,5-a]pyridin-2-amine



360A: (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoro-pyrimidin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to a solution of (2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid (0.150 g, 0.555 mmol) and (*R*)-2-chloro-4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoropyrimidine (0.206 g, 0.555 mmol) in 1,4-dioxane (8.0 mL) and H_2O (2.0 mL) was added potassium phosphate (0.354 g, 1.666 mmol). The reaction mixture was degassed for 10 minutes and [1,1'bis(diphenylphosphino)-ferrocene]dichloropalladium (II), complex with DCM (0.045 g, 0.056 mmol) was added. The mixture was heated to 80 °C and stirred for 2 h. Upon completion of reaction, the mixture was diluted with EtOAc and water. The organic layer was separated, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (230:400 silica gel), with 0-30% EA/Pet ether to yield (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoropyrimidin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.160 g, 0.214 mmol, 38.5 % yield) as white solid. MS ESI m/z 561.2 $(M+H)^+$.

360: (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoro-pyrimidin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to a solution of (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoropyrimidin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-methyl[1,2,4]-triazolo[1,5-a]pyridine (0.150 g, 0.268 mmol) in THF (3 mL), H_2O (1 mL) was added TFA

(1.031 mL, 13.38 mmol) slowly at room temperature. The reaction mixture was heated to 70 °C and stirred for 16 hours until all the starting materials get consumed as monitored by UPLC. After completion of the reaction, TFA was removed under vacuum. The residue was neutralized with saturated solution of sodium bicarbonate (15 mL) and extracted with DCM (100 mL). The organic layer was dried over sodium sulphate and concentrated under vacuum. The residue was purified by prep HPLC to afford (*R*)-7-(4-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-5-fluoropyrimidin-2-yl)-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.030 g, 0.062 mmol, 23.20 % yield) as white solid.

Preparative HPLC method:

Diluent: THF: water: ACN(50:20:30); Column: X Bridge C18(19 x150)mm, 5micron; Temperature : Ambient; Mobile phase A: 10mM Ammonium acetate in water; Mobile phase B: Acetonitrile; Flow :15mL/min; Time/Grad : 0/40,12/80.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.01 (d, J = 2.8 Hz, 1H), 8.79 (d, J = 1.2 Hz, 1H), 8.49 (dd, J = 0.40 Hz, 6.8 Hz, 1H), 8.37 (s, 1H), 7.75-7.78 (m, 2H), 7.42 (d, J = 6.80 Hz, 1H), 7.27-7.31 (m, 2H), 6.43 (t, J = 13.20 Hz, 1H), 6.08 (s, 2H), 2.72 (s, 3H), 1.67 (t, J = 19.20 Hz, 3H).

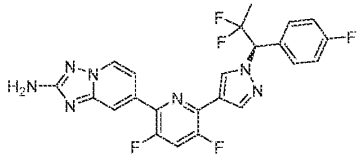
MS ESI m/z 483.1 $(M+H)^+$.

Chiral purity: 100% ee; RT:3.861 min.

SFC Method:

Cellulose-SC(250X4.6)mm 5μ_0.1% NH_4OH in Methanol_40_17.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 40.0 %; Make up Pump Flow : 0.5000 mL/min; Oven-B Temperature : 40°C; Oven-B Column Position :1; BPR Pressure : 100.0 bar; BPR Temperature: 50 C.

Example 361: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-4-yl)-3,5-difluoropyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine



361A: 7-(6-bromo-3,5-difluoropyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo-[1,5-a]pyridine:

In a 20 mL vial, to a solution of (2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid (0.5 g, 1.953 mmol) and 2,6-dibromo-3,5-difluoropyridine

(0.799 g, 2.93 mmol) in 1,4-dioxane (5 mL) and water (0.5 mL) was added potassium phosphate (1.24 g, 5.86 mmol). The reaction mixture was degassed for 10 minutes and [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.159 g, 0.195 mmol) was added to the reaction. The mixture was heated to 70 °C and stirred for 2 h. After completion of the reaction water was added and the mixture extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (230:400 silica gel), with 0-100% EA/Pet Ether to give 7-(6-bromo-3,5-difluoropyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.300 g, 0.742 mmol, 38.0 % yield). MS ESI m/z 404.0 $(M+H)^+$.

361B: (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-3,5-difluoropyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, to a solution of 7-(6-bromo-3,5-difluoropyridin- 2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.221 g, 0.546 mmol) and (*R*)-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.2 g, 0.546 mmol) in 1,4-dioxane (5 mL) and water (0.5 mL) was added potassium phosphate (0.348 g, 1.638 mmol). The reaction mixture was degassed for 10 minutes and [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.44 g, 0.055 mmol) was added. The mixture was heated to 80 °C and stirred for 2 h. Upon completion of reaction, the mixture was diluted with EtOAc and water. The organic fraction was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (230:400 silica gel), with 0-100% EA/Pet Ether to yield (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-3,5-difluoropyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.26 g, 0.461 mmol, 84 % yield) as off white solid. MS ESI m/z 564.2 $(M+H)^+$.

361: (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-3,5-difluoropyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 40 mL vial, to the solution of (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-3,5-difluoropyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.250 g, 0.444 mmol) in THF (6.0 mL) and water (2.0 mL) was added TFA (1.709 mL, 22.18 mmol) slowly at room temperature. The reaction mixture

was heated to 70 °C and stirred for 16 hours until all the starting materials get consumed as monitored by UPLC. After completion of the reaction, TFA was removed under vacuum. The residue was neutralized with saturated solution of sodium bicarbonate (25 mL) and extracted with DCM (100 mL). The organic layer was dried over sodium sulphate and concentrated under vacuum. The residue was purified by prep HPLC to afford (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-3,5-difluoropyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.032 g, 0.066 mmol, 14.77 % yield), as white solid.

Preparative HPLC method:

Diluent: THF: water: ACN(50:20:30); Column: X Bridge C18(19 x150)mm, 5micron; Temperature : Ambient; Mobile phase A: 10mM Ammonium acetate in water; Mobile phase B: Acetonitrile; Flow :15mL/min; Time/Grad : 0/80,12/80.

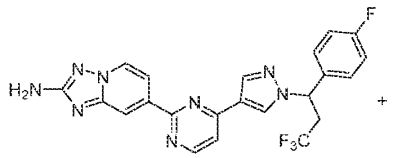
^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.68 (d, J = 0.80 Hz, 1H), 8.62 (s, 1H), 8.26 (s, 1H), 8.18 (t, J = 10.40 Hz, 1H), 7.90 (s, 1H), 7.74-7.77 (m, 2H), 7.49-7.51 (m, 1H), 7.26-7.30 (m, 2H), 6.36 (t, J = 13.20 Hz, 1H), 6.13 (s, 2H), 1.66 (t, J = 19.20 Hz, 3H). MS ESI m/z 486.2 $(M+H)^+$.

Chiral purity: 100% ee; RT:4.437 min.

SFC Method:

YMC Cellulose-SC (250mmX4.6X5u) _0.1% NH_4OH in methanol_40_3.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 40.0 %; Make up Pump Flow: 0.5000 mL/min; Oven-B Temperature : 40°C; Oven-B Column Position :6; BPR Pressure : 100.0 bar; BPR Temperature: 50 C.

Example 362: 7-(4-(1-(3,3,3-trifluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine



362A: 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(3,3,3-trifluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazole:

In a 100 mL vial, to a stirred solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (2 g, 10.31 mmol) and 3,3,3-trifluoro-1-(4-fluorophenyl)propan-1-ol (3.22 g, 15.46

mmol) in THF (30 mL) was added triphenylphosphine (5.41 g, 20.61 mmol). The reaction mixture was purged with nitrogen gas for 2 min and di-tert-butyl azodicarboxylate (4.75 g, 20.61 mmol) was added at ice cold temperature. The mixture was purged with nitrogen and stirred at room temperature for 16 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was evaporated. The residue was purified by silica gel column chromatography using 0-50% of EtOAc/Pet ether to afford 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(3,3,3-trifluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazole (1.5 g, 3.90 mmol, 37.9 % yield) as a light yellow solid. MS ESI m/z 385.2 $(M+H)^+$.

362B: 2-chloro-4-(1-(3,3,3-trifluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrimidine:

In a 40 mL vial, to a solution of 2,4-dichloropyrimidine (0.233 g, 1.562 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(3,3,3-trifluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazole (0.5 g, 1.301 mmol) in 1,4-dioxane (8 mL) and water (1 mL) was added tripotassium phosphate (0.829 g, 3.90 mmol). The reaction mixture was degassed for 10 minutes and [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.106 g, 0.130 mmol) was added. The mixture was heated to 80 °C and stirred for 2 h. Then the reaction mixture was diluted with EtOAc and water. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography, with 0-100% EA/Pet Ether to furnish 2-chloro-4-(1-(3,3,3-trifluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-pyrimidine (0.320 g, 0.863 mmol, 66.3 % yield), as off white solid. MS ESI m/z 371.0 $(M+H)^+$.

362C: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(4-(1-(3,3,3-trifluoro-1-(4-fluorophenyl)-propyl)-1*H*-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 40 mL vial, to a solution of 2-chloro-4-(1-(3,3,3-trifluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrimidine (0.310 g, 0.836 mmol) and (2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid (0.257 g, 1.003 mmol) in 1,4-dioxane (5 mL) and water (0.5 mL) was added potassium phosphate (0.532 g, 2.509 mmol).The reaction mixture was degassed for 10 minutes and [1,1'-bis(di-tertbutylphosphino)-ferrocene]dichloropalladium(II) (0.545 g, 0.084 mmol) was added. The mixture was heated to 80 °C and stirred for 2 h. Upon completion of reaction, the mixture was diluted with EtOAc (80.0 mL) and water (10.0 mL). the organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography, with 0-100% EA/Pet

Ether to yield 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(4-(1-(3,3,3-trifluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.345 g, 0.631 mmol, 75 % yield), as off-white solid. MS ESI m/z 547.2 $(M+H)^+$.

362: 7-(4-(1-(3,3,3-trifluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine; Peak-1 & Peak-2:

In a 40 mL vial, to the solution of 2-(2,5-dimethyl-1*H*pyrrol-1-yl)-7-(4-(1-(3,3,3-trifluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.3 g, 0.549 mmol) in THF (6 mL) and water (2 mL) was added TFA (2.114 mL, 27.4 mmol) slowly at room temperature. The reaction mixture was heated to 70 ºC and stirred for 16 h until all the starting materials get consumed as monitored by UPLC. TFA was removed under vacuum, the residue was neutralized with saturated solution of sodium bicarbonate (25 mL) and extracted with DCM (50 × 2 mL). The organic layer was dried over sodium sulphate and concentrated under vacuum. The residue was purified by the reverse phase preparative HPLC to obtain the racemate. The racemate was purified by SFC to separate enantiomer 1 and enantiomer 2.

Reverse phase preparative HPLC Purification method:

Diluent : THF: Acetonitrile (50:50), Column : Redisep 80g C18, 20-40 micron; Temperature : Ambient; Mobile phase A: 5mM Ammonium formate in water; Mobile phase B: ACN; Flow :40 mL/min.

Prep-SFC method:

Column/dimensions: Lux Cellulose-1(250 X 4.6)mm, 5 µm, Co solvent: 30 % of 0.2% NH_3 in MEOH, Flowrate : 100.0 mL/min; Back Pressure: 120bar; Temperature : 40°C.

362, Enantiomer 1:

7-(4-(1-(3,3,3-trifluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.035 g, 0.074 mmol, 13.55 % yield) (Peak 1) as light yellow solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.00 (s, 1H), 8.86 (d, J = 5.20 Hz, 1H), 8.67 (dd, J = 0.80, 7.2 Hz, 1H), 8.38-8.40 (m, 2H), 7.90 (dd, J = 2.00 Hz, 6.8 Hz, 1H), 7.72 (d, J = 5.60 Hz, 1H), 7.59-7.63 (m, 2H), 7.21-7.26 (m, 2H), 6.15 (s, 2H), 6.02-6.06 (m, 1H), 3.66-3.75 (m, 1H), 3.34-3.38 (m, 1H). MS ESI m/z 469.2 $(M+H)^+$.

Chiral purity: 98.9% ee; RT value: 4.789 min.

SFC Method: Cellulose-1(250mm×4.6×5u)_0.2% Ammonia in Methanol_30_3.lcd, Co solvent: 30%, Flowrate : 3.0000 mL/min; Back Pressure: 100bar; Temperature : 50°C;

363, Enantiomer 2:

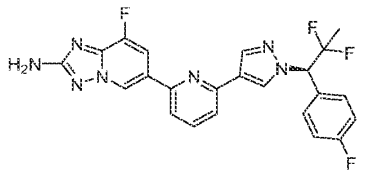
7-(4-(1-(3,3,3-trifluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.035 g, 0.074 mmol, 13.44 % yield) (Peak 2) as light yellow solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.00 (s, 1H), 8.86 (d, J = 5.20 Hz, 1H), 8.67 (dd, J = 0.40 Hz, 7.2 Hz, 1H), 8.38-8.40 (m, 2H), 7.90 (dd, J = 2.00, 6.8 Hz, 1H), 7.72 (d, J = 5.60 Hz, 1H), 7.59-7.63 (m, 2H), 7.22-7.26 (m, 2H), 6.15 (s, 2H), 6.03-6.06 (m, 1H), 3.66-3.75 (m, 1H), 3.32-3.34 (m, 1H). MS ESI m/z 469.2 $(M+H)^+$.

Chiral purity: 91.3% ee; RT value: 5.269 min.

SFC Method: Cellulose-1(250mmX4.6X5u) 0.2% Ammonia in Methanol_30_4.lcd, Co solvent: 30%, Flowrate: 3.0000 mL/min; Back Pressure: 100bar; Temperature : 50 °C.

Example 364: (R)-6-(6-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-3-yl)pyridin-2-yl)-8-fluoro-[1,2,4]-triazolo[1,5-a]pyridin-2-amine



364A: (*R*)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridine:

In a 40 mL vial, to a solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.346 g, 0.971 mmol) and (*R*)-2-bromo-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridine (0.385 g, 0.971 mmol) in 1,4-dioxane (8 mL) and water (2 mL) was added potassium phosphate (619 mg, 2.91 mmol). The reaction mixture was degassed for 10 minutes and [1,1'bis-(diphenylphosphino)ferrocene]dichloropalladium (II), complex with dichloromethane (0.79 g, 0.097 mmol) was added. The mixture was heated to 80 °C and stirred for 2 h. Upon completion of reaction, the mixture was diluted with EtOAc and water. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography, with 0-40% EA/Pet Ether to yield (*R*)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-

fluoro-[1,2,4]triazolo[1,5-a]pyridine (400 mg, 0.582 mmol, 59.9 % yield) as a colourless liquid. MS ESI m/z 546.2 $(M+H)^+$.

364: (*R*)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4 yl)pyridin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 40 mL vial, to a solution of (*R*)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H* pyrazol-4-yl)pyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]-pyridine (0.4 g, 0.582 mmol) in THF (9 mL) and water (3 mL) was added TFA (2.243 mL, 29.1 mmol). The reaction mixture was heated to 70 °C and stirred for 16 hours until all the starting materials got consumed as monitored by UPLC. TFA was removed under vacuum, the residue was neutralized with saturated solution of sodium bicarbonate (25 mL) and extracted with DCM (100 mL). The organic layer was dried over sodium sulphate and concentrated under vacuum. The residue was purified by reversed phase preparative HPLC to afford (*R*)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-8-fluoro-[1,2,4]-triazolo[1,5-a]pyridin-2-amine (0.040 g, 0.084 mmol, 14.37 % yield) as white solid.

Reverse phase preparative HPLC Method:

Diluent: THF: Acetonitrile (50:50); Column: Redisep 80gm C18, 20-40 micron; Temperature : Ambient; Mobile phase A: 5mM Ammonium Formate in water; Mobile phase B: Acetonitrile; Flow :60mL/min.

^{1}H-NMR (400 MHz, DMSO-*d*$_6$): 9.26 (d, J = 1.2 Hz, 1H), 8.71 (s, 1H), 8.33 (s, 1H), 8.23 (dd, J = 1.60, 12.00 Hz, 1H), 7.86-7.92 (m, 2H), 7.75-7.79 (m, 2H), 7.69 (dd, J = 1.60, 6.80 Hz, 1H), 7.25-7.30 (m, 2H), 6.32 (s, 2H), 6.26 (t, J = 12.8 Hz, 1H), 1.66 (t, J = 18.80 Hz, 3H).

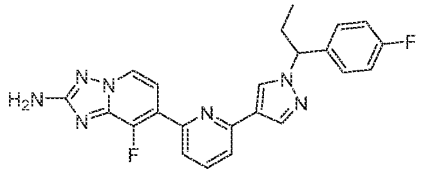
MS ESI m/z 468.1 $(M+H)^+$.

Chiral purity: 98.8% ee; RT: 2.859 min.

SFC Method:

(S,S)-WHELK-O1(150X4.6)mm 5µm_0.2% Ammonia in Methanol_30_2.lcd; Flowrate: 4.0000 mL/min; Co-Solvent: 30.0 %; Make up Pump Flow : 0.5000 mL/min; Oven-B Temperature : 40°C; Oven-B Column Position :4; BPR Pressure : 100.0 bar; BPR Temperature: 50 C.

Example 365: 8-fluoro-7-(6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-pyridin-2-yl)-[1,2,4]-triazolo[1,5-a]pyridin-2-amine



365A: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-fluoro-7-iodo-[1,2,4]triazolo[1,5-a]pyridine:

In a 30 mL microwave vial, to a stirred solution of 8-fluoro-7-iodo-[1,2,4]triazolo[1,5-a]pyridin-2-amine (1.5 g, 5.40 mmol) in toluene (8 mL) was added hexane-2,5-dione (3.69 g, 32.4 mmol) and acetic acid (1.544 mL, 27.0 mmol). The reaction mixture was heated to 140 °C in a microwave for 6 h. Upon completion of reaction, toluene was removed under vacuum. The residue was purified by silica gel column chromatography with 0-20% of EtOAc/Pet ether to afford 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-fluoro-7-iodo-[1,2,4]triazolo[1,5-a]pyridine (1.2 g, 3.10 mmol, 57.5 % yield) as white solid. MS ESI m/z 356.9 $(M+H)^+$.

365B: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL reaction vial, to a stirred solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-fluoro-7-iodo-[1,2,4]triazolo[1,5-a]pyridine (0.500 g, 1.404 mmol) and bis(pinacolato)diboron (0.713 g, 2.81 mmol) in 1,4-dioxane (10 mL) was added potassium acetate (0.413 g, 4.21 mmol). The reaction mixture was purged with nitrogen gas for 10 minutes. Then [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.115 g, 0.140 mmol) was added. The reaction mixture was purged with nitrogen gas for 2 min and allowed to stir at 100 °C for 8 h. Upon completion of the reaction, the mixture was filtered through celite. The celite pad was washed with ethyl acetate. The filtrate was concentrated and purified by reverse phase column chromatography to yield 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.300 g, 57.9% yield) as a white solid. MS ESI m/z 275.1 $(M+H)^+$.

365C: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-fluoro-7-(6-(1-(1-(4 fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 40 mL vial, to a solution of 2-bromo-6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-pyridine (0.15 g, 0.416 mmol) and (2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-fluoro-[1,2,4]-triazolo[1,5-a]pyridin-7-yl)boronic acid (0.137 g, 0.500 mmol) in 1,4-dioxane (8 mL), H_2O (2 mL), was added tripotassium phosphate (0.265 g, 1.249 mmol). The reaction mixture was degassed for 10 minutes and [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.034 g, 0.042 mmol) was added. The reaction mixture was heated to 80 °C and stirred for 2 hours until complete consumption of starting material as monitored by UPLC. The reaction mixture was diluted with EtOAc (80.0 mL) and water (10.0 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (230:400 silica gel), with 0-40% EA/Pet Ether to yield 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-fluoro-7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl) [1,2,4]triazolo[1,5-a]pyridine (0.153 g, 0.262 mmol, 62.9 % yield) as a white solid. MS ESI m/z 510.2 $(M+H)^+$.

365: 8-fluoro-7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]-triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to a solution of 2-(2,5-dimethyl-1*H*pyrrol-1-yl)-8-fluoro-7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.153 g, 0.300 mmol) in THF (6 mL) and water (2 mL) was added TFA (1.157 mL, 15.01 mmol). The reaction mixture was heated to 70 °C and stirred for 16 hours. After completion of the reaction, TFA was removed under vacuum, the residue was neutralized with saturated solution of sodium bicarbonate (25 mL) and extracted with DCM (100 mL). The organic layer was dried over sodium sulphate and concentrated under vacuum. The residue was purified by prep HPLC to afford 8-fluoro-7-(6-(1-(1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]-triazolo[1,5 a]pyridin-2-amine (0.012 g, 0.028 mmol, 9.21 % yield) as white solid.

Preparative HPLC method:

Diluent: THF: WATER: ACN(50:10:50); Column: X-select C18(150 x19)mm, 5micron; Temperature : Ambient; Mobile phase A: 10mM Ammonium formate in water; Mobile phase B: Acetonitrile; Flow :15mL/min; Time/Grad : 0/40,7/80.

^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 8.59 (s, 1H), 8.53 (d, J = 7.20 Hz, 1H), 8.17 (s, 1H), 7.94 (t, J = 7.60 Hz, 1H), 7.73-7.77 (m, 2H), 7.58 (t, J = 6.80 Hz, 1H), 7.45-7.49 (m, 2H),

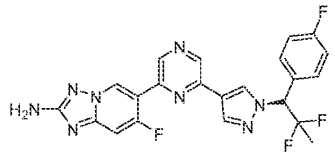
7.16-7.21 (m, 2H), 6.28 (s, 2H), 5.41-5.45 (m, 1H), 2.35-2.39 (m, 1H), 2.11-2.21 (m, 1H), 0.85 (t, J = 7.20 Hz, 3H). MS ESI m/z 432.1 $(M+H)^+$.

Chiral purity: 99.3% ee; RT: 3.701 min.

SFC Method:

Chiralpak IJ(250mmX4.6X5u)_0.1% TEA in Methanol_40_8.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 40.0 %; Make up Pump Flow : 0.5000 mL/min; Oven-B Temperature : 40°C; Oven-B Column Position :6; BPR Pressure : 100.0 bar; BPR Temperature: 50 C.

Example 366: (R)-6-(6-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-3-yl)pyrazin-2-yl)-7-fluoro-[1,2,4]-triazolo[1,5-a]pyridin-2-amine



366A: *O*-ethyl N-((5-bromo-4-fluoropyridin-2-yl)carbamothioyl)carbamate

In a 50 mL RBF, to a stirred solution of 5-bromo-4-fluoropyridin-2-amine (1.5g, 7.85 mmol) in 1,4-dioxane (10 mL) was added ethoxycarbonyl isothiocyanate (1.236 g, 9.42 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 h. Upon completion of the reaction, the mixture was evaporated and the crude material was washed with pentane. The filtrate was concentrated to give 2.4 g of **366A** as white solid, which was used for the next step without purification. MS ESI m/z 321.9 $(M+H)^+$.

366B: 6-bromo-7-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 250 mL RBF, to the stirred solution of **366A** (2.4 g, 7.45 mmol) in ethanol (40 mL) were added DIPEA (5.20 mL, 29.8 mmol) and hydroxylamine hydrochloride (2.59 g, 37.2 mmol). The reaction mixture was heated at 60 °C for 4 h. Upon completion of reaction, ethanol was removed under vacuum. The residue was dissolved with a minimum amount of DMSO and submitted for reverse phase purification to yield 6-bromo-7-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (1.2 g, 4.78 mmol, 64.1 % yield) as a brown solid. MS ESI m/z 230.9 $(M+H)^+$.

366C: 6-bromo-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-fluoro-[1,2,4]triazolo[1,5-a]pyridine:

In a 30 mL microwave vial, to a stirred solution of 6-bromo-7-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (1.2 g, 5.19 mmol) in toluene (8 mL) was added hexane-2,5-dione (3.56

g, 31.2 mmol) and acetic acid (1.487 mL, 26.0 mmol). The reaction mixture was heated at 140 °C in a microwave for 6 h. Upon completion of reaction, toluene was removed under vacuum. The residue was purified by silica gel column chromatography using 0-20% of EtOAc/Pet ether to afford 6-bromo-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-fluoro-[1,2,4]triazolo[1,5-a]pyridine (0.900 g, 2.73 mmol, 52.5 % yield) as white solid. MS ESI m/z 309.0 $(M+H)^+$.

366D: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL reaction vial, to a stirred solution of 6-bromo-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-fluoro-[1,2,4]triazolo[1,5-a]pyridine (0.300 g, 0.970 mmol) and bis(pinacolato)diboron (0.493 g, 1.941 mmol) in 1,4-dioxane (10 mL) was added potassium acetate (0.286 g, 2.91 mmol). The reaction mixture was purged with nitrogen gas for 10 minutes. Then [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.079 g, 0.097 mmol) was added. The reaction mixture was purged with nitrogen gas for 2 min and allowed to stir at 100 °C for 2 h. Upon completion of the reaction, the mixture was filtered through celite. The celite pad was washed with ethyl acetate. The filtrate was concentrated to give crude 6-bromo-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-fluoro-[1,2,4]triazolo[1,5-a]pyridine (0.300 g, 0.970 mmol) which was directly used without further purification. MS ESI m/z 275.2 $(M+H)^+$.

366E: 6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-fluoro-[1,2,4]triazolo[1,5-a]pyridine:

In a 40 mL vial, to a solution of (2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-fluoro-[1,2,4]triazolo[1,5-a]pyridin-6-yl)boronic acid (0.266 g, 0.582 mmol) and 2-chloro-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazine (0.205 g, 0.582 mmol) in 1,4-dioxane (8 mL) and H_2O (2 mL) was added potassium phosphate (0.371 g, 1.747 mmol). The reaction mixture was degassed for 10 minutes and [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.047 g, 0.058 mmol) was added. The mixture was heated to 80 °C and stirred for 2 h. Upon completion of reaction, the mixture was diluted with EtOAc and water. The organic layer was was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (230:400 silica gel), with 0-40% EA/Pet Ether to yield 6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1*H*-

pyrrol-1-yl)-7-fluoro-[1,2,4]triazolo[1,5-a]pyridine (0.230 g, 0.331 mmol, 56.9 % yield) as a dark brown liquid. MS ESI m/z 547.2 $(M+H)^+$.

366: 6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-7-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to a solution of 6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-fluoro-[1,2,4]triazolo[1,5-a]pyridine (0.230 g, 0.421 mmol) in THF (6 mL) and water (2 mL) was added TFA (1.621 mL, 21.04 mmol). The reaction mixture was heated to 70 °C and stirred for 16 hours. After completion of the reaction, TFA was removed under vacuum and the residue was neutralized with saturated solution of sodium bicarbonate (25 mL) and extracted with DCM (100 mL). The organic layer was dried over sodium sulphate and concentrated under vacuum. The residue was purified by Prep-HPLC to obtain (*R*)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-pyrazin-2-yl)-7-fluoro [1,2,4]triazolo[1,5-a]pyridin-2-amine (0.011 g, 0.023 mmol, 5.51 % yield) as white solid.

Prep-HPLC Purification Method:

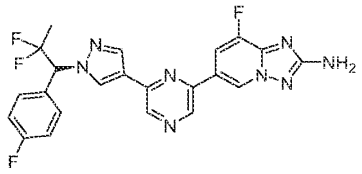
Diluent: THF: WATER: ACN(50:10:50); Column: X-select C18(250 x19)mm, 5micron; Temperature : Ambient; Mobile phase A: 5mM Ammonium formate in water; Mobile phase B: Acetonitrile; Flow :15mL/min; Time/Grad : 0/40,7/80.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.20 (d, J = 7.20 Hz, 1H), 9.06 (s, 1H), 8.82 (d, J = 2.4 Hz, 1H), 8.80 (s, 1H), 8.41 (s, 1H), 7.75-7.79 (m, 2H), 7.46 (d, J = 11.6 Hz, 1H), 7.26-7.31 (m, 2H), 6.26-6.30 (m, 3H), 1.67 (t, J =19.20 Hz, 3H). MS ESI m/z 469.1 $(M+H)^+$.

Chiral purity: 98.7% ee; RT: 3.264 min.

SFC Method: Column/Dimension: Chiralpak IB(250mmX4.6X5u)_0.2% NH3 in ACN MeOH(50_50)_35_10.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 35.0 %; Make up Pump Flow : 0.5000 mL/min; Oven-A Temperature : 40°C; Oven-A Column Position :1; BPR Pressure : 100.0 bar; BPR Temperature: 50 C.

Example 367: (R)-6-(6-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-3-yl)pyrazin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]-pyridin-2-amine



367A: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, 6-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridine (200 mg, 0.647 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.329 g, 1.29 mmol), [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.053 g, 0.065 mmol) and potassium acetate (0.19 g, 1.941 mmol) were placed, and the vial was flushed with nitrogen. Then, 1,4-dioxane (5 mL) was added and the mixture was purged with nitrogen and heated at 100 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was filtered through celite. The celite pad was washed with ethyl acetate. The filtrate was concentrated to give crude material (0.23 g), which was used for next step without further purification. MS ESI m/z 357.2 $(M+H)^+$.

367B: (*R*)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, 2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.23 g, 0.479 mmol), (*R*)-2-chloro-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazine (0.203 g, 0.575 mmol), [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.039 g, 0.048 mmol) and potassium phosphate (0.305 g, 1.437 mmol) were placed. The vial was flushed with nitrogen. Then, 1,4-dioxane/H_2O (4:1) (6 mL) was added, the mixture was purged with nitrogen and heated at 80 °C for 12 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified by silica gel column chromatography using 0-30% of EtOAc/Pet ether to afford (*R*)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-

fluoro-[1,2,4]triazolo[1,5-a]pyridine (0.17 g, 0.251 mmol, 52.4 % yield) as a colourless liquid. MS ESI m/z 547.2 $(M+H)^+$.

367: (*R*)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, to a well stirred solution of (*R*)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridine (0.17 g, 0.311 mmol) in THF (6 mL) and water (2 mL) was added TFA (1.198 mL, 15.55 mmol) and the mixture was allowed to stirred at 70 °C for 16 h. Upon completion of the reaction, the solvent was evaporated, excess TFA was quenched with 20 mL of saturated $NaHCO_3$ solution and compound was extracted with ethyl acetate (30 mL X 2). The organic layer was dried over anhydrous sodium sulphate, filtered and solvent evaporated. The residue was purified by reverse phase preparative HPLC, followed by preparative SFC purification to yield (*R*)-6-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.015 g, 0.032 mmol, 10.20 % yield) as an off white solid.

Reverse phase preparative HPLC method:

Diluent: THF:Water:ACN(50:20:30); Column: Redisep 80gm C18, 20-40 micron; Mobile phase A: 5mM Ammonium formate in water; Mobile phase B: Acetonitrile; Instrument 1D: Teledyne Isco-Combi flash; Compound elution (%): 42% Acetonitrile/ 5mM Ammonium formate in water; Flow Rate: 40 ml/min.

SFC Method: Column/dimensions: Chiralcel OJ-H(250 X 4.6)mm,5 µm; % CO2: 60%; % Co solvent: 40% of MEOH; Total Flow: 3.0g/min; Back Pressure: 100bar; Temperature : 40°C; UV: 220 nm.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.38 (s, 1H), 9.16 (s, 1H), 9.00 (s, 1H), 8.84 (s, 1H), 8.45 (s, 1H), 8.26 (d, J = 1.20 Hz, 1H), 7.78 (dd, J = 5.60, 8.80 Hz, 2H), 7.29 (t, J = 8.80 Hz, 2H), 6.42 (s, 2H), 6.28 (t, J = 13.60 Hz, 1H), 1.67 (t, J = 19.20 Hz, 3H). MS ESI m/z 469.0 $(M+H)^+$.

Chiral purity: 99.06% ee; RT value: 3.232 min.

SFC Method: Column/dimensions: Cellulose-1(250mmX4.6X5u)_0.1% NH4OH in Methanol_40_8.lcd; Flowrate : 4.0000 mL/min; Co-Solvent : 40.0 %; Make up Pump Flow : 0.5000 mL/min; Oven-B Temperature : 40°C; Oven-B Column Position:1; BPR Pressure : 100.0 bar; BPR Temperature : 50 C.

Example 368: 8-fluoro-7-(6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-pyrazin-2-yl)-[1,2,4]-triazolo[1,5-a]pyridin-2-amine

368A: 8-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 20 mL vial, 7-bromo-8-fluoro-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.1 g, 0.433 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.22 g, 0.886 mmol), [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.035 g, 0.043 mmol) and potassium acetate (0.127 g, 1.299 mmol) were placed. The vial was flushed with nitrogen. Then, 1,4-dioxane (5 mL) was added and the mixture was purged with nitrogen and heated at 100 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was filtered through celite. The celite pad was washed with ethyl acetate. The filtrate was concentrated to give crude product (0.1 g) which was used for next step without further purification. MS ESI m/z 353.2 $(M+H)^+$.

368: 8-fluoro-7-(6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]-triazolo[1,5-a]pyridin-2-amine:

In a 40 mL vial, 8-fluoro-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.12 g, 0.432 mmol), 2-chloro-6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazine (0.137 g, 0.432 mmol), [1,1'bis(diphenylphosphino)ferrocene]-dichloropalladium (II), complex with DCM (0.035 g, 0.043 mmol) and potassium phosphate (0.275 g, 1.295 mmol) were placed. The vial was flushed with nitrogen. Then, 1,4-dioxane/water (4:1) (5 mL) was added and the mixture was purged with nitrogen and heated at 80 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvent evaporated. The residue was purified by the reverse phase preparative HPLC to yield 8-fluoro-7-(6-(1-(1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.015 g, 0.034 mmol, 7.96 % yield) as an off white solid.

Reverse phase preparative HPLC method:

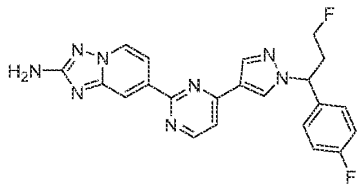
Diluent: THF:Water:ACN(50:10:40); Column: X-SELECT-C18 (250 x 19)mm, 5micron; Mobile phase A: 5mM AMOONIUM FORMATE in water; Mobile phase B: Acetonitrile; Flow:13mL/min.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.04 (s, 1H), 8.94 (s, 1H), 8.74 (s, 1H), 8.58 (s, 1H), 8.28 (s, 1H), 7.55 (t, J = 6.80 Hz, 1H), 7.46-7.49 (m, 2H), 7.17-7.21 (m, 2H), 6.34 (s, 2H), 5.45 (t, J = 6.40 Hz, 1H), 2.37-2.43 (m, 1H), 2.13-2.20 (m, 1H), 0.85 (t, J = 7.20 Hz, 3H). MS ESI m/z 433.0 $(M+H)^+$.

Chiral purity: 99.52% ee; RT value: 3.819 min.

SFC Method: Column/dimensions: Chiralcel OD-H(250mmX4.6X5u)_ACN IPA(50_50)_35_10.lcd; Flowrate : 3.0000 mL/min; Co-Solvent :35.0 %; Oven-B Temperature : 40°C; Oven B Column Position:1; BPR Pressure : 100.0 bar; BPR Temperature : 50 C.

Example 369: 7-(4-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine



369A: 1-(3-fluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole:

In a 40 mL vial, to the stirred solution of 3-fluoro-1-(4-fluorophenyl)propan-1-ol (1.0 g, 5.81 mmol) and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.127 g, 5.81 mmol) in toluene (20 mL) was added 2-(tributylphosphoranylidene)acetonitrile (4.21 g, 17.42 mmol) under nitrogen atmosphere. The reaction mixture was purged with nitrogen and heated at 110 °C for 3 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified by silica gel column chromatography using 0-20% of EtOAc/Pet ether to afford 1-(3-fluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.73 g, 1.824 mmol, 31.4 % yield) as a colourless liquid. MS ESI m/z 349.2 $(M+H)^+$.

369B: 2-chloro-4-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-pyrimidine (131):

In a 40 mL vial, 1-(3-fluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.25 g, 0.718 mmol), 2,4-dichloropyrimidine (0.128 g, 0.862 mmol), [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.058 g, 0.072 mmol) and potassium phosphate (0.457 g, 2.154 mmol) were placed. The vial was flushed with nitrogen. Then, 1,4-dioxane/water (10:1) (5 mL) was added and the mixture was purged with nitrogen and heated at 80 °C for 2 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvent evaporated. The residue was purified by silica gel column chromatography using 0-30% of EtOAc/Pet ether to afford 2-chloro-4-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidine (0.17 g, 0.467 mmol, 65.1 % yield) as a brown liquid. MS ESI m/z 335.0 $(M+H)^+$.

369C: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(4-(1-(3-fluoro-1-(4-fluorophenyl)-propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 40 mL vial, 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.182 g, 0.538 mmol), 2-chloro-4-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidine (0.15 g, 0.448 mmol), 1,1'-bis(di-t-butylphosphino)ferrocene palladium dichloride (0.029 g, 0.045 mmol) and tripotassium phosphate (0.285 g, 1.344 mmol) were placed. The vial was flushed with nitrogen. Then, 1,4-dioxane/water (10:1) (5 mL) was added and the mixture was purged with nitrogen and heated at 80 °C for 4 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvent evaporated. The residue was purified by silica gel column chromatography using 0-30% of EtOAc/Pet ether to afford 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(4-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.15 g, 0.247 mmol, 55.1 % yield) as a brown liquid. MS ESI m/z 511.2 $(M+H)^+$.

369: 7-(4-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]-triazolo[1,5-a]pyridin-2-amine; Peak 1 and Peak 2:

In a 20 mL vial, to a well stirred solution of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(4-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.13 g, 0.255 mmol) in THF (5 mL) and water (1 mL) was added TFA (0.981 mL, 12.73 mmol) and the reaction mixture was allowed to stir at 70 °C for 12 h. Upon completion of the reaction, the solvent was evaporated, quenched excess TFA with 10 mL of saturated $NaHCO_3$ solution and compound was compound was extracted with DCM (30 mL X 2). The organic layer was dried over anhydrous sodium sulphate, filtered and solvent evaporated. The residue was purified by the preparative HPLC to yield 0.02 g of 7-(4-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine as a racemate. Further, the racemate was purified by SFC to separate enantiomer 1 and enantiomer 2.

Preparative HPLC method:

Diluent: WATER:THF:ACN(10:60:30); Column : X-BRIDGE C18 (150 x19)mm, 5micron; Temperature: Ambient; Mobile phase A: 0.1% FORMIC ACID IN WATER; Mobile phase B: ACETONITRILE; Flow :15mL/min; Time/Grad : 0/40,7/80,10/80.

SFC method:

Column/dimensions: Chiralcel OJ-H(250 X 30)mm,5 µm; % CO2: 73%; % Co solvent: 27% of MeOH; Total Flow: 70.0g/min; Back Pressure: 100 bar; Temperature : 40°C; UV: 235 nm.

369, Enantiomer 1:

7-(4-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.008 g, 0.018 mmol, 7.22 % yield) (Peak 1) as a white solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 8.86 (d, J = 5.20 Hz, 1H), 8.66-8.67 (m, 1H), 8.39-8.40 (m, 2H), 7.90-7.92 (m, 1H), 7.72-7.73 (m, 1H), 7.52-7.55 (m, 2H), 7.20-7.25 (m, 2H), 6.14 (s, 2H), 5.75-5.79 (m, 1H), 4.28-4.53 (m, 2H), 2.79-2.89 (m, 1H), 2.60-2.64 (m, 1H). MS ESI m/z 433.0 $(M+H)^+$.

Chiral purity: 97.94% ee; RT value: 5.082 min.

SFC Method: Column/dimensions: Chiralcel-OJ-H (250X4.6)mm 5µ_Methanol_30_3.lcd; Flowrate : 3.0000 mL/min; Co-Solvent : 30.0 %; Make up Pump Flow : 0.5000 mL/min; Oven-A Temperature : 40°C; Oven A Column Position: 3; BPR Pressure: 100.0 bar; BPR Temperature : 50 C.

370, Enantiomer 2:

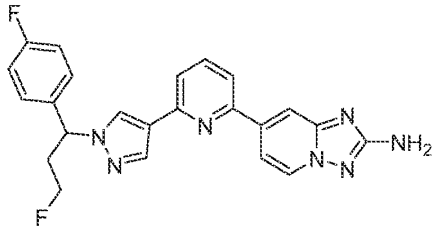
7-(4-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrimidin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.009 g, 0.021 mmol, 8.13 % yield) (Peak 2) as a white solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.96 (s, 1H), 8.86 (d, J = 5.20 Hz, 1H), 8.66-8.67 (m, 1H), 8.39-8.40 (m, 2H), 7.90-7.92 (m, 1H), 7.72-7.73 (m, 1H), 7.52-7.55 (m, 2H), 7.20-7.25 (m, 2H), 6.14 (s, 2H), 5.75-5.79 (m, 1H), 4.28-4.53 (m, 2H), 2.79-2.89 (m, 1H), 2.60-2.64 (m, 1H). MS ESI m/z 433.0 $(M+H)^+$.

Chiral purity: 94.02% ee; RT value: 5.591 min.

SFC Method: Column/dimensions: Chiralcel-OJ-H (250X4.6)mm 5µ_Methanol_30_3.lcd; Flowrate : 3.0000 mL/min; Co-Solvent : 30.0 %; Make up Pump Flow : 0.5000 mL/min; Oven-A Temperature : 40°C; Oven A Column Position: 3; BPR Pressure: 100.0 bar; BPR Temperature : 50 C.

Example 371: 7-(6-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-pyridin-2-yl)-[1,2,4]-triazolo[1,5-a]pyridin-2-amine



371A: 7-(6-chloropyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]-pyridine:

In a 20 mL vial, to the solution of (2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridin-7-yl)boronic acid (0.250 g, 0.976 mmol) and 2-bromo-6-chloropyridine (0.188 g, 0.976 mmol) in 1,4-dioxane (5 mL) and H_2O (0.5 mL) was added potassium phosphate (0.622 g, 2.93 mmol). The reaction mixture was degassed for 10 minutes and [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.071 g, 0.098 mmol) was added. The reaction mixture was heated to 80 °C and stirred for 2 h. Upon completion, the mixture was diluted with EtOAc and water. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography, with 0-30% EA/Pet Ether to yield 7-(6-chloropyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-

yl)-[1,2,4]-triazolo[1,5-a]pyridine (0.2 g, 0.574 mmol, 58.8 % yield) as a brown gummy liquid. MS ESI m/z 324.1 $(M+H)^+$.

371B: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(3-fluoro-1-(4-fluorophenyl)-propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 40 mL vial, to the solution of 7-(6-chloropyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.180 g, 0.556 mmol), 1-(3-fluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.194 g, 0.556 mmol) in 1,4-dioxane (5 mL) and H_2O (0.5 mL) was added potassium phosphate (0.354 g, 1.668 mmol). The reaction mixture was degassed for 10 minutes and [1,1'bis(diphenylphosphino)-ferrocene]dichloropalladium (II), complex with DCM (0.04 g, 0.056 mmol) was added. The above reaction mixture was heated to 80 °C and stirred for 2 h. Upon completion of the reaction, the mixture was diluted with EtOAc and water. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography with 0-100% EA/Pet Ether to yield 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.25 g, 0.422 mmol, 76 % yield) as a brown gummy liquid. MS ESI m/z 510.2 $(M+H)^+$.

371: 7-(6-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine; Peak-1 & Peak-2:

In a 40 mL vial, to the solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.25 g, 0.491 mmol) in THF (5 mL) and H_2O (0.5 mL) was added TFA (1.890 mL, 24.53 mmol) slowly at room temperature. The reaction mixture was heated to 70 °C and stirred for 16 h. After completion of the reaction, TFA was removed under vacuum and the residue was neutralized with saturated solution of sodium bicarbonate (25 mL) and extracted with DCM (50 × 2 mL). The organic layer was dried over sodium sulphate and concentrated under vacuum. The residue was purified by the preparative HPLC to afford racemic 7-(6-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.035 g) as a white solid. Further, the racemate was purified by SFC to separate enantiomer 1 and enantiomer 2.

Prep HPLC Method Information:

Diluent: THF:WATER:ACN(30:30:40); Column: XBridge Prep C8 (19x250mm) 5µ; Temperature: Ambient; Mobile phase A: 0.1% Formic Acid in Water; Mobile phase B: Acetonitrile; Flow :15 mL/min; Time/Grad : 0/30,7/70, 10/70.

Prep-SFC method:

Column/dimensions: Chiralpak AS-H (250 X 21)mm,5 µm, Co solvent: 30% of 0.1% NH4OH in MeOH, Total Flow: 70.0g/min; Back Pressure: 100 bar; Temperature : 40°C.

371, Enantiomer 1:

7-(6-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)[1,2,4]triazolo[1,5-a]pyridin-2-amine (17 mg, 0.038 mmol, 7.78 % yield) (peak-1) as an off-white solid.

^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 8.71 (s, 1H), 8.61(dd, d, J = 0.4, 6.8 Hz, 1H), 8.22 (s, 1H), 8.15-8.16 (m, 1H), 7.88-7.96 (m, 2H), 7.68-7.74 (m, 2H), 7.51-7.54 (m, 2H), 7.19-7.24 (m, 2H), 6.06 (s, 2H), 5.72-5.76 (m, 1H), 4.28-4.52 (m, 2H), 2.56-2.88 (m, 2H). MS ESI m/z 432.2 $(M+H)^+$.

Chiral purity: 100% ee; RT value: 4.171min.

SFC Method: Column/dimensions: CHIRALPAK-ASH (250X4.6) mm,5µm_0.1% NH$_4$OH in methanol_25_4.lcd, Co solvent: 25%, Flowrate : 3.0000 mL/min; Back Pressure: 100bar; Temperature : 50°C.

372, Enantiomer 2:

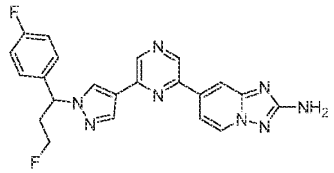
7-(6-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)[1,2,4]triazolo[1,5-a]pyridin-2-amine (14 mg, 0.032 mmol, 6.55 % yield) (peak-2) as an off-white solid.

^{1}H-NMR (400 MHz, DMSO-*d*$_6$): δ 8.71 (s, 1H), 8.61(d, J = 7.2 Hz, 1H), 8.22 (s, 1H), 8.15 (d, J = 1.2 Hz, 1H), 7.88-7.96 (m, 2H), 7.68-7.74 (m, 2H), 7.51-7.54 (m, 2H), 7.19-7.24 (m, 2H), 6.06 (s, 2H), 5.72-5.76 (m, 1H), 4.29-4.52 (m, 2H), 2.80-2.89 (m, 2H). MS ESI m/z 432.2 $(M+H)^+$.

Chiral purity: 98.6% ee; RT value: 4.576 min.

SFC Method: CHIRALPAK-ASH (250X4.6) mm,5µm_0.1% NH$_4$OH in methanol_25_3.lcd, Co solvent: 25%, Flowrate: 3.0000 mL/min; Back Pressure: 100bar; Temperature: 50 °C.

Example 373: 7-(6-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-pyrazin-2-yl)-[1,2,4]-triazolo[1,5-a]pyridin-2-amine



373A: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine:

In a 40 mL vial, to the solution of 7-(6-chloropyrazin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.2 g, 0.616 mmol), 1-(3-fluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.214 g, 0.616 mmol) in 1,4-dioxane (5 mL) and H_2O (0.1 mL) was added potassium phosphate (0.392 g, 1.847 mmol). The reaction mixture was degassed for 10 minutes and [1,1'bis(diphenylphosphino)ferrocene]-dichloropalladium (II), complex with DCM (0.045 g, 0.062 mmol) was added. The mixture was heated to 80 °C and stirred for 2 hours until complete consumption of starting material as monitored by UPLC. The reaction mixture was diluted with EtOAc and water. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography with 0-100% EA/Pet Ether to yield 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]-pyridine (0.2 g, 0.290 mmol, 47.1 % yield) as a brown gummy liquid. MS ESI m/z 511.2 $(M+H)^+$.

373: 7-(6-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]-triazolo[1,5-a]pyridin-2-amine; Peak-1 & Peak-2:

In a 20 mL vial, to the solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-7-(6-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.2 g, 0.392 mmol) in THF (5 mL) and H_2O (0.5 mL) was added TFA (1.509 mL, 19.59 mmol) slowly at room temperature. The reaction mixture was heated to 70 °C and stirred for 16 h until all the starting materials were consumed as monitored by UPLC. After completion of the reaction, TFA was removed under vacuum and the residue was neutralized with saturated solution of sodium bicarbonate (15 mL) and extracted with DCM (40 × 2 mL). The organic layer was dried over sodium sulphate and concentrated under vacuum. The residue was purified by the preparative HPLC to afford racemic 7-(6-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-[1,2,4]triazolo[1,5-a]pyridin-2-

amine (0.045 g) as a white solid. Further, the racemate was purified by SFC to separate enantiomer 1 and enantiomer 2.

Prep HPLC Method Information:

Diluent: THF:WATER:ACN(60:10:30); Column: XBridge Prep C8 (150x19mm) 5µ; Temperature: Ambient; Mobile phase A: 0.1% Formic Acid in Water; Mobile phase B: Acetonitrile; Flow:15 mL/min; Time/Grad : 0/30,7/70,10/70.

Prep-SFC method:

Column/dimensions: Chiralpak AS-H (250 X 21)mm,5 µm, Co solvent: 25% of 0.1% NH_4OH in MeOH, Total Flow: 70.0g/min, Back Pressure: 100 bar; Temperature : 40°C.

373, Enantiomer 1:

7-(6-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.02 g, 0.046 mmol, 11.70 % yield) (peak-1) as an off-white solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 1H), 9.00 (s, 1H), 8.85 (s, 1H), 8.69 (d, J = 6.8 Hz, 1H), 8.34 (s, 1H), 8.25 (d, J = 0.80 Hz, 1H), 7.75 (dd, J = 2.0, 8.80 Hz, 1H), 7.51-7.55 (m, 2H), 7.22-7.25 (m, 2H), 6.14 (s, 2H), 5.74- 5.78 (m, 1H), 4.29-4.52 (m, 2H), 2.81-2.90 (m, 1H), 2.58-2.63 (m, 1H). MS ESI m/z 433.1 $(M+H)^+$.

Chiral purity: 99.5% ee; RT value: 4.160 min.

SFC Method: CHIRALPAK-ASH (250X4.6) mm,5µm_0.1% NH_4OH in methanol_25_6.lcd, Co solvent: 25%, Flowrate : 3.0000 mL/min; Back Pressure: 100 bar; Temperature : 50°C.

374, Enantiomer 2:

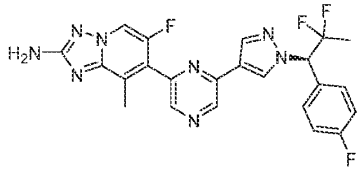
7-(6-(1-(3-fluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.019 g, 0.043 mmol, 11.04 % yield) as a white solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.20 (s, 1H), 9.00 (s, 1H), 8.85 (s, 1H), 8.69 (d, J = 6.80 Hz, 1H), 8.34 (s, 1H), 8.25 (d, J = 0.80 Hz, 1H), 7.75 (dd, J = 2.0, 8.80 Hz, 1H), 7.51-7.55 (m, 2H), 7.23-7.24 (m, 2H), 6.14 (s, 2H), 5.74- 5.78 (m, 1H), 4.27-4.52 (m, 2H), 2.79-2.90 (m, 1H), 2.56-2.63 (m, 1H). MS ESI m/z 433.1 $(M+H)^+$.

Chiral purity: 98.9% ee; RT value: 4.981 min.

SFC Method: CHIRALPAK-ASH (250X4.6) mm,5μm_0.1% NH_4OH in methanol_25_4.lcd, Co solvent: 25%, Flowrate: 3.0000 mL/min; Back Pressure: 100bar; Temperature : 50 °C.

Example 375: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-4-yl)pyrazin-2-yl)-6-fluoro-8-methyl-[1,2,4]triazolo[1,5-a]-pyridin-2-amine



375A: (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-6-fluoro-8-methyl-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, a mixture of 2-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)-6-(trimethylstannyl)pyrazine (0.298 g, 0.619 mmol) and 7-bromo-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-6-fluoro-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.200 g, 0.619 mmol) were placed in dioxane (2 mL). The reaction mixture was degassed for 10 minutes and [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.045 g, 0.062 mmol)) was added. The reaction mixture was heated to 100 °C and stirred for 12 hours until complete consumption of starting material as monitored by UPLC. The mixture was filtered through celite, washed with ethyl acetate (50 mL) and concentrated. The residue was purified by column chromatography with 0-40% EA/Pet ether to yield 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-6-fluoro-8- methyl-[1,2,4]triazolo[1,5-a]pyridine (0.140 g, 0.225 mmol, 36.3 % yield) as a yellow gummy liquid. MS ESI m/z 561.2 $(M+H)^+$.

375: (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-6-fluoro-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 40 mL vial, to the solution of 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-6-fluoro-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.140 g, 0.250 mmol) in THF (5 mL) and H_2O (1 mL) was added TFA (0.962 mL, 12.49 mmol). The reaction mixture was heated to 70 °C and stirred for 16 h. After completion of the reaction, TFA was removed under vacuum and the residue was neutralized with saturated solution of sodium bicarbonate (15 mL) and extracted with DCM (2 × 50 mL). The organic layer was dried over sodium sulphate and concentrated

under vacuum. The residue was purified by preparative HPLC to afford (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyrazin-2-yl)-6-fluoro-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.020 g, 0.042 mmol, 16.69 % yield) as a white solid.

Prep HPLC Method Information:

Diluent: THF:WATER:ACN(40:20:40); Column : x-select C18 (19 x150)mm, 5micron; Temperature : Ambient; Mobile phase A: 5mM Ammonium acetate in water; Mobile phase B: Acetonitrile; Flow :15 mL/min; Time/Grad : 0/30, 10/70.

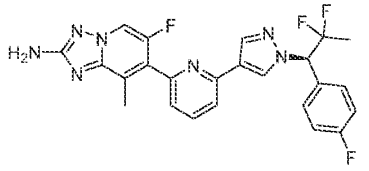
^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.13 (s, 1H), 8.93 (d, J = 4.40 Hz, 1H), 8.70 (s, 1H), 8.64 (d, J = 1.60 Hz, 1H), 8.33 (s, 1H), 7.73-7.76 (m, 2H), 7.25-7.29 (m, 2H), 6.31 (t, J = 13.20 Hz, 1H), 6.15 (s, 2H), 2.35 (s, 3H), 1.65 (t, J = 19.20 Hz, 3H). MS ESI m/z 483.1 $(M+H)^+$.

Chiral purity: 99.1% ee; RT: 4.896 min.

SFC Method:

Cellulose-4(250X4.6) mm,5µm_0.1% NH_4OH in methanol_50_18.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 50.0 %, Oven-B Temperature: 40°C; Oven-B Column Position :1; BPR Pressure: 100.0 bar; BPR Temperature: 50 C.

Example 376: (R)-7-(6-(1-(2,2-difluoro-1-(4-fluoro-phenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-6-fluoro-8-methyl-[1,2,4]triazolo[1,5-a]-pyridin-2-amine



376A: (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-6-fluoro-8-methyl-[1,2,4]triazolo[1,5-a]pyridine:

In a 20 mL vial, to the solution of 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-6-fluoro-8-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.2 g, 0.540 mmol) and 2-bromo-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridine (0.214 g, 0.540 mmol) in dioxane (5 mL) and water (0.5 mL) was added potassium phosphate (0.344 g, 1.621 mmol)). The reaction mixture was degassed for 10

minutes and [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.039 g, 0.054 mmol) was added. The mixture was heated to 80 °C and stirred for 2 h. Upon completion of the reaction, the mixture was diluted with EtOAc and water. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography with 0-30% EA/Pet Ether to yield 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-6-fluoro-8-methyl-[1,2,4]triazolo[1,5-a]pyridine (0.12 g, 0.167 mmol, 31.0 % yield) as a brown gummy liquid. MS ESI m/z 560.2 $(M+H)^+$.

376: (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-6-fluoro-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine:

In a 40 mL vial, to the solution of 7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-6-fluoro-8-methyl-[1,2,4]triazolo[1,5 a]pyridine (0.120 g, 0.214 mmol) in THF (5 mL) and H_2O (1 mL) was added TFA (0.826 mL, 10.72 mmol). The reaction mixture was heated to 70 °C and stirred for 16 hours until all the starting materials were consumed as monitored by UPLC. After completion of the reaction, TFA was removed under vacuum and the residue was neutralized with saturated solution of sodium bicarbonate (15 mL) and extracted with DCM (2 × 50 mL). The organic layer was dried over sodium sulphate and concentrated under vacuum. The reidue was purified by preparative HPLC to afford (*R*)-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1*H*-pyrazol-4-yl)pyridin-2-yl)-6-fluoro-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.018 g, 0.038 mmol, 17.63 % yield) as a white solid.

Prep HPLC Method Information:

Diluent: THF:WATER:ACN(10:30:60); Column : X-Bridge C18 (150 x19)mm, 5micron; Temperature : Ambient; Mobile phase A: 5mM Ammoniumformate; Mobile phase B: Acetonitrile; Flow :15 mL/min; Time/Grad : 0/40,12/80.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.85 (d, J = 0.80 Hz, 1H), 8.54 (s, 1H), 8.21 (s, 1H), 7.93-7.97 (m, 1H), 7.79-7.81 (m, 1H), 7.71-7.75 (m, 2H), 7.37 (d, J = 6.40 Hz, 1H), 7.24-7.36 (m, 2H), 6.23 (t, J = 12.80 Hz, 1H), 6.09 (s, 2H), 2.30 (s, 3H), 1.64 (t, J = 19.20 Hz, 3H).

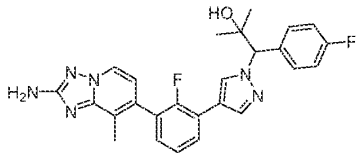
MS ESI m/z 483.1 $(M+H)^+$.

Chiral purity: 99.7% ee; RT: 2.720 min.

SFC Method:

Cellulose-4(250X4.6) mm, 5µm_0.1% NH4OH in methanol_50_17.lcd; Flowrate: 3.0000 mL/min; Co-Solvent: 50.0 %; Oven-B Temperature: 40°C; Oven-B Column Position :1; BPR Pressure: 100.0 bar; BPR Temperature: 50 C.

Example 377: 1-(4-(3-(2-amino-8-methyl-[1,2,4]-triazolo[1,5-a]pyridin-7-yl)-2-fluorophenyl)-1H-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol



Compound was prepared according to the methods described for **example 352**.

377, Enantiomer 1:

1-(4-(3-(2-amino-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)-2-fluorophenyl)-1H-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol (0.026 g, 0.055 mmol, 10.07 % yield) (Peak 1) as a white solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.44-8.46 (m, 2H), 8.03 (s, 1H), 7.81-7.85 (m, 1H), 7.66-7.69 (m, 2H), 7.31-7.35 (m, 1H), 7.14-7.26 (m, 3H), 6.78 (d, J = 6.80 Hz, 1H), 6.04 (s, 2H), 5.44 (s, 1H), 5.05 (s, 1H), 2.25 (s, 3H), 1.14 (s, 3H), 1.08 (s, 3H). MS ESI m/z 475.2 $(M+H)^+$.

Chiral purity: 100% ee; RT value: 3.23 min.

SFC Method: Column/dimensions: (R,R)WHELK-O1(250X4.6)mm,5u)_ACN IPA(50_50)_40_5.lcd; Flowrate: 3.0000 mL/min; Co-Solvent :40.0 %; Oven-A Temperature : 40; Oven A Column Position: 1; BPR Pressure : 100.0 bar; BPR Temperature: 50 C.

378, Enantiomer 2:

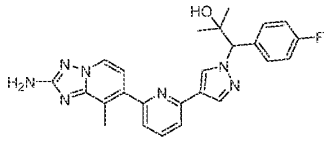
1-(4-(3-(2-amino-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)-2-fluorophenyl)-1H-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol (0.026 g, 0.055 mmol, 9.98 % yield) (Peak 2) as a white solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.44-8.46 (m, 2H), 8.03 (s, 1H), 7.81-7.85 (m, 1H), 7.66-7.69 (m, 2H), 7.31-7.35 (m, 1H), 7.14-7.26 (m, 3H), 6.78 (d, J = 6.80 Hz, 1H), 6.04 (s, 2H), 5.44 (s, 1H), 5.05 (s, 1H), 2.25 (s, 3H), 1.14 (s, 3H), 1.08 (s, 3H). MS ESI m/z 475.2 $(M+H)^+$.

Chiral purity: 99.1% ee; RT value: 3.957 min.

SFC Method: Column/dimensions: (R,R)WHELK-O1(250X4.6)mm,5u)_ACN IPA(50_50)_40_2.lcd; Flowrate: 3.0000 mL/min; Co-Solvent :40.0 %; Oven-A Temperature : 40; Oven A Column Position: 1; BPR Pressure : 100.0 bar; BPR Temperature : 50 C.

Example 379: 1-(4-(6-(2-amino-8-methyl-[1,2,4]triazolo-[1,5-a]pyridin-7-yl)-pyridin-2-yl)-1H-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol



Compound was prepared according to the methods described for **example 352**.

379, Enantiomer 1:

1-(4-(6-(2-amino-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyridin-2-yl)-1H-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol (0.026 g, 0.057 mmol, 15.18 % yield) (Peak 1) as a white solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.60 (s, 1H), 8.46 (d, J = 6.80 Hz, 1H), 8.13 (s, 1H), 7.90 (t, J = 7.60 Hz, 1H), 7.67-7.73 (m, 3H), 7.43 (dd, J = 0.80, 7.60 Hz, 1H), 7.15-7.19 (m, 2H), 7.02 (d, J = 7.20 Hz, 1H), 6.03 (s, 2H), 5.44 (s, 1H), 5.07 (s, 1H), 1.15 (s, 3H), 1.08 (s, 3H).

Note: 3H of CH_3 group is merging with DMSO-d_6. MS ESI m/z 458.2 $(M+H)^+$.

Chiral purity: 100% ee; RT value: 3.531 min.

SFC Method: Column/dimensions: (R,R)WHELK-O1(250X4.6)mm,5u)_ACN IPA(50_50)_40_4.lcd; Flowrate : 3.0000 mL/min; Co-Solvent :40.0 %; Oven-A Temperature : 40; Oven A Column Position: 1; BPR Pressure : 100.0 bar; BPR Temperature: 50 C.

380, Enantiomer 2:

1-(4-(6-(2-amino-8-methyl-[1,2,4]triazolo[1,5-a]pyridin-7-yl)pyridin-2-yl)-1H-pyrazol-1-yl)-1-(4-fluorophenyl)-2-methylpropan-2-ol (0.026 g, 0.057 mmol, 15.10 % yield) (Peak 2) as a white solid.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.60 (s, 1H), 8.46 (d, J = 6.80 Hz, 1H), 8.13 (s, 1H), 7.90 (t, J = 7.60 Hz, 1H), 7.67-7.73 (m, 3H), 7.43 (dd, J = 0.80, 7.60 Hz, 1H), 7.15-7.19

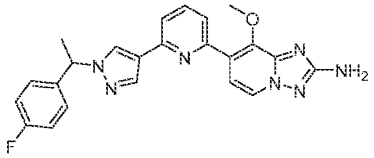
(m, 2H), 7.02 (d, J = 7.20 Hz, 1H), 6.03 (s, 2H), 5.44 (s, 1H), 5.07 (s, 1H), 1.15 (s, 3H), 1.08 (s, 3H).

Note: 3H of CH_3 group is merging with DMSO-*d*$_6$. MS ESI m/z 458.2 $(M+H)^+$.

Chiral purity: 98.50% ee; RT value: 4.256 min.

SFC Method: Column/dimensions: (R,R)WHELK-O1(250X4.6)mm,5u)_ACN IPA(50_50)_40_8.lcd; Flowrate : 3.0000 mL/min; Co-Solvent :40.0 %; Oven-A Temperature : 40; Oven A Column Position: 1; BPR Pressure : 100.0 bar; BPR Temperature: 50 C.

Example 381: 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1Hpyrazol-4-yl)-pyridin-2-yl)-8-methoxy-[1,2,4]-triazolo[1,5-a]pyridin-2-amine



381A: 1-(1-(4-fluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole:

In a 150 mL sealed tube, 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (8.31 g, 42.8 mmol), 1-(4-fluorophenyl)ethan-1-ol (6 g, 42.8 mmol) and triphenylphosphine (14.04 g, 53.5 mmol) were placed, THF (60 mL) was added and the reaction mixture was purged with nitrogen, with constant stirring, for 5 minutes. Then, di-tert-butyl azodicarboxylate (10.40 mL, 53.5 mmol) was added and the reaction mixture was stirred for 16 h at room temperature under nitrogen atmosphere. Upon completion of the reaction, the mixture was concentrated. The residue was purified by silica gel column chromatography using 0-100% of EtOAc/Pet ether to afford 1-(1-(4-fluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.65 g, 5.22 mmol, 12.19 % yield) as a colourless liquid. MS ESI m/z 317.2 $(M+H)^+$.

381B: 2-bromo-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridine:

In a 40 mL vial, 1-(1-(4-fluorophenyl)ethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.6 g, 5.06 mmol), 2,6-dibromopyridine (1.439 g, 6.07 mmol), [1,1'bis(diphenylphosphino)ferrocene]dichloropalladium (II), complex with DCM (0.413 g, 0.506 mmol) and potassium phosphate (3.22 g, 15.18 mmol) were placed. The vial was flushed with nitrogen. Then, 1,4-dioxane/water (9:1) (20 mL) was added and the mixture was purged with nitrogen and heated at 80 °C for 4 h under nitrogen atmosphere. Upon

completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvent evaporated. The residue was purified by silica gel column chromatography using 0-20% of EtOAc/Pet ether to afford 2-bromo-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridine (0.6 g, 1.120 mmol, 22.14 % yield) as a light yellow sticky liquid. MS ESI m/z 348.0 $(M+H)^+$.

381C: 2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-8-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4] triazolo[1,5-a]pyridine:

In a 40 mL vial, to a stirred solution of 7-bromo-2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (0.3 g, 0.934 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.356 g, 1.4 mmol) in 1,4-dioxane (15 mL) was added potassium acetate (0.275 g, 2.8 mmol). The reaction mixture was purged with nitrogen gas for 10 minutes. Then, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with DCM (0.041 g, 0.058 mmol) was added. The reaction mixture was purged with nitrogen gas for 2 min and allowed to stir at 100 °C for 2 h. Upon completion of the reaction, as monitored by UHPLC-MS, the mixture was filtered through celite. The celite pad was washed with ethyl acetate. The filtrate was concentrated to give 0.815 g crude, which was directly used for the next step without further purification. MS ESI m/z 369.2 $(M+H)^+$.

381D: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)-pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine:

In a 40 mL vial, 2-(2,5-dimethyl-1H-pyrrol-1-yl)-8-methoxy-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (0.3 g, 0.815 mmol), 2-bromo-6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridine (0.31 g, 0.896 mmol), [1,1'bis-(diphenylphosphino)-ferrocene]dichloropalladium (II), complex with DCM (0.036 g, 0.049 mmol) and potassium phosphate (0.426 g, 2.444 mmol) were placed. The vial was flushed with nitrogen. Then, 1,4-dioxane/water (20:1) (10 mL) was added and the mixture was purged with nitrogen and heated at 80 °C for 12 h under nitrogen atmosphere. Upon completion of the reaction, the mixture was quenched with water and compound was extracted by using ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, filtered and solvent evaporated. The residue was purified by silica gel column chromatography using 0-20% of EtOAc/Pet ether to afford 2-(2,5-dimethyl-1H-pyrrol-1-

yl)-7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (0.3 g, 0.461 mmol, 56.6 % yield) as a brown liquid. MS ESI m/z 508.0 $(M+H)^+$.

381: 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1Hpyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]-triazolo[1,5-a]pyridin-2-amine; Peak 1 and Peak 2:

In a 40 mL vial, to a well stirred solution of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridine (0.3 g, 0.591 mmol) in THF (10 mL) and water (1 mL) was added TFA (2.277 mL, 29.6 mmol) and the reaction mixture was allowed to stir at 70 °C for 12 h. Upon completion of the reaction, the solvent was evaporated, quenched excess TFA with 10 mL of saturated $NaHCO_3$ solution and compound was extracted with DCM (30 mL X 2). The organic layer was dried over anhydrous sodium sulphate, filtered and solvents evaporated. The residue was purified by the reversed phase preparative HPLC to yield 0.04 g of 7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine as a racemate. Further, the racemate was purified by SFC to separate enantiomer 1 and enantiomer 2.

Reverse phase preparative HPLC method:

Diluent: THF:Water:ACN(50:20:30); Column : Redisep 40gm C18 , 20-40 micron; Mobile phase A : 5mM Ammonium formate in water; Mobile phase B : Acetonitrile; Instrument 1D : Teledyne Isco-Combi flash; Compound elution (%) : 45% Acetonitrile/ 5mM Ammonium formate in water; Flow Rate : 30 ml/min.

SFC method:

Column/dimensions: (R,R)WHELK-O1(250X4.6)mm,5u)_Methanol_50_2.lcd; Flowrate: 3.0000 mL/min; Co-Solvent :50.0 %; Oven-A Temperature : 40; Oven A Column Position: 1

BPR Pressure: 100.0 bar; BPR Temperature : 50 C.

381, Enantiomer 1:

7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.007 g, 0.016 mmol, 2.68 % yield) (Peak 1) as a white solid.

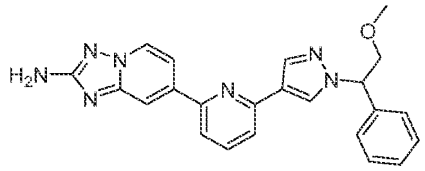
^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.52 (s, 1H), 8.36 (d, J = 6.80 Hz, 1H), 8.12 (s, 1H), 7.86 (t, J = 8.00 Hz, 1H), 7.77 (dd, J = 7.6, 0.80, Hz, 1H), 7.67 (dd, J = 8.00, 0.80, Hz, 1H),

7.42 (d, J = 6.80 Hz, 1H), 7.35-7.38 (m, 2H), 7.17 (t, J = 9.20 Hz, 2H), 6.10 (s, 2H), 5.71 (q, J = 7.2 Hz, 1H), 4.16 (s, 3H), 1.86 (d, J = 6.8 Hz, 3H). MS ESI m/z 430.0 $(M+H)^+$.
Chiral purity: 100% ee; RT value: 3.552 min.
SFC Method: Column/dimensions: (R,R)WHELK-O1(250X4.6)mm,5u)_Methanol_50_3.lcd
Flowrate: 3.0000 mL/min; Co-Solvent:50.0 %; Oven-A Temperature: 40;Oven A Column Position: 1; BPR Pressure : 100.0 bar; BPR Temperature: 50 C.

382, Enantiomer 2:

7-(6-(1-(1-(4-fluorophenyl)ethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-8-methoxy-[1,2,4]triazolo[1,5-a]pyridin-2-amine (0.007 g, 0.016 mmol, 2.67 % yield) (Peak 2) as a white solid.
^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.52 (s, 1H), 8.36 (d, J = 6.80 Hz, 1H), 8.12 (s, 1H), 7.86 (t, J = 8.00 Hz, 1H), 7.77 (dd, J = 7.6, 0.80, Hz, 1H), 7.67 (dd, J = 8.00, 0.80, Hz, 1H), 7.42 (d, J = 6.80 Hz, 1H), 7.35-7.38 (m, 2H), 7.17 (t, J = 9.20 Hz, 2H), 6.10 (s, 2H), 5.71 (q, J = 7.2 Hz, 1H), 4.16 (s, 3H), 1.86 (d, J = 6.8 Hz, 3H). MS ESI m/z 430.0 $(M+H)^+$.
Chiral purity: 99.62% ee; RT value: 4.832 min.
SFC Method: Column/dimensions: (R,R)WHELK-O1(250X4.6)mm,5u)_Methanol_50_3.lcd; Flowrate : 3.0000 mL/min; Co-Solvent :50.0 %; Oven-A Temperature : 40; Oven A Column Position: 1; BPR Pressure: 100.0 bar; BPR Temperature: 50 C.

Example 383: 7-(6-(1-(2-methoxy-1-phenylethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

383A:: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(2-methoxy-1-phenylethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine: In a 8 mL Chemglass reaction vial were combined 7-(6-(1H-pyrazol-4-yl)pyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (107 mg, 0.300 mmol), 2-methoxy-1-phenylethan-1-ol (100 mg, 0.660 mmol), triphenylphosphine (134 mg, 0.510 mmol) and anhydrous THF (2 mL)

with stirring. The resulting yellow solution was treated with di-*tert*-butyl azodicarboxylate (138 mg, 0.600 mmol) and the vial contents were stirred at RT overnight. The crude mixture was transferred to a 40 mL scintillation vial, then 2 g of Celite was added and the mixture was carefully concentrated in vacuo to provide a free-flowing powder. The dry-loaded material was purified by normal phase silica chromatography using a 12 g silica cartridge (elution 100% hexanes for 1 column volume (CV), then gradient 100% hexanes to 100% EtOAc over 15 CV, hold 100% EtOAc for 5 CV). Product eluted as the largest peak beginning at approximately 50% EtOAc in hexanes. The major peak fractions were combined and concentrated in vacuo to provide racemic 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(2-methoxy-1-phenylethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (147 mg, 0.300 mmol, quantitative). MS ESI m/z 490.3 $(M+H)^+$

383B:: 7-(6-(1-(2-methoxy-1-phenylethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate: A solution of racemic 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(2-methoxy-1-phenylethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (147 mg, 0.300 mmol) in EtOH (3 mL) was treated with hydroxylamine hydrochloride, 5M aqueous solution (1.20 mL, 6.00 mmol) and the mixture was heated to 100 °C for 6 h. The mixture was then concentrated under a gentle stream of nitrogen to provide a 2 mL sample which was purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 0.1% TFA; Mobile Phase B: 95:5 acetonitrile: water with 0.1% TFA; Gradient: 10-40% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). The material was further purified via preparative reverse phase chromatography with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 30-100% B over 10 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide racemic 7-(6-(1-(2-methoxy-1-phenylethyl)-1H-

pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (69.2 mg, 0.168 mmol, 56.1% yield).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.66 (s, 1H), 8.62 (d, *J*=6.9 Hz, 1H), 8.20 (s, 1H), 8.15 (s, 1H), 7.96 - 7.89 (m, 2H), 7.74 - 7.69 (m, 2H), 7.42 - 7.30 (m, 5H), 6.09 - 6.05 (m, 2H), 5.78 (dd, *J*=9.3, 4.9 Hz, 1H), 4.31 (t, *J*=9.8 Hz, 1H), 3.94 - 3.90 (m, 1H), 3.32 (s, 3H).

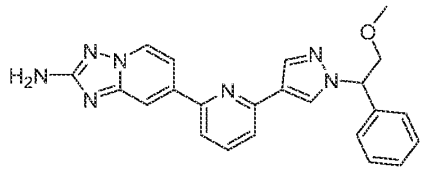
MS ESI m/z 412.3 $(M+H)^+$

383:: 7-(6-(1-(2-methoxy-1-phenylethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1: The racemic 7-(6-(1-(2-methoxy-1-phenylethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (69.2 mg, 0.168 mmol) obtained in the previous step was further separated into individual enantiomers via preparative chiral SFC chromatography with the following conditions: Column: Whelk-O1 (R,R), 21 mm x 250 mm, 5 μm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 20 mM ammonia; Elution Gradient: isocratic 30%B over 18 min; Flow Rate: 75 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (235 nm). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide 7-(6-(1-(2-methoxy-1-phenylethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (20.4 mg, 0.0496 mmol, 59.0% of the theoretical single isomer yield from preparative SFC).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.67 (s, 1H), 8.62 (d, *J*=7.0 Hz, 1H), 8.20 (s, 1H), 8.15 (s, 1H), 7.95 (d, *J*=7.7 Hz, 1H), 7.90 (t, *J*=7.6 Hz, 1H), 7.73 (d, *J*=7.0 Hz, 1H), 7.70 (d, *J*=7.3 Hz, 1H), 7.42 - 7.30 (m, 5H), 6.07 (s, 2H), 5.78 (dd, *J*=9.3, 4.5 Hz, 1H), 4.31 (t, *J*=9.8 Hz, 1H), 3.92 (dd, *J*=10.7, 4.7 Hz, 1H), 3.32 (s, 3H).

MS ESI m/z 412.1 $(M+H)^+$

Example 384: 7-(6-(1-(2-methoxy-1-phenylethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



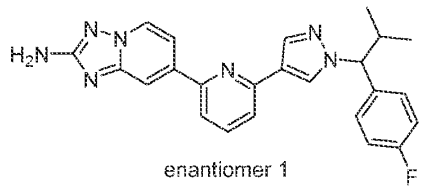
enantiomer 2

The title compound 7-(6-(1-(2-methoxy-1-phenylethyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (23.9 mg, 0.0576 mmol, 69.1% of the theoretical single isomer yield from preparative SFC) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of Example 383.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.67 (s, 1H), 8.62 (d, *J*=7.0 Hz, 1H), 8.20 (s, 1H), 8.15 (s, 1H), 7.95 (d, *J*=8.0 Hz, 1H), 7.90 (t, *J*=7.6 Hz, 1H), 7.73 (d, *J*=7.1 Hz, 1H), 7.70 (d, *J*=7.3 Hz, 1H), 7.42 - 7.30 (m, 5H), 6.07 (s, 2H), 5.78 (dd, *J*=9.5, 4.9 Hz, 1H), 4.31 (t, *J*=9.9 Hz, 1H), 3.92 (dd, *J*=10.4, 4.7 Hz, 1H), 3.32 (s, 3H).

MS ESI m/z 412.2 $(M+H)^+$

Example 385: 7-(6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

385A:: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine: In a 8 mL Chemglass reaction vial were combined 7-(6-(1H-pyrazol-4-yl)pyridin-2-yl)-2-(2,5-dimethyl-1H-pyrrol-1-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (107 mg, 0.300 mmol), benzenemethanol,4-fluoro-a-(1-methylethyl)- (111 mg, 0.660 mmol), triphenylphosphine (134 mg, 0.510 mmol) and anhydrous THF (2 mL) with stirring. The resulting yellow solution was treated with di-*tert*-butyl azodicarboxylate (138 mg, 0.600 mmol) and the vial contents were stirred at RT for 25 h. The crude mixture was transferred to a 40 mL scintillation vial, then 2 g of Celite was added and the mixture was carefully concentrated in vacuo to provide a free-flowing powder. The dry-loaded material was purified by normal phase silica chromatography using a 12 g silica cartridge (elution 100% hexanes for 1 column volume (CV), then gradient 100% hexanes to 100% EtOAc over 15 CV, hold 100% EtOAc for 5 CV). Product eluted as the largest peak beginning at approximately 50% EtOAc in hexanes. The major peak fractions were combined and concentrated in vacuo to provide racemic 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (122 mg, 0.241 mmol, 80 % yield).

MS ESI m/z 506.3 $(M+H)^+$

385B:: 7-(6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate: In a 4 mL Chemglass reaction vial, a mixture of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (121 mg, 0.239 mmol) in THF (1.8 mL) and Water (0.6 mL) was treated with TFA (461 µl, 5.98 mmol). The resulting yellow solution was heated at 70 °C overnight. The resulting mixture was concentrated under a gentle stream of nitrogen. The residue was dissolved in minimum DMF and filtered to provide a 2 mL sample which was purified by reverse phase preparative HPLC with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 26-56% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide racemic 7-(6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (28.5 mg, 0.0667 mmol, 27.2 % yield).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.65 - 8.61 (m, 2H), 8.18 - 8.14 (m, 2H), 7.96 - 7.87 (m, 2H), 7.72 (dd, *J*=7.0, 1.8 Hz, 1H), 7.69 - 7.63 (m, 3H), 7.20 (t, *J*=8.8 Hz, 2H), 6.09 - 6.05 (m, 2H), 5.09 (d, *J*=10.8 Hz, 1H), 2.81 - 2.74 (m, 1H), 0.81 (dd, *J*=19.1, 6.5 Hz, 6H).

MS ESI m/z 428.2 $(M+H)^+$

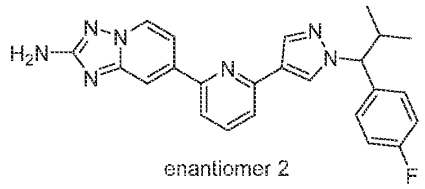
385:: 7-(6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1: The racemic 7-(6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (28.5 mg, 0.0667 mmol) obtained in the previous step was further separated into individual enantiomers via preparative chiral SFC chromatography with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 µm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1 % ammonium hydroxide; Elution Gradient: isocratic 20%B over 15 min; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (235 nm). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide 7-(6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-

[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (12.6 mg, 0.0295 mmol, 88.4 % of the theoretical single isomer yield from preparative SFC).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.65 - 8.61 (m, 2H), 8.20 - 8.14 (m, 2H), 7.95 - 7.87 (m, 2H), 7.72 (dd, *J*=7.0, 1.8 Hz, 1H), 7.69 - 7.63 (m, 3H), 7.20 (t, *J*=8.9 Hz, 2H), 6.10 - 6.05 (m, 2H), 5.11 - 5.06 (m, 1H), 2.82 - 2.74 (m, 1H), 0.81 (dd, *J*=19.1, 6.6 Hz, 6H).

MS ESI m/z 428.0 $(M+H)^+$

Example 386: 7-(6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



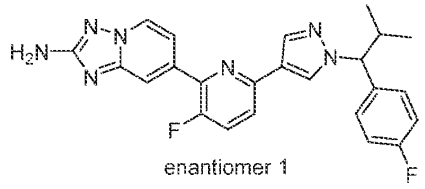
enantiomer 2

The title compound 7-(6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (11.5 mg, 0.0269 mmol, 80.7% of the theoretical single isomer yield from preparative SFC) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of **Example 385**.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.65 - 8.61 (m, 2H), 8.18 - 8.14 (m, 2H), 7.95 - 7.87 (m, 2H), 7.73 - 7.62 (m, 4H), 7.20 (t, *J*=8.3 Hz, 2H), 6.07 (s, 2H), 5.09 (d, *J*=11.1 Hz, 1H), 2.82 - 2.74 (m, 1H), 0.81 (dd, *J*=19.2, 6.5 Hz, 6H).

MS ESI m/z 428.2 $(M+H)^+$

Example 387: 7-(3-fluoro-6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1



enantiomer 1

387A:: 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(3-fluoro-6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine: In a 8 mL

Chemglass reaction vial were combined 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(3-fluoro-6-(1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (112 mg, 0.300 mmol), benzenemethanol,4-fluoro-a-(1-methylethyl)- (111 mg, 0.660 mmol), triphenylphosphine (134 mg, 0.510 mmol) and anhydrous THF (2 mL) with stirring. The resulting light brown suspension was treated with di-*tert*-butyl azodicarboxylate (138 mg, 0.600 mmol) which instantly resulted in a light brown solution, and the vial contents were stirred at RT for 25 h. The crude mixture was transferred to a 40 mL scintillation vial, then 2 g of Celite was added and the mixture was carefully concentrated in vacuo to provide a free-flowing powder. The dry-loaded material was purified by normal phase silica chromatography using a 12 g silica cartridge (elution 100% hexanes for 1 column volume (CV), then gradient 100% hexanes to 100% EtOAc over 15 CV, hold 100% EtOAc for 5 CV). Product eluted as the largest peak beginning at approximately 50% EtOAc in hexanes. The major peak fractions were combined and concentrated in vacuo to provide racemic 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(3-fluoro-6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (168 mg, quantitative yield asssumed) as an off-white glassy solid.

MS ESI m/z 524.3 $(M+H)^+$

387B:: 7-(3-fluoro-6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine racemate: In a 4 mL Chemglass reaction vial, a mixture of 2-(2,5-dimethyl-1H-pyrrol-1-yl)-7-(3-fluoro-6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridine (168 mg, 0.300 mmol) in THF (2.25 mL) and Water (0.75 mL) was treated with TFA (0.6 mL, 7.5 mmol). The resulting yellow solution was heated at 70 °C overnight. The resulting mixture was concentrated under a gentle stream of nitrogen. The residue was dissolved in minimum DMF and filtered to provide a 2 mL sample which was purified by reverse phase preparative HPLC with the following conditions: Column: Waters XBridge C18, 19 mm x 200 mm, 5 µm particles; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 27-57% B over 20 min; Flow Rate: 20 mL/min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide racemic

7-(3-fluoro-6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (45.8 mg, 0.103 mmol, 34.3 % yield).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.66 (d, *J*=7.0 Hz, 1H), 8.58 (s, 1H), 8.13 (s, 1H), 7.94 (s, 1H), 7.87 (t, *J*=9.4 Hz, 1H), 7.78 (dd, *J*=8.8, 3.0 Hz, 1H), 7.63 (dd, *J*=8.2, 5.6 Hz, 2H), 7.55 (d, *J*=7.2 Hz, 1H), 7.20 (t, *J*=8.7 Hz, 2H), 6.12 (s, 2H), 5.08 (d, *J*=10.7 Hz, 1H), 2.80 - 2.72 (m, 1H), 0.80 (dd, *J*=18.2, 6.5 Hz, 6H).

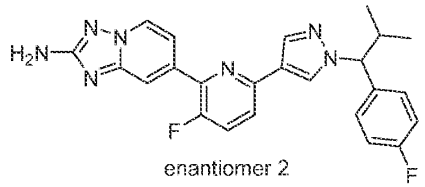
MS ESI m/z 446.3 $(M+H)^+$

387:: 7-(3-fluoro-6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1: The racemic 7-(3-fluoro-6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (45.8 mg, 0.103 mmol) obtained in the previous step was further separated into individual enantiomers via preparative chiral SFC chromatography with the following conditions: Column: Daicel Chiralcel OJ-H, 30 mm x 250 mm, 5 μm particles; Mobile Phase A: supercritical CO_2; Mobile Phase B: MeOH with 0.1 % ammonium hydroxide; Elution Gradient: isocratic 20%B over 15 min; Flow Rate: 100 mL/min; Column Temperature: 40 °C. Fraction collection was triggered by UV (235 nm). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide 7-(3-fluoro-6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 1 (19.5 mg, 0.0438 mmol, 85.2 % of the theoretical single isomer yield from preparative SFC).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.66 (d, *J*=7.0 Hz, 1H), 8.58 (s, 1H), 8.13 (s, 1H), 7.94 (s, 1H), 7.87 (dd, *J*=11.4, 8.7 Hz, 1H), 7.78 (dd, *J*=8.5, 3.1 Hz, 1H), 7.63 (dd, *J*=8.5, 5.7 Hz, 2H), 7.55 (d, *J*=7.2 Hz, 1H), 7.20 (t, *J*=8.9 Hz, 2H), 6.14 - 6.10 (m, 2H), 5.08 (d, *J*=10.8 Hz, 1H), 2.80 - 2.72 (m, 1H), 0.80 (dd, *J*=18.1, 6.6 Hz, 6H).

MS ESI m/z 446.2 $(M+H)^+$

Example 388: 7-(3-fluoro-6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2



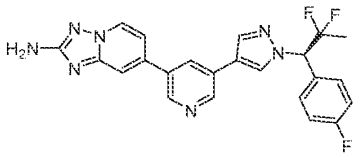
enantiomer 2

The title compound 7-(3-fluoro-6-(1-(1-(4-fluorophenyl)-2-methylpropyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine enantiomer 2 (19.6 mg, 0.0440 mmol, 85.6 % of the theoretical single isomer yield from preparative SFC) was obtained as the second eluting enantiomer from the preparative SFC column in the preparation of **Example 387**.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.66 (d, *J*=7.0 Hz, 1H), 8.58 (s, 1H), 8.13 (s, 1H), 7.94 (s, 1H), 7.86 (dd, *J*=11.3, 8.7 Hz, 1H), 7.78 (d, *J*=8.4 Hz, 1H), 7.63 (dd, *J*=8.7, 5.7 Hz, 2H), 7.55 (br d, *J*=7.3 Hz, 1H), 7.19 (t, *J*=8.9 Hz, 2H), 6.15 - 6.10 (m, 2H), 5.07 (d, *J*=10.8 Hz, 1H), 2.80 - 2.72 (m, 1H), 0.80 (dd, *J*=18.1, 6.5 Hz, 6H).

MS ESI m/z 446.2 $(M+H)^+$

Example 389: *(R)*-7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



389A:: *tert*-butyl *(R)*-(*tert*-butoxycarbonyl)(7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: In a 8 mL Chemglass pressure vial were combined *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (179 mg, 0.390 mmol) and 3-bromo-5-chloropyridine (75.0 mg, 0.390 mmol) in 1,4-dioxane (0.7 mL). To the mixture was added potassium phosphate tribasic, 2M aqueous solution (1.17 mL, 2.34 mmol). The resulting mixture was sparged with a gentle stream of nitrogen through a needle with stirring for 10 min, followed by addition of dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (15.9 mg, 0.0190 mmol). The mixture was again sparged with a stream of nitrogen with stirring for 5 min, and the vial was capped and heated to 60 °C for 6 h when the reaction was determined to be complete by LCMS. To this crude mixture was then added *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (143 mg, 0.390 mmol) dissolved in 1,4-dioxane (0.7 mL). The resulting mixture was gently sparged with nitrogen for a few minutes, and additional dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (15.9 mg, 0.0190 mmol)

was added and the mixture was sparged with nitrogen for a few more minutes before the reaction vial was sealed and heated 70 °C for 15 h. The aqueous phase was discarded and the organic phase was passed through a short plug of Celite and eluted with EtOAc. The eluted crude material was concentrated in vacuo to a dark brown residue which was dissolved in minimal DCM and loaded atop a hexanes preequilibrated 25g silica cartridge. Elution with 0.5 column volumes of hexanes, then gradient 100% hexanes to 100% EtOAc over 14 column volumes, hold 100% EtOAc for 6 column volumes provided the desired *tert*-butyl *(R)*-(*tert*-butoxycarbonyl)(7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (89.4 mg, 0.138 mmol, 35.3 % yield) as a yellow solid.

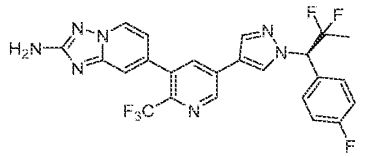
MS ESI m/z 650.3 $(M+H)^+$

389:: *(R)*-7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: A solution of *tert*-butyl *(R)*-(*tert*-butoxycarbonyl)(7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (89.4 mg, 0.138 mmol) in DCM (2 mL) was treated with TFA (1.0 mL, 13.0 mmol). The mixture was stirred overnight at RT. The mixture was concentrated under a gentle stream of nitrogen to a residue. The residue was dissolved in minimum DMF and filtered to give a 2 mL sample which was purified by reverse phase preparative HPLC with the following conditions: Column: XBridge C18, 19 mm x 200 mm, 5 µm particles; Flow Rate: 20 mL/min; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 17-47% B over 20 min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide *(R)*-7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (15.1 mg, 0.0336 mmol, 23.1 % yield).

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.94 (d, *J*=1.7 Hz, 1H), 8.89 - 8.86 (m, 1H), 8.70 - 8.65 (m, 2H), 8.48 (s, 1H), 8.30 (s, 1H), 7.89 (s, 1H), 7.77 (br dd, *J*=8.3, 5.8 Hz, 2H), 7.40 - 7.36 (m, 1H), 7.29 (t, *J*=8.8 Hz, 2H), 6.26 - 6.18 (m, 1H), 6.08 (s, 2H), 1.67 (br t, *J*=19.0 Hz, 3H).

MS ESI m/z 450.1 $(M+H)^+$

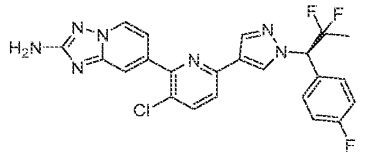
Example 390: *(R)*-7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-(trifluoromethyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



The title compound *(R)*-7-(5-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-2-(trifluoromethyl)pyridin-3-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (82.6 mg, 0.160 mmol, 41.6 % yield over 2 steps) was obtained via a similar procedure as that described for **Example 389**, where 3-bromo-5-chloro-2-(trifluoromethyl)pyridine was substituted for 3-bromo-5-chloropyridine in step **389A**.

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 9.11 (s, 1H), 8.76 (s, 1H), 8.66 (d, *J*=6.9 Hz, 1H), 8.34 (s, 1H), 8.31 (s, 1H), 7.75 (dd, *J*=8.3, 5.6 Hz, 2H), 7.43 (s, 1H), 7.30 - 7.25 (m, 2H), 6.92 (dd, *J*=6.8, 1.4 Hz, 1H), 6.24 (t, *J*=12.7 Hz, 1H), 6.13 (s, 2H), 1.65 (br t, *J*=18.9 Hz, 3H). MS ESI m/z 518.2 $(M+H)^+$

Example 391: *(R)*-7-(3-chloro-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



391A: *tert*-butyl *(R)*-(*tert*-butoxycarbonyl)(7-(3-chloro-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate: In a 8 mL Chemglass pressure vial were combined *(R)*-1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (120 mg, 0.328 mmol) and 6-bromo-2,3-dichloropyridine (74.3 mg, 0.328 mmol) in 1,4-dioxane (3.5 mL). To the mixture was added potassium phosphate tribasic, 2M aqueous solution (0.983 mL, 1.97 mmol) and the resulting mixture was sparged with a gentle stream of nitrogen through a needle with stirring for 10 min, followed by addition of dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (13.4 mg, 0.0160 mmol). The mixture was again sparged with a stream of nitrogen with stirring for 5 min and the

vial was capped and heated to 60 °C for 5 h when the reaction was determined to be complete by LCMS. To this crude mixture was added *tert*-butyl (*tert*-butoxycarbonyl)(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (151 mg, 0.328 mmol) and the result was gently sparged with nitrogen and stirring for 5 min. Then, additional dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (13.38 mg, 0.016 mmol) was added, and the mixture was again gently sparged with nitrogen for 5 min before the vial was sealed and heated to 70 °C for 15 h. The aqueous phase was discarded and the organic phase was passed through a short plug of Celite and eluted with EtOAc. The eluted crude material was concentrated in vacuo to a dark brown residue which was dissolved in minimal DCM and loaded atop a hexanes preequilibrated 25g silica cartridge. Elution with 0.5 column volumes of hexanes, then gradient 100% hexanes to 100% EtOAc over 14 column volumes, hold 100% EtOAc for 6 column volumes provided the desired *tert*-butyl *(R)*-(*tert*-butoxycarbonyl)(7-(3-chloro-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (193 mg, 0.234 mmol, 73.2 % yield at 85 % purity) as a thick yellow oil which was carried directly into the next step as-is.

MS ESI m/z 584.4, 684.4 $(M+H)^+$

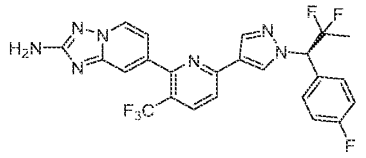
391:: *(R)*-7-(3-chloro-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine: A solution of *tert*-butyl *(R)*-(*tert*-butoxycarbonyl)(7-(3-chloro-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-yl)carbamate (193 mg, 0.234 mmol) in DCM (2 mL) was treated with TFA (1.0 mL, 13.0 mmol). The mixture was stirred overnight at RT. The mixture was concentrated under a gentle stream of nitrogen to a residue. The residue was dissolved in minimum DMF and filtered to give a 2 mL sample which was purified by reverse phase preparative HPLC with the following conditions: Column: XBridge C18, 19 mm x 200 mm, 5 µm particles; Flow Rate: 20 mL/min; Mobile Phase A: 5:95 acetonitrile: water with 10-mM ammonium acetate; Mobile Phase B: 95:5 acetonitrile: water with 10-mM ammonium acetate; Gradient: 25-65% B over 20 min; Column Temperature: 25 °C. Fraction collection was triggered by UV (220 nm) and MS (ESI +). Fractions containing the desired product were combined and dried via centrifugal evaporation to provide *(R)*-7-(3-chloro-6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-

pyrazol-4-yl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (64.2 mg, 0.133 mmol, 55.3 % yield).

^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.65 (d, *J*=7.0 Hz, 1H), 8.60 (s, 1H), 8.25 (s, 1H), 8.07 (d, *J*=8.5 Hz, 1H), 7.82 (d, *J*=8.5 Hz, 1H), 7.76 - 7.69 (m, 3H), 7.29 - 7.20 (m, 3H), 6.26 (t, *J*=13.0 Hz, 1H), 6.11 (s, 2H), 1.70 - 1.60 (m, 3H).

MS ESI m/z 484.2 $(M+H)^+$

Example 392: *(R)*-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3-(trifluoromethyl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine



The title compound *(R)*-7-(6-(1-(2,2-difluoro-1-(4-fluorophenyl)propyl)-1H-pyrazol-4-yl)-3-(trifluoromethyl)pyridin-2-yl)-[1,2,4]triazolo[1,5-*a*]pyridin-2-amine (60.1 mg, 0.116 mmol, 35.4 % yield over 2 steps) was obtained via a similar procedure as that described for **Example 391**, where 2,6-dichloro-3-(trifluoromethyl)pyridine was substituted for 6-bromo-2,3-dichloropyridine in step **391A**.

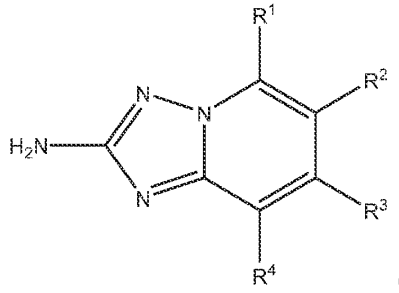
^{1}H NMR (500 MHz, DMSO-d$_6$) δ 8.69 - 8.63 (m, 2H), 8.33 - 8.29 (m, 2H), 8.00 (d, *J*=8.2 Hz, 1H), 7.73 (br dd, *J*=8.2, 5.7 Hz, 2H), 7.44 (s, 1H), 7.27 (t, *J*=8.8 Hz, 2H), 6.99 (br d, *J*=6.5 Hz, 1H), 6.26 (br t, *J*=13.0 Hz, 1H), 6.12 (s, 2H), 1.64 (br t, *J*=19.1 Hz, 3H).

MS ESI m/z 518.2 $(M+H)^+$

Numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

WHAT IS CLAIMED IS:

1. A compound having formula (I), or salt thereof,

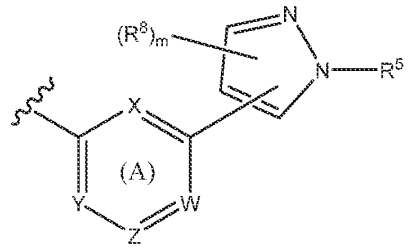


(I)

wherein, independently for each occurrence:

R^1 is –H, -T, -F, -OH, C_{1-3} alkyl, or C_{1-3} alkoxy;

one of R^2 or R^3 is -H, -T, -F, $-OCH_3$, or C_{1-3} alkyl; and the other is



W and Y are –N= or –$C(R^{10})$=;

Z is –N= or –$C(R^{11})$=;

X is –N= or –$C(R^9)$=;

wherein ring A contains 0-2 nitrogen atoms.

R^4 is –H, –F, -OH, C_{1-3} alkyl, or C_{1-3} alkoxy;

R^5 is, -$(CR^a R^b)$-$(CR^cH)_n$-R^{5a}, or -$(CR^a R^b)$-(CO)-R^{5a};

n, at each occurrence, is independently 0 or 1;

R^a is -H, -D, F, C_{1-4} alkyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkyl substituted with 0-2 of F or C_{1-3} alkyl, C_{1-4} deuteroalkyl, C_{1-4} haloalkyl, C_{1-4} hydroxyalkyl, C_{2-4} alkoxyalkyl, or oxetanyl; R^b is -H, -D, or C_{1-3} alkyl;

alternatively, R^a and R^b, along with the carbon to which they are attached, join to form a C_{3-6} cycloalkyl substituted with 0-2 F;

R^c is -H, C_{1-3} alkyl, or -OH;

R^{5a} is C_{6-10} carbocycle or a 5-6 membered heterocycle, the carbocycle or heterocycle being substituted with 0-3 R^6;

R^6 is H, -T, -F, ^{18}F, -Cl, –I, –CN, C_{1-3} alkyl, C_{1-3} alkoxy, nitro, C_{1-3} haloalkyl, or C_{1-3} haloalkoxy;

R^8 is –H, -T, -halo, -CN, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} haloalkyl;

R^9 is –H, -halo, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} haloalkyl;

R^{10} is –H, -T, -halo, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} haloalkyl;

R^{11} is –H, -CN, -C(O)NH_2, - C(O)OH, -halo, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} haloalkyl; and

m is 0 or 1.

2. The compound of claim 1, or salt thereof, wherein

X and Z are N;

Y is C(R^{10}); and

W is C(R^{10}).

3. The compound of claim 1, or salt thereof, wherein

X is N;

Y is C(R^{10});

Z is C(R^{11}); and

W is C(R^{10});

4. The compound of claim 1, or salt thereof, wherein

X is C(R^9);

Y is C(R^{10});

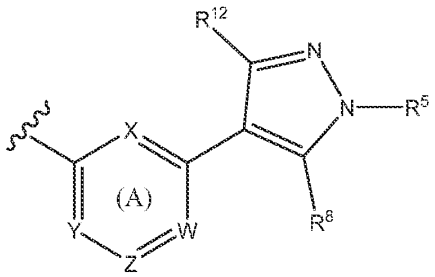
Z is C(R^{11}); and

W is C(R^{10});

5. The compound of claims 1-4, or salt thereof, wherein

R^2 is H; and

R^3 is



6. The compound of claims 1-5, or salt thereof, wherein

R^{5a} is phenyl, pyridyl, oxanyl, tetrahydronaphthalene, or dihydroindene, any of which are substituted with 0-2 R^6; and

R^6 is H, -F, -Cl, −CN, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} haloalkyl.

7. The compound of claims 1-6, or salt thereof, wherein

R^5 is -(CR^a R^b)$_n$-(CR^cH)$_n$-R^{5a}; and

R^a is H, D, C_{1-3} alkyl, C_{1-3} alkoxy, or $-CF_3$.

8. the compound of claims 1-7, or salt thereof, wherein

R^5 is $-(CR^a R^b)-(CR^cH)-R^{5a}$, $-(CR^aR^b)-R^{5a}$, or $-(CH_2)-(CH_2)-R^{5a}$.

9. The compound of claims 1-8, or salt thereof, wherein

R^8 is H;

R^9 is H or F;

R^{10} is H, F, Cl, CH_3, or OCH_3;

R^{11} is H, F, Cl, or CF_3; and

R^{12} is H.

10. The compound of claims 1-9, or salt thereof, wherein

R^4 is H;

R^8 is H;

R^9 is H or F;

R^{10} is H or F;

R^{11} is H; and

R^{12} is H.

11. The compound of claims 1-9, or salt thereof, wherein

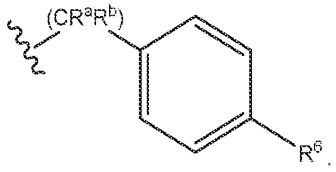
R^5 is $-(CR^aR^b)-R^{5a}$;

R^{5a} is phenyl or pyridyl, any of which are substituted with 0-2 R^6;

R^6 is H, -F, -Cl, CH_3, or OCH_3.

12. The compound of claims 1-9, or salt thereof, wherein

R^5 is



13. The compound of claim 1, or a salt thereof, wherein the compound is selected from the Examples.

14. A pharmaceutical composition comprising one or more compounds of claims 1-13, or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

15. A method of inhibiting casein kinase RIPK1 activity in a patient, comprising administering to the patient in need thereof, a therapeutically effective amount of one or more compounds according to claims 1-13.

16. A method for treating a disease comprising the administration to a subject in need thereof a therapeutically effective amount of at least one compound of claims 1-13, wherein the disease is selected from inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, rheumatoid arthritis (RA), NASH, and heart failure.

17. A method for treating a disease comprising the administration to a subject in need thereof a therapeutically effective amount of at least one compound of claims 1-13, wherein the disease is selected from multiple sclerosis, amyotrophic lateral sclerosis, or Alzheimer's.

18. A method for treating a disease comprising the administration to a subject in need thereof a therapeutically effective amount of at least one compound of claims 1-13, wherein the disease is selected from multiple sclerosis.

19. A method for treating a disease comprising the administration to a subject in need thereof a therapeutically effective amount of at least one compound of claims 1-13, wherein the disease is selected from amyotrophic lateral sclerosis.

20. A method for treating a disease comprising the administration to a subject in need thereof a therapeutically effective amount of at least one compound of claims 1-13, wherein the disease is selected from Alzheimer's.